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Dergimizin 57. cildinin üçüncü ve son sayısı ile tekrar karşınızdayız. Bir yılın bitip yeni bir yıla merhaba demeye hazırlandığımız bu günlerde dergimizi tekrar sizlerin beğenisine sunabilmenin mutluluğunu yaşıyoruz. Bu sayımızda da birbirinden kıymetli araştırmacılarımızın büyük emeklerle ortaya koydukları çalışmaları değerlendirme fırsatı bulacaksınız. Özellikle tıp alanında kullanılan veri kaynaklarının, dizinlerin, yapay zeka kullanımının detaylı şekilde irdelendiği derlemenin büyük bir ilgi çekeceğini düşünüyoruz. Yeni yılda, 58. Cildimizde, birbirinden güzel yeni çalışmalarla sizlerle tekrar buluşmayı umuyoruz.

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Özgün Çalışma / Original Article

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Anxiety-Depression and Sleep Quality in Healthcare Workers Working in the Covid Service During the Covid-19 Pandemic Period

Covıd-19 Pandemisi Döneminde Covid Servisinde Çalışan Sağlık Çalışanlarında Anksiyete-Depresyon ve Uyku Kalitesi

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ABSTRACT

AIM: Covid-19, which mainly causes respiratory tract infections, threatens the physical health of individuals and negatively affects their mental health. In this study we aim to examine the mental health and sleep quality of healthcare professionals working in the covid service during the Covid-19 pandemic.

MATERIAL AND METHOD: A total of 222 healthcare workers in Adana City Hospital, between the ages of 20 and 65 years, working in COVID and non-COVID wards, without any previous diagnosis of anxiety-depression and sleep disorders were included in the study. The BDI (Beck Depression Index) , and BAI (Beck Anksiety Index) , and PSQI (Pitsburg Sleep Quality Index) were applied to healthcare workers between February 15th, 2021 and March 15th, 2021. In addition, healthcare workers were divided into physicians, nurses, and allied health personnel (e.g. laboratory, technicians, cleaners) according to their profession. Those working in the COVID and non-COVID service were evaluated according to the PSQI, BDI , and BAI and compared with each other.

RESULTS: The depression scores of employees in the COVID service were observed to be higher (p=0.035). Although the total PSQI scores and Beck anxiety scores of employees working in the COVID service were higher than of those working in the non-COVID service, the difference was not statistically significant (p=0.19 and p=0.32, respectively).

CONCLUSION: This observational cross-sectional clinical study showed that working in the COVID service with patients with a high risk of infection caused psychological problems such as depression, anxiety, and sleep disorders in healthcare workers.

Key words: Mental health, SARS-COV2, sleep guality

ÖZET

AMAÇ: Ağırlıklı olarak solunum yolu enfeksiyonlarına neden olan Covid-19, bireylerin fiziksel sağlığını tehdit etmekte kalmayıp ruh sağlığını da olumsuz etkilemektedir. Bu çalışmada amacımız, Covid-19 pandemisi döneminde covid servisinde çalışan sağlık çalışanlarının ruh sağlığı ve uyku kalitesini incelemektir.

GEREÇ YÖNTEM: Çalışmaya Adana Şehir Hastanesi' nde COVID ve COVID dışı servislerde çalışan 20-65 yaş arası, daha önce anksiyete, depresyon ve uyku bozukluğu tanısı olmayan toplam 222 sağlık çalışanı dahil edildi. Sağlık çalışanlarına 15 Şubat 2021 ile 15 Mart 2021 tarihleri arasında BDI (Beck Depresyon Indexi), BAI (Beck Anksiyete Indeksi) ve PSQI (Pitsburg Uyku Kalitesi İndexi) uygulandı. Ayrıca sağlık çalışanları görevlerine göre hekim, hemşire ve yardımcı sağlık personeli (laboratuvar, teknisyen, temizlik görevlisi) olarak ayrıldı. COVID ve COVID dışı servislerde çalışanlar anksiyete, depresyon ve uyku kalitesi açısından değerlendirildi ve birbirleriyle karşılaştırıldı.

BULGULAR: COVID servisinde çalışanların depresyon puanlarının daha yüksek olduğu görüldü (p=0,035). COVID servisinde çalışanların toplam PSQI puanları ve Beck anksiyete puanları COVID dışı serviste çalışanlara göre daha yüksek olmasına rağmen aradaki fark istatistiksel olarak anlamlı değildi (sırasıyla p=0.19 ve p=0.32).

SONUÇ: Bu gözlemsel kesitsel klinik çalışma, COVID servisinde enfeksiyon riski yüksek hastalarla çalışmanın sağlık çalışanlarında depresyon, anksiyete ve uyku bozuklukları gibi psikolojik sorunlara neden olduğunu göstermiştir.

Anahtar kelimeler: Ruh sağlığı, SARS-COV2, uyku kalitesi

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INTRODUCTION

The virus that caused many unexplained pneumonia cases in December 2019 was named by WHO (World Health Organization) severe acute respiratory syndrome coronavirus 2 (SARS-COV2).The WHO declared a pandemic in March 2020 and stated that 1716 of the 44,672 infected cases were healthcare workers . [1]This virus, which mainly causes respiratory tract infections, threatens the physical health of individuals and negatively affects their mental health. Besides the general population and patients, health workers are also affected physically and mentally due to intense and risky working conditions.

During the H1N1 pandemic in 2009-2010, approximately 3 million healthcare workers (physcians,nurses,laboratory technicians, cleaning staff,medical waste handlers) were affected by this virus .[2] All healthcare workers were at risk of both infection and death in the COVID-19 pandemic . [3]In previous pandemics, as with all the public, especially healthcare workers have experienced more stress and anxiety about being infected. In the early part of the COVID-19 pandemic, as in the SARS epidemic, various signs of anxiety were shown among healthcare workers .[4]The negative effects on the mental health of healthcare workers, who are at the frontline of the pandemic, may prevent an effective fight against the pandemic. Few healthcare systems have drawn attention to the importance of mental health and sleep habits in effective pandemic management. Many studies have been conducted by researchers to effectively combat the virus. Studies on Covid-19 are usually related to the physical complaints caused by the disease. However, it is very important to deal with the mental health of both patients and healthcare professionals in order to intervent well with the pandemic .[5,6] Due to the SARS-COV2 pandemic in our country, there are a limited number of studies examining the sleep quality and mental health of healthcare professionals working in the covid service.

In this study, we aimed to evaluate the mental health and sleep habits of healthcare professionals working in the covid service and to compare them with those working in non-covid services during the COVID-19 pandemic.

MATERIAL AND METHOD

A total of 222 healthcare workers in Adana City Hospital, between the ages of 20 and 65 years, working in COVID and non-COVID service , without any previous diagnosis of anxiety-depression and sleep disorders were included in the study. The BDI, BAI, and PSQI were applied to healthcare workers between February 15th, 2021 and March 15th, 2021. Those who did not meet the study criteria were excluded from the study. The study was approved by the local ethics committee (decision no. 1257, date 13.01.2021). Patients were informed about the research, it is explained that the information obtained will be kept confidential, and written or verbal consent was obtained from those who volunteered to participate in the study.

The patients were evaluated according to age, sex, educational status, work experience, marital status, number of children, smoking, household type and fear of contagion to family members. In addition, healthcare workers were divided into physicians, nurses, and aallied health personnel (e.g. laboratory, technicians, cleaners) according to their profession. Those working in the COVID and non-COVID service were evaluated according to the PSQI, BDI, and BAI and compared with each other.

Pittsburgh Sleep Quality Index (PSQI): The Self-consistent and repeatable PSQI is used to assess each person's sleep quality over the past 1 month .[7] The PSQI includes 19 questions and is used to evaluate the quality and quantity of sleep, the presence and severity of sleep disorders. It was completed by the same physician through one-to-one interviews with the patients. The PSQI consists of seven items that evaluate subjective sleep quality, sleep delay, sleep duration, sleep efficiency, sleep disturbance, use of sleeping pills, and deterioration in daytime work. The response of each is scored between 0-3 according to symptom frequency. Scoring is 0 if it has never happened during the past month, 1 if it is less than once a week, 2 if it is once or twice a week, and 3 if it is three or more times a week. The sleep quality assessment in the questionnaire is scored as 0 very good, 1 very good, 2 very badly, and 3 very bad. The obtained global score ranges from 0 to 21, and high values indicate poor sleep quality and high levels of sleep disturbance. A global score of 6 or above indicates that the quality of sleep is clinically significantly worse. It has a diagnostic sensitivity of 89.6% and a specificity of 86.5% .[7,8]Agargün et al. adapted the PSQI questionnaire to Turkish patients .[9]

Beck Depression Index (BDI): The BDI was developed to measure the risk of depression, the level of depressive symptoms, and the change in severity in adults (Beck 1961). The Turkish validity and reliability study was conducted by Hisli (1989). It measures the physical, emotional, and cognitive symptoms seen in depression. The scale includes 21 symptom categories with four options each. The individual is asked to mark the sentence that best expresses how they felt in the past week, including the day of practice. Each item is given a score between 0-3, and the depression score is calculated by summing the answers to all questions. A high total score indicates a high level of severity of depression. The total score obtained from the inventory indicates 0-9 normal, 10-18 mild, 19-29 moderate, 30 and above severe depression symptoms .[10]

Beck Anxiety Index (BAI): The BAI, by Beck et al. (1988), is a self-rating scale used to determine the frequency of anxiety symptoms experienced by individuals. The Turkish validity and reliability study was performed by Ulusoy et al. in 1998 .[11] It evaluates the frequency of anxiety symptoms experienced by the individual. It is a self-assessment scale consisting of 21 items and scored between 0-3. The patient is questioned about how much the feeling of distress has bothered them in the last week. Higher scores indicate greater anxiety. The total score obtained from the inventory indicates 0-7 normal, 8-15 mild, 16-25 moderate, 26-63 severe anxiety symptoms.

Statistical analysis: The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk test. Analyses were performed using non-parametric methods because the data did not conform to normal distribution. The Mann-Whitney U test was used for comparisons of two independent groups, and the Kruskal-Wallis test was used for comparisons of more than two groups. The linear relationship between the two continuous variables was evaluated using the Spearman Rho correlation coefficient. In the analysis of categorical data, Chi-square and Fisher's exact tests were used. Data analysis was performed using the SPSS 21 program. The statistical significance level was taken as 0.05.

RESULTS

A total of 222 people, 93 people working in the COVID service and 129 people working in the non- COVID service , were included in the study. Age, sex, education level, work experience, marital status, number of children, smoking, fear of contagion to family members, household type, and the number of people living together showed homogeneous distribution ($p>0.05$) Occupational distributions differed between those working in the COVID service and those working in the non-COVID service ($p<0.001$).

Table 1: Demographic data of healthcare workers and characteristic features

	Covid service (n:93)		Non- Covid service (n:129)		Total (n:222)		
	N	%	n	%	N	%	P
Age							
20-30	22	23.7	13	10.1	35	15.8	0.055
30-40	38	40.9	65	50.4	103	46.4	
40-50	21	22.6	33	25.6	54	24.3	
50 ≤	12	12.9	18	14.0	30	13.5	
Sex							
Male	34	36.6	62	48.1	96	43.2	0.088
Female	59	63.4	67	51.9	126	56.8	
Work experience							
0-5 years	19	20.4	11	8.5	30	13.5	0.088
6-10 years	20	21.5	32	24.8	52	23.4	
11-15 years	23	24.7	37	28.7	60	27.0	
16 ≤ years	31	33.3	49	38.0	80	36.0	
Occupational							
Doctor	60	64.5	97	75.2	157	70.7	**<0.001**
Nurse	29	31.2[t]	14	10.9	43	19.4	
Allied health care professional	4	4.3	18	14.0[t]	22	9.9	
Fear of contagion to family members							
Yes	92	98.9	124	96.1	216	97.3	0.405*
No	1	1.1	5	3.9	6	2.7	

p: Chi-square test *Fisher Exact test [t]expresses the higher ratio (compare column proportions with Z-score) (p<0.05)

Although there was no significant difference in PSQI and anxiety scores according to age groups, depression scores were different(p=0.034). Depression scores were higher in the 20-30 years' age group and those aged over 50 years (p<0.05). There was no significant difference in terms of PSQI and depression scores according to sex, but anxiety scores were higher in women (p<0.001). There was no significant difference in PSQI and anxiety scores according to work experience, but depression scores of employees for 11-15 years were lower (p=0.024), and higher in those who were employed for 0-5years and 16 years and over (p<0.05).There was no significant difference in PSQI and depression scores according to occupational groups, but anxiety scores were lower among physicians (p=0.001), and higher among the others (p<0.05).There was no significant difference in PSQI scores according to the fear of contagion to family members, but depression and anxiety scores were higher in those with a fear of contagion to family members (p<0.05). PSQI, depression, and anxiety scores did not differ according to education level, marital status, number of children, smoking, and house type (p>0.05).

Table 2: The relationship of total PSQI, depression and anxiety score with age, sex, work experience, occupation, , fear of contagion to family members

	PSQI score		Depression score		Anxiety score	
	Mean±SD (min-max)	Median[IQR]	Mean±SD (min-max)	Median[IQR]	Mean±SD (min-max)	Median[IQR]
Age						
20-30	8.09±5.79 (2-37)	7 [5-10]	15.69±7.9 (1-35)	15 [10-22]	12.83±11.18 (0-37)	13 [2-21]
30-40	6.63±3.22 (1-17)	6 [4-9]	12.44±9.97 (0-51)	11 [4-17][4]	10.7±9.54 (0-50)	9 [3-16]
40-50	7.24±3.64 (2-17)	6 [4-10]	15.13±9.99 (0-38)	14.5 [6-23]	14.31±13.2 (0-52)	10 [3.75-23.5]
50 ≤	7.17±2.93 (1-13)	7 [5-10]	15.23±8.01 (1-34)	15 [9-22]	12.73±9.63 (0-39)	11.5 [5-18.5]
p[k]	0.400		**0.034**		0.467	
Sex						
Male	6.92±4.26 (1-37)	6.5 [4-9]	12.75±9.34 (0-40)	11 [5.25-17]	9.18±8.74 (0-35)	7 [2-13]
Female	7.21±3.44 (1-17)	7 [4-9]	14.92±9.52 (0-51)	13.5 [8-21.25]	14.48±11.72 (0-52)	11.5 [5-21]
p[m]	0.376		0.074		**<0.001**	
Work experience						
0-5 years	8.37±6.03 (3-37)	8 [5-10]	15.6±8.97 (0-35)	15 [9.25-24]	13.57±11.13 (0-37)	13 [2.5-21]
6-10 years	6.69±3.23 (1-15)	6 [4-9]	13.31±10.19 (0-51)	11 [6.5-18]	9.88±8.13 (0-33)	10 [2.25-14.75]
11-15 years	6.22±2.73 (2-15)	6 [4-8]	11.6±8.92 (1-40)	10.5 [4-16.75][4]	10.53±10.34 (0-50)	8.5 [2.25-16.75]
16 ≤years	7.5±3.68 (1-17)	7 [5-10]	15.6±9.36 (0-38)	15 [8.25-22.75]	14.41±12.22 (0-52)	11 [5-21.75]
p[k]	0.093		**0.024**		0.131	
Occupational						
Doctor	6.96±3.87 (1-37)	7 [4-9]	13.46±10.26 (0-51)	11 [5-20.5]	10.59±10.23 (0-52)	8 [2-16]
Nurse	7.42±3.6 (2-16)	7 [4-9]	15.81±7.28 (2-35)	14 [11-22]	14.91±11.08 (0-43)[t]	13 [7-22]
Allied health care professional	7.27±3.92 (3-17)	6 [4-10]	14.09±7.05 (1-31)	15 [7.75-19]	18.32±11.79 (1-50)[t]	16 [11-26.25]
p[k]	0.802		**0.085**		**0.001**	
Fear of contagion to family members						
yes	7.07±3.81 (1-37)	7 [4-9]	14.22±9.46 (0-51)	13 [7-20]	12.27±10.54 (0-52)	10 [4-19]
no	7.33±4.23 (4-15)	6 [4-10.5]	5.33±6.25 (0-14)	3.5 [0-11.75]	9.33±19.98 (0-50)	1 [0-15.5]
p[m]	0.972		**0.013**		**0.046**	

pk:Kruskal Wallis test (more than two independents group comparisons) . pm: Mann Whitney U test (two independents group comparisons)

Except for component 4, PSQI components were found to be high in covid service workers (p>0.05).Although the total PSQI scores and Beck anxiety scores of employes working in the COVID sevice were higher than of those working in the non-COVID service, the difference was not statistically significant (p=0.19and p=0.32, respectively). The depression scores of employees in the COVID service were observed to be higher (p=0.035)

Table 3: PSQI, Beck depression and Beck anxiety scores in the covid service and non-covid service

	Covid service			Non- Covid service			Total			P
	Mean±SD	Median[IQR]	Min-Max	Mean±SD	Median[IQR]	Min-Max	Mean±SD	Median[IQR]	Min-Max	
Component 1: sleep quality	1.43±0.73	1 [1-2]	0-3	1.32±0.79	1 [1-2]	0-3	1.36±0.77	1 [1-2]	0-3	0.294
Component 2: sleep latency	1.65±1.03	2 [1-2]	0-3	1.43±0.98	1 [1-2]	0-3	1.52±1.01	2 [1-2]	0-3	0.099
Component 3: sleep duration	0.72±0.84	1 [0-1]	0-3	0.56±0.79	0 [0-1]	0-3	0.63±0.81	0 [0-1]	0-3	0.099
Component 4: sleep efficiency	0.12±0.32	0 [0-0]	0-1	0.18±0.38	0 [0-0]	0-1	0.15±0.36	0 [0-0]	0-1	0.222
Component 5. Sleep disturbance	1.37±0.6	1 [1-2]	1-3	1.32±0.61	1 [1-2]	0-3	1.34±0.61	1 [1-2]	0-3	0.850
Component 6: Use of sleeping medication	0.24±0.71	0 [0-0]	0-3	0.18±0.65	0 [0-0]	0-3	0.2±0.68	0 [0-0]	0-3	0.309
Component 7: Daytime dysfunction	2.02±3.51	1 [0-3]	0-31	1.78±1.86	1 [0-3]	0-6	1.88±2.68	1 [0-3]	0-31	0.997
Global PSQI score	7.54±4.39	7 [5-9.5]	2-37	6.75±3.31	6 [4-9]	1-17	7.08±3.81	7 [4-9]	1-37	0.190
Beck anxiety score	12.57±10.29	11 [4-19]	0-52	11.91±11.24	9 [3-18]	0-50	12.19±10.84	10 [3-19]	0-52	0.322
Beck depression score	15.49±9.61	14 [9-20.5]	0-51	12.89±9.28	11 [5.5-19]	0-40	13.98±9.48	13 [6-19.25]	0-51	**0.035**

p: Mann Whitney U test (two independents group comparisons)

DISCUSSION

In our country, as in the whole world, Covid-19 has affected healthcare workers both physically and mentally, as well as the general public. Many health workers have had sleep disorders and mental health problems, and some even needed treatment. While studies on the disease and patients are being carried out during the pandemic period, studies on healthcare professionals are quite insufficient. In our study, we found that the symptoms of depression were significantly higher in those working in the COVID service compared with those working in the non-COVID service. We observed more depression symptoms in those with a fear of contagion to family members, in those aged 20-30 years and over 50 years, with less than 5 years of professional experience and more than 16 years. Moreover ; we observed more anxiety symptoms in women, allied health personnel and those with fear of contagion to their family members.

Lai et al. found 50.4% depressive symptoms and 44.6% anxiety symptoms in 1257 healthcare workers during the COVID-19 pandemic .[12] They used the Patient Health Questionnaire-9(PHQ-9) for dep-

ression, the Generalized Anxiety Disorder-7(GAD-7) questionnaire for anxiety, and the Insomnia Severety Index(ISI) questionnaire for sleep disorders. Liu et al. , on the other hand, found 50.7% depressive symptoms, 44.7% anxiety symptoms,and 36.1% sleep disturbances in 1563 healthcare workers during the COVID-19 pandemic . [13] In their study, Liu et al. used the same questionnaires .However, Lai et al. accepted anxiety scores above 5 as significant, whereas Liu et al. accepted above 8 as significant. In our study, 61.7% of 222 healthcare workers had depression symptoms, 59% had anxiety symptoms, and 62.2% had sleep disorders. We used the , BDI ,BAI, PSQI scale. Differences between studies may be due to differences in lifestyles between countries and the use of different types of questionnaires to assess mental health and sleep quality.

During the COVID-19 pandemic, medical healthcare workers (physicians, nurses) showed a higher prevalence of insomnia, anxiety, depression and somatization disorder, compared with non-medical healthcare workers (secretaries, technicians) .[14] In contrast, a study was conducted in Singapore showing that non-medical healthcare workers have a higher prevalence of anxiety than others .[15] Our study is not as health workers and non-medical health workers; we divided them into 2 groups as covid service and non covid service.We found the depression symptoms of all staff working in the COVID service to be significantly higher. In the treatment and care of patients with COVID-19, healthcare workers take very strict precautions to protect themselves from high virus exposure. Long-term use of protective equipment, difficulty in eating, dealing with patients and their relatives who do not comply with safety instructions causes physical and mental fatigue.This may cause depression, insomnia, and sleep rhythm disorder .[16] These studies show that support mechanisms are needed for all healthcare workers during the COVID-19 pandemic, regardless of their job role and exposure to the virus.

In a study conducted during the COVID-19 pandemic in China, 50.4% of healthcare workers reported depression, 44.6% of anxiety, 34.0% of insomnia and 71.5% of distress symptoms. · Nurses, women, frontline healthcare workers had more severe symptoms than other healthcare workers .[12] In our study similar to this study, anxiety and depression symptoms were more common in women, and women's sleep quality was found to be worse. Here, we think that sex hormones may be effective and may cause women to take more responsibility in family and child care. However, in our study, we found that anxiety symptoms were higher in allied health personnel, not nurses. This may be due to less medical information about the outbreak, lack of personal protective equipment, less education on infection control measures, and less access to psychological support . [15]

In a study conducted to evaluate the psychological responses of physicians and related factors during the COVID-19 epidemic, 64.7% of the participants showed depression, 51.6% anxiety, and 41.2% stress symptoms. Risk factors included being female, younger age, being single, having less work experience, and working on the frontlines . [17] In our study, we examined all healthcare professionals, not just physicians, and we saw more depressive symptoms in those aged 20-30 years and over 50 years. The reason for this may be the lack of professional experience at a young age and the fear of death due to the virus, which increases with the accompanying comorbid diseases if aged over 50 years. In addition, depressive symptoms were more common in those with less than 5 years' professional experience and more than 16 years in our study. The reason for this difference between studies may be that pandemic management, working conditions, access to protective equipment, and support services vary from country to country.

Some studies have shown that medical personnel in China treating patients with COVID-19 had poor sleep quality and increased anxiety levels . [18] Also, compared with other occupational groups (teachers, institution workers), healthcare workers had lower sleep quality during the COVID-19 pandemic . [19] According to Leila and Wang, shift work and exposure to patients with COVID-19 were stated as the most important risk factors affecting sleep quality .[1,20] In our study, we did not compare health care workers with other occupational groups, but we divided them into two as COVID service and non-COVID service workers. Many studies have used the PSQI total score, and we divided the PSQI questionnaire into seven components in our study .[18-21] Subjective sleep quality, sleep latency, sleep duration, sleep disturbance, drug use and daytime function scores were found to be higher and more sleep disturbances were observed in the COVID service employees. We concluded that working in the COVID service increased sleep disorders.

The COVID-19 outbreak has had a dramatic impact on healthcare workers around the world. For healthcare workers, COVID-19 has a high risk of infection and a high risk of death. In addition to fears about COVID-19 exposure, lack of personal protective equipment, heavy workload and working hours due to the rapid increase in the number of patients, and staying away from the family due to a high infection rate may cause psychological problems in healthcare workers .[3] Healthcare workers working on the front lines are afraid of being infected and infecting their relatives at home due to the increasing virus load. Not only the risk of death and disability on health workers of covid 19, but also the economic, social and secondary psychological conditions that will affect the family in case of a possible death and disability are also very important. In our study, 98.9% of those working in the COVID service and 96.1% of those working in the non-COVID service were found to be afraid of contagion to a family member. This fear has been found to significantly increase symptoms of anxiety and depression. The development of more specific procedures and treatment protocols, as well as educational activities and increased knowledge of disease prevention and coping, will contribute to boosting the morale of healthcare workers dealing with the pandemic . [4]

Limitation: Our study was conducted in a single center and with a limited number of patients. Multicenter, prospective studies with more patients are needed in the future. In addition, the Beck Depression and Beck Anxiety Scale can only inquire about symptoms, not make a diagnosis of depression and anxiety. Health care workers should be examined with more detailed and prospective tests.

CONCLUSION

This observational cross-sectional clinical study showed that working in the COVID service with patients with a high risk of infection caused psychological problems such as depression, anxiety, and sleep disorders in healthcare workers. In such a life-threatening pandemic, psychological evaluations should be routine.

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Normal İşiten Tinnitus Hastalarında Yüksek Frekans Odyometrinin Rolü

The Role of the High Frequency Audiometry in Tinnitus Patients with Normal Hearing

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ÖZET

AMAÇ: Konvansiyonel odyometri testi normal olan tinnitus hastalarında yüksek frekans odyometri testinin önemini ve olası patolojilerin erken saptanmasındaki rolünü araştırmak.

GEREÇ VE YÖNTEM: Ocak 2018-Ocak 2021 tarihleri arasında İzmir Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi KBB Kliniğine belirgin işitme kaybı olmaksızın uğultu ve çınlama şikayeti ile başvuran ve konvansiyonel odyometri sonuçları normal olan 18-45 yaş arası 60 hasta ile herhangi bir şikayeti olmayan konvansiyonel odyometri sonuçları normal olan 54 hasta çalışmaya dahil edildi. Çalışmaya dahil edilen tüm hastalara yüksek frekanslı odyometri de yapıldı.

BULGULAR: Çalışmaya katılan tüm hastaların sağ ve sol kulakları için saf ses ve yüksek frekans ortalamaları karşılaştırıldığında, her iki kulakta saf ses ve yüksek frekans değerleri arasında istatistiksel olarak anlamlı fark bulundu.

SONUÇ: Mevcut bulgular ışığında saf ses odyometrinin koklea ve işitmeyi tam olarak değerlendiremediği görülmektedir. Yüksek frekanslı odyometride tespit edilen bulguların tinnituslu hastaların tedavisine yönelik yapılacak araştırmalar için ufuk açıcı olduğuna ve yüksek frekans odyometrinin işitme kaybının erken teşhisi için değerli veriler sağladığına inanıyoruz. Kurulacak yeni odyometri ünitelerinde ve mevcut altyapının modernizasyonunda mutlaka yüksek frekanslı odyometri cihazlarının ekipmanlara dahil edilmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: Tinnitus, Yüksek Frekans Odyometri, Saf Ses Odyometri

ABSTRACT

AIM: To investigate the importance of high frequency audiometry test and its role in early detection of possible pathologies in tinnitus patients with normal conventional audiometry test.

MATERIAL AND METHOD: 60 patients, aged between 18-45 years, who applied to İzmir Bakırçay University Çiğli Training and Research Hospital ENT Clinic between January 2018 and January 2021 with the complaint of buzzing and ringing in the ear without significant hearing loss and had normal conventional audiometry results, also 54 patients who had normal conventional audiometry results without any complaints were included in the study. High frequency audiometry was also performed on all patients included in the study.

RESULTS: When pure tone and high frequency averages for the right and left ears of all patients participating in the study were compared, a statistically significant difference was found between pure tone and high frequency values in both ears.

CONCLUSION:: In the light of current findings, it can be seen that pure tone audiometry can not fully evaluate the cochlea and hearing. We believe that the findings detected in high frequency audiometry are stimulating for research to be conducted on the treatment of patients with tinnitus and that high frequency audiometry provides valuable data for the early diagnosis of hearing loss. We think that high frequency audiometry devicess hould definitely be included in the equipment in the new audiometry units to be established and the modernization of the existing infrastructure.

Keywords: Tinnitus, High Frequency Audiometry, Pure Tone Audiometry

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GİRİŞ

İşitmenin objektif ve subjektif yollarla değerlendirilmesi Dünya Sağlık Örgütü'nün bir halk sağlığı problemi olarak ilan ettiği işitme kaybının önlenmesi ve uygun müdahale yöntemlerinin belirlenmesi için çok önemlidir. Yaş, gürültüye maruziyet ve ototoksik ilaç kullanımı gibi birçok faktörün işitmeyi etkilediği bilinmektedir. İşitme kaybını en aza indirmek için ise hem işitme kaybının erken tespiti hem de erken müdahale şarttır. İşitme, geleneksel saf ses odyometri (125-8000 Hz) ile değerlendirilir.[1] Ancak insan kulağının 20000 Hz'e kadar ulaşan bir işitsel aralığı vardır. Literatürde, 9000 ile 20000 Hz arasındaki frekanslara genişletilmiş yüksek frekanslar denir.[2, 3]Yüksek frekanslar, işitme hasarındaki eşik kaymasının ilk gözlenebildiği frekanslardır.[4] Bu frekansların özellikle konuşulanları anlama ve gürültülü ortamlarda konuşmayı ayırt etme performansını etkilediği bilinmektedir.[1, 5]

Tinnitus, ortada bir dış kaynak olmaksızın ses algılanmasıdır. Tinnitusun birçok formu olabilir ve çeşitli faktörler etiyolojisine katkıda bulunabilir. Bununla birlikte, işitme kaybının tinnitus için en önemli risk faktörünü temsil ettiği iyi bilinmektedir.[6] Tinnitus şikayeti olan hastaların birçoğunda geleneksel saf ses odyometride normal bulgular olduğu gözlenmektedir. Bu nedenle geleneksel saf ses odyometrinin koklear hasarı objektif olarak yansıtmayacağı öne sürülmektedir.[7] Yapılan güncel çalışmalarda normal odyogramı olan tinnitus hastalarında, kontrol gruplarına göre koklear ölü bölgelere daha sık rastlandığı ve dış tüy hücre hasarının olduğu, genişletilmiş yüksek frekans bölgesinde işitme eşiklerinde bozulmaların görülebildiği saptanmıştır.[8, 9]Ayrıca bir diğer çalışmada normal işitmesi olan tinnituslu hastalarda işitsel beyin sapı yanıtlarında 1. dalga amplitüdü düşük saptanmıştır, bu da tüy hücrelerinin ve işitme sinir liflerinin saf ses odyometri sonuçları normalken bile hasar görebildiğini düşündürmektedir.[7] Tüm çalışmalar birlikte ele alındığında, tinnitus hastalarında "gizli işitme kaybı" teorisini desteklemektedir. Fakat tinnitus hastalarının rutin değerlendirmesinde yüksek frekanslı odyometrinin standart bir tanı prosedürü olarak önerilip önerilmeyeceği sorusu halen devam etmektedir.[10] Geleneksel saf ses odyometri ile değerlendirilmeyen yüksek frekansların yaşa bağlı işitme kaybı, ototoksisite ve akustik travma gibi faktörlerle bozulduğu bilinmektedir. Yaşla birlikte işitme yeteneği yavaş yavaş azalır; bu kayıp en yüksek frekanslarda başlar ve giderek en düşük frekanslara doğru uzanır.[2] Benzer şekilde, sisplatin gibi ototoksik ilaçların etkilerinin erken saptanması noktasında da yüksek frekans odyometrinin önemli rol oynayabileceği düşünülmektedir.[11]

Geleneksel saf ses odyometri ile saptanamayan işitme kayıplarının erken tanısının, bu bireylerin koruyucu önlemler alarak işitme kayıplarının ilerlemesinin engellenerek koruyucu hekimlik noktasında önemli bir kazanım sağlanılacağı düşünülmektedir. Bu çalışmanın amacı, tinnitus şikayetiyle polikliniğe başvuran ve geleneksel saf ses odyometri testlerinde normal işitme tanısı almış olan bireylere yüksek frekans odyometri testi uygulayarak teste yansımamış patolojilerin erken tespit edip edilemeyeceğini araştırmak ve yüksek frekans odyometri testinin tinnitus yakınması olan bireylerde öneminin vurgulanmasıdır.

GEREÇ VE YÖNTEM

İzmir Bakırçay Üniversitesi Çiğli Eğitim Araştırma Hastanesi Kulak Burun Boğaz (KBB) Kliniğine Ocak 2018-Ocak 2021 tarihleri arasında başvuran 18-45 yaş aralığındaki toplamda 114 hasta çalışmaya dahil edilmiştir. Çalışma kontrol ve çalışma olmak üzere iki gruptan oluşmaktadır. Çalışma grubu işitme kaybı şikayeti olmayıp kulakta uğultu veya çınlama şikayetiyle başvuran ve geleneksel saf ses odyometri sonuçlarına normal işitme tanısı almış, 60 hastadan oluşmaktadır. Kontrol grubu ise çınlama şikayeti olmayan ve normal işitmeye sahip 54 hastadan oluşmaktadır. 20 dB ve altındaki işitme eşikleri normal işitme olarak kabul edilmiştir. Kulakta uğultu ve çınlama şikayeti tarifleyen hastalardan pulsatil tinnitus sorgulanarak; tarifleyenler çalışma dışı bırakıldı. 45 yaş üzerindeki hastalar presbiakuziye bağlı etiyolojik faktörler nedeniyle çalışma dışı bırakıldı. Gürültüye maruziyet, akustik travma ve ototoksik ilaç kullanım öyküsü olan hastalar da çalışma dışı bırakılmıştır. Çalışma için İzmir Bakırçay Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan izin alınmış, tüm etik ilke ve bildirgelere uyularak çalışma gerçekleştirilmiştir.

Enstrümantasyon ve Prosedür

Çalışmaya dahil edilen tüm hastalara yüksek frekans odyometrisi yapılmıştır. Farklı frekanslarda (125-20000Hz) işitme eşiğini belirlemek için hava iletimli saf ses odyometri testi yapılmıştır.

Geleneksel saf ses odyometri testi (125-8000Hz) Madsen Orbiter 922 klinik odyometre ve supra-aural Telephonics TDH-39 kulaklıklar ile tamamlanmıştır. Yüksek frekans odyometrisi (9000-20000Hz) aynı odyometre ve Koss HV/1A circumaural kulaklık ile yapıldı. Tüm odyometrik malzeme, üretici tavsiyelerinin yanı sıra ISO 389-112 ve IEC 60645-113 standartlarına göre kalibre edilmiştir. Dönüştürücüler ISO 389-112 standartlarına göre kalibre edilmiştir.

Odyometrik testler, eğitimli personel tarafından, ISO 8253-114 standartlarına uygun olarak, ses geçirmez bir kabin içerisinde manuel olarak gerçekleştirilmiştir. İşitme eşikleri, Modifiye Hughson-Westlake yöntemine göre belirlenmiştir. Tüm frekanslardaki işitme eşikleri desibel işitme seviyesinde (dB HL) sunulmuştur. Geleneksel saf ses odyometri ve yüksek frekans odyometrisinde elde edilen işitme eşikleri her frekans için (250-20000 Hz) kaydedilmiştir. Hastaların 500-1000-2000-4000 Hz için saf ses ortalamaları belirlenmiştir. Tüm frekanslarda ortalama işitme eşikleri belirlenerek, standart sapmaları hesaplanmıştır. Sağ ve sol kulak için saf ses ve yüksek frekans değerlerinin karşılaştırılmasında eşleştirilmiş örneklem t testi kullanılmıştır. P değeri hesaplanmış, $p<0,05$ anlamlı olarak kabul edilmiştir.

BULGULAR

Çalışmaya katılan hastalarda en küçük yaş 18, en büyük yaş ise 45'ti. Hastaların ortalama yaşı ise 36,3 olarak hesaplandı. Çalışmaya dahil edilen hastaların 30'u (%26,3) erkek 84'ü (%73,7) ise kadındı. Hastaların 500-1000-2000-4000 Hz için sağ ve sol kulak için saf ses ortalamalarına ait veriler Tablo 1'de özetlenmiştir.

Tablo 1: Çalışmaya katılan hastaların Odyometri Sonuçlarına İlişkin Veriler

Saf Ses Hava Yolu İşitme Eşiği	Minimum	Maximum	Ortalama	Standart Sapma
Sağ Geleneksel Saf Ses Odyometri	5 dB	20 dB	15,8 dB	3,991
Sol Geleneksel Saf Ses Odyometri	5 dB	20 dB	15,1 dB	4,864
Sağ Yüksek Frekans Odyometri	10 dB	55 dB	41,9 dB	11,609
Sol Yüksek Frekans Odyometri	5 dB	55 dB	41,1 dB	11,526

Hastaların sağ ve sol kulak için saf ses ortalamaları sırasıyla karşılaştırıldığında istatistiksel anlamlı fark bulunmamıştır ($p=0,183$ ve $p=0,808$).

Çalışmaya katılan tüm hastaların sağ kulak için saf ses ve yüksek frekans ortalamaları karşılaştırıldığında saf ses ve yüksek frekans değerleri arasında istatistiksel olarak anlamlı fark bulunmuştur ($p=0$). Benzer şekilde, tüm hastaların sol kulak için saf ses ve yüksek frekans ortalamaları karşılaştırıldığında saf ses ve yüksek frekans değerleri arasında istatistiksel olarak anlamlı fark bulunmuştur ($p=0$).

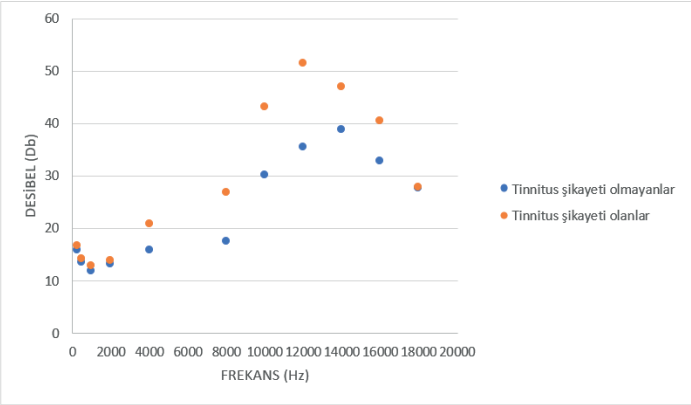
Kontrol ve çalışma grupları arasında sağ ve sol kulak için 500-1000-2000-4000 Hz saf ses ortalamaları karşılaştırıldığında istatistiksel anlamlı fark saptanmamış olup (sırasıyla; $p=0,183$ ve $p=0,808$); yüksek frekans odyometri ortalama sonuçları arasında hem sağ hem sol kulak için istatistiksel olarak anlamlı fark saptanmıştır (sırasıyla; $p=0$ ve $p=0,012$).

Tinnitus şikayeti olmayan hastalarda sağ ve sol kulakta işitme eşiği ortalamaları sırasıyla 250 Hz için 15,8 dB ve 15,6 dB, 500 Hz için 13,5 dB ve 13,4 dB, 1000 Hz için 11,9 dB ve 11,9 dB, 2000 Hz için 13,2 dB ve 13,5 dB, 4000 Hz 15,9 dB ve 17,7 dB, 8000 Hz 17,5 dB ve 19,8 dB, 10000 Hz için 30,2 dB ve 29,4 dB, 12000 Hz için 35,4 dB ve 38,8 dB, 14000 Hz için 38,75 dB ve 40,3 dB, 16000 Hz için 32,8 dB ve 36,2 dB, 18000 Hz için 27,6 dB ve 27,2 dB olarak hesaplanmıştır.

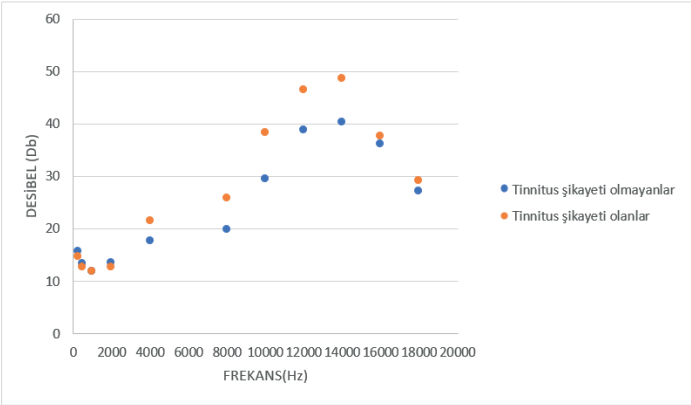
Tinnitus şikayeti olan hastalarda sağ ve sol kulakta işitme eşiği ortalamaları sırasıyla 250 Hz için 16,7 dB ve 14,7 dB, 500 Hz için 14,2 dB ve 12,6 dB, 1000 Hz için 12,9 dB ve 11,8 dB, 2000 Hz için 13,75 dB ve 12,75 dB, 4000 Hz için 20,9 dB ve 21,5 dB, 8000 Hz için 26,8 dB ve 25,8 dB, 10000 Hz için 43,2 dB ve 38,25 dB, 12000 Hz için 51,5 dB ve 46,5 dB, 14000 Hz için 46,9 dB ve 48,7 dB, 16000Hz için 40,5 dB ve 37,7 dB, 18000 Hz için 27,75 dB ve 29,2 dB olarak hesaplanmıştır. Sağ ve sol kulak için bu değerler tinnitusu olan ve olmayan hastalar

için Tablo 2 ve 3'te özetlenmiştir.

Tablo 2: Sağ Kulak İçin Tüm Frekanslardaki İşitme Eşiği Ortalamaları



Tablo 3: Sol Kulak İçin Tüm Frekanslardaki İşitme Eşiği Ortalamaları



TARTIŞMA

Çalışmamıza katılan hastalarda sağ ve sol kulak için saf ses ortalamaları ile yüksek frekans ortalamaları arasında anlamlı fark saptanmıştır. Geleneksel odyogram sonuçları normal olan hastalarda yüksek frekans odyometride saptanan bozulma ileride gelişecek işitme problemleri için erken uyarı niteliği taşıyor olabilir. Yapılan çalışmalarda geleneksel saf ses odyometrinin koklear hasarı güvenilir bir şekilde yansıtmadığı ileri sürülmüştür. Test edilen frekanslar arasındaki veya 8 kHz üzerindeki frekansları kodlayan tüy hücrelerinin hasarı, geleneksel odyometri tarafından tespit edilmez. Buna göre, normal odyogramı olan hastalarda koklear ölü bölgeler, dış tüy hücresi hasarları ve buna bağlı olarak genişletilmiş yüksek frekans bölgesinde işitme eşiğinde bozulmalar saptanabilir.[8, 9] Çalışmamızdaki veriler de bu bilgileri desteklemektedir. Çalışmamızda özellikle 12 kHz ve 14 kHz seviyelerinde işitme eşiklerinde belirgin yükselme saptanmıştır. Yüksek sesle müzik dinleyen genç erişkinler üzerine yapılan bir çalışmada da yüksek frekans işitme eşik seviyelerinde yükselme olduğu saptanmıştır[4] Bizim çalışmamızda da saptanan yüksek frekanslardaki bu bozulma üzerine spesifik frekanslara özel ileri çalışmalar yapılması gerektiği ortadadır. Nitekim patlama gürültüsüne mesleki maruziyeti inceleyen güncel bir çalışmada da yüksek frekanslar incelenmese de meslek yılı arttıkça özellikle 4 kHz ve 8kHz'de belirgin etkilenme olduğu ortaya konulmuştur[12]. Alınacak önlemlerle çalışmamızda yüksek frekans odyometride saptanan bu bozulma ile hastaların işitme kaybına sebep olabilecek etiyolojik faktörlerden korunması ileride gelişebilecek ileri düzey işitme kayıplarını engelleme noktasında önemli kazanımlar sağlayabilir.

Güncel bir çalışmada özellikle gürültülü ortamlarda konuşmayı algılamada yüksek frekansların önemli rol oynadığı gösterilmiştir. Geleneksel odyometride normal işiten fakat gürültülü ortamlarda konuşmayı ayırt etmekte zorlanan hastalarda; yüksek frekanslarda çalışmamızdaki hipotezle uyumlu olarak kayıp saptanmıştır.[13] Bazı hayvan ve insan çalışmalarından elde edilen kanıtlar, gürültüye maruz kalmanın ve yaşlanmanın, tüy hücrelerinde herhangi bir azalma veya işitme eşiklerinde yükselme meydana gelmeden önce iç tüy hücreleri ve koklear sinir lifleri arasındaki sinaps kaybıyla ilişkili olduğuna dair kanıtlar sunmuştur.[14, 15] Bu koklear "sinaptopati" ilk olarak daha yüksek frekanslarda ortaya çıkar ve insan çalışmalarında "belirsiz işitsel işlev bozukluğu" ve "gizli işitme kaybı" dahil olmak üzere çeşitli isimlerle bilinen bir dizi zorluğa katkıda bulunduğu varsayılmıştır.[7, 14, 16] Standart odyometrinin nörodejenerasyonun bu tür erken belirtilerini tespit etmedeki başarısızlığının ardından, bazı çalışmalar gürültüye maruz kalma, ototoksisite ve yaşlanmanın neden olduğu gizli işitme kaybının tespitinde genişletilmiş yüksek frekanslı odyometrinin tanısal faydasını incelemiştir ve yüksek frekans odyometrinin bu bozulmaya ilişkin veriler sunabildiği gösterilmiştir.[1, 2, 4]

Çalışmamızda çınlama şikayeti olan hastaların saf ses odyometri sonuçları ile yüksek frekans odyometri sonuçları arasında istatistiksel olarak anlamlı fark saptanmıştır. Bu durum geleneksel saf ses odyometrinin çınlama şikayeti tarifleyen hastalarda tüm yönleriyle değerlendirme sağlamakta yetersiz kalabildiği hipotezini desteklemektedir. Yapılan güncel bir çalışmada; normal odyogram bulguları olan tinnitus hastalarında yüksek frekans odyometride işitme eşiklerinde düşüşler saptanmıştır. Tinnitus tariflenen tarafta bu bulgular daha belirgin olarak saptanmıştır[17] Çalışmamızla uyumlu olarak saptanan bu veriler tinnitus hastalarında geleneksel odyometrinin değerlendirme noktasında yetersiz kaldığını göstermektedir. Bu noktadan hareketle yüksek frekans odyometri tinnitus hastalarında değerli veriler saptamaktadır.

SONUÇ

Yüksek frekansların rolüne ilişkin bilinmez birçok nokta mevcuttur. Mevcut bulgular ışığında saf ses odyometrinin kokleayı ve işitmeyi tam olarak değerlendiremediği görülebilmektedir. Yüksek frekans odyometride saptanan bulguların tinnituslu hastaların tedavisine yönelik yapılacak araştırmalar için ufuk açıcı olduğunu ve yüksek frekans odyometrinin işitme kayıplarının erken tanısı noktasında değerli veriler sağladığına inanıyoruz. Bu nedenle özellikle genç popülasyonda yüksek frekans odyometride saptanan kayıpların, hastaların başlarda standart testlere yansımayan yüksek sesle müzik dinleme gibi işitme kaybı etiyolojik faktörlerinden erken kaçınması ile koruyucu hekimlik açısından değerli bir tarama testi olduğuna inanıyoruz. Yeni kurulacak odyometri ünitelerinde ve mevcut altyapının modernizasyonunda mutlaka yüksek frekans odyometri cihazlarının da ekipmana dahil edilmesi gerektiğini düşünüyoruz.

Yazarlık Katkıları

Fikir/Kavram: CA, TU, TM, Çalışma Tasarımı ve Dizayn: CA, TU, TM, Kaynak ve literatür değerlendirmesi: CA, TU, TM, Veri Toplama ve/veya İşleme: CA, TU, TM, Analiz ve/veya Yorum: CA, TU, TM, Yazım: CA, TU, TM

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Özgün Çalışma / Original Article

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Antihypertensive Treatment Compliance in Stroke Patients with Hypertension

Hipertansiyonlu İnmeli Hastalarda Antihipertansif Tedavi Uyumu

Esra TAŞKIRAN [1], Bilgin ÖZTÜRK[2]

ABSTRACT

AIM: Stroke is responsible for approximately 6 millions of all the annual deaths worldwide. An effective method to prevent stroke and its comorbidities is the adequate control of the risk factors. This study aimed to evaluate the compliance of stroke patients in their antihypertensive treatment and the frequency of measuring blood pressure.

MATERIAL AND METHOD: Patient's files were retrieved from the hospital patients database using the ICD codes (I60-64, I67-69). In total, 5289 files were accessed. The age, sex, hypertension diagnosis, treatment compliance, the frequency of blood pressure measurements, and the presence of hypertensive crisis during admission were evaluated. Data about compliance with drug treatment and blood pressure monitoring was accepted only if it was received directly from the patient or their relatives. These parameters were also obtained from epicrisis retrospectively.

RESULTS: In this study, 478 files [female: male, 201 (42.1%):277 (57.9%)] with complete data were included. Among the patients, 76.3% had a good to very good treatment compliance and 29.8% had a good to very good frequency of blood pressure measurement. During admission, 23% of patients were in hypertensive crisis.

CONCLUSION: In patients with poor drug compliance and who did not have their blood pressure regularly measured, hypertensive crises occurred significantly more often. Strict blood pressure monitoring and regular doctor follow-ups are neglected by patients. Drug compliance is insufficient to prevent stroke and blood pressure monitoring and follow-ups are also important points to consider.

Key words: Blood pressure, Hypertension, Patient compliance, Stroke

ÖZET

AMAÇ: İnme, dünya çapında tüm yıllık ölümlerin yaklaşık 6 milyonundan sorumludur. İnmeyi ve eşlik eden hastalıklarını önlemenin en etkili yöntemi, risk faktörlerinin yeterli şekilde kontrol altına alınmasıdır. Bu çalışmada, inme hastalarının antihipertansif tedaviye uyumunu ve kan basıncı ölçüm sıklığını değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM: Hastane veri tabanından ICD kodları (I60-64, I67-69) kullanılarak toplam 5289 dosyaya erişildi. Bu dosyalardan yaş, cinsiyet, hipertansiyon tanısı, tedavi uyumu, kan basıncı ölçüm sıklığı ve başvuru sırasında hipertansif kriz varlığı bilgileri değerlendirildi. İlaç tedavisine uyum ve kan basıncı takibine ilişkin veriler epikrizlerden retrospektif olarak incelenerek doğrudan hasta veya yakınlarından alındığı takdirde kabul edildi.

BULGULAR: Bu çalışmaya, verileri eksiksiz olan 478 dosya (kadın: erkek, 201 (%42,1):277 (%57,9)) dahil edildi. Hastaların %76,3'ü iyi-çok iyi tedavi uyumuna ve %29,8'i iyi-çok iyi tansiyon ölçüm sıklığına sahipti. Başvuru sırasında hastaların %23'ü hipertansif krizdeydi.

