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Attitudes of first and sixth year medical faculty students towards sexual assault victims: a cross-sectional study

Birinci ve altıncı sınıf tıp fakültesi öğrencilerinin cinsel saldırı mağdurlarına karşı tutumları: kesitsel bir çalışma

Fatih Turan, Volkan Zeybek

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Abstract

Purpose: Sexual violence encompasses a range of coercive behaviors, from verbal harassment to forced penetration, and includes from social pressure and intimidation to the application of physical force. Sexual violence has numerous mental and physical health consequences on the individual. Although physicians recognize their crucial role in caring for sexual violence victims, various attitudes and behaviors hinder their fulfillment of these roles. In our study, the aim was to determine the attitudes of first and sixth year medical faculty students towards sexual assault victims and the socio-demographic factors influencing these attitudes.

Materials and methods: A total of 370 voluntary first- and sixth-year students enrolled in the 2021-2022 academic year at Manisa Celal Bayar University Faculty of Medicine were administered a questionnaire comprising socio-demographic characteristics, the "Social Attitudes Scale Towards Sexual Assault Victims", and questions assessing their knowledge of forensic medicine regarding sexual assault.

Results: In our study, it was found that 55.9% of the medical faculty students who participated were female, with an average age of 20.83±2.85 years. 56.5% were first-year students. 18.9% reported that they or someone close to them had been subjected to behavior considered as sexual assault. The average score of the participants in the Social Attitudes Scale towards Sexual Assault Victims was determined to be 95.29. It was statistically significant that women, those aged between 17-22, and those with a high monthly family income had higher average scores on the scale. It was found that 17.3% of the participants answered all six forensic medical questions correctly. The total scores of female students on the Social Attitudes Scale Towards Sexual Assault Victims and the scores of the behavior and thought sub-dimensions were found to be statistically significantly higher than those of male students.

Conclusion: It was determined that participants generally held a positive attitude towards sexual assault victims. Factors contributing to this positive attitude included higher levels of parental education, the influence of education received during medical school and preceding periods, and social environments.

Keywords: Sexual assault, medical faculty student, attitude, forensic medicine education.

Turan F, Zeybek V. Attitudes of first and sixth year medical faculty students towards sexual assault victims: a cross-sectional study. Pam Med J 2024;17:602-613.

Öz

Amaç: Cinsel şiddet, sözlü tacizden zorla penetrasyona kadar değişen eylemleri ve sosyal baskı ile sindirmeden fiziksel güç uygulanmasına kadar bir dizi zorlama türünü kapsar. Cinsel şiddetin kişi üzerinde çok sayıda zihinsel ve fiziksel sağlık sekelleri vardır. Hekimler, cinsel şiddet mağdurlarını bakımında kilit rolleri olduğunu tanımlasa da çeşitli tutum ve davranışları bu rolleri yerine getirmelerini engellemektedir. Çalışmamızda, tıp fakültesi birinci ve altıncı sınıf öğrencilerinin cinsel saldırı mağdurlarına karşı tutumları ve bu tutumları etkileyen sosyodemografik etkenlerin belirlenmesi amaçlanmıştır.

Gereç ve yöntem: Manisa Celal Bayar Üniversitesi Tıp Fakültesi'nde 2021-2022 akademik yılında öğrenim gören 370 gönüllü dönem 1 ve dönem 6 öğrencisine, sosyo-demografik özellikleri ile "Cinsel Saldırı Mağdurlarına Karşı Toplumsal Tutum Ölçeği" ve cinsel saldırı hususunda adli-tıbbi bilgilerini değerlendirmek amacıyla hazırlanan soruları içeren toplam 38 maddelik bir anket formu uygulandı.

Bulgular: Çalışmamıza katılan tıp fakültesi öğrencilerinin %55,9'unun kadın olduğu, ortalama yaşın 20,83±2,85 bulunduğu, %56,5'inin birinci dönem öğrencisi olduğu, %18,9'unun kendisinin veya yakın çevresinin suç sayılan cinsel amaçlı davranışa maruz kaldığını belirttiği, çalışmaya katılan öğrencilerin Cinsel Saldırı Mağdurlarına Karşı Toplumsal Tutum Ölçeği'ndeki ortalama puanının 95,29 saptandığı, kadınların, 17-22 yaş aralığında olanların ve aylık aile gelir durumu yüksek bulunanların ölçek toplam puan ortalamalarının istatistiksel olarak anlamlı şekilde yüksek olduğu, katılımcıların %17,3'ünün kendilerine yöneltilen 6 adli-tıbbi sorunun tamamına doğru cevap verdiği belirlenmiştir. Kadın öğrencilerin Cinsel Saldırı Mağdurlarına Karşı Toplumsal Tutum Ölçeği toplam puan ortalamaları ile davranış ve düşünce alt boyutu puan ortalamaları erkeklere göre istatistiksel olarak anlamlı şekilde yüksek bulunmuştur.

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Sonuç: Katılımcılarda, cinsel saldırı mağdurlarına karşı tutum olarak olumlu bir bakış açısının hâkim olduğu saptanmıştır. Bu olumlu bakış açısının oluşmasında; aile eğitim düzeylerinin yüksek olması, tıp fakültesi ve öncesindeki dönemlerde almış oldukları eğitim ile bulundukları sosyal ortamların etkilerinin olduğu anlaşılmıştır.

Anahtar kelimeler: Cinsel saldırı, tıp fakültesi öğrencisi, tutum, adli tıp eğitimi.

Turan F, Zeybek V. Birinci ve altıncı sınıf tıp fakültesi öğrencilerinin cinsel saldırı mağdurlarına karşı tutumları: kesitsel bir çalışma. Pam Tıp Derg 2024;17:602-613.

Introduction

Sexual violence covers a spectrum of coercive behaviors, extending from verbal abuse to compelled intercourse, and includes various forms of coercion such as intimidation through social pressure and the application of physical force. The concept of sexual assault involves engaging in behavior with sexual content, aimed at sexual gratification, using coercive methods such as physical force, threats, fear, deceit, and manipulation against a person who does not consent or whose consent is not recognized [1]. Despite regional differences, most studies indicate the widespread occurrence of sexual assault [2].

Sexual assault leads to myriad. psychological and physiological ramifications for the victim. Those who have endured sexual violence face increased susceptibility to conditions such as asthma, diabetes, irritable bowel syndrome, migraines, persistent discomfort, painful intercourse, sleep disturbances, and general deterioration in both mental and physical well-being [3]. Therefore, individuals who have experienced sexual violence are frequent users of various health services where primary care and specialist physicians, such as emergency departments, forensic medicine, urology, psychiatry, and gynecology clinics [4]. It is acknowledged that personal and societal barriers in physicians who has received education from a medical faculty that may hinder sexual violence victims from accessing necessary health services [5]. There is a range of myths and misunderstandings about sexual assault that can lead to inappropriate management. Increased awareness, early diagnosis, and appropriate management of sexual violence among all physicians from medical students to experienced physicians can be beneficial [6]. In Türkiye and many countries, there is limited coverage of sexual assault in medical school curricula. Additionally, there are few specialized services available for sexual violence victims [7, 8]. Due to the widespread nature of sexual violence and inadequate healthcare infrastructure, the World Health Organization has developed a series of guidelines outlining the services needed for survivors of sexual assault [9]. Survivors of sexual assault necessitate comprehensive, gender-sensitive healthcare provisions to address the physical and psychological aftermath of their ordeal and facilitate their recuperation from an exceedingly distressing and traumatic incident. Besides immediate medical assistance, the healthcare sector can serve as a pivotal referral hub for ancillary services that survivors might require subsequently, such as social welfare and legal aid. Such substantiation frequently proves indispensable in prosecuting cases of sexual violence [1, 9].

Although physicians acknowledge their pivotal roles in caring for sexual violence victims, various attitudes and behaviors hinder their fulfillment of these roles. There is limited research investigating what prevents physicians from addressing sexual violence with their patients. Particularly, there is a scarcity of studies in the literature that specifically explore physicians' perceptions of providing care to sexual violence victims [10]. In our study, it was aimed to determine the attitudes of first and sixth-year medical students towards sexual assault victims and the socio-demographic factors influencing these attitudes. Literature review during the study did not reveal any previous research on the attitudes of medical students towards sexual assault victims in our country. The fact that there has been no previous study in a similar setting in our country and the importance of increasing the positive attitudes of physicians towards sexual assault victims in the long term and guiding interventions for sexual assault victims is significant.

Materials and methods

During the academic year 2021-2022, there were a total of 453 first- and sixth-year students enrolled in Manisa Celal Bayar University Faculty of Medicine. A questionnaire consisting of socio-demographic characteristics, the "Social Attitudes Scale Towards Sexual Assault Victims" developed by Bostancı and colleagues, and questions assessing their knowledge of forensic medicine regarding sexual assault, totaling 38 items, was administered. A collective of 370 students (comprising 81.7% of the total) filled out the questionnaire during in-person sessions, and their responses were incorporated into the analysis.

The Social Attitudes Scale Towards Sexual Assault Victims consists of a total of 22 items, with 12 of them reverse-coded, using a 5-point Likert scale. The scale comprises three sub-dimensions: emotion, thought, and behavior. The assessment of the scale relies on computing the total score, with a higher score reflecting a more favorable outlook towards sexual assault survivors. The Social Attitudes Scale Towards Sexual Assault Victims form is presented in Table 1. The Cronbach's Alpha coefficient for internal consistency of the scale is noted to be 0.87, with the behavior sub-dimension at 0.87, the thought sub-dimension at 0.84, and the emotion sub-dimension at 0.15 [11].

In this study, descriptive statistics were evaluated. The reliability of the scales was checked. Confirmatory Factor Analysis, one of the Structural Equation Modeling (SEM) analyses, was used to demonstrate the validity of the scales. The AMOS 23 program was used.

The initial stage of the statistical analysis involved assessing the assumption of normality using the Shapiro-Wilk test. For comparing the means of two groups lacking normal distribution, the Mann-Whitney U test was employed. The Kruskal-Wallis test was utilized for comparing the means of three or more groups without normal distribution. Post hoc Bonferroni test was applied to pinpoint any differing groups. Spearman correlation was employed to gauge the relationship between continuous variables lacking normal distribution. Fisher's Exact test analyzes were applied to examine the relationships between the responses of the participating students to the forensic medical evaluation questions and the students' classes. The analyses were executed using IBM SPSS 25 software. $P<0.05$ was considered significant. Findings were tabulated, graphed, and discussed accordingly.

The research received ethical clearance from the Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee.

Results

Among the 370 students participating in the study, 209 (56.5%) were first-year students, and 161 (43.5%) were sixth-year students. Regarding gender distribution, 207 (55.9%) were female, and 163 (44.1%) were male. When examined by class level, it was found that among first-year students, 124 (59.3%) were female and 85 (40.7%) were male, while among sixth-year students, 83 (51.6%) were female and 78 (48.4%) were male. The mean age of the students was 20.83±2.86 years (minimum 17, maximum 30).

Reliability analyses were conducted for the Sexual Assault Victims' Social Attitudes Scale (SAVSAS) and its sub-dimensions. It was established that the behavior sub-dimension exhibited a high level of reliability, demonstrating a Cronbach's Alpha coefficient of 0.857. The thought sub-dimension was sufficiently reliable with Cronbach's Alpha coefficients of 0.672, while the emotion sub-dimension had coefficients of 0.642. Overall, the SAVSAS exhibited a high level of reliability with a Cronbach's Alpha coefficient of 0.836.

According to the results of the SEM, SAVSAS was significant at $p=0.000$ level, indicating its association with the 22-item scale structure. Improvements are being made in the model. During the refinement process, variables that compromised model fit were identified, and new covariances were introduced for those exhibiting high covariances among residual values (e12-e15; e10-e11; e9-e10; e5-e6; e1-e8). The initially calculated fit indices and the acceptable values for fit indices after refinement are outlined in Table 2. Upon scrutinizing the goodness-of-fit indices of the scale developed based on the results of the multi-factor confirmatory factor analysis, the fit indices were found to be as follows: RMSEA 0.058; GFI 0.897; AGFI 0.870; CFI 0.904; and a χ^2 value of 451.686 ($p=0.000$), indicating an acceptable level of fit (Figure 1).

Table 1. The social attitudes scale towards sexual assault victims

	Behavior-Emotion-Thought Evaluation	Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
1	I would help a person who has experienced sexual assault.					
2	I trust a person who has experienced sexual assault.					
3	I approach a person who has experienced sexual assault warmly.					
4	I would be friends with a person who has experienced sexual assault.					
5	I keep my distance from a person who has experienced sexual assault.					
6	I behave rudely towards a person who has experienced sexual assault.					
7	I don't hesitate to chat with a person who has experienced sexual assault.					
8	I share my secrets with a person who has experienced sexual assault.					
9	I advocate for the rights of a person who has experienced sexual assault.					
10	I treat a person who has experienced sexual assault kindly.					
11	I am compassionate towards a person who has experienced sexual assault.					
12	If a person who has experienced sexual assault was drunk when the assault happened, I consider this incident to be normal.					
13	The religious feelings of a person who has experienced sexual assault are weak.					
14	I think that the honor of a person who has experienced sexual assault has been tarnished.					
15	I consider it normal for a person who works in the sex industry to experience sexual assault.					
16	A person who has experienced sexual assault should not raise children.					
17	I believe that the individual who has been sexually assaulted deserved the assault.					
18	I consider it normal for a person who identifies as LGBT (lesbian, gay, bisexual, transgender, etc.) to experience sexual assault.					
19	I feel sorry for a person who has experienced sexual assault.					
20	I get stressed around a person who has experienced sexual assault.					
21	I believe that a person who has experienced sexual assault will be lacking in self-confidence.					
22	I feel depressed around a person who has experienced sexual assault.					

Table 2. Fit indices of the multi-factor confirmatory factor analysis for the SAVSAS

RMSEA	NFI	CFI	IFI	GFI	TLI	AGFI	CMIN	CMIN/df
0.084	0.739	0.794	0.796	0.842	0.769	0.806	744.788	3.612
RMSEA	**NFI**	**CFI**	**IFI**	**GFI**	**TLI**	**AGFI**	**CMIN**	**CMIN/df**
0.058	0.841	0.904	0.905	0.897	0.890	0.870	451.686	2.247

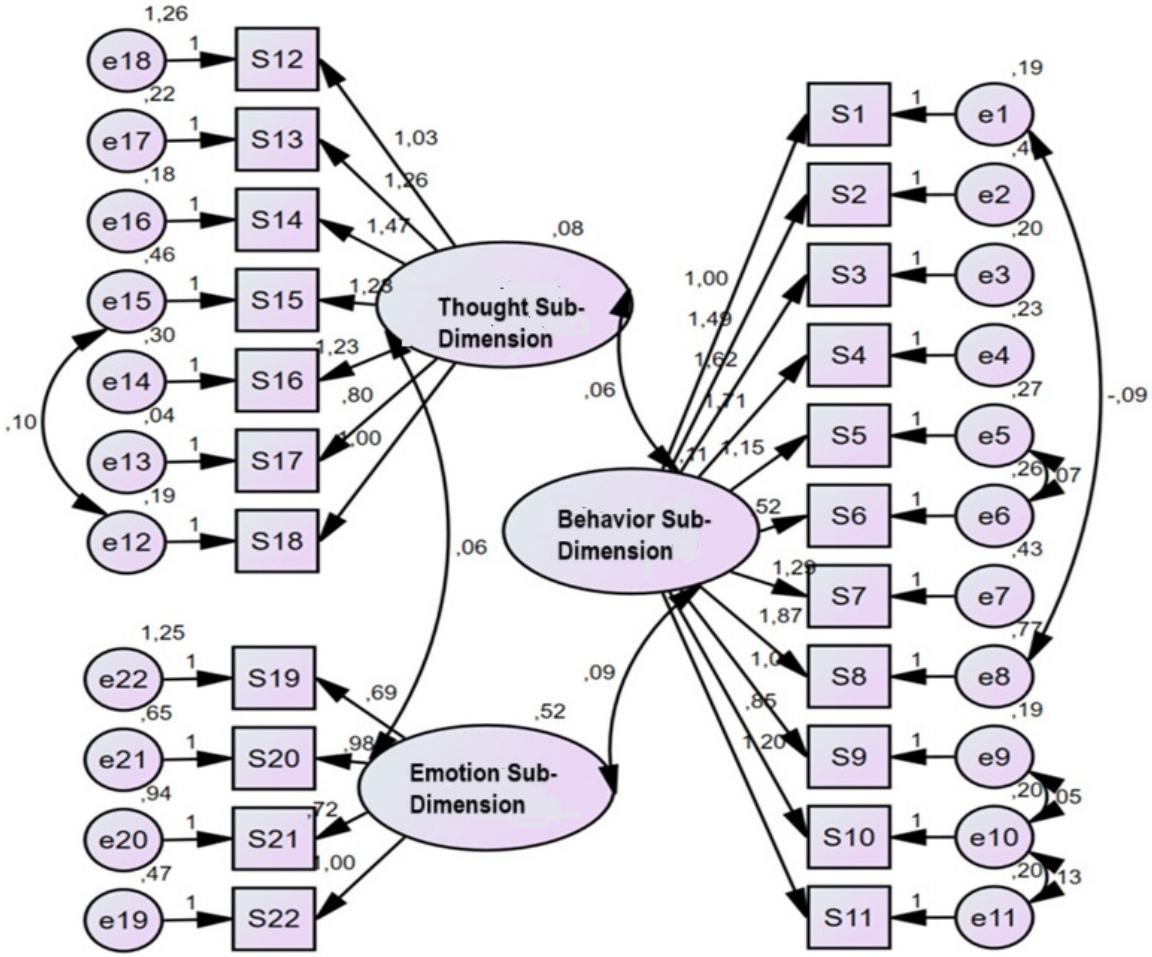

Figure 1. Multi-factor confirmatory analysis for the SAVSAS

The distribution of total scores obtained from the SAVSAS and its sub-dimensions by the participating students is examined in Table 3.

According to the analysis utilizing Spearman correlation, a statistically significant, positive, moderate-level relationship was uncovered between the behavior sub-dimension and the thought sub-dimension, yielding a correlation coefficient of 0.387. Likewise, a statistically significant, positive, moderate-level relationship was detected between the behavior sub-dimension and the emotion sub-dimension, producing a correlation coefficient of 0.323. Furthermore, a statistically significant, positive, high-level relationship was noted between the behavior sub-dimension and the total scale score, exhibiting a correlation coefficient of 0.861. The relationship between the SAVSAS and its sub-dimensions is examined in Table 4.

Upon testing the hypotheses to investigate the differences in total scores obtained from the SAVSAS according to the demographic characteristics of the participating students, there was a difference in the rank order means of scale total scores among age groups (p<0.05). Specifically, individuals in the age group of 17-22 had higher means compared to those in the age group of 23-30. And, there was a difference in the rank order means of scale total scores between genders (p<0.05), with females having higher means than males. Furthermore, a difference was found in the rank order means of scale total scores based on monthly family income (p<0.05). According to the Bonferroni test, statistically significant differences were found between the groups with a monthly family income of 9000 TL and above compared to those with incomes of 0-3000 TL and 3000-9000 TL (p=0.042 and p=0.012, respectively). It was determined that individuals with a monthly family income of 9000 TL and above had higher means compared to those with incomes of 0-3000 TL and 3000-9000 TL. Additionally, the group with a monthly family income of 9000 TL and above was found to be the differentiating segment (Table 5).

Assumptions were assessed for testing hypotheses regarding differences in total scores derived from the Behavior Sub-dimension of the SAVSAS across demographic characteristics of participating students. Specifically, females exhibited higher means compared to males.

Table 3. Descriptive statistics for the SAVSAS and its sub-dimensions

Scale and Sub-dimensions	n	Minimum	Maximum	Mean	Standard Deviation
Behavior Sub-dimension	370	27.00	55.00	48.98	4.98
Thought Sub-Dimension	370	20.00	35.00	32.83	2.82
Emotion Sub-Dimension	370	5.00	20.00	13.48	3.05
Scale Total	370	60.00	110.00	95.29	8.24

Table 4. The relationship between the SAVSAS and its sub-dimensions

		Thought Sub-Dimension	Emotion Sub-Dimension	Scale Total
Behavior Sub-Dimension	Rho	0.387	0.323	0.861
	p	0.000*	0.000*	0.000*
Thought Sub-Dimension	Rho		0.221	0.625
	p		0.000*	0.000*
Emotion Sub-Dimension	Rho			0.653
	p			0.000*

*p<0.05

Table 5. Comparison of the total scores of the SAVSAS according to the demographic characteristics of the participating students

		n	Mean	Standard Deviation	Min	Max	Test Values	*p*
Age	17-22	216	95.90	8.52	60.00	110.00	U:14370.5	0.026*
	23-30	154	94.44	7.77	62.00	110.00		
Gender	Female	207	97.32	6.62	78.00	110.00	U: 11963.0	0.000*
	Male	163	92.71	9.32	60.00	108.00		
Class	First-Year	209	95.72	8.52	60.00	110.00	U:15175.5	0.106
	Sixth-Year	161	94.74	7.85	62.00	110.00		
Mother's education level	Illiterate	4	92.25	12.97	77.00	104.00	kw: 6.728	0.242
	Primary school graduate	65	93.47	8.64	62.00	108.00		
	Secondary school graduate	27	94.29	7.67	79.00	106.00		
	High school graduate	87	95.01	7.71	68.00	110.00		
	Bachelor's degree	160	96.44	8.10	60.00	110.00		
	Master's degree	27	95.25	9.15	79.00	109.00		
Father's education level	Primary school graduate	33	93.54	8.66	76.00	108.00	kw: 6.060	0.300
	Secondary school graduate	22	93.77	10.34	60.00	104.00		
	High school graduate	74	95.13	7.89	68.00	110.00		
	Bachelor's degree	196	95.29	7.92	62.00	110.00		
	Master's degree	44	97.45	8.56	75.00	109.00		
Number of siblings	Only child	50	95.30	8.05	78.00	110.00	kw: 1.052	0.591
	2 siblings	204	95.82	7.80	68.00	110.00		
	3 siblings and more	116	94.36	9.01	60.00	108.00		
Where you lived until you went to university	Urban	348	95.35	8.18	60.00	110.00	U: 3709.5	0.807
	Rural	22	94.40	9.17	76.00	108.00		
Income status	0-3000 TL	41	91.97	11.29	60.00	105.00	kw:10.645	0.005*
	3000-9000 TL	181	94.62	7.50	75.00	110.00		
	Above 9000 TL	148	97.03	7.75	75.00	110.00		
Where you live	With family	76	94.92	7.83	76.00	110.00	U: 3430.5	0.450
	Dormitory/Apartment/ Student House etc.	294	95.39	8.35	60.00	110.00		
Have you or anyone close to you ever been subjected to criminal sexual conduct?	Yes	70	97.47	7.76	60.00	110.00	U:10487.0	0.409
	No	300	94.79	8.27	62.00	110.00		

*p<0.05, U: Mann Whitney U test or, kw: kruskal Wallis variance analysis

A statistically significant difference was found in the rank order means of the thought sub-dimension total scores according to the father's education level (p<0.05). According to the Bonferroni test, differences were found between the groups of primary school graduates and graduates of middle school, high school, undergraduate, and graduate school (p=0.006, p=0.047, p=0.009, and p=0.004, respectively). The means of graduates of middle school, high school, undergraduate, and graduate school were higher than the mean of primary school graduates. Moreover, it was determined that the group of primary school graduates was the differentiating segment.

After verifying the assumptions for testing hypotheses regarding differences in total scores derived from the Emotion sub-dimension of the SAVSAS across demographic characteristics of participating students, several significant findings emerged. Firstly, a difference in the rank order means of the emotion sub-dimension total scores was detected based on age groups (p<0.05). Specifically, individuals aged 17-22 exhibited higher means compared to those aged 23-30. Secondly, a statistically significant difference in the rank order means of the emotion sub-dimension total scores was observed concerning the academic terms of the students (p<0.05). Notably, the mean of students in term 1 surpassed that of students in term 6. Additionally, difference was found in the rank order means of the emotion sub-dimension total scores based on income level (p<0.05). Differences were seen between the groups with an income of 9000 TL and above and those with incomes of 0-3000 TL and 3000-9000 TL (p=0.035 and p=0.005, respectively). It was established that the mean of individuals with an income of 9000 TL and above surpassed the means of those with incomes of 0-3000 TL and 3000-9000 TL, with the group earning 9000 TL and above being the distinguishing segment.
The relationships between the classes of the participating students and their responses to the forensic medical evaluation questions are shown in Table 6.

Table 6. The relationship and cross-table between the responses of the participating students to the forensic medical evaluation questions and the students' classes

			Class			
			First-Year	Sixth-Year	Test Values	*p*
1. It is necessary for individuals who have been subjected to sexual assault to be reported to the judicial authorities by the healthcare institution they have applied to after the incident.	Right	n	184	161	24.660**	0.000*
		%	53.3	46.7		
		%S	88.0	100.0		
	Wrong	n	4	0		
		%	100.0	0.0		
		%S	1.9	0.0		
	No idea	n	21	0		
		%	100.0	0.0		
		%S	10.1	0.0		
2. Individuals who have suffered sexual assault must present a letter of authorization from the judiciary for examination purposes.	Right	n	67	114	60.499**	0.000*
		%	37.0	63.0		
		%S	32.1	70.8		
	Wrong	n	31	20		
		%	60.8	39.2		
		%S	14.8	12.4		
	No idea	n	111	27		
		%	80.4	19.6		
		%S	53.1	16.8		

Table 6. The relationship and cross-table between the responses of the participating students to the forensic medical evaluation questions and the students' classes (continued)

			Class		Test Values	*p*
			First-Year	Sixth-Year		
3. Only a Forensic Medicine Specialist conducts the examination of individuals who have been subjected to sexual assault.	Right	n	30	11	115.072**	0.000*
		%	73.2	26.8		
		%S	14.3	6.8		
	Wrong	n	58	134		
		%	30.2	69.8		
		%S	27.8	83.2		
	No idea	n	121	16		
		%	88.3	11.7		
		%S	57.9	10		
4. Even if individuals who have been sexually assaulted do not give consent for the examination, necessary examinations are conducted.	Right	n	28	14	15.322**	0.000*
		%	66.7	33.3		
		%S	13.4	8.7		
	Wrong	n	106	114		
		%	48.2	51.8		
		%S	50.7	70.8		
	No idea	n	75	33		
		%	69.4	30.6		
		%S	35.9	20.5		
5. Individuals who have been sexually assaulted undergo genital examination initially.	Right	n	23	11	105.255**	0.000*
		%	67.6	32.4		
		%S	11.0	6.8		
	Wrong	n	53	126		
		%	29.6	70.4		
		%S	25.4	78.3		
	No idea	n	133	24		
		%	84.7	15.3		
		%S	63.6	14.9		
6. The Turkish Penal Code contains separate articles regarding harassment, indecent assault, sexual abuse, and sexual assault.	Right	n	96	130	47.429**	0.000*
		%	42.5	57.5		
		%S	45.9	80.7		
	Wrong	n	7	4		
		%	63.6	36.4		
		%S	3.3	2.5		
	No idea	n	106	27		
		%	79.7	20.3		
		%S	50.8	16.8		

*p<0.05, **S: Percentage of the class itself, **Fisher's Exact test

The hypotheses testing the differences in total scores of the Social Attitudes Scale towards Sexual Assault Victims and its subscales, based on the number of correct responses to the forensic medical evaluation questions provided by the participating students, were examined after checking the assumptions. Following the analysis, a statistically noteworthy variance was evident in the mean total scores of the thought subscale in relation to the number of correct responses (p<0.05). Subsequent Bonferroni examination delineated a statistically significant contrast between the mean scores of students without any correct answers and those with five correct responses (p=0.042).

Discussion

When looking at the total scores obtained by the participating students based on their responses to the Social Attitudes Scale towards Sexual Assault Victims, it is observed that the lowest score obtained was 60, while the highest score was 110. The mean score was determined to be 95.29. Given that the scale ranges from a minimum of 22 to a maximum of 110, where higher scores reflect a more favorable attitude, it is evident that the participating students attained a notably high average score. This underscores a prevailing positive disposition towards sexual assault victims among the study's participants. Other studies examining the attitudes of medical students and physicians working in emergency departments towards sexual assault victims have also generally shown positive attitudes [12-14].

In our study, the total score averages of female students participating in the study on the Social Attitudes Scale towards Sexual Assault Victims, as well as the scores for the behavior and thought sub-dimensions, were found higher compared to males. Similar studies conducted in Türkiye and other countries have also indicated that women tend to exhibit more positive attitudes in this regard [13, 15, 16].

In a research endeavor conducted in Spain, it was noted that participants demonstrated increasingly less favorable attitudes towards sexual assault victims with advancing age [17]. Another study suggested that as age increases, negative attitudes towards sexual assault victims may arise due to traditional gender roles [18]. In our study, the data we obtained showed that the 17-22 age group had a more positive outlook compared to the 23-30 age group, which is consistent with the literature. It was concluded that as age increases, there may be a decrease in tolerance towards attitudes that could be considered towards sexual assault victims.

In a study conducted by Yalçın, it was noted that a positive attitude towards sexual assault victims became increasingly predominant as the level of education increased [19]. Similarly, other studies in the literature have indicated a decrease in blaming attitudes as the level of education increases [17, 20]. In our study, as the family education levels of the participating students increased, a positive outlook towards sexual assault victims was observed. This result corresponds with the existing body of literature, which suggests that the positive attitudes increasing in parallel with education levels also occur when there is an increase in participants' family education levels. Hence, it can be deduced that there is a connection between the increase in students' academic achievements and the advancement of their attitudes towards a more optimistic outlook.

A study on gender attitudes conducted in Edirne revealed that students native to urban locales had the most egalitarian attitudes towards gender, while those born and raised in rural areas tended to have more traditional attitudes [21]. Similarly, in other studies involving medical students, it was found who spent the longest time in rural areas had more traditional gender attitudes, whereas those who lived in metropolitan areas had more egalitarian attitudes [22, 23]. While no analogous studies are available in the existing literature, the outcomes concerning gender attitudes in our study resonate with the findings. They indicate that students hailing from urban locales harbor more favorable attitudes towards sexual assault victims, aligning with the egalitarian viewpoint prevalent in the literature. This is probably due to the easier access to education and social opportunities in urban areas, which fosters a more diverse and inclusive environment.

In a study by Yalçın, it was found that individuals with lower income levels tended to exhibit higher levels of victim blaming towards sexual assault victims compared to those with higher incomes [19]. This finding is supported

by another study as well [24]. The proportional increase in positive attitudes towards sexual assault victims among students in our study according to their income levels is consistent with the literature. Nevertheless, it is concluded that besides an individual's own income status, family income status also contributes to similar outcomes.

Pre-graduation forensic medicine training has been reported to make medical students feel more competent in evaluating cases of sexual abuse/assault, writing forensic reports, and conducting autopsies [25, 26]. According to the right answers to the forensic medical assessment questions, it was observed that sixth-year students statistically significantly outperformed first-year students. Furthermore, a statistically significant disparity was observed in the total scores of the thought dimension based on the number of correct answers. It is believed that there is a mutual interaction in the emergence of this situation, and that a positive attitude towards the attitude and the curiosity and ongoing education level that will arise will increase the extent of knowledge.

Of the participating students, 70 (18.9%) answered 'Yes' to the question 'Have you or someone close to you experienced any action considered as a sexual offense?' These personal experience rates remind us not only to prepare our students effectively to work with those who have experienced sexual violence but also to be aware that there are many individuals among our student population who have experienced sexual violence.

In conclusion, it is believed that the formation of a positive attitude towards sexual assault victims is influenced by the high level of family education, the education received during medical school and prior periods, as well as the social environments in which individuals are situated. Overall, the ongoing problem arises from the negative attitudes experienced by sexual assault victims following their trauma. It is believed that by instilling a positive outlook towards sexual assault victims among medical students, coupled with an increase in their forensic medical knowledge, they will be better equipped to achieve more knowledgeable and accurate results in their careers.

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

References

1. Garcia Moreno C, Guedes A, Knerr W. Understanding and addressing violence against women. Geneva; 2012. Available at: https://www.who.int/publications/i/item/WHO-RHR-12.43. Accessed February 14, 2024
2. Dworkin ER, Krahé B, Zinzow H. The global prevalence of sexual assault: a systematic review of ınternational research since 2010. Psychol Violence 2021;11:497-508. https://doi.org/10.1037/VIO0000374
3. Muehlenhard CL, Peterson ZD, Humphreys TP, Jozkowski KN. Evaluating the one-in-five statistic: women's risk of sexual assault while in college. The Journal of Sex Research 2017;54:549-576. https://doi.org/10.1080/00224499.2017.1295014
4. Koss MP, Woodruff WJ, Koss PG. Relation of criminal victimization to health perceptions among women medical patients. J Consult Clin Psychol 1990;58:147-152. https://doi.org/10.1037//0022-006X.58.2.147
5. Cannon LM, Sheridan Fulton EC, et al. Understanding the healthcare provider response to sexual violence in Ghana: a situational analysis. PLoS One 2020;15:e0231644. https://doi.org/10.1371/JOURNAL.PONE.0231644
6. Williams L, Forster G, Petrak J. Rape attitudes amongst British medical students. Med Educ 1999;33:24-27. https://doi.org/10.1046/J.1365-2923.1999.00296.X
7. Varol ZS, Çiçeklioğlu M, Şafak T. Bir tıp fakültesi birinci sınıf öğrencilerinde toplumsal cinsiyet algı düzeyi ve ilişkili faktörlerin değerlendirilmesi. Ege Tıp Dergisi 2016;55:122-128. https://doi.org/10.19161/ETD.344208
8. Dielissen P, Verdonk P, Waard MW de, Bottema B, Lagro Janssen T. The effect of gender medicine education in GP training: a prospective cohort study. Perspect Med Educ 2014;3:343-356. https://doi.org/10.1007/S40037-014-0122-3/TABLES/5
9. World Health Organization. Guidelines for medico-legal care for victims of sexual violence. Geneva; 2003. Available at: https://www.un.org/sexualviolenceinconflict/wp-content/uploads/2019/05/report/guidelines-for-medico-legal-care-for-victims-of-sexual-violence/924154628X.pdf. Accessed October 09, 2023
10. Amin P, Buranosky R, Chang JC. Physicians' perceived roles, as well as barriers, toward caring for women sex assault survivors. Women's Health Issues 2017;27:43-49. https://doi.org/10.1016/J.WHI.2016.10.002
11. Bostancı E, Kalender B, Akyol A, Suatoğlu B, Temizkan O, Gökçe B. Cinsel saldırı mağdurlarına karşı toplumsal tutum ölçeği (pilot çalışma). Paper presented at: IV. Sosyal Psikoloji Kongresi, İzmir, Türkiye, 2022.

12. Perenc L, Podgórska Bednarz J, Guzik A, Drużbicki M. Selected correlates of attitudes towards rape victims among polish medical students. Int J Environ Res Public Health 2022;19:5896. https://doi.org/10.3390/IJERPH19105896
13. Anderson I, Quinn A. Gender differences in medical students' attitudes towards male and female rape victims. Psychology, Health & Medicine 2008;14:105-110. https://doi.org/10.1080/13548500802241928
14. Wong AYS, Wong TW, Lau PF, Lau CC. Attitude towards rape among doctors working in the emergency department. Eur J Emerg Med 2002;9:123-126. https://doi.org/10.1097/MEJ.0000000000000907
15. Belma ZG, Yavuz MF, Yavuz MS. Turkish university students' attitudes toward rape. Sex Roles 2003;49:653-661.
16. Marsh F, Wager NM. Restorative justice in cases of sexual violence: exploring the views of the public and survivors. Probation Journal 2015;62:336-356. https://doi.org/10.1177/0264550515619571
17. Sirvent Garcia del Valle E. Acceptability of sexual violence against women in Spain: demographic, behavioral, and attitudinal correlates. Violence Against Women 2020;26:1080-1100. https://doi.org/10.1177/1077801219854536
18. Anderson KB, Cooper H, Okamura L. Individual differences and attitudes toward rape: a meta-analytic review. Pers Soc Psychol Bull 1997;23:295-315. https://doi.org/10.1177/0146167297233008
19. Yalçın MA. Cinsel Saldırı Suçu Mağduru Kadınlara Karşı Toplumsal Tutumlar. Yayınlanmamış Yüksek Lisans Tezi. İstanbul Üniversitesi, Adli Tıp Enstitüsü, Sosyal Bilimler Ana Bilim Dalı, İstanbul, 2016.
20. Grubb AR, Harrower J. Understanding attribution of blame in cases of rape: an analysis of participant gender, type of rape and perceived similarity to the victim. Journal of Sexual Aggression 2009;15:63-81. https://doi.org/10.1080/13552600802641649
21. Baş D. Trakya üniversitesinin merkez ilçede eğitim gören öğrencilerinin şiddet eğilimleri ve toplumsal cinsiyete ilişkin tutumları. Yayınlanmamış Uzmanlık Tezi. Trakya Üniversitesi Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, Edirne, 2020.
22. Akkaya B, Çelik Seyitoğlu D, Güneş G, Çöl M. Tıp öğrencilerinin toplumsal cinsiyet rolleriyle ilgili tutumları: iki üniversite karşılaştırması. 3 Uluslararası 21 Ulusal Halk Sağlığı Kongresi Kitabı, Antalya, 2019:717-723.
23. Zeybek V, Kurşun M. Tıp fakültesi öğrencilerinin toplumsal cinsiyet rollerine ilişkin tutumları. Pam Tıp Derg 2019;12:225-233. https://doi.org/10.31362/PATD.468353
24. Nagel B, Matsuo H, McIntyre KP, Morrison N. Attitudes toward victims of rape. J Interpers Violence 2005;20:725-737. https://doi.org/10.1177/0886260505276072
25. Zeybek V, Acar K, Kurtuluş Dereli A, Kara CO. Yapılandırılmış senaryo eşliğinde maket üzerinde adli ölü muayenesi eğitiminin değerlendirilmesi. Adli Tıp Bülteni 2018;23:6-12. https://doi.org/10.17986/blm.2018136913
26. Salaçin S, Çekin N, Özdemir MH, Kalkan Ş. Mezuniyet öncesi adli tıp eğitimi almış öğrencilere yönelik bir anket çalışması. The Bulletin of Legal Medicine 1997;2:21-24. https://doi.org/10.17986/blm.199721199

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Author contribution

This study is a part of the first author's medical dissertation. F.T. developed the theory and arranged/ edited the material and method section, has done the evaluation of the data in the results and discussion sections. V.Z. constructed the main idea and hypothesis of the study, provided editorial advice. All authors reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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A combined treatment strategy of Legg-Calve-Perthes disease with BEST quartet

Legg-Calve-Perthes hastalığının BEST dörtlüsü ile bir kombine tedavi stratejisi

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Abstract

Purpose: The main pathology of Legg-Calvé-Perthes Disease (LCPD) is the disruption of blood flow of the femoral head resulting ischemic necrosis which leads hip joint incongruency. The most frequent methods in the treatment are the methods improving the containment of the femoral head. There are limited studies in the literature addressing the treatment of necrosis using methods such as epiphyseal drilling or distraction osteogenesis. Our study aimed to investigate the mid-long-term outcomes of LCPD patients treated with the BEST method, which aims to improve congruency and containment simultaneously.

Materials and methods: LCPD patients (23 male, 1 female) who were treated with (B)leeding the epiphysis by drilling, (E)vacuation of the joint synovitis, contained with (S)alter's Osteotomy, and distracted with skin (T)raction investigated retrospectively. Only patients who reached skeletal maturity at latest follow-up were included in the study. Patients' final radiographs were classified according to the Stulberg classification, Mose classification, and Tönnis osteoarthritis classification.

Results: The mean follow-up of the patients was 10.44±1.35 (8.5-13) years, and the mean age at the last follow-up was 17.71±1.73 (15.25-20.83) years. According to the Stulberg classification, 11 (45.8%) of the patients had a Class-I hip; 6 (25%) a Class-II hips; 3 (12.5%) a class-III hips, 4 (16.7%) a class-IV hips. According to the Mose classification, 12 (50%) of the patients had good results; 5 (20.8%) had fair results; 7 (29.1%) had poor results.

Conclusion: BEST treatment method for LCPD is a combined procedure which addresses to all pathologies of disease at the same time. This combined treatment protocol may be preferred for severely affected LCPD cases who with subluxation especially in higher lateral pillar class that are prone to nonspherical incongruency.

Keywords: Legg-Calve-Perthes disease, Salter's osteotomy, femoral head osteonecrosis.

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Öz

Amaç: Legg-Calvé-Perthes hastalığının (LCPH) temel patolojisi, femur başındaki kan akışının bozulması sonucunda kalça ekleminde uyumsuzluğa yol açan iskemik doku nekrozudur. Tedavide sık uygulanan yöntemler femur başının kapsamasını artıran yöntemlerdir. Epifizin delinmesi veya distraksiyon osteogenezi gibi nekroz tedavisine değinen nadir yayın vardır. Çalışmamızın amacı, uyum ve kapsamayı aynı anda geliştirmeyi amaçlayan BEST yöntemiyle tedavi ettiğimiz LCPH hastalarının orta-uzun dönem sonuçlarını araştırmaktı.

Gereç ve yöntem: LCPH tanısı ile 24 (23 erkek, 1 kadın) hastaya uygulanan epifizi delme yoluyla kanlandırma (B), eklem ponksiyonu ile fazla eklem sıvısının boşaltılması (E), Salter Osteotomisi (S) ile femur başı kapsamasının artırılması ve cilt (T)raksiyonu ile eklemdeki basıncın azaltılması yöntemlerinin birlikte kullanıldığı kombine yöntem araştırıldı. Çalışmaya sadece iskelet olgunluğuna ulaşan hastalar dahil edildi. Hastaların son radyografileri Stulberg sınıflaması, Mose sınıflaması ve Tönnis osteoartrit sınıflamasına göre sınıflandırıldı.

Bulgular: Hastaların ortalama takip süresi 10,44±1,35 (8,5-13) yıl, son takip yaş ortalaması ise 17,71±1,73 (15,25-20,83) yıldı. Stulberg sınıflamasına göre hastaların 11'inde (%45,8) sınıf I kalça, 6 hastada (%25) sınıf II kalça, 3 hastada (%12,5) sınıf III kalça, 4 hastada (%16,7) sınıf IV kalça görüldü. Mose sınıflamasına göre hastaların 12'sinde (%50) iyi sonuç, 5'inde (%20,8) orta sonuç, 7'sinde (%29,1) kötü sonuç elde edildi.

Sonuç: LCPH için BEST tedavi yöntemi, hastalığın tüm patolojilerine aynı anda hitap eden kombine bir prosedürdür. Bu kombine tedavi protokolü, özellikle asferik uyumsuzluğa eğilimli, yüksek lateral pillar sınıfında, subluksasyonlu ve ciddi şekilde etkilenmiş LCPH vakalarında tercih edilebilir.

Anahtar kelimeler: Legg-Calve-Perthes hastalığı, Salter osteotomisi, femur başı osteonekrozu.

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Introduction

The main pathological event of Legg-Calvé-Perthes Disease (LCPD) is the disruption of 3 blood flow of the femoral head resulting in ischemic tissue necrosis [1]. After a century from the first description, a widely accepted treatment algorithm could not be established yet. Improving the containment (surgically or conservatively) is a frequently used method to reduce the local loads on the femoral head to prevent deformity and obtain a spherical and congruent joint using the molding effect of the acetabulum during the healing period [2-14].

Recently, publications have reported that drilling can be used in LCPD, which is also used in adult osteonecrosis of the femoral head [15-18]. However, the drawback of drilling is that it may cause physeal damage, resulting in premature physeal closure and consequent deterioration in growth. However, Park et al. [19] observed premature physeal closure in 21 (77.8%) of 27 unilateral LCPD patients treated conservatively and stated that premature physeal closure was associated with the Herring class of the disease (more in Herring B/C and 14 C), but not the Stulberg class.

It may be possible to increase the success rate by combining various methods in treating LCPD. Thus, drilling of the necrotic area (to reduce intraosseous pressure and enhance revascularization), evacuation of hip joint excess fluid (to reduce intra-articular pressure), Salter's osteotomy (to increase containment), and skin traction (to reduce intra-articular pressure and to obtain distraction osteogenesis) can be performed together. We abbreviate this combination as BEST. B is bleeding by drilling, E is the evacuation of the excessive joint fluid, S is Salter's osteotomy and T is skin traction. The present study aimed to investigate the mid-long-term outcomes of patients with LCPD that we treated with the BEST method retrospectively.

Material and methods

Our indications for BEST treatment in LCPD are; (1) symptoms started after the age of six (2) severe involvement of the epiphysis of the femoral head (Catterall 3-4 or lateral pillar B, B/C, C) (3) subluxation of the femoral head (regardless of the involvement of the femoral head). These patients got indications whenever they showed these criteria (first admission or at follow-ups).

BEST procedure

All patients were operated on and treated by a single physician (ET). After routine preparation, adductor tenotomy was performed with a mini-incision in all cases. The necrotic area in the femoral head was drilled by 1.5 mm smooth Kirschner wire from the lateral trochanteric region percutaneously under fluoroscopy (BLEEDING) (Figure 1). Drilling was administered twice or three times depending on the size of the necrosis from the same entry points but in different directions. An anterior iliofemoral approach was used for Salter's innominate osteotomy. Hip joint fluid evacuation was performed before osteotomy by a needle (EVACUATION) (Figure 1). The classical Salter's innominate osteotomy was administered using a Gigli saw (SALTER) (Figure 1). No rigid immobilization method was used, including a spica cast. Skin traction was applied to the extremity and 0.5 kg weight was suspended from the distal to ensure continuous traction on the joint (TRACTION) (Figure 1). Skin traction was discontinued for the 4th week (the first three days in the hospital, then at home). At the end of four weeks, skin traction was terminated and passive joint movements were started. Mobilization by partial weight-bearing with crutches and active ROM exercises was started at the end of the 8th week. Full weight-bearing was allowed at the end of the 12th week. After the 12th week, the patients were followed-up at 3-month intervals in the first year and then at 6-month intervals until the end of the healing period. After mobilization, parents were informed about activity restrictions and not being interested in heavy sports.