SONUÇ: İlaç uyumsuzluğu olan ve kan basıncı düzenli olarak ölçülmeyen hastalarda, hipertansif krizler önemli ölçüde daha sık meydana geldiği gözlendi. Sıkı tansiyon takibi ve düzenli doktor takipleri hastalar tarafından ihmal edilmektedir. İlaç uyumu inmeyi önlemede yetersiz olarak görülmüş olup tansiyon takibi ve hastaların kontrolleri de dikkat edilmesi gereken önemli noktalardır.

Anahtar kelimeler: Kan basıncı, Hipertansiyon, Hasta uyumu, İnme

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INTRODUCTION

Stroke is responsible for approximately 6 million of all the annual deaths throughout the world and constitutes a very important part of the health expenditures [1,2]. In the UK, £100 million can be annually saved if 80% of patients affected by stroke can remain compliant with their antihypertensive treatment. Mennini in 2015 has reported that a 70% increase in antihypertensive treatment compliance would save more than £300 million in five European countries (Germany, Italy, France, Spain, United Kingdom) [3].

The best method of preventing stroke and its associated complications is the elimination or control of the risk factors. Hypertension plays a significant role in stroke risk factors. In the USA, deaths associated with hypertension have increased up to 61.8% between 2000 and 2013 [4]. Other studies have shown that hypertension control can reduce the incidence of stroke by 30%–40% [5,6]. Therefore, national, and international guidelines recommend the screening, treatment, and control of hypertension [7,8].

Several agents, such as calcium channel blockers, diuretics, beta blockers, angiotensin-converting enzyme inhibitors and receptor blockers are used for controlling blood pressure. However, it is estimated that approximately 50% of the patients have poor treatment compliance. Treatment compliance is proportional to the improvement in blood pressure, decrease in hospitalization rate and mortality, and lower treatment costs [9,10]. Various studies have evaluated the incidence of stroke and treatment compliance [5,6,11-16].

The aim of the present study was to evaluate antihypertensive treatment compliance and the frequency of measuring blood pressure in stroke patients and their relationship with hypertensive crisis.

MATERIAL AND METHOD

Patients treated in our service between 2011 and 2016 were selected from the hospital system using the stroke ICD codes (I60-64, I67-69). In total, 5289 files were accessed. The parameters evaluated included age, sex, the presence of hypertension prior to stroke, compliance with antihypertensive treatment, the frequency of blood pressure measurements, and the presence or absence of hypertension during admission. Only 478 patients with the complete data of these parameters were included. Data about compliance with drug treatment and blood pressure monitoring was accepted only if it was received directly from the patient or their relatives. These parameters were obtained from epicrisis retrospectively. A scale of 0–4 (0: None-Patient never uses drugs, 1: Bad-Use only if patient feels bad, 2: Moderate-Use half of what is prescribed, 3: Good- Forgets only a few doses monthly, and 4: Very Good-Use exactly as prescribed) was used to assess the level of treatment compliance. For assessing the frequency of tension measurement, the scale of 0–4 (0: None-No controls, 1: Bad- Checks only if patient feels bad, 2: Moderate-1-2 checks monthly, 3: Good- 1-2 checks weekly, and 4: Very good- Checks everyday) was used. For evaluating hypertension attacks, systolic blood pressure >180 mmHg and diastolic blood pressure > 110 mmHg were used.

Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, and maximum). More than two groups that are independent and not compatible with normal distribution were compared using the Kruskal–Wallis test. Comparison of two groups that were independent and not compatible with normal distribution was performed using the Mann–Whitney U test. The chi-square (or Fisher's exact test in appropriate situations) was used for the relationship between categorical variables. Statistical significance level was set at $p > 0.05$. MedCalc Statistical Software version 12.7.7 was used for analyses (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

This study was approved by the ethics committee of the Haydarpaşa Training and Research Hospital (1491-137-15/1539).

RESULTS

Files of 5289 stroke patients were reviewed, and 478 patients with complete information of all parameters were included. The mean age of patients was 76.5 ± 9.9 years, and 201 (42.1%) were females and 277 (57.9%) were males (Table 1).

Table 1: Distribution of parameters

		N	%
Sex	Female	201	42.1
	Male	277	57.9
Hypertension	None	160	33.5
	Yes	318	66.5
Treatment compliance	None	12	3.8
	Poor	10	3.2
	Moderate	21	6.7
	Good	47	14.9
	Very Good	225	71.4
Tension controls	None	40	12.7
	Poor	78	24.8
	Moderate	103	32.7
	Good	69	21.9
	Very Good	25	7.9
Arrival hypertension crisis	None	368	77.0
	Yes	110	23.0

Only 76.3% of patients reported good to very good treatment compliance and 29.8% reported good to very good frequency of blood pressure measurement. Among the 478 stroke patients, 23% had a systolic blood pressure of >180 mmHg and a diastolic blood pressure of >110 mmHg.

When the ages of patients were examined according to their sex, females were found to have stroke 4.5 years later than males (Mann–Whitney U-text, $p < 0.001$). With regard to the presence of hypertension, there was a statistically significant difference in terms of age distribution (Mann–Whitney U test, $p < 0.05$). Thus, the incidence of hypertension was higher in elderly patients. With regard to the drug compliance and blood pressure control, there was no statistically significant difference in terms of age distribution (Kruskal–Wallis test, both $p > 0.05$)

Table 2: Significancy of age

	Sex	n	Mean	Min.	Maks.	p
Age	Female	201	79,1	50	101	**<0,001***
	Male	277	74,6	28	97	
	Hypertension					
	No	160	74,9	28	96	**0,026****
	Yes	318	77,3	51	101	
	Drug compliance					
	No	12	71,1	58	87	0,192***
	Bad	10	80,1	61	94	
	Moderate	21	77,9	60	92	
	Good	47	77,8	58	95	
	Very good	225	77,3	51	97	
	Blood pressure control					
	No	40	78,8	61	94	0,634****
	Bad	78	76,8	58	95	
	Moderate	103	77,2	56	96	
	Good	69	76,6	57	97	
	Very good	25	78,6	51	97	

*Statistically significant (Mann-Whitney U p<0.001)

** Statistically significant (Mann-Whitney U p<0.05)

*** Statistically NOT significant (Kruskal Wallis p>0,05)

**** Statistically NOT significant (Kruskal Wallis p>0,05)

Hypertension was more frequent in women with stroke than in men (chi-square test, p < 0.05). There was no statistically significant difference between sex and drug compliance (Fisher's exact test, p > 0.05) and between sex and treatment controls (Fisher's exact test, p > 0.05)

Table 3: Significancy of sex

		Female	Male	p
Hypertension	No	57 (28,4)	103 (37,2)	**0,044***
	Yes	144 (71,6)	174 (62,8)	
Drug compliance	No	5 (3,5)	7 (4,0)	0,722**
	Bad	4 (2,8)	6 (3,5)	
	Moderate	10 (7,0)	11 (6,4)	
	Good	17 (12,0)	30 (17,3)	
	Very good	106 (74,6)	119 (68,8)	
Blood pressure control	No	21 (14,8)	19 (11,0)	0,405***
	Bad	29 (20,4)	49 (28,3)	
	Moderate	47 (33,1)	56 (32,4)	
	Good	35 (24,6)	34 (19,7)	
	Very good	10 (7,0)	15 (8,7)	

* Statistically significant (Chi-square test, p < 0.05)

** Statistically NOT significant (Fisher's Exact p>0,05)

*** Statistically NOT significant (Fisher's Exact p>0,05)

Hypertensive crisis was more frequently detected in patients with previous hypertension diagnosis (Fisher's exact test, p < 0.05)

Table 4: Hypertension and Hypertensive crisis

		Hypertension		
		No	Yes	p
Hypertensive crisis	No	136 (85,0)	232 (73,0)	**0,002***
	Yes	24 (15,0)	86 (27,0)	

* Statistically significant (Fisher's Exact p<0,05)

In the analysis of drug compliance and blood pressure control, the p-value was not calculated because the number of subgroup patients was low

Table 5: Drug compliance vs Blood pressure control

		Drug compliance				
		None	Poor	Moderate	Good	Very Good
Blood pressure controls	None	9 (75.0)	8 (80.0)	4 (19.0)	4 (8.5)	15 (6.7)
	Poor	3 (25.0)	2 (20.0)	14 (66.7)	22 (46.8)	37 (16.4)
	Moderate	0 (0.0)	0 (0.0)	3 (14.3)	17 (36.2)	83 (36.9)
	Good	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.5)	65 (28.9)
	Very Good	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	25 (11.1)

Since the number of patients was low, the p value could not be calculated.

The incidence of hypertensive crises was significantly higher in patients with poor drug compliance and in those who did not have their blood pressure regularly measured (Fisher's exact test, p < 0.001)

Table 6: Blood pressure control vs Hypertension crisis

		Hypertension crisis		
		No	Yes	p
Blood pressure control	None	19 (8.3)	21 (24.7)	**<0.001***
	Poor	31 (13.5)	47 (55.3)	
	Moderate	86 (37.4)	17 (20.0)	
	Good	69 (30.0)	0 (0.0)	
	Very Good	25 (10.9)	0 (0.0)	

*Fisher's Exact p<0.001

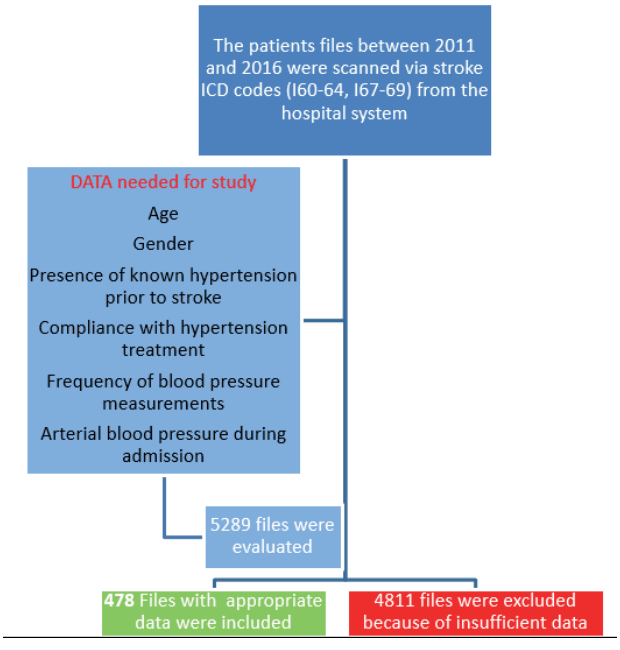

Figure 1: Flowchart of the study

DISCUSSION

In this retrospective clinical study, 478 patients with the diagnosis of stroke within a period of 6 years were evaluated. The results revealed an increase in the incidence of hypertension in proportion to age. Female patients had a stroke at younger ages than the male patients, and hypertension was more frequently monitored in females with a stroke than males. Hypertensive crisis was more frequent in patients with a previous diagnosis of hypertension and in those who did not have any regular blood pressure measurements and had poor antihypertensive treatment compliance.

Hypertension is an important risk factor for stroke, and attempts have been made to develop adequate treatment strategies for the regulation of hypertension. In that regard, regular doctor appointment to follow-up antihypertensive treatment, frequent blood pressure monitoring, and drug compliance are the most common methods.

High blood pressure is a very important and controllable risk factor in stroke. Similarly, other studies have revealed a direct relationship between patient compliance and antihypertensive treatment with the prevention of stroke [17-19]. In these studies, a decrease in the incidence of stroke was shown to correlate with health expenditures, hospital admission rates, reductions in emergency admission, and mortality rates [6, 13, 14, 16, 20].

In the meta-analysis by Abegaz et al., 45.2% of hypertensive patients had poor treatment compliance and females had lower drug compliance than males [21]. In another study by Kettani et al., a treatment compliance of >80% was shown to reduce the risk of cerebrovascular diseases by 22% [6]. Other studies have suggested that treatment compliance is suboptimal in >50% of patients with uncontrolled hypertension [22]. In the cohort study by Blaschke et al., 16907 patients were examined; 40% of these patients did not follow any treatment in the first year and 4% of these patients did not receive any treatment in the first year [23]. It is determined that decreasing the systolic blood pressure by 10 mmHg decreases the cardiovascular disease risk by 20%, stroke risk by 27%, and mortality risk related to all reasons by 13% [24].

Bruno et al declared that adherence to HTN medications was significantly lower among black patients and those without health insurance [25]. Additionally, as a result of the study conducted by Bawand et al. involving 530 patients, it was concluded that stroke-related mortality and morbidity rates could be significantly altered by persuading individuals to regularly monitor their blood pressure and maximize adherence to antihypertensive medications. The same study also indicated that increasing health literacy and reducing smoking rates would play a crucial role in achieving these goals [26].

The studies conducted thus far have investigated whether patients use antihypertensive drugs using several different methods. The effects of treatment compliance on stroke, complications, and health expenditures are also examined. However, in our daily practice, although some patients have very good compliance, they do not have their blood pressure regularly measured and have high blood pressures because of insufficient treatments received. However, other studies have reported such patients to have very good treatment compliance. However, because their blood pressure values are high, they should be accepted as high risk in terms of complications due to hypertension. Therefore, patients who had stroke for the first time in our study were examined for the presence of hypertension, treatment compliance, frequency of blood pressure measurements, and hypertensive crisis.

CONCLUSION

Hypertension control is very important in the etiology of stroke, and it has been determined that this control can be achieved via regular doctor appointments, strict blood pressure monitoring, and drug compliance. It has been observed that treatment compliance is independent of age and sex. Therefore, there is a need for prospective, randomized, double-blind, multi-center, and long-term follow-up studies involving a larger number of patients to demonstrate the efficacy and strength of these strategies in controlling hypertension.

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Özgün Çalışma / Original Article

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Phyllodes Tumors of the Breast: Recurrence and the Importance of Clinical Follow-up

Memenin Filloid Tümörleri: Nüks ve Klinik Takibin Önemi

Berkay KILIÇ[1], Burak İLHAN[2]

ABSTRACT

AIM: Phyllodes tumors, including benign and borderline types, have a substantial potential for recurrence. The objective of this study was to evaluate histologic features that can help predict recurrences and to emphasize the importance of close follow-up in this regard.

MATERIAL AND METHOD: The cilinopathologic characteristics of patients, treatment approaches, and follow-up data of the 64 patients treated between 2006 and 2022 at the Institute of Oncology, Istanbul University, with the diagnosis of phyllodes tumors, were evaluated retrospectively by examining the patient files and pathology records.

RESULTS: The median age was 41 (range: 26–63) years, and the median tumor size was 52 (range: 11–210) mm. The phyllodes tumors were classified as benign (n=36, 56.27%), borderline (n=11, 17.24%), and malign (n=17, 26.49%). High mitotic number, cellular pleomorphism, stromal overgrowth, tumoral heterogeneity, and tumor margin irregularity were independent prognostic factors in the development of local recurrence. The common feature of tumor recurrence in the process of benign and borderline phyllodes tumors was tumor margin irregularity. The median recurrence time for phyllodes tumors was 29.5 (range: 10–64) months. In the study, seven out of 10 recurrences were when excision was performed with an insufficient surgical margin of closer than 1 cm and in three cases when a clear surgical margin was far more than 1 cm (p=0.045).

CONCLUSION: Phyllodes tumors were benign, borderline, and malignant. A negative surgical margin of ≥1cm plays a major role in the management. The study may emphasize the importance of close follow-up, given that the recurrence period is short, especially if tumor margin irregularity is detected on definitive pathological examination, even if it is benign or borderline.

Keywords: Phyllodes tumor, breast surgery, margin status

ÖZET

AMAÇ: Benign ve borderline tipleri de dahil olmak üzere filloid tümörlerin önemli bir nüks potansiyeli vardır. Bu çalışmanın amacı nüksleri öngörmeye yardımcı olabilecek histolojik özellikleri değerlendirmek ve bu konuda yakın takibin önemini vurgulamaktır.

GEREÇ VE YÖNTEM: Çalışmada 2006-2022 yılları arasında İstanbul Üniversitesi Onkoloji Enstitüsü'nde filloid tümör tanısıyla tedavi edilen 64 hastaların klinikopatolojik özellikleri, tedavi yaklaşımları ve takip verileri hasta dosyaları ve patoloji kayıtları üzerinden retrospektif olarak incelenerek değerlendirildi.

BULGULAR: Medyan yaş 41 (aralık: 26–63) yıl ve medyan tümör boyutu 52 (aralık: 11–210) mm idi. Filloid tümörler şu şekilde sınıflandırıldı: Benign (n=36, %56,27), borderline (n=11, %17,24) ve malign (n= 17, %26,49). Yüksek mitotik sayı, hücresel pleomorfizm, stromal aşırı büyüme, tümöral heterojenite ve tümör sınırı düzensizliğinin lokal nüks gelişiminde bağımsız prognostik faktörler olduğu bulundu. Benign ve borderline filloid tümörlerde nüksün ortak özelliği tümör sınırı düzensizliğiydi. Filloid tümörlerin tekrarlama süresi medyan 29,5 (aralık: 10–64) ay olarak belirlendi. Çalışmada 1 cm'den daha yakın yetersiz cerrahi sınır ile eksizyon yapıldığında 10 olgudan yedisinde, 1 cm'den uzakta temiz cerrahi sınır elde edilen üç olguda ise nüks gözlendi (p=0,045).

SONUÇ: Filloid tümörler benign, borderline ve malign olarak sınıflandırıldı. Tedavisinde ≥1 cm'lik negatif cerrahi sınır önemli bir rol oynar. Çalışmamız, nüks süresinin kısa olması nedeniyle, özellikle benign veya borderline tipte olsa bile, kesin patolojik incelemede tümör sınırında düzensizlik saptanması durumunda yakın takibin önemini vurgulamaktadır.

Anahtar Kelimeler: Filloid tümör, meme cerrahisi, cerrahi sınır

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INTRODUCTION

The etymology of "Phyllodes" can be traced back to its Latin origin, "Phyllodium" where the essence of leaf-like characteristics is unveiled through microscopic observation. In 1838, German physician Johannes Müller first described phyllodes tumor (PT) as cystosarcoma phyllodes despite the uncommon cystic component of these tumors and the rarity of malignancy.[1,2] The term PT was first reported by the World Health Organization in 1981, with Rosen providing a histological subclassification into benign, borderline, and malignant categories.[3] A significant proportion of phyllodes tumors, ranging from 35% to 64%, are classified as benign, while the remainder falls into the borderline and malignant categories.[4] Local recurrence (LR) rates vary, with benign PT having a recurrence rate of 17% and malignant PT at 27%.[5] If inadequately managed, malignant PT can demonstrate a tendency for rapid growth and the potential for metastasis.

The histologic grading of PT generally correlates with prognosis; however, histologic features might not always reflect the clinical behavior in individual patients.[6,7] These lesions diagnosed as malign or benign with fine needle aspiration remain difficult preoperatively. While the risk of misdiagnosis is very high with fine needle biopsy, both epithelial and stromal elements should be seen and evaluated for diagnosis in core needle biopsy (CNB).[8] In this way, CNB can provide important information about tumor features. An accurate preoperative pathological diagnosis enables precise surgical planning, optimizing excision margin assessment and reducing the risk of tumor recurrence.[9-11]

Surgical excision is the cornerstone of treatment for phyllodes tumors. It is crucial to remove these tumors with a safe surgical margin. If a clear surgical margin is not achieved, a re-excision may be necessary, as LR primarily occurs when adequate margins are not established.[12,13] Barth Jr RJ reported local recurrence rates following breast-conserving surgery (BCS) at 8% for benign phyllodes tumors and between 21% and 36% for borderline and malignant types.[14]

The role of adjuvant radiotherapy (RT) in the management of phyllodes tumors is still a subject of debate. In cases of borderline and malignant tumors, where there may be concerns about achieving clear surgical margins following BCS or mastectomy due to large tumor size, RT is thought to potentially lower the risk of LR. Recent studies indicate that administering RT in these scenarios may effectively mitigate the risk of LR.[15]

The role of chemotherapy (CT) in managing these tumors is a topic of debate. Chemotherapy may be suitable for aggressive malignant tumors, but the decision to proceed with CT should involve careful consideration of its potential benefits and drawbacks, discussed with the patient. For hormone-sensitive tumors that contain an epithelial component, adjuvant hormone therapy is a possible treatment option, though its effectiveness has not been established.[16]

This study aimed to identify specific tumor characteristics associated with recurrence and to determine key factors to consider for ongoing follow-up.

MATERIAL AND METHOD

Study population

Tumor features and patient-related factors were analyzed to predict tumor progression after surgical treatment of 64 patients diagnosed with PT, treated between May 2006 and December 2022, at the Institute of Oncology, Istanbul University. The exclusion criteria were those who did not receive further treatment at our institution or did not have pathology slides available. Each case of PT was reviewed by a dedicated breast pathologist at our institution to confirm the histological diagnosis. The study was approved by the Ethics Committee of Istanbul University (form number: 2023/402; Date: 17.03.2023). A written informed consent form was obtained from all patients.

Clinical presentation

Patients presenting with a rapidly growing but clinically benign breast lump were assessed for family history and underwent thorough physical examinations. In some cases, the lesion may have been present for several years before suddenly increasing in size and causing symptoms. The tumors vary in size, ranging from small to very large, and typically exhibit a mobile, multinodular appearance that is not painful. Although rare, ulceration and adherence to the chest wall can occur even in malignant tumors. Clinical adenopathy has been reported in 20% of patients; however, the occurrence of metastatic disease in the axilla is uncommon.

Mammography (MG) and ultrasonography (USG) are standard imaging techniques used for evaluating breast lumps. Mammography typically reveals a well-circumscribed oval or lobulated mass with rounded edges, sometimes accompanied by a radiolucent halo and coarse calcifications around the lesion. Color Doppler ultrasonography generally shows marked hypoechogenicity, posterior acoustic shadowing, and poorly defined tumor margins. Magnetic resonance imaging (MRI) may also be employed. On MRI, a heterogeneous internal structure with non-enhancing septation displays hypointense signals on T1-weighted images and hyper- or isointense signals on T2-weighted images. Benign phyllodes tumors typically exhibit slow initial enhancement with a persistent delayed phase, while malignant tumors show rapid initial enhancement with a wash-out phenomenon. Following clinical evaluation and imaging, core biopsy is primarily used for pathological diagnosis.

Surgical procedure

After the initial diagnosis, lumpectomy was performed aiming for a macroscopic surgical margin of 1 cm. If the surgical margin was found to be close, positive, or unknown, re-excision was conducted. In cases where BCS was deemed unsuitable due to the tumor size-to-breast ratio, mastectomy (with or without reconstruction) was performed. Axillary interventions were carried out in select cases based on the surgeon's discretion.

Pathological examination

Phyllodes tumors are classified based on the grading system established by the World Health Organization in 2012[5] and revised in 2019.[17] Tumors are classified into three categories: benign, borderline, and malignant, based on specific criteria. Benign tumors are characterized by fewer than 5 mitoses observed per 10x magnification field, low stromal excess, minimal atypia, and low cellularity, with evident growth patterns and intact surgical margins. Borderline tumors show 5 to 9 mitoses per 10x magnification field, exhibit moderate stromal atypia and cellularity, and may have excessive growth, with either intact or infiltrated surgical margins. In contrast, malignant tumors present more than 10 mitoses per 10x magnification field, accompanied by high levels of stromal cellularity, atypia, pleomorphism, and stromal overgrowth, as well as infiltrating surgical margins. The Ki-67 index is also included in the pathological evaluations when applicable

Table 1. WHO subclassification of phyllodes tumors

	Benign	Borderline	Malign
Mitosis of Per 10 HPF	<5	5-9	≥10
Stromal overgrowth	Absent	Absent/focal	Present
Stromal atypia	Mild	Mild-Moderate	Marked
Stromal cellularity	Mild	Mild-Moderate	Marked
Cellular pleomorphism	Mild	Mild-Moderate	Marked
Intratumoral heterogenity	Variability in structure and stromal cellularity or atypia in a single tumor		
Tumor margin	Projections of tumor stroma into the peritumoral stroma or adipose tissue		
Leaflike pattern	Enhanced intracanalicular pattern, characterized by projection of cellular stroma into epithelial-lined clefts of cystic spaces		
HPF: high-power field, WHO: World Health Organization			

The pathologist assesses the surgical margins and potential invasion of the pectoral muscle in each specimen. During the pathological analysis performed intraoperatively, a surgical margin was deemed positive if any tumor margin was in contact with the ink or if the margin was less than 2 mm, necessitating re-excision. A surgical margin of two mm or greater is considered negative.

Statistical analysis

Patient demographics, tumor characteristics, surgical methods, and postoperative tumor progression data were compiled using Microsoft Excel software (Microsoft Luxembourg S.a.r.l., 20 Rue Eugene Ruppert, Luxembourg). For the analyses, Fisher's exact test or the χ^2 test was employed for two-tailed univariate assessments. The independent sample t-test was utilized to compare the mean values between two independent groups. Variables that were available for all cases and were statistically significant in the univariate analyses were incorporated into the multivariate analyses using binary logistic regression. A p-value of less than 0.05 was deemed statistically significant. Statistical analyses were performed using version 21.0 of the Statistical Package for the Social Sciences (IBM Corp.).

Table 2. Differences between benign, borderline and malign phyllodes tumors

		Benign & Borderline n=47	Malign n=17	p
Age, years, median		36 (26–51)	42 (34–63)	0.029
Tumor size, mm, median		42 (11–85)	75 (45–210)	0.006
Tumor grade	**1-2**	46 (97.92%)	1 (5.86%)	<0.001
	3	1 (2.08%)	16 (94.14%)	
Mitotic number of Per 10 HPF, mean		3.42 (±3.11)	31.62 (±13.32)	<0.001
Stromal atypia	**Mild/ Moderate**	45 (95.69%)	3 (17.62%)	<0.001
	Marked	2 (4.31%)	14 (82.38%)	
Cellular pleomorphism	**No**	46 (97.89%)	3 (17.61%)	<0.001
	Yes	1 (2.11%)	14 (82.39%)	
Stromal overgrowth	**No**	45 (95.68%)	2 (11.82%)	<0.001
	Yes	2 (4.32%)	15 (88.18%)	
Tumoral heterogeneity	**No**	44 (93.59%)	2 (11.79%)	<0.001
	Yes	3 (6.41%)	15 (88.21%)	
Tumor margin irregularity	**No**	35 (74.51%)	2 (11.78%)	<0.001
	Yes	12 (25.49%)	15 (88.22%)	
Ki-67, mean		2.43 (±3.63)	36.21 (±8.52)	<0.001
Initial surgery	**BCS**	45 (95.74%%)	11 (64.71%)	0.003
	Mastectomy	2 (4.26%)	6 (35.29%)	
Margin positivity		4 (8.52%)	5 (29.41%)	0.048
Overall surgery	**BCS**	42 (89.43%)	8 (47.18%)	0.001
	Mastectomy	5 (10.57%)	9 (52.82%)	
Local recurrence		4 (8.52%)	6 (35.32%)	0.017
HPF: high-power field, BCS: breast-conserving surgery				

RESULTS

Patient characteristics

Phyllodes tumors were classified as follows: benign (n=36, 56.27%), borderline (n=11, 17.24%), and malign (n=17, 26.49%). The median age was 41 (range: 26–63) years, and the tumor size was 52 (range: 11–210) mm. Patients with malign PT were older than patients with benign & borderline PT (p=0.029), and tumors of malignant tumors were larger than those tumors of benign & borderline tumors (p=0.006). While the tumor grade of malign tumors was usually three, it was grade one or two for benign & borderline tumors (p<0.001). The mitotic number was significantly higher in malign phyllodes tumors (p<0.001). Marked stromal atypia, cellular pleomorphism, stromal overgrowth, tumoral heterogeneity, and tumor margin irregularity tended significantly more to exist in malign tumors compared with benign & borderline ones. The Ki-67 index of a malign PT was higher than the benign and borderline ones (p<0.001).

Fifty-six patients had BCS, whereas eight patients underwent a mastectomy. Three patients underwent axillary sampling, and no nodal metastases were found. Three patients had re-excisions added to BCS, and six patients underwent mastectomy due to positive margins following BCS. Margin positivity was observed in nine out of 56 (16.14%) breast-conserving surgeries: five were malignant, two were borderline, and two were benign phyllodes tumors. Patients with malignant tumors underwent mastectomy more frequently than breast-conserving surgery (p=0.003).When the cases converted to mastectomy due to margin positivity were added, patients with malign PT still had more mastectomies (p=0.001). The overall mastectomy rate was 14/64 (21.92%). Local recurrence was observed more often in patients with malign PT than in patients with benign & borderline PT during the follow-up period (p=0.017).

Local recurrence

The median follow-up period was 72 (range: 12–124) months. Eight LR (three benign PT, one borderline PT, and four malign PT), one single distant metastasis (malign PT), and two LR plus distant metastasis (malign PT) occurred in follow-up, with a total of 10 LR. One LR developed following mastectomy, and the remaining nine following BCS. There is no relationship between recurrence and patient age (p=0.53). Large tumor size, tumor grade of three, high mitosis score, marked stromal atypia, cellular pleomorphism, stromal overgrowth, tumoral heterogeneity, tumor margin irregularity, and high ki-67 index had a role in the development of recurrence in univariate analyses. Among the factors affecting recurrence according to univariate analyses, other than large tumor size and tumor grade of three, others were also determined as independent significant risk factors in multivariate analysis. There was no difference in the recurrence rate following overall mastectomy and BCS (p=0.299). Seven patients developed LR with a surgical margin ≥1 cm that could not be obtained, and three patients with a 1 cm clear margin (p=0.045). Therefore, a surgical margin of ≥1 cm was critical in the LR. Tables 3 and 4 summarize the factors of recurrence.

Table 3. Features of recurrent phyllodes tumors

Local recurrence		**No n=54**	**Yes n=10**	**p**
Age, years, mean		39.22 (±11.91)	36.62 (±11.92)	0.532
Tumor size, mm, mean		47.12 (±41.93)	85.51 (±56.53)	0.019
Tumor grade	**1-2**	42 (77.82%)	5 (50.0%)	<0.001
	3	12 (22.18%)	5 (50.0%)	
Mitotic number of Per 10 HPF, mean		8.22 (±11.41)	25.12 (±20.91)	0.001
Stromal atypia	**Mild/ Moderate**	43 (79.63%)	5 (50.0%)	0.06
	Marked	11 (20.37%)	5 (50.0%)	
Cellular pleomorphism	**No**	45 (83.32%)	4 (40.0%)	0.008
	Yes	9 (16.69%)	6 (60.0%)	
Stromal overgrowth	**No**	43 (79.64%)	4 (40.0%)	0.017
	Yes	11 (20.36%)	6 (60.0%)	
Tumoral heterogeneity	**No**	42 (77.83%)	4 (40.0%)	0.024
	Yes	12 (22.17%)	6 (60.0%)	
Tumor margin irregularity	**No**	37 (68.52%)	0	<0.001
	Yes	17 (31.53%)	10 (100.0%)	
Ki-67, mean		6.12 (±6.61)	17.82 (±15.31)	0.001
Overall surgery	**BCS**	41 (82.0%)	9 (90.0%)	0.299
	Mastectomy	13 (18.0%)	1 (10.0%)	
Margin	**2-10 mm**	19 (35.22%)	7 (70.0%)	0.045
	>10 mm	35 (64.78%)	3 (30.0%)	
HPF: high-power field, BCS: breast-conserving surgery				

Table 4. Multivariate analysis on recurrence

	Odds Ratio	p	95% C.I. for EXP(B)	
			Lower	Upper
Tumor size ≥50 mm	1.27	0.071	0.88	1.43
Tumor grade 1-2 vs. 3	1.25	0.082	0.86	1.41
Mitotic number of ≥20 per 10 HPF	1.76	0.025	1.40	2.44
Cellular pleomorphism	2.02	0.015	1.75	3.21
Stromal overgrowth	1.77	0.017	1.41	2.45
Tumoral heterogeneity	1.66	0.022	1.27	2.68
Tumor margin irregularity	2.98	0.004	0.22	6.72
Ki-67 ≥20	2.04	0.014	1.76	3.25
Nagelkerke R Square	0.63			
Hosmer and Lemeshow Test	0.97			
HPF: high-power field, CI: 95% confidence interval				

Among patients with malign PT, two patients received adjuvant CT plus RT, and one patient received only CT following mastectomy. Three patients who underwent conservative surgery had CT and RT, and four received only RT. Lung metastasis developed in the eleventh month, and bone metastasis in the eighth month after surgery. Three recurrences developed in patients following conservative surgery who received RT. Nine of 17 patients with malign PT in our series received RT. Three of six malignant phyllodes cases with LR were among the patients who received adjuvant RT, and three LRs developed in the remaining 11 cases with malign PT who did not receive RT. In addition, LR developed in two of six patients who received adjuvant CT during the follow-up.

Study endpoint

Regarding recurrent phyllodes tumors, a common tumor feature to predict recurrence for benign & borderline and also for malign tumors was tumor margin irregularity. In addition, LR developed in three of four benign phyllodes tumors and one of four borderline tumors with tumor margin irregularity based on definitive pathological examination. The median recurrence time was 29.5 (range: 10–64) months. Five re-excisions could be performed in patients with recurrence within the first three years (mean, 13.82 months) after conservative surgery. However, patients required four mastectomies (mean, 50.52 months) due to the prolonged recurrence detection process. A possible explanation was that it was due to the rapid growth pattern of these tumors. All recurrent benign & borderline tumors underwent conservative surgeries, and excisions were within a 2-5 mm surgical margin, which led to the interpretation that this surgical margin may not be sufficient for benign and borderline tumors with margin irregularity. Features of recurrent phyllodes tumors are shown in Table 5.

Table 5. Recurrent phyllodes tumors

Tumor type	Age	Size, mm	Grade	Mitotic number	P/O/H	M.I.	Surgery	Margin, mm	LRFS, months	Overall surgery
Benign	26	23	1	1	-	+	BCS	2–5	10	Rx
Benign	28	40	1	1	-	+	BCS	2–5	18	Rx
Benign	33	130	1	1-2	-	+	BCS	2–5	43	Mas
Borderline	27	20	1	5	-	+	BCS	2–5	56	Mas
Malign	43	54	3	45	+	+	BCS	>10	14	Rx
Malign	29	110	3	40	+	+	BCS	5–10	39	Mas
Malign	53	210	3	50	+	+	Mas	5–10	26	Rx-Mas
Malign	41	70	3	50	+	+	BCS	>10	11	Rx
Malign	33	40	3	20	+	+	BCS	>10	64	Mas
Malign	38	55	3	40	+	+	BCS	5–10	16	Rx

LRFS: local recurrence-free survival, BCS: breast-conserving surgery, Rx: re-excision, mm: millimeter, Mas: mastectomy, P/O/H: pleomorphism, overgrowth, heterogeneity, M.I.: margin irregularity

DISCUSSION

Phyllodes tumors account for 0.5% of all breast neoplasms.[18] These tumors peak between 35–49 years of age, while fibroadenomas (FA), which can be difficult to differentiate diagnostically, are usually observed at a younger age.[19] The median age of our series was 41 (range: 26–63) years. In addition, patients with malign PT were older than patients with other PT subtypes.

Typically a PT appears on ultrasound and mammography as a clinically fast-growing mass with a smoothly circumscribed or slightly lobulated contour.[20] All patients in this series underwent USG and MG, except in some cases MG due to young age. In some studies performed with MRI, there were no significant differences between benign PT and FA. However, malignant PT usually had a higher contrast enhancement pattern in T1-weighted sections than benign PT.[21] In our series, all patients with preoperative diagnosis of mixed histology or malignant PT underwent a magnetic resonance imaging, but not in all cases with benign PT diagnosis.In this study, marked stromal atypia, cellular pleomorphism, stromal overgrowth, tumoral heterogeneity, and tumor margin irregularity tended significantly more to exist in malign tumors compared with benign & borderline ones. In addition, while 60–70% of these tumors were benign in other series, this rate was 56.3% in our series, with a relatively lower rate of benign tumors.[22] A possible explanation was due to the tendency of surgeons to probably not refer patients diagnosed with benign PT to a cancer center.

The literature indicates that the average size of phyllodes tumors typically ranges from 4 to 7 cm.[23] Additionally, Mallick et al. noted that the median size of malignant tumors can reach as high as 13.6 cm.[24] In our study, the median tumor size was 52 (range: 11–210) mm, with malignant tumors measuring larger (75 mm) compared to the benign and borderline subtypes (42 mm).

According to the National Comprehensive Cancer Network (NCCN), the standard approach involves excision with a safe margin of at least 1 cm, without axillary staging. Ensuring a wide margin during excision is essential, as narrower surgical margins are linked to an increased risk of local recurrence.[25] A simple mastectomy may be necessary whenever margin control may not be sufficient or large or multiple tumors.[25,26] Demian et al. reported a mastectomy rate of 48.5%. Patients in this report underwent 56/64 (87.5%) BCS and 14/64 (21.8%) mastectomy. These small tumor sizes and relatively low mastectomy rates may be due to the rapid presentation of patients and successful screening programs in our case series. In the same study, the positive margin rate was 24% and 15% for malignant tumors and borderline subtypes, respectively.[27] In our study, the likelihood of margin positivity following breast-conserving surgery (BCS) was significantly greater in patients with malignant phyllodes tumors

compared to those with benign and borderline tumors (45% versus 9%). This higher rate of margin positivity may be attributed to our inclination to perform BCS (with or without reconstruction) and the inability to achieve a clear surgical margin of 1 cm in all cases of malignant phyllodes tumors.

Although studies show that adjuvant RT contributes to decreasing the recurrence rate for malignant tumors, it is still controversial. In this series, LR developed in one patient who underwent a mastectomy and received RT, and three LR developed in patients following conservative surgery who received RT. Nine of 17 patients with malign PT in our series received RT. Three of six malignant phyllodes cases with LR were among the patients who received adjuvant RT, and three LR developed in the remaining 11 cases with malign PT who did not receive RT. During the follow-up period, LR occurred in two out of six patients who received adjuvant CT. The effectiveness of CT remains a contentious issue. In our series, four patients with malignant phyllodes tumors underwent CT, with two developing distant metastasis and one experiencing local recurrence. As a result, this study could not definitively demonstrate a positive impact of RT and CT.

The overall rate of local recurrence in our study was 15.6% (10 out of 64 patients), and 18% (nine out of 50 patients) following breast-conserving surgery, which is relatively high compared to the literature, which reports rates ranging from 8% to 19%.[28] According to the National Comprehensive Cancer Network (NCCN) guidelines, a minimum negative surgical margin of 1 cm is recommended to lower the risk of recurrence.[26] In our retrospective study, the threshold for a clear tumor-free margin for re-excision was set at 2 mm, resulting in none of the cases having a clear margin of 1 cm. This finding may account for the elevated recurrence rate observed.

A large meta-analysis by Yu C-Y et al. identified several risk factors for recurrence, including stromal atypia, high cellularity, stromal overgrowth, a mitotic count of five or more, border irregularity, and margin positivity, in addition to tumor size exceeding 5 cm.[29] Our study corroborated these potential risk factors associated with the occurrence of local recurrence.

Again, according to the NCCN guidelines, the recommendation for borderline and malign tumors was close follow-up for three years.[25] In our study, re-excision is sufficient instead of mastectomy in recurrences detected in the first three years. In our series, patients underwent mastectomy in relapses exceeding three years, possibly due to rapid growth patterns. In conclusion, our study may support the interpretation that all types of PT require a 3-year close follow-up after surgery.

Of course, the limitation of our study is that contrary to the current guidelines, there was no surgical margin of 1 cm in all borderline or malignant PT cases. This finding may present insufficient information regarding post-surgical outcomes or possible CT and RT contributions.

CONCLUSION

Phyllodes tumors are rare fibroepithelial neoplasms with substantial potential for local recurrence and distant metastasis. In particular, the recommendation should be to remove a malignant PT with a surgical margin of at least 1 cm in line with current guidelines. In addition, LR developed in three of four benign tumors and one of four borderline tumors with tumor margin irregularity based on definitive pathological examination. These surgical margins were within a 1 cm surgical margin. Therefore, the study may suggest that the excision of benign or borderline tumors should be in the same way as a malignant PT, at least to provide a clear surgical margin of 1 cm macroscopically. In addition, for patients with benign and borderline PT, even if the patient is young, especially if tumor margin irregularity is detected as a result of definitive pathological examination because recurrences generally occur in a short period, the study may extrapolate that a minimum of three years of close follow-up should be kept to avoid mastectomy due to recurrence, perhaps.

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Özgün Çalışma / Original Article

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Complicated Intraabdominal Infections; Epidemiology of Microorganisms, Resistance Profiles and Risk Factors Associated with Mortality

Komplike İntraabdominal Enfeksiyonlar; Mikroorganizmaların Epidemiyolojisi, Direnç Profilleri ve Mortalite ile İlişkili Risk Faktörleri

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ABSTRACT

AIM: The threat of antimicrobial resistance has been identified as one of the major challenges in the management of complicated intra-abdominal infections(cIAIs). In this study, we aimed to describe the clinical, microbiological and resistance profiles of complicated intra-abdominal infections and to assess the risk factors related to resistance and mortality.

MATERIAL AND METHOD: Seventy-nine patients undergoing surgery or interventional drainage for cIAIs with a positive microbiological culture were documented.

RESULTS: Among these patients 79,7% were affected by health care associated IAIs while remaining 20,3% cases were identified as cIAI in the community. In 79 cases, 143 microorganisms were isolated and the leading microorganism was E.coli (34.9%) followed by Enterococcus spp. (17.4%). Among Enterobacteriaceae (n:96), 53.6% of the strains had ESBL and 36.8% were Multi Drug Resistant (MDR) bacteria. The overall mortality rate was 22.8%. According to univariate analysis, the use of broad spectrum antibiotics between initial intervention and re-operation was a significant risk factor for presence of ESBL. By multivariate analysis of the data; isolation of MDR bacteria, Enterococcus spp as an etiologic agent and presence of chronic obstructive pulmonary disease were statistically significant indicators for mortality.

CONCLUSION: These data indicate that local community and nosocomial resistance patterns should guide empiric antimicrobial therapy. To have the efficient data for resistance patterns, culture of the materials should not be neglected in either hospital or community acquired IAIs.Due to the increase in the prevalence of ESBL positive and MDR bacteria, demonstration of the epidemiological data in populations and each hospital is crucially important for accurate selection of initial empirical antibiotherapy

Anahtar Kelimeler: Intraabdominal infection, resistance, mortality

ÖZET

AMAÇ: Antimikrobiyal direnç tehdidi, komplike intraabdominal enfeksiyonların(cIAI) tedavisindeki en büyük zorluklardan biridir.Bu çalışmada komplike intraabdominal enfeksiyonların klinik ve mikrobiyolojik özelliklerin, etkenlerin direnç profillerinin tanımlanması, direnç ve mortalite ile ilişkili risk faktörlerinin belirlenmesi amaçlandı.

GEREÇ VE YÖNTEM: Komplike intraabdominal enfeksiyon tanısıyla takip edilen, perkutan drenaj ya da açık cerrahi ile alınan mikrobiyolojik kültürleri pozitif olan 79 hasta dökümente edildi.

BULGULAR: Hastaların %79,7'si sağlık hizmeti ilşkili intraabdominal enfeksiyon ve geri kalan %20,3'ü toplumda edinilmiş intraabdominal enfeksiyon olarak sınıflandırıldı. 143 mikroorganizma izole edildi. En sık izole edilen mikroorganizma E.coli (34.9%), sonrasında Enterococcus spp.(17.4%) olduğu görüldü. Enterobacteriaceae (n:96) türleri içerisinde %53.6 ESBL pozitif ve %36.8 çoklu ilaca dirençli (MDR) bakteri olarak saptandı. Mortalite oranı %22.8'di. Tek değişkenli analizlere göre iki cerrahi girişim arasında geniş spektrumlu antibiyotiklerin kullanımı ESBL varlığı için risk faktörüydü. Verilerin çok değişkenli analizlerine göre ise MDR bakteri izolasyonu, etkenin Enterococcus spp. olması ve kronik obstrüktif akciğer hastalığı varlığı istatistiksel olarak anlamlı mortalite belirleyicisiydi.

SONUÇ: Bu veriler bölgesel toplumsal ve nozokomiyal direnç paternlerinin, ampirik antibiyotik tedavisini yönlendirmesi gerektiğine işaret etmektedir. Yeterli verinin sağlanabilmesi için toplum kökenli ya da sağlık hizmeti ilişkili intraabdominal enfeksiyonlarda kültür alınmalıdır. ESBL pozitif ve MDR bakteri sıklığındaki artış nedeniyle, toplumda ve hastanede epidemiyolojik verilerin bilinmesi başlangıç ampirik antibiyotik tedavisinin seçiminde önemlidir.

Anahtar Kelimeler: İntraabdominal enfeksiyon, direnç, mortalite

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INTRODUCTION

Treating complicated intraabdominal infections (cIAIs) is an ongoing challenge for clinicians because of the high complication risk and increased risk of death in severely ill patients. Complicated intra-abdominal infections are defined as infections that extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis. Uncomplicated infection involves intramural inflammation of the gastrointestinal tract and has a substantial probability of progressing to complicated infection if not adequately treated.[1] Prompt diagnosis, adequate resuscitation, appropriate systemic antibacterial therapy, early and effective source control, reassessment of the clinical response, and appropriate adjustment of the management strategy are paramount for the successful treatment of cIAIs.[2]

Knowledge of the patient's risk for isolation of resistant pathogens, such as; immunodeficiency and prolonged antibacterial exposure and the source and severity of the infection are essential. Following this, treatment should start with the most appropriate regimen immediately. Healthcare-associated intraabdominal infections (HCA-IAIs) are commonly caused by more resistant bacteria, although the resistance level is also significant in community-acquired infections. The rapid spread of multi-drug resistant (MDR) and extended-spectrum beta-lactamases (ESBL) that have produced gram-negative bacteria is a major threat to antimicrobial therapy. Detecting and monitoring any change in the resistance patterns of pathogens, locally and regionally, plays a crucial role in managing antimicrobial therapy.[3]

Therefore, we documented the clinical and microbiological profiles of cIAIs at our institution to describe the pathogens of infection and the resistance patterns, to obtain data that could lead to better empirical treatment and therapeutic strategies for selecting appropriate antibiotics based on local resistance/susceptibility. We also aimed to investigate risk factors related to mortality and assess the prognostic features linked to resistant pathogens causing cIAIs.

MATERIAL AND METHOD

Patients hospitalized at the emergency surgery clinic and surgical intensive care unit of a tertiary hospital between January and December 2015, who had surgery or percutaneous drainage for cIAIs and whose tests resulted in positive microbiological culture were included in the study. Their medical charts and microbial profiles were reviewed retrospectively.

Cases were classified into two groups: "community onset-complicated intra-abdominal infections (CO-cIAIs)" and "HCA-IAIs". Patients admitted to the hospital for more than two days at the time of infection and patients with post-operative infections were placed in the latter group. Despite applying from community because of inadequate and reliable anamnesis regarding the previous 12 months, the remaining cases could not be classified as "community-acquired". Therefore, a new category, "community onset-complicated intra-abdominal infections (CO-cIAIs)" was suggested.

The following data were collected from patients' medical records: demographic features; age and gender, initial diagnosis which included the following; post-operative intraabdominal abscess, colon anastomosis leakage, perforated appendicitis, gastric anastomosis leakage, gallbladder perforation, small intestine perforation, colon perforation, gastric anastomosis leakage, peptic ulcer perforation comorbid diseases; diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF), immunosuppressive therapy, cardiovascular disease, malignancy and hypertension (HT).

The categorization of surgical interventions was based on the operating surgeons' decisions and divided into four classes: clean, clean-contaminated, contaminated, and dirty. Surgical wound classification was defined as the National Academy of Sciences.[4] The operations' type and timing were open or laparoscopic and urgent or elective, respectively.

Data regarding microbiologic examination of the liquid aspirated during the operation or postoperative period and the antimicrobial susceptibility test results of infecting microorganisms were collected. The infection was considered monomicrobial or polymicrobial according to the number and type of isolated microorganisms.

Along with examination of isolated Enterobacterales for ESBL, gram-negative pathogens resistant to three or more different classes of antibiotics through cephalosporins, aminoglycosides, fluoroquinolones, carbapenems, and penicillin were accepted as MDR.

The following risk factors that may be related to the development of cIAIs with ESBL or MDR gram-negative pathogens were recorded: hospitalization occurring within 12 months before the first operation, having been prescribed antibiotics within the last seven days and having taken antibiotics in the period between two interventions for patients who were re-operated.

Mortality refers to any cause of death occurring at a hospital. The relationship between mortality and all the parameters mentioned above (demographic features, underlying diseases, isolation of resistant microorganisms, community-onset infection or healthcare-associated infection) was statistically determined.

Statistical analysis

SPSS for Windows 11.5 was used to gather and analyze the collected data. The Kolmogorov–Smirnov test was chosen to ensure the distribution of intermittent numerical variables was close to normal. Descriptive statistics were shown as having a mean ± standard deviation or median (minimum–maximum) for intermittent numerical variables, and the percentage (%) and number of cases were given for categorical variables. To assess the significant difference between the mean values of groups and compare categorical variables between different groups, the Student's t-test and Pearson's chi-square or Fisher's exact chi-square tests were preferred. To investigate the co-effects of all possible risk factors that were effective or thought to be effective on mortality as a result of univariate statistical analysis, multivariate analysis was carried out using stepwise logistic regression analysis. Variables identified as $p < 0.25$ as a result of univariate statistical analysis were added to multivariate models as candidate risk factors. Finally, adjusted odds ratios and their 95% confidence intervals for each variable were provided. Statistical significance was defined as $p < 0.05$.

Ethical approval was obtained from Ankara Numune Training and Education Hospital Clinical Research Ethics Committee (Permission Date 05.09.2013, Permission number E-724.01).

RESULTS

Among the 79 cIAI cases, 16 were CO-cIAIs (20.3%) and 63 healthcare-associated (79.7%) infections were observed. In most cases (42 out of 79 patients; 53.2%), more than one species were cultured (polymicrobial) without any statistically significant difference between the CO-cIAIs and the HCA-IAIs groups ($p = 0.402$). The overall number of bacteria cultured from abdominal swabs totaled 143. In CO-cIAIs and HCA-IAIs groups, at a frequency of 50 strains, Escherichia coli was the most common microorganism, followed by 25 Enterococcus spp. strains. The distribution of other isolated microorganisms was also similar among the two groups. Although the Pseudomonas species were more common in the postoperative cases, the difference was not significant. A complete overview of the cultured microorganisms is presented in Table 1.

Table 1: Distribution of microorganisms isolated from peritoneal fluid in community onset complicated intra-abdominal infections (CO-cIAIs) and healthcare-associated- intra-abdominal infections (HCA-IAIs).