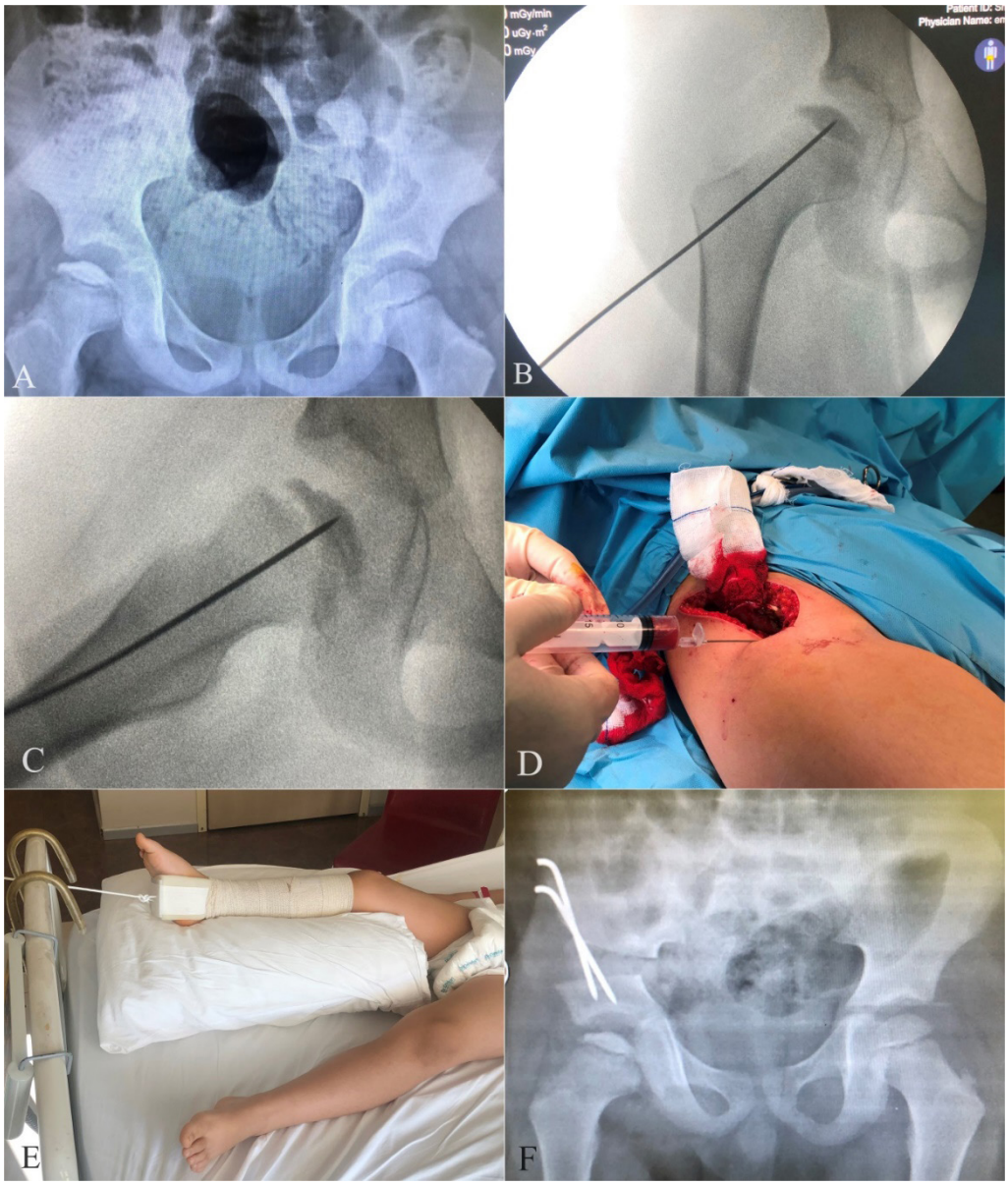

Figure 1. A seventy-three months of age boy with LCPD in his right hip (A). The patient who was decided to apply BEST treatment; The epiphysis of the femoral head was drilled with a 1.5mm Kirschener wire and its blood supply was increased (Bleeding) (B, C). Excess and harmful fluid in the hip joint is evacuated (Evacuation) (D). After the Salter innominate osteotomy was performed, the patient's right lower extremity was placed under skin traction (Traction) (E). Post-operative radiograph of the patient (Salter Innominate osteotomy) (F)
Note the increased the containment of femoral head by acetabulum after the Salter innominate osteotomy (This patient was not included in the study)

Study design

Ethics committee approval was obtained before this retrospective study. Patients diagnosed with LCPD in our hospital and treated with the BEST method were investigated. Twenty-five patients (twenty-four boys, one girl) who reached skeletal maturity were included in this study. Patients were invited to the hospital for final evaluation except one (who couldn't be reached). Twenty-four patients (twenty-three boys, one girl) participated in the final evaluation. Informed consent was obtained from the patients for the present study.

Clinical evaluation

Pre- and post-treatment examinations and surgical notes taken from hospital records were analyzed. In the final physical evaluation, range of motion and leg lengths were measured, and the Trendelenburg sign was noted for each patient. In addition, in their last follow-up, the patients were asked to fill a questionnaire for the Harris Hip Score (HHS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The duration of surgery, the amount of bleeding and complications were obtained from the surgery notes.

Radiological evaluation

The radiographs of the patients before the treatment were all obtained and examined from the hospital records. Pelvic X-rays were taken in the AP and frog-leg positions of the patients in their final evaluations. The preoperative radiographs were classified according to the lateral pillar classification [10], the Catterall [2] classification, and the Waldenström [20] staging. The presence and number of risk signs (lateral calcification, lateral subluxation, gage sign, horizontal growth plate and diffuse metaphyseal reaction) indicated by Catterall [2] were investigated and Wiberg's Central Edge (CE) angle [21] was measured pretreatment radiographs. Final radiographs were classified according to the Stulberg et al. [22] classification and Tönnis osteoarthritis classification [23]. The sphericity of the femoral head was evaluated using the Mose [24] method. The result was considered good if the femoral head was spherical in the AP and lateral projections with no deviation of the concentric rings. A deviation of 2 mm or less was considered fair and a deviation greater than 2 mm was considered poor. CE angles were measured on the final radiographs again. In the final evaluation, the Risser [25] index was considered the criterion for patients to reach skeletal maturity.

To provide an accurate and reliable radiographic evaluation, two independent experienced orthopedic surgeons (one was in treatment and study, one was not) and a radiologist classified the radiographs according to the Stulberg classification, and the Herring classification independently. Both intra- and inter-observer reliability radiographic evaluations were performed three weeks apart.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables were summarized as median and IQR. The chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. For comparison of continuous variables between two groups, Mann-Whitney U test was used. For non-normal distributed data, the Kruskal Wallis test was used to compare more than two groups. Bonferroni adjusted Mann-Whitney U test was used for multiple comparisons of groups. For comparison of preop-postop CE angle values, Wilcoxon signed-rank test was used. To evaluate the correlations between measurements, Spearman Rank Correlation Coefficient was used. To measure intra- and inter- observer reliability, Intraclass Correlation Coefficient (ICC) was used. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

The patients (23 males, 1 female) included in this study were with unilateral (6 right, 18 left) involvement and a mean age of 7.3±1.12 (6.16-9.91) years at the time of surgery. All the patients had limp and/or hip pain and limited hip joint movements during the examination before surgery. Pre-treatment radiographic findings of the hips are given in Table 1.

Table 1. Pre-treatment radiographic findings and measurements of hips

	n (%)
Waldenström Staging	
Initial (Necrosis)	6 (25%)
Fragmantation	18 (75%)
Catterall Classification	
3	7 (29%)
4	17 (71%)
Lateral Pillar Classification	
B	9 (37.5%)
B/C	0 (0%)
C	15 (62.5%)
Number of Risk Signs	
1	6 (25%)
2	9 (37.5%)
3	2 (8.3%)
4	6 (25%)
5	1 (4.2%)

The mean surgery time was 74.3±10.2 (50-90) minutes, and the mean amount of bleeding during surgery was 77.9±10.9 (60-100) ml. None of the patients experienced complications during the surgery and did not need a transfusion. There was no wound healing problem or infection detected in the follow-ups. Implant removal procedures were routinely performed 6-8 months after surgery.

The mean follow-up period of the patients was 10.44±1.35 (8.5-13) years, and the mean age at the last follow-up was 17.71±1.73 (15.25-20.83) years. In the last follow-up examination, an average of 5.2±2.13 (4-10) mm limb shortening was detected clinically in only seven (29.1%) patients and limited joint rotation in four (16.7%) patients. Trendelenburg sign was present in five (20.8%) patients. The mean HHS was 94.9±11.4 (54-100), and the mean WOMAC index was 5.3±13 (0-53). According to the HHS grading system, 20 patients (83.3%) had an excellent outcome; one patient (4.2%) had a good result; two patients (8.3%) had a fair result; and one patient (4.2%) had a poor result (Figure 2).

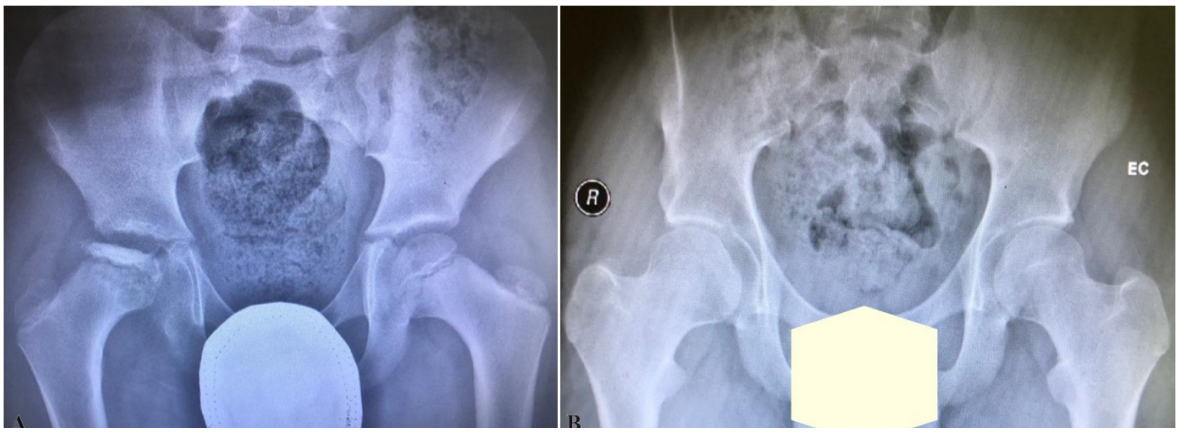

Figure 2. A 6.1 years old age boy had been sustained from hip pain for 4 months and was limping while walking

After the examination, it was determined that there was LCPD in the right hip (A). There was more than 50% depression in lateral pillar (lateral pillar C). The femoral head had three radiological risk factors; diffuse metaphyseal reaction, lateral calcification and lateral subluxation. Radiograph after 9.5 years after BEST treatment, showing good remodeling of the femoral head (B)

All radiological results are given in Table 2. Inter-observer variability revealed no significant difference in lateral pillar classification and Stulberg classification measurements between the observers (ICC >0.90). Likewise, intra-observer variability showed no significant differences between measurements taken by the same observers (ICC >0.90). No significant relationship was noted in the analysis between the age of surgery, follow-up duration, Waldenström stage [20], Catterall class and number of risk signs on Stulberg classification. However, the relation between lateral pillar classification and Stulberg classifications showed that Class B hips of lateral pillar classification ended in a better Stulberg class than Class C hips (Table 3). This relationship was also valid for the Mose [24] index (Table 4) (Figure 3). The CE angles of the patients at the last follow-up were higher than before the operation (p<0.001) (Figure 4).

Table 2. Final radiographic measurements and results

	n (%)
Stulberg Classification	
Class 1	11 (45.8%)
Class 2	6 (25%)
Class 3	3 (12.5%)
Class 4	4 (16.7%)
Class 5	0 (0%)
Mose Classification	
Good	12 (50%)
Fair	5 (20.8%)
Poor	7 (29.1%)
Presence of Osteoarthritis	
Yes	6 (25%)
Tönnis Grade 1	5 (20.8%)
Tönnis Grade 2	1 (4.2%)
No	18 (75%)

Table 3. Analysis of Stulberg classification

	Stulberg Class				***p***
	1	**2**	**3**	**4**	***statistics***
Age at surgery, years, median (IQR)	7 (1.45)	6.5 (2.09)	6.4 (1.1)	7.3 (2.19)	0.737 KW:1.265
Follow-up time, years, median (IQR)	10 (1)	10.5 (1.5)	10 (1.5)	10.7 (2.3)	0.573 KW:1.998
Waldenström stage					
Initial (necrosis)	2 (33.3%)	2 (33.3%)	2 (33.3%)	0 (0%)	0.198
Fragmantation	9 (50%)	4 (22.2%)	1 (5.5%)	4 (22.2%)	FE:4.004
Catterall class					
3	6 (85.8%)	1 (14.2%)	0 (0%)	0 (0%)	0.178
4	5 (29.4%)	5 (29.4%)	3 (17.6%)	4 (23.5%)	FE:4.449
Lateral pillar class					
B	8 (89%)	1 (11%)	0 (0%)	0 (0%)	**0.011**
C	3 (20%)	5 (33%)	3 (20%)	4 (27%)	FE:9.714
Risk sign number, median (IQR)	2 (1)	3 (3)	2 (0)	3 (2)	0.382 KW:2.527

KW: Kruskall Wallis Test, FE: Fisher-Exact Test

Table 4. Analysis of Mose classification

	Mose Class			*p* Statistics
	Good	**Fair**	**Poor**	
Age at surgery, years, median (IQR)	7 (1.7)	7.5 (2)	6.8 (1.7)	0.958 KW:0.087
Follow-up duration, years, median (IQR)	10.1 (1.1)	10.6 (1.5)	10.5 (1.9)	0.558 KW:1.166
Waldenström stage				
Initial (necrosis)	2 (33.3%)	2 (33.3%)	2 (33.3%)	0.585 FE:1.357
Fragmantation	10 (55.5%)	3 (16.7%)	5 (27.8%)	
Catterall class				
3	6 (85.8%)	1 (14.2%)	0 (0%)	0.064 FE:5.249
4	6 (35.3%)	4 (23.6%)	7 (41.1%)	
Lateral pillar class				
B	8 (88.9%)	1 (11.1%)	0 (0%)	**0.010** FE:8.903
C	4 (26.7%)	4 (26.7%)	7 (46.6%)	
Risk sign number, median (IQR)	2 (2)	2 (3)	3 (2)	0.391 KW:1.876

KW: Kruskall Wallis Test, FE: Fisher-Exact Test

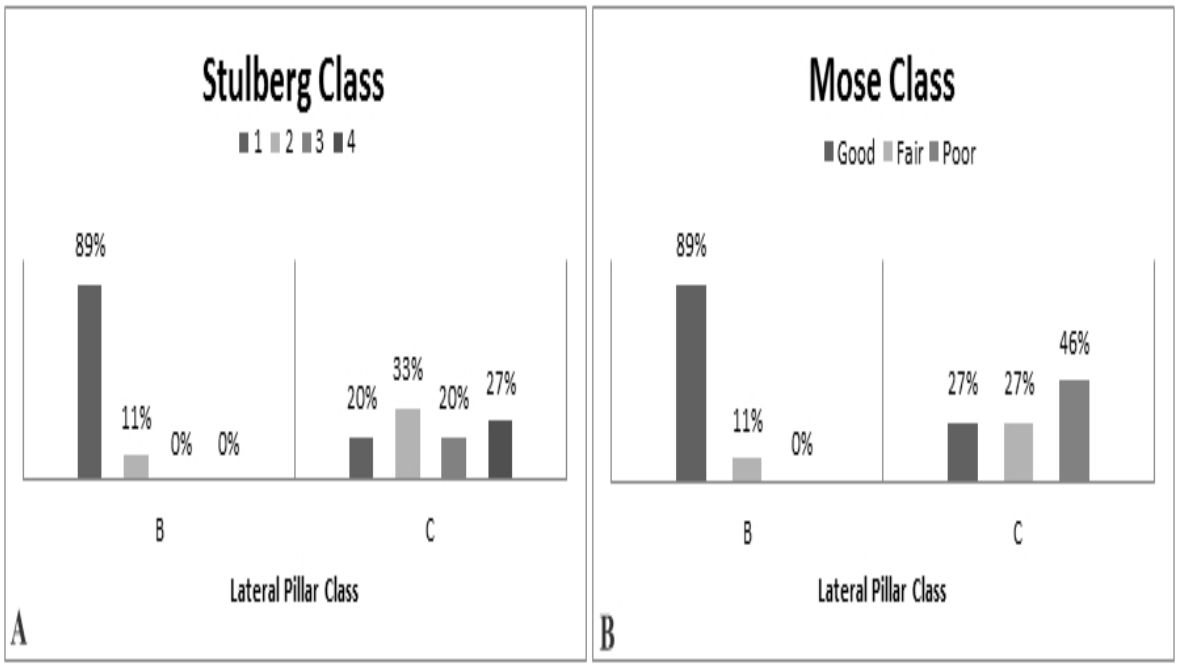

Figure 3. Lateral pillar classes according to Stulberg classes (A) and Mose classes (B)

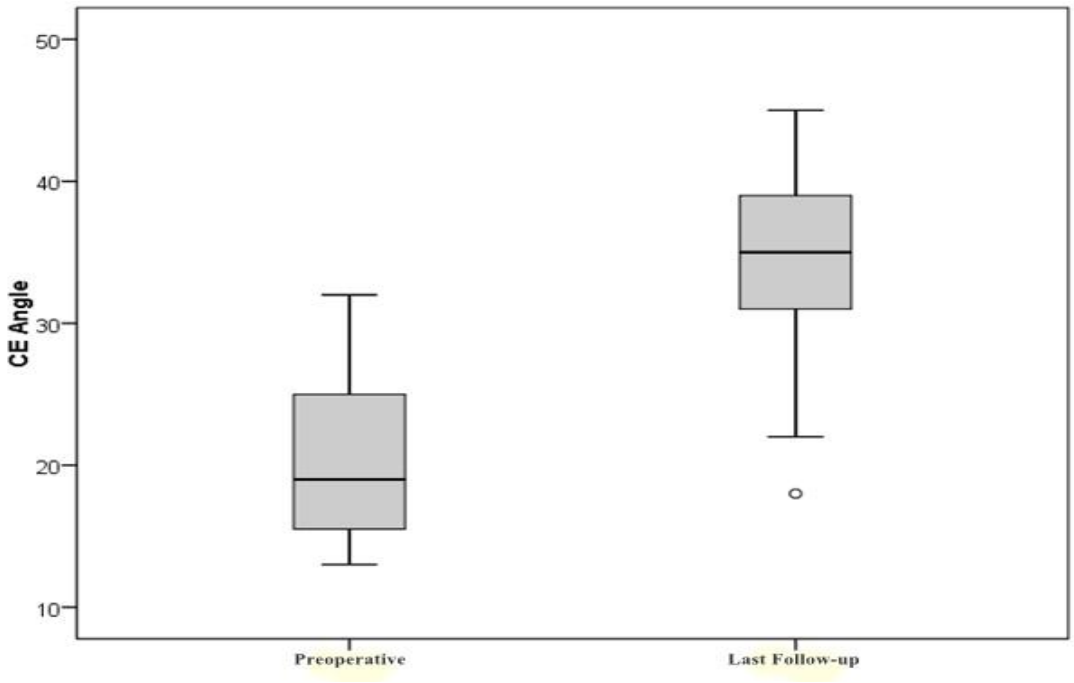

Figure 4. The CE angle showing centralization of the femoral head was higher at the last follow-up than before the operation

Preoperative CE angle Median: 19 (IQR:10), Last follow-up CE angle Median:35 (IQR:9), $p<0.001$

Discussions

Although more than a century has passed since the definition of the LCPD a common consensus has not been established on its treatment yet. The ultimate goal of treatment is to achieve a spherical and congruent hip joint. Joseph et al. [26] reported that spherical femoral head development could not be achieved in 76% of untreated LCP patients. The most accepted and practiced method is to improve the containment of the head by the acetabulum by the molding effect of the socket during the period when the head is susceptible to deformation. Many conservative and surgical methods can be applied to increase containment [2-14].

In treating of LCPD, brace and orthosis can be used as conservative methods to increase containment [27, 28]. Rich and Schoenecker [27] stated that 89% of lateral pillar B and 67% of lateral pillar C hips were spherical and congruent at maturity by orthosis. However, Wiig et al. [28], in their study comparing femoral varus osteotomy and orthosis treatment, reported that 43% spherical and congruent hips were obtained in patients older than six years of age who underwent surgery, while this rate was 20% in orthosis treatment. Terjesen et al. [29] stated that surgical treatment could be more successful in patients with Catterall 4, Lateral pillar C, more than six years of age, and less than 80% femoral head coverage, which they identified as risk factors.

Pelvic osteotomies could be performed to increase containment, including Salter innominate osteotomy, triple pelvic osteotomy, Chiari osteotomy, and shelf osteotomy [3, 4, 6, 7, 13, 30, 31]. Salter innominate osteotomy further increases the coverage of the anterolateral part of the femoral head, where the load is higher. Its advantages are that it medializes the acetabulum by 1-1.5 cm, reduces the load on the joints, increases blood supply to the femoral head, does not cause shortening, and easy remove implants [4]. In the literature reporting the results of Salter's Osteotomy in the treatment of LCPD, it is not possible to make a direct comparison because many factors, such as the timing of the treatment, severity of the disease, and age, cannot be standardized. In various small series published, the rate of obtaining excellent-good results with Salter osteotomy (Stulberg 1-2) varies from 46% to 74% [6-8, 11]. In a series of 35 patients with a mean follow-up of 9.4 years, where Kaneko et al. [12] reported 74% excellent

and good results, 20% of the patients were in the lateral pillar C group. Volpon [8] reported 46% good-excellent results in their series of 28 cases. However, there are no data about the number of patients in the lateral pillar groups in their publications. In our series, of 24 patients, 11 (45.8%) patients were Stulberg Class-1, six (25%) were Stulberg Class-2, 3 (12.5%) were Stulberg Class-3, and 4 (16.7%) were Stulberg Class-4. Fifteen of these patients were in lateral pillar C class. All nine patients with lateral pillar class B were excellent or good (8 Stulbeg-1 class, 1 Stulberg-2 class).

Recently, studies in the treatment of LCPD have focused on shortening the course of the disease and accelerating regeneration. Oh et al. [31] stated that the prolongation of the initial and fragmentation phases affected the results negatively, and that especially shortening the fragmentation period would positively affect the results. Drilling of the femoral head is the method that can be applied to increase revascularization and thus enhance blood supply. Kong et al. [15] stated that multiple drilling of the femoral head accelerated revascularization in their study on immature piglets. Wang et al. [17] stated that adding adipose tissue-derived stem cells and BMP -2 to drilling could induce new bone formation and prevent the collapse of the femoral head epiphysis in the early stages of femoral head necrosis. Herrera Soto and Price [16], in addition to shelf acetabuloplasty in the treatment of juvenile avascular necrosis of the femoral head allow removal of the necrotic segment and improve vascularization in the affected area. We think that accelerating the revascularization by drilling the necrotic area in the treatment of LCPD will shorten the course of the disease, thus minimizing the deformity that may occur in the femoral head. In addition, decreasing the duration of necrosis and fragmentation periods will save more time for remodeling, so that a more spherical femoral head and congruent hip joint will be obtained. We strongly recommend performing the BEST procedure during the necrosis stage and/or before fragmentation to shorten the necrosis stage.

The main drawback of drilling given in the literature is the risk of permanent cessation of the growth plate. However, Bowen et al. [32] reported that premature physeal closure was observed in 23% of patients with LCPD, and it was more common in patients who did not undergo surgery. Park et al. [19] observed premature physeal closure in 21 (77.8%) of 27 unilateral LCPD patients they treated conservatively and stated that premature physeal closure was associated with the Herring class of the disease (more in Herring B/C and C) but not the Stulberg class. In other words, premature closure of the femoral head physis does not seem to cause inferior results of the disease. In summary, the main goal should be obtaining spherical femoral heads in which the limb can be shorter than the other extremity, rather than having equal leg lengths but with aspheric non-congruency. Seven of our patients (29.1%) had an average leg length discrepancy of 5.2 mm. This rate was well below the 77% premature physeal closure rate encountered in patients treated conservatively determined by Park et al. [19].

Skin traction is a conservative treatment method with some success in treating of LCPD. Wagenaar et al. [33] observed that patients treated with long-term traction achieved similar success to patients treated with femoral varus osteotomy. However, they stated that long-term application might cause problems due to muscle atrophy, osteopenia, negative social and psychological effects. Thus, it is not very suitable for today's conditions and can be applied for a short time by combined with other treatment methods. We recommend skin traction for four weeks to enhance osteogenesis and angiogenesis by distraction and secure the pelvic osteotomy fixation by its immobilization effect.

Synovitis of the affected hip joint is a common feature of LCPD, producing pain, loss of hip motion and chondrolysis. Additionally, medial and inferior seating of the excess synovial fluid in the joint may cause reflected pain on the medial knee by obturator nerve innervation. It may also cause a lateral shift of the femoral head in the acetabulum. Kamiya et al. [34] stated that the IL-6 level of the synovial fluid is significantly higher in LCPD, which may have significant effects on healing. In addition, Upasani et al. [35] stated that the increase in intraarticular pressure negatively affects blood flow to the femoral head in their study on animals. Thus, evacuation of the fluid with pathological content, which both causes an increase in the pressure

in the joint and negatively affects the blood flow to the head, and has the potential to have a negative effect on healing, may contribute to the acceleration of healing. We also postulated that evacuation of the fluid lowers the pressure in the inferomedial pocket of the capsule, which further relieves the pain reflected in the knee and also helps increase the containment. Therefore, we include the evacuation of pathological fluid in the joint in our treatment protocol for its physical and chemical benefits.

Our study had some limitations. First, our study was a retrospective study with no control group. We had no chance to compare our method with any other treatment method. Second, the number of our patients was relatively low. This did not give an idea about which stage of the treatment would be more successful. Prospective studies with many patients are needed to make stronger recommendations.

In conclusion the BEST treatment method for LCPD is a combined procedure that addresses all pathologies of the disease at the same time. We recommend this combined treatment protocol (BEST procedure) for severely affected LCPD cases over six years of age and subluxation, especially in the higher lateral pillar class. We need a longer follow-up duration and larger numbers in our series to strengthen our conclusion for our method in LCPD treatment.

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References

1. Kim HK, Herring JA. Pathophysiology, classifications, and natural history of Perthes disease. Orthop Clin North Am 2011;42:285-295. https://doi.org/10.1016/j.ocl.2011.04.007
2. Catterall A. Legg-Calvé-Perthes syndrome. Clin Orthop Relat Res 1981;158:41-52.
3. Conroy E, Sheehan E, O' Connor P, Connolly P, McCormack D. Triple pelvic osteotomy in Legg-Calve-Perthes disease using a single anterolateral incision: a 4-year review. J Pediatr Orthop B 2010;19:323-326. https://doi.org/10.1097/BPB.0b013e32833822a4
4. Thompson GH. Salter osteotomy in Legg-Calvé-Perthes disease. J Pediatr Orthop 2011;31:192-197. https://doi.org/10.1097/BPO.0b013e318223b59d
5. Shim SS, Day B, Leung G. Circulatory and vascular changes in the hip following innominate osteotomy: an experimental study. Clin Orthop Relat Res 1981;160:258-267.
6. Yavuz U, Demir B, Yildirim T, Beng K, Karakas ES. Salter innominate osteotomy in the treatment of late presentation Perthes disease. Hip Int 2014;24:39-43. https://doi.org/10.5301/hipint.5000086
7. Park KS, Cho KJ, Yang HY, Eshnazarov KE, Yoon TR. Long-term results of modified salter innominate osteotomy for Legg-Calvé-Perthes disease. Clin Orthop Surg 2017;9:397-404. https://doi.org/10.4055/cios.2017.9.4.397
8. Volpon JB. Comparison between innominate osteotomy and arthrodistraction as a primary treatment for Legg-Calvé-Perthes disease: a prospective controlled trial. Int Orthop 2012;36:1899-1905. https://doi.org/10.1007/s00264-012-1598-2
9. Saran N, Varghese R, Mulpuri K. Do femoral or salter innominate osteotomies improve femoral head sphericity in Legg-Calvé-Perthes disease? A meta-analysis. Clin Orthop Relat Res 2012;470:2383-2393. https://doi.org/10.1007/s11999-012-2326-3
10. Herring JA, Kim HT, Browne R. Legg-Calve-Perthes disease. Part II: Prospective multicenter study of the effect of treatment on outcome. J Bone Joint Surg Am 2004;86:2121-2134.
11. Cıtlak A, Kerimoğlu S, Baki C, Aydın H. Comparison between conservative and surgical treatment in Perthes disease. Arch Orthop Trauma Surg 2012;132:87-92. https://doi.org/10.1007/s00402-011-1382-6
12. Kaneko H, Kitoh H, Mishima K, et al. Comparison of surgical and nonsurgical containment methods for patients with Legg-Calvé-Perthes disease of the onset ages between 6.0 and 8.0 years: Salter osteotomy versus a non-weight-bearing hip flexion-abduction brace. J Pediatr Orthop B 2020;29:542-549. https://doi.org/10.1097/BPB.0000000000000710
13. Wenger DR, Pring ME, Hosalkar HS, Caltoum CB, Lalonde FD, Bastrom TP. Advanced containment methods for Legg-Calvé-Perthes disease: results of triple pelvic osteotomy. J Pediatr Orthop 2010;30:749-757. https://doi.org/10.1097/BPO.0b013e3181f5a0de
14. Leitch JM, Paterson DC, Foster BK. Growth disturbance in Legg-Calvé-Perthes disease and the consequences of surgical treatment. Clin Orthop Relat Res 1991;262:178-184.
15. Kong SY, Kim HW, Park HW, Lee SY, Lee KS. Effects of multiple drilling on the ischemic capital femoral epiphysis of immature piglets. Yonsei Med J 2011;52:809-817. https://doi.org/10.3349/ymj.2011.52.5.809
16. Herrera Soto JA, Price CT. Core decompression and labral support for the treatment of juvenile osteonecrosis. J Pediatr Orthop 2011;31:212-216. https://doi.org/10.1097/BPO.0b013e318223b4d4
17. Wang ZL, He RZ, Tu B, et al. Drilling combined with adipose-derived stem cells and bone morphogenetic protein-2 to treat femoral head epiphyseal necrosis in juvenile rabbits. Curr Med Sci 2018;38:277-288. https://doi.org/10.1007/s11596-018-1876-3

18. Novais EN, Sankar WN, Wells L, Carry PM, Kim YJ. Preliminary results of multiple epiphyseal drilling and autologous bone marrow implantation for osteonecrosis of the femoral head secondary to sickle cell disease in children. J Pediatr Orthop 2015;35:810-815. https://doi.org/10.1097/BPO.0000000000000381
19. Park KW, Rejuso CA, Cho WT, Song HR. Timing of premature physeal closure in Legg-Calve-Perthes disease. Int Orthop 2014;38:2137-2142. https://doi.org/10.1007/s00264-014-2394-y
20. Waldenström H. The definite form of the coxa plana. Acta Radiol 2016;57:79-94. https://doi.org/10.1177/0284185116642923
21. Wiberg G. Studies on dysplastic acetabula and congenital subluxation of the hip joint: with special reference to the complication of osteoarthritis. Acta Chir Scand 1939;83:58.
22. Stulberg SD, Cooperman DR, Wallensten R. The natural history of Legg-Calvé-Perthes disease. J Bone Joint Surg Am 1981;63:1095-1108.
23. Clohisy JC, Carlisle JC, Beaulé PE, et al. A systematic approach to the plain radiographic evaluation of the young adult hip. J Bone Joint Surg Am 2008;90:47-66. https://doi.org/10.2106/JBJS.H.00756
24. Mose K. Methods of measuring in Legg-Calvé-Perthes disease with special regard to the prognosis. Clin Orthop Relat Res 1980;150:103-109.
25. Risser JC. The Iliac apophysis; an invaluable sign in the management of scoliosis. Clin Orthop 1958;11:111-119.
26. Joseph B, Varghese G, Mulpuri K, Narasimha Rao K, Nair NS. Natural evolution of Perthes disease: a study of 610 children under 12 years of age at disease onset. J Pediatr Orthop 2003;23:590-600. https://doi.org/10.1097/00004694-200309000-00005
27. Rich MM, Schoenecker PL. Management of Legg-Calvé-Perthes disease using an A-frame orthosis and hip range of motion: a 25-year experience. J Pediatr Orthop 2013;33:112-119. https://doi.org/10.1097/BPO.0b013e318281ab44
28. Wiig O, Terjesen T, Svenningsen S. Prognostic factors and outcome of treatment in Perthes' disease: a prospective study of 368 patients with five-year follow-up. J Bone Joint Surg Br 2008;90:1364-1371. https://doi.org/10.1302/0301-620X.90B10.20649
29. Terjesen T, Wiig O, Svenningsen S. The natural history of Perthes' disease. Acta Orthop 2010;81:708-714. https://doi.org/10.3109/17453674.2010.533935
30. Rosello O, Solla F, Oborocianu I, et al. Advanced containment methods for Legg-Calvé-Perthes disease: triple pelvic osteotomy versus Chiari osteotomy. Hip Int 2018;28:297-301. https://doi.org/10.5301/hipint.5000569
31. Oh HS, Sung MJ, Lee YM, Kim S, Jung ST. Does the duration of each waldenström stage affect the final outcome of Legg-Calvé-Perthes disease onset before 6 years of age? Children 2021;8:118(e1-6). https://doi.org/10.3390/children8020118
32. Bowen JR, Schreiber FC, Foster BK, Wein BK. Premature femoral neck physeal closure in Perthes' disease. Clin Orthop Relat Res 1982;171:24-29.
33. Wagenaar FB, Maathuis CG, van Erve RH. Treatment outcome in the most severely affected Legg-Perthes patients, comparing prolonged traction in abduction with femoral varus derotation treatment. J Child Orthop 2011;5:89-95. https://doi.org/10.1007/s11832-010-0309-z
34. Kamiya N, Yamaguchi R, Adapala NS, et al. Legg-Calvé-Perthes disease produces chronic hip synovitis and elevation of interleukin-6 in the synovial fluid. J Bone Miner Res 2015;30:1009-1013. https://doi.org/10.1002/jbmr.2435
35. Upasani VV, Badrinath R, Farnsworth CL, et al. Increased hip intracapsular pressure decreases perfusion of the capital femoral epiphysis in a skeletally immature porcine model. J Pediatr Orthop 2020;40:176-182. https://doi.org/10.1097/BPO.0000000000001284

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Authors' contributions to the article

R.C., E.T., and C.O. constructed the main idea and hypothesis of the study. R.C. and C.O. developed the theory and arranged the material and method section. R.C. and E.T. have evaluated the data in the results section. Discussion section of the article written by R.C., E.T., and C.O.

R.C., and C.O. reviewed, corrected, and approved. In addition, all authors discussed the entire study and approved the final version.

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Volumetric analysis of pain centers in migraine patients

Migren hastalarında ağrı merkezlerinin volümetrik analizi

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Abstract

Purpose: To investigate patterns of abnormalities in pain centers among patients with chronic pain, particularly those with migraines. The study aims to explore the potential correlation with pain duration and migraine types, and to propose new interventions for managing chronic pain.

Materials and methods: Radiologic data of 32 migraine patients and 28 healthy controls underwent three-dimensional iso T1-weighted brain MRI between 2019 and 2023 at our university hospital were examined. Patients with a minimum migraine duration of three years were included and divided into two groups: patients without aura (MwoA group) and patients with aura (MwA group). Additionally, patients were categorized based on the frequency of their migraine attacks, either episodic (EM) or chronic (CM). A control group (Group C) was also established for comparison. Volumetric analysis, including cortical and subcortical pain-related structures, was performed using volBrain software.

Results: Significant differences were observed in grey matter (p=0.037), cortical grey matter (p=0.022), cerebrum grey matter (p=0.026), anterior cingulate cortex (ACC) (p=0.017), middle cingulate cortex (MCC) (p=0.014), and posterior cingulate cortex (PCC) (p=0.008) volumes among the groups. Group comparisons revealed significant differences in the ACC, MCC, and PCC between Groups C and MwoA (p=0.047, p=0.040, and p=0.047, respectively) and PCC between Groups C and MwA (p=0.026), possibly related to aura pathogenesis. Patients without aura exhibited non-significantly thinner postcentral gyrus (p=0.079), suggesting potential cortical involvement.

Conclusions: This study provides insights into pain center abnormalities in migraine patients and their potential relevance to pain duration and migraine type.

Keywords: Chronic pain, neuroimaging, voxel-based morphometry (VBM), migraine with aura, pain processing centers.

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Öz

Amaç: Kronik ağrısı olan, özellikle migren hastalarında ağrı merkezlerindeki anormallik paternlerini araştırmak. Çalışma, ağrı süresi ve migren tipleri ile olası korelasyonu keşfetmeyi ve kronik ağrı yönetimi için yeni müdahaleler önermeyi amaçlamaktadır.

Gereç ve yöntem: Üniversite hastanemizde 2019-2023 yılları arasında üç boyutlu izo T1 ağırlıklı beyin MRG'si çekilen 32 migren hastası ve 28 sağlıklı kontrolün radyolojik verileri incelendi. En az 3 yıllık migren süresi olan hastalar çalışmaya dahil edildi ve aura yokluğu (Grup MwoA) veya varlığına (Grup MwA) göre iki gruba ayrıldı. Ek olarak hastalar migren ataklarının sıklığına göre epizodik (EM) veya kronik (CM) olarak sınıflandırıldı. Karşılaştırma için bir kontrol grubu da (Grup C) oluşturuldu. Kortikal ve subkortikal ağrıyla ilişkili yapılar dahil olmak üzere volümetrik analiz volBrain yazılımı kullanılarak yapıldı.

Bulgular: Gruplar arasında gri madde (p=0,037), kortikal gri madde (p=0,022), serebrum gri maddesi (p=0,026), ön singulat korteks (ACC) (p=0,017), orta singulat korteks (MCC) (p=0,014) ve arka singulat korteks (PCC) (p=0,008) hacimlerinde anlamlı farklılıklar gözlendi. Grup karşılaştırmalarında ACC, MCC ve PCC'de Grup C ve MwoA arasında (sırasıyla p=0,047, p=0,040 ve p=0,047) ve PCC'de Grup C ve MwA arasında (p=0,026) muhtemelen aura patogeneziyle ilişkili anlamlı farklılıklar ortaya konuldu. Aurası olmayan hastalarda, potansiyel kortikal tutulumu düşündüren, istatistiksel olarak anlamlı olmayan (p=0,079) daha ince postcentral girus görüldü.

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Sonuç: Bu çalışma, migren hastalarında ağrı merkezi anormalliklerine ve bu durumun ağrı süresi ve migren tipi ile potansiyel ilişkisine dair anlayış sağlamaktadır.

Anahtar kelimeler: Kronik ağrı, nörogörüntüleme, voksel bazlı morfometri (VBM), auralı migren, ağrı işleme merkezleri.

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Introduction

Chronic pain persists for more than three months, occurring every day or on ≥50% of days for six months and extending beyond the expected healing period; also, unlike acute pain, it does not have a warning function [1, 2]. Patients with chronic pain have decreased quality of life that also leads to increasing costs for medical care, disability, and productivity [1, 2]. The development of imaging technologies makes a possible objective assessment of pain. These developments may provide new insight into understanding and treating chronic pain. Significantly, knowledge affecting centers in chronic pain could help better understand the central localization of pain, providing further intervention to these centers.

Migraine is a chronic neurovascular disorder with episodic headache manifestations and an enormous socioeconomic impact [3, 4]. The pathophysiology of migraine is not well understood. Despite migraine being considered a benign disease, its long-term effects are still unclear. Recent neuroimaging studies show that migraine could be associated with functional and structural brain changes. Most of the changes were researched for the altered morphology of cerebral, cerebellar, and brainstem structures [3, 4]. There is still a lack of research on pain centers.

Research on the structure of the cerebral cortex could provide more precise and reliable insights into the underlying neurophysiological mechanism associated with chronic pain. The main objective of this study was to perform a comprehensive analysis of changes in cortical morphology and limbic structures (ACC, MCC, PCC, and anterior insula) among patients with long-duration migraine (chronic pain), and explore the alteration of these centers, also the potential connection these changes with the duration of pain and type of migraine. Due to previous neuroimaging research on chronic pain, we hypothesized that pain-related regions would be altered in migraine patients [3-8]. In this article, we aimed to explore patterns of pain center abnormalities in patients with chronic pain due to long-duration migraine.

Materials and methods

This retrospective cohort study included 32 migraine patients and 28 matched healthy control subjects admitted to the Neurosurgery and Neurology Outpatient Clinics at our university hospital between 2019 and 2023. After obtaining approval from Trakya University Non-Interventional Clinical Research Ethics Committee (TÜTF-GOBAEK 2023/287), three-dimensional brain MRI was obtained using iso-T1-weighted imaging. Patients with vasculitis, previous stroke, intracranial mass, previous intracranial surgery, alcoholism, smoking, obesity (BMI >30 kg/m^2), and the presence of another headache, pregnancy, claustrophobia, or incompatible metallic devices were excluded from the study.

Questionnaires were used to gather clinical data, including age, gender, disease duration since migraine diagnosis, average pain intensity, and medication use. Patients with at least 3 years of migraine duration were included in the study. The participants were divided into two groups based on the presence or absence of aura, according to migraine phenotype: Group MwA (Migraine with aura) and Group MwoA (Migraine without aura). Their results were then compared to those of a control group (Group C) consisting of normal individuals without pain.

Moreover, patients were divided into two groups based on migraine frequency: episodic migraine (EM), with less than 15 migraine attacks per month (Group EM), and chronic migraine (CM), with more than 15 migraine attacks per month (Group CM). These groups were then compared to a normal group (Group C).

Finally, all migraine patients (MwoA and MwA groups) were compared with Group C to evaluate the effects of pain.

Brain MRI imaging was obtained using a Siemens 1.5 Tesla device in a 32-channel phased-array coil. The imaging protocol included T1-weighted, high-contrast, 3D isotropic voxel images acquired in the sagittal plane and reconstructed in the three orthogonal planes.

Volumetric analysis was conducted using volBrain software, which automatically analyzes brain MRI data and provides volumes of subcortical structures, cerebellum, brainstem, brain hemispheres, brain tissues, and the intracranial cavity (Figure 1-3).

Voxel-based morphometry (VBM) was performed for volumetric measurements, including total brain volume, cortex volume, subcortical volume, cerebral white matter volume, total gray matter volume, cortical thickness, and measures of specific regions such as the postcentral gyrus (somatosensory area), anterior insula, anterior cingulate cortex (ACC), midcingulate cortex (MCC), posterior cingulate cortex (PCC), putamen, thalamus, nucleus accumbens (n. accumbens), pallidum, hippocampus, parahippocampus (PHG), and cerebellum (Figure 4).

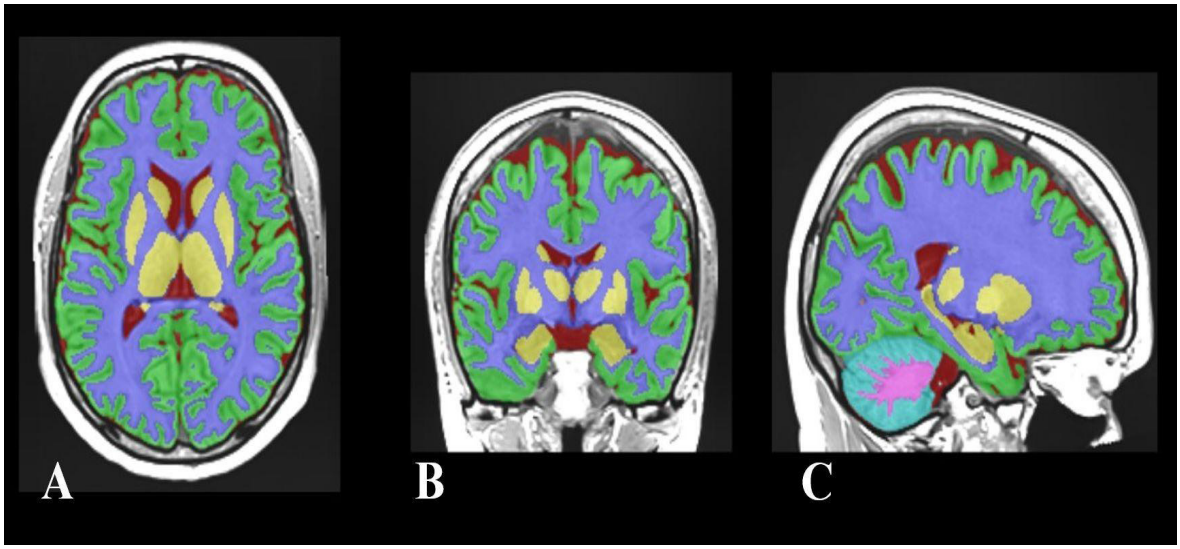

Figure 1. Tissue segmentation to cortical and subcortical structures
A. Axial view. B. Coronal view. C. Sagittal view

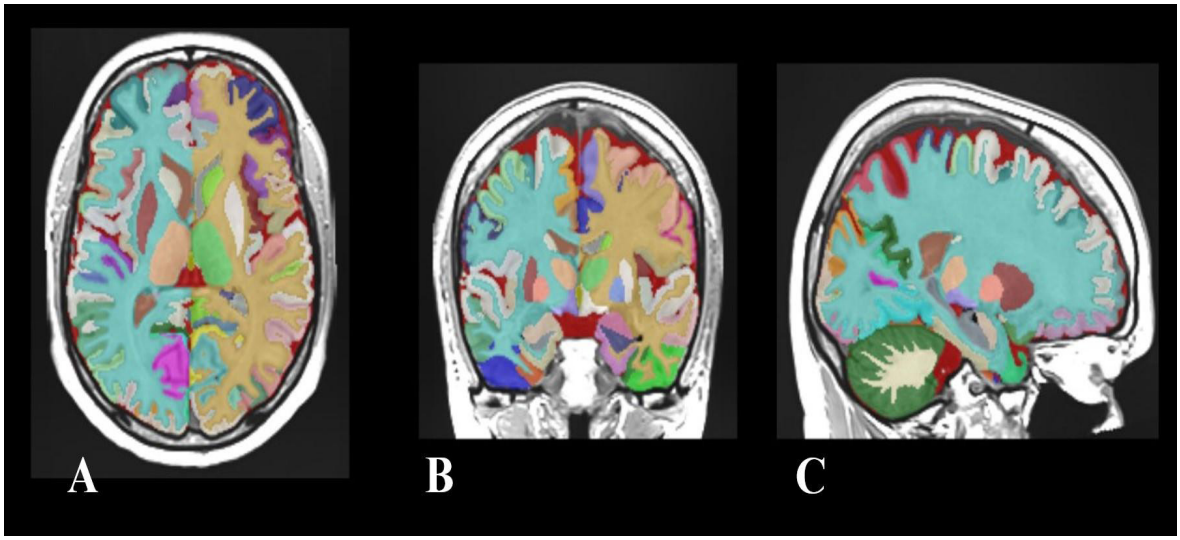

Figure 2. Structure segmentation of cortical and subcortical structures
A. Axial view. B. Coronal view. C. Sagittal view