	CI-cIAI (n: 32)	HCA-IAI (n: 111)	p
Gram-negative			
Escherichia coli	12	38	0.733
Klebsiella spp.	3	14	0.764
Pseudomonas spp.	2	6	1.000
Acinetobacter spp.	0	12	0.068
Other *Enterobacterales*	1	8	0.684
Gram-positive			
Streptococcus spp.	3	6	0.419
Enterococcus spp.	8	17	0.204
Staphylococcus spp.	2	5	0.653
Candida spp.	1	5	1.000

CO-cIAIs:Community onset-complicated intra-abdominal infections, HCA-IAI: Healthcare-associated- intra-abdominal infections, spp: species

Among Enterobacterales (n: 96), 53% of the strains had ESBL and 36.8% were detected as MDR. Regarding CO-cIAIs, the number of ESBL and MDR E.coli strains were 5/12 and 3/12, respectively. In concordance with these results, the resistance rates were also high for the Klebsiella species (ESBL: 3/3, MDR: 1/3). No MDR Acinetobacter baumannii strains were found in the community onset patients. Regarding ESBL and MDR, positively observed in the E.coli and Klebsiella spp. strains, there was no difference between CO-cIAIs and HCA-IAIs

Table 2: Resistance rates of gram-negative bacteria in the community onset complicated intra-abdominal infections(CO-cIAIs) and healthcare-associated- intra-abdominal infections (HCA-IAIs).

Gram-negative	CI-cIAIs (n: 17)	HCA-IAIs (n: 78)	P
Escherichia coli	12	38	0.102
ESBL (+)	5	25	0.832
MDR (+)	3	9	0.445
Klebsiella spp.	3	14	1.000
ESBL (+)	3	9	0.445
MDR (+)	1	7	1.000
Pseudomonas spp.	2	6	0.631
ESBL (+)	1	2	0.450
MDR (+)	0	1	1.000
Acinetobacter spp.	0	12	0.116
MDR (+)	0	12	0.116
Other Enterobacterales	1	8	1.000
ESBL (+)	1	5	1.000
MDR (+)	1	1	0.327

CO-cIAIs: Community onset-complicated intra-abdominal infections, HCA-IAI: Healthcare-associated- intra-abdominal infections, ESBL: Extended-spectrum beta-lactamases, MDR: Multi-drug resistant, spp:species

As for the risk factors, 12 patients had a hospitalization history before the first operation. Before the initial surgery, only four patients disclosed information about antibiotic usage; however, 49 patients had antibiotic therapy between the first and subsequent operations. Univariate analysis showed that the use of antibiotics between the initial intervention and re-operation was a significant risk factor for ESBL (p = 0.017), but none of these risk factors were associated with the presence of MDR bacteria

Table 3: Rates of ESBL (+) and MDR bacteria according to the presence of risk factors.

Variables	ESBL (–) (n: 28)	ESBL (+) (n: 51)	p	MDR (–) (n: 56)	MDR (+) (n: 23)	p
Groups			0.847			1.000
CO-cIAI	6 (21.4%)	10 (19.6%)		11 (19.6)%	5 (21.7%)	
HCA-IAI	22 (78.6%)	41 (80.4%)		45 (80.4%)	18 (78.3%)	
Before initial intervention			0.196			0.738
Hospitalization (–)	26 (92.9%)	41 (80.4%)		48 (85.7%)	19 (82.6%)	
Hospitalization (+)	2 (7.1%)	10 (19.6%)		8 (14.3%)	4 (17.4%)	
Before initial intervention			1.000			1.000
Use of antibiotics (–)	27 (96.4%)	48 (94.1%)		53 (94.6%)	22 (95.7%)	
Use of antibiotics(+)	1 (3.6%)	3 (5.9%)		3 (5.4%)	1 (4.3%)	
Between initial intervention and re-operation			0.017			0.198
Use of antibiotics (–)	9 (40.9%)	6 (14.3%)		13 (28.3%)	2 (11.1%)	
Use of antibiotics (+)	13 (59.1%)	36 (85.7%)		33 (71.7%)	16 (88.9%)	

CO-cIAIs:Community onset-complicated intra-abdominal infections, HCA-IAI: Healthcare-associated- intra-abdominal infections, ESBL: Extended-spectrum beta-lactamases, MDR: Multi-drug resistant, spp:species

The overall mortality rate was 22.8% and according to univariate analysis, none of the patient characteristics (age, gender, and comorbidities) were associated with mortality. In addition, the type and timing of the operation and unexpectedly, contamination type were not predictive of death. Among IAI diagnoses, only small intestinal anastomosis leakage was statistically associated with mortality (p = 0.010) and all three patients with this type of infection died (p = 0.010)

Table 4: Demographic and clinical features of cases from the survival and exitus groups

Variables	Survival (n: 61)	Exitus (n: 18)	p	OR (95% CI)
Age (years)	52.5 ± 17.6	60.3 ± 17.4	0.103	1.026 (0.994–1.059)
Gender				
Female	24 (39.3%)	10 (55.6%)	-	1.000
Male	37 (60.7%)	8 (44.4%)	0.222	0.519 (0.179–1.501)
Comorbidities				
DM	8 (13.1%)	6 (33.3%)	0.075	3.313 (0.968–11.333)
COPD	6 (9.8%)	5 (27.8%)	0.113	3.526 (0.931–13.356)
HT	13 (21.3%)	6 (33.3%)	0.350	1.846 (0.581–5.864)
CRF	4 (6.6%)	0 (0.0%)	0.569	-
Malignancy	17 (27.9%)	6 (33.3%)	0.654	1.294 (0.419–4.000)
Immunosuppressive therapy	3 (4.9%)	1 (5.6%)	1.000	1.137 (0.111–11.652)
Cardiovascular Disease	4 (6.6%)	2 (11.15)	0.615	1.781 (0.299–10.623)
Groups				
CO-cIAIs	13 (21.3%)	3 (16.7%)	-	1.000
HCA-IAIs	48 (78.7%)	15 (83.3%)	1.000	1.354 (0.340–5.398)
Diagnosis of cIAIs				
Intraabdominal abscess	34 (55.7%)	6 (33.3%)	0.095	0.397 (0.132–1.196)
Colon anastomosis leakage	6 (9.8%)	2 (11.1%)	1.000	1.146(0.211–6.237)
Gallbladder perforation	6 (9.8%)	1 (5.6%)	1.000	0.539 (0.061–4.798)
Small intestine perforation	4 (6.6%)	2 (11.1%)	0.615	1.781 (0.299–10.623)
Colon perforation	4 (6.6%)	2 (11.1%)	0.615	1.781 (0.299–10.623)
Perforated appendicitis	4 (6.6%)	0 (0.0%)	0.569	-
Small intestine anastomosis leakage	0 (0.0%)	3 (16.7%)	0.010	-
Peptic ulcer perforation	2 (3.3%)	1 (5.6%)	0.545	1.735 (0.148–20.318)
Gastric anastomosis leakage	1 (1.6%)	1 (5.6%)	0.406	3.529 (0.210–59.428)
Timing of operation				
Elective	25 (41.0%)	11 (61.1%)	-	1.000
Urgent	36 (59.0%)	7 (38.9%)	0.132	0.442 (0.151-1.296)
Type of surgery				
Laparoscopic	9 (14.8%)	2 (11.1%)	-	1.000
Open	52 (85.2%)	16 (88.9%)	1.000	1.385 (0.271–7.077)
Type of contamination				
Dirty	25 (41.0%)	5 (27.8%)	-	1.000
Clean contamination	15 (24.6%)	9 (50.0%)	0.089	3.000 (0.845–10.649)
Contamination	21 (34.4%)	4 (22.2%)	0.947	0.952 (0.226–4.008)

CO-cIAIs:Community onset-complicated intra-abdominal infections, HCA-IAI: Healthcare-associated- intra-abdominal infections, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CRF: Chronic renal failure, HT: Hypertension, OR:Odds Ratio, CI:Confidence Interval

A statistically significant difference between the survival and the exitus groups in terms of MDR positivity was observed (p = 0.026). Mortality in the MDR (+) group was 3,357 times higher than (95% confidence interval: 1.118–10.084) that of the MDR (–) group. The mortality rate statistically significantly increased 3.833 times and 7.127 times by growing enterococcus and Acinetobacter in culture (95% confidence interval: 1.280–11.484) (p = 0.013) (95% confidence interval: 1.909–26.605) statistically (p = 0.004)

Table 5: Distribution of cases in terms of agents according to survival and exitus groups.

Variables	Survival (n: 61)	Exitus (n: 18)	p	OR (95% CI)
Polymicrobial	30 (49.2%)	12 (66.7%)	0.191	2.067 (0.687–6.215)
ESBL	37 (60.7%)	14 (77.8%)	0.182	2.270 (0,667–7.722)
MDR	14 (23.0%)	9 (50.0%)	0.026	3.357 (1.118–10.084)
E.coli	42 (68.9%)	8 (44.4%)	0.059	0.362 (0,123–1.062)
Klebsiella spp.	14 (23.0%)	3 (16.7%)	0.749	0.671 (0.170–2.658)
Enterococcus spp.	15 (24.6%)	10 (55.6%)	0.013	3.833 (1.280–11.484)
Pseudomonas spp.	6 (9.8%)	2 (11.1%)	1.000	1.146 (0.211–6.237)
Acinetobacter spp.	5 (8.2%)	7 (38.9%)	0.004	7.127 (1.909–26.605)
Other Enterobacterales	5 (8.2%)	4 (22.2%)	0.198	3.200 (0.759–13.497)

ESBL: Extended-spectrum beta-lactamases, MDR: multi-drug resistant, spp:species, OR:Odds Ratio, CI: Confidence Interval

Multiple logistic regression analysis analyzed all possible risk factors that are potential determinants for distinguishing between the survival and exitus groups. Especially the presence of Acinetobacter spp. and Enterococcus spp. infections and COPD were related to higher mortality rates. Interestingly, dirty operations negative correlated with mortality

Table 6: Examination of the effects of all possible risk factors which may be determinants for distinguishing between the survival and exitus groups; risk factors were analyzed by multiple logistic regression with multivariate stepwise logistic regression analysis.

Variables	Odds ratio	95% confidence interval		p
		Lower limit	*Upper limit*	
Initial Model				
Age	1.027	0.968	1.089	0.378
Male	0.641	0,.093	4.425	0.652
DM	1.169	0.147	9.290	0.882
COPD	6.963	0.533	90.929	0.139
Urgent	5.052	0.141	180.625	0.375
Contamination	0.090	0.005	1.527	0.095
Dirty	0.009	0.000	1.119	0.056
Polymicrobial	0.179	0.018	1.759	0.140
ESBL	5.269	0.431	64.435	0.193
MDR	0.230	0.017	3.044	0.265
E.coli	0.213	0.031	1.463	0.116
Enterococcus spp.	22.141	2.278	215.217	0.008
Acinetobacter spp.	83.517	3.261	2138.697	0.007
Other microorganisms	8.309	0.828	83.331	0.072
Intraabdominal abscess	0.399	0.068	2.339	0.309
Final model				
COPD	5.770	1.060	31.416	0.043
Contamination	0.229	0.042	1.246	0.088
Dirty	0.127	0.022	0.723	0.020
Enterococcus spp.	8.122	1.869	35.286	0.005
Acinetobacter spp.	12.638	2.461	64.896	0.002

DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, ESBL: Extended-spectrum beta-lactamases, MDR: multi-drug resistant, spp:species

DISCUSSION

This single-center, retrospective study demonstrated the relation between mortality and the causative agents, resistance rates and clinical and microbiological characteristics community-onset and healthcare-associated cIAIs. Although routinely obtaining peritoneal fluid culture is not recommended in lower-risk patients with community acquired cIAIs, knowledge of local microbiological and resistance patterns is essential for selecting the appropriate antibiotic therapy.[5]

As previous national and international studies also reported high resistance rates in gram-negative isolates obtained from extra-abdominal regions, it is not surprising that we also observed higher resistance rates in community-onset and nosocomial isolates in this study.[6-8] However, the rates compared are not for cIAIs, and the number of national studies on this topic is still limited. Nevertheless there is not enough data from our country regarding the epidemiology of microorganisms that cause community and hospital-acquired intra-abdominal infections, ESBL rate in gram-negative bacteria in community-acquired infections was found to be 12.3% in one study.[9] Since these data include only community-acquired infections, resistance rates are much lower compared to ours. Also, our high resistance rates in community-onset infections were associated with the lack of reliable data on 12-month healthcare utilization. In a multinational study involving centers from around the world, both community and hospital-acquired intraabdominal infections were evaluated, and the ESBL rate among Gram-negative bacteria was found to be 16.4%.[10] Given that antimicrobial resistance in our country is known to be high according to the antimicrobial surveillance data published by the World Health Organization, this rate is an expected finding.[11] Acinetobacter baumannii, a causative agent of other hospital-acquired infections (pneumonia, sepsis) at our institution, was isolated at a higher rate than previous reports on HCA-IAIs.

Previous exposure to antibiotics increases ESBL positivity and is associated with the development of resistant bacteria. This fact was supported by our finding that using antibiotics between two operations represented a risk factor for isolating ESBL-positive gram-negative bacteria.[12-13] While the relationship between other risk factors and the development of resistant bacteria was previously demon-

strated in the literature, these risk factors and the development of resistant bacteria were not significantly associated with ESBL positivity and MDR development in this study. This may be due to the limited data (preoperative hospitalization occurred for only 15.2% of patients and preoperative antibiotherapy in 5.1%).

Age, infection severity, surgical intervention type, microbial factors, the timing and adequacy of antimicrobial therapy, comorbidities, and Acute Physiology and Chronic Health Evaluation-II (APACHE-II) and Sequential organ failure assessment (SOFA) scores on admission have been examined as mortality predictors in the literature.[14] In recent studies, the failure of initial antibiotic therapy and the isolation of resistant pathogens are risk factors for mortality.[15,16] Surgical guidelines emphasize that empiric therapy should be directed according to local microbiological data and resistance patterns.[2,3] Mortality was associated with MDR bacteria only during univariate analysis, while it was associated with isolation of Acinetobacter in both univariate and multivariate analyses in the present study. As most of the cases in the study were postoperative infections, the isolation of MDR pathogens and the correlation between the rates of resistant bacteria and mortality were as expected. There was similarity between the mortality rate in this study (22%) and the rates previously reported in the literature for postoperative infections.[14,17]
While medical guidelines recommend using empirical anti-enterococcal treatment in high-risk patients, the isolation of Enterococci from cIAIs was previously associated with treatment failure and mortality in several studies in the literature.[18,19] In our study, where Enterococci were the second most isolated species, univariate and multivariate analyses supported the previous findings. Riche et al.s' findings show that the isolation of Enterococci species from peritoneal fluids represents a poor prognostic factor, demonstrating the need for additional prospective studies evaluating the effective systemic antibiotic therapy for these microorganisms.[20]
Similar to our findings, Riche previously reported similar mortality rates between community-acquired and nosocomial infections and identified septic shock as the main determinant of mortality. Likewise, Claridge et al. demonstrated that whether an infection was community-acquired or nosocomial had less impact on the patient mortality rate than intrinsic patient characteristics.[21] In our study, only a history of COPD among the comorbidities was associated with increased mortality, based on the multivariate analyses. However, this finding should be further evaluated in future studies.
While a relationship was not found between the type of contamination and mortality in Van Ruler's study, we believe that the lower rate of mortality observed for dirty operations in this study could be explained by the fact that surgeons generally ask for consultation from emergency infectious diseases departments in the presence of dirty infections. Large-spectrum antimicrobial therapy is initiated earlier in those patients.[17]
Our study has some limitations. The patients' status at presentation was described as a mortality predictor, and it included the Charlson and APACHE indexes and septic shock, but we could not investigate these prognostic parameters.[20,22] Nevertheless, our data can contribute to the currently limited regional resistance rates and show the importance of local microbiological patterns of IAIs. In addition, the risk factors affecting mortality support previous studies in the literature.

CONCLUSION

Due to the increase in the prevalence of ESBL-positive and MDR bacteria, the epidemiological data in populations and in each hospital / (locally/regionally) is essential for accurate selection of initial empirical antibiotherapy. The risk factors for developing resistant bacteria should be carefully observed and assessed in community-acquired infections. MDR bacteria and Acinetobacter species are a serious threat to cIAI cases. At the same time, Enterococcus species also appear as a more significant concern than before.

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Is There Any Relationship Between Clinical Progress and Vitamin-D Levels In Critically Ill Children?

Çocuk Yoğun Bakım Ünitesinde Yatan Kritik Hastalığı Olan Çocuklarda D Vitamini Düzeyi ile Klinik İzlem Arasında İlişki Var mı?

Tuğçe GÜZELKAŞ[1], Handan ALP[2]

ABSTRACT

AIM: Vitamin-D is a hormone that affects infections, the autoimmune system, the cardiovascular system, and the central nervous system; therefore, it is considered important for critically ill patients. This study aimed to examine the relationship between vitamin-D levels and Paediatric Risk of Mortality (PRISM) III score and mortality rates in critically ill children.

MATERIAL AND METHOD: A total of 200 patients who were admitted to Atatürk University Paediatric Intensive Care Unit between January 2016 to January 2017 were included in this study. Demographic data, PRISM III score, serum calcium, phosphorus, alkaline phosphatase, parathormone, and 25-Hydroxy-Vitamin-D [25(OH) D] levels were recorded. 25(OH)D levels were grouped as deficiency (below 12 ng/ml), insufficiency (12-20 ng/ml), sufficiency (20-100 ng/ml), and excess (above 100 ng/ml).

RESULTS: Vitamin-D levels of 23.5% of the patients were deficient, 24.5% were insufficient, and 52% were sufficient. A negative correlation was found between vitamin-D and age (r=-0.42, p<0.01). PRISM III score was found to be lower in patients with sufficient vitamin-D (p<0.01). Although the mortality rate of cases with vitamin-D deficiency was higher, it was not found to be significant. No significant relationship was found between vitamin-D level and duration of hospitalization, duration of mechanical ventilation, chronic disease status, or vasopressor need.

CONCLUSION: PRISM scoring system is a scoring system frequently used in paediatric intensive care units to predict mortality. The higher PRISM III score in patients with insufficient or deficient vitamin-D levels may suggest that vitamin-D insufficiency or deficiency is a risk factor for mortality.

Keywords: Vitamin D, mortality, pediatric intensive care, PRISM III

ÖZET:

GİRİŞ: D vitamini enfeksiyonlar, otoimmün sistem, kardiyovasküler sistem ve merkezi sinir sistemi üzerine etki gösteren bir hormondur; bu nedenle kritik hastalar için önemli olduğu düşünülmektedir. Bu çalışmada, kritik hastalığı olan çocuklardaki D vitamini düzeyi ile Pediatrik Mortalite Riski (PRISM)III skoru ve mortalite oranları arasındaki ilişkinin incelenmesi amaçlanmıştır.

GEREÇ VE YÖNTEM: Bu çalışmaya Atatürk Üniversitesi Çocuk Yoğun Bakım Ünitesine Ocak 2016 ile Ocak 2017 tarihleri arasında yatırılan toplamda 200 hasta dahil edildi. Demografik veriler, PRISM III skoru, serum kalsiyum (Ca), fosfor (P), alkalen fosfataz (ALP), parathormon (PTH) ve 25-Hidroksi-Vitamin-D [25(OH)D] seviyeleri kaydedildi. 25(OH)D seviyeleri eksiklik (12 ng/ml altı), yetersizlik (12-20 ng/ml), yeterlilik (20-100 ng/ml) ve fazlalık olarak gruplandırıldı (100 ng/ml üzeri).

BULGULAR: Hastaların %23,5'inin D vitamini düzeyi eksik, %24,5'inin yetersiz, %52'sinin yeterliydi. D vitamini ile yaş arasında negatif korelasyon saptandı (r=-0,42, p<0,010). D vitamini yeterli olan hastalarda PRISM III skoru daha düşük bulundu (p<0,010). D vitamini eksikliği olan hastaların ölüm oranı daha yüksek olmakla beraber anlamlı bulunmadı. D vitamini düzeyi ile hastanede yatış süresi, mekanik ventilatör süresi, kronik hastalık durumu ya da vazopressör ihtiyacı arasında anlamlı ilişki saptanmadı.

SONUÇ: PRISM skorlama sistemi mortaliteyi öngörme açısından çocuk yoğun bakım ünitelerinde sıklıkla kullanılan bir skorlama sistemidir. D vitamini seviyesi yetersiz veya eksik olan hastalarda PRISM III skorunun daha yüksek olması, D vitamini yetersizliği veya eksikliğinin mortalite için bir risk faktörü olduğunu düşündürebilir.

Anahtar Kelimeler: D vitamini, Mortalite, Çocuk Yoğun Bakım, PRISM III

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INTRODUCTION

Vitamin-D plays a critical role in bone metabolism, and its deficiency can result in the development of rickets[1]. Studies have demonstrated that vitamin-D has a protective effect on autoimmune diseases, inflammatory diseases, and some infectious agents through the immune system[2,3]. Although severe deficiency is now rare, the growing awareness of subclinical vitamin-D deficiency has drawn attention to its potential impact on neurological, cardiovascular, respiratory, and immune health and its possible effects on morbidity and mortality rates. Recent research suggest that vitamin-D may positively affect the course of critical illness due to its pleiotropic effects[4-6]. Low levels of vitamin-D have been reported to be associated with mechanical ventilation requirement, prolonged mechanical ventilation day, a worse Acute Physiology and Chronic Health Evaluation (APACHE) II score, length of stay, organ dysfunction, severe infections, and the mortality rate of critically ill adult and child patient[6-19]. Moreover, vitamin-D status has been reported to be associated with differential metabolic homeostasis during critical illness[7].

Although studies on the association between serum vitamin-D and morbidity/mortality in critically ill children have primarily been conducted in developed countries, limited data exist in developing countries, especially in Turkey[8]. Moreover, most studies in Turkey have focused on adults[9-11]. A recent study focused on children from the northern Anatolia region of Turkey found a high prevalence of vitamin-D deficiency in critically ill children, which was associated with higher vasopressor requirement but not mortality[8].

Because of vitamin-D levels are influenced by geographic factors, ethnic differences, and latitude, more research is needed in Turkey to explore the association between vitamin-D and mortality and morbidity in children with critical illness. Therefore, we aim to obtain the vitamin-D deficiency of children with critical illness and the association between vitamin-D deficiency and the PRISM III score, which is frequently used to predict mortality, among patients admitted to the Paediatric Intensive Care Unit (PICU).

MATERIAL AND METHOD

This retrospective study was conducted at the Paediatric Intensive Care Unit (PICU) of Atatürk University Faculty of Medicine in Erzurum, Turkey, in paediatric patients who were admitted to the intensive care unit between January 2016 and January 2017. Only the first hospitalizations of patients with a history of recurrent hospitalization within the specified period were included. Patients hospitalized for vitamin D toxicity and rickets were excluded from the study. Of the 216 cases, 14 were excluded due to recurrent hospitalizations and 2 were excluded due to vitamin-D toxicity, resulting in a total of 200 cases included in the study. This study was approved by the Ethics Committee of Atatürk University Faculty of Medicine (decision no: B.03.2.ATA.0.01.00 / 110, date: 05/05/2017).

The demographic and clinical characteristics of the patients, including their age, weight, height, body mass index (BMI), gender, hospitalization season, presence of any chronic diseases, need for mechanical ventilation, duration of mechanical ventilation day, length of PICU stay, requirement for vasopressor and/or inotropic treatment, history of vitamin-D prophylaxis (daily 400 IU vitamin-D prophylaxis given free of charge to infants under 1 year of age, conducted by the Ministry of Health) or treatment, as well as levels of calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin-D, and parathyroid hormone level were recorded. The patients were classified according to the primary reason for hospitalization, which included cardiovascular, respiratory, gastrointestinal, haematological, endocrinologic and metabolic, oncological, nephrological, neurological diseases, trauma, and poisonings.

The PRISM III score was calculated to evaluate the mortality risk of the cases. PRISM III parameters, calculated based on the worst values in the first 24 hours after the child is admitted to intensive care, consist of systolic blood pressure, body temperature, creatinine, blood urea nitrogen (BUN), Glasgow Coma Score, pupillary response, cardiac rate, leukocyte and platelet count, pH, total CO2, PaCO2, PaO2, PT/aPTT, potassium, glucose, and bicarbonate. It is a commonly used method to determine the predicted mortality risk of critically ill patients based on their clinical and laboratory findings at the time of admission to the paediatric intensive care unit[12,13].

The serum 25(OH)D level was measured using the Beckman Coulter brand UniCel DxI 800 autoanalyzer through the immunoassay method. Serum 25(OH)D levels are classified according to vitamin-D levels and are defined as deficiency (below 12 ng/ml), insufficiency (12-20 ng/ml), sufficiency (20-100 ng/ml) and excess (above 100 ng/ml).[14]. Because 400 IU vitamin-D prophylaxis is routinely recommended for infants under the age of one, a separate evaluation was conducted for this age group. Patients with 25(OH)D levels below 20 ng/ml were treated with stoss therapy[14]. Serum Ca, P, and Alkaline phosphatase (ALP) levels were analysed using spectrophotometry on a Beckman Coulter brand AU5800 autoanalyzer, while serum PTH levels were determined using chemiluminescence on a Beckman Coulter brand UniCel DxI 800 autoanalyzer. If the serum calcium level calculated according to age was below, the patient was given 1-2 ml/kg of intravenous 10% Calcium Gluconate[15].

The data was analysed using SPSS 20 package program. Categorical measurements were determined as numbers and percentages, while normally distributed data were reported as mean ± standard deviation and non-normal distribution as the median. Chi-Square test was used for categorical data, and the risk ratio was calculated for comparisons between independent groups, to compare 2 groups with numerical data that did not show normal distribution, the Mann Whitney U test was used and the Kruskal Wallis test was used when there were more than 2 groups. One-way ANOVA was used in the presence of more than 2 groups and Student-T tests were used in the presence of 2 groups in numerical analyses showing normal distribution. Correlation tests were used to determine the direction and strength of the linear relationship between vitamin-D and other variables. 5% error level was used in all statistical analysis. P value of less than 0.05 was considered to be statistically significant.

RESULTS

The mean age of the patients was 53.82±60.41 months, ranging from 1 month to 16 years. Eighty-nine (44.50%) of them were female and 111 (55.5%) were male. The most common reason for hospitalization was neurological diseases 66(33%). Of the patients, 104 (52%) had a chronic disease, with cerebral palsy being the most common (12.50%). The mean length of PICU stay was 11.72±26.34 days, 46% (n=92) 92(46%) of the patients required mechanical ventilation, while 26.50% (n=53) needed vasopressor and/or inotropic support. The mean PRISM III score was 9.64±12.51, and the mortality rate was 42(21%).

Table 1. Demographic Characteristics of the Cases

Specifications	n=200
Age (month) †	53.82 ± 60.41(1-203)
Gender*	
Girl	89(44,50)
Boy	111(55,50)
Season of the hospitalization*	
Summer	59(29,50)
Autumn	54(27)
Winter	54(27)
Spring	33(16,50)
Diagnosis*	
Neurological Diseases	66(33)
Respiratory System Diseases	41(20,50)
Cardiovascular System Diseases	25(12,50)
Trauma	22(11)
Oncological Diseases	11(5,50)
Gastrointestinal System Diseases	10(5)
Nephrological Diseases	7(3,50)
Intoxication	7(3,50)
Endocrinologic and Metabolic Diseases	6(3)
Haematological Diseases	5(2,50)
Comorbidity*	
Cerebral palsy	25(12,50)
Epilepsy	17(8,50)
Congenital Heart Disease	17(8,50)
Down Syndrome	6(3)
Chronic Lung Disease	6(3)
Lymphoma	5(2,50)
Hydrocephalus	3(1,50)
Chronic Renal Insufficiency	4(2)
Type 1 Diabetes	2(1)
Other Diseases **	19(9,50)
No Chronic Illness	96(48)
Biochemical parameters†	
25(OH)D (ng/ml)	22,82 ± 13,78 (1,5-81,6)
PTH (pg/ml)	78,31±94,93 (2,9-585,7)
Ca (mg/dl)	8,72±1,02 (4,1-11,4)
P (mg/dl)	4,58±1,64 (1,1-11,5)
ALP (U/L)	183,23±113,08 (36-647)
Mechanical Ventilatory Support*	92(48)
Duration of Hospitalization (Days)†	11.72±26.34 (1-298)
Mechanical Ventilation Day†	7,12±23,73(0-270)
Vasopressor / Inotrope Requirement*	53(26,5)0
PRISM III †	9.64±12.51(0-59)
Outcome	
Mortality*	42(21)
Transfer to Related Clinic,*	158(79)

*: n(%), †: mean±SD (Min-Max), PRISM III: The Pediatric Risk of Mortality Score **:Nephrological, Haematological, Oncological Diseases, Gastrointestinal System Diseases, Endocrine and Metabolic Diseases, BMI: Body Mass Index

A significant relationship was found between the season of hospitalization and the presence of chronic disease (p=0.042). Patients with chronic disease had a longer hospitalization stay (13.12±20.01 days) compared to those without chronic disease (10.38±31.81 days) (p=0.033).

Mean 25(OH)D, PTH, Ca, P, ALP level were 22.82±13.78 ng/ml, 78.33±94.87 pg / ml, 8.72±1.02 mg / dl, 4.59±1.61 mg / dl,183.27±113.41 U / L, respectively. The serum vitamin-D levels were insufficient or deficient in 96 (48%) of the patients. A significant relationship was observed between decreasing levels of vitamin-D and decreasing levels of calcium, as well as increasing levels of parathyroid hormone (p=0.008 and p=0.022, respectively). There was a positive correlation between vitamin-D levels and Ca (r=0.20, p=0.006), while there was a negative correlation with PTH (r=-0.19, p=0.008) and age (r=-0.42, p=0.008).

The mean age of the patients with vitamin-D deficiency, insufficiency, sufficiency was 82.01±69.84 months, 73.47±62.69 months, and 31.87±44.92 months, respectively (Table II). As the vitamin-D levels decreased, body weight and height increased significantly (p=0.002), and there was a significant relationship between vitamin-D and BMI (p=0.013). There was no significant relationship between the patients' hospitalization seasons and vitamin-D levels (p=0.581). There was no significant association between vitamin-D levels and the presence of chronic disease (p=0.062), the mechanical ventilatory support (p=0.463), length of hospital stay (p=0.512), length of mechanical ventilatory support (p=0.342), and the use of vasopressor and/or inotropic agents (p=0.981)

Table 2. Demographic Characteristics of the Cases According to Vitamin D Levels

	Vitamin D Level			
Specifications	**Deficiency**	**Insufficiency**	**Sufficiency**	**p**
Age (month) †	82,01±69.84	73,47±62,69	31,87±44,92	**0,002**
Weight (kg) †	20,91±16,62	21,41±15,72	11,52±10,71	**0,003**
Height (cm) †	105,01±34,58	106,39±33,09	79,62±27,33	**0,002**
BMI (kg/m²)*	15,69±3,79	16,12±2,59	14,70±3,08	**0,013**
Gender *				0,761
Girl	20(42,55)	24(48,98)	45(43,27)	
Boy	27(57,44)	25(51,02)	59(56,73)	
Season of the hospitalization*				0,581
Winter	15(31,91)	13(26,53)	26(25,00)	
Spring	9(19,15)	10(20,41)	14(13,46)	
Summer	9(19,15)	14(28,57)	36(34,62)	
Autumn	14(29,79)	12(24,49)	28(26,92)	
Diagnosis*				**0,003**
Neurological Diseases	5(10,64)	7(14,29)	29(27,88)	
Respiratory System Diseases	20(42,55)	14(28,57)	32(30,77)	
Cardiovascular System Diseases	9(19,15)	10(20,41)	22(21,15)	
Trauma and Intoxication	4(8,51)	8(17,02)	17(16,34)	
Other Diseases **	9(19,15)	10(20,41)	4(3,85)	
Duration of Hospitalization (Days)†	13,24±21,62	7,31±10,87	13,17±32,60	0,512
Comorbidity*	29(61,70)	19(38,78)	56(53,85)	0,062
Biochemical parameters †				
25(OH)D (ng/ml)	22,82 ± 13,78 (1,5-81,6)			**0,008**
PTH (pg/ml)	111,3±127,6	83,3±89,3	61,1±74,8	**0,022**
Ca (mg/dl)	8,7±1,0 (4,1-11,4)			
P (mg/dl)	4,6±1,6 (1,1-11,5)			
Mechanical Ventilatory Support*	25(53,19)	20(40,81)	47(45,19)	0,463
Vasopressor / Inotrope Requirement*	12(25,53)	13(26,53)	28(26,92)	0,981
Mechanical Ventilation Day†	8,61±19,92	2,82±6,29	8,33±29,71	0,342
PRISM III†	10,42±8,64	12,81±15,82	7,83±11,91	**<0,01, (r=-0,211)**
Outcome				0,243
Mortality*	12(25,53)	13(26,53)	17(16,34)	
Transfer to Related Clinic*	35(74,47)	36(73,47)	87(83,65)	
Total	47(100)	49(100)	104(100)	

*:n(%), †: mean±SD (Min-Max) **:Nephrological, Haematological, Oncological Diseases, Gastrointestinal System Diseases, Endocrine and Metabolic Diseases, BMI: Body Mass Index

The mean PRISM III score was 7.81±11.94 in cases with sufficient vitamin-D levels and 10.42±8.64 in cases with deficient vitamin-D levels, indicating a significantly higher score in patients with vitamin-D deficiency (p=0.005). Moreover, a negative correlation was found between vitamin-D levels and the PRISM III score (r=-0.21, p=0.003)

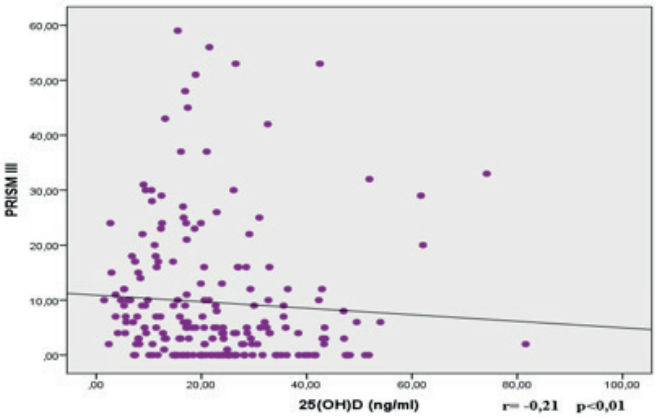

Figure 1. Vitamin D-PRISM III Correlation Graph

The rate of mortality was 17 (16.35%), 13 (26.53%), and 12 (25.53%) in children with vitamin-D sufficiency, insufficiency, and deficiency, respectively (p=0.241). The vitamin-D levels of survived patients were higher than non-survive, although this difference was not statistically significant (23.54±13.91 ng/ml vs. 20.32±13.09 ng/ml, p=0.119) (Table II).

DISCUSSION

This study showed that the PRISM III score was higher in critically ill children with vitamin-D deficiency. In the literature, no consensus has been reached regarding the association between vitamin-D deficiency and PRISM III score[8,16-19]. Although some previous studies have found no relationship between vitamin-D deficiency and PRISM III score[17-20], others reported higher PRISM III scores were associated with vitamin-D deficiency[16,21]. McNally et al. reported that every additional increase in the PRISM III score, the likelihood of vitamin-D deficiency increased by 8%[22]. Similarly, Madden et al reported that lower admission 25(OH)D level was inversely associated with PRISM III score, with a 5 ng/mL decrease in 25(OH)D levels corresponding to a 1.19-fold increase for a 1-quartile rise in PRISM III score[16]. These differences between studies may be due to sample characteristics, exposure to sunlight, geographical and ethnic features, differences in dietary or supplemental vitamin-D intake, and genotype variation in proteins involved in vitamin-D transport, functioning, and metabolism[23]. It has been shown that vitamin-D levels should be checked in patients in PICU.

Our study showed that the 48% of critically ill children have vitamin-D deficiency and insufficiency at admission to the PICU. The prevalence of vitamin-D deficiency and sufficiency was similar to that reported in a previous study from Turkey, which found that vitamin-D deficiency was observed in 58% of critically ill children[8]. Moreover, the prevalence of vitamin-D deficiency was higher in children older than one year old. Although the infants under one year of age, the frequency of vitamin-D deficiency/insufficiency was 26.9%, it is increased to 58.6% in children over one year old. Since 2005, the Ministry of Health has provided 400 IU of vitamin-D prophylaxis free of charge to infants under one year old, reducing the rate of vitamin-D deficiency in this age group[24]. These findings suggest that it is important to assess vitamin-D levels in children admitted to the PICU, especially those aged over one year, who are at a higher risk of vitamin-D deficiency or insufficiency.

Although most patients with vitamin-D deficiency (61.7%) in our study were hospitalized during the winter and autumn seasons, no correlation was found between the seasons and vitamin-D levels. A previous study in Turkey found that vitamin-D levels were significantly affected in patients admitted to the paediatric intensive care unit, especially during winter [8]. Another study of 4168 adults and children showed that vitamin-D levels were higher in spring and summer months[25]. A cohort study of critically ill adults in France found that ICU admission in spring (following winter months) was an independent predictor of severe vitamin-D deficiency (level < 30 nmol/L)[26]. Sunlight and climate conditions are known to have an impact on vitamin-D synthesis. Since there is no strong evidence on this subject in the literature, we believe that studies designed to detect the difference in seasonal variations are needed.

One of the factors that contribute to serious morbidity among critically ill paediatric patients is the presence of the chronic diseases. However, studies evaluating the vitamin-D levels of patients with chronic diseases are scarce in the literature, with most studies focusing on adult patients[27-29]. In Madden et al.'s study, 82.4% of the patients hospitalized in the PICU had an underlying chronic disease, with respiratory or neurological conditions being the most common. Patients with seizures and oncological problems had significantly higher vitamin-D levels[16]. In our study, a lower percentage of patients had an underlying chronic condition compared to Madden et al. Our percentage was similar to other studies in our country[8,30,31]. Specifically, 52% of the patients in our study had chronic diseases, with cerebral palsy being the most common diagnosis. Surprisingly, we found that chronic disease status did not significantly affect the vitamin-D levels. Although dietary and feeding problems are more common, and exposure to sunlight may also be a challenge in patients with chronic diseases, we believe that vitamin D preparations may be used more frequently in these children due to frequent hospital admissions, examinations, and blood tests [32,33]

Previous studies suggested that vitamin-D has regulatory effects on cardiac contractility and has antiatherosclerotic and renoprotective properties[34,35]. Ponnarmeni et al. (31) suggested that the vitamin-D deficiency correlated with an increased need for vasopressors. Furthermore, a meta-analysis showed that vitamin-D deficiency is associated with a 1.9 fold increase in vasopressor use [22]. However, in our study, we did not find a statistically significant relationship between vitamin-D levels and the need for vasopressors. In future research exploring the effects of vitamin-D on conditions such as hypotension and cardiac failure, it may be worthwhile to re-evaluate the use of vasopressors after controlling for 25(OH)D levels on certain days following treatment for vitamin-D deficiency.

In our study, although the vitamin-D levels of survive patients were higher than those who did non-survive, this difference was not statistically significant. One meta-analysis systematically reviewed observational cohort studies of vitamin-D deficiency in the intensive care unit, including 9.715 critically ill patients showed that vitamin-D deficiency increases the susceptibility to serious infections and mortality in critically ill patients[36]. In the other meta-analysis, reported an increase in deaths in the group with vitamin-D deficiency, but it was found to be statistically significant only in the study in Chile[37]. When developing countries were excluded from the study, the relationship with mortality was stronger and greater statistical significance was obtained (OR 2.6, p=0.003). However, since vitamin-D deficiency is seen with a rare frequency of 5% in developed countries, the sample was more limited[37]. In a meta-analysis by Su et al., it was found that the risk of mortality 1.77 times in children with vitamin-D deficiency[38]. On the other hand, there are some studies reported that vitamin-D deficiency had no effect on mortality[20,21,39,40]. These results suggest that the effect of vitamin-D on mortality is likely a result of its pleiotropic effects, leading to faster resolution of mortality and organ dysfunction, and an improvement in the quality of life.

The strength of our study is that it was a study conducted in the paediatric intensive care unit of the largest city in the region where vitamin-D deficiency is most common in our country. In addition, the exclusion of diseases that directly affect vitamin-D metabolism is another strength. The limitations of our study are that it includes 1-year data of our center and we do not have a control group. Our patient count is insufficient for such a study and power analysis could not be performed. Another limitation is that we only measured the vitamin-D levels of our patients at the time of admission.

CONCLUSIONS

Vitamin-D deficiency is a common problem in critically ill children in Turkey. In our study, although we did not find a significant relationship between vitamin-D level and mortality, we found that patients with vitamin-D deficiency had a higher PRISM III score compared to those with sufficient vitamin-D levels. Further studies are needed

to determine the relationship between vitamin-D deficiency and/or insufficiency in children hospitalized in the intensive care unit, and mortality scores and mortality.

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Özgün Çalışma / Original Article

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Erken evre Mikozis fungoides nedeniyle darband ultraviyole B fototerapisi alan hastaların değerlendirilmesi

Evaluation of patients receiving narrow-band ultraviolet B phototherapy for early stage Mycosis fungoides

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ÖZET

AMAÇ: Bu çalışmanın amacı, erken evre Mikozis fungoides (MF) nedeniyle darband ultraviyole B (dbUVB) fototerapisi alan hastaların demografik, hastalık ve tedavi özelliklerinin karşılaştırılmasıdır.

GEREÇ VE YÖNTEM: Bu çalışmaya Şubat 2020 ile Şubat 2024 yılları arasında üçüncü basamak bir sağlık kuruluşunun fototerapi ünitesinde, klinik ve histopatolojik olarak MF tanısı doğrulanmış ve en az 12 hafta dbUVB monoterapisi alan hastalar kabul edildi. Çalışma için değerlendirme değişkenleri; demografik bilgiler, semptomlar, dermatolojik muayene ve histopatolojik bulgular, dbUVB tedavi bulguları olarak seçilmiştir. Değişkenler istatistiksel olarak analiz edilmiştir.

BULGULAR: Çalışmaya 50 hastanın verileri dahil edildi. Hastaların yaş ortalaması 50,1±17,8'di Hastaların %50'si (n=25) erkekti, %50'si (n=25) kadındı. Hastaların ortalama tanı alma süreleri 75,37±9,05 aydı. Kaşıntı semptomu hastaların %30'unda (n=15) bildirilmişti. Hastaların %58'i (n=29) tedaviden tam yanıt aldı. Hastaların ortalama tedavi süreleri 14,2±7,2 aydı. Hastalar median 121 (36-324) seans dbUVB tedavisi almıştı. Evre 1A olan hastaların %65,6'sı (n=21), Evre 1B olan hastaların %44,4'ü (n=8) tedaviden fayda görmüştü. Hastaların %42'sinde (n=21) hafif eritem ve pruritus yan etkisi görülmüştü. Yanıt grupları arasında çalışma değişkenleri açısından yapılan değerlendirmede istatistiksel anlamlı farklılık bulunamamıştı. Evre grupları arasında çalışma değişkenleri açısından istatistiksel anlamlı farklılık sadece tanı alma süreleri arasındaki farktı (p<0,05).

SONUÇ: DbUVB fototerapisi erken evre MF için efektif ve yan etki profili güvenilir bir tedavi yöntemidir.

Anahtar kelimeler: fototerapi, mikozis fungoides

ABSTRACT

AIM: To compare the demographic, disease and treatment characteristics of patients receiving darband ultraviolet B (dbUVB) phototherapy for early stage mycosis fungoides (MF).

MATERIAL AND METHOD: The study included patients with a clinically and histopathologically confirmed diagnosis of MF who received dbUVB monotherapy for at least 12 weeks in the phototherapy unit of a tertiary healthcare instution between February 2020 and February 2024. The evaluation variables for the study were demographic information, symptoms, dermatological examination and histopathological findings, and dbUVB treatment findings. The variables were analysed statistically.

RESULTS: Data of 50 patients were included in the study. The mean age of the patients was 50.1±17.8 years. 50% (n=25) of the patients were male and 50% (n=25) were female. The mean duration of diagnosis was 75.37±9.05 months. Itching symptom was reported in 30% (n=15) of the patients. 58% (n=29) of the patients had a complete response to treatment. The mean duration of treatment was 14.2±7.2 months. Patients received a median of 121 (36-324) sessions of dbUVB treatment. 65.6% (n=21) of stage 1A patients and 44.4% (n=8) of stage 1B patients benefited from the treatment. Mild erythema and pruritus side effects were observed in 42% (n=21) of the patients. There was no statistically significant difference in the evaluation of study variables between the response groups. The only statistically significant difference between the stage groups in terms of study variables was the difference in the time to diagnosis (p<0.05).

CONCLUSION: NbUVB phototherapy is an effective treatment modality for early stage MF with a reliable side effect profile.

Keywords: phototherapy, mycosis fungoides

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GİRİŞ

Mikozis fungoides (MF), Kutanöz T hücreli lenfomanın yüksek prevalans (%50) oranına sahip tipidir. Çalışmalarda MF'in yıllık insidansı 0,3-1,02 vaka /100.000 kişi olarak bulunmuştur.[1,2] MF'nin patogenezi net olarak ortaya koyulamamıştır. Hastalığın ortaya çıkmasında genetik, çevresel ve immünolojik faktörlerin rol oynadığı düşünülmektedir. Genetik olarak, Myc (myelositomatoz) geninde amplifikasyon, p53 (protein 53) ve CDKNA2A (siklin bağımlı kinaz inhibitörü) ve 2B genlerinde ekspresyon kaybının hastalık patogenezinde önemli olduğu raporlanmıştır. Çevresel faktörler; mesleki maruziyeti, İnsan T Lenfotrofik Virüs ve Ebstein Barr Virus enfeksiyonları olarak gösterilmiştir. İmmunolojik olarak da artmış Th2 sitokinleri ve azalmış Th1 aracılı antitümör yanıt suçlanmıştır.[3] MF, karakteristik olarak yama, plak ve tümör evreleri olan bir lenfoma tipidir. Başlangıç deri lezyonlarının predileksiyon alanları gluteal alan gibi kapalı vücut alanlarıdır. Lezyonlar sıklıkla anüler, polisiklik veya atnalı şeklinde olabilir. [4] Hastalığın tanısı, şüpheli deri lezyonlarından yapılan histopatolojik değerlendirme ve immünfenotiplendirme ile konur. Yama dönemi lezyonlarının histopatolojik değerlendirilmesinde yüzeyel band tarzında veya likenoid lenfositik infiltrat, papiller fibrozis vardır. Serebriform hiperkromatik nükleuslu atipik hücreler mevcuttur. Bu atipik hücreler, periferik halosu olan tek hücreler şeklinde epidermis bazal membrana tek sıra lineer birikim yaparlar.[4,5] Atipik lenfositler intraepidermal kümeler oluşturarak Pautrier mikroabselerini temsil ederler. Atipik hücreler, immunfenotiplendirmede CD3+, CD4+, CD45RO+ ve CD8- tespit edilmektedir.[6]

Mikozis fungoides tanısı konulduktan sonra tedavi planı için evrelendirme yapılmaktadır. Günümüzde MF evrelemesinde TNMB (tümör, lenf nodu, metastaz ve kan) sistemi uygulanmaktadır. Evreleme sistemine göre Evre 1A, Evre 1B ve Evre 2A erken dönem MF'i temsil etmektedir. Yama ve plakların vücut yüzey alanının %10'undan daha azını tuttuğu ve lenf nodunun tutulmadığı durum Evre 1A'yı, %10'dan daha fazla tutulum ise Evre-1B'yi, yama ve plak döneminde klinik olarak anormal lenf nodu saptanması ise Evre-2A'yı temsil etmektedir.[7] Evreleme sonrası uygun tedavi planı yapılmaktadır. Tedaviler, deriye yönelik tedaviler ve sistemik tedaviler olarak ikiye ayrılır. Deriye yönelik tedavilerin günümüzde en önemli temsilcisi fototerapilerdir. Fototerapinin MF üzerindeki patofizyolojik mekanizması net olmamakla birlikte, UV maruziyetinin Langerhans hücrelerinin antijen sunumunu kısıtlayarak, IL-2, IL-6 ve TNF-alfa seviyelerini artırarak ve neoplastik lenfositleri apoptozise uğratarak etkili olduğu düşünülmektedir.[8] Bu fototerapi yöntemlerinden en ulaşılabilir ve yan etki profili düşük olan tedavi seçeneği darband UVB (dbUVB)'dir.[8] Çalışmalarda erken dönem MF'te dbUVB'nin tedavi yanıtı yüzdesi %75'in üzerindedir. [9-11] Bu çalışmadaki amacımız, fototerapi ünitemizde erken dönem MF nedeniyle dbUVB alan hastalarımızın profilini incelemek ve yanıt farkı olan hastaların özelliklerini karşılaştırmaktır.

GEREÇ VE YÖNTEM

Çalışmanın tasarımı retrospektif kohorttur. Bu çalışmaya Şubat 2020 ile Şubat 2024 yılları arasında üçüncü basamak bir sağlık kuruluşunun fototerapi ünitesinde, klinik ve histopatolojik olarak MF tanısı doğrulanmış ve en az 12 hafta dbUVB monoterapisi alan Evre-1A ve Evre-1B hastalar kabul edildi. Işığa duyarlılığı olan veya ışığa duyarlılık yapan ilaçlarla tedavi edilen hastalar hariç tutulmuştur. Çalışma için Ankara Eğitim ve Araştırma Hastanesi etik kurulundan 17.04.2024 tarihinde E-93471371-514.10-241617640/ E-24-73 numarayla etik onay alınmıştır.

Çalışma için değerlendirme değişkenleri; yaş, cinsiyet, kaşıntı varlığı, daha önceki tedaviler, tanı alma süresi, vücut tutulum alanları, histopatolojik bulgular, fototerapi toplam dozu, fototerapi seans sayısı, fototerapi yanıtı, fototerapi yan etkileri olarak seçilmiştir. Vücut tutulum alanları; baş/boyun, alt ekstremite, üst ekstremite ve gövde olarak gruplandırıldı. Hastaların evreleri TNM evrelemesine göre seçildi.[7] Histopatolojik bulgular; atipik lenfosit, epidermotropizm, yüzeyel perivasküler lenfosit infiltrasyonu, papiller fibrozis, Pautrier mikroabseleri olarak gruplandırıldı. [12] Tam yanıt grubu, lezyonların tutulum alanında %95'den fazla azalma olanlar şeklinde tanımlandı. Bu kritere uymayan hastalar ise yanıtsız/ kısmi yanıtlı grubu şeklinde tanımlandı [13].