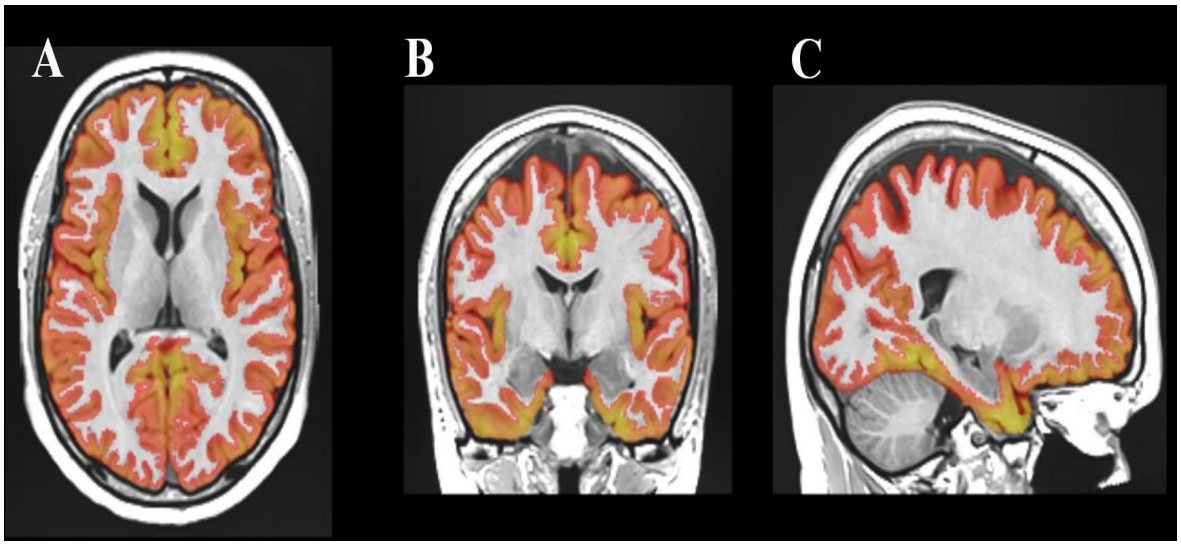

Figure 3. Cortical gray matter. A: Axial view, B: Coronal view, C: Sagittal view

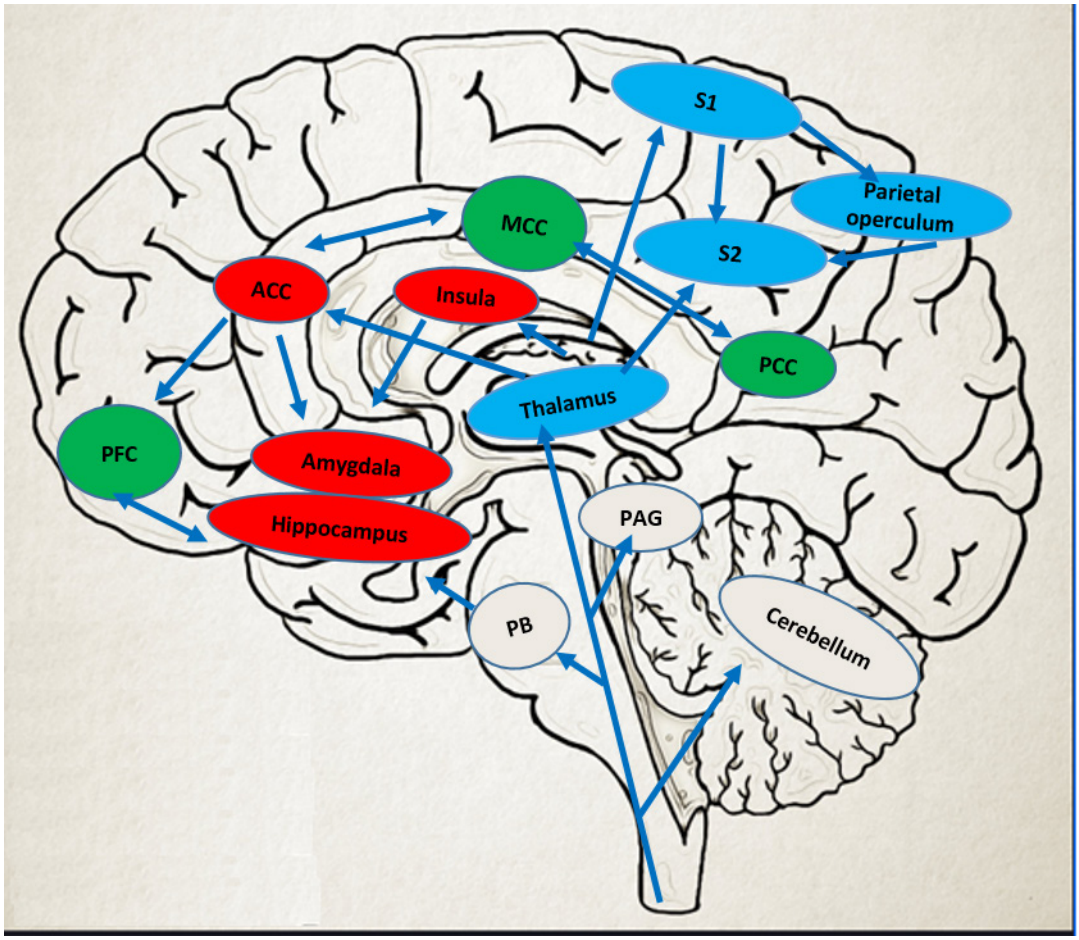

Figure 4. Schematic illustrations of neural networks associated with pain

The arrows illustrate the central connections between pain-related regions
ACC: anterior cingulate cortex, MCC: medial cingulate cortex, PCC: posterior cingulate cortex PFC: prefrontal cortex
PAG: periaqueductal gray, S1: primary somatosensory cortex, S2: secondary somatosensory cortex, PB: parabrachial nucleus
The areas involved in pain perception and location are highlighted in blue, while the red highlights indicate areas involved in the affective motivational part of pain. The green highlights indicate areas involved in the cognitive component of pain

Statistical analysis was conducted using Jamovi (version 2.3) software. The normality of the data was examined using the Shapiro-Wilk tests. Results were presented as mean ± standard deviation for parametric continuous variables and as percentages for categorical variables. Two-group comparisons were made using Mann Whitney U for numerical variables, χ^2 tests for categorical variables, and Fisher's exact test. Kruskal-Wallis tests were used to compare means or medians of continuous variables (age) between different groups, with a significance level set at $p \leq 0.05$. To conduct a post hoc pairwise comparison, a Dwass-Steel-Critchlow-Fligner test was performed to assess the volumetric differences between the groups.

Results

The study included a total of 60 participants, with 17 patients in Group MwoA, 15 in Group MwA, and 28 in Group C. Furthermore, related to the number of attacks, there were 26 patients in Group EM and 6 in Group CM, as well as 28 in Group C. The age range of the patients was between 18-45 years, and all participants were female. The mean duration since migraine diagnosis was 14.97 years.

Descriptive measurements of cortical and subcortical centers are given in Table 1. Despite no statistically significant differences, patients without aura showed thinner measurements in the n. accumbens (0.648±0.119 group MwoA, 0.709±0.095 in group MwA), hippocampus (6.93±2.39 group MwoA, 7.39±1.59 in group MwA), and thalamus (11.7±1.12 group 1, 12.5±1.03 in group MwA). In contrast, patients with aura had thinner measurements in the parahippocampus (5.82±0.486 group MwA, 5.40±1.04 in group MwoA) and anterior insula (8.12±0.92 group MwA, 7.86±1.42 in group MwoA). However, it is essential to note that these differences did not reach statistical significance.

Dwass-Steel-Critchlow-Fligner pairwise comparisons revealed statistically significant differences in cortical gray matter (p=0.041), cerebrum gray matter (p=0.047), ACC (p=0.020), MCC (p=0.020), and PCC (p=0.011) volumes among the groups (Table 1). However, no statistically significant differences were found in other variables, such as total gray matter, white matter, the volumes of total brain volume, cerebellum, n. accumbens, hippocampus, pallidum, putamen, thalamus, postcentral gyrus, parahippocampus, and anterior insula among the groups.

In comparison of Group C and MwoA, there were significant differences between ACC (p=0.047), MCC (p=0.040), and PCC (p=0.047). In comparison of Group C and MwA were noted differences between PCC (p=0.026), which probably could be involved in pathogenesis patients with aura. Moreover, despite there being no statistically significant differences, patients without aura showed thinner measurements in the postcentral gyrus (Group C-MwoA (p=0.079) compared to Group C-MwA (p=0.597)), which could be related to cortical involvement in pathogenesis patients with absence aura.

Mann Whitney U test was used for comparing all migraine patients (groups MwoA and MwA) with the Group C, were noted significant differences in structures, such as gray matter (p=0.017), cortical gray matter (p=0.012), cerebrum gray matter (p=0.013), ACC (p=0.006), MCC (p=0.005), and PCC (p=0.003) (Table 2).

Furthermore, Kruskal Wallis analyzed between groups to compare the effects of episodic and chronic migraine (Groups EM, CM, and C). Significant differences were observed in structures such as gray matter (p=0.011), cortical gray matter (p=0.007), cerebrum gray matter (p=0.008), and PCC (p=0.033). Despite this, ACC and MCC have no significant differences between all migraines and control groups (p=0.070 and 0.069), and between groups C and EM in both structures, significant differences (p=0.018 and 0.018). Also, significant differences were noted between groups EM and CM (ACC, p=0.009, MCC, p=0.005) (Table 3).

Table 1. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with (MwA)/without aura (MwoA) and control group (C)

	Median (IQR)	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner pairwise comparisons					
				C-MwoA		C-MwA		MwoA- MwA	
	C (n=28) **MwoA** (n=17) **MwA** (n=15)	χ^2	*p*	W	*p*	W	*p*	W	*p*
GM	665 (59.6) 638 (89.9) 644 (39.3)	5.794	0.055	-3.013	0.084	-2.487	0.184	0.774	0.848
Cortical GM	523 (60.6) 495 (66.4) 504 (31.5)	**6.395**	**0.041**	-2.830	0.112	-3.063	0.077	-0.027	1.000
WM+GM	1175 (116) 1127 (84.0) 1135 (99.8)	2.146	0.342	-1.920	0.364	-1.405	0.581	0.401	0.957
WM	471 (62.0) 465 (46.0) 456 (52.8)	0.493	0.781	-0.728	0.864	-0.901	0.800	-0.080	0.998
Cerebrum GM	564 (60.6) 535 (72.8) 544 (36.3)	**6.127**	**0.047**	-2.847	0.109	-2.919	0.097	-0.027	1.000
Cerebellum	123 (10.4) 123 (9.57) 127 (12.2)	1.177	0.555	-0.066	0.999	1.406	0.581	1.308	0.625
N. Accumbens	0.690 (0.112) 0.640 (0.009) 0.680 (0.075)	3.216	0.200	-1.839	0.395	0.866	0.814	2.487	0.184
Hippocampus	7.79 (0.792) 7.80 (0.900) 7.63 (0.895)	0.975	0.614	-1.391	0.587	-.0811	0.834	0.240	0.984
Pallidum	2.73 (0.277) 2.60 (0.350) 2.81 (0.165)	2.41	0.300	-1.19	0.677	1.19	0.677	2.25	0.251
Putamen	8.29 (0.648) 8.26 (0.910) 8.68 (1.03)	1.69	0.430	-0.017	1.000	1.604	0.493	1.682	0.460
Thalamus	12.0 (1.04) 11.7 (1.58) 12.5 (1.55)	4.14	0.126	-1.97	0.345	1.50	0.541	2.64	0.148
Postcentral gyrus	18.8 (3.21) 17.7 (3.33) 18.0 (1.79)	4.54	0.103	-3.05	0.079	-1.37	0.597	1.18	0.684
ACC	10.9 (1.89) 9.77 (1.82) 9.86 (0.48)	**7.80**	**0.020**	**-3.344**	**0.047**	-3.117	0.071	0.668	0.884
MCC	10.6 (1.68) 9.45 (1.84) 9.49 (0.77)	**7.83**	**0.020**	**-3.443**	**0.040**	-3.027	0.082	0.454	0.945

Table 1. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with (MwA)/without aura (MwoA) and control group (C) (continued)

	Median (IQR)	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner pairwise comparisons					
				C - MwoA		C-MwA		MwoA- MwA	
	C (n=28) MwoA (n=17) MwA (n=15)	**χ2**	***p***	**W**	***p***	**W**	***p***	**W**	***p***
PCC	10.6 (2.10) 9.28 (1.28) 9.37 (1.72)	**9.09**	**0.011**	**-3.344**	**0.047**	**-3.658**	**0.026**	-0.401	0.957
Parahippo-campus	5.76 (0.86) 5.91 (0.73) 5.48 (0.66)	2.88	0.237	1.738	0.436	-0.883	0.807	-2.323	0.228
Anterior insula	8.36 (1.34) 7.94 (1.53) 8.14 (1.60)	1.20	0.548	-1.424	0.573	-1.117	0.710	-0.187	0.990

GM: Gray Matter, ACC: Anterior Cingulate Cortex, MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

Table 2. Descriptive values and Mann-Whitney U test for all migraine patients (chronic pain) and control group

	Control group	All migraine patients (chronic pain)	Mann Whitney U	
	Median (SE)	**Median (SE)**	**U value**	***p***
GM	664.980 (10.905)	641.015 (11.552)	288	**0.017**
Cortical GM	522.760 (9.92)	496.810 (9.09)	278	**0.012**
WM+GM	1174.570 (16.372)	1132.190 (18.204)	351	0.154
WM	471.415 (7.422)	457.015 (9.114)	401	0.494
Cerebrum GM	563.755 (10.266)	535.640 (9.494)	281	**0.013**
Cerebellum	123.445 (2.44)	125.610 (2.212)	411	0.591
N. Accumbens	0.690 (0.016)	0.675 (0.02)	417	0.646
Hippocampus	7.790 (0.115)	7.705 (0.36)	384	0.343
Pallidum	2.730 (0.045)	2.730 (0.039)	445	0.970
Putamen	8.295 (0.14)	8.495 (0.149)	404	0.519
Thalamus	12.000 (0.161)	12.005 (0.20)	430	0.795
Postcentral gyrus	18.775 (0.471)	17.915 (0.323)	318	0.055
ACC	10.870 (0.323)	9.840 (0.289)	261	**0.006**
MCC	10.570 (0.26)	9.475 (0.222)	260	**0.005**
PCC	10.600 (0.279)	9.325 (0.218)	246	**0.003**
Parahippocampus	5.765 (0.119)	5.610 (0.143)	420	0.684
Anterior insula	8.360 (0.189)	8.040 (0.207)	374	0.276

GM: Gray Matter, WM: White Matter, ACC: Anterior Cingulate Cortex, MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

Table 3. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with episodic migraine (Group EM) and chronic migraine (Group CM) and control group (C)

	Median (IQR)	**Kruskal-Wallis**		**Dwass-Steel-Critchlow-Fligner pairwise comparisons**					
				C - EM		**C - CM**		**EM - CM**	
	C (n=28) **EM (**n=26) **CM (**n=6)	χ^2	***p value***	**W**	***p***	**W**	***p***	**W**	***p***
GM	**665** (59.6) 644 (69.0) 614 (22.1)	**9.01**	**0.011**	-2.50	0.181	**-3.71**	**0.024**	-2.94	0.095
Cortical GM	**523** (60.6) 504 (58.3) 471 (12.1)	**9.87**	**0.007**	-2.73	0.130	**-3.77**	**0.021**	-3.07	0.076
WM+GM	1175 (116) 1141 (109) 1103 (76.3)	4.98	0.083	-1.18	0.684	-3.13	0.069	-2.39	0.209
WM	471 (62.0) 455 (65.1) 462 (61.9)	1.10	0.578	-0.514	0.930	-1.66	0.469	-0.89	0.805
Cerebrum GM	**564** (60.6) 546 (61.6) 512 (13.4)	**9.68**	**0.008**	-2.64	0.148	**-3.77**	**0.021**	-3.07	0.076
Cerebellum	123 (10.4) 126 (12.9) 120 (7.75)	3.50	0.174	1.54	0.520	-1.66	0.469	-2.46	0.191
N. Accumbens	0.690 (0.112) 0.680 (0.105) 0.640 (0.063)	2.08	0.353	0.025	1.000	-2.08	0.305	-1.78	0.420
Hippocampus	7.79 (0.792) 7.61 (1.03) 7.79 (0.650)	1.11	0.575	-1.065	0.732	-1.342	0.609	-0.546	0.921
Pallidum	2.73 (0.277) 2.77 (0.228) 2.58 (0.345)	0.056	0.972	0.037	1.000	-0.288	0.977	-0.342	0.968
Putamen	8.29 (0.648) 8.57 (0.932) 8.11 (1.00)	0.821	0.663	1.249	0.651	-0.447	0.947	-0.615	0.901
Thalamus	12.0 (1.04) 12.1 (1.53) 12.0 (1.43)	0.147	0.929	-0.269	0.980	-0.447	0.947	-0.478	0.939
Postcentral gyrus	18.8 (3.21) 17.9 (2.35) 17.5 (2.88)	4.17	0.124	-2.33	0.227	-2.24	0.254	-1.06	0.735
ACC	10.9 (1.89) 9.90 (1.66) 9.46 (0.482)	9.39	**0.009**	**-3.12**	0.070	-3.83	**0.018**	**-1.71**	0.449

Table 3. Descriptive values and Kruskal Wallis Variance Analysis, including Dwass-Steel-Critchlow-Fligner pairwise comparisons for migraine patients with episodic migraine (Group EM) and chronic migraine (Group CM) and control group (C) (continued)

	Median (IQR)	Kruskal-Wallis		Dwass-Steel-Critchlow-Fligner pairwise comparisons					
				C - EM		C - CM		EM - CM	
	C (n=28) **EM (**n=26) **CM (**n=6)	χ^2	***p* value**	**W**	***p***	**W**	***p***	**W**	***p***
MCC	10.6 (1.68) 9.69 (1.36) 8.95 (1.47)	10.67	**0.005**	**-3.13**	0.069	-3.83	**0.018**	**-2.80**	0.117
PCC	**10.6** (2.10) 9.39 (1.60) 8.45 (1.51)	**11.12**	**0.004**	-3.54	**0.033**	-3.71	0.024	**-2.46**	0.191
Parahippo-campus	5.76 (0.857) 5.74 (0.625) 5.36 (0.633)	2.99	0.224	1.26	0.646	-1.50	0.538	-2.46	0.191
Anterior insula	8.36 (1.34) 8.13 (1.46) 7.17 (1.50)	3.88	0.144	-0.759	0.853	-2.75	0.127	-2.32	0.229

GM: Gray Matter, WM: White Matter, ACC: Anterior Cingulate Cortex MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

Correlation of volume of different brain regions and pain centers

The correlation matrix showed significant positive and negative correlations between various brain regions and the duration of disease. The correlation revealed a statistically significant positive correlation of n. accumbens with several brain structures, including postcentral gyrus (p<0.001), ACC (p<0.001), MCC (p<0.001), and PCC (p<0.001), suggesting that the volume or characteristics of the n. accumbens region was related to these other brain regions. Moreover, postcentral gyrus and cerebrum gray matter demonstrated a positive correlation with ACC (p<0.001), MCC (p<0.001), and PCC (p<0.001). The parts of the cingulate cortex (ACC, PCC, MCC) demonstrated a strong positive correlation with each other (p<0.001).

Lastly, the parahippocampus and anterior insula also showed a positive correlation (p<0.001), indicating a moderate association between these structures. These findings provide valuable insights into understanding chronic pain between different brain regions in the study population.

There is a statistically significant negative correlation between duration and gray matter (p=0.003), cortical gray matter (p=0.002), total brain volume (p=0.009), cerebrum gray matter (p=0.002), postcentral gyrus (p=0.022), ACC (p=0.001), MCC (p<0.001), and PCC (p=0.001). This indicates that as the duration of migraine (chronic pain) increases, there is a tendency for a decrease in the volume of the ACC, MCC, PCC, cortical gray matter, total brain volume, cerebrum gray matter, and the postcentral gyrus (Table 4).

Table 4. Correlation matrix between duration and pain-related centers

		Duration	Gray matter	N. Accumbens	Postcentral gyrus	ACC	MCC	PCC
Duration	Pearson's r *p*-value	—-						
Gray matter	Pearson's r *p*-value	-0.375 0.003	—-					
N. Accumbens	Pearson's r *p*-value	-0.176 0.177	0.475 < .001	—-				
Postcental gyrus	Pearson's r *p*-value	-0.295 0.022	0.722 < .001	0.325 0.011	—-			
ACC	Pearson's r *p*-value	-0.402 0.001	0.851 < .001	0.397 0.002	0.606 < .001	—-		
MCC	Pearson's r *p*-value	-0.475 < .001	0.801 < .001	0.407 0.001	0.684 < .001	0.823 < .001	—-	
PCC	Pearson's r *p*-value	-0.408 0.001	0.811 < .001	0.422 < .001	0.576 < .001	0.756 < .001	0.776 < .001	—-

ACC: Anterior Cingulate Cortex MCC: Middle Cingulate Cortex, PCC: Posterior Cingulate Cortex

The correlation analysis revealed negative correlations between the duration of migraine and the volumes of specific brain regions, including the anterior insula (Pearson's r=-0.229), white matter (Pearson's r=-0.210), nucleus accumbens (Pearson's r=-0.176), hippocampus (Pearson's r=-0.106), pallidum (Pearson's r=-0.089), putamen (Pearson's r=-0.213), and thalamus (Pearson's r=-0.140). However, it is essential to note that these correlations were not statistically significant for the anterior insula (p=0.079), white matter (p=0.107), nucleus accumbens (p=0.177), hippocampus (p=0.420), pallidum (p=0.499), putamen (p=0.102), and thalamus (p=0.284).

Discussion

This retrospective cohort study provides insights into abnormalities in pain centers among patients with chronic pain, their potential relevance to pain duration and migraine type, and suggests new interventions for chronic pain management. This study has yielded significant findings based on the comprehensive analysis of cortical morphological changes in patients with chronic pain caused by long-duration migraines. The results revealed volumetric alterations in specific brain regions, particularly a decrease in the volumes of the anterior, middle, and posterior cingulate cortex, cortical gray matter, total brain volume, and the postcentral gyrus, which were all found to be negatively correlated with the duration of chronic pain. These regions play essential roles in pain processing and sensory perception, making these findings highly relevant to our understanding of the neurophysiological mechanisms related to chronic pain. Furthermore, we noticed in migraine patients without aura, there were significant differences between ACC, MCC, and PCC, compared with the presence of aura, which revealed differences in PCC, which probably could be involved in pathogenesis patients with aura. Moreover, patients without aura showed thinner measurements in the n. accumbens, hippocampus, and thalamus; conversely, patients with aura had thinner measurements in the parahippocampus and anterior insula.

The study utilized VBM to detect volumetric changes in brain tissue [8]. VBM is a computational approach that compares brain images with a template to measure differences in local brain tissue concentration at a voxel level. The observed volumetric changes showed either a decrease or increase in gray matter or white matter volumes, possibly related to the underlying pathophysiology of migraines involving recurrent ischemia due to reduced blood flow during both ictal and interictal phases [3-8]. Consistent with these findings, all migraine

patients showed thinning of gray matter, white matter, and cerebrum gray matter, which was significantly different from the control group.