Çalışma değişkenleri, elektronik kayıt sisteminden her hasta için kaydedildi. Değişkenler açısından eksik verileri olan hastalar, çalışma dışı bırakıldı.

Fototerapi için Waldman marka UV5040K tipi dbUVB cihazı 311-313 nm dalga boyunda kullanıldı. Hastaların başlangıç dbUVB dozları, minimal eritem dozlarının %70'i olacak şekilde ayarlanmıştır. Hastaların tedavisi 3 seans/hafta ile başlamıştır. dbUVB dozları, hasta tolere edilebildiği kadar her seansta %10-15 arttırılmıştır. DbUVB, lezyonlarda %95 azalma olana kadar haftada 3 seans olacak şekilde uygulandı. Daha sonra hastanın klinik bulgularına göre seans sıklığında 4-8 haftada bir olacak şekilde 2 seans/hafta, 1 seans/hafta, 1 seans/2 hafta, 1 seans/ 4 hafta azaltmalar yapıldı. Bu şekilde idame tedavisi planlandı.

Araştırma verileri Sosyal Bilimler İstatistik Paketi (SPSS.22, IBM SPSS İstatistikleri for Windows, Sürüm 22.0. Armonk, New York: IBM Corp.) aracılığıyla değerlendirildi. Tanımlayıcı istatistikler ortalama (±) standart sapma, frekans dağılımı ve yüzde olarak kaydedildi. Verilerin normallik analizleri Shapiro-Wilk testi ile yapıldı. Kategorik değişkenler için gruplar arasında frekans farkı olup olmadığı Pearson ki-kare kullanılarak karşılaştırıldı. Normal dağılan ortalamaları değerlendirmek için t testi kullanıldı. Normal dağılmayan ortalamaları değerlendirmek için Mann-Whitney U testi kullanıldı. Bu çalışmanın istatistiksel anlamlılık değeri $p<0,05$ olarak kabul edildi.

BULGULAR

Çalışmaya 50 hastanın verileri dahil edildi. Hastaların yaş ortalaması 50,1±17,8'di Hastaların %50'si (n=25) erkekti, %50'si (n=25) kadındı. Çalışma değişkenleri açısından hastaların bilgileri Tablo-1'de gösterildi.

Tablo-1: Çalışma katılımcılarının çalışma değişkenleri açısından bilgileri

	Hasta (n=50)
Yaş, (yıl) ort±Std	50,1±17,8
Cinsiyet, n (%)	
Kadın	25 (50)
Erkek	25 (50)
Tanı alma süresi, (ay) ort±Std	75,37±9,05
Kaşıntı, n (%)	15 (30)
Tutulum alanları, n (%)	
Baş/boyun	4 (8)
Üst ekstremite	25 (50)
Alt ekstremite	42 (84)
Gövde	18 (36)
Evre, n (%)	
Evre 1A	32 (64)
Evre 1B	18 (36)
Histopatolojik bulgular, n (%)	
Atipik lenfosit	35 (70)
Epidermotropizm	46 (92)
Süperfisyal likenoid infiltrat	11 (22)
Papiller dermal fibrozis	5 (10)
Pautrier mikroabsesi	11 (22)
dbUVB seans sayısı, median	121
dbUVB dozu (J/cm2), ort±Std	211,5±132
Yan etkiler, n (%)	
Eritem ve pruritus	21 (42)
Herpes zoster/labialis	2 (4)
Nevüs artışı	1 (2)
Tam yanıt seansı, ort±Std	76,8±52,8

n: sayı, Std: Standart deviasyon, ort: ortalama, dbUVB: darband ultraviyole B

Hastaların %24'ünde (n=12) tedavisi esnasında seans sıklığı azaltılırken yeni lezyon çıkışları olduğu için, tekrar seans sıklığı arttırılmıştı.

Hastaların %58'i (n=29) tedaviden tam yanıt aldı. Tedaviden tam yanıt gören hastalar ortalama 76,8±52,8 seansta tam yanıta ulaşmıştı. Yanıt grupları arasında çalışma değişkenleri açısından yapılan değerlendirmede istatistiksel anlamlı farklılık bulunamamıştı

Tablo-2: Yanıt gruplarının çalışma değişkenleri açısından değerlendirilmesi

	Tam yanıt (29)	Kısmi/Yanıtsız (21)	P değeri
Yaş, (yıl) ort±Std	51,2±18	48,6±17,7	0,5*
Cinsiyet, n (%)			0,7**
Kadın	14 (48,3)	11 (52,4)	
Erkek	15 (51,7)	10 (47,6)	
Kaşıntı, n (%)	7 (25)	8 (38,1)	0,5**
Tanı alma süresi, (ay) ort±Std	83,8±98,2	66,2±98,8	0,5*
Evre, n (%)			0,1**
Evre 1A	21 (72,4)	11 (52,4)	
Evre 1B	8 (27,6)	10 (47,6)	
Histopatolojik bulgular, n (%)			
Atipik lenfosit	21 (72,4)	14 (66,7)	0,9**
Epidermotropizm	27 (93,1)	19 (90,5)	0,8**
Süperfisyal likenoid infiltrat	7 (24,1)	4 (19)	0,9**
Papiller dermal fibrozis	3 (10,3)	2 (9,5)	0,9**
Pautrier mikroabsesi	8 (27,6)	3 (14,3)	0,2**
dbUVB seans sayısı, ort±Std	155,8±82,4	122,4±95,7	0,08***
dbUVB dozu (J/cm^2), ort±Std	232,5±123	183±143,2	0,4*

n: sayı, Std: Standart deviasyon, ort: ortalama, dbUVB: darband ultraviyole B

*: T test, **: Ki-kare, ***: Mann-Whitney U test

Evre 1A olan hastaların %65,6'sı (n=21) ve Evre 1B olan hastaların %44,4'ü (n=8) tedaviden tam fayda görmüştü. Evre grupları arasında çalışma değişkenleri açısından istatistiksel olarak anlamlı farklılık yalnızca tanı alma süreleri arasında saptandı (p<0,05). Geri kalan değişkenlerde istatistiksel anlamlı bir farklılık yoktu

Tablo-3: Evre gruplarının çalışma değişkenleri açısından değerlendirilmesi

	Evre 1A (32)	Evre 1B (18)	P değeri
Yaş, ort±Std	49,31±18,4	51,7±16,9	0,9*
Cinsiyet ,n (%)			0,76**
Kadın	17 (53,1)	8 (44,4))	
Erkek	14 (46,9)	10 (55,6)	
Kaşıntı, n (%)	9 (28,1)	6 (35,3)	0,8**
Tanı alma süresi, (ay)±Std	113,8±116	27,3±24,4	**0,02***
Histopatolojik bulgular, n (%)			
Atipik lenfosit	20 (62,5)	15 (83,3)	0,1**
Epidermotropizm	28 (87,5)	18 (100)	0,1**
Süperfisyal likenoid infiltrat	7 (21,9)	4 (22,2)	0,9**
Papiller dermal fibrozis	4 (12,5)	2 (5,6)	0,9**
Pautrier mikroabsesi	8 (27,6)	3 (14,3)	0,2**
dbUVB seans sayısı, ort±Std	139,8±83,2	142,9±93,2	0,58*
dbUVB dozu (J/cm^2), ort±Std	214,3±132,5	208,3±124,8	0,9***
Tam yanıt aldığı seans sayısı, ort±Std	63,6±50,1	86,45±63,2	0,36*
Tam tedavi yanıt, n (%)	21 (65,6)	8 (44,4)	0,14**

n: sayı, Std: Standart deviasyon, ort: ortalama, dbUVB: darband ultraviyole B

*: T test, **: Ki-kare, ***: Mann-Whitney U test

Hastalarda tedavi sonlandırılması sonrası ortalama 57,8±41,9 hafta takip edilmişti. Tam yanıt veren hastaların %20'sinde (n=6) bu süre boyunca relaps tespit edildi. Bu hastaların hepsi Evre-1B hastasıydı.

TARTIŞMA

Mikozis fungoidesin epidemiyolojik verilerini inceleyen çalışmalarda, hastalığın daha çok 50'li yaşların sonunda ve daha çok erkeklerde görüldüğü vurgulanmıştır.[2] Bizim çalışmamızda yaş ortalaması literatüre göre daha düşük ve kadın/erkek oranı eşit çıkmıştır. Çalışmanın retrospektif yapısı nedeniyle bu sonucun ortaya çıktığını düşünmekteyiz.

Literatürde dbUVB'nin MF'te etkinliğini değerlendiren çalışmalar farklı ülkelerden tek merkez tecrübe raporlarından oluşmaktadır. İlk defa 1999 yılında Hofer ve ark. ortalama 6 hafta ve 16,3 J/cm2 kümülatif doz sonrasında 6 erken MF hastasının 5'inde tam yanıt bildirmiştir. [14] Daha sonra konunun popülerliği artmış ve araştırmacılar bu konuyla ilgili tecrübelerini bildirmeye başlamışlardı. Bu çalışmalara 6-68 arası hasta katılmış, erkek hastaların oranı %38,8-%89,6 arası ve yaş ortalamaları 49,6- 61,1 yıl arasındaydı. [9,10,13-24] Çalışmamız da literatürdeki raporlarla benzer hasta profillerine sahipti.

Mikozis fungoides'in erken evre semptomları, egzama ve Psoriasis gibi enflamatuvar deri hastalıklarına benzemektedir. O nedenle MF'in erken evrelerinde tanısı oldukça güçtür. Hastalar, semptomlarının başladıktan tanı alana kadar çoğunluklar bir den fazla yanlış tanı ve yanıtsız tedavileri tecrübe ederler. Tanı gecikmelerinin bir diğer sebebi de MF'in erken dönem histopatolojik değerlendirilmesinin güçlüğüdür [25]. Literatürde erken evre MF nedeniyle dbUVB tedavisi alan hastalarda tanı alma süresi 11,75- 60 ay arasıydı. [9,17,19-24] Bizim hastalarımızda ise bu süre literatürdeki değerlere nazaran daha uzundu. Bu duruma, hastalarımızın çoğunluğunun lokal semptomlarının (Evre 1A) oluşu ve sağlık hizmetlerine ulaşmada zorluk (randevu sistemi) sebep olmuş olabilir.

Mikozis fungoides'in her evresinde hafif veya şiddetli kaşıntı şikayeti görülebilir. Kaşıntı genelde geç evrelerde, erken evrelere nazaran daha şiddetli olma eğilimindedir. Buna geç dönemde periferal eozinofil, Th2 sitokin profili ve stafilokokkal kolonizasyonun neden olduğu düşünülmektedir. Literatürde erken evre MF nedeniyle dbUVB verilen hastalarda kaşıntı ortalaması %31-42,9 arasıydı. [20,21] Çalışmamızda da bu oran literatürle uyumluydu. Yanıt grupları arasında ise kaşıntı varlığı açısından anlamlı fark yoktu. Hastalarımızda kaşıntı semptomunun dbUVB tedavisi sonrası gerileyip gerilemediği çalışmanın retrospektif yapısı nedeniyle kayıtlarından ulaşılamadı. Kaşıntılı deri hastalıklarında dbUVB uzun zamandır kullanılan bir yöntemdir.[26] Kaşıntısı olan MF hastalarında dbUVB'nin etkinliğini inceleyen çalışmalara ihtiyaç vardır.

Çalışmamızda dbUVB tedavisi öncesi histopatolojik bulgular, tedavi yanıtı grupları arasında ve evre grupları arasında karşılaştırılmış; bulgular açısından istatistiksel anlamlı farklılıklar saptanmamıştır. Literatürde bu konuda bildiğimiz kadarıyla henüz bir çalışma bulunmamaktadır. Gelecekte, MF hastalarında tedavi öncesi baskın bulunan histopatolojik bulguların tedavi yanıtını öngörmede bir faktör olup olamayacağı yapılacak çalışmalarla değerlendirilmelidir.

Hastalığın erken tanısı, uygun tedavi ile birlikte hastalığın progresyonunu önlemede ve yan etki profili geniş sistemik tedavilerden korumada önemlidir. Fototerapi bu açıdan MF hastalığının tedavisinde önem arz etmektedir. DbUVB'nin MF'te etkinliğini değerlendiren çalışmalarda tam yanıt oranları değişkendir. Bu çalışmalarda ortalama tedavi süreleri 1,5-14 ay arası, ortalama tedavi seans sayısı 19- 112 seans arası, ortalama kümülatif UV dozu 16,3- 108.8 arasındaydı. Bu tedavi parametrelerinin sonucunda hastaların dbUVB'ye tam yanıt oranları %57-95 arasındaydı. [9,10, 13-24] Bizim çalışmamızda da tam yanıt oranı benzer iken, ortalama tedavi süresi, ortalama tedavi seans sayısı ve ortalama kümülatif UV dozu yüksekti. Literatür verilerinin bu açılardan farklı oluşunun birden fazla nedeni olabilir. Bunlar; çalışmalarda kabul edilen tam yanıt kriterleri, lezyon kalınlıkları dağılımı (yama veya plak), lezyonların yaygınlığı dağılımı (Evre 1A, Evre 1B ve parapsoriasis), hastaların deri fototip varlığı ve fototerapi tedavi şeması farklılıklarıdır. Çalışmalarda tam yanıt, lezyonlarda %90-100 silinme olarak tanımlanmıştı. Bu açıdan çalışmalar bir standardizasyon sağlayamamıştı. [9,17,18,20] DbUVB'nin penetrasyonu yama lezyonlara daha yüzeyel olması nedeniyle daha kolaydır. O nedenle plak lezyonlara derin penetrasyon yeteneği nedeniyle Psoralen Ultraviyole A önerilmektedir [27]. Bazı çalışmalarda, plak lezyonları olan hastalar da çalışmalara dahil edilmişti. [9,15,16,24] Bu çalışmalarda aynı zamanda lezyon dağılımını temsil eden Evre 1A ve Evre 1B hasta dağılımları farklıydı. Çalışmaların bazılarında hastalar daha çok Evre1A iken [14,23,24], bazıların da Evre 1B idi. [21,22] Bizim de gözlemimiz, Evre 1B olan hastalarımızda tedavi yanıtı düşüktü. Ancak Gokdemir ve ark. , çalışmasında hastalarının büyük bir kısmı Evre 1B (%75) olmasına rağmen yanıt oranı %90'lardaydı.[9] Bu durum lezyon yaygınlığının tedavi yanıtına etkisini şüpheli hale getirmektedir. Yanıtı etkileyen bir diğer faktör, hastaların deri fototipi olabilir. Deri fototipi IV-V olan hastalarda fototerapi etkinliğinin düşük olduğu gösterilmişti.[19,22] Bu duruma artan melanositlerin fotoprotektif etkisiyle UVB'yi absorbe etmesiyle açıklanabilir. Bizim çalışmamızın retrospektif doğası nedeniyle hastaların fototipleri bilgisi elde edilemedi. Bu çalışmaların tam yanıt oranlarının farklı olmasının bir diğer sebebi de uygulanan fototerapi şeması farklılıklarıdır. Bazı çalışmalarda haftada 3 seans yerine, haftada 2 seans şeklinde tedavi uygulanmıştı.[18] Çalışmamızdaki ortalama tedavi süresi, ortalama tedavi seans sayısı ve ortalama kümülatif UV dozu yüksekliğinin birden fazla nedeni olduğunu düşünüyoruz. Öncelikle bizim hastalarımız, literatürdeki hastaların aksine idame tedavisi almışlardı. Bir diğer neden ise hastaları değerlendiren hekimlerin farklı olmasıydı. Günümüzde dbUVB tedavisinin MF'te standardize edilmiş bir şeması yoktur. Daha çok tecrübeye dayanarak tedavi planlaması yapılmaktadır. Ayrıca bazı hastalarımız seans sıklığında azaltma yapılırken, hastalıklarında relaps meydana gelmiş ve seans sıklıkları arttırılmıştı. Bu nedenlerin hepsi literatürün aksine çalışmamızda daha uzun tedavi süresi, daha çok tedavi seansı ve kümülatif doza sebep olmuş olabilir.

Mikozis fungoides nedeniyle dbUVB tedavisi almış hastaların tedavi sonlanmasını takiben hastalık relapsını inceleyen çalışmalardan elde edilen sonuçlar değişkendir. Çalışmalarda hastalar ortalama 6,7-77 ay boyunca takip edilmiş, bu süre aralığında ortalama relaps oranı %4,7-100 arasında izlenmiştir.[16-21,23,24] Çalışmamızın sonuçları literatürle uyumlu olmakla birlikte relaps oranı diğer çalışmalara nazaran daha düşüktü. Bunu idame tedavisi vermemizle ilişkilendirebiliriz. Literatürde benzer şekilde idame tedavisi verilmiş bazı çalışmalar da relaps oranları düşüktü. [9,20,24] Ancak Gara ve ark. bir çalışmasında idame tedavisi almış ve almamış MF hasta grupları arasında relaps oranları arasında fark saptamamıştı. Bu çalışmada fototerapi ile idame tedavinin bir takım çekinceleri belirtilmişti. Bunlar; idame fototerapi ile tedaviye rezistan malign hücreleri arttırmak ve melanom dışı deri kanseri riskini arttırmaktır.[28] Görünen o ki, MF'te fototerapi ile idame tedavinin yeri henüz aydınlatılamamıştır. Bu konuda daha çok çalışmaya ihtiyaç olduğu açıktır.

Literatürde dbUVB ile MF hastalarında ciddi yan etki bildirilmemişti.[9,10,13-24] Bizim çalışmamızda da bu konuda benzer bir yan etki profili vardı. Hastalarımızda tedaviyi sonlandırmaya neden olacak ciddi bir yan etki görülmemişti.

Bu çalışmamızın bazı kısıtlılıkları vardı. Çalışmamız tek merkezden az sayıda katılımcılı olan retrospektif kohort bir çalışmadır.

SONUÇ

Çalışmamız, dbUVB tedavisin erken evre MF için efektif ve yan etki profili güvenilir bir tedavi yöntemi olduğunu göstermişti. Çalışmamız, lezyon yaygınlığı arttıkça tedavi yanıtının düşme eğiliminde olduğunu ve idame tedavi ile literatüre kıyasla daha düşük relaps oranları gözlemlediğimizi göstermiştir. Ancak, bu bulgular istatistiksel anlamlılık taşımamaktadır. O nedenle çok merkezli, katılımcı sayısının fazla olduğu çalışmalara ihtiyaç vardır.

Yazarlık Katkıları:

Konsept ve tasarım: B.T, Veri toplama: B.T, İ.K., Analiz: B.T, İ.K., N.K
Literatür derleme, araştırma: B.T, İ.K, N.K, Makalenin yazımı: B.T,
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Evaluation of Liver Function Indices in Intrahepatic Cholestasis of Pregnancy: Diagnostic Utility and Neonatal Outcomes

Gebelik İntrahepatik Kolestazında Karaciğer Fonksiyon Endekslerinin Değerlendirilmesi: Tanı Yararlığı ve Yenidoğan Sonuçları

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ABSTRACT

AIM: Intrahepatic cholestasis of pregnancy (ICP) is a hepatic condition that occurs in 0.2-2% of pregnancies. It is characterized by intense itching and increased levels of bile acids in the bloodstream. Precise identification and anticipation of adverse neonatal outcomes are crucial. This study evaluates the diagnostic performance of liver-related scores—APRI (aspartate aminotransferase- platelet), ALBI (albumin-bilirubin), PALBI (platelet- albumin-bilirubin), and FAR (fibrinogen/albumin ratio) —in ICP patients and examines their relationship to pregnancy outcomes.

MATERIAL AND METHOD: This study was a retrospective analysis of 180 patients who were treated at Ankara Etlik City Hospital between January 2023 and January 2024. 90 ICP patients (Group 1) and 90 control patients (Group 2) were compared. The PALBI, ALBI, APRI scores, and FAR were calculated using third-trimester laboratory values. Neonatal outcomes, including birth weight, APGAR scores, NICU (neonatal intensive care unit) admission, sepsis, RDS (respiratory distress syndrome), and neonatal death were recorded. Statistical analyses included ROC (Receiver Operating Characteristics) curve analysis and Spearman correlation.

RESULTS: The PALBI, ALBI, APRI scores, and FAR were significantly higher in ICP patients (p<0.001). The APRI score showed the highest diagnostic performance (area under curve 0.870). Cut-off values were >-2.58 for PALBI (sensitivity 62%, specificity 81%), >-2.47 for ALBI (sensitivity 67%, specificity 81%), and >0.3 for APRI (sensitivity 78%, specificity 68%). Neonatal outcomes did not differ significantly between the groups. There was no correlation between fasting bile acid levels and liver damage markers with negative outcomes in newborns.

CONCLUSION: In facilities where it is not possible to test fasting bile acid levels, PALBI, ALBI, APRI scores and FAR value offer an alternative approach to the evaluation of individuals with intrahepatic cholestasis of pregnancy (ICP). Future studies with larger patient groups are needed to increase the reliability of these parameters.

Keywords: Intrahepatic cholestasis of pregnancy; PALBI score; fasting bile acids

ÖZET

AMAÇ: Gebelikte intrahepatik kolestaz (ICP), gebeliklerin %0,2-2'sinde görülen bir karaciğer hastalığıdır. Yoğun kaşıntı ve kan dolaşımında safra asitlerinin artmasıyla karakterizedir. Olumsuz neonatal sonuçların kesin olarak tanımlanması ve öngörülmesi çok önemlidir. Bu çalışma, ICP hastalarında karaciğerle ilgili APRI (aspartat aminotransferaz-trombosit), ALBI (albümin-bilirubin), PALBI (trombosit-albümin-bilirubin) ve FAR (fibrinojen/albümin oranı) değerinin tanısal performansını değerlendirmekte ve bunların gebelik sonuçlarıyla olan ilişkisini incelemektedir.

GEREÇ VE YÖNTEM: Bu çalışma Ocak 2023-Ocak 2024 tarihleri arasında Ankara Etlik Şehir Hastanesi'nde tedavi gören 180 hastanın retrospektif analizidir. 90 ICP hastası (Grup 1) ile 90 kontrol hastası (Grup 2) karşılaştırıldı. PALBI, ALBI, APRI skorları ve FAR üçüncü trimester laboratuvar değerleri kullanılarak hesaplandı. Doğum ağırlığı, APGAR skorları, yenidoğan yoğun bakım ünitesine kabul, sepsis, solunum sıkıntısı ve neonatal ölümü içeren neonatal sonuçlar kaydedildi. İstatistiksel analiz, ROC (Receiver Operating Characteristics) eğrisi analizi ve Spearman korelasyonu ile yapıldı.

BULGULAR: ICP hastalarında PALBI, ALBI, APRI skorları ve FAR anlamlı olarak yüksekti (p<0,001). APRI puanı en yüksek tanısal performansı gösterdi (AUC: 0.870). PALBI skoru için cut-off değeri >-2,58 (sensivite %62, spesifite %81), ALBI skoru için >-2,47 (sensitive %67, spesifite %81), APRI skoru için >0,3 (sensivite %78, spesifite %68) idi. Yenidoğan sonuçları gruplar arasında anlamlı farklılık göstermedi. Yenidoğanlarda açlık safra asidi düzeyleri ve karaciğer hasarı belirteçleri ile olumsuz sonuçlar arasında bir korelasyon yoktu.

SONUÇ: Açlık safra asidi düzeylerinin test edilmesinin mümkün olmadığı merkezlerde PALBI, ALBI, APRI skorları ve FAR değeri intrahepatik gebelik kolestazı olan bireylerin değerlendirilmesinde alternatif bir yaklaşım sunmaktadır. Bu parametrelerin güvenilirliğini arttırmak için daha geniş hasta gruplarıyla gelecek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Gebelikte intrahepatik kolestaz; PALBI skoru; açlık safra asitleri

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a common liver disease that occurs in 0.2-2% of women during pregnancy.[1,2] It is more common during the latter stages of pregnancy and can be reversed.[3] The condition is marked by severe itching, especially on the soles of the feet and palms of the hands, and increased levels of bile acids in the blood.[4,5]the association between LMPI values, total bile acid (TBA It poses significant risks to neonatal health, with sudden intrauterine death being the most severe outcome.[3]

Genetic, hormonal, and environmental factors significantly contribute to the development of ICP.[6] While serum bile acid measurement is a reliable biochemical indicator for diagnosing and following intrahepatic cholestasis of pregnancy (ICP), it cannot be measured in every center and necessitates fasting overnight.[7] Moreover, bile acid levels are not elevated in all ICP patients and can also rise in other liver diseases, highlighting the need for further research into ICP's pathogenesis and diagnostic methods.[8] This situation raises the need for further research into the pathogenesis and diagnostic methods in ICP patients. Although the pathogenesis of ICP is not clear, the primary organ affected is the liver. ALBI (albumin-bilirubin) score, APRI (aspartate aminotransferase- platelet) score, PALBI (platelet- albumin-bilirubin) score and FAR (fibrinogen/albumin ratio) are indices related to liver function and fibrosis.[9–12]the severity of which is currently assessed by the Child-Pugh (C-P PALBI score, APRI score, PALBI score and FAR can be easily calculated from routine laboratory values and are inexpensive.

Precise identification of intracranial pressure (ICP) and the anticipation of unfavorable newborn consequences are essential for efficient prenatal and postnatal healthcare.[3] This study investigates the diagnostic performance of liver-related scores (APRI, ALBI, PALBI, and FAR) in ICP patients and examines their relationship to negative pregnancy outcomes.

MATERIAL AND METHOD

This retrospective study was conducted between January 2023 and January 2024 in the Perinatology Clinic of Ankara Etlik City Hospital. The study protocol received approval from the Ethics Committee of Ankara Etlik City Hospital (approval number: AESH-EK1-2023-771, 20.12.2023), and the study followed the guidelines outlined in the Declaration of Helsinki by the World Medical Association.

The study population comprised 180 patients, divided into two groups: 90 patients diagnosed with intrahepatic cholestasis of pregnancy (ICP) (Group 1) and 90 control patients (Group 2) selected according to randomization rules and who met the inclusion criteria.

The diagnosis of ICP was based on the presence of pruritus on the palms and soles, particularly at night, a fasting bile acid level >10 µmol/L, and the exclusion of other causes of liver dysfunction.[13] The exclusion criteria were prolonged illness in the mother, multiple pregnancies, smoking, alcohol consumption, congenital malformations, and inaccessible medical records. Demographic data such as age, gravidity, parity, and body mass index (BMI) were collected for all patients. The gestational age of the study patients was calculated on the basis of the first day of the patient's last menstruation and confirmed by ultrasound. The control patients were selected according to the rules of randomization and in accordance with the maternal age and gestational age of the patient group. AST (aspartate aminotransferase), ALT (alanine aminotransferase), total bilirubin, direct bilirubin, creatinine, urea, albumin, GGT (gamma-glutamyl transferase), ALP (alkaline phosphatase), LDH (lactate dehydrogenase), APTT (activated partial thromboplastin time), PT (prothrombin time), INR (international normalized ratio), fibrinogen, hemoglobin, WBC (white blood count), platelet, neutrophil, lymphocyte and monocyte levels were examined from maternal venous blood. The PALBI score, the ALBI score, the APRI score and the FAR values were calculated on the basis of the laboratory test results of the ICP patients and the control patients in the third trimester.

In the third trimester, the PALBI score, ALBI score, APRI score, and FAR values were calculated for both ICP and control patients using the following formulas: ALBI score = -0.085 × (albumin g/L) + 0.66 × (total bilirubin µmol/L) and this score is graded as ≤ −2.60 Grade 1, between −2.60 and −1.39 Grade 2, and > −1.39 Grade 3.[9]the severity of which is currently assessed by the Child-Pugh (C-P PALBI score= (2.02 × Log10 bilirubin µmol/L) + [−0.37 × (Log10 bilirubin)2] + (−0.04 × albümin g/dL) + (−3.48 × Log10 platelet 10^3/µL) + [1.01 × (Log10 platelet^2 10^3/µL)] and this score was calculated as Grade 1 when it was ≤−2.53, Grade 2 when it was between −2.53 and −2.09, and Grade3 when it was >−2.09.[14] APRI score= [(Aspartate aminotransferase (AST) (U/L) /upper limit of AST) /platelet count 10^3/µL] × 100 (upper limit of AST= 33 U/L in our hospital)[15]but the data is limited. As dengue epidemics are common in our country with limited healthcare resources, we believe APRI can help emergency physicians/primary physicians in predicting the severity of dengue and plan for the appropriate use of limited healthcare resources.\n\nObjective:\n1 and FAR= fibrinogen/albumin ratio. Neonatal outcomes such as birth weight, APGAR scores at 1 and 5 minutes, need for neonatal intensive care, neonatal sepsis, presence of respiratory distress syndrome (RDS), and neonatal death were recorded.

All statistical studies were conducted using RStudio (version: 2024.09.1+394 -Boston, USA) to analyze the data. The variables were assessed for normal distribution using visual techniques such as graphs and chance maps, as well as analytical methods like the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Levene test was employed to evaluate the uniformity of the variance. The descriptive analyses were conducted by calculating the means and standard deviations for variables that followed a normal distribution. The independent sample t-test was used to compare these parameters among the groups. Analyzed the irregularly distributed data using medians and quartiles (Q1-Q3) for descriptive analysis. The Mann-Whitney U test was conducted to compare these parameters among the groups. Frequency and percentage were used to offer descriptive analyses for the categorical variables. The Chi-square test or Fisher's exact test were used to investigate the relationship between categorical variables. The Fisher's exact test was employed in cases where the assumptions of the Chi-square test were not satisfied due to low anticipated cell numbers. The capacity of various parameters that can be used to predict ICP and adverse neonatal outcomes were analyzed using ROC (Receiver Operating Characteristics) curve analysis. When a significant cut-off value was observed, the sensitivity, specificity and AUC (Area Under Curve) were presented. The Spearman test was used to calculate the correlation coefficients and their significance for exploring the relationships between non-normally distributed variables. A p-value below 0.05 was accepted for statistical significance.

RESULTS

Ninety ICP patients and ninety control patients were included in the study. Table 1 presents the maternal characteristics and perinatal outcomes of the participants.

Table 1. Maternal Characteristics and Perinatal Outcomes

	ICP n: 90	Control n: 90	p
Maternal age (year)	28 (24-31)	28 (24-32)	0.790
Blood sample collection time (week)	33 (31-35)	34 (33-35)	0.094
BMI	28.4 (25.7-31.3)	29.5 (27.0-33.7)	0.100
Weight gained during pregnancy (kg)	10 (8-13)	10 (8-15)	0.177
Gravida	2 (1-3)	2 (1-3)	0.287
Parity	0 (0-1)	1 (0-1)	0.106
Glucose (mg/dl)	86 (76-97)	86 (73-96)	0.700
AST (U/L)	47 (22-86)	13 (11-17)	**<0.001**
ALT (U/L)	65 (22-137)	10 (8-13)	**<0.001**
Total bilirubin (mg/dl)	0.44 (0.28-0.70)	0.24 (0.18-0.36)	**<0.001**
Direct bilirubin (mg/dl)	0.28 (0.14-0.42)	0.11 (0.09-0.14)	**<0.001**
Creatinine (mg/dl)	0.53 (0.47-0.59)	0.48 (0.44-0.54)	**0.008**
Urea (mg/dl)	15.2 (12.0-20.7)	13.6 (11.1-16.2)	**0.012**
Albumin (g/dL)	35 (12-32.8)	36.0 (34.7-38.1)	**0.005**
GGT (U/L)	16 (10-28)	8 (6-11)	**<0.001**
ALP (U/L)	169 (132-227)	120 (94-144)	**<0.001**
LDH (U/L)	219 (184-255)	197 (178-217)	**0.003**
APTT (sn)	26.6 (24.4-28.0)	26.3 (24.9-27.9)	0.799
PT (sn)	7.93 (7.64-8.21)	8.22 (7.97-8.53)	**<0.001**
INR	0.90 (0.86-0.93)	0.88 (0.86-0.92)	0.112
Fibrinogen (mg/dL)	562 (489-610)	481 (433-529)	**<0.001**
Hemoglobin (g/L)	11.30 (10.30-12.43)	11.55 (10.38-12.60)	0.409
WBC (10^3/µL)	10.29 (8.74-12.41)	10.14 (8.81-12.11)	0.828
Platelet (10^3/µL)	251±73.9	249±57.8	0.831
Neutrophil (10^3/µL)	6.63 (5.72-8.38)	7.32 (6.18-8.89)	0.069
Lymphocyte (10^3/µL)	1.83 (1.37-2.39)	1.95 (1.62-2.17)	0.387
Monocyte (10^3/µL)	0.66 (0.50-0.80)	0.71 (0.60-0.82)	0.049
PALBI score	-2.44 (-2.77; -2.12)	-2.92 (-3.14; -2.62)	**<0.001**
ALBI score	-2.38 (-2.61; -2.16)	-2.64 (-2.83; -2.50)	**<0.001**
APRI score	0.7 (0.3-1.4)	0.2 (0.1-0.3)	**<0.001**
FAR	15.5 (13.8-18.0)	13.2 (11.8-14.9)	**<0.001**
History of ICP	6 (6.7)	0 (0)	**0.029**
Antenatal corticosteroid therapy	31 (34.4)	6 (6.7)	**<0.001**
Preterm birth (<37 week)	28 (31.1)	9 (10)	**0.001**
Fetal distress	3 (3.3)	8 (8.9)	0.213
Gestational age at delivery (week)	37 (36-37)	39 (38-40)	**<0.001**
Birth weight (gram)	2858±376.9	3245±412.6	**<0.001**
Birth method			
Normal spontaneous vaginal birth	34 (37.8)	46 (51.1)	
Primary cesarean section	35 (38.9) *	20 (22.2) *	**0.048**
Previous cesarean section history	21 (23.3)	24 (26.7)	
APGAR Score at 1st minute	9 (8-9)	9 (9-9)	**0.029**
APGAR Score at 5th minute	10 (9-10)	10 (10-10)	**0.049**
NICU admission	22 (24.4)	10 (11.1)	**0.032**
Neonatal hypoglycemia	0 (0)	3 (3.3)	0.246
TTN	8 (8.9)	5 (5.6)	0.565
Respiratory distress syndrome	6 (6.7)	1 (1.1)	0.118
Need for CPAP	8 (8.9)	6 (6.7)	0.781
Need for mechanical ventilator	6 (6.7)	1 (1.1)	0.118
Need for phototherapy	10 (11.1)	7 (7.8)	0.610
Neonatal sepsis	5 (5.6)	0 (0)	0.059

ICP: Intrahepatic cholestasis of pregnancy, BMI: Body mass index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma glutamyl transferase, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, APTT: Activated partial thromboplastin time, PT: Prothrombin time, INR: International normalized ratio, WBC: White blood count, PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, NICU: Neonatal intensive care unit, TTN: Transient tachypnea of the newborn, CPAP: Continuous positive airway pressure

* There is a significant difference between the groups only in the primary cesarean section.

Data are expressed as mean±SD, median and quartiles (Q1–Q3), or number (percentage) where appropriate. A p value of <0.05 indicates a significant difference.

There were no significant differences between the two groups regarding maternal age, time of blood sampling, BMI, weight gained during pregnancy, gravidity, and parity (p = 0.790, p = 0.094, p = 0.100, p = 0.177, p = 0.287, p = 0.106, respectively.) Laboratory values, including glucose, APTT, INR, hemoglobin, WBC, platelets, neutrophils, lymphocytes, and monocytes, were similar in both groups (p = 0.700, p = 0.799, p = 0.112, p = 0.409, p = 0.828, p = 0.831, p = 0.069, p = 0.387, p = 0.049, respectively). However, AST, ALT, total bilirubin, direct bilirubin, creatinine, urea, GGT, ALP, LDH, and fibrinogen levels were higher in the ICP group, while albumin and PT levels were higher in the control group (p < 0.001 for AST, ALT, total bilirubin, direct bilirubin, GGT, ALP, fibrinogen; p = 0.008 for creatinine; p = 0.012 for urea; p = 0.003 for LDH; p = 0.005 for albumin; p < 0.001 for PT). The average fasting bile acid level in the ICP group was 17.4 µmol/L (range: 12.0-32.8). The ICP group had significantly greater PALBI, ALBI, APRI scores, and FAR compared to the control group (p <0.001 for all). Perinatal outcomes did not differ significantly between the two groups in terms of fetal distress, neonatal hypoglycemia, TTN (transient tachypnea of the newborn), respiratory distress syndrome, need for CPAP (continuous positive airway pressure), need for mechanical ventilation, need for phototherapy, and neonatal sepsis (p=0.213, p=0.246, p=0.565, p=0.118, p=0.781, p=0.118, p=0.610, p=0.059). Antenatal corticosteroid therapy, preterm birth, primary cesarean section, and NICU admission were significantly higher in the ICP group, while gestational age at birth, birth weight, and APGAR scores at the first and fifth minutes were significantly lower (p < 0.001 for antenatal corticosteroid therapy, preterm birth, gestational age at birth, birth weight, APGAR scores; p = 0.001 for neonatal intensive care unit (NICU) admission; p = 0.048 for primary cesarean section; p = 0.032 for gestational age at birth; p = 0.029 for birth weight).

Table 2. Receiver Operating Characteristic (ROC) Analysis to Evaluate PALBI Score, ALBI Score, APRI Score and FAR in Detecting ICP Patients

	Cut-off	Sensivity	Specificity	AUC	CI	P value
PALBI score	>-2.58	62%	81%	0.749	0.679-0.811	**<0.001**
ALBI score	>-2.47	67%	81%	0,756	0.687-0.817	**<0.001**
APRI score	>0.3	70%	91%	0.870	0.812-0.916	**<0.001**
FAR	>13.68	78%	68%	0.713	0.663-0.796	**<0.001**

ICP: Intrahepatic cholestasis of pregnancy, PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, AUC: Area under the curve, CI: Confidence interval

Table 2 shows the ROC (receiver operating characteristic) analysis of the PALBI, ALBI, APRI scores, and FAR values in detecting ICP patients. The cut-off value for the PALBI score was>-2.58, with a sensitivity of 62% and a specificity of 81% (p <0.001). For the ALBI score, the cut-off value was >-2.47, with a sensitivity of 67% and a specificity of 81% (p <0.001). The APRI score had a cut-off value of >0.3, with a sensitivity of 78% and a specificity of 68% (p <0.001), and the highest AUC (area under the curve) was 0.870 for the APRI score

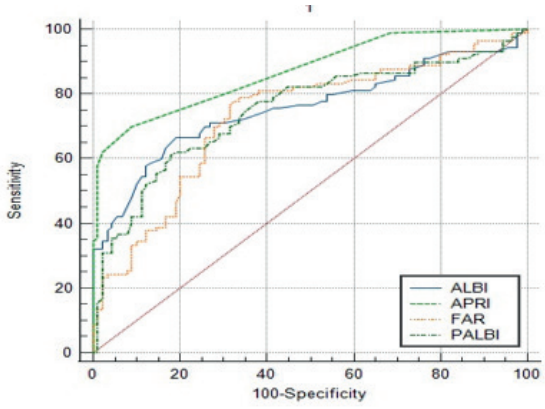

Figure 1. Receiver operating characteristic (ROC) curves to assess the usefulness of APRI (Aspartate aminotransferase-platelet) score, ALBI (Albumin-bilirubin) score, FAR (fibrinogen/albumin ratio) and PALBI (platelet-albumin-bilirubin) score

When the cut-off values and AUCs are compared with the ROC analysis, the APRI score is higher than the ALBI score (p = 0.04), the

PALBI score (p = 0.05) and FAR (p = 0.02).

Table 3. Receiver Operating Characteristic (ROC) Analysis to Evaluate Fasting Bile Acid, PALBI Score, ALBI Score, APRI Score and FAR in Predicting Adverse Neonatal Outcomes in ICP Patients

	Cut-off	Sensivity	Specificity	AUC	CI	P value
Fasting bile acid	>67.1	18%	97%	0.500	0.393-0.608	0.997
PALBI score	>-2.7	55%	28%	0.502	0.395-0.609	0.980
ALBI score	>-2.29	55%	71%	0.539	0.431-0.645	0.625
APRI score	≤ 0.2	27%	84%	0.518	0.410-0.625	0.809
FAR	>16.59	50%	71%	0.545	0.437-0.651	0.530

ICP: Intrahepatic cholestasis of pregnancy, PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, AUC: Area under the curve, CI: Confidence interval

Adverse neonatal outcomes: NICU (Neonatal intensive care unit) admission, TTN (Transient tachypnea of the newborn), Need for CPAP (Continuous positive airway pressure), Need for phototherapy, Neonatal sepsis

Table 3 shows the ROC analysis evaluating the association of fasting bile acid, PALBI score, ALBI score, APRI score, and FAR values with adverse neonatal outcomes in ICP patients. Fasting bile acid, PALBI score, ALBI score, APRI score, and FAR values were not associated with adverse neonatal outcomes in ICP patients.

Table 4. Receiver Operating Characteristic (ROC) Analysis to Evaluate PALBI Score, ALBI Score, APRI Score, and FAR in Predicting Adverse Neonatal Outcomes in All Patients

	Cut-off	Sensivity	Specificity	AUC	CI	P value
PALBI score	>-2.13	25%	59%	0.512	0.437-0.587	0.831
ALBI score	>-2.29	36%	85%	0.519	0.443-0.594	0.751
APRI score	>0.1	94%	19%	0.539	0.463-0.613	0.460
FAR	>16.59	36%	80%	0.555	0.479-0.629	0.313

PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio, AUC: Area under the curve, CI: Confidence interval

Adverse neonatal outcomes: NICU (Neonatal intensive care unit) admission, TTN (Transient tachypnea of the newborn), Need for CPAP (Continuous positive airway pressure), Need for phototherapy, Neonatal sepsis

Table 4 shows the ROC analysis evaluating the association between PALBI score, ALBI score, APRI score and FAR values with adverse neonatal outcomes in all patients. When all patients enrolled in the study are evaluated, the PALBI, ALBI, APRI scores and FAR values cannot predict adverse neonatal outcomes.

Table 5. Spearman's Correlation Between Fasting Bile Acid Concentration and Maternal-Perinatal Characteristics

	r	p
APGAR Score at 1st minute	-0.023	0.832
APGAR Score at 5th minute	0.007	0.947
PALBI score	0.348	**0.001**
ALBI score	0.312	**0.003**
APRI score	0.041	0.705
FAR	0.216	**0.041**

PALBI: Platelet-albumin-bilirubin score, ALBI: Albumin–bilirubin score; APRI: Aspartate aminotransferase platelet ratio index, FAR: Fibrinogen-to-albumin ratio

Table 5 shows the Spearman's correlation between fasting bile acid and maternal-perinatal characteristics. Fasting bile acid was associated with PALBI score (r = 0.348, p = 0.001), ALBI score (r = 0.312, p = 0.003), and FAR (r = 0.216, p = 0.041).

DISCUSSION

In this study, we found that the PALBI score, ALBI score, APRI score and FAR value were significantly higher in ICP patients and could be predictive in differentiating ICP patients. When the cut-off values and AUCs are compared with the ROC analysis, the APRI score is higher than the ALBI score, the PALBI score and FAR. PALBI score, ALBI score, APRI score, and FAR values were not associated with adverse neonatal outcomes in ICP patients.

ICP is associated with adverse neonatal outcomes such as fetal distress, preterm birth, meconium in the amniotic fluid and intrauterine fetal loss. Diagnosis and treatment of ICP is extremely important to avoid these adverse outcomes. Despite being implicated in the development of fetal illness, bile acids are the most reliable and specific biochemical indicator employed for the diagnosis and monitoring of ICP.[7,16] However, the exact cause of ICP is not completely understood, several researches have focused on establishing a relationship between maternal serum biochemistry and fetal outcomes. Some markers have been scrutinized for their ability to predict ICP patients, however bile acid is commonly employed for diagnosis.[17] The study conducted by Chen et al. found that irisin levels in maternal serum and cord blood were high in patients diagnosed with ICP and that irisin levels correlated with disease severity.[18] In the study conducted by Agaoglu et al., maternal calprotectin levels were found to be higher in ICP patients than in control patients and it was shown that this marker could be a diagnostic marker for ICP patients.[19] In the study conducted by Kırbas et al., higher IL-17 levels were found in ICP patients compared to control patients.[20] Similarly, Biberoğlu et al. investigated a marker that may be effective in the diagnosis and pathology of ICP patients, and IL-6 was detected at higher levels in ICP patients than in the control group.[21]the most common liver disease in pregnancy, is characterized by elevated serum total bile acid and/or transaminase concentration, and pruritus. Interleukin-6 (IL-6 Desteli et al. demonstrated that pregnancy-associated plasma protein-A (PAPP-A), a component of the first trimester screening test, can serve as an indicator for intrahepatic cholestasis of pregnancy (ICP). They found that a reduction in PAPP-A levels is related with an elevated chance of developing ICP.[22] None of these markers, which have been shown to be involved in the pathogenesis of ICP and predict its diagnosis, can be measured in routine laboratory tests. This situation brings new investigations.

Recent studies have evaluated liver-based scores for diagnosing ICP. Tolunay et al. showed that the APRI score, calculated in the first trimester, predicted ICP in the third trimester.[23] The APRI score was developed by Wai et al. in 2003.[24]most models for predicting liver fibrosis are complicated and separate formulas are needed to predict significant fibrosis and cirrhosis. The aim of our study was to construct one simple model consisting of routine laboratory data to predict both significant fibrosis and cirrhosis among patients with CHC. Consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period were divided into 2 sequential cohorts: training set (n = 192 This score enables the assessment of liver fibrosis without invasive procedures.[24,25]most models for predicting liver fibrosis are complicated and separate formulas are needed to predict significant fibrosis and cirrhosis. The aim of our study was to construct one simple model consisting of routine laboratory data to predict both significant fibrosis and cirrhosis among patients with CHC. Consecutive treatment-naive CHC patients who underwent liver biopsy over a 25-month period were divided into 2 sequential cohorts: training set (n = 192 Obut et al. demonstrated the utility of APRI and ALBI scores in predicting ICP [26]. The ALBI score, developed by Johnson et al., was initially used to assess liver function in hepatocellular carcinoma patients.[9]the severity of which is currently assessed by the Child-Pugh (C-P Xu et al. later confirmed its relevance for non-malignant liver diseases.[27] The PALBI score was developed based on the consideration that the ALBI score is not an objective determinant of liver disease and by adding the platelet count to this score.[28]which are recently reported to be simple and objective measurements for liver reserve in HCC. Methods Between 2002 and 2014, consecutive 3182 HCC patients were enrolled to follow up their survival. The area under receiver-operator-characteristic curve (AUC A study conducted in patients with hepatocellular carcinoma

has shown that the PALBI score is a decisive factor for the occurrence of liver dysfunction after resection.[29] Albumin and fibrinogen are secreted in the liver. The FAR, the ratio of these two parameters, is considered an important parameter for predicting the prognosis of cancer patients.[30] In our study, PALBI score, ALBI score, APRI score and FAR values, which are indicators of liver damage, predicted ICP. The laboratory values used to calculate these scores and ratios can be easily checked in any hospital.

Glantz et al. found no increased fetal risk in ICP patients with bile acid levels <40 µmol/L but noted a 1-2% increase in fetal risk for each µmol/L of bile acid above this threshold.[31] Lee et al. reported an 18% incidence of meconium-stained amniotic fluid in severe ICP patients, with a 19.7% increased risk for each 10 µmol/L increase in bile acid levels.[32] A meta-analysis by Ovadia et al. showed that the risk of stillbirth was significantly increased in ICP patients with a serum bile acid level of >100 µmol/L[33]but the association with the concentration of specific biochemical markers is unclear. We aimed to quantify the adverse perinatal effects of intrahepatic cholestasis of pregnancy in women with increased serum bile acid concentrations and determine whether elevated bile acid concentrations were associated with the risk of stillbirth and preterm birth.\n\nMethods\nWe did a systematic review by searching PubMed, Web of Science, and Embase databases for studies published from database inception to June 1, 2018, reporting perinatal outcomes for women with intrahepatic cholestasis of pregnancy when serum bile acid concentrations were available. Inclusion criteria were studies defining intrahepatic cholestasis of pregnancy based upon pruritus and elevated serum bile acid concentrations, with or without raised liver aminotransferase concentrations. Eligible studies were case-control, cohort, and population-based studies, and randomised controlled trials, with at least 30 participants, and that reported bile acid concentrations and perinatal outcomes. Studies at potential higher risk of reporter bias were excluded, including case reports, studies not comprising cohorts, or successive cases seen in a unit; we also excluded studies with high risk of bias from groups selected (eg, a subgroup of babies with poor outcomes were explicitly excluded. In our study, we found no significant correlation between fasting bile acid levels and adverse neonatal outcomes, with a cut-off value of >67.1 µmol/L, sensitivity of 18%, and specificity of 97%. Similarly, liver damage markers did not correlate with adverse neonatal outcomes.

Our study had some limitations. Due to an inadequate number of ICP patients, it was not possible to categorize them based on severity. As a result, we were unable to describe the individual prediction abilities of these scores for mild and severe cases. Nevertheless, the study's main advantage is that ICP can be anticipated by utilizing scores obtained from standard maternal blood tests. These tests are available in any clinical setting. Moreover, this is the first study which evaluates the PALBI score and FAR values in ICP patients.

CONCLUSION

In conclusion, the PALBI score, ALBI score, APRI score, and FAR value can be used to diagnose ICP. In facilities where it is not possible to test fasting bile acid levels, these scores provide an alternative approach to evaluate individuals with intrahepatic cholestasis of pregnancy (ICP). Future studies with larger patient cohorts are necessary to enhance the reliability of these parameters.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Efficacy and Outcomes of Laser Treatment in Pilonidal Sinus Disease

Pilonidal Sinüs Hastalığında Lazer Tedavisinin Etkinliği ve Sonuçları

Merter GÜLEN [1], Ahmet Cihangir EMRAL[1]

ABSTRACT

AIM: In recent years, minimally invasive treatment methods have introduced significant innovations in the surgical management of pilonidal sinüs disease. This study aims to comprehensively evaluate the efficacy of laser treatment for pilonidal sinus disease, focusing on treatment success, recurrence rates, complications, and patients' return to normal life.

MATERIAL AND METHOD: In this study, data from patients treated with laser ablation for pilonidal sinus disease between August 2020 and August 2023 were retrospectively analyzed. Patients aged 18-40 who were treated with laser for pilonidal sinus disease were included in the study. Patients with recurrence, those who had undergone chemotherapy/radiotherapy in the anorectal or sacrococcygeal region, those with concurrent malignancies, those with a history of inflammatory bowel disease, those on chronic steroids, diabetics, and patients with autoimmune diseases were excluded from the study.

RESULTS: A total of 49 patients (5 females, 44 males) who underwent laser ablation for pilonidal sinus disease were included in the study. It was found that 16 (32.7%) of the included patients had a history of abscess drainage due to pilonidal sinus disease. In the postoperative period, the median (min-max) wound healing time was 28 (20-52) days. A total of 4 patients (8.3%) experienced recurrence.

CONCLUSION: Considering pilonidal sinus disease as a subcutaneous infectious condition, laser ablation should be regarded as one of the primary treatment options for pilonidal sinus surgery, given its acceptable recurrence rates, low complication risk, rapid return to normal activities, and cosmetic advantages.

Keywords: laser, pilonidal sinus disease, minimally invasive

ÖZET

AMAÇ: Son yıllarda, minimal invaziv tedavi yöntemleri pilonidal sinüs hastalığının cerrahi yönetiminde önemli yenilikler getirmiştir. Bu çalışmanın amacı, pilonidal sinüs hastalığında lazer tedavisinin etkinliğini, tedavi başarısı, nüks oranları, komplikasyonlar ve hastaların normal yaşantıya dönüş süresi açısından kapsamlı bir şekilde değerlendirmektir.

GEREÇ VE YÖNTEM: Bu çalışmada, Ağustos 2020 ile Ağustos 2023 arasında pilonidal sinüs hastalığı nedeniyle lazer ablasyon yöntemiyle tedavi edilen hastaların verileri retrospektif olarak incelendi. 18-40 yaş arası pilonidal sinüs hastalığı nedeniyle lazer ile tedavi edilen hastalar çalışmaya dahil edildi. Nüks yaşayan hastalar, anorektal veya sakrokoksigeal bölgede kemoterapi/radyoterapi uygulanan hastalar, eş zamanlı malignitesi olan hastalar, inflamatuar barsak hastalığı öyküsü bulunan hastalar, kronik steroid kullanan hastalar, diabeti olan hastalar ve otoimmün hastalığı bulunan hastalar çalışma dışı bırakıldı.

BULGULAR: Toplamda 49 hasta (5 kadın, 44 erkek) pilonidal sinüs hastalığı nedeniyle lazer ablasyon tedavisi uygulandı. Dahil edilen hastalardan 16'sında (%32.7) daha önce abse drenajı öyküsü olduğu belirlendi. Postoperatif dönemde, median (min-maks) yara iyileşme süresi 28 (20-52) gün olarak görüldü. Toplamda 4 hastada (%8.3) nüks gözlemlendi.

SONUÇ: Pilonidal sinüs hastalığını subkutanöz enfeksiyöz bir durum olarak değerlendirildiğinde, lazer ablasyon, kabul edilebilir nüks oranları, düşük komplikasyon riski, hızlı normal yaşantıya dönüş ve kozmetik avantajları nedeniyle pilonidal sinüs cerrahisi için ilk tercih edilecek tedavi yöntemlerinden biri olarak kabul edilebilir.

Anahtar kelimeler: Lazer, pilonidal sinüs hastalığı, minimal invaziv

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INTRODUCTION

Pilonidal Sinus Disease (PSD) is an infectious condition frequently observed in the sacrococcygeal region and is more common among young males. Although its etiology is not fully elucidated, PSD is generally considered to be an acquired disease. Risk factors include genetic, obesity, prolonged sitting, poor hygiene, and excessive body hair.[1,2]

Several methods for the treatment of PSD have been developed and applied. However, no gold standard treatment method has yet been established [3,4]. Conventional surgical techniques involve the complete removal of the infected skin and subcutaneous tissues, followed by secondary healing, primary repair, or flap techniques. Nonetheless, these methods often lead to problems such as large wounds, prolonged healing times, and poor cosmetic outcomes.[4,5]

In recent years, minimally invasive treatment methods have introduced significant innovations in the surgical management of PSD. These methods are generally considered less invasive and offer a more comfortable recovery process for patients. Postoperative pain is usually minimal, and the risk of complications is low. Additionally, patients can return to their normal activities more quickly. High success rates and low recurrence rates enhance the appeal of these treatment methods. Laser therapy, for example, represents one of these minimally invasive approaches and is considered an important alternative in the treatment of the pilonidal sinus disease.[6-8]

This study aims to comprehensively evaluate the efficacy of laser treatment for pilonidal sinus disease, focusing on treatment success, recurrence rates, complications, and patients' return to normal life.

MATERIAL AND METHOD

In this study, data from patients treated with laser ablation for pilonidal sinus disease between August 2020 and August 2023 were retrospectively analyzed. The data were obtained from prospectively standardized clinical notes. Demographic information of the patients was recorded. Data from preoperative and perioperative periods (operation day, postoperative day 1, 1st week, 1st month,3th month, and 1st year) were used based on examination notes. Complete healing was defined as the full closure of the sinus cavity epithelium. Patients who did not begin epithelialization within 1 month were considered persistent. Recurrence was defined as the appearance of an asymptomatic pit or the development of an abscess/infection in the natal cleft during the 1-year postoperative follow-up of patients who had completely healed after treatment. All patients were discharged at the 4th postoperative hour. Postoperative care included a 5-day course of antibiotic therapy (Amoxicillin-clavulanic acid 2x1000mg).

Patients aged 18-40 who were treated with laser for pilonidal sinus disease were included in the study. Patients with recurrence, those who had undergone chemotherapy/radiotherapy in the anorectal or sacrococcygeal region, those with concurrent malignancies, those with a history of inflammatory bowel disease, those on chronic steroids, diabetics, and patients with autoimmune diseases were excluded from the study.

Surgical Procedure

All patients were positioned prone and underwent the procedure under sedation combined with local anesthesia (bupivacaine). Intravenous prophylaxis with 1 gram of Cefazolin was administered. Hair and debris from the pit openings and sinus cavities were cleaned and curettaged. Subsequently, a NeoV V1470 Diode Laser (neoLaser Ltd, Caesarea, Israel) with a 2 mm probe was used to perform ablation along each sinus tract with 10 W power, 5-second pulse duration, and 5 pulses (total 250 J). After ablation, a 1-minute cold application with sterile ice was applied to the pit opening. No sutures were used

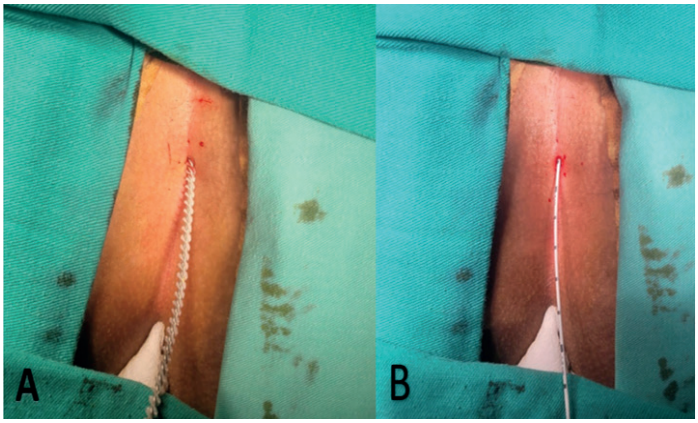

Figure 1. Curettage (A) and the application of laser ablation (B) in pilonidal sinus disease

illustrates curettage and the application of laser ablation in pilonidal sinus disease.

Statistical Analysis

Analyses were carried out with SPSS v26 (IBM-SPSS, Chicago, IL, USA). The distribution is checked by looking at Skewness and Kurtosis. Normally distributed data are presented as the mean ± standard deviation (SD). Non-normally distributed data are presented as the median (minimum-maximum). The categorical variables were expressed as number of patients and percentage of patients. A p value of less than 0.05 was considered to be statistically significant.

Ethics committee approval number '48' dated 22.12.2023 was received from Atılım University Medicana Hospital for this study.

RESULTS

A total of 49 patients (5 females, 44 males) who underwent laser ablation for pilonidal sinus disease were included in the study according to the criteria. The demographic data and preoperative characteristics of the patients are presented in

Table 1. Demographic and Preoperative Characteristics of the Patients

Characteristics	Value
Age, years (mean±SD)	26±3.7
Female/Male	5/44
Body Mass Index (BMI, kg/m^2, mean±SD)	27.5±1.9
Previous Abscess Drainage, n (%)	16 (32.7)
Number of Pits (mean±SD)	1.8±1.2

It was found that 16 (32.7%) of the included patients had a history of abscess drainage due to PSD. The average number of pits among patients based on preoperative evaluation was 1.8.

In the postoperative period, the median (min-max) wound healing time was 28 (20-52) days. Postoperative infections were identified in two male patients. In these patients, the infections were managed with daily local wound care using rifampicin 125 mg/2 ml for one week and no abscesses developed. One of these patients was a 33-year-old male with a Body Mass Index (BMI) of 29.9 and 5 midline pits. Persistent disease developed in this patient, and laser ablation was repeated after 1 month. Following the repeat laser ablation, the patient achieved complete healing in 22 days, and no recurrence was observed in postoperative follow-ups. The other patient with an infection was a 28-year-old male with a BMI of 29.8 and 4 midline pits. This patient achieved complete healing in 38 days without the need for additional procedures. Both patients with infections had a history of pilonidal abscess. Apart from these two patients with infections, no complications were observed in the remaining patients.

A total of 4 patients (8.3%) experienced recurrence. All patients with recurrence were male, and 3 of these patients had a history of pi-

lonidal abscess. None of the patients with recurrence experienced additional complications in the postoperative period. Postoperative outcomes of the patients are summarized in

Table 2. Postoperative outcomes of patients

Variable	Value
Wound Healing Time, median (range)	28 (20-52)
Complication, n (%)	2 (4.1)
Recurrence, n(%)	4 (8.3)
Persistent, n(%)	1 (2)
Postoperative Day 1 VAS (mean±SD)	1.3±1.4
Postoperative Day 7 VAS, median (range)	0 (0-4)
Return to Daily Activitiy (days), median (range)	2 (1-8)

DISCUSSION

Although conventional pilonidal sinus surgeries generally yield successful results, these methods often require extensive excision of all diseased skin and subcutaneous tissues, leading to large wound areas. This can result in delayed healing, increased risk of infection, and delays in return to normal activities. Emile et al.[9] reported complication rates of 26.9% for Karydakis flap (KF) and 19.3% for Limberg flap (LF) in a meta-analysis involving 1943 patients. In contrast, the study by Li et al.[5] found no complications following laser ablation. Şahin et al.[8] observed a wound infection rate of 8.3% after laser ablation. In this study, the complication rate following laser ablation was 4.1%, with only local infections that were controlled with wound care. Laser ablation appears to offer advantages over conventional surgical methods in terms of complications, as it is a minimally invasive procedure. Complications commonly encountered after flap techniques, such as wound infections, wound dehiscence, hematoma, seroma, and flap edema, are not expected following laser ablation.

The median wound healing time in this study was calculated to be 28 (20-52) days. Although this duration may seem prolonged, the absence of sutures in laser ablation means that patients do not require the movement restrictions recommended from the first postoperative days as seen in flap surgeries. Additionally, the low postoperative VAS scores positively influence the patients' early return to normal activities.

Recurrence rates following laser treatment have been reported as 2.1% by Li et al.[5], 15% by Taşkin et al.[10], and 14.9% by Dessily et al.[11] This study observed a recurrence rate of 8.3%, which aligns with the literature. Recurrence rates for conventional surgical techniques have been reported to be between 3.7-4.4%.[9] In cases where recurrence occurs after laser ablation, success rates for repeat laser ablation procedures have been found to be between 75-78.3%. [5,11,12] Thus, it is believed that repeat laser ablation can be beneficial if recurrence occurs. While recurrence rates may appear lower with conventional flap surgeries, literature indicates that minimally invasive surgical techniques are more successful in terms of postoperative complications, pain, and return to daily activities.[9,13,14]

A major limitation of this study is the limited number of patients and the lack of comparison with other surgical methods.

CONCLUSION

Considering pilonidal sinus disease as a subcutaneous infectious condition, laser ablation should be regarded as one of the primary treatment options for pilonidal sinus surgery, given its acceptable recurrence rates, low complication risk, rapid return to normal activities, and cosmetic advantages.

Author contributions

Conceptualization, M.G. and A.C.E.; methodology, M.G.; formal analysis, M.G.; investigation, A.C.E.; resources, A.C.E. and M.G.; data curation, M.G.; writing-Original draft preparation, M.G.; writing-Review and editing, M.G. and A.C.E. All authors have read and agreed to the published version of the manuscript. M.G. is the guarantor of the paper.

Informed consent was obtained from all individual participants included in the study.

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Assessment of Olfactory Functions in Patients with Acne vulgaris Under Systemic Treatment: A Prospective Study

Sistemik Tedavi Alan Akne Vulgaris Hastalarında Koku Fonksiyonlarının Değerlendirilmesi: Prospektif Bir Çalışma

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ABSTRACT

AIM: The loss of smell is a common disease and can affect a patient's quality of life. Olfactory disturbance leads to problems such as safety and eating. Acne vulgaris is a prevalent disease in the daily clinical practice of a dermatologist. Doxycycline and isotretinoin are the most preferred systemic drugs for severe acne. This study aimed to investigate the possible effects on olfactory function in patients with acne vulgaris receiving isotretinoin and doxycycline therapy by using the Brief Smell Identification Test.

MATERIAL AND METHOD: A total of 60 patients with acne vulgaris were included in the study. The patients were divided into two groups, each consisting of 30 patients. One group received oral doxycycline, while the other received oral isotretinoin. The olfactory function of each patient in both groups was assessed at the beginning and third month of treatment by using the Brief Smell Identification Test.

RESULTS: There was no statistically significant difference between the total scores of the Brief Smell Identification Test at 0. and 3. months in both the isotretinoin group and the doxycycline group.

CONCLUSION: The results of the present study showed that both drugs are safe and have no undesirable effect on olfactory function. However, the certain effects of both drugs on olfactory functions still remain unknown. New studies are needed to shed light on this issue.

Keywords: Acne, isotretinoin, doxycycline, olfactory function, smell

ÖZET

AMAÇ: Koku kaybı sık görülen bir hastalıktır ve hastanın yaşam kalitesini etkileyebilir. Koku alma bozukluğu hastaların günlük hayatında güvenlik ve yeme gibi sorunlara yol açar. Akne vulgaris, bir dermatoloğun günlük klinik pratiğinde sık görülen bir hastalıktır. Doksisiklin ve isotretinoin, şiddetli akne için en çok tercih edilen sistemik ilaçlardır. Bu çalışmada, 'Brief Smell İdentification Test' kullanılarak isotretinoin ve doksisiklin tedavisi alan akne vulgarisli hastalarda koku alma fonksiyonu üzerindeki olası etkiler araştırılmıştır.

GEREÇ VE YÖNTEM: Çalışmaya toplam 60 akne vulgaris hastası dahil edildi. Hastalar her biri 30 hastadan oluşan iki gruba ayrıldı. Bir grup oral doksisiklin alırken, diğer grup oral isotretinoin aldı. Her iki gruptaki her hastanın koku alma fonksiyonu, tedavi başlangıcında ve üçüncü ayda 'Brief Smell Identification Test' kullanılarak değerlendirildi.

BULGULAR: Hem isotretinoin grubunda hem de doksisiklin grubunda 0. ve 3. aylardaki 'Brief Smell Identification Test'toplam skorları arasında istatistiksel olarak anlamlı bir fark yoktu.

SONUÇ: Mevcut çalışmanın sonuçları her iki ilacın da güvenli olduğunu ve koku alma fonksiyonu üzerinde istenmeyen bir etkisinin olmadığını göstermiştir. Ancak her iki ilacın da koku alma fonksiyonları üzerindeki kesin etkileri hala bilinmemektedir. Bu konunun aydınlatılabilmesi için yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akne, izotretinoin, doksisiklin, koku fonksiyonu, koku

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INTRODUCTION

The loss of smell is a common disease which can significantly affect patients' quality of life. The disease has been underlined and accepted as a public health concern during the coronavirus disease 2019 (COVID-19) pandemic.[1]

There are many different causes of olfactory dysfunction, such as head traumas, upper respiratory tract infections and exposure to toxins. [2] Olfactory disturbance may lead to many problems in daily life, especially in the areas of safety and eating. An anosmic or hiposmic patient may not be able to detect the warning odours of spoiled food, smoke, or leaking gas. In addition to all these disadvantages, a loss of sense of smell can lead to a lack of food taste.[3,4]

Acne vulgaris is one of the most common dermatological diseases in daily clinical practice. It usually affects adolescents and young adults and sometimes may have the potential to cause scarring. Systemic treatment is necessary in patients with severe acne to prevent psychological and social impairment. There are several choices of systemic therapy for acne, including oral antibiotics (mainly doxycycline), isotretinoin and hormonal treatment. [5]

Oral antibiotics may be the treatment choice for acne in individuals resistant to topical treatments. Among other alternatives, oral tetracyclines are the most preferred ones all around the world. [6] Doxycycline is the only form which is on sale in our country. Thus, it is the most commonly prescribed oral antibiotic form. Isotretinoin is a synthetic analogue of vitamin A, which is indicated for recalcitrant acne. Both systemic medications may have some side effects, but most of them are mild and tolerable.

There are many studies in the literature investigating the side effects of systemic acne treatment. Only a few reported the possible effects of isotretinoin and doxycycline on olfactory functions. Some of these studies reported positive effects on olfactory function, on the other hand, some of them reported negative effects. [7-13] The certain effects on olfactory functions in the patients receiving systemic acne treatment remain unknown. This study aimed to investigate the possible impact on olfactory function in patients with acne vulgaris receiving isotretinoin and doxycycline therapy using the Brief Smell Identification Test.

MATERIAL AND METHOD

A total of 60 patients with acne vulgaris who were admitted to the Department of Dermatology of xxx Hospital between October 2022 and October 2023 and who received either isotretinoin or doxycycline were included in the study. The local ethics committee approved the study (E-22-896). All participants were informed about the study, and a written consent form was obtained. The study was performed by the latest version of the 'Helsinki Declaration' and 'Guidelines for Good Clinical Practice'.

The study consisted of two groups, each of which included 30 patients. One group received oral doxycycline, while the other received oral isotretinoin. All of the patients underwent a careful rhinological examination at the ENT and Head and Neck Surgery Clinic of xxx Hospital before including in the study. Patients with septal deviation, allergic rhinitis, nasal polyposis or rhinosinusitis, diabetes mellitus or neurological defects were not included. The ones who were smokers or were receiving drugs that could affect olfaction, such as calcium channel blockers, ACE inhibitors, diuretics, statins or antidepressants, were also not included. Additionally, the patients using vitamin A supplements or who had a recent history of any psychiatric disorder were also excluded. Those who were pregnant or under 18 years of age were not included in either group.

The demographic characteristics of each patient group, such as age and sex, were recorded. A daily dose of 0,5-1 mg/kg isotretinoin was initiated in the isotretinoin group. Doxycycline was initiated as 100 mg/day together with topical benzoyl peroxide in the doxycycline group. The total cumulative dose of isotretinoin was also calculated and recorded.

The olfactory function of each patient in both groups was assessed at the beginning and third month of treatment by using the Brief Smell Identification Test. The Brief Smell Identification Test (BSIT) is a brief, easily administered, and convenient instrument that was developed as a quick tool to measure odor identification deficits. It is a shortened version of Pennsylvania Smell Identification Test (UPSIT) with 40-items. [14] The Turkish version of the modified BSIT (Sensonics Inc.; Haddon Heights, NJ, USA) was used in this study. In previous studies, it was reported that the UPSIT included some smells which were not distinguished by the Turkish population, and therefore, they modified the UPSIT to contain odours recognized by the Turkish population. That's the reason why we used the Turkish version of BSIT. The BSIT comprises 12 items selected from the 40-item UPSIT (Sensonics Inc.; Haddon Heights, NJ, USA). The two tests are highly correlated. The BSIT is a 'scratch and sniff' test, including four options for each question. All of the patients were asked to release the smell and select the option that identified the odour. The patients were requested to answer all of the 12 questions, and if they were not sure, they were asked to choose the closest one. A mini period of 30 seconds was given to the patients between each odour. The test was administered by the same doctor in a well-ventilated room. The applying doctor did not use perfume or powdered gloves. The BSIT included 12 odors: mint, banana, clove, gas oil, strawberry, pine, cinnamon, smut, lemon, soap, baby powder and rose. In the end, a total score was calculated. The score reflected the number of correct answers. [15] The patients with a total score of 9-12 were classified as normal olfactory nerve function; while those with a score of fewer than 9 were classified as decreased olfactory nerve function. The test was applied at the beginning and third month of the treatment in both groups.

Statistical Analysis

All data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) version 21.0. The normality distribution of scale variables was checked using the Kolmogorov-Smirnov test. Data were expressed as median (interquartile range) or mean ± standard deviation for those with nonparametric or parametric distribution, respectively. Independent samples were compared with the Student's T test or Mann-Whitney U test, whichever is appropriate. Dependent samples were compared with the Wilcoxon signed rank test. Correlation analysis in nonparametric data was done with Spearman's rho test. Pearson's chi-square test was used for categorical variables, and Fisher's Exact test was used if at least one cell had an expected count of less than 5. Dependent categorical variables were compared with McNemar's test. Two-sided p-values less than 0.05 were considered statistically significant.

RESULTS

In this prospective comparative study consisting of 60 patients with acne vulgaris, there were 30 patients in the isotretinoin group and 30 patients in the doxycycline group. Isotretinoin group and doxycycline study group had similar sex, age, severity and duration of acne vulgaris (p=0.573, p=0.176, p=1, p=0,747, respectively)

Table 1: Demographic and clinical characteristics of isotretinoin and doxycycline groups

	Isotretinoin group (n=30)		Doxycycline group (n=30)	P
Sex (n /%)				
Female	22 (73.3%)		20 (66.7%)	
Male	8 (26.7%)		10 (33.3%)	0.573
Age (Mean±SD, years)	21.03±4.86		22.97±6.01	0.176
Severity of acne vulgaris (n /%)				
Moderate	20 (66.7%)		21 (70%)	1*
Severe	9 (30%)		9 (30%)	
Very Severe	1 (3.3%)		0 (0%)	
Duration of acne vulgaris (median/minimum, maximum, IQR, months)	21 (min:5, max:120, IQR:31.5)		24 (min:3, max:96, IQR:36)	0.747

SD: standard deviation, IQR: interquartile range

Data were expressed as mean±SD, median, minimum, maximum and IQR in continuous variables and n (%) in categoric variables.

Categorical data were compared using the Chi-Square test. Fisher's exact test was used to compare the severity of acne between groups. Severe and very severe subgroups were combined since they had expected counts less than 5.

Independent samples were compared with the Student's T and Mann–Whitney U tests.

Median total cumulative drug dose in the isotretinoin group was 2400 mg (min:600, max:3600, IQR:1200).

The mean BSIT score before treatment in the isotretinoin group was 9 (min:6, max:11, IQR:2) and 8.5 (min:5, max:12, IQR:3) in the doxycycline group. The mean scores in the third month of treatment were 9 (min:3, max:11, IQR:2) in the isotretinoin group and 9 (min:5, max:12, IQR:3) in the doxycycline group, respectively. There was no statistically significant difference in the total score of the brief smell identification test applied at the beginning of treatment (month 0) and in the 3rd month of treatment (month 3) between the isotretinoin group and doxycycline study group (p=0.247, p=0.845, respectively) (Table 2). There was no statistically significant difference between the total scores of the brief smell identification test at 0. and 3. months in both the isotretinoin group and the doxycycline group (p=0.240, p=0.578, respectively)

Table 2: Comparison of the total score of brief smell identification test at the beginning of treatment (month 0) and in the 3rd month of treatment in isotretinoin and doxycycline groups

	Isotretinoin group (n=30)	Doxycycline group (n=30)	P
Total score, month 0 (median/minimum, maximum, IQR)	9 (min:6, max:11, IQR:2)	8.5 (min:5, max:12, IQR:3)	p=0.247*
Total score, month 3 (median/minimum, maximum, IQR)	9 (min:3, max:11, IQR:2)	9 (min:5, max:12, IQR:3)	p=0.845*
	p=0.240**	p=0.845**	

Continuous variables expressed data as median (minimum, maximum, interquartile range).
Independent samples were compared with the Mann-Whitney U test; dependent samples were compared with the Wilcoxon Signed Rank test.
* Mann Whitney U test
** Wilcoxon Signed Rank test
IQR: Interquartile range

No statistically significant difference was found between males and females in terms of having decreased and normal olfactory nerve function according to BSIT at baseline and in the 3rd month of treatment in either the isotretinoin group, or in the doxycycline group (isotretinoin group month 0, month 3: p=0.643, p=0.417; doxycycline group month 0, month 3: p=0.245, p=0.602, respectively).

No statistically significant difference was found in the number of patients with decreased and normal olfactory nerve function according to BSIT applied at the beginning of treatment (month 0) and in the 3rd month of treatment between the isotretinoin group and doxycycline study group (p=0.063, p=0.598, respectively)

Table 3: Comparison of olfactory nerve function according to brief smell identification test at the beginning of treatment (month 0) and in the 3rd month of treatment in isotretinoin and doxycycline groups

	Isotretinoin group (n=30)		Doxycycline group (n=30)		P
	Month 0	Month 3	Month 0	Month 3	
Decreased olfactory nerve function n/%	8 (26.7%)	11 (36.7%)	15 (50%)	13 (43.3%)	Month 0: p=0.063*
Normal olfactory nerve function n/%	22 (73.3%)	19 (63.3%)	15 (50%)	17 (56.7%)	Month 3: p=0.598*
	Month 0 vs Month 3: p=0.549**		Month 0 vs Month 3: p=0.774**		

Data were expressed as n/% in categorical variables.
Categorical independent data were compared using the Chi-Square test. McNemar's test compared categorical independent data. If at least 1 cell had expected count of less than 5, binominal distribution was used.
*Chi-Square ** McNemar's test

There was also no statistically significant difference between the number of patients with decreased and normal olfactory nerve function according to BSIT applied at 0. and 3. months in both the isotretinoin group and the doxycycline group (p=0.549 p=0.774, respectively) (Table 3). There was no statistically significant correlation between the total cumulative dose of isotretinoin and the total score of BSIT in the isotretinoin group (r=-0.098, p=0.606)

DISCUSSION

Acne vulgaris, which is one of the most common diseases in dermatology, is associated with physical and psychological morbidity and results in a considerable expense annually for each country. Systemic antibiotics may be prescribed for moderate to severe acne or inflammatory acne, that is resistant to topical therapies. Oral isotretinoin is the best choice for a physician when the patient has severe nodular acne or moderate acne, when it causes scarring and when the patient is distressed. Serious side effects are uncommon with either systemic therapy. [16]

The fact that isotretinoin causes many multisystem side effects is already known. Mucocutaneous side effects, such as xerosis, skin fragility, erythemal changes, pruritus or rashes, are the most common and less severe adverse events. But the drug may also cause other side effects, including other systems (ophthalmic, nasopharyngeal, oral, mood and neurological, musculoskeletal, gastrointestinal, liver function test abnormalities, lipid panel abnormalities, blood count abnormalities, urine and kidney function test abnormalities). [17] Nasopharyngeal changes include dry nose, epistaxis, and dryness of other mucosal tissues. These changes are usually dose-related and moisturising the mucous membranes usually decreases their severity. [18]In the literature, only a few case reports and studies report its adverse effects on the sense of smell. [7,8, 19-23]

Heise et al. reported an interesting case with an olfactory and taste disturbance after acne treatment with isotretinoin. The patient was a 36-year-old man with severe acne and was advised to use isotretinoin at a daily dose of 0,5-0,75 mg/kg for 4 months. He reported an olfactory disturbance after 4 months and experienced a change in taste after 6 months. He also had 12 kg weight loss within 2 months. The patient did not have any history of viral infection, head trauma or other medications. Endoscopic examination of the nose and a CT scan showed no evidence of polyposis, chronic sinusitis or neoplasm. His status had been reported as not changed after stopping the treatment and beginning systemic steroids after 11 months . [8] Kartal et al. reported a study in which 45 patients with acne treated with isotretinoin underwent olfactory function tests (Sniffin' Sticks Test) at baseline and third month of treatment. They found a statistically significant difference in olfactory functions of the patients in favour of improving olfactory functions. The authors concluded that isotretinoin therapy improved the sense of smell. [7] Kuş et al. [19] investigated 102 acne patients using oral isotretinoin or topical treatments during the COVID-19 pandemic. They concluded that the use of oral isotretinoin did not cause an increase or decrease in the risk of COVID-19 transmission when compared with the topical treatment group. Still, the patients using oral isotretinoin had a lower incidence of taste/smell loss and headache. The authors cited studies that were carried out on mice and reported that retinoic acid treatment in mice increased the number of macrophages expressing retinoic acid receptors, leading to a faster recovery of olfactory function. [10,20] They suggested that the lower incidence of taste/smell loss in the oral isotretinoin group could be related to the faster recovery of olfactory function with isotretinoin. [19] Haglin et al. analysed male and fema-

le mice to investigate the cellular and molecular basis of metaplasia and declining neurogenesis in the ageing olfactory epithelium. Their study demonstrated that CYP26B1, a neural activity-regulated gene, is an essential spatial stem cell regulator in a neuroepithelium where changes in retinoic acid influence age-related tissue pathology. They suggested that retinoic acid serves to delay olfactory stem cell ageing. [21] Chung TW et al. reported a pilot study investigating the effect of short-course oral vitamin A (25000 IU/day for 14 days) and aerosolised diffuser olfactory training in the treatment of persistent olfactory dysfunction in long COVID. They concluded that a combination of these therapies would be effective on the symptoms of the patients suffering from olfactory dysfunction in long COVID. They suggested that their findings sustain the potential for vitamin A as a supportive therapy in promoting neuronal recovery. It was revealed that vitamin A could be applied to various olfactory neurosensory disorders, and also it could be a good topic in investigating regenerative medicine beyond the olfactory system. [22]

In this study, the mean scores of BSIT before and at the 3rd month of isotretinoin treatment were not statistically significantly different. Although the sense of smell of a few patients was examined to increase or decrease within 3 months, there seemed to be no significant effect on the sense of smell in total. This result may be due to the small number of patients. To determine the exact role of retinoids on olfactory dysfunction, prospective, controlled and long-term studies with a larger number of patients are needed.

Doxycycline was first approved by the FDA in 1967, and it is the first tetracycline derivative to come to market. It is more lipophilic when compared to tetracycline, making it more optimal for penetrating and accumulating in the sebaceous gland. The drug's side effects are more tolerable than tetracycline, but still, there are potential adverse effects that the clinician should be aware of. Phototoxicity, gastrointestinal disturbance, and tooth discoloration in individuals with developing teeth, are some common and well-known side effects. Fortunately, it is possible to avoid these side effects by paying attention to certain rules and taking precautions. Its success in treating acne is not only related to antimicrobial activity but also its anti-inflammatory activity as well. [23] There are no case reports or studies in the present literature investigating the potential effects of doxycycline on olfactory functions in acne patients. However, there are some studies revealing the potential positive effects on olfactory functions in those patients treated with doxycycline in indications other than acne . [11-13]

Çetin et al. reported that an add-on therapy with doxycycline in patients diagnosed with chronic rhinosinusitis with nasal polyp (CRSwNP), which has a high symptom burden, could be considered and found to be effective, especially CRSwNP comorbid with asthma. [11] In another study, Nabavi et al. also revealed that CRSwNP is a complex disorder, and effective treatment remains a major challenge. Antibiotics with anti-inflammatory properties, such as doxycycline, could have the potential to be an adjunct therapy in the management of chronic airway inflammation. They found that doxycycline improves the quality of life of patients with CRSwNP and also has beneficial effects on improving the sense of smell. [12] Jenkins et al. investigated the effects of oral administration of metronidazole and doxycycline on the olfactory capability of explosives detection dogs. While metronidazole administration resulted in the degradation of the detection threshold for 2-3 explosives, no significant effect was found in the degradation of detection thresholds with doxycycline administration. Finally, doxycycline was offered as a safe drug for use in explosives detection dogs . [13]

This study found no significant effect on olfactory functions in patients with acne vulgaris receiving doxycycline therapy. This result could be again due to the small number of patients. Since this is the first study investigating the drug's possible effects on acne patients, more studies are needed to come to an exact conclusion about the real impact on olfactory functions of acne patients.

As revealed before, the study has some limitations. Firstly, a larger number of patients are needed. Also, a longer follow-up duration, including a period after stopping the treatments, could be added. Another limitation is that the study does not include a healthy control group.

CONCLUSIONS

This study investigated the possible effects of systemic acne treatment with isotretinoin and doxycycline on olfactory functions. It can be concluded that both drugs are safe and have no undesirable effect on olfactory function. However, the exact effects of both drugs-either positive or negative-on olfactory functions still remain unknown. We hope this study will call attention to this interesting topic and find more satisfactory answers in future studies.

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Shadows of Birth Order: Affective Temperament, Perceived Parental Attitudes, and Substance Use Disorders

Doğum Sırasının Gölgesinde: Afektif Mizaç, Algılanan Ebeveyn Tutumları ve Madde Kullanım Bozuklukları

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ABSTRACT

AIM: In personality development temperamental traits, along with parental attitudes and birth order play a crucial role. These factors—temperamental traits, birth order, perceived parental attitudes—can influence substance use and its continuation. This study aims to explore the relationship between Adler's birth order theory, temperamental traits and perceived parental attitudes in the context of substance use disorders (SUDs).

MATERIAL AND METHOD: The study included 37 SUD patients from Ankara Training and Research Hospital's Alcohol and Substance Treatment and Training Centre (AMATEM) and 37 siblings without substance use. Participants temperamental traits and parental attitudes were assessed using the Temperament Evaluation of Memphis, Pisa, Paris, San Diego Autoquestionnaire (TEMPS-A) and the Short Form of the Perceived Parental Attitudes Scale-Child Form (s-EMBU). Independent samples t-test, one-way analysis of variance, Spearman correlation coefficient, and binary logistic regression analysis were used in data analysis.

RESULTS: Individuals with SUD had significantly higher depressive, cyclothymic, irritable, and anxious temperaments than their siblings ($p < 0.05$), and these traits were linked to perceived rejecting parental attitudes. Birth order analysis showed higher cyclothymic temperament in the first and last children. However, contrary to our hypotheses, no relationship was observed between birth order and perceived parental attitudes in any groups. According to regression analysis, individuals who were last-born had a 5.34 times higher likelihood of developing SUD compared to others.

CONCLUSION: Assessing challenges based on birth order can aid in providing effective addiction treatment services. Our study found a link between perceived parental attitudes and temperamental traits, but not with birth order. This suggests temperamental traits may moderate the effect of birth order on perceived parental attitudes. Given the strong link between affective temperamental traits and rejecting parental attitudes, we recommend implementing behavioral parent training programs to reduce parental anger and hostility.

Keywords: Affective temperament, birth order, perceived parental attitudes, substance use disorder

ÖZET

AMAÇ: Kişilik gelişiminde, bireylerin mizaç özelliklerinin yanı sıra anne baba tutumları ve doğum sıraları önemli bir rol oynamaktadır. Mizaç özellikleri, doğum sıraları ve algıladıkları anne-baba tutumları, bireylerin madde kullanımlarını ve bu davranışı sürdürmelerini etkileyebilir. Bu çalışmada, Adler'in doğum sırası teorisinin, bireylerin mizaç özellikleri ve algılanan anne baba tutumları ekseninde madde kullanım bozukluklarıyla (MKB) ilişkisinin araştırılması planlanmıştır.

GEREÇ VE YÖNTEM: Çalışmaya, Ankara Eğitim ve Araştırma Hastanesi Alkol ve Madde Bağımlılığı Tedavi Merkezi' ne (AMATEM) başvuran 37 MKB tanılı hasta ve 37 madde kullanımı olmayan kardeşi dahil edilmiştir. Katılımcıların mizaç özellikleri ve ebeveyn tutumları Temperament Evaluation of Memphis, Pisa, Paris, San Diego Autoquestionaire (TEMPS-A Mizaç Ölçeği) ve Kısaltılmış Algılanan Ebeveyn Tutumları Ölçeği-Çocuk Formu (KAET-Ç) kullanılarak değerlendirilmiştir. Veri analizinde, bağımsız örneklemler t-testi, tek yönlü varyans analizi, Spearman korelasyon katsayısı ve ikili lojistik regresyon analizi uygulanmıştır.

BULGULAR: MKB tanılı bireylerin depresif, siklotimik, irritabl ve anksiyöz mizaç düzeylerinin kardeşlerine göre anlamlı derecede yüksek ($p < 0.05$) olduğu ve algılanan reddedici ebeveyn tutumlarıyla da ilişkili olduğu bulunmuştur. Doğum sırasına göre yapılan analizlerde, tüm gruplarda siklotimik mizaç düzeylerinin ilk ve son çocuklarda daha yüksek olduğu; öte yandan, hipotezlerimizin aksine, hiçbir grupta doğum sırasıyla algılanan anne baba tutumları arasında bir ilişki olmadığı gözlemlenmiştir. Regresyon analizi sonuçlarında, en son doğan bireylerin diğerlerine göre MKB geliştirme olasılığının 5,34 kat daha fazla olduğu bulunmuştur.

SONUÇ: Bireylerin aile içindeki doğum sırası perspektifinden yaşadıkları zorlukların değerlendirilmesi, bağımlılık tedavisinde etkili hizmetlerin sunulmasına yardımcı olabilir. Çalışmamızda algılanan ebeveyn tutumları ile mizaç özellikleri arasında bir ilişki varken, doğum sıralarıyla böyle bir ilişkinin olmayışı, mizaç özelliklerinin doğum sırasının algılanan anne-baba tutumlarına etkisini modere edebileceğini düşündürtmektedir. Bağımlı bireylerin MKB olmayan kardeşlerine göre baskın affektif mizaç özelliklerinin, reddedici ebeveyn tutumlarıyla anlamlı ilişkili olduğu göz önünde bulundurulduğunda, ebeveyn öfke ve düşmanlığını azaltabilecek davranışsal ebeveyn eğitim programlarının yaygınlaştırılmasını öneriyoruz.

Anahtar Kelimeler: Afektif mizaç, algılanan ebeveyn tutumları, doğum sırası, madde kullanım bozuklukları

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INTRODUCTION

Substance use disorders are a chronic health problem in which multiple factors play a role in the etiology, which is increasing day by day all over the world and creates problems for the individual, his/her environment and the whole society.[1]

One of the important factors in the etiology of substance use disorders is communication and interaction within the family.[2] Decreased interaction and conflict within the family, as well as contradictory and inconsistent messages given by parents to their children, may cause individuals to turn to addictive substances.[2] The family, which is the first social interaction area in which the child lives, is one of the fundamental institutions of society.[3] The way parents approach their children is one of the most important factors shaping their personality and other individual characteristics.[3] In addition, the child-rearing methods that parents apply to their children according to the order in which they were born may differ from each other.[4,5] These differences also reveal the importance of birth order, which Adler emphasized.[6]

Adler studied the relationship between birth order and personality and drew attention to the effects of these relationships on the child's development.[7] Adler conceptualized the birth order theory by stating that each child born in the same family is born into a different psychological environment than the previous child.[5,8] Adler mentions different positions of siblings, including their actual birth order as well as the roles and personality traits they adopt when interacting with others (single, eldest, second, middle, youngest, etc.).[8]

According to Adler, firstborn children are the focus of family attention and feel special.[6] When the second child is born, the first child has to share the parents' love, care and attention with another individual. The last child in the family shares parental attention with all other siblings.[7] First children may feel that they lose their power when other siblings are born.[6] On the other hand, younger siblings see their older siblings as role models and struggle to be as successful as them.[9,10]

Studies have shown that alcohol and substance abuse as well as some psychiatric disorders are more prevalent especially in the last-born children raised in nuclear families compared to other birth orders.[11] Similarly, some studies have suggested that being the eldest child is a protective factor in terms of substance abuse and last-born children use alcohol more than first-born children.[12,13] Again, in some studies, it has been stated that individuals who have an older sibling are more likely to exhibit criminal behaviours or to use alcohol and substances compared to older children.[14]

The attitudes and behaviors of parents, who are the first people with whom the child communicates, have a significant impact on the formation of the child's personality.[15] When parents raise their first child, they are generally inexperienced in child rearing; however, their attitudes and expectations towards their children may change as a result of their experiences and they become more knowledgeable about how to raise a child from the second child onwards.[16] In studies, it was found that families attribute more responsibility to firstborn children and tend to control and discipline first-born children more.[16]

In addition to parental attitudes and birth order of individuals in personality development, temperament, which determines the attitude and approach of the individual in communication with the outside world and other people and is thought to be innate and stable throughout life, also plays an important role.[17] Besides the undeniable effect of environmental factors on the initiation and maintenance of substance use, hereditary factors such as temperament are also known to have significant effects on substance use disorder (SUD).[18] The relationships between depressive, irritable and anxious temperament characteristics, especially cyclothymic temperament, and SUD have been shown in many studies.[19-24] Individuals' temperament characteristics, birth order and parental attitudes may affect their substance use and maintenance of this behaviour through mutual interactions.

Our aim in conducting this study is to investigate the effects of Adler's birth order theory on substance use disorders (SUDs) in terms of individuals' temperament characteristics and perceived parental attitudes, and to contribute to the literature and to make suggestions especially in areas such as child development and child rearing in case of finding significant relationships that we anticipate to be possible.

MATERIAL AND METHOD

Power Analysis

Before starting the research, a priori power analysis was conducted to determine the necessary minimum sample size. The conditions for the power analysis were set as follows: confidence level of 95% ($\alpha = 0.05$), power level of 80% ($1-\beta = 0.20$), two-tailed hypothesis, and large effect size ($d = 0.80$ and below). It was determined that the minimum number of participants required for each group is 26.

Sample group

The study included 37 patients diagnosed with SUD and 37 siblings without substance abuse who were admitted to Ankara Training and Research Hospital's Alcohol and Substance Treatment and Training Centre (AMATEM). The inclusion criteria for the patient group were as follows: receiving inpatient treatment at AMATEM since the beginning of the study and being diagnosed with SUD according to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) diagnostic criteria, not having diagnoses of mental retardation, schizophrenia, bipolar disorder, dementia, depression with psychotic features, being between 18-65 years of age and accepting to participate in the study. The control group was formed by selecting a sibling of the individuals diagnosed with SUD who had no history of substance abuse and who agreed to participate in the study. The exclusion criteria for the control group were mental retardation, schizophrenia, bipolar disorder, dementia, and depression with psychotic features. The subject and purpose of the study were explained to the individuals diagnosed with SUD and their siblings and an informed consent form was obtained from the participants who agreed to participate in the study. The necessary approval for the study was obtained from the ethics committee of our hospital (date: 24/08/2022 no: E-22/1010).

Scales used

Sociodemographic data form: Sociodemographic parameters such as age, gender, marital status, number of siblings and number of children of their parents, educational status, occupation, employment status, and criteria such as how long they had been using substances (years), the age at which they first started using substances, whether they had committed a crime before, how long they had received addiction treatment, whether they had been hospitalized for addiction treatment before, history of multiple substance use, and whether their families were aware of their substance use of the participants diagnosed with SUD were evaluated.

Temperament Evaluation of Memphis, Pisa, Paris, San Diego Autoquestionaire (TEMPS-A Temperament Scale): This scale, developed by Akiskal in 2005 and consisting of 99 yes-no questions, assesses whether individuals have a dominant affective temperament.[25] A yes answer means 1 point and a no answer means 0 points. It has 5 sub-dimensions including dysthymic (18 items), cyclothymic (19 items), irritable (18 items), anxious (24 items) and hyperthymic (20 items) temperaments. Turkish validity and reliability study was conducted by Vahip et al.[26]

Abbreviated Perceived Parental Attitudes Scale-Child Form (PAASC-Ch): This scale assesses adults' attitudes towards their parents during childhood. Developed by Arrindell et al. (1999), the PAASC-Ch is essentially a shortened version of the Parenting Styles Scale with 23 items and 4-point Likert type (1=no, never, 4=yes, most of the time).[27] The same questions are scored separately for both mother and father. It has three sub-dimensions: rejection, overprotective attitudes and emotional warmth. The minimum score that can be obtained from the scale is 23 and the maximum score is 92. The psychometric properties of the PAASC-Ch in Turkish language were analysed by Dirik et al. (2004).[28]

Statistical Analysis

Data Analysis

In data analysis, descriptive statistical measures (frequency and percentage for categorical variables; mean and standard deviation for continuous variables) were used respectively. Skewness and kurtosis coefficients were used to examine the distribution of variables. Independent samples t-test and one-way analysis of variance (ANOVA) were used to determine the differences between the groups. Spearman correlation coefficient was used to examine the relationship between variables. Binary logistic regression analysis was used to determine the factors affecting substance use. SPSS (version 25) package program was used for data analysis. Alpha level of .05 was used for statistical significance.

Normality analysis and Descriptive Statistics

When the skewness and kurtosis values of the measurements obtained for both groups, it has been observed that most of the values are within the range of ±2.00. This result indicates that the majority of the measurements obtained from both groups have a normal distribution. In addition, since sample size in each group is 30 or more, the normality assumption is not a concern for difference analyses. In this context, parametric tests were used in the difference analyses since the distributions were normal and there was sufficient sample size. In correlation analyses, Spearman correlation coefficient, which does not have a normal distribution assumption, was used.

RESULTS

The study group of the research consisted of 74 people, 37 substance addicts and 37 siblings. Descriptive statistics regarding the socio-demographic information of both groups participating in the study are given in Table 1.

Table 1. Frequencies and percentages of socio-demographic information of the substance abuser and sibling group

		Dependent		Brother		χ^2 (*p*)
Variables	Variable levels	f	%	f	%	
Gender	Male	32	86.49	16	43.24	15.17 (p = .000)
	Woman	5	13.51	21	56.76	
Marital Status	Married	12	32.44	17	45.95	5.73 [1] (p = .060)
	Single	20	54.05	20	54.05	
	Divorced	5	13.51	--	--	
Number of siblings	2 siblings	8	21.62	8	21.62	0.00 (p = 1.000)
	3 siblings	17	45.95	17	45.95	
	4 siblings	6	16.22	6	16.22	
	5 siblings and above	6	16.21	6	16.21	
Sibling ranking	1.	9	24.32	13	35.14	12.63 [1] (p = .046)
	2.	7	18.92	14	37.84	
	3.	13	35.14	7	18.92	
	4th and onwards	8	21.62	3	8.10	
Adler sequence	First sibling	9	24.32	13	35.14	10.08 (p = .006)
	Last sibling	21	56.76	8	21.62	
	Other	7	18.92	16	43.24	
Mother Education level	Illiterate	5	13.51	5	13.51	0.53 [1] (p = 1.000)
	Literate	2	5.41	2	5.41	
	Primary School	19	51.35	19	51.35	
	Middle School	6	16.22	6	16.22	
	High School	4	10.81	4	10.81	
	University	1	2.70	1	2.70	
Father's education level	Literate	1	2.70	1	2.70	0.54 [1] (p = 1.000)
	Primary School	14	37.84	14	37.84	
	Middle School	10	27.03	10	27.03	
	High School	11	29.73	11	29.73	
	University	1	2.70	1	2.70	
Employment status	Not working	22	59.46	14	37.84	3.46 (p = .063)
	Working	15	40.54	23	62.16	
Education level	Primary education	20	54.05	13	35.14	9.82 [1] (p = .013)
	High School	16	43.25	13	35.14	
	License	1	2.70	8	21.62	
	Undergraduate	--	--	3	8.10	
The substance currently used	Heroin	19	51.35	--	--	--
	Methamphetamine	11	29.73	--	--	
	Pregabalin	7	18.92	--	--	
First substance used	Cannabis	29	78.38	--	--	--
	Volatile	4	10.81	--	--	
	Heroin	2	5.41	--	--	
	Cocaine	1	2.70	--	--	
	Pregabalin	1	2.70	--	--	
Crime story	Yes	14	37.84	--	--	17.27 (p = .000)
	No.	23	62.16	37	100.00	
Receiving treatment before	Yes	28	75.68	--	--	--
	No.	9	24.32	--	--	
MKB type	Monodrug	17	45.95	--	--	--
	Polydrug	20	54.05	--	--	
Total		37	100.00	37	100.00	
		Mean	SD	Mean	SD	
Age (years)		28.11	5.08	30.59	6.79	1.78 (p = .079)
Income level (TL)		10650	7378	12405	5786	1.14 (p = .259)
Age at first substance use (years)		16.59	3.44	--	--	--

[1] Fisher Exact test

After analyzing the socio-demographic information of the participants, the comparisons of the temperament and parental attitude levels of both groups are given in Table 2.

Table 2. Comparisons of the temperament and parental attitude levels of groups

Variables	Group	N	Average	SD	*p*	t
Depressive temperament	Dependent	37	7.30	3.35	**.003**	3.07
	Brother	37	5.03	3.00		
Cyclothymic temperament	Dependent	37	11.54	4.51	**.000**	4.20
	Brother	37	6.92	4.94		
Hyperthymic temperament	Dependent	37	11.65	4.58	.752	0.32
	Brother	37	11.32	4.20		
Irritable temperament	Dependent	37	7.92	5.09	**.000**	3.85
	Brother	37	3.81	4.03		
Anxiosis temperament	Dependent	37	9.65	6.31	**.004**	2.97
	Brother	37	5.54	5.56		
Father emotional warmth	Dependent	37	17.92	5.64	.166	1.40
	Brother	37	19.65	4.96		
Father overprotectiveness	Dependent	37	22.32	5.33	.054	1.96
	Brother	37	20.00	4.86		
Father rejectionism	Dependent	37	13.65	6.04	**.005**	2.89
	Brother	37	10.16	4.16		
Emotional warmth of the mother	Dependent	37	19.68	5.29	.117	1.57
	Brother	37	21.41	4.00		
Maternal overprotectiveness	Dependent	37	23.32	5.33	**.019**	2.40
	Brother	37	20.49	4.83		
Mother rejectionism	Dependent	37	12.95	5.74	**.001**	3.33
	Brother	37	9.46	2.77		

When Table 2 is examined, it demonstrates that depressive, cyclothymic, irritable and anxious temperament levels of substance abusers are higher than their siblings and this difference is statistically significant (p .05).

When the differentiation of perceived maternal and paternal attitudes according to the groups was examined, it was found that substance dependent individuals had higher perceptions of paternal and maternal rejectionism than their siblings and this difference was statistically significant. Furthermore, it was found that substance dependent individuals' perceptions of maternal overprotectiveness were higher than their siblings and this difference was statistically significant.

The relationships between the participants' birth order, temperament characteristics, and perceived parental attitudes are presented in Table 3.