Several previous studies have reported volume loss in various cortical regions in migraine patients compared to healthy controls, involving frontal/prefrontal, parietal, temporal, and occipital areas, bilateral insula, ACC, basal ganglia, and the cerebellum [3, 4, 9]. However, in this study, no significant differences were found among the basal ganglia structures (n. accumbens volume, pallidum, putamen, thalamus) among the groups [10-13]. Furthermore, correlation analysis with duration was not statistically significant for white matter (p=0.107), n. accumbens (p=0.197), hippocampus (p=0.408), pallidum (p=0.511), putamen (p=0.105), and thalamus (p=0.284), suggesting that further investigation is needed to understand their role in chronic pain.

Significant positive and negative correlations were observed in the correlation matrix between different brain regions, age, and disease duration. There is a statistically significant negative correlation between the duration of chronic pain and ACC (Pearson's r=-0.399, p=0.002), MCC (Pearson's r=-0.333, p<0.001), PCC (Pearson's r=-0.210, p=0.001), cortical gray matter (Pearson's r=-0.211, p=0.002), total brain volume (Pearson's r=-0.292, p=0.024), and the postcentral gyrus (Pearson's r=-0.290, p=0.024). These results indicate that as the duration of chronic pain increases, there is a tendency for a decrease in the ACC, MCC, PCC, cortical gray matter, total brain volume, and the postcentral gyrus.

The basal ganglia, located in the deep gray matter, are crucial in integrating various functions such as sensory, motor, motivation, cognitive, and procedural learning [10]. Previous studies have revealed changes in the volume, functional connectivity alterations, and iron deposition in the basal ganglia among migraine patients [11-13]. Furthermore, another essential structure is the thalamus, which is vital for various functions, such as pain processing, regulation of awareness, sleep-wake cycle, modulation of visual information, and cognitive behaviors [14]. Previous studies reported the volume decrease of the thalamic nuclei [15] or alterations in the microstructure of the thalamus [16] among migraine patients. These changes support the basal ganglia's role in migraine patients' pathophysiology. Like these studies, Chen et al. [17] reported enlarged right putamen and increased thalamic volume among episodic and chronic migraine patients.

Furthermore, in our study, we also measured n. accumbens and putamen. On the contrary, these studies did not find significant differences in basal ganglia structures, such as n. accumbens volume, pallidum, putamen, thalamus, and volumes among the groups [11-17]. However, we found that patients with absence aura showed thinner measurements in the n. accumbens (0.648±0.119), which suggests that further investigation is needed to understand their role in chronic pain.

Several studies explored the variation between hippocampus volume and migraine patients. Maleki et al. [18] reported that in migraine patients, the bilateral hippocampi were larger in those experiencing 1-2 headache days compared to those having 8-14 headache days per month. Furthermore, they found a negative correlation between hippocampus volumes and the estimated total number of migraine attacks. We found that patients without aura showed thinner measurements in the hippocampus volume; however, they did not reveal differences in hippocampus volumes (p=0.575), as shown in Maleki's study [18].

The ACC is known for its role in pain processing and its functions in cognition and emotion. Therefore, it is considered involved in affective pain [19]. Functional magnetic resonance imaging (fMRI) studies demonstrated activation of the ACC during pain conditions [20, 21]. In clinical studies, it has been observed that cingulotomy (surgical ablation of the ACC) or blocking the pathway to the ACC resulted in a reduction of the sensory component of pain [22, 23]. Mo et al. [24], with a mean disease duration of 5.41±4.71 years, observed significantly decreased ACC, MCC, and PCC among trigeminal neuralgia patients. In our study, with a mean pain duration of 14.98 years, significant changes were seen in ACC (p=0.006), MCC (p=0.005), and PCC (p=0.003) among migraine patients. These findings are consistent with previous research indicating that chronic pain conditions may lead to structural alterations in specific brain regions involved in pain processing and perception [8, 9]. The

observed changes in the ACC, MCC, and PCC among patients with chronic pain suggest potential long-term adaptations in chronic pain perception.

In summary, the results suggest that the duration of chronic pain, specifically long-duration migraines, may be associated with volumetric changes in specific brain regions, particularly a decrease in the volumes of the gray matter (cerebrum and cortical), MCC, ACC, and PCC. However, it is essential to note that the observed negative correlations indicate potential associations, but the lack of statistical significance suggests that these findings should be interpreted cautiously. Further research with larger sample sizes may be needed to validate and better understand the impact of duration on brain volume changes chronic pain patients.

A functional study on migraine showed increased insular activity in the insula during the interictal period, suggesting that repeated migraine attacks could modify the function of the insula throughout life [25]. Additionally, other studies have revealed increased connectivity of the anterior insula and the dorsal pons, as well as the primary visual and auditory cortices. In contrast, the posterior insula showed reduced connectivity with the thalamus and several cortical regions [25, 26]. Mammadkhanli et al. [27] reported significant differences in various insular regions, particularly the posterior insula, the parietal operculum and the whole insular cortex, when comparing chronic pain groups (migraine patients) with normal groups. The study also investigated the clinical manifestations of migraine, such as photophobia, phonophobia, and smell, through volumetric measurements This study focuses on cortical and subcortical structures. We only measured the anterior insula and did not include clinical manifestations. Patients were divided according to migraine phenotype and frequency. We did not reveal differences in anterior insula volumes (p=0.276), as shown in Tso's study [26].

When comparing with the pathophysiological mechanism and evaluation methods in the current literature:

Neumann et al. [28] conducted a study on three groups of individuals with chronic pain conditions (chronic back pain, migraine, and craniomandibular disorder) and compared them to controls. The study found significantly less gray matter volume (GMV) in clusters of the left dorsal anterior insula/temporal pole, bilateral paracingulate/ACC, left posterior insula, and the left hippocampal/PCC region in the chronic pain groups compared to the controls. Our study focused solely on patients with migraines, excluding those with chronic low back and craniomandibular pain, resulting in a more homogeneous patient group. We conducted measurements on both cortical and subcortical structures, including all gray matter measurements without separating left and right. However, we did not include measurements of the posterior insula.

Yin et al. [29] reported that gray matter structural changes in the medial inferior temporal gyrus, particularly the parahippocampus, were the crucial and initial pathological features in Migraine without aura patients. In contrast to their study, we did not observe a significant difference in PHG in our study. This may be because our patient population consisted of both migraine with aura and migraine without aura, and the sample size was smaller.

To understand the pathophysiology of migraine, Silva et al. [30] analyzed volumetric white matter lesions and concluded that aura frequency was particularly correlated with temporal lobe white matter lesions. However, our study did not investigate white matter lesions. Instead, we focused on cortical and subcortical structures.

In their systematic review and neuroimaging meta-analysis of fMRI studies based on regional homogeneity (ReHo), Chen et al. [31] revealed that the left thalamus and brainstem were significantly activated regions. However, we did not use functional MRI in our study. The focus of our study is to understand the structures involved in the chronicization of pain through volumetric measurements of the relevant structures in pain pathophysiology. Perhaps in future prospective studies, the involvement of a certain center will serve as an objective indicator of the chronicization of pain.

In their systematic review and meta-analysis of VBM, Zhang et al. [32] revealed GM alterations in multiple cortical and subcortical brain regions.

These alterations were mostly related to sensation, affection, cognition, and descending modulation aspects of pain. The study found that patients with migraines had an elevation of grey matter in the left parahippocampus and a reduction in the left insula. This was discovered using two neuroimaging meta-analysis methods: anisotropic effect size-signed differential mapping (AES-SDM) and activation likelihood estimation (ALE), which are specifically designed for analyzing functional MRI data, not structural MRI. Our study utilized volumetric analysis, excluding the use of AES-SDM and ALE methods. The results indicate that patients experiencing chronic pain, specifically prolonged migraines, had thinner GM.

Cao et al. [33] conducted a study on MwoA patients and found a correlation between changes in GM volume and altered functional connectivity in MwoA patients. These results suggest that the middle frontal cortex plays an important role in the pathophysiology of migraines. Additionally, the study found decreased functional connectivity in the left PCC and significantly increased functional connectivity in the left cerebellum lobule VI. Similar to the previous study, our study also found a significant change in PCC between the MwoA and control groups. Significant differences were observed in ACC and MCC measurements. In terms of GM volume differences, our study found significant differences between the control group and all migraine patients.

Masson et al. [34] reported that they could not detect any brain anatomical differences in migraine patients regarding GM volume, cortical surface (thickness, gyrification, and sulcus depth) as evaluated by surface-based morphometry (SBM), and WM integrity as evaluated by tract-based spatial statistics (TBSS). Diffusion tensor imaging (DTI) also demonstrated that WM volume was reduced in migraine patients in the left superior longitudinal fasciculus (SLF). Our study only used volumetric analysis and did not include surface-based morphometry (SBM), tract-based spatial statistics (TBSS), or DTI methods. Our results suggest that patients experiencing chronic pain, specifically prolonged migraines, may have thinner gray matter due to chronic cortical ischemia.

This study has limitations, such as a retrospective study, a relatively limited sample size, and the exclusion of patient groups. Therefore, further research with larger and more diverse cohorts is essential to confirm and generalize these findings. Nevertheless, the novel findings of this study may contribute to the knowledge of the pathophysiology of chronic pain in long-term migraine.

In conclusion, our study revealed significant volumetric changes in specific brain regions related to pain that are associated with long-duration migraines (chronic pain). These regions include the anterior, middle, and posterior cingulate cortex, cortical gray matter, total brain volume, postcentral gyrus, nucleus accumbens, hippocampus, thalamus, parahippocampus, and anterior insula.

The negative correlations observed indicate that longer durations of chronic pain may lead to volumetric reductions in particular brain structures involved in pain processing. This information has the potential to advance our understanding of chronic pain in long-standing migraine and could guide the development of novel treatment strategies targeting pain-related brain regions for the clinical management of chronic pain.

Conflict of interest: The authors did not declare any conflicts of interest.

References

1. Treede, RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain 2015;156:1003-1007. https://doi.org/10.1097/j.pain.0000000000000160
2. Davis KD, Flor H, Greely HT, et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat Rev Neurol 2017;13:624-638. https://doi.org/10.1038/nrneurol.2017.122
3. Kim JH, Suh SI, Seol HY, et al. Regional grey matter changes in patients with migraine: a voxel-based morphometry study. Cephalalgia 2008;28:598-604. https://doi.org/10.1111/j.1468-2982.2008.01550.x
4. Valfrè W, Rainero I, Bergui M, Pinessi L. Voxel-based morphometry reveals gray matter abnormalities in migraine. Headache 2008;48:109-117. https://doi.org/10.1111/j.1526-4610.2007.00723.x
5. Qin Z, He XW, Zhang J, et al. Structural changes of cerebellum and brainstem in migraine without aura. J Headache Pain 2019;20:93(e1-9). https://doi.org/10.1186/s10194-019-1045-5

6. Palm Meinders IH, Arkink EB, Koppen H, et al. Volumetric brain changes in migraineurs from the general population. Neurology 2017;89:2066-2074. https://doi.org/10.1212/WNL.0000000000004640
7. Schwedt TJ, Dodick DW. Advanced neuroimaging of migraine. Lancet Neurol 2009;8:560-568. https://doi.org/10.1016/S1474-4422(09)70107-3
8. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology 2013;81:1260-1268. https://doi.org/10.1212/WNL.0b013e3182a6cb32
9. Bonanno L, Lo Buono V, De Salvo S, et al. Brain morphologic abnormalities in migraine patients: an observational study. J Headache Pain 2020;21:39(e1-6). https://doi.org/10.1186/s10194-020-01109-2
10. Kreitzer AC, Malenka RC. Striatal plasticity and basal ganglia circuit function. Neuron 2008;60:543-554. https://doi.org/10.1016/j.neuron.2008.11.005
11. Kruit MC, Launer LJ, Overbosch J, van Buchem MA, Ferrari MD. Iron accumulation in deep brain nuclei in migraine: a population-based magnetic resonance imaging study. Cephalalgia 2009;29:351-359. https://doi.org/10.1111/j.1468-2982.2008.01723.x
12. Yuan K, Zhao L, Cheng P, et al. Altered structure and resting-state functional connectivity of the basal ganglia in migraine patients without aura. J Pain 2013;14:836-844. https://doi.org/10.1016/j.jpain.2013.02.010
13. Rocca MA, Messina R, Colombo B, Falini A, Comi G, Filippi M. Structural brain MRI abnormalities in pediatric patients with migraine. J Neurol 2014;261:350-357. https://doi.org/10.1007/s00415-013-7201-y
14. Younis S, Hougaard A, Noseda R, Ashina M. Current understanding of thalamic structure and function in migraine. Cephalalgia 2019;39:1675-1682. https://doi.org/10.1177/0333102418791595
15. Magon S, May A, Stankewitz A, et al. Morphological abnormalities of thalamic subnuclei in migraine: a multicenter MRI study at 3 tesla. J Neurosci 2015;35:13800-13806. https://doi.org/10.1523/JNEUROSCI.2154-15.2015
16. Granziera C, DaSilva AF, Snyder J, Tuch DS, Hadjikhani N. Anatomical alterations of the visual motion processing network in migraine with and without aura. PLoS Med 2006;3:e402(1915-1921). https://doi.org/10.1371/journal.pmed.0030402
17. Chen XY, Chen ZY, Dong Z, Liu MQ, Yu SY. Regional volume changes of the brain in migraine chronification. Neural Regen Res 2020;15:1701-1708. https://doi.org/10.4103/1673-5374.276360
18. Maleki N, Becerra L, Brawn J, McEwen B, Burstein R, Borsook D. Common hippocampal structural and functional changes in migraine. Brain Struct Funct 2013;218:903-912. https://doi.org/S0896-6273(01)00533-5
19. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288:1769-1772. https://doi.org/10.1126/science.288.5472.1769
20. Bliss TV, Collingridge GL, Kaang BK, Zhuo M. Synaptic plasticity in the anterior cingulate cortex in acute and chronic pain. Nat Rev Neurosci 2016;17:485-496. https://doi.org/10.1038/nrn.2016.68
21. Xiao X, Ding M, Zhang YQ. Role of the anterior cingulate cortex in translational pain research. Neurosci Bull 2021;37:405-422. https://doi.org/10.1007/s12264-020-00615-2
22. Davis KD, Taub E, Duffner F, et al. Activation of the anterior cingulate cortex by thalamic stimulation in patients with chronic pain: a positron emission tomography study. Neurosurg Focus 2000;8:1-6. https://doi.org/10.3171/foc.2000.8.2.7
23. Talbot J, Villemure JG, Bushnell MC, Duncan GH. Evaluation of pain perception after anterior capsulotomy: a case report. Somatosens Mot Res 1995;12:115-126. https://doi.org/10.3109/08990229509101503
24. Mo J, Zhang J, Hu W, Luo F, Zhang K. Whole-brain morphological alterations associated with trigeminal neuralgia. J Headache Pain 2021;22:95(e1-10). https://doi.org/10.1186/s10194-021-01308-5
25. Zhang J, Su J, Wang M, et al. The posterior insula shows disrupted brain functional connectivity in female migraineurs without aura based on brainnetome atlas. Sci Rep 2017;7:16868(e1-12). https://doi.org/10.1038/s41598-017-17069-8
26. Tso AR, Trujillo A, Guo CC, Goadsby PJ, Seeley WW. The anterior insula shows heightened interictal intrinsic connectivity in migraine without aura. Neurology 2015;84:1043-1050. https://doi.org/10.1212/WNL.0000000000001330
27. Mammadkhanli O, Kehaya S, Solak S, Yagmurlu K. Insular cortex involvement in migraine subjects with chronic pain: a volumetric radiological and clinical study. Journal of Clinical Neuroscience 2024;123:157-161. https://doi.org/10.1016/j.jocn.2024.03.034
28. Neumann N, Domin M, Schmidt CO, Lotze M. Chronic pain is associated with less grey matter volume in the anterior cingulum, anterior and posterior insula and hippocampus across three different chronic pain conditions. Eur J Pain 2023;27:1239-1248. https://doi.org/10.1002/ejp.2153
29. Yin T, Lan L, Tian Z, et al. Parahippocampus hypertrophy drives gray matter morphological alterations in migraine patients without aura. J Headache Pain 2023;24:53(e1-12). https://doi.org/10.1186/s10194-023-01588-z
30. Silva NO, Maciel NM, Nather JC Jr, et al. White matter lesions identified by magnetic resonance in women with migraine: a volumetric analysis and clinical correlations. Diagnostics (Basel) 2023;13:799(e1-13). https://doi.org/10.3390/diagnostics13040799

31. Chen ZH, Cui YL, Sun JT, et al. The brain structure and function abnormalities of migraineurs: A systematic review and neuroimaging meta-analysis. Front Neurol 2022;13:1022793. https://doi.org/10.3389/fneur.2022.1022793

32. Zhang X, Zhou J, Guo M, et al. A systematic review and meta-analysis of voxel-based morphometric studies of migraine. J Neurol 2023;270:152-170. https://doi.org/10.1007/s00415-022-11363-w

33. Cao Z, Yu W, Zhang Z, et al. Decreased gray matter volume in the frontal cortex of migraine patients with associated functional connectivity alterations: a VBM and rs-FC Study. Pain Res Manag 2022;2022:2115956. https://doi.org/10.1155/2022/2115956

34. Masson R, Demarquay G, Meunier D, et al. Is migraine associated to brain anatomical alterations? New data and coordinate-based meta-analysis. Brain Topogr 2021;34:384-401. https://doi.org/10.1007/s10548-021-00824-6

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Authors' contributions to the article

O.M. and K.Y. conceptualized the main idea and hypothesis of the study. O.M. and S.K. developed the theory and structured/edited the Materials and methods section. O.M., S.K., E.S. and A.T.A. (and/or other names) conducted the data evaluation in the Results section. The Discussion section of the article was authored by O.M. and K.Y.

O.M., K.Y., S.K. and O.S. reviewed, corrected, and approved the manuscript. Additionally, all authors contributed to the drafting or editing of parts of the manuscript and endorsed the final version.

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Evaluation of brainstem auditory-evoked potentials in infants with iron deficiency anemia

Demir eksikliği anemisi olan infantlarda beyin sapı işitsel uyarılmış potansiyel yanıtlarının değerlendirilmesi

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Abstract

Purpose: To evaluate and compare the brain functions of infants with and without Iron Deficiency anaemia (IDA) electrophysiologically with brainstem auditory potentials (BAEPs).

Materials and methods: BAEP tests were performed on 26 healthy infants and 26 infants with iron deficiency anaemia, aged 6-24 months, who were followed through the Paediatric Haematology Department at SDU Faculty of Medicine. Children were classified as anaemic if their haemoglobin (Hb) level fell below -2 standard deviations for their age. All patients diagnosed with iron deficiency anaemia received 5 mg/kg/day of divalent iron glycine sulphate complex in three doses daily for a duration of 12 weeks, to be taken on an empty stomach. Both group were orally administered Chloral hydrate at a dosage of 50 mg/kg prior to the BAEP test to induce sedation. The BAEP was recorded at a sound intensity level of 90 decibels, with a frequency of 10 Hertz, and with click stimuli ranging from 1000 to 2000. The BAEP test was administered to the IDA group before and after treatment, as well as to the control group, with a 3-month interval between tests.

Results: 14 (53.8%) of the IDA patients were males, and 16 (61.5%) of the control group were females. Patients with IDA had an average age of 14.4±3.09 months, while the control group patients have an average age of 11.2±4.04 months. Patients with iron deficiency anaemia had lower pre-treatment levels of Hb, Hct, MCV, MCH, MCHC, transferrin saturation percentage, and ferritin compared to the control group, whereas platelet and RDW values were greater (p<0.05). The study compared the Brainstem Auditory Evoked Potential (BAEP) values of patients with Iron Deficiency Anaemia (IDA) before treatment with those of control patients. The results indicated that the III-V interval, showing nerve conduction time, was significantly prolonged in the pre-treatment BAEPs (p=0.002). There was no significant difference in interpeak latencies between the control group and patients with iron deficiency anaemia (IDA) following therapy (p<0.05). Significant differences were found in the I-III, III-V, and I-V interpeak latencies of individuals with iron deficiency anaemia before and after treatment (p<0.05).

Conclusion: Iron deficiency anaemia appears to affect the functional development of the auditory system. Untreated iron deficiency anaemia, especially in infancy, may have long-term effects on the central auditory system. Consequently, this can result in changes in the maturation of neuro-functional.

Keywords: Iron deficiency anaemia, myelination, BAEP.

Altin H, Akhan G, Tunc B. Evaluation of brainstem auditory-evoked potentials in infants with iron deficiency anemia. Pam Med J 2024;17:644-652.

Öz

Amaç: Demir eksikliği anemisi (DEA) olan ve olmayan bebeklerin beyin fonksiyonlarını beyin sapı işitsel potansiyelleri (BAEPs) ile elektrofizyolojik olarak değerlendirmek ve karşılaştırmaktır.

Gereç ve yöntem: SDÜ Tıp Fakültesi Pediatrik Hematoloji Bilim Dalı'nda takip edilen, yaşları 6-24 aylık, 26 DEA'lı olan ve 26 DEA'lı olmayan sağlıklı çocuğa BAEP testi uygulandı. Hemoglobin (Hb) değeri yaşına göre -2SD'nin altında olan çocuklar anemik olarak kabul edildi. DEA'lı tüm hastalara aç karnına 12 hafta boyunca 3 dozda 5 mg/kg/gün iki değerlikli demir glisin sülfat kompleksi verildi. Sedasyon için testten önce kloral hidrat (50 mg/kg/doz) oral olarak verildi. BAEP, 90dB, frekans 10 Hz ve 1000-2000 klik uyaranla kaydedildi. Bu test, DEA grubuna tedaviden önce ve sonra olmak üzere iki kez, kontrol grubuna ise 3 ay arayla iki kez uygulandı.

Bulgular: DEA hastalarının 14'ünü (%53,8) erkekler, kontrol grubunun 16'sını (%61,5) kadınlar oluşturdu. DEA'lı hastaların yaş ortalaması 14,4±3,09 ay, kontrol grubu hastalarının yaş ortalaması ise 11,2±4,04 aydır. DEA'lı hastaların tedavi öncesi Hb, Hct, MCV, MCH, MCHC, transferrin satürasyon yüzdesi ve ferritin değerleri kontrol grubundan daha düşükken, trombosit ve RDW değerleri daha yüksektir (p<0,05). DEA'lı grubunun tedavi öncesi ile kontrol grubunun interpik latansları karşılaştırıldığında, DEA'lı grubun III-V interpik latansında uzama tespit edilmiştir (p=0,002). Kontrol grubunun ve DEA'lı grubun tedavi sonrası interpik latansları karşılaştırıldığında, interpik latans değerlerinde anlamlı fark tespit edilmedi p>0,05). DEA hastaların tedavi öncesi ve tedavi sonrası I-III, III-V ve I-V interpik latans değerlerinde anlamlı fark tespit edildi (p<0,05).

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Sonuç: Demir eksikliği anemisinin işitsel sistemin fonksiyonel gelişimini etkilediği görülmektedir. Tedavi edilmeyen demir eksikliği anemisi, özellikle bebeklik döneminde, merkezi işitme sistemi üzerinde uzun vadeli etkileri olabilir. Bu durum nöro-fonksiyonel yapıların maturasyonunda değişikliklere yol açabilir.

Anahtar kelimeler: Demir eksikliği anemisi, miyelinizasyon, BAEP.