Table 3. Associations between Birth Order, Temperament Traits, and Perceived Parenting Attitudes

Variables		Patient	Sibling	Whole group
Depressive temperament	r	-.31	-.08	-.19
	p	.059	.641	.106
Cyclothymic temperament	r	-.44	-.34	-.35
	p	**.007**	**.037**	**.002**
Hyperthymic temperament	r	.33	-.09	.07
	p	**.047**	.561	.552
Irritable temperament	r	-.28	-.16	-.20
	p	.098	.335	.088
Anxiosis temperament	r	-.39	.23	-.10
	p	**.016**	.171	.399
Father emotional warmth	r	.09	.09	.11
	p	.579	.614	.374
Father overprotectiveness	r	-.12	.07	-.02
	p	.465	.678	.837
Father rejectionism	r	-.12	.19	.01
	p	.480	.257	.910
Emotional warmth of the mother	r	.19	-.18	-.02
	p	.274	.278	.898
Maternal overprotectiveness	r	-.11	-.01	-.11
	p	.532	.961	.375
Mother rejectionism	r	-.24	.22	-.04
	p	.151	.183	.740

When Table 3 is examined, it has been found that there is a negative and medium level significant relationship between birth order and cyclothymic temperament, a positive and low level significant relationship with hyperthymic temperament and a negative and low level significant relationship with anxiotic temperament in the dependent group. In the sibling group, it was found that there was a negative and low level significant relationship between birth order and cyclothymic temperament. It was determined that the correlation values related to birth order and maternal and paternal attitudes were not statistically significant (p.05).

To determine the effects of birth order, temperament characteristics, and perceived parental attitudes on substance use, a binary logistic regression analysis was conducted, and the findings are presented in Table 4.

Table 4. Variables affecting substance use

						95% CI	
Variables	B	SH	Wald	p	Exp(B)	Lower	Upper
Fixed	-3.96	1.57	6.35	.012	0.02	--	--
Birth order	--	--	6.35	.042	--	--	--
Birth_order(1)	**1.67**	**0.71**	**5.52**	**.019**	**5.34**	**1.32**	**21.58**
Birth order(2)	0.41	0.77	0.28	.597	1.51	0.33	6.87
Depressive temperament	0.12	0.14	0.73	.392	1.12	0.86	1.47
Cyclothymic temperament	0.11	0.08	2.11	.147	1.12	0.96	1.31
Hyperthymic_temperament	0.08	0.08	1.18	.278	1.09	0.94	1.26
Irritable temperament	0.06	0.11	0.31	.576	1.06	0.86	1.31
Anxiosis temperament	0.02	0.08	0.05	.828	1.02	0.88	1.18

When Table 4 is analyzed, it is found that the variable that has a statistically significant effect on substance use is the birth order. It is determined that compared to the last child, there is a significance in birth order number 1. According to this, if an individual is the last child, then he/she is 5.34 times more prone to be a substance addict than other child ranks.

Relationships between perceived parental attitudes and temperament types in the patient group presented in Table 5.

Table 5. Relationships between mother and father attitudes and temperament types (patient group)

Variables		Depressive temperament	Cyclothymic temperament	Hyperthymic temperament	Irritable temperament	Anxiosis temperament
Father emotional warmth	r	-.36	-.13	.19	-.09	-.27
	p	**.029**	.431	.257	.592	.113
Father overprotectiveness	r	.39	.02	.26	.30	.28
	p	**.018**	.889	.126	.068	.088
Father rejectionism	r	.519	.253	.084	.330	.451
	p	**.001**	.131	.622	**.046**	**.005**
Emotional warmth of the mother	r	-.35	-.26	.01	-.21	-.28
	p	**.036**	.118	.953	.209	.093
Maternal overprotectiveness	r	.29	.03	.13	.21	.27
	p	.080	.857	.447	.206	.107
Mother rejectionism	r	.46	.40	.11	.41	.50
	p	**.004**	**.013**	.500	**.012**	**.002**

Table 5 shows the relationships between the temperament characteristics of the addicted group and parental attitudes. Accordingly, it was found that depressive temperament had a low level and statistically significant relationship with mother's and father's emotional warmth in a negative direction. In addition, depressive temperament was found to have a moderate and positively significant relationship with the father's rejectionism attitude and a low level positive significant relationship with overprotectiveness. Moreover, both irritable and anxiotic temperament were found to have a low and statistically significant positive relationship with father's rejectionism attitude. Unlike all other perceived parental attitudes, perceived rejecting mother attitude was found to have statistically significant relationships with all temperament levels (depressive, cyclothymic, irritable and anxiotic temperaments) except for hyperthymic temperament (p .05).

There was no statistically significant relationship observed between the temperament characteristics of the sibling group and parental attitudes.

DISCUSSION

In present study, we aimed to investigate the relationship between birth order and affective temperament characteristics and perceived parental attitudes in individuals with SUD and their non-substance using siblings. In this study, it was found that those who were the last child according to birth order were diagnosed with SUD at a rate 5 times higher than other birth orders. In addition to this, it was observed that the depressive, cyclothymic, irritable and anxious temperament levels of individuals diagnosed with SUD were significantly higher than their siblings without SUD. Finally, the perceived maternal and paternal rejection and maternal overprotectiveness levels of individuals with SUD were also found to be significantly higher compared to their siblings without SUD. In all groups, no relationship was observed between perceived parental attitudes and birth order.

In one of the studies conducted regardless of whether they were associated with psychiatric disorders (axis-1 diagnoses in DSM-4), patients with alcohol use disorder scored significantly higher on cyclothymic and depressive scales compared to the control group.[22] In another study, individuals with heroin use disorder showed significantly higher cyclothymic and irritability scores than controls.[21] In a study conducted by Iliceto et al., it was reported that patients with heroin use disorder had higher scores of anxious, depressive, cyclothymic and irritable temperament compared to age- and gender-matched randomly selected control group; on the other hand, there was no difference between the groups in hyperthymic temperament scores.[24] In a study comparing 31 patients with psychiatric disorders who had substance use comorbidity with psychiatric patients who did not have substance use comorbidity, it was shown that substance users had higher dysthymic, cyclothymic, anxious and irritable temperament scores and lower hyperthymic scale scores.[29] The fact that the depressive, cyclothymic, irritable and anxious temperament levels of individuals with SUD in our study were significantly higher than their siblings without SUD is compatible with the data in the literature.

In present study, the unique variable that had a statistically significant effect on substance use was the birth order. In our study, it was observed that those who were the last children in birth order were approximately 5 times more likely to have an SUD diagnosis than those in other birth orders. Most of the studies on birth order and substance use, have found that being the last child is associated with alcohol and substance use.[11,13,14] A study has shown that, in addition to some psychiatric disorders, alcohol and substance abuse are more common in the youngest children growing up in nuclear families compared to other birth orders.[11] Similarly, in the study conducted by Valkov, individuals with a history of SUD were evaluated according to birth order and it was found that the majority were last born children.[30] Another study conducted in Latin America yielded results supporting the importance of birth order in substance use disorder; being the first child was found to be a protective factor against substance use.[12] Analyzing data from the National Longitudinal Survey of Youth, Argys et al. found that last born individuals were significantly more likely to use substances and be sexually active than first-borns.[14] A study of 770,000 people in Sweden found that later-born siblings were more likely to be hospitalized for alcohol use than the first-borns, and that later birth order was associated with an increased risk of hospitalization.[31] The finding in our study that those who were the last child were more likely to be diagnosed with SUD compared to other birth orders is consistent with the data in the literature.

There may be several reasons for the increased risk of substance use in the last-born children. Last-born children can be outgoing and affectionate, but also rebellious, critical, short-tempered, spoiled and impatient.[6,32] According to Adler, while some of the latter may strive to be noticed and succeed, others may tend to avoid responsibilities because they have grown up pampered and cannot surpass the academic and social achievement levels of their siblings.[6] Some of the last children who have been spoiled and raised without limits by their parents may use substances to cope with difficult life situations outside the home environment when they grow up, since they have not gained independence.[6,30,33] In addition to their comfortable upbringing, last-born children may also be introduced to alcohol and drugs at a younger age through older siblings.[31] Finally, the fact that last-born children are slightly more likely to be raised by a single parent or by other people may be another risk factor for substance use.[34]

In present study, the perceived maternal and paternal rejection and maternal overprotectiveness levels of individuals diagnosed with SUD were found to be significantly higher compared to their siblings without SUD. It is noteworthy that perceived maternal rejection levels, one of these variables, were positively correlated with depressive, cyclothymic, irritable and anxious temperament levels, which were significantly higher in individuals with SUD compared to their siblings. In our study, a significant negative correlation was also found between perceptions of parental emotional warmth and patients' depressive temperament levels.

Studies have shown that parents' lack of emotional warmth is associated with children's various depressive temperament traits such as low self-esteem, depressive feelings and a negative worldview.[35-38] Studies have also found that perceived lack of parental warmth is associated with less prosocial behaviors and concurrent symptoms of depression in children with high irritability.[39,40] In our study, the high

level of depressive temperament in patients who perceived their parents as less emotionally warm is consistent with the results in the literature.

Studies have shown that there is a relationship between perceived rejecting parental attitudes and childhood depression as well as parental emotional warmth.[35,41] In a study examining the relationship between various sub-dimensions of parenting and childhood depression, it was found that rejecting parental attitudes towards the child was the most strongly sub-dimension associated with childhood depression.[35] It has also been shown that children with high irritability lead to rejectionist parental attitudes such as anger and hostility, and that such parental attitudes further increase children's anger and irritability in a vicious cycle.[42-44] Research has shown that for children with high irritability, maternal rejection is associated with greater externalizing behaviors (stealing, lying, antisocial behaviors, etc.).[45-48] In our study, the relationships between perceived rejecting parental attitudes and depressive and irritable temperament levels of individuals with SUD are consistent with this information in the literatüre. In children with high irritability, a negative parent-child relationship may cause anger or restlessness that prevents internalization of rules and manifests itself in negative behaviors such as substance use.

In the literatüre, there are several studies on the relationship between birth order and character and personality.[11,32,49-53] However, to the best of our knowledge, there is no study in the literature demonstrating the relationship between affective temperament traits and birth order. In our study, it was found that the cyclothymic temperament levels of the first and last children of the families were higher than the other birth order children. However, no relationship was found between birth order and perceived parental attitudes.

Parents may treat children in the same family in different ways depending on their age, gender, personal characteristics and life experiences.[54-56] Besides, environmental factors such as parental attitudes during the developmental process may affect individuals in different ways; some individuals may be highly permeable or sensitive to environmental conditions, while others may be largely unaffected by environmental conditions.[57]

The high cyclothymic temperament levels of children who are the first and last children of families in our study may be related to the nature of the sample, as well as the many-sided relationship between parental attitudes and emotional sensitivity and experience differences between siblings.[58,59] Because the presence of a sibling can change the course of both the older and younger sibling's temperament, children with siblings have different family experiences than single children and this can affect the stability of their temperament.

One reason for the lack of a relationship between birth order and perceived parental attitudes in our study may be that these individuals have different temperament characteristics according to their birth order. This may cause individuals with different birth order to perceive parental attitudes differently and thus make it difficult to establish a direct relationship. In our study, while there was a relationship between perceived parental attitudes and temperament traits, there was no such relationship with birth order, suggesting that temperament traits may moderate the effect of birth order on perceived parental attitudes.

It should be noted that possible confounding effects of anxiety disorders or personality disorders cannot be excluded in our study without a more thorough structured assessment. Secondly, it should be noted that the sample size and statistical power of this study were limited due to the difficulties we had in reaching the siblings of most individuals with SUD because of the problematic family relationships. Another limitation of our study is related to the cross-sectional study design of our study, which does not allow us to evaluate the temporal course of the relationship between substance use and affective temperaments. Eventually, when the number of participants was analyzed, the number of males in the group diagnosed with SUD was 2 times that of the control group and the number of females was one fourth of the control group. This difference in gender distribution may have affected the results of the study.

CONCLUSION

The correlation between being the youngest child and substance use disorder in our study does not mean that birth order causes substance use disorders. However, given that many studies in the literature have reached similar findings, it may be particularly important for families to be aware of the substance use risks of their youngest children. In this context, we recommend that parents and teachers closely monitor possible substance use-related behavioral problems and academic performance issues that may arise in these children.

Another noteworthy result in our study is that cyclothymic temperament levels are higher in addicts than in healthy controls and are associated with birth order. Considering the relationship between cyclothymia and addictive disorders, we would like to make a strong caution about the need to identify a psychopathological threshold regarding cyclothymic temperament levels, which has also been emphasized in previous studies.[23] So as to better understand the relationship between cyclothymic temperament and birth order, controlled studies examining the relationship between affective temperament and birth order should be performed and the findings obtained should be tested in different sample groups.

Many studies have shown that the perception of emotional warmth towards parents has no correlational effect on the prediction of various externalizing problems such as substance abuse, lying, stealing, etc., on the other hand, perceived rejecting maternal attitudes are associated with externalizing problems, especially for children with high irritability.[40,45-47] Considering the findings in this study that are similar to the results of the literature, the affective temperament characteristics of dependent individuals are mostly associated with rejecting parental attitudes (especially the mother). Therefore, we suggest that behavioral parent training programs that can reduce parental hostility/aggression should be continued and made widespread, especially in our country.[60-61]

The results of this study suggest that the relationships between birth order, perceived parenting attitudes and affective temperament and their possible effects on substance use may be multifaceted. In order to understand the relationships between parental attitudes and temperament towards substance use behavior, it may be appropriate to conceptualize these variables within a developmental framework that considers how they mutually affect each other over time, as well as the direct effects of parental attitudes or temperament in a given time period. In this context, in terms of substance use behavior, individuals may adapt to parental attitudes at a specific time point to certain extents depending on their temperamental characteristics, while the continuity of parental attitudes may negatively operate the effect of this adaptation. Moreover, different parental attitudes triggered by individuals' temperament traits over time may also shape individuals' temperament traits through mutual interactions.

Assessing the difficulties experienced by individuals and the privileges they have gained through the birth order window for their families may be useful in providing appropriate treatment services in the field of addiction.[12] Studies with larger samples investigating the associations of birth order, temperament characteristics and parental attitudes with each other and with substance use may provide a more comprehensive understanding of these associations.

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Conflict of Interest Statement

The authors declare no conflict of interest

Author Contributions

MD: Concept, drafting the article, writing, critical review

GZI: Data collection, literature research

KSK: Data analysis and interpretationHC: Data collection

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Maksillofasiyal travmaların epidemiyolojisi ve tedavi sonuçları: 9 yıllık retrospektif çalışma

Epidemiology and treatment results of maxillofacial trauma: A 9-year retrospective study

Etkin BOYNUYOĞUN[1], Cebrail AYGÜN[1], Uğur KOÇER[1]

ÖZET

AMAÇ: Maksillofasiyal travmaların epidemiyolojik özellikleri, oluş mekanizmaları, travmanın lokalizasyonu, tedavi yöntemi ve komplikasyonları ortaya konarak, bu yaralanmaların gerek önlenmesi gerek etkili tedavisi için klinik ve araştırma önceliklerinin belirlenmesine katkı sunulması, bu hastaların yönetimine yardımcı olması amaçlanmaktadır.

GEREÇ VE YÖNTEM: Kliniğimize Ocak 2015-Ocak 2024 tarihleri arasında maksillofasiyal travma nedeniyle başvuran hastalar retrospektif olarak dahil edildi. Hastaların yaşı, cinsiyeti, ek hastalıkları, travma etyolojisi, kırıkların lokalizasyonu, tedavi yöntemleri ve ameliyat sonrası komplikasyonları kaydedildi. Kırıkların tanısı anemnez ve fizik muayene sonrası, 3 boyutlu ince kesitli bilgisayarlı tomografi incelemeleri ile konuldu ve anatomik lokalizasyonuna göre sınıflandırıldı.

BULGULAR: Bu retrospektif çalışmada toplam 392 hastada meydana gelen 539 maksillofasiyal fraktür dahil edilmiştir. Bu hastaların 319'u erkek, 73'ü kadındır. Yaşları 1 ile 96 arasında sıralanmış olup, ortalama yaş 36,9 olarak bulunmuştur. Oluş mekanizmasına göre gruplandırıldığında, 169 hastada darp ile en sık sebep olarak görülürken, fraktür lokalizasyonuna göre sınıflandırıldığında, 106 hasta ile nazal kemik, maksillofasiyal bölgede en sık görülen kırık lokalizasyonu olarak bulunmuştur.

SONUÇ: Maksillofasiyal travmalar, farklı yaş ve cinsiyet dağılımlarında, çeşitli anatomik lokalizasyonlarda ve etiyolojik faktörlerle görülebilmektedir. 20-29 yaş aralığındaki erkekler en sık etkilenen grubu oluşturmakla birlikte, darp maksillofasiyal kırıklarının etiyolojisinde en sık neden olarak yer almaktadır. En sık kırık lokalizasyonu nazal kemik olmakla birlikte, konservatif izlem ve açık redüksiyon internal fiksasyon, tedavide en sık kullanılan yöntemler olarak saptanmıştır.

Anahtar Kelimeler: Epidemiyoloji, Etiyoloji, Fraktür, Fiksasyon, Travma

ABSTRACT

AIM: The aim of this study is to determine the epidemiological characteristics, injury mechanisms, localization of the injury, treatment method and complications of maxillofacial traumas, to contribute to the determination of clinical and research priorities for surgical intervention, and to help the management for individuals.

MATERIAL AND METHOD: Patients were admitted to our clinic due to maxillofacial trauma between January 2015 and January 2024 were included retrospectively. Patients' age, gender, comorbidities, trauma etiology, fracture localization, treatment methods and postoperative complications were recorded. Fractures were diagnosed after history and physical examination, with 3D thin section computed tomography examinations and classified according to anatomic localization.

RESULTS: This retrospective study included 539 maxillofacial fractures occurring in 392 patients. 319 of these patients were male and 73 were female. Their ages ranged from 1 to 96, with a mean age of 36.9. According to the mechanism of injury, the most common cause was assault in 169 patients, while classified according to fracture localization, the nasal bone was found the most common fracture localization in the maxillofacial region in 106 patients.

CONCLUSION: Maxillofacial traumas can be seen in different age and gender distributions, in various anatomical locations and etiological factors. Males between the ages of 20-29 are the most frequently affected group, and assault is the most common cause in the etiology of maxillofacial fractures. The most common fracture location is the nasal bone, and conservative follow-up and open reduction internal fixation are the most used methods in treatment.

Keywords: Epidemiology, etiology, fracture, fixation, trauma

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GİRİŞ

Travma, dünya genelinde mortalite ve morbiditenin en sık nedeni olmakla birlikte, maksillofasiyal yaralanmalar, travma merkezlerine yapılan başvuruların en sık nedenlerindendir. En sık nedenleri arasında trafik kazaları, darp, düşmeler, spor ve iş kazaları bulunmakta olup, trafik kazaları yüz kırıklarının en önde gelen nedeni olarak görülmektedir[1,2].

Maksillofasiyal yaralanmalar, bireyin genel fiziksel ve psikolojik sağlığı üzerindeki önemli olumsuz etkilerine ek olarak, aynı zamanda göz ardı edilemeyecek sosyoekonomik sonuçları nedeniyle önemli bir halk sağlığı sorunudur[3]. Ayrıca bu yaralanmalara, diğer anatomik bölgelerin de travmalarının eşlik edebilmesi, bu sorunu daha da karmaşık hale getirebilmektedir[2,4]. Fasiyal travmaların yönetiminde konservatif izlem yapılabilmekle birlikte, daha ağır travmalarda intermaksiller tespit ve plak-vidalarla açık redüksiyon internal fiksasyon gibi yöntemler, temel tedavi modaliteleri olarak gösterilmektedir. Bununla birlikte hastanın tedavi protokolü, kırığın tipi ve lokasyonunun yanı sıra cerrahın deneyimi ve tercihine göre değişebilmektedir[5].

Yüz kırıklarının epidemiyolojisi, çalışılan popülasyona bağlı olarak tip, şiddet ve etiyolojik açıdan farklılıklar gösterebilir. Maksillofasiyal kırıkların popülasyonlar arasındaki bu farklılıkları, ülkeler arasındaki risk faktörlerinin ve kültürel farklılıkların sonucu olarak görülmektedir[4]. Maksillofasiyal travmaların epidemiyolojik analizi, travma yükünü belirlemek, kaynak tahsisini planlamak ve önleyici tedbirlerin geliştirilmesine ve değerlendirilmesine olanak sağlamak adına önemlidir[6]. Bu nedenle, 9 yıllık bir süre boyunca kliniğimize başvuran maksillofasiyal travmaların epidemiyolojik özellikleri, oluş mekanizmaları, travmanın lokalizasyonu, tedavi yöntemi ve komplikasyonları ortaya konarak, bu yaralanmaların gerek önlenmesi gerek etkili tedavisi için klinik ve araştırma önceliklerinin belirlenmesine katkı sunulması, bireylere yönelik tedavinin kalitesinin değerlendirilmesi ve geliştirilmesine yardımcı olması amaçlanmaktadır.

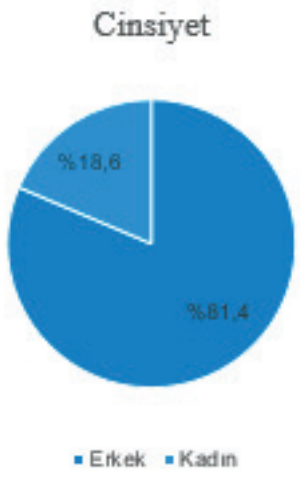
GEREÇ VE YÖNTEM

Bu çalışma, Ankara Eğitim ve Araştırma Hastanesi etik kurulu tarafınca onaylanmıştır (Karar no: E-24-39). Çalışmaya, Ankara Eğitim ve Araştırma Hastanesi Plastik, Rekonstrüktif ve Estetik Cerrahi Kliniği'ne Ocak 2015-Ocak 2024 tarihleri arasında maksillofasiyal travma nedeniyle başvuran hastalar retrospektif olarak dahil edildi. Hastaların yaşı, cinsiyeti, ek hastalıkları, travma etyolojisi, kırıkların lokalizasyonu, tedavi yöntemleri ve ameliyat sonrası komplikasyonları kaydedildi.

Kırıkların tanısı anemnez ve fizik muayene sonrası, 3 boyutlu ince kesitli bilgisayarlı tomografi incelemeleri ile konuldu ve anatomik lokalizasyonuna göre sınıflandırıldı: Mandibula (dento-alveoler, simfiz/parasimfiz, corpus, angulus, ramus, koronoid proses, kondil), Maksilla (damak-alveoler, Le Fort 1, Le Fort 2, Le Fort 3), Nazal, Orbital rim (supraorbital, infraorbital), Orbita (taban, medial, lateral, superior, posterior), Zigomatik (tripod kırığı, izole ark kırığı) ve Frontal sinüs[7]. Trafik kazaları, darp, düşme, iş kazaları ve spor yaralanması yaralanma nedenleri olarak kategorize edilmiştir. İstatistiksel analizler IBM SPSS versiyon 23 (IBM Corp, Armonk, NY) üzerinden yapılmış olup, kategorik değişkenlerin analizi için ki-kare testi kullanılmıştır. $p<0.05$ olması, istatistiksel olarak anlamlı kabul edilmiştir.

BULGULAR

Bu retrospektif çalışmada toplam 392 hastada meydana gelen 539 maksillofasiyal fraktür dahil edilmiştir. Bu hastaların 319'u erkek, 73'ü kadındır.



Grafik 1: Cinsiyet Dağılımı

Yaşları 1 ile 96 arasında sıralanmış olup, ortalama yaş 36,9 olarak bulunmuştur. En sık görülen yaş aralığı 93 hasta ile 20-29 yaş aralığı olup, bunu 72 hasta ile 30-39 yaş grubu takip etmektedir.

Tablo 1: Yaş grupları

Yaş Aralığı	**Hasta Sayısı** (n[%])
0-9	16 (4)
10-19	51 (13)
20-29	93 (24)
30-39	72 (18)
40-49	58 (15)
50-59	35 (8)
60-69	30 (8)
70-79	26 (7)
80-89	7 (2)
90-99	4 (1)
Toplam	392 (100)

Pediatrik yaş grubunda 61 hasta saptanmış olup 45 hasta erkek, 16 hasta kadındır.

Maksillofasiyal travmalar oluş mekanizmasına göre gruplandırıldığında, 169 hastada darp ile en sık sebep olarak görülürken, diğer nedenler Tablo 2'de özetlenmiştir.

Tablo 2: Maksillofasyal travma oluş mekanizması

Etyoloji	**Hasta Sayısı** (n[%])
Darp	169 (43)
Düşme	92 (23)
Trafik kazası	64 (16)
İş kazası	41 (11)
Spor yaralanması	26 (7)
Toplam	392

Pediatrik grupta ise 29 düşme, 21 darp, 9 trafik kazası ve 2 spor yaralanması bulunmuştur.

Fraktür lokalizasyonuna göre sınıflandırıldığında, 106 hasta ile nazal kemik, maksillofasiyal bölgede en sık görülen kırık lokalizasyonu olarak bulunmuştur. 91 hasta ile maksilla fraktürü ve 83 hasta ile blow-out fraktürü sırasıyla nazal kemiği takip etmektedir. Ayrıca, blow-out ve orbita duvar kırıkları, blow-out ve tripod kırıkları, maksilla ve nazal kemik kırıkları en sık bir arada görülen kırıklar olarak tespit edilmiştir. Pediatrik hastalarda 13 nazal fraktür, 11 mandibula, 10 maksilla, 10 frontal kemik, 9 blow-out fraktürü ve 7 hastada orbital fraktür görülmüştür. Fraktür lokalizasyonuna göre dağılımlar ve ayrıntılı analizi Tablo 3'te verilmiştir.

Tablo 3: Fraktürlerin anatomik lokalizasyonları

Fraktür Lokalizasyonu	Izole	Kompleks	Toplam
Nazal	86	20	106
Tripod	7	12	19
Zigomatik Ark	29	31	60
Orbita	6	53	59
- Medial	4	36	
- Lateral		20	
- Superior		6	
- Posterior	2	2	
Mandibula	54	7	61
- Ramus	11	1	12
- Simfizis	15		15
- Korpus	14		14
- Parasimfizis	10	2	12
- Subkondil	10	2	12
- Kondil	12	2	14
- Angulus	17		17
- Alveolar Proçes	1		1
Frontal	22	16	38
- On		32 (Nondeplase: 19, Deplase: 13)	
- On + Arka		6 (Nondeplase: 5, Deplase: 1)	
Maksilla	33	58	91
- Lefort-1		1	1
- Lefort-2	2		2
- Lefort-3	1		1
- Maksilla Duvar	30	57	87
Blow Out	27	56	83
Blow In	1		1
Supraorbital Rim	2	2	4
Infraorbital Rim		7	7
Temporomandibular Eklem Subluksasyon			5
Panfasiyal			5
Toplam			539

Düşme, darp, iş kazası, trafik kazası ve spor yaralanması olmak üzere beş ayrı etiyolojik sebebe göre; fraktür lokalizasyonu arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır ($p>0.05$).

Tedavi sonuçlarında, 335 hastada takiplerde herhangi bir problem meydana gelmemiştir. Tedavi sonrası meydana gelen komplikasyonlar incelendiğinde, 32 hastada nazal deformite, 13 hastada maloklüzyon, 8 hastada plak enfeksiyonu ve 4 hastada mal-union gözlenmiştir. Pediatrik grupta ise 56 hastada takiplerde komplikasyon gözlenmemiş olup, 3 hastada nazal deformite ve 2 hastada plak enfeksiyonu görülmüştür. Bu bağlamda, hasta yaşı ile komplikasyon gelişimi arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır ($p>0.05$).

Hastanın yaşı, travmanın oluşum mekanizması ve komorbidite durumlara ek olarak, kırık lokalizasyonu, deplasman derecesi gibi değişkenlere göre, farklı tedavi yöntemleri kullanılabilmektedir. En sık kullanılan yöntem, 105 hastada titanyum plak-vidalar ile açık redüksiyon ve internal fiksasyon olarak bulunmuştur. Ayrıca 92 hastada mesh ile onarım, 51 hastada minimal invaziv olarak ark elevasyonu, 37 hastada intermaksiller fiksasyon tedavide kullanılmıştır. İntermaksiller fiksasyon mandibula ve maksilla kırıklarında, mesh ile onarım blow-out kırıklarında ve ark elevasyonunun zigomatik ark kırıklarında kullanılmış olup, bu yöntemlerin bölgesel kırıklara spesifik olarak uygulandığı görülmüştür. Pediatrik grupta ise 24 hastanın travması konservatif takip edilmiş olup, 16 hastada açık redüksiyon internal fiksasyon, 11 hastada kapalı redüksiyon, 9 hastada mesh kullanılmıştır. Kullanılan tedavi modaliteleri Tablo 4'te ele alınmıştır.

Tablo 4: Tedavi yöntemleri

Tedavi Yöntemi	Uygulama Sayısı
Açık redüksiyon-internal fiksasyon	105
Intermaksiller fiksasyon	37
Mesh ile onarım	92
Minimal invaziv (Gillies) ark elevasyonu	51
Perkütan redüksiyon	2
Açık redüksiyon-internal fiksasyon ile sinüs obliterasyonu	2
Açık redüksiyon-internal fiksasyon ile duraplasti ve sinüs obliterasyonu	3
Kapalı redüksiyon	90
Konservatif	102
Ex	4

Maksillofasiyal travmaya sekonder, bazı ek komorbiditeler de yaralanmaya eşlik edebilmektedir. Örneğin, 29 hastada intrakraniyal yaralanma, 11 hastada ekstremitede fraktür ve 5 hastada vertebra fraktürü görülmüştür. 4 hastada ise takipleri sırasında ex olmuştur. Üç hasta yüksekten düşme, panfasiyal fraktür, 1 hasta ise trafik kazası sonrası zigoma ve maksilla kırıklarına ek olarak, çoklu vücut travması ve genel durum bozukluğu sonucunda ex olmuştur. Bu ek yaralanmalar Tablo 5'te ayrıntılı olarak incelenmiştir.

Tablo 5: Ek travmalar

Ek Travma	Hasta Sayısı
Intrakraniyal Yaralanmalar	29
Epidural Kanama	7
Subaraknoid Kanama	6
İntraparankimal Kanama	6
Pnömosefali	7
Subdural Hematom	3
Ekstremitede Fraktür	11
Vertebra Fraktürü	5
Intraabdominal Yaralanma	2
Intratorasik Organ Yaralanmaları	7
Kalvaryal Kemik Fraktürü	11
Kulak Zarı Perforasyonu	1
Toplam	66

TARTIŞMA

Travma, yaşamın ilk 40 yılında mortalitenin en sık nedenidir. Ayrıca travmatik yaralanmalar, daha çok üretken yaşlarda meydana gelmesi nedeniyle, ciddi iş gücü kaybına neden olmaktadır. Maksillofasiyal travmalar darp, trafik kazaları ve endüstriyel kazalardan kaynaklanan çoklu travmanın yaygın bir bileşeni olabilmekle birlikte, izole olarak da meydana gelebilmektedir. Maksillofasiyal kırıklar, kafatası kırıkları, intrakraniyal kanama ve servikal omurga yaralanmaları ve diğer ek travmalar açısından büyük risk taşır ve travma hastalarının hava yolu yönetimi, görüntüleme yöntemleri ve cerrahi onarım zamanlaması üzerinde önemli etkilere sahiptir[4 8]. Ayrıca bu hastalar uzun dönem takiplerinde, kemik deformiteleri, görme sorunları, koku almada değişiklik, çiğneme ve nefes almada zorluk gibi yaralanmaya bağlı geç dönem sorunlar yaşayabilmektedir. Tüm bunlar bir arada düşünüldüğünde, fiziksel, psikolojik ve sosyo-ekonomik olarak hasta üzerinde olumsuz etkileri bulunmaktadır[9]. Bu nedenle, travmaya uğrayan kişilerin işe dönmesine yardımcı olmak hem bireyin sağlığına fayda sağlamak hem de işsizliğin toplumsal maliyetlerini azaltmak için her hastanın tedavi planının bir parçası olmalıdır[10]. Maksillofasiyal travmaya ilişkin birçok epidemiyolojik çalışma, ulusal sağlık sistemlerinin travmayla ilişkili maliyetleri belirlemesine ve popülasyonların ihtiyaçlarına göre ayarlamak için kaynak tahsisini planlamasına yardımcı olmuştur. Dahası, bu çalışmalar önleyici programların ve yasal değişikliklerin geliştirilmesini de kolaylaştırmıştır[11 12]. Bu bağlamda, maksillofasiyal travmaların epidemiyolojik özellikleri, oluş mekanizmaları, travmanın lokalizasyonu, tedavi yöntemi ve komplikasyonları ortaya konarak, bu yaralanmaların önlenmesi için klinik ve araştırma önceliklerinin belirlenmesine katkı sunulması, bu hastaların yönetimine yardımcı olması amaçlanmaktadır.

Genel olarak bulgularımız, benzer sosyo-ekonomik bölgelerde yapılan çalışmaların bulguları ile paralellik göstermektedir. Çalışmamızda literatüre benzer olarak[13 14], erkek hakimiyeti ön planda olup, erkek: kadın oranı 4,4:1 olarak saptanmıştır. Roccia ve ark. yaptıkları literatür taramasında, ortalama başvuru yaşı 37.2, en sık yaş aralığı ise 20-29 yaş (%25,2) olarak bulunmuştur[15]. Mu ve ark. yaptıkları bir başka çalışmada ise ortalama yaş 33,4 olarak saptanmış olup, en sık yaş aralığı %28 ile 20-29 yaş aralığıdır[16]. Literatüre benzer olarak çalışmamızda ortalama yaş 36.9, en sık başvurunun olduğu yaş aralığı ise 20-29 olarak (%24) bulunmuştur.

Maksillofasiyal travmaların oluş mekanizmasına bakıldığında, özellikle Asya ve Afrika kıtalarında, trafik kazaları halen birinci sırada yer almaktadır[15]. Kırk epidemiyolojik çalışmanın incelendiği bir taramada, trafik kazalarının yüksek sayıda olmasının altında yatan nedenlerin arasında yol düzenlemelerinin ve bunların uygulanmasında eksiklik olması, zorunlu emniyet kemeri ve kask konusunda mevzuat eksiklikleri, riskli sürüş, kötü yol kalitesi, araçların daha az güvenli olması ve motorlu taşıt ve bisiklet kullanımının artması olduğu belirtilmiştir[17]. Örneğin McMullin ve ark. yaptıkları çalışmada 1993-2005 yılları arasında emniyet kemeri kullanımı ve hava yastığı gibi önlemlerle yıllar içerisinde anlamlı ölçüde trafik kazalarına bağlı maksillofasiyal travmaların azaldığı gösterilmiştir[18]. Yine 2000-2005 yılları arasındaki maksillofasiyal travmaların incelendiği ülkemizden bir çalışmada, trafik kazalarına bağlı yüz travmalarının oranı %67 iken[5], çalışmamızda %16,3 olarak bulunmuştur. Bununla birlikte, 2000-2007 döneminde trafik kazası nedeniyle yüz kırığı olan hastaların yüzdesinin, 1987-1999 dönemiyle karşılaştırıldığında, özellikle gelişmiş ülkelerde önemli ölçüde azaldığı gösterilmiştir[11]. 2015 yılında Avrupa Maksillofasyal Travma (EURMAT) çalışmasında da benzer bir şekilde darp ve düşme, trafik kazalarını geride bırakarak, maksillofasiyal travmaların en sık sebebi olarak bulunmuştur[1]. Literatüre paralel olarak, çalışmamızda %43,1 ile darp en sık ve %23,5 ile düşme en sık ikinci sebep olarak bulunmuştur. Trafik kazaları ise %16,3 ile 3. sırada yer almıştır. Zorunlu emniyet kemeri ve kask kullanımını, hız sınırının kamerayla izlenmesi, alkollüyken araç kullanmayı yasaklayan kurallara ek olarak aynı zamanda ehliyetlerde puan sisteminin getirilmesini, araç kullanırken cep telefonu kullanımının kısıtlanması gibi kuralların, bu düşüşte etkili olduğu düşünülmektedir[19 20]. Ayrıca, dünyada ve ülkemizde yaşlı nüfusun artmasıyla, düşme kaynaklı travmaların artışının devam etmesi muhtemeldir [11 21].

Çalışmamızda, maksillofasiyal kırıkların 267'sinin tek bir kemiğe izole kaldığı, 262 kırığın ise birden fazla kırıkla beraber meydana geldiği görülmüştür. Nazal fraktür, 106 ile en sık görülen fraktür olmuştur. Maksilla, 91 adet fraktür ile en sık ikinci, 83 adet ile de blow-out fraktürü üçüncü sırada yer almıştır. Mandibula fraktürü ise 61 hastada görülmüş olup, en sık anatomik lokalizasyonu 26 hastada görülen kondil kırığıdır. Roccia ve ark. yaptıkları çalışmada, maksillofasiyal kırıkların %50,3'ü yüzün orta üçte birinde, %46,2'si alt üçte birinde ve kalan %3,5'i ise üst üçte birinde saptanmış olup, en sık görülen kırıklar maksillo-zigomatik-orbital kompleks ve burun kemiği kırıkları iken, alt üçte birlik kısımda en sık görülen kırıklar kondiler ve parasimfiz kırıkları şeklinde raporlanmış[15]. Bir başka çalışmada, maksillo-zigomatik-orbital kırıklar en sık görülen, ardından mandibular kırıklar ve orbital kırıklar şeklinde sıralanmıştır[22]. Pediatrik kırıkların araştırıldığı bir çalışmada ise, en sık nazal fraktür, ikinci sırada mandibula ve üçüncü sırada orbita kırıkları görülmüştür[23]. Çalışmamızda ise, pediatrik yaş grubunda 13 hasta ile en sık nazal fraktür, 11 mandibula fraktürü, 10 maksilla fraktürü, 10 frontal kemik, 9 blow-out fraktürü ve 7 hastada orbital fraktür görülmüştür. 24 hastanın travması konservatif takip edilmiş olup, 16 hastada açık redüksiyon internal fiksasyon, 11 hastada kapalı redüksiyon, 9 hastada mesh kullanılmıştır. Mandibula kırıklarının kendi içerisinde analiz edildiği bir başka çalışmada ise, kırıkların %28,4'ü parasimfiz, %23,6'sı angulus ve %21,5 kondil-subkondil bölgesinde görüşmüştür[24]. Yaş gruplarına göre kırık lokalizasyonlarının sıklığı gösterebilmektedir. Çalışmamızda gerek pediatrik gerek erişkin hasta grubunda nazal fraktür en sık rastlanan kırık lokalizasyonu olmasına rağmen, pediatrik grupta mandibula, erişkin hastalarda ise maksilla fraktürü, nazal fraktürü takip etmektedir.

Maksillofasiyal travmaların cerrahi tedavisinin amacı, fonksiyon ve estetiğin tam olarak geri kazandırılmasıdır[3]. Bu amaç doğrultusunda birçok tedavi modalitesi uygulanabilmekle birlikte, kullanılacak olan yöntem, kırığın türüne ve yerine, hasta özelliklerine ve cerrahın deneyimine ve tercihine göre değişebilmektedir. Her hasta ve kırığın kendine özgü özellikleri olması nedeniyle, standart bir tedavi yönteminden bahsetmek mümkün değildir[5]. Konservatif izlem, açık redüksiyon internal fiksasyon, kapalı redüksiyon, intermaksiller fiksasyon, ark için elevasyon, mesh ile onarım, perkütan redüksiyon veya bu yöntemlerin kombine olarak uygulanması mümkün olabilmektedir[25]. Çalışmamızda, konservatif izlem ve açık redüksiyon internal fiksasyon, en sık kullanılan tedavi modaliteleri olarak görülmektedir.

Maksillofasiyal kırıkları olan hastalarda eş zamanlı vücutta ek travmatik yaralanma riski daha yüksektir. Travmatik maksillofasiyal yaralanmaların %12-45,5›inde eş zamanlı olarak ek intrakraniyal veya servikal-spinal kord yaralanmalarının görüldüğü bildirilmiştir. Travmatik intrakraniyal kanama, maksillofasiyal travması olan hastalarda mortalite ve morbiditenin en önemli nedenidir. Bu nedenle, intrakraniyal patolojilerin erken teşhisi önem arz etmektedir[26 27]. Çalışmamızda da 29 hastada intrakraniyal yaralanma tespit edilmiştir. Yine 5 hastada servikal vertebra yaralanması görülmüştür. İntrakraniyal yaralanmalara ek olarak, intratorasik, intraabdominal veya ekstremite yaralanmaları da maksillofasiyal kırıklara eşlik etmiştir. Bu yaralanmaların erken tanısı ve doğru yönetimi, hastaların mortalite ve morbidi-

tesi açısından önem arz etmektedir [23 27].
Çalışmamızın kısıtlılıkları arasında, verilerin retrospektif olarak alınması ve çalışmanın tek merkezli olarak yürütülmesi bulunmaktadır.

SONUÇ

Maksillofasiyal travmalar, farklı yaş ve cinsiyet dağılımlarında, çeşitli anatomik lokalizasyonlarda ve etiyolojik faktörlerle görülebilmektedir. 20-29 yaş aralığındaki erkekler en sık etkilenen grubu oluşturmakla birlikte, darp maksillofasiyal kırıklarının etiyolojisinde en sık neden olarak yer almaktadır. En sık kırık lokalizasyonu nazal kemik olmakla birlikte, konservatif izlem ve açık redüksiyon internal fiksasyon, tedavide en sık kullanılan yöntemler olarak saptanmıştır. Bu hasta grubunda, birden fazla kırık geçirme ve ek yaralanma geliştirme riski akılda tutulmalıdır. Her hastanın ve kırığın kendine özgü özellikleri olmakla birlikte, tedavi sürecinde hasta ve eşlik eden travmaları ayrı ayrı değerlendirilmelidir. Bu değerlendirme sonucunda, hastaya ve yaralanmasına uygun tedavi planı oluşturulmalıdır.

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Determining Predictive Factors for Refractory Disease in Oligoarticular Juvenile Idiopathic Arthritis

Oligoartiküler Juvenil İdiopatik Artritte Dirençli Hastalığı Öngörücü Faktörlerin Belirlenmesi

Emine Nur SUNAR YAYLA[1], Elif ARSLANOĞLU AYDIN[1]

ABSTRACT

AIM: This study aims to compare the clinical and demographic characteristics of patients diagnosed with oligoarticular juvenile idiopathic arthritis (JIA) treated with conventional disease-modifying antirheumatic drugs (cDMARDs) versus those requiring additional biologic DMARDs (bDMARDs). Additionally, it aims to identify the factors that necessitate the inclusion of bDMARDs in the treatment regimen and to determine predictors of long-term treatment resistance.

MATERIAL AND METHOD: Patients diagnosed with oligoarticular JIA were classified into two groups based on their response to cDMARDs: responders and resistant.

RESULTS: The study included 71 patients with oligoarticular JIA on cDMARDs. Knee joint complaints were most common (83.1%), followed by ankle joint (29.6%). All patients were started on non-steroidal anti-inflammatory drugs (NSAIDs) at diagnosis, and cDMARDs were initiated at a median of one month (IQR: 3 months). The most commonly initiated treatment in these patients was methotrexate (MTX) (97.2%). cDMARDs were effective in 21 patients (29.5%), while 50 patients (70.4%) were resistant to cDMARDs and required the initiation of bDMARDs. In comparing cDMARD-responsive and resistant groups starting bDMARDs, family history was more common in responders (23.8%, p=0.044), while ankle involvement was higher in resistant group (38%, p=0.016). Univariate analysis highlighted ankle/toe joint involvement as a risk factor for resistance (p=0.027, CI 95%), and family history as protective (p=0.043, CI 95%). When multivariate analysis was performed with the variables that were significant in univariate analysis, there was statistical significance only in the involvement of ankle/toe joints (ankle/toe joints OR=5.29 CI 95% (1.08-25.83), p=0.040, family history OR=0.24 CI 95% (0.05-1.19), p=0.080).

CONCLUSION: In patients with oligoarticular JIA, the involvement of ankle/toe joints at diagnosis increases the risk of resistance to cDMARDs therapy. Therefore, careful monitoring of these patients is warranted during follow-up.

Keywords: Disease-modifying antirheumatic drugs, oligoarticular juvenile idiopathic arthritis, predictive factors, refractory disease

ÖZET

AMAÇ: Bu çalışma, oligoartiküler jüvenil idiyopatik artrit (JİA) tanısı almış ve konvansiyonel hastalık modifiye edici antiromatizmal ilaç (kDMARDs) tedavisi alan hastalar ile biyolojik DMARDs (bDMARDs) tedavisine ihtiyaç duyan hastaların klinik ve demografik özelliklerini karşılaştırmayı amaçlamaktadır. Ayrıca, tedavi rejimine bDMARDs eklenmeyi gerektiren faktörleri ve uzun vadeli tedavi direncinin öngörücülerini belirlemeyi hedeflemektedir.

GEREÇ VE YÖNTEM: Oligoartiküler JİA tanısı almış hastalar, kDMARDs yanıtlarına göre iki gruba ayrıldı: yanıt verenler ve dirençli olanlar. İki grup arasında klinik ve demografik özellikler karşılaştırıldı.

BULGULAR: Çalışmaya, kDMARDs kullanan 71 oligoartiküler JİA hastası dahil edildi. Hastalar en sık diz eklemi (%83,1) ardından ayak bileği eklemi (%29,6) şikayetleri ile başvurdu. Tüm hastalara tanı anında nonsteroid antiinflamatuar ilaç (NSAİİ), ortanca birinci ayda (ÇAA: 3 ay) ise kDMARDs başlandı. Bu hastalarda en sık başlanan tedavi metotreksat (MTX)(%97,2) idi. kDMARDs 21 hastada (%29,5) etkili olurken, 50 hasta (%70,4)'nın kDMARDs tedavisine direnç gösterip bDMARDs'a ihtiyaç duyduğu saptandı. kDMARDs'a yanıt veren grup ile dirençli grup karşılaştırıldığında, aile öyküsü yanıt verenlerde daha yaygındı (%23,6, p=0,044), ayak bileği tutulumu ise dirençli grupta daha sıktı (%38, p=0,016). Tek değişkenli analizde, ayak bileği/ayak parmağı eklemi tutulumu kDMARDs tedavisine direnç açısından risk faktörü (p=0,027, %95 GA), aile öyküsü olması ise koruyucu faktör olarak (p=0,043, %95 GA) belirlenmiştir. Tek değişkenli analizde anlamlı olan değişkenlerle çok değişkenli analiz yapıldığında, sadece ayak bileği/ayak parmağı eklemi tutulumu istatistiksel olarak anlamlı bulunmuştur (ayak bileği/ayak parmağı eklemi OR=5,29 %95 GA (1,08-25,83), p=0,040, aile öyküsü OR=0,24 %95 GA (0,05-1,19), p=0,080).

SONUÇ: Oligoartiküler JİA'lı hastalarda, tanı anında ayak bileği/ayak parmağı eklemi tutulumu, kDMARDs tedavisine direnç riskini artırmaktadır. Bu nedenle, bu hastaların takiplerinde dikkatli izlem gerekmektedir.

Anahtar Kelimeler: Hastalık modifiye edici antiromatizmal ilaçlar, oligoartiküler jüvenil idiyopatik artrit, öngörücü faktörler, dirençli hastalık

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease of childhood. This term encompasses a heterogeneous group of arthritis types in terms of genetic factors, etiopathogenesis, age of onset, and outcomes.[1]Oligoarticular JIA is the most common subtype, affecting fewer than five joints and accounting for approximately 50% of JIA cases, and it is divided into two subgroups. Persistent oligoarticular JIA is defined as having no additional joint involvement after the first six months of disease, whereas extended oligoarticular JIA starts with four or fewer joints affected within the first six months but involves five or more joints over time.[2]

In the management of active oligoarthritis, initial treatment typically involves non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular corticosteroid injections (IACS). If these options prove insufficient, conventional disease-modifying antirheumatic drugs (cDMARDs) are introduced. However, if there's still inadequate response or intolerance to NSAIDs and/or IACS despite cDMARDs therapy, transitioning to biological DMARDs (bDMARDs) becomes necessary. It's noteworthy that certain cases of oligoarticular disease may progress to chronic destructive arthritis. Factors such as involved joints, presence of erosive disease or enthesitis, delayed diagnosis, elevated inflammatory markers, and symmetrical disease are critical indicators for prognosis and influence treatment strategies.[3]

Recent advancements in targeted therapies for JIA have led to improved disease outcomes both in the short and long term. Over the past decade, evidence has demonstrated that early and aggressive treatment of the disease with a targeted approach increases the likelihood of achieving and maintaining clinical remission.[1]Anticipating patients who will be transitioned to bDMARDs also enables more rigorous and precise monitoring of these patients. Therefore, there is a need for biomarkers that can predict resistance to cDMARDs in oligoarticular JIA. Until biomarkers for determining the risk of resistant disease become available, it is useful to identify markers that can be employed in clinical practice.

In this study, our objective is to compare the clinical and demographic characteristics of patients diagnosed with oligoarticular JIA treated with cDMARDs to those who received additional bDMARDs. Additionally, we aim to determine the factors that require the inclusion of bDMARDs in the treatment plan and to identify the predictors of long-term disease resistance.

MATERIAL AND METHOD

This retrospective study included 71 pediatric patients aged 0-18 years who were diagnosed with oligoarticular JIA according to ILAR (International League of Associations for Rheumatology) criteria [2] and followed up in the Pediatric Rheumatology Clinic of Ankara Etlik City Hospital between October 2022 and April 2024. Inclusion criteria included patients who received cDMARDs for at least three months and were followed up for one year. The study excluded other subtypes of JIA and patients with concurrent rheumatologic conditions (e.g., familial Mediterranean fever). The data were sourced from patient medical records. Parameters recorded included patient demographics (age, gender), clinical findings, symptom duration, oligoarticular JIA subtype (persistent or extended), complications, presence of concomitant uveitis, laboratory findings at diagnosis (complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), rheumatoid factor, HLA-B27), treatments (NSAIDs, IACS, cDMARDs and bDMARDs) and disease activity assessed using the Juvenile Arthritis Disease Activity Score 27 (JADAS 27) at diagnosis, 3 months, 6 months and 12 months.

The JADAS was calculated using the following components: 1. Physician's global assessment of disease activity (scored on a 10-cm VAS where 0 represents no activity and 10 represents maximum activity), 2. Parent's global assessment of well-being (scored on a 0-10 VAS), 3. Number of active joints (either 71, 27, or 10 joints), 4. ESR (mm/hour)-20/10 or CRP (mg/L)-10/10. Based on this parameter, JADAS is classified as follows: JADAS ≤1 indicates inactive disease, JADAS between 1.1 and 2 indicates low disease activity, JADAS between 2.1 and 4.2 indicates moderate disease activity, JADAS ≥4.2 indicates high disease activity[4].

Clinical remission was defined based on Wallace criteria, which evaluate remission under three conditions: clinically inactive disease, characterized by the absence of active arthritis, systemic symptoms, and uveitis, normal ESR and/or CRP levels, optimal physician's global assessment, and morning stiffness lasting less than 15 minutes; remission on medication, defined as the maintenance of clinically inactive disease for at least six months while continuing anti-rheumatic and/or anti-uveitis medication; and remission off medication, which requires sustained inactive disease for 12 months without any medications[5].

The initiation of bDMARDs treatment for patients diagnosed with oligoarticular JIA is defined as resistant disease when there is no achievement of an ACR30 response despite a minimum of three months of treatment with at least one cDMARDs. Treatment response is evaluated using the ACR Pediatric criteria, where ACR Pediatric 30 indicates at least 30% improvement in three or more core set criteria, with no more than one component worsening by more than 30%. Similarly, ACR Pediatric 50, 70, and 90 represent 50%, 70%, and 90% improvement in three or more core set criteria, respectively[6].

Permission for the current study was received from our hospital's ethics committee on June 05, 2024, with decision number 2024/379.

Statistical analysis

SPSS version 21 software (SPSS, Chicago, USA) was used to analyze the data. Categorical data were presented as numbers and percentages, and quantitative data were presented as median and interquartile range (IQR) (non-normally distributed). When comparing the groups with and without biologic therapy in patients with oligoarticular JIA, the Chi-Square test or Fisher's Exact test was used to compare categorical data. Mann-Whitney U test was used to compare quantitative data. Factors associated with the use of biological therapy in oligoarticular JIA patients were evaluated by binary logistic regression analysis, and multivariate analyses were performed with variables considered statistically significant in univariate analyses. Odds ratios (ORs) calculated as a result of these analyses were presented using 95% confidence intervals. $p<0.05$ was considered statistically significant.

RESULTS

The study included 71 patients with oligoarticular JIA receiving DMARDs. Forty-two (59.2%) of the patients were female. Median age at diagnosis was 56 (IQR:75) months and median age at symptom onset was 53 (IQR:73) months. Family history was present in 11.3% and 9.9% of the patients had concomitant uveitis. Joint swelling was the presenting complaint in 64 (90.1%) patients, while 61 (85.9%) patients had morning stiffness. The most common complaints were in the knee joint (83.1%), followed by the ankle joint (29.6%). Laboratory characteristics revealed ANA positivity in 26 (36.6%) patients. At the time of diagnosis, the median ESR was 21 mm/h (IQR: 34 mm/h) and the median CRP was 7.1 mg/L (IQR: 15.5 mg/L). When the disease activities of the patients at presentation were evaluated, the median value of the number of active joints was 2 (IQR:1). The median values of physician global assessment score and patient/parent VAS (visual analogue scale) at the time of diagnosis were 6 (IQR:1) and 6 (IQR:2), respectively, and the median value of JADAS 27 was 13.7 (IQR:5.7)

Table 1. Characteristics of oligoarticular JIA patients at the time of diagnosis

	N=71 Oligoarticular JIA
Gender, female†	42 (59.2)
Age at diagnosis, months‡	56 (75)
Age at symptom onset, months‡	53 (73)
Clinical characteristics	
Family history †	8 (11.3)
History of uveitis†	7 (9.9)
Extended oligoarticular JIA	2 (2.8)
Complaint/findings at diagnosis	
Arthritis †	64 (90.1)
Arthralgia †	7 (9.9)
Morning stiffness †	61 (85.9)
Affected joints at the time of diagnosis	
Knee†	59 (83.1)
Ankle†	21 (29.6)
Fingers†	6 (8.5)
Wrist†	4 (5.6)
Hip†	2 (2.8)
Toes†	1 (1.4)
Elbow†	1 (1.4)
Assessment of disease activity	
Number of active joints‡	2 (1)
Number of active enthesitis‡	0 (0)
Physician global assessment score‡	6 (1)
Patient/parent VAS‡	6 (2)
JADAS 27 (at diagnosis) ‡	13.7 (5.7)
Serological, genetic, and laboratory/radiological features	
ANA positivity†	26 (36.6)
HLA B27†	1 (1.4)
Hb, gr/dL‡	12.2 (2)
WBC, $10^3/\mu L$‡	8360 (3810)
ESR, mm/hour‡	21 (34)
CRP, mg/L‡	7.1 (15.5)

ANA antinuclear antibody, CRP C-reactive protein, ESR erythrocyte sedimentation rate, HLA B27 Human Leukocyte Antigen B27, JADAS 27 Juvenile Idiopathic Arthritis Disease Activity Score 27, JIA juvenile idiopathic arthritis, VAS visual analogue scale

†Data presented as numbers and percentages.
Values are presented as median and interquartile range.

At the time of diagnosis, all patients were started on NSAIDs, and cDMARDs were initiated at the median one month (IQR: 3). Of these patients, 69 (97.2%) were on methotrexate, 4 (5.6%) on leflunomide, and 1 (1.4%) on sulfasalazine. Glucocorticoids were used as bridge therapy in 36 patients (50.7%) and IACS in 41 patients (57.7%). cDMARDs were effective in 21 patients (29.5%), while 50 patients (70.4%) were resistant to cDMARDs and required the initiation of bDMARDs. The reasons for transitioning to bDMARDs treatment included an inadequate response to cDMARDs in 32 patients (64%), disease flare after remission in 13 patients (26%), and adverse effects from cDMARDs in 5 patients (10%). These adverse effects included gastrointestinal intolerance in 3 patients and elevated liver function tests in 2 patients.

Among patients receiving bDMARDs, 34 (68%) used etanercept, 20 (40%) used adalimumab, 2 (4%) used tocilizumab, 2 (4%) used infliximab, and 1 (2%) used tofacitinib

Table 2. Comparison of Response and Resistance to Conventional DMARD Therapy

	Responsive OligoJIA N=21	Resistant OligoJIA N=50	
Gender, female	11 (52.4)	31 (62)	0.452*
Age at onset of symptoms, months	55 [69.5]	52 [74.25]	0.480†
Age at diagnosis, months	56 [71]	57 [75.75]	0.724†
Duration of follow-up, months	39 [41.5]	57 [56.5]	0.108†
Family history	5 (23.8)	3 (6)	**0.044****
ANA positivity	5 (23.8)	21 (42)	0.146*
HLA B27 positivity	0	1 (2)	>0.999**
Disease activity markers (at presentation)			
Morning stiffness	19 (90.5)	42 (84)	0.712**
Uveitis	1 (4.8)	6 (12)	0.665**
Number of active joints	1 [1]	2 [1]	0.129†
JADAS 27	12.4 [6.2]	13.5 [5.45]	0.148†
CRP, mg/L	6 [16.2]	8.2 [15.9]	0.355†
ESH, mm/hour	16 [28]	22 [33]	0.098†
Affected joints			
Knee	20 (95.2)	39 (78)	0.094**
Ankle	2 (9.5)	19 (38)	**0.016***
Toe	0	1 (2)	>0.999**
Finger	1 (4.8)	5 (10)	0.662**
Wrist	0	4 (8)	0.312**
Hip	1 (4.8)	1 (2)	0.507**
Elbow	0	1 (2)	>0.999**
Treatments (cumulative)			
Glucocorticoid	12 (57.1)	24 (48)	0.482*
İntraarticular steroid	9 (42.9)	32 (64)	0.100*
Methotrexate	21 (100)	48 (96)	>0.999**
Leflunomide	1 (4.8)	3 (6)	>0.999**
Sulfasalazine	0	1 (2)	>0.999**
Etanercept	0	34 (68)	-
Adalimumab	0	20 (40)	-
Tocilizumab	0	2 (4)	-
İnfliximab	0	2 (4)	-
Tofacitinib	0	1 (2)	-

ANA antinuclear antibody, CRP C-reactive protein, DMARD disease-modifying anti-rheumatic drug, ESR erythrocyte sedimentation rate, HLA B27 Human Leukocyte Antigen 27, JADAS 27 Juvenile Idiopathic Arthritis Disease Activity Score 27, JIA juvenile idiopathic arthritis

*Chi-square test was employed.

**Fisher's exact test was utilized.

†Mann-Whitney U test was conducted.

When the groups that responded to cDMARDs therapy and those that were resistant to cDMARDs therapy and started bDMARDs therapy were compared, family history was more common in the DMARDs-responsive group (23.8%) (6%) (p=0.044), while ankle involvement was more common in the resistant group (38%) (9.5%) (p=0.016).

Univariate analysis was performed with clinical and laboratory findings that may be associated with resistant disease. Involvement of the ankle/toe joints at presentation increased the risk of resistant disease (p=0.027, CI 95%), while the presence of a family history decreased the risk of resistant disease (p=0.043, CI 95%)

Table 3. Univariate and multivariate analysis of factors associated with refractory disease

	Univariate Analysis (95% CI)	P value	Multivariate Analysis (95% CI)	P value
Gender, male	0.67 (0.24-1.89)	0.453	-	-
Age at diagnosis, months	0.99 (0.98-1.01)	0.704	-	-
Age at symptom onset, months	0.99 (0.98-1.01)	0.461	-	-
Family history	0.20 (0.44-0.95)	**0.043**	0.24 (0.05-1.19)	0.080
Knee	0.18 (0.02-1.47)	0.109	-	-
Ankle/toe involvement	5.82 (1.22-27.85)	**0.027**	5.29 (1.08-25.83)	**0.040**
Wrist/finger involvement	3.81 (0.45-31.57)	0.222	-	-
Uveitis	2.73 (0.31-24.17)	0.367	-	-
Number of active joints	2.04 (0.89-4.68)	0.091	-	-
Physician global assessment	1.00 (0.67-1.50)	0.979	-	-
Patient/parent VAS	1.11 (0.72-1.69)	0.639	-	-
JADAS 27 (at diagnosis)	1.09 (0.94-1.27)	0.246	-	-
ANA positivity	2.32 (0.73-7.32)	0.152	-	-
ESR, mm/hour	1.02 (0.99-1.04)	0.211	-	-
CRP, mg/L	0.99 (0.98-1.01)	0.677	-	-

ANA antinuclear antibody, CRP C-reactive protein, ESR erythrocyte sedimentation rate, JADAS 27 Juvenile Idiopathic Arthritis Disease Activity Score 27, VAS visual analogue scale

CI; confidence interval, OR: odds ratio

When multivariate analysis was performed with the variables that were significant in univariate analysis, there was statistical significance only in the involvement of ankle/toe joints (ankle/toe joints OR=5.29 CI 95% (1.08-25.83), p=0.040, family history OR=0.24 CI 95% (0.05-1.19), p=0.080).

DISCUSSION

This research is one of the notable studies in the literature that examines the factors predicting resistance to cDMARDs therapy in patients with oligoarticular JIA. Through multivariate analysis, we identified that the involvement of the ankle/toe joints is the only significant predictor of refractory disease.

Oligoarticular JIA is more prevalent in females at a ratio of 3:1, with the disease peaking between the ages of 1 and 3. In oligoarticular JIA, the affected joint typically exhibits swelling and sometimes increased warmth, but there is generally little pain or tenderness. The lower limbs are predominantly affected in this type.[7, 8] In a study conducted with 64 patients diagnosed with oligoarticular JIA, it was reported that the most commonly affected joints were one or both knees (89%), with the ankles affected in 36% of cases.[9] In our research, the majority of the patients were female. The most common presentation involved morning stiffness following joint swelling, with the knee being the most frequently affected joint, followed by the ankle.

The therapeutic approach in patients with oligoarticular JIA typically follows a stepwise progression. Initial treatment with NSAIDs and/or IACS is administered, and for those who do not achieve an adequate response, cDMARDs are initiated. Among cDMARDs therapy options, MTX is known to be superior to leflunomide, sulfasalazine and hydroxychloroquine.[3] In prior studies, the initiation rates of cDMARDs in patients with oligoarticular JIA were reported to range from 64.7% to 75%. MTX was identified as the most frequently initiated cDMARDs, with initiation rates between 89% and 94%, followed by sulfasalazine and leflunomide.[10-12] In our research, while the initiation of MTX as the most frequently prescribed cDMARDs aligns with previous findings, we observed a notably higher overall rate of cDMARDs initiation compared to earlier studies.

In the treatment of oligoarticular JIA, when patients exhibit either a lack of response or intolerance to cDMARDs, the recommendation is to transition to bDMARDs.[3] An investigation determined that 45% of oligoarticular JIA patients received biologic DMARDs, with 96% of these patients commencing treatment with tumor necrosis factor inhibitors (TNFi). Etanercept was the most commonly used TNFi, followed by adalimumab and infliximab.[11] Another study indicated that bDMARDs therapy was initiated in 34.2% of 187 oligoarticular JIA patients, with etanercept being the most frequently prescribed biologic agent.[12] In addition, a different research found that bDMARDs therapy was started in 10% of 574 oligoarticular JIA patients, with etanercept again being the most commonly used agent.[13] The use of biologic agents (70.4%) is significantly higher in our study compared to previous studies. This may be due to differences in clinical approaches and the increasing adoption of biologic therapies in recent years. Consistent with previous studies, etanercept was the most frequently initiated bDMARDs in our research, followed by adalimumab and infliximab. Etanercept, approved in 2001 as the first biologic therapy for JIA.[14] Probably for this reason, it remains the most frequently used agent by clinicians, as observed in our clinic.

Uveitis, one of the most serious complications of oligoarticular JIA, develops in 20-25% of patients.[15, 16] Additionally, approximately 50% of JIA patients present with the oligoarticular type, and among this group, 50% develop extended oligoarticular JIA over time.[17] It is well known that extended oligoarticular JIA has a poorer prognosis. In these patients, initiating DMARDs therapy in the early stages of the disease may be considered.[18] In our study, the observed rates of uveitis (9.9%) and the progression to extended oligoarticular JIA (2.8%) were significantly lower compared to the rates reported in the literature.[11, 12] We believe that the low frequency of complications and the reduced progression to extended oligo JIA, can be attributed to the initiation of cDMARDs and bDMARDs therapies in the majority of our patients.

In patients with oligoarticular JIA, ankle involvement, wrist involvement, symmetrical joint involvement, and elevated acute phase reactants at presentation are known poor prognostic factors.[19] In a cohort of 440 JIA patients, ankle involvement was observed in 57% during the first eight years of the disease. This manifestation was most prevalent in extended oligo JIA and RF-negative polyarticular JIA. Patients with ankle involvement within the first year exhibited lower remission rates and increased physical disability. Consequently, assessing ankle involvement is recommended for determining prognosis and tailoring treatment strategies.[20] According to Al-Matar et al., an evaluation of the initial six months' characteristics of 205 oligoarticular JIA patients revealed that ankle and/or wrist involvement predicted joint extension and erosion, indicating disease progression.[21] Further research involving 88 oligoarticular JIA patients examined predictors of inactive disease and relapse. Ankle involvement at disease onset was identified as a significant risk factor for relapse.[22] In our study, ankle/toe joints involvement was identified as a predictor for transitioning to biologic agents. In contrast to prior investigations [12, 19] wrist joint involvement, symmetric joint involvement, elevated acute phase reactants and high JADAS values at diagnosis were not identified as predictive factors for refractory disease.

Our study had some limitations, including its single-center and retrospective design. However, a notable strength of our study is its contribution to the existing literature on predicting the initiation of biologic agents in oligoarticular JIA, despite the extensive research on prognosis in this subgroup. Our findings provide valuable insights for the management of these patients.

CONCLUSION

In conclusion in patients diagnosed with oligoarticular JIA, the involvement of ankle/toe joints at the time of diagnosis increases the risk of resistance to cDMARDs therapy. Therefore, careful monitoring of these patients is warranted during follow-up.

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Tıpta Uluslararası Kaynaklara Kapsamlı Bakış: Bilimsel Dergi İndeksleri, Veri Tabanları, Kataloglar, Bilgi Matrisleri, Açık Erişim Altyapıları, Kütüphaneler, Alan İndeksleri, Yayıncılık Etiği Platformları ve Yapay Zekâ ile İlgili Veri Kütüphaneleri (Sistematik İnceleme)

Comprehensive Overview of International Resources in Medicine: Scientific Journal Indexes, Databases, Catalogs, Information Matrices, Open Access Infrastructures, Libraries, Field Indexes, Publishing Ethics Platforms and Data Libraries Related to Artificial Intelligence (Systematic Review)

Ali DAL[1], Mehmet ÇITIRIK[2]

ÖZET

Bilim, yapılan araştırmaların birikimiyle ilerler. Yeni bir çalışma yapılırken, önceki çalışmalardan yola çıkarak yeniden aynı şeyi yapmamak ya da bu çalışmalardan faydalanmak için literatür taraması esastır. Bu taramalar sırasında bilimsel kaliteye sahip, uzmanlarca onaylanmış yayınlara başvurmak önemlidir. Bu kalite değerlendirmesini sistemli bir şekilde yapan oluşumlara "indeksler" denir. İndeksler yağmacı dergileri uzak tutarak, dergileri bir nevi eleyerek araştırmacıların işlerini kolaylaştırmaktadır. Araştırmacılar için indeksler, tanınırlık, atıf alma ve akademik kariyer ilerlemesi açısından hayati öneme sahiptir. Bununla birlikte, resmi olarak bir indeks olmamakla birlikte, araştırmacılar tarafından sıkça kullanılan veri tabanları, kataloglar, bilgi matrisleri, açık erişim alt yapıları ve kütüphaneler vardır. Her indeks ve arama motoru kendi özgün özellikleriyle öne çıkar. Yayıncılıkta en önemli konulardan bir tanesi de etik konusudur. Bu konuda rehberlik hizmetleri gören ve standardizasyon çalışması yürüten uluslararası yayıncılık etiği platformunda oluşumlar mevcuttur. Bu platformlar, şeffaflığı artırma, çıkar çatışmalarını yönetme ve bilimsel topluluğun güvenini sürdürme amacıyla kapsamlı rehberlik sunar. Bu makalede, indeks ve arama motorlarının kapsamı ve özellikleri detaylı bir şekilde ele alınmış, literatür ışığında öne çıkan özellikleri tartışılmıştır. Ayrıca yayıncılık etiği konusunda uluslararası oluşumlar ve özellikleri başlıklar halinde değerlendirilmiştir. Amacımız, dergi indekslerini, veri tabanlarını ve arama motorlarının özelliklerini tanıtarak hem literatür taraması esnasında hem de çalışmalarını dergilerde yayımlatmayı planlayan araştırmacılara, dergi seçimi esnasında dikkat etmeleri gereken hususlar hakkında bilgi vermek ve bilimsel dergi dizinlerinin karşılaştırmalı değerlendirilmesini ortaya koymaktır.

Anahtar Kelimeler: Arama motoru, Bilimsel Dergi, İndeks, Veri Tabanı, Yapay Zekâ, Yayıncılık Etiği.

ABSTRACT

Science progressed through the accumulation of research. When conducting a new study, it is essential to conduct a literature review to avoid redoing what has been done previously or to benefit from prior studies. During these reviews, it was crucial to refer to scientifically approved publications that were verified by experts. These systematic quality evaluations are referred to as "indices." For researchers, indices are vital in terms of recognition, citations, and academic career progression. However, databases, catalogs, knowledge matrices, open-access infrastructure, and libraries are frequently used by researchers that are not officially indexed. Each index and search engine had unique features. Ethics is one of the most critical issues in publishing research. International publishing ethics platforms provide guidance and standardization in this regard. This article extensively discusses the scope and features of indices and search engines and discusses their prominent features in light of the literature. International formations and their features regarding publishing ethics were evaluated under specific headings. We aimed to introduce the features of journal indexes, databases, and search engines to inform researchers who plan to publish their studies both during literature searches and in journals about the issues they should pay attention to during journal selection, and to present a comparative evaluation of scientific journal indexes.

Keywords: Artificial Intelligence, Databases, Index, Publication Ethics, Scientific Journal, Search Engine.

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Bilim, kendinden önceki bireylerin koyduğu tuğlanın üstüne bir tuğla koyarak inşa edilen bir yapıdır. Bilimsel yayınlar, araştırmacıların çalışmalarını paylaşmaları için bir platform sağlar ve diğer araştırmacıların aynı konu üzerine kendi çalışmalarını inşa etmelerine olanak tanır. Bu durum, uluslararası iş birliklerini teşvik eder. Bilimsel yayınlar, yayımlanmadan önce genellikle akran değerlendirmesi (peer-review) sürecinden geçer. Bu süreç, bir araştırmanın metodolojisinin, sonuçlarının ve tartışmalarının bilimsel standartlara uygun olup olmadığını değerlendirir. Bilimsel değer atfeden çalışmalar dergilerde yayınlanır. İşleyişin düzgün bir şekilde olduğu değerlendirilen dergiler ise indekslenir. Dizin (İndeks); araştırılan kavramlar, kelimeler ve temaların yayımlanan makaleler veya diğer akademik içeriklerde nerede bulunduğunu sistematik bir şekilde gösteren rehberlerdir. Bu tür bilgilerin düzenlenmesi ve kategorilendirilmesi, kullanıcıların ihtiyaç duyduğunda kolaylıkla başvurabilmeleri için gereklidir. Her bir araştırmacı makalenin güvenilirliğini detaylı şekilde bilemez. İndeksler yağmacı dergileri uzak tutarak ve yayınları belli kalitede olması adına dergileri bir nevi eleyerek araştırmacıların işlerini kolaylaştırmaktadır. Ulusal ve uluslararası ölçekte birçok farklı indeks platformu bulunmakta ve bu platformlar, belirledikleri özel kriterlere uygun dergi içeriklerini kullanıcıların erişimine sunmaktadırlar.[1] Prestijli bir bilimsel dergi indeksi, makalenin geniş bir akademik kitleye ulaşmasını kolaylaştırarak atıf potansiyelini artırır.[2] Yayımlanan bilimsel çalışmalar, araştırmacının akademik kariyerinde de önemli rol oynar. Akademik kariyerde özellikle belirli indekslerin kapsamında yer alan dergilerde yayın yapılması istenmektedir.[3]
İndeks olarak kabul edilmemekle birlikte, pek çok araştırmacı ve akademisyen tarafından günlük pratikte neredeyse "indeks" kadar değerli kabul edilen ve sıkça başvurulan diğer veri tabanları da mevcuttur. Pubmed ve Google Scholar bu tür veri tabanlarındandır. Ayrıca, bazı özel alanlara odaklanmış, belirli konularda derinlemesine bilgi sunan, ancak resmi olarak "indeks" olmayan diğer veri tabanları da bulunmaktadır. Bu tür veri tabanları, konuya özgü derinlemesine bilgilere erişim sağlamada oldukça faydalıdır.
Bilimsel kalitenin yanında bir diğer önemli husus da yayıncılık etiğidir. Yayıncılık etiği, bilimsel araştırma ve yayın süreçlerinin temelini oluşturan kritik bir konsepttir. Bu bağlamda, yayıncılık etiği platformları, araştırmacılara, editörlere ve yayıncılara, etik ilkelere uygunluğu sağlama ve etik dışı uygulamaları önleme konusunda rehberlik eder. Bu platformlar, şeffaflığı artırma, çıkar çatışmalarını yönetme ve bilimsel topluluğun güvenini sürdürme amacıyla kapsamlı rehberler ve eğitim materyalleri sunar.
Bu makale, uluslararası bilimsel dergi indekslerinin çalışma mekanizmalarını, bu indekslerin literatürde nasıl bir rol oynadığını, bilimsel araştırma ve yayın dünyasında neden bu kadar kritik bir öneme sahip olduklarını ve yayın etiği platformlarını incelemeyi amaçlamaktadır. Ayrıca indeks olmamakla birlikte indeks gibi değerlendirilen veri tabanları işleyişi ve özelliklerini detaylandırmak suretiyle indeksten farkları değerlendirilmiştir.

A) Bilimsel Dergi Kriterleri

Bilimsel dergi indeksleri, dergilerin kalitesini ve bilimsel katkılarını değerlendiren ve bu dergilere kolay erişim sağlamak amacıyla oluşturulmuş bilgi depolarıdır. Bir derginin indekslenip indekslenmeyeceğine karar verirken dikkate alınan genel kriterlerden bazıları şunlardır:
Yayın Standartları: Derginin yayın süreçleri, editoryal içerik ve yapısal kalite gibi temel standartlara uyup uymadığına bakılır.
İçerik: Derginin sunmuş olduğu bilimsel katkının orijinallik, bilimsel kalite ve kapsamı değerlendirilir.
Bilimsel Topluluk Tarafından Atıf: Derginin diğer bilimsel çalışmalarda ne kadar sık atıflandığı, atıf frekansı analiz edilir.
Editoryal Kurul: Derginin editoryal kurulunun bilimsel topluluk içindeki durumu, uzmanlık seviyesi ve itibarı incelenir.
Uluslararası Çeşitlilik: Derginin yazarları, editörleri ve danışma kurulu üyelerinin coğrafi çeşitliliği değerlendirilir.
Dergi Politikaları: Derginin etik kurallar, yazar hakları, açık erişim politikaları gibi konulardaki politikaları kontrol edilir.
Akran Değerlendirme- Peer-review: Hakem değerlendirme sürecinin kalitesi, hızı ve şeffaflığı göz önünde bulundurulur.
Yayın Tarihi ve Sürekliliği: Derginin düzenli olarak ve belirtilen zaman diliminde yayınlandığına bakılır.
Derginin Dışsal Durumu: Derginin diğer indekslerdeki durumu, prestij ve bilimsel topluluktaki itibarı gibi dış faktörler de dikkate alınabilir.
0Yayın Dili: Derginin yayın dili, genellikle İngilizce olması tercih edilen bir kriterdir, ancak diğer dillerdeki dergiler de kabul edilebilir.
Bu kriterler genel bir rehber olarak düşünülebilir, ancak her dergi için uygulanan özel kriterler veya değerlendirmeler değişiklik gösterebilir.
Dergi Etki Faktörü (Journal Impact Factor, IF): Bilimsel derginin kalitesini ve etkisini ölçmek için kullanılan bir metriktir. Etki faktörü, belirli bir yıl içinde yayımlanan makalelere son iki yıl içerisinde yapılan toplam atıfların sayısının, aynı derginin bu iki yıl içinde yayımladığı toplam makale sayısına bölünmesiyle hesaplanır. Etki faktörü, bir derginin bilimsel toplulukta ne kadar tanındığını ve referans alındığını gösteren bir gösterge olarak kabul edilir, ancak tek başına bir derginin kalitesini belirlemek için yeterli değildir. Etki faktörü (İmpact Factor), her yıl Thomson Reuters'in (şu anda Clarivate Analytics olarak bilinir) Journal Citation Reports (JCR) adlı yayınında yayınlanır.[4]

B) Önemli Uluslararası Bilimsel Dergi İndeksleri

1.Web of Science – WoS (Bilim Ağı): 1964 yılında Bilimsel Bilgi Enstitüsü'nden Eugene Garfield tarafından oluşturulan WoS, ilk başta 700 dergiyi kapsayan bir atıf indeksi olarak hizmet vermeye başladı. Bu platform zamanla gelişerek 1973'te Sosyal Bilimler, 1978'de Sanat ve Beşerî Bilimler ve 2011'de Kitap Atıf İndeksleri'ni bünyesine kattı. 1997'de tüm bu indeksler, WoS adı altında internet üzerinden erişilebilir hale geldi.[5] Daha sonra 2015 yılında, dergilerin klasik indekslere dahil edilmeden önce erken bir değerlendirme süreci olarak Yükselen Kaynaklar Atıf Dizini (Emerging Sources Citation Index- ESCI) tanıtıldı. Şu anki sahibi Clarivate Analytics olan bu platform, 2020 verilerine göre 74,8 milyondan fazla akademik içeriği ve 1,5 milyar atıf kaynağını barındırmaktadır.[6] Yayıncıya göre indeks, bölgesel öneme sahip ve yeni ortaya çıkan bilimsel alanlardaki hakemli yayınları içermektedir. ESCI'ye diğer Clarivate indeksleriyle birlikte WoS üzerinden erişilebilir. Haziran 2021 itibarıyla ESCI'de indekslenen tüm dergiler dergi atıf raporlarında da yer almaktadır. Bu dergiler bir sonraki yıla kadar etki faktörü alamasa da diğer dergilerin etki faktörlerinin hesaplanmasına atıf katkısında bulundular. Clarivate Analytics tarafından işletilen WoS'un dergi değerlendirme süreci oldukça kapsamlıdır ve birkaç farklı indeks veya veri tabanını bünyesinde barındıran bir platformdur. Bu indeksler, bilimsel araştırma çıktılarının farklı yönlerini ve disiplinlerini kapsar. WoS'un en bilinen alt indeksleri şunlardır:

1.a. Science Citation Index – SCI (Bilim Atıf Dizini): Science Citation Indeks (SCI), bilimsel literatürdeki makaleler arasındaki atıf ilişkilerini izleyerek bilimsel çalışmaların etkisini değerlendiren bir indekstir. SCI, başlangıçta bilimsel makalelerin kâğıt tabanlı indekslerini oluşturmak için tasarlandı, ancak teknolojinin gelişmesiyle dijital ortama taşındı. SCI bir makalenin başka hangi makaleler tarafından atıf aldığını belgelemektedir. Bu, bilimsel araştırmaların etkisini ve alandaki bilgi akışını analiz etmek için kritik bir araçtır. SCI, doğa bilimleri ve bazı sosyal bilimler dahil olmak üzere geniş bir disiplin yelpazesini kapsar. Bir derginin SCI'ye dahil edilip edilmeyeceği, derginin bilimsel kalitesi, yayın politikası, düzenliliği ve diğer birçok kriter göz önünde bulundurularak belirlenir.

1.b. Science Citation Index Expanded – SCIE (Genişletilmiş Bilim Atıf Dizini): Bilimsel literatürdeki makaleler arasındaki atıf ilişkilerini takip eden bir indeks olup özellikle doğa bilimleri, mühendislik ve teknoloji alanları olmak üzere çok sayıda disiplini kapsar. SCIE, dergi seçiminde birçok kritere dikkat eder. Bu titiz seçim sürecinin bir sonucu olarak, SCIE, dünya genelinde binlerce dergiyi indeksler ve bu dergilerde yer alan makalelerin atıf analizlerini sağlar. Böylece akademisyenlere ve araştırmacılara kendi çalışmalarını konumlandırma ve literatürdeki güncel gelişmeleri takip etme olanağı sunar. SCIE tarafından indekslenen dergi sayısı zamanla değişiklik gösterebilmektedir. SCIE, SCI'nin daha büyük versiyonu olarak kabul edilebilir ve iki fark dışında SCI'ye benzerdir.

a) Dergi Sayısı: SCIE, SCI'nin kapsadığı dergilerin yanı sıra çok daha fazla sayıda dergiyi içerir. Bu ek dergiler, araştırmacılara daha geniş bir disiplinler arası kaynak seti sunar.

b) Depolama formatı: Hem SCI hem de SCIE çevrimiçi olarak mevcuttur. SCI, CD/DVD formatında da mevcuttur ancak SCIE bu formatta mevcut değildir.
Yeni dergilerin eklenmesi, bazı dergilerin indeksten çıkarılması gibi durumlar nedeniyle bu sayı sürekli olarak güncellenir. Bu yazının yazıldığı tarihe kadar olan verilere göre SCIE'de, 9.000'den fazla dergi indekslenmektedir.[7]
1.c. Social Sciences Citation Index – SSCI (Sosyal Bilimler Atıf Dizini): Clarivate Analytics'in sunduğu bir diğer prestijli indeks olan SSCI, sosyal bilimler alanında yayınlanan dergilere odaklanır. Sosyoloji, antropoloji, hukuk, iletişim bilimleri, eğitim ve psikoloji gibi birçok disipli-

ni kapsayan bu indeks, dahil edilen dergilerin bilimsel etki faktörüne dayanarak seçilmesiyle bilinir. Bu indeksleme, sosyal bilimlerdeki araştırmacılar için çalışmalarının global çapta tanınmasını, geniş bir okuyucu kitlesi tarafından erişilmesini ve daha fazla atıf almasını mümkün kılar.[7]

1.d. Arts & Humanities Citation Index – AHCI (Sanat ve Beşerî Bilimler Atıf Dizini): AHCI, sanat ve beşerî bilimler alanında önemli ve etkili dergileri kapsayan prestijli bir indekstir. Edebiyat, felsefe, müzik, sanat tarihi, dil bilimleri ve benzeri disiplinlerdeki yayınlara odaklanır.[7]

1.e. Emerging Sources Citation Index – ESCI (Yükselen Kaynaklar Atıf Dizini): ESCI, bilimsel kalite ve yenilikçi içerik taşıyan, ancak diğer indekslerin ana koleksiyonları için belirlenen kriterleri tam olarak karşılamayan dergilere ev sahipliği yapar. ESCI, akademik topluluğun dikkatini çekmeye başlamış, ancak henüz tam olarak yerleşik hale gelmemiş yayınlara vitrin oluşturur. Bu indeks içerisinde yer almak, dergiler için bilimsel kabul sürecine adım atmış olmanın bir göstergesidir. Clarivate'e göre dergileri değerlendirmek ve ESCI'ye mi yoksa SCIE'ye mi dahil edileceklerine karar vermek için 28 farklı kriter kullanılmaktadır. Genel olarak bu kriterlerin 24'ü kaliteyle, geri kalan dördü ise etkiyle ilgilidir. Kalite kriterlerini karşılayan dergiler ESCI'de yer alırken hem kalite kriterlerini hem de etki kriterlerini karşılayan dergiler SCIE'de listelenmektedir.[7]

2. Scopus: 2004 yılında Elsevier tarafından oluşturulan Scopus veri tabanı, bilimsel dergiler, kitaplar ve konferans bildirilerini içeren büyük bir veri tabanıdır. İçerik seçimini danışma kurulunun (Content Selection and Advisory Board-CSAB) belirlediği kapsama kriterleriyle yayınları indeksler. 2004'te 1966-2004 dönemine ait 27 milyon yayın kaydıyla başlayan Scopus, şu anda 1788 yılından itibaren olan yayınları kapsamakta ve her yıl yaklaşık 3 milyon yeni kayıt eklenmektedir. Aktif olarak 23,452 dergi başlığı, 120,000 konferans ve 206,000 kitap içerir. Farklı konu alanlarındaki dergi ve konferans makalelerini kapsayan tek bir atıf indeksine sahip olan Scopus, toplamda yaklaşık 77,8 milyon ana kayıt içermektedir. Kullanıcılara araştırma çıktıları üzerinde detaylı arama ve analiz imkânı sunar.[8] Scopus; bilim, teknoloji, tıp ve sosyal bilimler araştırma alanındaki bağımsız dergilere odaklanırken, SCIE indekslemesi doğa ve sosyal bilimler dahil teknik ve bilimsel yayınlara odaklanır. Scopus, PubMed ve WoS'a göre daha geniş bir dergi yelpazesi içerir, atıf analizi WoS'un atıf analizinden daha hızlıdır ve daha fazla makale içerir. Öte yandan WoS'un sunduğu atıf analizi, Scopus'un atıf analizine göre daha iyi grafikler sağlar ve daha ayrıntılıdır.[9]

3. Directory of Open Access Journals – DOAJ (Açık Erişim Dergiler Dizini): DOAJ, kısıtlama olmadan tamamen açık erişimli hakemli bilimsel dergilere özgü bir arama hizmetidir. 2023'te, dünya genelindeki hakemli bilimsel dergilerin %27'sini temsil eden 9.000'den fazla dergiye ev sahipliği yapmaktadır. 2007'de bu oran %10 iken zamanla hızla artmıştır. Tüm akademik alanlar temsil edilirken, bazı alanlar ve özellikle tıp, diğerlerinden daha baskındır. 128 ülkeyi ve birçok dili kapsayan DOAJ, küresel bir çeşitlilik sunmaktadır. DOAJ, açık erişim dergilerinde yayımlanmak isteyen yazarlar için ideal bir mecradır ve kütüphaneler için önemli bir kaynaktır. Kütüphanelerin üyeliği hem kendi tanıtımları hem de açık erişimin tanıtımı için değerlidir.[10]

4. Education Resources Information Center -ERIC (Eğitim Kaynakları Bilgi Merkezi): 1966'da Amerika Birleşik Devletleri Eğitim Bakanlığı tarafından kurulan, eğitimle ilgili araştırmaları kapsayan büyük bir veri tabanıdır. Eğitimle ilgili dergi makaleleri, konferans bildirileri, araştırma raporları ve diğer yayınları içerir. Hem geleneksel akademik yayınları hem de gri literatür olarak bilinen yayımlanmamış materyalleri kapsar. ERIC, eğitimciler, araştırmacılar ve politika yapıcılar için güncel ve kaliteli eğitim literatürüne erişim sağlama amacıyla oluşturulmuştur ve ayda bir kez güncellenmektedir.[11]

5. PsycINFO: American Psychological Association (APA) tarafından oluşturulan ve sürdürülen bir bilimsel ve profesyonel psikoloji literatürü veri tabanıdır. PsycINFO, psikoloji ve ilgili alanlarda (eğitim, iletişim, iş, tıp, hemşirelik, hukuk ve sosyal çalışma gibi) yapılan araştırmaları kapsayan kaynaklara erişim sağlar. Veri tabanı, dergi makaleleri, kitap bölümleri, kitap incelemeleri ve tezler gibi çok çeşitli yayın türlerini indeksler. Psikoloji ve ilgili alanlarda literatüre erişim sağlar.[12]

6. Index Copernicus International- ICI (Kopernik Uluslararası Dizini): Polonya merkezli bir araştırma platformudur ve bilimsel dergilerin kalitesini sıralama ve değerlendirme amacıyla oluşturulmuştur. ICI, dergilerin içeriğinden yayın sürekliliğine kadar çeşitli kriterleri temel alarak bir puanlama sistemi sunar. ICI'de iki başlık öne çıkmaktadır. Bunlardan biri olan ICI World of Journals (ICI Dünya Dergileri), dünya çapındaki bilimsel dergileri içeren küresel bir veri tabanıdır. İki başlıktan diğeri olan ICI Journal Master List (ICI Dergileri Ana Listesi) veri tabanının amacı, dünyanın her yerindeki bilimsel dergilere şeffaf editoryal uygulamalar, özellikle şeffaflık uyarısı ve yağmacı uyarısı açısından doğrulama olanağı oluşturmaktır. ICI Dünya Dergileri arama motoru, bilim dünyasının bilimsel dergilerle ilgili bilgilerin tek bir yerde toplanması ihtiyaçlarına bir yanıttır. Sunulan araçlar sayesinde, ICI Dergiler Ana Listesinde indekslenen dergiler listesinde (ICV puanlaması) veya Bilim ve Yüksek Öğretim Bakanlığı (Ministry of Science and Higher Education -MEiN scoring, MEiN puanlaması) tarafından güncel dergi sıralamasında dergi araması yapmak mümkündür. Her iki bilgiyi birleştirerek en uygun dergiyi seçmek mümkündür.[13]

ICI Dergileri Ana Listesi, yaklaşık 20 yıldan bu yana gönderilen süreli yayınları değerlendiren, bilimsel dergilerin yer aldığı uluslararası indeksleme veri tabanıdır. Veri tabanında indekslenmenin şartı 100'ün üzerinde kritere dayalı, çok boyutlu olumlu bir değerlendirmeden geçmektir. Değerlendirme süreci ücretsiz olup, ICI Dünya Dergileri veri tabanına kayıtlı her dergi için geçerlidir. Veri tabanında indekslemenin öncelikli şartı, şeffaf editoryal uygulamaların sağlanması ve bunların onaylanmasıdır. Hem resmî hem de başlangıç indeksleme koşullarını karşılayan dergiler, dergilerin gelişmişlik düzeyini gösteren bir puan olan ve bir yıl geçerliliğe sahip Index Copernicus Value- ICV (Kopernik Dizin Değeri) alırlar. ICI Dergileri Ana Listesi veri tabanında ayrıca ICI Publishing Stars (ICI Yayıncılık Yıldızları) adı verilen dergilerin gelişimini ölçen bir model bulunmaktadır. Bu model, bilimsel dergilerin yayın ofisleri tarafından, dağıtım oranlarında ve alıntı oranlarında artışa yol açan, örneğin yayın istikrarı, etik ve editoryal standartlar, dijitalleşme derecesi ve uluslararası hale gelme gibi işlevsel alanlarda elde edilen başarıları ölçme olanağı sağlar.[13]

C) Diğer Uluslararası Bilimsel Dergi İndeksleri

1. Directory of Research Journals Indexing – DRJI (Araştırma Dergileri İndeksleme Rehberi): Daha çok, gelişmekte olan ülkelerden gelen dergilere erişim sağlama ve bu dergilere görünürlük kazandırma misyonuna sahip ve gelişmekte olan bir indekstir.[14]

2. EuroPub: Bilimsel literatürün geniş bir özetini kapsar ve özellikle Avrupa'da yer alan araştırma makaleleri, dergiler, konferans bildirileri ve diğer akademik yayınları barındırır. Araştırmacılar ve akademisyenler için farklı disiplinlerdeki en güncel bilimsel çalışmalara erişim sağlama amacıyla oluşturulmuş bir indeksleme hizmetidir.[15]

3. Scientific Indexing Services- SIS (Bilimsel İndeksleme Hizmetleri): Bilimsel dergileri ve konferans bildirilerini indeksleyen bir platformdur. Diğer indekslerden farkı, geniş kapsamlı bir indeksleme hizmeti sunmasına rağmen bazı akademik çevrelerde diğer önde gelen indekslere göre daha az tanınmış olmasıdır. SIS'in en önemli özelliği, sunduğu "Citation Analysis-Atıf Analizi" ile dergi ve makalelerin atıf analizlerini sağlamasıdır.[16]

4. Eurasian Scientific Journal Index – ESJI (Avrasya Bilimsel Dergi Dizini): Avrasya bölgesindeki araştırmaların tanıtılmasını teşvik etmek amacıyla kurulmuş olup, uluslararası alanda dergilerin görünürlüğünü artırmayı hedefler. ESJI, dergilerin kalitesini ve bilimsel katkısını değerlendiren özel bir algoritma ile çalışır.[17]

5. Cumulative Index to Nursing and Allied Health Literature- CINAHL (Hemşirelik ve Yardımcı Sağlık Literatüründe Kümeli Dizin): Hemşirelik, yardımcı sağlık ve biyomedikal alanlarındaki dergi makalelerini indeksleyen bir veri tabanıdır. 1940'larda başlatılan bu proje, 1961'de Hemşirelik Literatürü'nün Kümeli Dizini olarak yayınlanmaya başladı ve 1977'de yardımcı sağlık alanını da kapsayacak şekilde genişletilerek adı değiştirildi. 2003'te EBSCO yayıncılık tarafından satın alındıktan sonra, 2006'da CINAHL, yalnızca EBSCOhost platformunda sunulmaya başlandı.[18]

6. Open Academic Journals Index – OAJI (Açık Akademik Dergiler Dizini): Açık erişimli bilimsel dergilerin tam metinli bir veri tabanıdır.[19] 2013 yılında bilimsel dergiler için bir veri tabanı olarak tasarlanan bu veri tabanı, ilave olarak 2014 yılında hakemli makalelerin sunulması için tam metinli bir platform haline getirildi. Çok yaygınlaşamayan bu dizinin veri tabanına Cherkas Global Üniversitesi'nin bilimsel bilgi de-

partmanı tarafından hizmet verilmektedir.

D) Veri Tabanları, Kataloglar, Bilgi Matrisleri, Açık Erişim Alt Yapıları ve Kütüphaneler

Öncelikle belirtmek gerekir ki, bu başlıkta yer alanlar indeks/dizin değildir. Yanlış bir kullanım ile indeks başlığı altında verilebilmektedir.

1. Scimago Journal & Country Rank – SJCR (SCImago/Scimago Dergi ve Ülke Sıralaması): Scopus veri tabanına dayalı bilimsel dergi sıralamaları ve ülke bilimsel gösterge metrikleri sağlayan bir araştırma grubudur. Bu göstergeler bilimsel alanları değerlendirmek ve analiz etmek için kullanılmaktadır. Dergiler ayrı ayrı karşılaştırılabilir veya analiz edilebilir. Ülke sıralamaları ayrı ayrı da karşılaştırılabilir veya analiz edilebilir. Dergiler konu alanına (27 ana tematik alan), konu kategorisine (309 belirli konu kategorisi) veya ülkeye göre gruplandırılabilir. Alıntı verileri, 5.000'den fazla uluslararası yayıncının 34.100'den fazla başlığından ve dünya çapında 239 ülkeden ülke performans ölçümlerinden alınmıştır. Bu platform, adını SCImago tarafından yaygın olarak bilinen Google PageRank™ algoritmasından geliştirilen SCImago Journal Rank – SJR (SCImago Dergi Sıralaması) göstergesinden almaktadır. Bu gösterge Scopus® veri tabanında yer alan dergilerin 1996 yılından itibaren görünürlüğünü gösterir. SJR, bir derginin bilimsel prestijini ölçer. Farklı olarak, SJR sadece atıf sayısına değil, atıf yapan dergilerin prestijine de dayanır; bu nedenle yüksek prestijli dergilerden gelen atıflar daha değerlidir. Bu araçlar, dergilerin bilimsel etkisini anlamak için kullanılır.[20]

2. Scope Database: Scopus ile karıştırılabilmektedir ama farklıdır. 2008'de kurulmuş, kâr amacı gütmeyen bir eğitim organizasyonudur. Akademik ve bilimsel dergiler, konferans bildirileri, ticaret dergileri ve kitap serilerini kapsayan geniş bir bibliyografik atıf veri tabanına sahiptir. Dünya genelinde birçok araştırma kurumunun kullandığı bu veri tabanı, Bilim, Mühendislik, Teknoloji, Yönetim, Tıp, Sosyal Bilimler, Sanatlar ve Beşerî Bilimler gibi farklı alanlarda araştırma başarılarının kapsamlı bir özetini sunar. Kullanıcılara, yazar, makale ve kurum araştırmaları gibi özelliklere erişim sağlar. Ayrıca, indekslenen içerikler için yayıncılara ve yazarlara sertifikalar da sunmaktadır. 2021 itibariyle, Scope Database 5.260.800 makale, 3.540 dergi başlığı, 1.209 konferans bildirisi ve 12.280 kitap serisini indekslemiştir.[21]

3. WorldCat: Dünyanın en kapsamlı kütüphane kataloglama ve ağ tabanlı bibliyografik veri tabanıdır. Aralık 2021 itibariyle WorldCat, 483 dilde 540 milyondan fazla bibliyografik kaydı ve 3 milyardan fazla fiziksel ve dijital kütüphane varlığını temsil etmekteydi.[22] Online Bilgisayar Kütüphane Merkezi (Online Computer Library Center- OCLC) tarafından işletilen bu veri tabanı, kitaplar, müzik CD'leri, video kayıtları, dijital kaynaklar, gazeteler, dergiler ve diğer basılı ve dijital materyallerin kayıtlarını içerir. Aslında bir indeks değildir. WorldCat; kütüphanelerin koleksiyonlarını ve kataloglarını bir araya getiren birleşik bir kataloglama sistemidir.

4. Information Matrix for the Analysis of Journals- MIAR (Dergilerin Analizi için Bilgi Matrisi): Dergilerin hangi indekslerde listelendiğini gösteren bir bilgi matrisidir. Farklı indekslerdeki dergi listelemelerini toplayarak bir değer oluşturur, ancak bu değer derginin kalitesini değil, indeksleme varlığını yansıtır. Bu matris, araştırmacılara ve yayıncılara dergilerin indeksleme durumları hakkında hızlı bir genel bakış sunar. Kendisi bir indeks değildir.[23]

5. Open Access Infrastructure for Research in Europe – OpenAIRE (Avrupa'da Araştırma İçin Açık Erişim Altyapısı): Avrupa'da açık erişim ve açık bilim faaliyetlerini desteklemek için kurulmuş bir altyapıdır. Bilimsel yayınlara ve araştırma verilerine erişimi kolaylaştırır, ancak geleneksel bir indeksleme servisi değildir.[24]

6. Directory of Open Access Scholarly Resources – ROAD (Açık Erişim Bilimsel Kaynaklar Rehberi): Ücretsiz erişimli akademik kaynakların global bir dizinidir. UNESCO tarafından desteklenen bu platform, dergiler, konferanslar ve kitaplar gibi farklı türdeki akademik içerikleri kapsar.[25]

7. Global Provider of Research and Learning Resources – GALE (Küresel Araştırma ve Öğrenme Kaynakları Sağlayıcısı): Dünya genelinde eğitim kurumları, kütüphaneler ve işletmeler için bilgi çözümleri sunan bir eğitim yayıncılığı şirketidir. Adını kurucusu Frederick Gale'den almıştır. Cengage Learning'in bir bölümü olarak faaliyet gösteren GALE, birçok farklı konuda veri tabanları, e-kitaplar ve diğer dijital öğrenme kaynakları sunmaktadır. Şirket, tam metinli dergi ve gazete veri tabanları, Gale OneFile (eski adıyla Infotrac) ve kütüphanelerin abone olduğu diğer çevrimiçi veri tabanlarının yanı sıra özellikle din, tarih ve bilim alanlarında çok ciltli referans çalışmalarıyla tanınmaktadır. Gale'in sahibi olduğu siteler ve hizmetlerden birisi olan Gale Dizin Kütüphanesi 2017 tarihinde arşivlenmiş ve dijital platformda düzinelerce basılı dizin içermektedir. Ayrıca kurgu ve kurgu dışı kitap başlıklarından oluşan Kitaplar ve Yazarlar adında indeksli veri tabanı mevcuttur.[26]

8. Hinari: Gelişmekte olan ülkelerin biyomedikal alandaki ve sağlık alanındaki literatüre erişebilmeleri amacıyla Dünya Sağlık Örgütü ve büyük yayınevleri tarafından kurulan bir programdır. Program, sağlık kuruluşlarının ulaşabileceği birçok e-dergi ve online kitaba erişim imkânı sağlar.[27]

9. British Library (İngiliz Kütüphanesi): Birleşik Krallık'ta bulunan ulusal bir kütüphanedir ve dünyanın en büyük ve en kapsamlı kütüphanelerinden biridir. British Library, kendi koleksiyonunu kataloglamak ve araştırmacılara erişim sağlamak için kendi kataloglama sistemini kullanır. Bu katalog, kitaplar, dergiler, el yazmaları, haritalar ve diğer birçok materyali içerir. "Kütüphane koleksiyonunda yaklaşık 14 milyon kitap ve MÖ 2000'lere kadar geçmişe uzanan birçok el yazması vardır.[28] Araştırmacılar, British Library'nin çevrimiçi kataloğunu kullanarak koleksiyonlarındaki materyallere erişebilirler. Ancak bu, akademik dergi indeksleme servisleriyle karıştırılmamalıdır.