Altın H, Akhan G, Tunç B. Demir eksikliği anemisi olan infantlarda beyin sapı işitsel uyarılmış potansiyel yanıtlarının değerlendirilmesi. Pam Tıp Derg 2024;17:644-652.

Introduction

Iron deficiency is the predominant nutritional problem globally. This inadequacy persists as a significant public health issue worldwide, particularly notable in countries with low to middle socioeconomic levels [1, 2]. The global prevalence of anaemia in children aged 6-59 months is over 40% [3]. The prevalence of anaemia in children in Türkiye ranges from 15.2% to 62.5% [4]. Anaemia is defined as a haemoglobin (Hb) level that is more than 2 standard deviations below the average for the age of the individual [5]. Infants and young children are susceptible to iron deficiency anaemia because of their rapid growth, whereas adolescent girls are at risk due to menstrual blood loss [6]. Iron is present in the composition of our body's haemoglobin, myoglobin, and other enzymes. Iron is involved in various crucial tasks such oxygen transfer, adenosine triphosphate (ATP) and deoxyribonucleic acid (DNA) synthesis, mitochondrial activities, myelination, neurotransmitter regulation, and serotonin production [7]. Research has demonstrated that infants with iron deficiency (ID) perform worse in mental and motor development assessments compared to infants with adequate iron levels [8]. Iron is essential for the production of myelin. Research on rats has demonstrated that iron deprivation leads to hypomyelination. Iron deficiency has a long-term impact on neuronal conduction and the development of the central nervous system. Myelination or nerve conduction speed decreases as interpeak latencies increase. Reduced interpeak latency is linked to improved myelination [9, 10]. The Brainstem Auditory Evoked Potential (BAEP) test evaluates the auditory pathways in the brainstem of young children, which cannot be assessed through behavioural audiological testing. This study aims to evaluate and compare the brain functions of infants with and without iron deficiency anaemia (IDA) using brainstem auditory potentials (BAEPs).

Materials and methods

This study was conducted between 1.07.2002 and 1.06.2004 at the haematology outpatient clinic of Süleyman Demirel University (SDU) Faculty of Medicine, Department of Child Health and Diseases.

Thirty-four infants between the ages of 6 months and 24 months diagnosed with iron deficiency anaemia and 26 healthy infants in the same age group without iron deficiency or anaemia were included in the research. The study excluded those who had a history of prenatal asphyxia, neonatal hyperbilirubinemia needing treatment, central nervous system infection, preterm, family history of hearing loss, low birth weight, malnutrition, and external auditory canal and middle ear abnormalities. Individuals within a specific age range were classified as having iron deficiency anaemia (IDA) if their haemoglobin (Hb) level was below -2 standard deviations and their ferritin level was below 10ng/ml [5]. The same laboratory tests were performed on the control group at the beginning of the study. The patients were categorised into two groups: the group with IDA (N: 34) and the group without IDA (N: 26). The IDA group received daily oral ferrous sulphate (ADEKA Pharmaceuticals Industry and Trade Inc., Samsun, Türkiye) at a dosage of 5mg/kg per dose for a duration of 12 weeks.

BAEP measurements were conducted twice in each group. BAEP testing was conducted at the study's beginning and again 12 weeks later. BAEPs were recorded and processed with the Nihon Kohden MEB-5504 device in a quiet and poorly light room. Both groups were orally administered 50mg/kg/dose of Chloral hydrate (Galenik Pharmaceuticals and Chemical Substances Domestic and Foreign Industry Trade Inc., İzmir, Türkiye) before the test for sedation. It was dissolved in water. Chloral hydrate sedation does not affect

BAEP parameters [11]. The active electrode was positioned on the earlobes, the vertex reference electrode on the vertex, and the neutral electrode on the forehead. The stimulus was shown to both ears at the same time. The stimulus strength was set at 90 decibels, the frequency at 10 Hertz, and the analysis time at 10 milliseconds. 1000-2000 clinical stimuli were used for each test. The potentials were visualised as a waveform on the monitor, and the I, II, III, IV, and V waves were identified using a cursor. Absolute interpeak latencies (IPL) were then determined. The BAEP recordings were evaluated based on the latency and interpeak latency of the waves. A single value was calculated by averaging the latency values obtained for both the left and right ears. The procedure of our study is summarised in Figure 1.

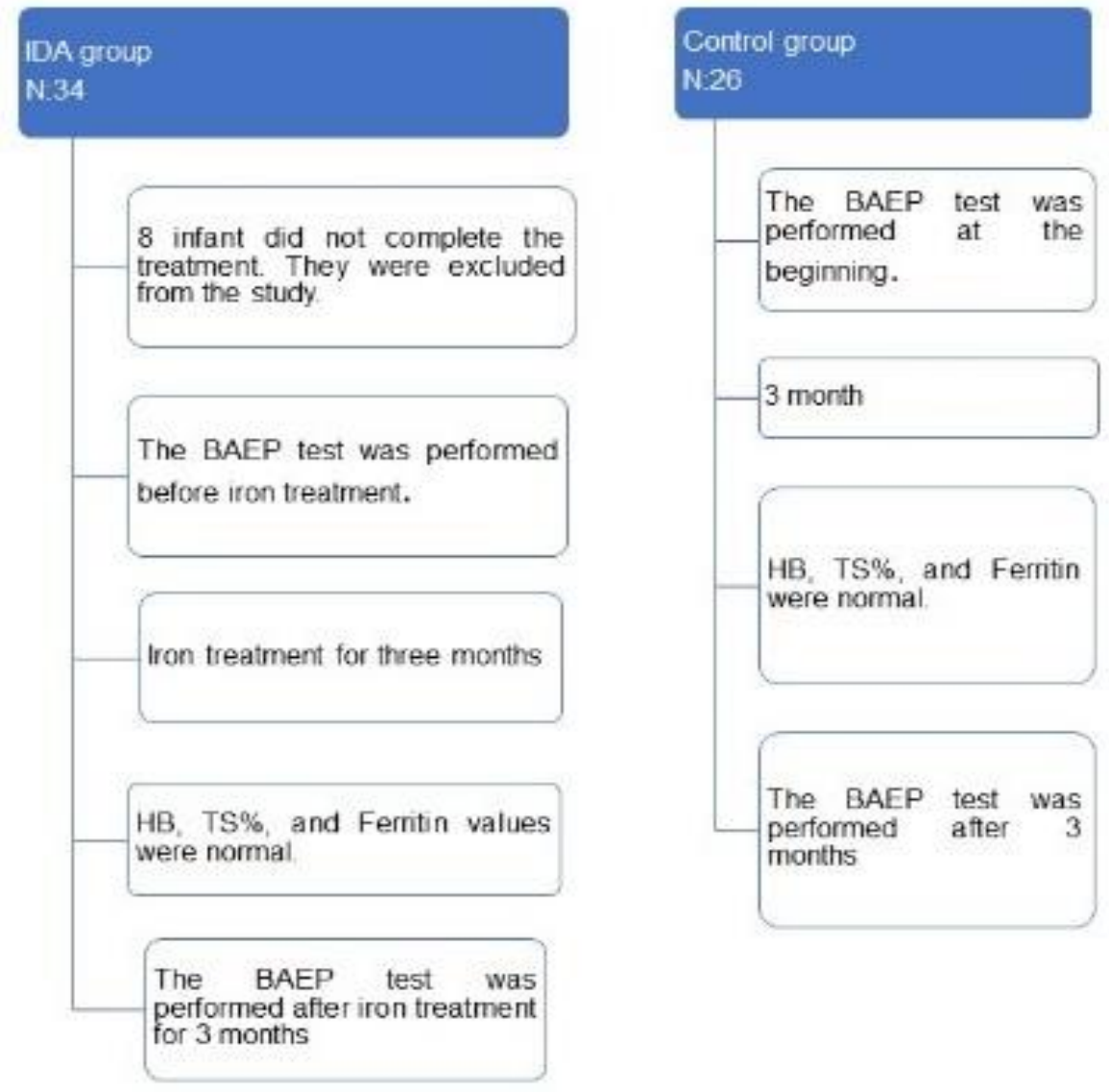

Figure 1. The procedure of our study

Statistical analyses

The study was conducted on a computer using the SPSS 15.0 (Statistical Package for the Social Sciences) statistical package program. In the survey, descriptive statistics of categorical variables were given with frequency and percentage, and descriptive statistics of continuous variables were given with mean and standard deviation values. Kurtosis and Skewness values were calculated to determine whether the BAEP values of the groups with and without iron deficiency anaemia fit the normal distribution. As a result of the calculations, it was resolved that the kurtosis and skewness values of the BAEP values were between +2 and –2, as required in the literature. Pre-treatment and post-treatment values were analysed with paired samples t test. The before and after treatment brainstem auditory evoked potential values of the IDA group were compared with those of the control group without IDA using an Independent Samples t-test. In all statistical analyses, if the *p*-value was below 0.05, it was considered statistically significant.

Informed consent was obtained from each parent participating in the study. The study was conducted by the rules of the Declaration of Helsinki. The SDU Research Fund supported this work under project number 605. The study was produced from the undergraduate thesis prepared before 2020. Suleyman Demirel University Clinical Research Ethics Committee approved of the study protocol before starting up the study.

Results

Eight patients in the IDA group were excluded from the study because they did not use iron therapy regularly. The study was completed with 26 children in the IDA group and 26 children in the control group without IDA and ID. The average age in the IDA group was 14.4±3.09 months, and the average age in the control group was 11.2±4.04 months. There is a significant difference in the haematological test findings between the two groups at the start of the trial. Before starting therapy, patients with iron deficiency anaemia had lower levels of Hb, Hct, MCV, MCH, MCHC, transferrin saturation percentage, and ferritin compared to the control group (p=0.001). Platelet and RDW values shown an increase in comparison (p=0.013, p=0.001) (Table 1).

Comparing the Hb, Hct, MCV, MCHC, transferrin saturation percentage, and ferritin results of the IDA group before and after therapy showed that they were lower before treatment (p=0.001). Platelet and RDW values were considerably elevated compared to other values (p=0.023, p=0.001) (Table 2).

The analysis revealed that the average before-treatment III-V interpeak latency for the iron deficiency anaemia group was 2.19±0.11, whereas the IIII-V interpeak latency average for the control group was 2.06±0.16. A significant difference was found in the before-treatment mean III-V interpeak latency values between the iron deficient anaemia group and the control group p=0.002 as shown in Table 3.

Table 1. Hematological test results of IDA and control groups at the beginning of the study

	Group with IDA N=26 Mean±SD	Control Group N=26 Mean±SD	*t*	*p* value
Hemoglobin (g/dl)	9.5±0.50	12.2±0.38	-21.078	0.001*
HCT	29.5±2.14	36.1±1.7	-11.284	0.001*
MCV	62.4±6.39	78.7±3.1	-11.640	0.001*
MCHC	31.6±2.06	36.7±1.20	-10.784	0.001*
RDW	16.5±2.38	13.7±0.63	5.485	0.001*
Platelet	488x10^3±162	392x10^3±98	2.588	0.013*
TF%	4.20±2.64	27.60±5.93	-17.837	0.001*
Ferritin (mg/L)	4.97±2.51	27.80±11.4	-9.936	0.001*

*= p<0.05, Independent samples t test was conducted on independent groups, t was the test value of the independent samples
N=Number of patients, SD=Standard Deviation, IDA=Iron deficiency anaemia, MCV=Mean Corpuscular Volume, TF=Transferrin Saturation MCHC=Mean Corpuscular Hemoglobin Concentration, RDW=Red cell Distribution Width

Table 2. Haematological test results of the IDA group before and after treatment

	IDA Group Before Treatment N=26 Mean±SD	IDA Group After Treatment N=26 Mean±SD	*t*	*p*-value
Haemoglobin (g/dl)	9.5±0.50	13.1±5.07	-3.633	0.001*
HCT	29.5±2.14	36.1±1.69	-10.601	0.001*
MCV	62.4±6.39	78.5±3.27	-12.016	0.001*
MCHC	31.6±2.06	34.3±1.18	-6.258	0.001*
RDW**	16.5±2.38	13.7±0.74	5.021	0.001*
Platelet	$488x10^3$±162	$392x10^3$±98	2.425	0.023*
TF%	4.20±2.64	26.6±3.11	-30.875	0.001*
Ferritin (mg/L)	4.97±2.51	24.3±10.6	-9.217	0.001*

*=p<0.05, Paired Samples T-test was conducted on dependent groups, t was the test value of the paired samples
N=Number of patients, SD=Standard Deviation, IDA=Iron deficiency anaemia, MCV=Mean Corpuscular Volume, TF=Transferrin Saturation MCHC=Mean Corpuscular Hemoglobin Concentration, RDW=Red cell Distribution Width

Table 3. Brainstem evoked potentials at 90 dB of IDA and control groups at the beginning of the study

	Group with IDA N=26 Mean±SD	Control Group N=26 Mean±SD	*t*	*p* value
Wave I	1.54±0.10	1.56±0.13	0.787	0.435
Wave III	3.79±0.20	3.75±0.30	-0.543	0.589
Wave V	5.88±0.23	5.91±0.27	0.452	0.654
IPL I - III	2.25±0.15	2.18±0.27	–1.067	0.291
IPL III - V	2.19±0.11	2.06±0.16	-3.316	0.002*
IPL I - V	4.33±0.23	4.34±0.25	0.115	0.909

*= p<0.05, p<0.05 was considered statistically significant
Independent samples t test was conducted on independent groups, t was the test value of the independent samples. N=Number of patients IDA=Iron deficiency anaemia, IPL=Interpeak latencies, SD=Standard Deviation

The analysis showed that there was no significant difference in the average BAEP values between the iron deficient anaemia group after treatment and the control group (p>0.05) (Table 4).

The mean interpeak latency values for peak I-III, III-V, and I-V in the iron deficiency anaemia group were 2.25±0.15, 2.19±0.11, and 4.33±0.23 before treatment, and 2.17±0.15, 2.04±0.19, and 4.22±0.20 after treatment, respectively. The mean interpeak latency differences of peak I-III, III-V, and I-V in the iron deficient anaemia group before and after therapy show statistical significance (p<0.05) as indicated in Table 5.

Table 4. Brainstem evoked potentials at 90 dB of IDA and control groups at the end of the study

	Group with IDA N=26 Mean±SD	Control Group N=26 Mean±SD	*t*	*p* value
Wave I	1.58±0.94	1.56±0.13	-0.424	0.673
Wave III	3.75±0.30	3.75±0.30	0.000	0.999
Wave V	5.93±0.20	5.91±0.25	-0.402	0.689
IPL I - III	2.17±0.15	2.18±0.27	0.253	0.801
IPL III - V	2.04±0.19	2.09±0.09	1.234	0.223
IPL I - V	4.22±0.20	4.30±0.24	1.210	0.232

p<0.05 was considered statistically significant
Independent samples t test was conducted on independent groups, t was the test value of the independent samples. N=Number of patients IDA=Iron deficiency anaemia, IPL=Interpeak latencies, SD=Standard Deviation

Table 5. Brainstem evoked potentials at 90 dB of the IDA group before and after treatment

	IDA Group Before Treatment N=26 Mean±SD	IDA Group After Treatment N=26 Mean±SD	*t*	*p* value
Wave I	1.54±0.10	1.58±0.94	-1.774	0.088
Wave III	3.79±0.20	3.75±0.30	0.601	0.553
Wave V	5.88±0.23	5.93±0.20	-1.105	0.280
IPL I - III	2.25±0.15	2.17±0.15	2.100	0.046*
IPL III - V	2.19±0.11	2.04±0.19	4.200	0.001*
IPL I - V	4.33±0.23	4.22±0.20	2.156	0.041*

*= $p<0.05$, $p<0.05$ was considered statistically significant
Paired Samples T-test was conducted on dependent groups, t was the test value of the paired samples
N=Number of patients, IDA=Iron deficiency anaemia, IPL=Interpeak latencies, SD=Standard Deviation

Discussion

This study assessed the brainstem auditory responses of children aged 6-24 months with and without iron deficiency anaemia (IDA) using the Brainstem Auditory Evoked Potential (BAEP) test, a non-invasive procedure. We examined and compared the Brainstem Auditory Evoked Potentials (BAEPs) of both groups at 90 dB at the start and conclusion of the trial. At the beginning of the trial, the IDA group showed significantly extended III-V interpeak latencies ($p<0.05$). After three months of iron treatment, the anomalies in Brainstem Auditory Evoked Potentials (BAEP) in the group with Iron Deficiency Anaemia (IDA) improved as the haematological parameters improved. Oligodendrocytes require iron for the production of myelin. The development of the brainstem auditory pathways continues until the age of two. Research has demonstrated that iron insufficiency and iron deficiency anaemia have a detrimental impact on myelin production. We theorise that the results of our investigation could be attributed to the delayed secondary myelination caused by iron shortage. We believed that conduction was delayed as a result of iron deficient anaemia, resulting in extended III-V interpeak delays.

Sundagumaran and Seethapathy [12] conducted Auditory Brainstem Response (ABR) tests at 70, 50, and 30 dB to patients with and without iron deficient anaemia. The group with anaemia showed extended III-V and I-V interpeak latencies at 50 and 30 dB. Extended III-V interpeak latencies were observed, consistent with our research findings. The authors suggested that the extended ABR III-V interval could be attributed to delayed myelination. They did not investigate brainstem auditory responses post-treatment, unlike our investigation.

Zheng et al. [13] conducted a Brainstem Auditory Evoked Potential (BAEP) investigation on 48 infants with Iron Deficiency Anaemia (IDA) aged 6 to 36 months, finding anormal results in 26 cases. Like our research, they found that brainstem auditory responses showed enhancement following iron treatment in four instances.

Sarici et al. [14] in their study, categorised infants aged 6 to 24 months into two groups: one with iron deficient anaemia and the other as a control group. The brainstem auditory-evoked potential values showed no significant differences between the before-treatment and control group. Additionally, there was no statistically significant variance observed in the BAEP of the study group before and after a three-month period of oral iron therapy. They attributed the lack of difference in BAEP results to the mild to moderate severity of iron deficiency anemia in their patients. In our study showed improvements in Brainstem Auditory Evoked Potential (BAEP) values following three months of iron treatment in patients with iron deficiency anaemia.

Kürekçi et al. [15] in their study, categorised infants aged 6-24 months into three groups: iron deficit, iron deficiency anaemia, and a control group. The BAEP test was performed to all three groups both before and after the treatment. No differences in peak interpeak latencies were found between the groups before and after therapy. They clarified that they did not observe

any distinction due to the mild and moderate iron status in the iron deficiency and iron deficiency anaemia groups.

Roncagliolo et al. [16] analysed the brainstem auditory responses of 6-month-old infants with and without iron deficiency anaemia using the ABR test before treatment and at 6, 12, and 18 months after treatment. While the haematological indicators showed improvement following therapy in the group with anaemia, it was found that the dysfunction in brainstem auditory responses persisted at the 12th and 18th months. Their investigation did not find any enhancement in brainstem auditory responses following iron therapy. Chloral hydrate was used for sedation in our research. Roncaglio et al. [16] measured ABR values during natural sleep without sedation. Methodological differences may exist between our study and their investigation. As we did not investigate the long-term effects of iron deficiency anaemia using the BAEP test in our study, we are unable to provide information on its long-term consequences.

Research indicates that while medication can improve haematological parameters in infants with iron deficient anaemia, long-term motor, sensory, behavioural, and cognitive abnormalities persist [17-20]. Studies have shown that individuals who had iron deficiency anaemia during infancy had worse scores on behavioural performance tests [21]. Neuro-behavioral development, gross motor skills, fine motor skills, and compliance development performance values were poorer in children with iron deficiency compared to those without. An inverse relationship has been discovered between iron deficient anaemia and neurobehavioral development [13]. Studies on animals have demonstrated that a lack of iron in the early stages of life can have lasting impacts on the central nervous system [22].

Lou et al. [23] an investigation revealed that infants born with low ferritin levels and anaemia at 10 months of age exhibited a prolonged III-V interpeak latency.

Amin and et al. [24] studied the relationship between cord serum ferritin levels and auditory brainstem evoked response (ABR) interpeak latencies in infants born at or after 35 weeks of gestational age (GA). Infants with low iron levels (cord serum ferritin: 11-75 ng/mL) were compared to those with normal iron levels (>75 ng/mL). Findings showed that children with latent iron deficit had notably extended interpeak latencies, indicating a link between prenatal iron shortage and atypical auditory neural myelination in infants born at or after 35 weeks gestational age. Their findings supported our study's results.

Elalfy et al. [25] conducted a study with 50 participants diagnosed with iron deficiency anaemia (IDA) and 50 healthy mothers chosen as controls. They conducted Auditory Brainstem Response (ABR) tests on babies within 48 hours after birth and then repeated the procedures at 3 months. The study revealed that neonates of mothers with iron deficiency anaemia (IDA) had higher ABR interpeak latencies compared to the control group. The study found a significant association between ABR test outcomes and the extent of iron insufficiency in mothers and babies. In our study, similar to their results, I-III, III-V and I-V inter-peak latencies were significantly prolonged in the group with iron deficiency anaemia before treatment compared to after treatment (p<0.05).

Iron requirements are most significant during the initial 1000 days of life. Infants aged 6 to 24 months are particularly susceptible to iron insufficiency and iron deficiency anaemia. The initial 1000 days of life are the most critical period for the risk of iron deficiency and its lasting neurological effects. Iron plays a role in brain energy metabolism, neurotransmitter metabolism (particularly dopamine and serotonin), myelin production, and memory processes. Iron is essential for typical neurodevelopment, as evidenced by numerous animal investigations [26]. During this period, it is advisable to conduct comprehensive screening for all infants around 12 months of age, incorporating assessments such as hemoglobin testing and evaluation of iron levels, such as ferritin. These recommendations are predominantly based on expert guidance and clinical assessment [27].

Our study's limitation is that we conducted before and after treatment monitoring of our groups for 3 months and contucted BAEP tests. We could not investigate the prolonged impacts of iron deficient anaemia on brainstem auditory responses. The number of infants in the group could have been slightly higher. The patient

sample size within the groups have been slightly increased.

In conclusion, iron deficiency anaemia adversely affects brainstem auditory responses, although the exact cause is not yet known. Further comprenhensive research is required to elucidate the connection between iron deficiency, iron deficiency anaemia, and auditory functions.