10. Sherpa/RoMEO: Dergi bazında dünyanın dört bir yanındaki yayıncıların açık erişim politikalarını toplayan ve analiz eden bir çevrimiçi kaynaktır. Yayıncının telif hakkı ve açık erişim arşivleme politikalarının özetlerini sağlar. Yazarların yayınlanmış makalelerinin telif hakkı durumunu belirlemelerine ve dünya genelindeki dergiler için açık erişim arşivleme politikalarını öğrenmelerine yardımcı olur.[29]

11. Essential Science Indicators – ESI (Temel Bilim Göstergeleri): Dergilere, ülkelere, kurumlara ve bilim insanlarına yönelik olarak analizler gerçekleştiren ve çeşitli yönlerden sıralamalar yapan bir değerlendirme platformudur. Web of Science Core Collection'da en iyi performansı gösteren araştırmaları belirlemenize yardımcı olan analitik bir araçtır. ESI, yayın ve alıntı performansına dayalı olarak yazarları, kurumları, ülkeleri ve dergileri sıralamak için dünyanın dört bir yanından 11.000'den fazla dergiyi araştırır. Veriler 10 yıllık bir dönemi kapsar ve sıralamalar ve alıntı sayılarına ilişkin iki ayda bir yapılan güncellemeleri içerir. Ayrıca ESI, "highly cited papers" ve "hot papers" gibi çok fazla sayıda atıf yapılan çalışmaları ve araştırmacıları öne çıkaran ek özellikleri de içermektedir.[30]

Bu liste, bilimsel indekslerin sadece bir kısmını temsil etmektedir. Her akademik alana özgü birçok özel indeks (EconLit: Ekonomi literatürüne erişim sunar, Chemical Abstracts Service-CAS: Kimya ve ilgili alanlardaki literatüre odaklanır vb.) bulunmaktadır.

E) Bir dergi indeksi olmamakla birlikte pratikte indeks gibi kullanılan veri tabanları

1. PubMed: PubMed, Amerika Birleşik Devletleri Ulusal Tıp Kütüphanesi (National Library of Medicine-NLM) bünyesinde faaliyet gösteren, biyomedikal literatür için öncü bir araştırma motorudur. PubMed kendi başına bir "indeks" değildir; fakat içerisinde MEDLINE gibi önemli indekslenmiş koleksiyonları barındırır. Bu nedenle, bazen insanlar MEDLINE ile PubMed arasındaki farkı karıştırabilirler. Ancak, pratiğe döküldüğünde, birçok araştırmacı "PubMed'de indekslenmiş" ifadesini kullanarak bir derginin ya da makalenin kalitesine veya saygınlığına işaret etmeye yönelmektedir.
Daha önceleri Medline olarak bilinen bilgiler, 1996'da PubMed altında birleştirilmiştir. 1966'dan günümüze kadar olan yayınları kapsayan PubMed, çoğunlukla Medline veri tabanındaki özetleri içerir ve bu özetler, genellikle yaşam bilimleri ve biyomedikal konulardaki bilimsel dergi makalelerini kapsar. PubMed sistemi, herkese Haziran 1997'den itibaren ücretsiz olarak sunulmaya başlamıştır.[31] Aynı zamanda PubMed Central adında, tam metin makalelere ücretsiz erişim imkânı sunan bir arşivle de bağlantılıdır. PubMed, 23 Mayıs 2023 tarihinde yaklaşık 36 milyon makaleye sahip olup, her yıl 1 milyondan fazla makale eklenmektedir.[32] Bu verilerin bir kısmının 1865 yılına kadar geri gittiği bilinmektedir. Aynı tarihe kadar, PubMed'in kayıtlarının 24,6 milyonu özetleriyle listelenmiştir ve 26,8 milyon kayıt tam metin versiyonlarına bağlantıya sahiptir (bunların 10,9 milyon makalesi üc-

retsiz olarak tam metin olarak mevcuttur). Tam olarak indeks olmadığından yağmacı dergilerin sızıntıları olabildiği unutulmamalıdır.[33]

2. Google Scholar (GS): 2004 yılında Google tarafından hizmete sunulan, akademik literatürü indeksleyen ve kullanıcılara sunan bir arama motorudur. Bilimsel makaleler, tezler, kitaplar, konferans bildirileri ve diğer bilimsel çalışmaları kapsayan geniş bir veri tabanına sahiptir. Ayrıca, atıf analizi yapma yeteneği sayesinde, bilimsel çalışmaların etki ve referans sayısını izleme imkânı sunar. Bu özellikleriyle, akademik araştırmalar için kapsamlı ve çok yönlü bir araç olarak ön plana çıkar. Tam bir indeks olmasa da geniş kapsamı ve erişilebilirliği nedeniyle bilim dünyasında yaygın olarak kullanılır. Google Scholar, dergileri değerlendirmemesi ve bünyesine yağmacı dergileri dahil etmesi nedeniyle eleştirilmektedir.[34]

3. EBSCOhost: Çeşitli akademik ve ticari veri tabanlarına erişim sağlayan önde gelen bir online referans kaynak servisidir. EBSCOhost'un (EltonBStephensCO) sunduğu veri tabanlarından bazıları, belirli disiplinlere veya konu alanlarına odaklanan özgün indeksleme ve özetleme servisleridir. EBSCO, veri tabanlarının 1500'den fazla yayıncıdan bir milyonun üzerinde e-kitap ve 90.000 sesli kitap içerdiğini belirtilmektedir. Böylece, EBSCOhost kullanıcılarına geniş bir bilgi havuzu sunar, fakat platformun kendisi doğrudan bir indeks değil, çok sayıda veri tabanını bir araya getirip sunan bir araçtır.[35]
4. Research Gate (Araştırma Kapısı): 2008'de kurulan bir sosyal ağ ve iş birliği platformudur, özellikle araştırmacılar ve bilim insanları için tasarlanmıştır. Üyeler, yayınladıkları makaleleri paylaşabilir, bilimsel sorular sorabilir ve diğer araştırmacılarla iş birliği yapabilirler. Bu platform, bilimsel bilgi ve bulguların geniş bir kitleyle paylaşılmasını teşvik eder.[36]
5. Dimensions (Boyutlar): 2018'de oluşturulan en yeni akademik veri tabanıdır. Digital Science adında, Londra merkezli bir teknoloji firmasının bünyesinde faaliyet gösterir. Başlangıçta 90 milyon yayınla başlatılmış, 2023'ün Temmuz ayı itibarıyla, platform 1,8 milyardan fazla atıfla birlikte 140 milyon civarında yayını içermektedir. Bu veri tabanı, 74.000'den fazla dergi girdisine sahiptir ve birçok küçük yayıncıyı kapsar. Web of Science ve Scopus'tan farklı olarak, Dimensions, Crossref ve PubMed'den veri toplar ve bu veriyi çeşitli kaynaklardan zenginleştirir. Dimensions, farklı erişim seviyeleriyle üç farklı formda kullanılabilir ve geniş bir veri yelpazesi sunar.[37]
6. Research Square (Araştırma Meydanı): Denetimden sonra gönderilmek üzere onaylanan ancak hakem değerlendirmesi almayan elektronik ön baskılar için açık erişimli bir platformdur. Bu, araştırmacıların çalışmalarını resmi hakem değerlendirmesinden geçmeden önce paylaşmalarına olanak tanıyan bir web sitesidir.[38]
7. Research Bible- ResearchBib (Araştırma Kitabı): Akademik dergi ve konferansları indeksleyen bir online platformdur. Özellikle açık erişimli dergiler, konferanslar ve iş raporları için bir indeksleme servisidir. Bu platform, araştırmacıların ilgili literatüre hızlı ve kolay erişim sağlamalarına yardımcı olur.[39]

F) Alan indeksi:

Alan indeksi, bilinen anlamda dizinlemeyi içermemekte ve bazı veri tabanları ile arama motorlarını da içine almaktadır. Bu yüzden "indeks" ifadesi yerine başka bir tanımlama kullanılmasının daha doğru olabileceği düşünülmektedir. Örneğin sadece tıp alanında veya sadece kimya alanında yayınlanan makaleleri içeren yapılar, alan indeksi olarak kabul edilmektedir. Doğru ifadeyle alan indeksi; belirli bir konu alanında, seçim kriterleri ile yayın kabul eden ve yayınların en az bibliyografik bilgilerinin verildiği (makalelerin/kitapların/tezlerin künyelerinin ve kimi zamanda özetlerinin yer aldığı) indekstir. Alan indeksleri olarak aşağıdaki başlıklar ön plana çıkmaktadır; Sociological Abstract, Psychological Abstract, Library and Information Science Abstract, ERIC, Index Medicus/Medline, PUBMED, Geobase, PsycInfo, Chemical Abstracts, Food Sciences and Technology Abstracts, MathSci, Biological Abstract, CAB, Engineering Index.[40]

G) Yayıncılık Etiği Platformları

Yine belirtmek gerekir ki, bu başlıkta yer alanlar da indeks/dizin olmayıp yanlış bir kullanım ile indeks başlığı altında verilebilmektedir.
1. Committee on Publication Ethics- COPE (Yayın Etiği Komitesi): Yayıncılık etiği konularında rehberlik sağlayan uluslararası bir örgüttür. Bilimsel dergi editörleri ve yayıncıları için etik ilkelere uyum ve en iyi uygulama standartları hakkında tavsiyelerde bulunur. Ancak COPE, bir derginin kalitesini ölçen bir indeksleme servisi değildir.[41]
2. International Committee of Medical Journal Editors- ICMJE (Uluslararası Tıp Dergisi Editörleri Komitesi): Yayın için biyomedikal dergilere gönderilen yazıların etiğini, hazırlanmasını ve formatını standartlaştırmak için Uluslararası Tıp Dergileri Editörleri Komitesi tarafından üretilen bir dizi kılavuzdur. ICMJE tavsiyelerine uyum, önde gelen biyomedikal dergilerin çoğu tarafından zorunludur. Daha önce Vancouver Grubu olarak bilinen ICMJE açık bir organizasyon olmayıp genel tıp dergilerinden oluşan küçük bir gruptur.[42]
3. World Association of Medical Editors- WAME (Dünya Tıbbi Editörler Birliği): Dünya Tıp Editörleri Birliği, tıp dergilerinin editörlerinden oluşan uluslararası, sanal bir organizasyondur. İlk olarak 1995 yılında, ICMJE'nin "çok küçük, kendi kendine hizmet eden ve ayrıcalıklı" hale gelmesinden endişe duyan ICMJE'nin bir grup üyesi tarafından kuruldu. Tıp dergilerinin editörleri arasında daha fazla uluslararası iş birliği sağlanması için görev yapar. Hakemli bir biyomedikal derginin herhangi bir editörü WAME'ye katılma hakkına sahiptir.[43]
4. Council of Science Editors- CSE (Bilim Editörleri Konseyi): Eski adıyla Biyoloji Editörleri Konseyi olan ve 2000 yılında Bilim Editörleri Konseyi adına alan bu yapı, bilimsel yazarlar arasında editoryal uygulamayı destekleyen kâr amacı gütmeyen bir kuruluştur. CSE, çevrimiçi hizmet ve tavsiye sağlamanın yanı sıra, dergi editörlüğü, yayın yönetimi, makale düzenleme ve dergi ölçümleri gibi konularda kısa kurslar içeren yıllık toplantı düzenler.[44]
5. European Association of Science Editors- EASE (Avrupa Bilim Editörleri Birliği): Bilim iletişimi ve düzenleme ile ilgilenen kişiler için kâr amacı gütmeyen, 1982 yılında Fransa'da kurulan ve halihazırda uluslararası üyeliğe sahip bir kuruluştur. EASE'in sadece Avrupa'da değil dünyanın diğer yerlerinde de olmak üzere yaklaşık 50 ülkede yaşayan üyesi bulunmaktadır. Üyeler birçok disiplinde ve meslekte çalışmaktadır: editörler, akademisyenler, bilim çevirmenleri, yayıncılar, web ve multimedya personeli, indeksleyiciler, istatistik editörleri, bilim ve teknik yazarlar, yazar editörleri, gazeteciler, kurumsal iletişimciler, redaktörler, üretim personeli, yönetici editörler vb. Üyelerin sadece %10'undan azı bilim dergilerinin baş editörüdür.[45]
6. World Medical Association- WMA (Dünya Tabipler Birliği): Dünya çapında hekimleri temsil eden uluslararası, bağımsız bir ücretsiz profesyonel tıp birlikleri konfederasyonudur. Birliğin temel amacı, hekimlerin etik davranış ve bakımlarına ilişkin mümkün olan en yüksek standartları oluşturmak ve desteklemektir. Bu hedef doğrultusunda, tıbbi profesyonellik, hasta bakımı, insan denekler üzerine araştırmalar ve halk sağlığı ile ilgili bir dizi etik konuya ilişkin küresel politika beyanlarını benimsemiştir. DTB Konseyi ve onun daimî komiteleri mevcut politikaları düzenli olarak gözden geçirip günceller ve ortaya çıkan etik sorunlar hakkında sürekli olarak yeni politikalar geliştirir.[46]

H) Yapay Zekâ ile İlgili Veri Kütüphaneleri

Yapay zekâ ile ilgili veri kütüphaneleri, yapay zekâ (AI) ve makine öğrenimi (ML) modellerini tasarlamak, geliştirmek ve eğitmek için kullanılan programlama kütüphaneleridir. Bu kütüphaneler, özellikle tıbbi görüntüleme ve hastalık teşhisinde yoğun bir şekilde kullanılmaktadır. MR, CT, röntgen ve ultrasonografi gibi çeşitli tıbbi görüntüleme teknikleri, TensorFlow, PyTorch ve benzeri yapay zekâ kütüphaneleri kullanılarak analiz edilir.[47] Bu analizler, görüntülerdeki anormallikleri—malignite, fraktür, damar tıkanıklıkları gibi—tespit etmek için kullanılır ve bu da erken teşhis koymayı mümkün kılar.[47] Bu teknolojiler aynı zamanda, hastalıkların seyri ve tedaviye yanıtların izlenmesinde de önemli bir role sahiptir. Örneğin, yapay zekâ modelleri, tedavi öncesi ve sonrası görüntülerdeki değişiklikleri analiz ederek, tedavinin etkinliğini objektif bir şekilde değerlendirebilir.[48] Ek olarak, yapay zekâ kütüphaneleri, genetik veri analizinde de kullanılarak, hastalıkların genetik temellerini anlamada ve hatta kişiselleştirilmiş tıp uygulamalarında, hastalara özel tedavi yöntemleri geliştirilmesinde yardımcı olmaktadır.[49]

Ayrıca, AI teknolojileri, açık erişim altyapıları ve kütüphanelerdeki bilgi matrisleri arasındaki entegrasyonu kolaylaştırmaktadır. AI destekli araçlar, metaveri analizi, otomatik etiketleme ve sınıflandırma ile bilgiye erişimi hızlandırırken, yayıncılık etiği platformlarında AI, yazarlık ve alıntı yanlılıklarını tespit ederek bilimsel bütünlüğü korumada yardımcı olmaktadır.[50] Bu tür sistemler, araştırmacıların çalışmalarını daha geniş bir kitleye ulaştırırken etik standartları korumasına ve bilimsel iletişimin doğruluğunu artırmaya önemli katkılar sağlamaktadır.

I) İndekslerin Karşılaştırılması

Ulusal ve uluslararası indeksler, belirledikleri özel kriterlere göre seçtikleri ve dahil ettikleri dergi içeriklerini, belirli zaman aralıklarında ve farklı yöntemler kullanarak okuyucularına sunan kapsamlı veri tabanları olarak hizmet vermektedirler. Her bir indeks veya arama motorunun avantajları ve dezavantajları vardır. Hedefler öncülüğünde seçim tavsiye edilmektedir.

Web of Science'ın seçici ekleme yaklaşımı, bilim ve internetteki bilgi artışına hızla adapte olamama sorununa yol açabileceğinden bahsedilmektedir. Seçici ekleme yapmayan diğer arama motorları (Google Scholar, Pubmed vb) ise yağmacı dergi diye tarif edilen ve çalışmanın kalitesi tam olarak sınanmamış yayınlardan kendini koruyamamaktadır.[51] Özellikle bilim dünyasındaki en hızlı büyüyen araştırma alanlarında WoS'un diğer veri tabanlarına kıyasla dergi makalelerini kapsama oranı düşmektedir. Örneğin, Avustralya üniversitelerinin yayın çıktıları üzerinde yapılan bir analizde, bazı bilim dallarında WoS tarafından indekslenen dergilerdeki yayınlar yüksekken, sosyal bilimler, yönetim ve eğitim gibi alanlarda bu oranın oldukça düşük olduğu gözlemlenmiştir.[52] Dahası, bazı bilim insanlarının çalışmalarının GS'de (Google Scholar) WoS'a kıyasla çok daha yüksek atıflandığı tespit edilmiştir. Bu, WoS'un yüksek etkili araştırmaları gözden kaçırma riski taşıdığını göstermektedir. GS ve WoS, bilimsel literatürde farklı kapsamlara sahiptir. GS'nin biyoloji, fizik ve kimya gibi disiplinlerde WoS'e kıyasla daha az atıf sağladığını; ancak bilgi teknolojisi, insan-bilgisayar etkileşimi, sosyal bilimler, ekonomi, yönetim, mühendislik ve matematik gibi alanlarda WoS'ten daha üstün atıf sayılarına ulaştığını ortaya koyan çalışmalar mevcuttur.[53]

2021 tarihinde yapılan bir araştırmada, üç veri tabanının (WoS, Scopus ve Dimensions) dergi kapsamının karşılaştırmalı bir analizi yapılmıştır.[54] Analiz için üç veri tabanının en güncel ana dergi listeleri kullanılmıştır. Sonuçlar, veri tabanlarının önemli ölçüde farklı dergi kapsamına sahip olduğunu göstermektedir; WoS en seçici iken Dimensions en kapsamlıdır. WoS'ta indekslenen dergilerin %99,11'i Scopus'ta ve %96,61'i Dimensions'ta da indekslenmektedir. Scopus'ta indekslenen dergilerin %96,42'si Dimensions tarafından da kapsanmaktadır. Dimensions veri tabanı en kapsamlı dergi kapsamına sahiptir; Web of Science'dan %82,22 daha fazla ve Scopus'tan %48,17 daha fazla dergiye sahip olduğu bulunmuştur. WoS'un Scopus'a göre bir avantajı, tam WoS veri tabanının 1945'e kadar uzanan kapsama derinliğidir. Scopus'un geçmişi 1966'ya kadar uzanmaktadır.[55]

Visser ve arkadaşlarının yaptığı çalışmada, WoS, Scopus, Dimensions gibi çeşitli bibliyografik veri kaynaklarının makale kapsamları ele alınmıştır.[56] 2008-17 yıllarını kapsayan bu süre zarfında, WoS 22,9 milyon, Scopus 27 milyon, Dimensions ise 36,1 milyon makaleye ev sahipliği yapakta olduğu bildirilmiştir. Bu veri tabanları arasında Scopus'un makaleleri temel alınarak bir örtüşme analizi yapıldığında, Scopus'un makalelerinin yaklaşık %65'inin WoS ile, %78'inin ise Dimensions ile benzerlik gösterdiği bulunmuştur. Bu bağlamda, Dimensions'ın yeni bir platform olduğunu ve 2017/2018 sonrasında büyük bir büyüme kaydettiğini belirtmek önemlidir. Ek olarak, her derginin yayınladığı makale sayısı farklı olabileceği için, makale ve dergi bazlı örtüşme oranları arasında farklar olması doğaldır. Genel olarak, bu çalışma WoS'un en seçici platform olduğunu, Scopus'un daha geniş bir kapsama sahip olduğunu ve Dimensions'ın diğer iki platforma kıyasla çok daha geniş bir içeriğe sahip olduğunu göstermektedir.

Sonuç olarak dergi indeksleri çalışmanın okunurluğunu artıran bir mecradır. Günümüz teknolojisinde bilim hızla ilerlemekte ve çok sayıda çalışmalar yapılmaktadır. Yapılan çalışmanın kalitesini gösteren verilerden bir tanesi de derginin hangi indekste olduğudur. Çok sayıda indeks bulunmakla birlikte birbirlerine üstünlükleri ve farklılıkları vardır. Bazı platformlar yanlışlıkla indeks olarak adlandırılmakta veya kullanılmaktadır. Bu veri tabanlarında yağmacı dergi ayrımı yapılmadığı göz önünde bulundurulmalıdır. İndekslerde seçici ekleme politikası da adaptasyon hızında sorunlara neden olabilmektedir. Hedef kitleye göre her bir indeksin artı ve eksilerinin mevcut olduğu unutulmamalıdır.

Çıkar Çatışması:

Yazarların ve/veya aile bireylerinin herhangi bir çıkar çatışması potansiyeli yoktur.

Yazar Katkıları:

Fikir/Kavram: Mehmet Çıtırık; Tasarım: Mehmet Çıtırık, Ali Dal; Denetleme/Danışmanlık: Mehmet Çıtırık; Veri Toplama ve/veya İşleme: Ali Dal, Mehmet Çıtırık; Analiz ve/veya Yorum: Ali Dal, Mehmet Çıtırık; Kaynak Taraması: Ali Dal, Mehmet Çıtırık; Makalenin Yazımı: Ali Dal, Mehmet Çıtırık; Eleştirel İnceleme: Mehmet Çıtırık.

KAYNAKLAR

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YAYIN KURALLARI

GENEL BİLGİLER

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi; Ankara Eğitim ve Araştırma Hastanesi' nin süreli bilimsel yayın organıdır. Nisan, ağustos ve aralık aylarında olmak üzere yılda üç sayı olarak yayımlanır. Tıbbın her dalı ile ilgili olabilecek retrospektif, prospektif veya deneysel araştırma, (davetli) derleme, olgu sunumu, editoryal yorum / tartışma, editöre mektup, tıbbi ve cerrahi tedavi teknikleri, tıbbi kitap değerlendirmeleri ve tıp gündemini belirleyen güncel konuları yayımlayan, ulusal ve uluslararası tüm tıp camiasına ulaşmayı hedefleyen bilimsel bir dergidir.

AMAÇ VE KAPSAM

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi; Ankara Eğitim ve Araştırma Hastanesi' nin süreli bilimsel yayın organı olup 1966 yılında yayın hayatına başlamıştır. Nisan, ağustos ve aralık aylarında olmak üzere yılda üç sayı olarak yayımlanır.
Tıbbın her dalı ile ilgili olabilecek retrospektif, prospektif veya deneysel araştırma, (davetli) derleme, olgu sunumu, editoryal yorum / tartışma, editöre mektup, tıbbi ve cerrahi tedavi teknikleri, tıbbi kitap değerlendirmeleri ve tıp gündemini belirleyen güncel konuları yayımlayan, ulusal ve uluslararası tüm tıp camiasına ulaşmayı hedefleyen, önyargısız ve çift-kör hakemlik ilkeleri çerçevesinde yayın yapan açık erişimli bilimsel bir dergidir.
Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi, kapsam olarak tıbbın her dalı ile ilgili retrospektif, prospektif veya deneysel araştırma, (davetli) derleme, olgu sunumu, editöryal yorum / tartışma, editöre mektup, tıbbi kitap değerlendirmeleri yayımlayan bilimsel, uluslararası hakemli bir dergidir.
Derginin yazım kurallarına göre gönderilen çalışmalar TÜBİTAK-DERGİPARK online yayın platformu üzerinden kabul edilmektedir. Derginin yayın dili Türkçe ve İngilizce'dir. Yayımlanmak için gönderilen makalelerin daha önce başka bir yerde yayımlanmamış veya yayımlanmak üzere gönderilmemiş olması gerekir.
Dergiye gönderilen makale biçimsel esaslara uygun ise editör ve en az iki danışmanın incelemesinden geçip gerek görüldüğü takdirde, istenen değişiklikler yazarlarca yapıldıktan sonra yayımlanır.
Amacımız, bilime katkı yapmaya çalışan değerli araştırmacılarımızın yoğun emeklerinin eseri olan çalışmalarının karar verme ve yayımlanma sürecini en kısa sürede sonuçlandırmaktır. Dergimizin bilimsel kalitesini yükseltmek için yazar, hakem ve okuyucularımızın değerli görüş, öneri, bildirim ve yapıcı eleştirilerine açık olduğumuzu, bunlara gereken hassasiyeti gösterdiğimizi bildiririz.

AÇIK ERİŞİM VE MAKALE DEĞERLENDİRME

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi, açık erişimli bir dergidir.
Dergi, elektronik ortamda online olarak yayımlanan sayılara ve sayı içeriğinde yer alan makalelerin tam metinlerine, yayınlandığı anda ücretsiz erişim sağlar.
Dergi, tüm kullanıcılara makalelerin tam metinlerini okuma, indirme, kopyalama, dağıtma, yazdırma, arama veya bağlantı verme, dizine eklemek için tarama, veri olarak yazılıma aktarma veya başka herhangi bir yasal amaç için kullanma izni verir.
Yazar(lar)dan yazılarının yayımı için herhangi bir ücret talep edilmez.
Okuyucular dergi içeriğini akademik veya eğitsel kullanım amaçlı olarak ücretsiz indirebilirler.
Dergi herkese, her an ücretsizdir. Bunu sağlayabilmek için dergi Ankara Eğitim ve Araştırma Hastanesi' nin fiziksel imkanlarından, DERGİPARK bilimsel dergi yayın platformunun ücretsiz makale değerlendirme ve online yayın sisteminden ve editörlerin ve hakemlerin süregelen gönüllü çabalarından yararlanmaktadır.

BİLİMSEL SORUMLULUK

Yayımlanmak üzere gönderilen çalışmalarda ismi yer alan tüm yazarların akademik-bilimsel olarak doğrudan katkısı olmalıdır. Yazar olarak belirlenen isim aşağıdaki özelliklerin tamamına sahip olmalıdır.
*Makaledeki çalışmayı planlamalı veya yapmalı,
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Çalışmaların bilimsel kurallara uygunluğu yazarların sorumluluğundadır. Gönderilen tüm çalışmalarda, yazarların çalışmaya verdiği katkılar açıkça belirtilmiş olmalıdır.
Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi, Uluslararası Tıp Dergileri Editörleri Kurulu'nun (International Committee of Medical Journal Editors) standartlarını uygulamayı kabul etmiştir. Yazarlar "Biyomedikal Dergilere Gönderilen Makalelerin Uyması Gereken Standartlar: Biyomedikal Yayınların Yazımı ve Baskıya Hazırlanması (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication)'daki yazarlık kriterlerini karşılamalıdır. Bu konudaki bilgiye www.icmje.org adresinden ulaşılabilir.

ETİK SORUMLULUK

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi' ne gönderilen çalışmaların etik ve bilimsel standartlara uygun olması gerekmektedir. Yayımlanan makalelerin bilimsel, etik ve hukuki sorumlulukları yazar(lar)a ait olup editör, editörler kurulu ve yayın kurulu üyelerinin görüşlerini yansıtmaz.
Dergi, yayımladığı makalelerde, konu ile ilgili en yüksek etik ve bilimsel standartlarda olması ve ticari kaygılar olmaması şartını gözetmektedir. Bu çerçevede herhangi bir ticari ürün reklamına yer vermemektedir. Editörler ve yayın kurulu, yayımlanan makalelerde yer verilen ticari ürünlerin özellikleri ve açıklamaları konusunda hiçbir garanti vermemekte ve sorumluluk kabul etmemektedir.

Yayımlanmak için gönderilen çalışmaların daha önce başka bir yerde yayımlanmamış veya yayımlanmak üzere gönderilmemiş olması gerekir. Eğer çalışmada daha önce yayımlanmış; alıntı yazı, tablo, resim vs. mevcut ise çalışmanın sorumlu yazarı, yayın hakkı sahibi ve yazarlarından yazılı izin almak ve bunu çalışmada belirtmek zorundadır. Dergiye gönderilen çalışma biçimsel esaslara ve gönderildiği dilin yazım kurallarına uygun ise editör / alan editörü ve en az iki danışmanın incelemesinden geçip gerek görüldüğü takdirde, istenen değişiklikler yazarlarca yapıldıktan sonra yayımlanır.
Deney hayvanları ile yapılan çalışmalar dahil, tüm prospektif ve retrospektif çalışmalar ile yürürlükteki mevzuat gereği etik kurul onayı alınması gereken diğer çalışmalar için Etik Kurul Onayı alınmalı ve yazının "Gereç ve Yöntem" bölümünde Etik Kurul Onayının alındığı kurum, onay numarası ve alındığı tarih (gün-ay-yıl) belirtilmelidir.
Dergi, insan öğesinin içinde bulunduğu tüm çalışmalarda Helsinki Deklarasyonu Prensipleri' ne uygunluk (https://www.wma.net/ policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) ilkesini kabul eder. Bu tip çalışmaların varlığında yazarlar, çalışmanın "Gereç ve Yöntemler" bölümünde bu prensiplere uygun olarak çalışmayı yaptıklarını, etik kurul onayı ve çalışmaya katılmış insanlardan "Bilgilendirilmiş rıza (informed consent)" aldıklarını belirtmek zorundadırlar.

Çalışmada 'hayvan' öğesi kullanılmış ise yazarlar, çalışmanın "Gereç ve Yöntemler" bölümünde, "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 çalışmalarında hayvan haklarını koruduklarını ve hayvan deneyleri etik kurulu onayı aldıklarını belirtmek zorundadırlar.
Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza (informed consent)" alınmalı ve çalışma içinde bu durum belirtilmelidir. Kişisel Verilerin Korunması Hakkında Kanun Çerçevesinde onam alınması ve yetkili merciler tarafından talep edilmesi halinde sunulması, yazarların sorumluluğundadır.
Eğer çalışmada doğrudan veya dolaylı ticari bağlantı ya da çalışma için maddi destek alınan kurum mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma ile hiçbir ticari ilişkilerinin olmadığını veya bir ilişkileri varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar, vb), editöre sunum sayfasında bildirmek zorundadır. Çalışmaların etik kurallara uygunluğu yazarların sorumluluğundadır.

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İNTİHAL TARAMASI

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi intihale sıfır tolerans politikası izlemektedir. Bu politikanın bir sonucu olarak Dergiye gönderilen tüm çalışmalar yazarları tarafından lisanslı bir uygulama (iThenticate ya da Turnitin) ile taranmalı ve benzerlik raporu makale dosyaları ile birlikte sisteme yüklenmelidir. Kabul edilebilir benzerlik oranı %20' nin altıdır. Belirlenen oranın üzerinde benzerliğe sahip yazılar değerlendirmeye alınmadan reddedilir.

EPİDEMİYOLOJİK VE İSTATİSTİKSEL DEĞERLENDİRME

İstatistiksel inceleme yapılan tüm retrospektif, prospektif ve deneysel araştırma makaleleri dergiye gönderilmeden önce biyoistatistik incelemelerin geçerliliği ve gücü açısından değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir. Editörler, gerekli gördükleri takdirde istatistiksel incelemeye ait ham verileri isteme haklarını saklı tutarlar

YAZIM DİLİ YÖNÜNDEN DEĞERLENDİRME

Derginin yayın dili Türkçe ve İngilizce' dir. Türkçe çalışmalarda Türk Dil Kurumu'nun Türkçe sözlüğü veya "https://sozluk.gov.tr/" adresinde yer alan çevrimiçi sözlük esas alınmalıdır. Varsa ilgili branş derneklerinin kendi terim sözlükleri de kullanılabilir. İngilizce çalışmalar ve İngilizce **özet**ler, dergiye gönderilmeden önce İngilizce dil uzmanı ve/veya ana dili İngilizce olan (native speaker) bir kişi tarafından değerlendirilmelidir. Çalışmayı, İngilizce yönünden değerlendiren kişi yazarlardan biri değil ise bu kişinin ismi makalenin sonunda bulunan "Teşekkür (Acknowledgement)" bölümünde belirtilmelidir. Dergimize yayımlanmak üzere gönderilen ve değerlendirme sonucunda yayıma kabul edilen çalışmalardaki yazım ve dilbilgisi hatalarının yazarlar tarafından düzeltilmesi gerekmekle beraber, gerek görüldüğü taktirde, çalışmanın bilimsel içeriğine dokunmadan, redaksiyon komitesi tarafından ayrıca düzeltilebilir. Yazarlar bu düzeltmeleri kabul etmiş sayılırlar.

MAKALE DEĞERLENDİRME SÜRECİ

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi'ne gönderilen çalışmalardan yayımlanabilir olduğu düşünülenler sıkı bir double-blind peer review sürecinden geçirilmektedir.
Dergiye yayımlanması dileğiyle gönderilen her çalışma, yazım kurallarına uygunluk açısından bir ön incelemeye tabi tutulmaktadır. Ön incelemeden geçen çalışmalara konusuna uygun olarak bir alan editörü belirlenir ve çalışma bu editöre yönlendirilir.
İlgili Alan editörü çalışmaya en az iki hakem atayarak çalışmanın bilimsel değerlendirme sürecini başlatır. Hakem seçimi çalışmanın konusuna göre yapılır.
Çalışmada yer alan yazarlarının kimlikleri, çalıştıkları kurumlar ve çalışmanın yapıldığı kurum/kurumlar hakemlerden gizli tutulmaktadır. Hakemler, dolduracakları "makale değerlendirme formu" ile alan editörlerine, çalışmanın bilimsel değeri, metodolojisi, istatistiksel değerlendirmelerin yerindeliği, verilerin tartışılmasının yeterliliği ve varılan sonuçların verilerle uyumlu olup olmadığı gibi konularda kendi bilimsel görüşlerini iletirler. İstatistik açısından daha detaylı incelenmesi gerektiği düşünülen çalışmalar istatistik uzmanlarına gönderilir. İlgili Alan editörü hakem değerlendirme formlarını da kapsayan genel bir değerlendirme ile kanaatini Dergi Editörler Kurulu'na sunar.
Hakem yorumları, değerlendirmeleri, eleştiri ve öneriler elektronik olarak çalışmanın sorumlu yazarına iletilir. Çalışmaların hakeme gönderilmesinde olduğu gibi bu süreçte de hakem kimlikleri yazara iletilmez ve gizli tutulur. Hakemler tarafından istenen düzeltmelerin yapılması için yazarlara geri gönderilen çalışmalarda Derginin daha önceden ilan ettiği süre içinde gerekli düzeltmelerin yapılarak, yeniden değerlendirmeye sunulması beklenir.
İstenen düzeltmelerin yapılması için geri gönderilen çalışmaların takip sorumluluğu yazarlara aittir. Hakem önerileri doğrultusunda düzeltilip derginin belirlediği süre içinde sisteme yüklenmeyen çalışmalar reddedilecektir.

YAYIN PLATFORMU

Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi, elektronik ortamda TÜBİTAK-DERGİPARK online bilimsel dergi yayıncılık platformu üzerinden yayımlanmaktadır.
Derginin web adresi: https://dergipark.org.tr/tr/pub/aeahtd
Dergiye çalışma gönderimi ve süreç takibi DERGİPARK sistemi üzerinden yürütülmektedir. Çalışma gönderebilmek için öncelikle DERGİPARK platformuna üye olunmalıdır.
Derginin yayın kurallarına https://dergipark.org.tr/tr/pub/aeahtd/writing-rules adresinden elektronik olarak ulaşılabilir.
Çalışmanın DERGİPARK' a yüklenmesini takiben, Derginin e-posta adresine de makalenin DERGİPARK ID numarası ve başlığını da içeren bir bilgilendirme e-postası gönderilmesi gerekmektedir.
İletişim için e posta adresi: ankarahastanesidergisi@gmail.com

YAYIN HAKKI

Yazarlar, "Yayın Hakları Formu" nu doldurup, çalışma ile birlikte göndermelidirler. Yayın Hakları Formu olmadan gönderilen çalışmalar değerlendirmeye alınmayacaktır.

YAZI ÇEŞİTLERİ

Dergiye yayımlanmak üzere gönderilecek yazı çeşitleri şu şekildedir.

EDİTÖRDEN:
Dergide yayımlanarak bilimsel çevrelere ulaştırılmasına gerek görülen editör, editör yardımcıları ya da davetli yazar (lar) tarafından kaleme alınan kısa yazılardır.

MAKALE YORUMU:
Yayımlanan orijinal araştırma makaleleri ile ilgili olarak araştırmanın yazarlarından olmayan, araştırma konusunun uzmanı farklı bir bilim insanı tarafından yapılan değerlendirmedir.

ÖZGÜN ÇALIŞMA:

Prospektif ya da retrospektif her türlü deneysel ve klinik çalışmalar yayımlanabilmektedir.
Özgün çalışmalar aşağıdaki bölümlerden oluşmalıdır:
Özet (**Abstract**): Türkçe ve İngilizce olarak ayrı ayrı en fazla 300 kelime içermelidir. Amaç (aim), gereç ve yöntem (material and method), bulgular (results), sonuç (conclusion) bölümlerinden oluşmalıdır.
Anahtar Kelimeler (**Keywords**): Türkçe ve İngilizce olmak üzere en az 3, en fazla 5 kelimeden oluşmalı, Medical Subject Headings (MeSH)' e uygun olarak verilmelidir.
Giriş (Introduction): çalışmanın kısa ve anlaşılır şekilde amacının açıklandığı kısımdır.

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Gereç ve Yöntem (Material and Method): Çalışmada kullanılan gereç, yöntem, istatistik değerlendirme vb nin detaylı şekilde açıklandığı kısımdır. Etik kurul onayı alınması gereken çalışmalar için etik kurul onayının alındığı kurum, tarih ve sayısı açık bir şekilde bu kısımda belirtilmelidir. Etik kurul onayı / bilgilendirilmiş onam formu olmayan yazılar değerlendirmeye alınmadan reddedilecektir.
Bulgular (Results): Çalışmada elde edilen bulguların detaylı şekilde açıklandığı kısımdır
Tartışma (Discussion): Elde edilen bulguların güncel literatür eşliğinde tartışıldığı kısımdır.
Sonuç (Conclusion): Elde edilen bulgular ve tartışma sonunda yazarların vardığı sonucun açıklandığı kısımdır.
Teşekkür (**Acknowledgements**): Çalışmaya katkıda bulunmakla beraber yazarlar içinde yer almayan kişilerle çalışmada katkısı olan kurum ve kuruluşların açıklandığı ve kendilerine teşekkür edilen kısımdır. Çalışmada herhangi bir kişi, kurum ya da kuruluştan maddi destek sağlanmış ise bu bölümde belirtilmelidir. Çalışmada herhangi bir çıkar çatışması olup olmadığı da bu bölümde açıklanmalıdır.
Kaynaklar (References): Makale içinde geçiş sırasına göre tüm kaynakların verildiği kısımdır.

DERLEME:

Dergi sadece davetli derleme kabul etmektedir. Editörler kurulu tarafından belirlenen tıbbi bir konuda en son tıbbi gelişmeleri de kapsayacak şekilde davet edilen yazar ya da yazarlar tarafından hazırlanır. Yazar / yazarların ilgili konu ile ilgili basılmış yayınlarının olması özellikle tercih nedenidir. Derleme makalelerinin yapısı aşağıdaki bölümlerden oluşmalıdır:
Özet (**Abstract**): Türkçe ve İngilizce olarak ayrı ayrı en fazla 250 kelime içermelidir. Derleme makalelerin özetlerinde bölüm olması zorunlu değildir.
Anahtar Kelimeler (**Keywords**): Türkçe ve İngilizce olmak üzere en az 3, en fazla 5 kelimeden oluşmalı, MeSH İndeksine uygun olarak verilmelidir.
Temel bölümler ardışık olarak numaralandırılmalıdır. Alt bölümler 1.1, 1.2 gibi alt başlıklarla belirtilmelidir. Derlemelerin başlıkları içerdikleri konuyu açıklayıcı olmalıdır.
Kaynaklar (References): Makale içinde geçiş sırasına göre tüm kaynakların verildiği kısımdır.

OLGU SUNUMU:

Nadir görülen, tanı ve tedavide farklılık ya da yenilik gösteren olguların sunulduğu makalelerdir. Yeterli sayıda fotoğraflarla ve şemalarla desteklenmiş olmalıdır. Olgu sunumlarının yapısı aşağıdaki gibi olmalıdır:
Özet (**Abstract**): Türkçe ve İngilizce olarak ayrı ayrı en fazla 150 kelime içermelidir. Bölümsüz olmalıdır.
Anahtar Kelimeler (**Keywords**): Türkçe ve İngilizce olmak üzere en az 3, en fazla 5 kelimeden oluşmalı, MeSH İndeksine uygun olarak verilmelidir.

Giriş (Introduction): Olgunun sunum gerekçesinin kısaca belirtildiği, tanı, tedavi, laboratuvar verilerinin detaylı olarak açıklandığı kısımdır.
Tartışma (Discussion): Olgunun tartışıldığı kısımdır.
Kaynaklar (References): En fazla 12 tane olmalıdır.
Olgu sunumunda sunulan hastalardan (18 yaşından küçükler için yasal vasisinden) "bilgilendirilmiş onam formu (informed consent)" alınmalı ve çalışma içeriğinde belirtilmelidir.

EDİTÖRE MEKTUP:

Son bir yıl içinde dergide yayımlanan makaleler ile ilgili olarak, okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 500 kelimelik yazılardır. Başlık ve özet bölümleri yoktur. Kaynak sayısı 5 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.

TIBBİ EĞİTİM:

Güncel tıbbi konularda okuyucuya mesaj veren son klinik ve laboratuvar uygulamaların da desteklediği bilimsel makalelerdir. Yapısı aşağıdaki gibi olmalıdır:
Özet (**Abstract**): Türkçe ve İngilizce olarak ayrı ayrı en fazla 150 kelime içermelidir.
Temel bölümler ardışık olarak numaralandırılmalıdır. Alt bölümler 1.1, 1.2 gibi alt başlıklarla belirtilmelidir.
Kaynaklar (References)

TIBBİ KİTAP DEĞERLENDİRMELERİ:

Güncel değeri olan ulusal veya uluslararası kabul görmüş kitapların değerlendirmeleridir.

YAZIM KURALLARI

Yazım kurallarına uygun olmayan çalışmalar değerlendirmeye alınmayacaktır. Derginin yazım kurallarına uygun taslak formlara https://dergipark.org.tr/tr/pub/aeahtd/writing-rules adresinden ya da Derginin basılı halinin son kısmından ulaşılabilir. Dergiye yayınlanması için gönderilen çalışmalarda aşağıdaki biçimsel esaslara uyulmalıdır.
Çalışma, PC uyumlu bilgisayarlarda Microsoft Word Programı ile "Times New Roman" yazı formatında, 11 punto büyüklüğünde ve 1,5 satır aralığı verilerek yazılmalıdır. Özgün araştırma çalışmalarının toplam uzunluğu 5000 kelimeyi geçmemelidir.
Çalışmalar, Derginin internet sitesinde "formlar" kısmında, basılı halinde son sayfalarında yer alan "çalışma gönderimi için son kontrol listesi" ne göre kontrol edildikten sonra sisteme yüklenmelidir.

Editöre Sunum Sayfası:

Çalışmadan ayrı bir sayfa olarak "editöre sunum" başlığı ile gönderilmelidir. Gönderilen çalışmanın kategorisi, daha önce başka bir dergiye gönderilmemiş olduğu, varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu kuruluşların yazarlarla olan ilişkileri, çalışma İngilizce ise İngilizce yönünden kontrolünün, araştırma makalesi ise biyoistatiksel kontrolünün yapıldığı belirtilmelidir. Örnek sayfaya Derginin internet sitesinde "formlar" kısmından ya da Derginin basılı halinin son sayfalarından ulaşılabilir.

Başlık Sayfası:

Çalışmadan ayrı bir sayfa olarak "başlık sayfası" başlığı ile gönderilmelidir. Makalenin başlığı (Türkçe ve İngilizce), tüm yazarların ad- soyadları, kurumları, ORCID numaraları, telefon numaraları, e-posta ve yazışma adresleri belirtilmelidir. Başlık sayfasında sorumlu (başlıca) yazar belirtilmelidir. Çalışma daha önce herhangi bir bilimsel toplantıda sunulmuş ise tebliğ yeri ve tarihi belirtilmelidir. Örnek sayfaya Derginin internet sitesinde "formlar" kısmından ya da Derginin basılı halinin son sayfalarından ulaşılabilir.

Özetler:

Yazı çeşitleri bölümünde belirtilen şekilde Türkçe ve İngilizce hazırlanarak, makale metni ile birlikte gönderilmelidir.

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Anahtar Kelimeler:
En az 3, en fazla 5 adet, Türkçe ve İngilizce yazılmalıdır. Anahtar kelimeler 'Medical Subject Headings (MeSH)' e uygun olarak verilmelidir (www.nlm.nih.gov/mesh/MBrowser.html).Anahtar kelimeler özet sayfasının en alt kısmında yer almalıdır.

Kısaltmalar:
Kelimenin ilk geçtiği yerde parantez içinde verilir ve tüm metin boyunca aynı kısaltmalar kullanılır. Uluslararası kabul görmüş kısaltmalar için "Bilimsel Yazım Kuralları" kaynağına başvurulabilir.
Özet kısmında kısaltma kullanılamaz.
Herkes tarafından genel kabul görmüş ve kısaltma hali ile kullanılan kelimeler (DNA, RNA vb.) açık hali verilmeden de kullanılabilir.

Şekil, Resim, Tablo ve Grafikler:
Şekil, resim, tablo ve grafikler çalışmada işleniş sırasına uygun olarak numara verilip, kaynaklar kısmından sonra her biri ayrı sayfada olmak üzere gönderilmelidir. Şekil, resim, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmelidir. Şekil ve resimler için altında, tablo ve grafikler için üstünde olacak şekilde açıklamaları eklenmelidir.
Çalışmanın Word dosyasına eklenecek şekil, resim, tablo ve grafik, 1 MB dan büyük ise, ayrı bir jpg dosyası olarak ta sisteme eklenebilir. Bu durumda, jpg dosyasına, çalışmanın Word şeklinin içinde geçen numaralara göre isim verilmelidir. Baskı kalitesinde standardın sağlanabilmesi için şekil, resim, tablo ya da grafiklerin en az 300 dpi çözünürlükte hazırlanarak sisteme eklenmesi gerekmektedir.
Şekil, resim, tablo ve grafiklerde kullanılan kısaltmalar ilgili görselin açıklamasında belirtilmelidir.
Şekil, resim ve grafikler, en fazla 16*20 cm, en az 8 cm büyüklükte olmalı ve büyütülerek ya da küçültülerek deforme edilmemiş olarak gönderilmelidir.
Daha önce başka bir yerde basılmış ya da yayımlanmış şekil, resim, tablo ve grafik kullanılmış ise yayın hakkı sahibinden yazılı izin alınmalıdır. Bu izin şekil, resim, tablo ve grafik açıklamasında belirtilmelidir.
Çalışma içerisinde ve eklerinde geçen uzunluk, yükseklik, hacim ölçümleri metrik ünitelerle (metre, kilogram ya da litre) ve bunların ast ve üst katları şeklinde verilmelidir. Sıcaklık ölçümleri derece santigrad (0 C), kan basıncı ölçümleri milimetre civa olarak (mmHg) belirtilmelidir. Laboratuvar değerleri International System of Units' e (SI) uygun olarak belirtilmelidir. SI karşılığı olmayan değerler metin içinde açıklanmak kaydıyla kullanılabilir.
Dört ve üzeri haneli sayılarda binlik basamaklar arasında boşluk bırakılmalıdır (Örnek: 1 000 000). Çift haneli sayılar, yazı içinde rakamla, tek haneli sayılar ise yazıyla verilmelidir. Ancak değerleri belirten ifadelerde tek haneler rakamla verilmelidir (Örnek: 1 cm). Yazı içinde ve tablolarda yüzdelik değerler virgülden sonra iki basamak, p değerleri virgülden sonra üç basamak olarak verilmelidir. Yazı, tablo ve şekillerde yer alan ondalık sayılar Türkçe yazılarda virgül ile İngilizce yazılarda nokta ile ayrılmalıdır.

Kaynaklar:
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Altı ve daha az yazar varsa: Özcan NN, Özçam G, Koşar P, Özcan A, Başar H, Kaymak Ç. Correlation of computed tomography, magnetic resonance imaging and clinical outcome in acute carbon monoxide poisoning. Braz J Anesthesiol. 2016; 66(5): 529-32. doi: 10.1016/j. bjane.2014.05.006

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Türkçe yayın: Sözen TH. Bruselloz. Topçu AW, Söyletir G, Doğanay M, editörler. İnfeksiyon Hastalıkları ve Mikrobiyoloji. Cilt 1. Sistemlere Göre İnfeksiyonlar.1. Baskı, İstanbul: Nobel Tıp Kitabevleri; 2002.s.636-42
Yabancı dilde yayınlanan kitaplar için: Philips SJ, Whistant JP. Hypertension and stroke. In: Laragh JH, Brenner BM; eds. Hypertension: Pathophysiology, diagnosis and management. 2nd ed. New York: Raven Pr;1995.p.466-78

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Türkçe yayın: Sümbüloğlu K, Sümbüloğlu V. Önemlilik testleri. Sümbüloğlu K, Sümbüloğlu V, editörler. Biyoistatistik. 8. Baskı. Ankara: Hatipoğlu Yayınevi;1998.s.76-156.
Yabancı dilde yayınlanan kitaplar için: Solcia E, Capella C, Kloppel G. Tumors of the exocrine pancreas. In: Solcia E, Capella C, Kloppel G, eds. Tumors of the Pancreas.2nd ed.Washington: Armed Forces Institute of Pathology. 1997.p.145-210.
Kongre bildirileri için:
Ozsoy MH, Koca G, Dincel E, et al."Surgery and adjuvant Yttrium–90 radiosynovectomy in the treatment of diffuse pigmented villonodular synovitis (DPVNS) of the knee". 5th Meeting of the European Federation of Associations of Orthopaedic Sports Traumatology (EFOST); 67pp, November 26–30, 2008, Antalya, Turkiye

Tezler için:
Karaca G. Kolon Anastomozlarında, Harmonic Scalpel, Bisturi ve Monopolar Elektrokoter Kullanılarak Yapılan Rezeksiyon Sonrası Anastomozlarda, Bu Araçların Anastomoz Sağlığı ve İyileşmesi Üzerine Etkileri. T.C. Sağlık Bakanlığı Ankara Eğitim ve Araştırma Hastanesi, Tıpta Uzmanlık Tezi, Ankara, Türkiye, 2010.

Elektronik ortamda yayımlanan makaleler için:
Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm. Erişim tarihi:25.09.2018 (Accessed September 25,2018)
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Musculoskeletal MRI Atlas. Available at: http://www.gla.med.va.gov/mriatlas/lndex.html. Erişim tarihi 25.09.2018. (Accessed September 25,2018.)

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More than six authors: Wells CR, Townsend JP, Pandey A, Moghadas SM, Krieger G, Singer B, et al. Optimal COVID-19 quarantine and testing strategies. Nat Commun. 2021;12(1):356. doi: 10.1038/s41467-020-20742-8. PMID: 33414470; PMCID: PMC7788536.
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