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

References

1. Lopez A, Cacoub P, Macdougall IC, Peyrin Biroulet L. Iron deficiency anaemia. Lancet 2016;387:907-16. https://doi.org/10.1016/S0140-6736(15)60865-0
2. Hess SY, Wessells KR, Haile D, et al. Comparison of published estimates of the national prevalence of iron, vitamin A, and zinc deficiency and sources of inconsistencies. Adv Nutr 2023;14:1466-1478. https://doi.org/10.1016/j.advnut.2023.08.011
3. Stevens GA, Paciorek CJ, Flores Urrutia MC, et al. National, regional, and global estimates of anaemia by severity in women and children for 2000-19: a pooled analysis of population-representative data. Lancet Glob Health 2022;10:627-639. https://doi.org/10.1016/S2214-109X(22)00084-5
4. Özdemir N. Iron deficiency anemia from diagnosis to treatment in children. Turk Pediatri Ars 2015;50:11-9. https://doi.org/10.5152/tpa.2015.2337
5. Fish JD, Lipton JM, Lanzkowsky P. Lanzkowsky's Manual of Pediatric Hematology and Oncology. Seventh Edition. Fish JD, Lipton JM, Lanzkowsky P, editors. Lanzkowsky's Manual of Pediatrics Hematology and Oncology 2022;767-780.
6. Lopez A, Cacoub P, Macdougall IC, Peyrin Biroulet L. Iron deficiency anaemia. Lancet 2016;27:907-916. https://doi.org/10.1016/S0140-6736(15)60865-0
7. Kayıran SM, Gürakan B. Çocuklarda demir eksikliğinin motor gelişim ve bilişsel fonksiyonlar üzerine etkisi. TSK Koruyucu Hekimlik Bülteni 2010;9:529-534. Available at:https://search.trdizin.gov.tr/tr/yayin/detay/111944/cocuklarda-demir eksikliginin-motor-gelisim-ve-bilissel-fonksiyonlar-uzerine-etkisi. Accessed Semptember 12, 2023
8. Akman M, Cebeci D, Okur V, Angin H, Abali O, Akman AC. The effects of iron deficiency on infants' developmental test performance. Acta Paediatr 2004;93:1391-1396.
9. Lee DL, Strathmann FG, Gelein R, Walton J, Mayer Pröschel M. Iron deficiency disrupts axon maturation of the developing auditory nerve. J Neurosci 2012;4:5010-5015. https://doi.org/10.1523/JNEUROSCI.0526-12.2012
10. Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res 2003;53:217-223. https://doi.org/10.1203/01.PDR.0000047657.23156.55
11. Valenzuela DG, Kumar DS, Atkins CL, Beers A, Kozak FK, Chadha NK. Chloral hydrate sedation for auditory brainstem response (ABR) testing in children: safety and effectiveness. Int J Pediatr Otorhinolaryngol 2016;83:175-178. https://doi.org/10.1016/j.ijporl.2016.02.006
12. Sundagumaran H, Seethapathy J. Auditory brainstem response in infants with iron deficiency anaemia. Int J Pediatr Otorhinolaryngol 2019;117:78-81. https://doi.org/10.1016/j.ijporl.2018.11.017
13. Zheng J, Liu J, Yang W. Association of iron-deficiency anemia and non-iron-deficiency anemia with neurobehavioral development in children aged 6-24 months. Nutrients 2021;13:3423(e1-11). https://doi.org/10.3390/nu13103423
14. Sarici SU, Serdar MA, Dündaröz MR, et al. Brainstem auditory-evoked potentials in iron-deficiency anemia. Pediatr Neurol 2001;24:205-208. https://doi.org/10.1016/s0887-8994(00)00270-8
15. Kürekçi AE, Sarici SU, Karaoglu A, et al. Effects of iron deficiency versus iron deficiency anemia on brainstem auditory evoked potentials in infancy. Turk J Pediatr 2006;48:334-669.
16. Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Evidence of altered central nervous system development in infants with iron deficiency anemia at 6 mo: delayed maturation of auditory brainstem responses. Am J Clin Nutr 1998;68:683-690. https://doi.org/10.1093/ajcn/68.3.683
17. Greer FR, Baker RD. Early childhood chronic iron deficiency and later cognitive function: the conundrum continues. Pediatrics 2022;150:e2022058591(e1-2). https://doi.org/10.1542/peds.2022-058591
18. Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 2010;126:1040-50. https://doi.org/10.1542/peds.2010-2576
19. Jáuregui Lobera I. Iron deficiency and cognitive functions. Neuropsychiatr Dis Treat 2014;10:2087-2095. https://doi.org/10.2147/NDT.S72491
20. Lozoff B, Klein NK, Nelson EC, McClish DK, Manuel M, Chacon ME. Behavior of infants with iron-deficiency anemia. Child Dev 1998;69:24-36.
21. Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. Pediatr Res 2003;53:217-223. https://doi.org/10.1203/01.PDR.0000047657.23156.55

22. Chen Q, Connor JR, Beard JL. Brain iron, transferrin and ferritin concentrations are altered in developing iron-deficient rats. J Nutr 1995;125:1529-1535. https://doi.org/10.1093/jn/125.6.1529
23. Lou J, Mai X, Lozoff B, et al. Prenatal iron deficiency and auditory brainstem responses at 3 and 10 months: a pilot study. Hong Kong J Paediatr 2016;20:71-79.
24. Amin SB, Orlando M, Wang H. Latent iron deficiency in utero is associated with abnormal auditory neural myelination in ≥ 35 weeks gestational age infants. J Pediatr 2013;163:1267-1271. https://doi.org/10.1016/j.jpeds.2013.06.020
25. ElAlfy MS, El Farrash RA, Taha HM, Ismail EA, Mokhtar NA. Auditory brainstem response in full-term neonates born to mothers with iron deficiency anemia: relation to disease severity. J Matern Fetal Neonatal Med 2020;33:1881-1888. https://doi.org/10.1080/14767058.2018.1533940
26. McCarthy EK, Murray DM, Kiely ME. Iron deficiency during the first 1000 days of life: are we doing enough to protect the developing brain? Proc Nutr Soc 2022;81:108-118. https://doi.org/10.1017/S0029665121002858
27. Greer FR, Baker RD. Early childhood chronic iron deficiency and later cognitive function: the conundrum continues. Pediatrics 2022;150:e2022058591. https://doi.org/10.1542/peds.2022-058591

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Consent of publication: Additional informed consent was obtained from all individual participants for identifying information in this article.

Ethics committee approval: The study was produced from a Licence thesis before 2020. Suleyman Demirel University Clinical Research Ethics Committee approved of the study protocol before starting up the study (Date: 28.12.2002 and File number: 5/6).

The authors' contributions to the article

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

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Assessment of wound cultures in an oncology hospital

Onkoloji hastanesindeki hastaların yara kültürlerinin değerlendirilmesi

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Abstract

Purpose: The aim of this study is to evaluate the patient's demographic, clinical and laboratory data to determine whether the bacteria isolated from wound cultures are causative agents or colonization, and to determine their antimicrobial susceptibilities. This study aims to assess the demographic, clinical, and laboratory data of patients to distinguish between pathogenic bacteria and colonization in wound cultures, while also determining their antimicrobial susceptibilities.

Materials and methods: This retrospective research was conducted in Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 1, 2021 and December 31, 2022. Two hundred thirty six isolates from 186 patients wound cultures were included in the study. Demographic data, clinical data and laboratory results of the patients were evaluated. The isolated bacteria and their antimicrobial susceptibilities were determined. The Q score system was used to evaluate the microbiological quality of wound samples.

Results: One hundred fifty nine cases (85%) were inpatients. Totally 119 (63.9%) patients were diagnosed with infection. The Q score for 136 samples (85.5%) was assessed as Q3. The most common isolated microorganisms were coagulase negative-staphylococci (CoNS) (19%), Escherichia coli (14.8%), and Staphylococcus aureus (13.1%), respectively in wound bacterial cultures. The methicillin resistance rate was 55.5% in CoNS and 54.1% in Staphylococcus aureus. Gram-negative bacteria were isolated in 81 (59.9%) infected patients.

Among patients with infected wounds, 39 (32.7%) patients had surgical site infections, 25 (21%) prosthesis infections, and diabetic foot infections 3 (2.5%). Infection rates were statistically significantly higher in patients with surgery, prosthesis, and diabetic foot (p=0.054).

Conclusion: The Q score serves as a strong indicator for identifying the causative agent in wound infection and distinguishing it from colonization, thus aiding in the prevention of unnecessary antibiotic use. Regular review of local antibiotic susceptibility data is crucial in the clinical treatment of specific patient groups with oncological conditions.

Keywords: Wound culture, Q score, oncology patient, antimicrobial susceptibility.

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Öz

Amaç: Bu çalışmanın amacı, yara kültürlerinden izole edilen bakterilerin etken/kolonizasyon ayrımının yapılmasında; hastaya ait demografik, klinik ve laboratuvar verilerinin değerlendirilmesi ve etken bakterilerin antimikrobiyal duyarlılıklarının belirlenmesidir.

Gereç ve yöntem: Bu retrospektif araştırma, 1 Ocak 2021-31 Aralık 2022 tarihleri arasında Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. Çalışmaya, 186 hastaya ait 236 yara kültürü dahil edildi. Hastalara ait demografik veriler, klinik veriler ve laboratuvar sonuçları değerlendirildi. İzole edilen bakteriler ve antimikrobiyal duyarlılıkları belirlendi. Yara örneklerinin mikrobiyolojik kalitesini değerlendirmek için Q skor sistemi kullanıldı.

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Bulgular: Vakaların 159'u (%85) yatan hastalardı. Toplam 119 (%63,9) hastada etken olarak kabul edildi. Q puanı 136 örnek için (%85,5) Q3 olarak değerlendirildi. Yara bakteri kültürlerinde en sık izole edilen mikroorganizmalar sırasıyla koagülaz negatif stafilokoklar (KNS) (%19), E. coli (%14,8) ve S. aureus (%13,1) oldu. Metisilin direnci oranı KNS'lerde %55,5; S. aureus'ta ise %54,1 olarak belirlendi. Enfeksiyöz hastaların 81'inde (%59,9) Gram negatif bakteri izole edildi. Enfekte yarası olan hastaların 39'unda (%32,7) cerrahi alan enfeksiyonu, 25'inde (%21) protez enfeksiyonu, 3'ünde (%2,5) diyabetik ayak enfeksiyonu vardı. Ameliyatlı, protezli ve diyabetik ayaklı hastalarda enfeksiyon oranları istatistiksel olarak anlamlı derecede yüksekti (p=0,054).
Sonuç: Q skorlaması yara enfeksiyonunda etkenin saptanması ve kolonizasyonun dışlanmasında güçlü bir belirteçtir ve gereksiz antibiyotik kullanımının önlenmesine yardımcı olur. Onkolojik hastalar gibi özel hasta gruplarının ampirik tedavilerinin verilmesinde lokal antibiyotik duyarlılık verilerinin güncel olarak incelenmesi gereklidir.

Anahtar kelimeler: Yara kültürü, Q skoru, onkoloji hastaları, antimikrobiyal duyarlılık.

Arslan F, Tavukcu E, Demirhan B, Mumcuoğlu İ, Ulaş T, Süzük Yıldız S, Güreser AS, İnan N, İskender G, Dal T. Onkoloji hastanesindeki hastaların yara kültürlerinin değerlendirilmesi. Pam Tıp Derg 2024;17:654-663.

Introduction

Wound infections are one of the most common causes of healthcare-associated infections (HCAIs) and lead to high mortality and morbidity. Timely and accurate evaluation of wound infections is vital. Determining the causative pathogens and their antimicrobial susceptibility increases the effectiveness of treatment and reduces mortality and morbidity. Management of wound infections will also contribute to the Sustainable Development Goals. According to 2017 data from the National Healthcare-Associated Infections Surveillance Network (USHIESA), 8,194 cases (1.3%) out of 617,745 total healthcare infections were attributed to surgical site infections (SSIs) [1].

The aim of this study is to differentiate whether the bacteria isolated from wound cultures are pathogens or colonization, to determine the antimicrobial susceptibility of bacteria interpreted as causative agents, and to evaluate the demographic, clinical and laboratory data of the patients.

Material and methods

Cultures of 186 patients were included in the study between January 1, 2021 and December 31, 2022. Demographic data, clinical data and laboratory results of the patients (including C-reactive protein-CRP levels, procalcitonin levels and leukocyte counts) were evaluated. Clinical samples sent to the Medical Microbiology Laboratory were stained with Gram stain and microscopic examination was performed. Culture samples were simultaneously inoculated into 5% sheep blood agar and eosin methylene blue agar and evaluated after the appropriate incubation period. The isolated bacteria were identified using traditional microbiological methods and the VITEK® 2 automated system (BioMérieux, France). Antibiotic susceptibility test results were determined according to EUCAST standards. Antibiotic susceptibility tests were performed both with the disc diffusion method and the VITEK® 2 automatic system (BioMérieux, France). Sensitive (S) and sensitive increasing exposure (I) results were considered sensitive.

In this retrospective study, demographic and clinical findings of the patients were obtained from the hospital data system. CRP and procalcitonin level were determined by AU5800 (Beckman Coulter INC) and Centaur XP (Siemens Healthcare), and leukocyte count levels were evaluated using the Automated Hematology Analyzer (Mindray BC-6200, Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China).

Colonization was characterized by the isolation of microorganisms from the wound without local and/or systemic signs and symptoms of infection. Local infection was defined by the presence of signs and symptoms of infection, which included erythema, local warmth, swelling, purulent discharge, delayed wound healing beyond expected timelines, the appearance of new or intensified pain, and increased foul odor [2]. Surgical site infections (SSI) are defined as infections that affect the incisional wound created during the surgical procedure or occur near the surgical site or organ. SSI was diagnosed according to the criteria of the Center for Disease Control and Prevention (CDC). Infections that occurred

within 30 days after surgery and 90 days when an implant (e.g., hip prosthesis) was used were designated as SSIs [3].

The Q score system was used to evaluate sample quality and determine the required extent of culture investigation for potential pathogens (PP). The Q score assigns positive values to the number of polymorphonuclear cells (PMNs) and negative values to the number of squamous epithelial cells (SECs) observed directly in the Gram-stained smear. The number resulting from the addition of these values creates the "Q score". Starting with a maximum value of 3, the score then continues to decrease values, maintaining the lower limit of zero; Negative numbers are always rounded to zero in the final calculation of the Q score [4, 5].

Statistical analysis

Statistical data were analysed using SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The categorical data were expressed as percentage, and numbers; continuous variables were expressed as median, minimum and maximum. The Chi-square test was used to compare the categorical data. *P* value <0.05 was considered to be significant statistically.

This research was approved by the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-Interventional Clinical Research Ethics Committee.

Results

Of the 186 patients with positive wound cultures, 71 (38.2%) were male and 115 (61.8%) were female. The average age of the patients was 61.72 years. One hundred twenty-nine (69.4%) of the cases were inpatients and 27 (14.5%) were outpatients. Thirty (16.1%) patients were from intensive care unit. One hundred forty-two (76.3%) of the samples consisted of wound swabs, and 44 (23.7%) consisted of tissue, debridement, and drainage fluids. According to CDC criteria, 119 (64%) of the bacteria isolated from wound cultures were identified as causative agents and 42 (22.6%) were identified as colonization (Table 1).

Table 1. Demographic and clinical characteristics of patients

Demographic characteristics	
The average age (years)	61.7
Gender	
Female	115 (61.8%)
Male	71 (38.2%)
Hospital Unit	
Inpatient	129 (69.4%)
Outpatient	27 (14.5%)
Intensive care patients	30 (16.1%)
Distribution of wound samples	
Wound swab	142 (76.3%)
Tissue, debridement	44 (23.7%)
Infection	119 (64%)
Colonization	42 (22.6%)
Undetermined sample	25 (13.4%)

Out of 154 samples with available Gram stain results, in 53 samples (34.4%), the leukocyte count was ≥25, and no epithelium was observed under x10 magnification microscopy. The Q score for these 53 samples was assessed as Q3. In 41 samples (26.6%), the leukocyte count during the x10 scan fell within the range of 1-9, and epithelium was absent. The Q score for these 41 samples was also Q3. For 42 samples (27.2%) where no cells were detected, the Q Score was designated as Q3. The Q score for these 136 samples (88.2%) was assessed as

Q3. In 11 samples (7.2%), only 1-9 squamous epithelial cells were visible in each x10 scan area, and no leukocytes were detected so the Q score was determined as Q0.

Bacterial or yeast cells were observed in only seven samples (4.6%) by direct microscopy. The most frequently isolated microorganisms from wound cultures were coagulase-negative staphylococci (CoNS) (19%), *Escherichia coli* (14.8%) and *Staphylococcus aureus* (13.1%), respectively (Table 2). A single agent was isolated in 155 of the patients included in the study, two agents were isolated in 29 patients, and three or more different microorganisms were isolated in two patients. It was observed that the microorganism isolated from wound cultures was simultaneously isolated from non-wound samples in 25 of the patients. Especially *E. coli* (8 cases), *Staphylococcus* spp. (5 cases) and *Candida* spp. (5 cases) were the most common isolates in these concurrent samples.

The methicillin resistance rate was 55.5% in CoNS and 54.1% in *S. aureus* (Table 3). Antimicrobial susceptibility of *Enterobacterales* to cephalosporins and carbapenem was observed 49.9% and 78.3%, respectively. In non-fermenter Gram-negative bacteria, ceftazidime and carbapenem susceptibility was 32% and 52%, respectively (Table 4). In particular, ceftazidime-avibactam susceptibility was performed for multidrug resistance 42 Gram-negative isolates and 88% (37/42) was susceptible.

Table 2. The distribution of microorganism species isolated in wound cultures

Microorganism	Number (n=236)	Percent (%)
Coagulase negative staphylococci	46	19.4
Escherichia coli	35	14.8
Staphylococcus aureus	31	13.1
***Klebsiella* spp.**	26	11
Enterococcus faecalis/faecium	18	7.6
Acinetobacter baumannii	13	5.5
Pseudomonas aeruginosa	12	5
***Enterobacter* spp.**	11	4.6
***Candida* spp.**	8	3.3
***Proteus* spp.**	6	2.5
Others	30	13.2

Table 3. Distribution of antibiotic susceptibility of Gram-positive microorganisms isolated in wound culture

	AM (%)	GN (%)	GNHR (%)	CIP (%)	LEV (%)	E (%)	DA (%)	LNZ (%)	VA (%)	TEC (%)	FA (%)	SXT (%)	FOX (%)
CoNS (n=46)	NA	NA	NA	23.2*	27.2*	26.6	97	97.8	100	100	41.3	71.7	44.5
S. *aureus* (n=31)	NA	NA	NA	62.5*	NA	67.7	77.4	96.7	100	100	89.2	90.3	45.9
***Enterococcus* spp. (n=18)**	50	75	40	36.6	50	IR	IR	100	72.2	77.7	IR	IR	NA

AM: Ampicillin, GN: Gentamicin, GNHR: Gentamicin high dose resistance, CIP: Ciprofloxacin, E: Erythromycin, DA: Clindamycin, LNZ: Linezolid VA: Vancomycin, TEC: Teicoplanin, FA: Fusidic acid, SXT: Trimethoprim-Sulphamethoxazole, FOX: Cefoxitin, NA: Not applicable
(*): Susceptible, increased exposure, IR: Intrinsic Resistance

Table 4. Distribution of antibiotic susceptibility of Gram-negative microorganisms isolated in wound cultures

	CN (%)	AK (%)	AM (%)	TPZ (%)	CXM (%)	CAZ (%)	CRO (%)	FEP (%)	ETP (%)	MEM (%)	IMP (%)	CIP (%)	LEV (%)	TGC (%)	SCF (%)	SXT (%)
E. coli (n=35)	84	100	22.8	60.6	6.2	54.8	51.5	52.9	88.5	100	100	50	61.5	81.4	89.9	54.2
Klebsiella spp. (n=26)	46.1	54.1	IR	36.3	5.8	30.7	30.7	36	57.6	57.6	66.6	38.4	25	80	50	42.3
Enterobacter spp. (n=11)	70	100	IR	72.7	0	63.6	54.5	70	90.9	100	100	72.7	NA	NA	77.7	72.7
Proteus spp. (n=6)	40	100	16.6	100	0	100	83.3	100	100	100	100	50	100	16.6	100	33.3
Pseudomonas aeruginosa (n=12)	16.6	100	NA	33.3	NA	66.6	NA	100	NA	90.9	66.6	50	66.6	IR	100	NA
Acinetobacter baumannii(n=13)	36.3	58.3	NA	15.3	NA	27.2	NA	NA	NA	23	50	9	0	87.5	33.3	41.6

CN: Gentamicin, AK: Amicasin, AM: Ampicillin, TPZ: Piperacillin-tazobactam, CXM: Cefuroxime, CAZ: Ceftazidime, CRO: Ceftriaxone, FEP: Cefepime, ETP: Ertapenem MEM: Meropenem, IMP: Imipenem, CIP: Ciprofloxacin, LEV: Levofloxacin, TGC: Tigecycline, SCF: Cefoperazone/sulbactam, NA: Not applicable IR: Intrinsic Resistance SXT: Trimethoprim/sulfamethoxazole

In our study, we evaluated the clinical, laboratory data and treatment schedule and divided the patients into two groups: infection and colonization; (Table 5). Since we could not access the data of 25 patients, we evaluated infection or colonization in a total of 161 patients (Table 5). There was no significant difference in the presence of fever, local infection symptoms, CRP level, procalcitonin level and leukocyte count in patients with infection and colonization (p>0.05) (Table 5). However, in 77.6% (125/161) of the cases, CRP levels were above normal limits, with an average of 98.4. Regarding procalcitonin, high levels were observed in 17.4% (28/161) of the patients tested. Empirical treatment and post-culture treatment was significantly compatible (p≤0.05). Wound isolates identified as pathogens were diagnosed with cancer in 65 cases (54.6%), while among those considered as colonization, 22 cases (52.3%) were diagnosed with cancer. Patients with infectious wounds, 39 (32.8%)

had surgical site infection, 25 (21%) had prosthesis infection, and 3 (2.5%) had diabetic foot infection. Infection rates were higher in patients with surgery, prosthesis and diabetic feet (p=0.054). While gram-negative bacteria were isolated in 81 (60%) of the patients with infectious wounds, gram-positive bacteria were isolated in 30 (71.4%) of the patients with colonization.

Table 5. Clinical and laboratory findings of patients with wound infection/colonization

	Infection n=119, (%)	Colonization n=42, (%)	Values/*p*
Clinical findings			
Fever	26 (21.8)	5 (11.9)	1.932/0.381
Local signs of infection			
Fever, erythema, pain, tenderness	13 (10.9)	4 (9.5)	1.560/0.906
Serous discharge	22 (18.5)	6 (14.2)	
Fistula	3 (2.5)	1 (2.3)	
Purulent discharge	23 (19.3)	7 (16.6)	
Local signs of infection ≥1	27 (22.7)	8 (19)	
Laboratory findings			
Increased CRP (C-reactive protein)	98 (82.3)	27 (64.2)	92.497/0.437
Increased Procalcitonin	19 (15.9)	9 (21.4)	2.356/0.502
Increased Leukocyte count	41 (34.4)	15 (35.7)	15.585/0.792
Receiving empirical treatment	90 (75.6)	28 (66.6)	4.316/0.497
Compliance with empirical therapy and post-culture therapy			
The same with post-culture treatment	38 (32)	21 (50)	1.142/0.378
Narrowed Post-culture therapy	14 (11.8)	0	0.798/0.508
Extended post-culture therapy	43 (36.1)	11 (26.2)	1.326/0.315
Antibiotic started patients for the first time after culture	16 (13.4)	2 (4.8)	1.762/0.184
Patients not given antibiotics	8 (6.7)	8 (19)	3.735/0.053
The presence of cancer	65 (54.6)	22 (52.3)	0.063/0.802
The presence of prosthesis	28 (23.5)	8 (19)	1.744/0.187
Clinic/followed unit			
Outpatient	16 (13.5)	6 (14.3)	0.030/0.985
Inpatient	81 (68)	28 (66.7)	
Intensive care unit	22 (18.5)	8 (19)	
Wound types			
Surgical side	39 (32.8)	8 (19)	7.693/0.103
Prosthesis	25 (21)	6 (14.3)	
Diabetic foot	3 (2.5)	2 (4.8)	
Other	52 (43.7)	26 (61.9)	
History of hospitalization in the last three months	51 (42.8)	14 (33.3)	0.366/0.545
Culture result	**n=135**	**n=42**	
Gram negative isolation	81 (60)	7 (16.6)	9.704/0.018
Gram positive isolation	51 (37.8)	30 (71.4)	4.892/0.026
Candida isolation	3 (2.2)	5 (12)	6.071/0.103

The Pearson Chi-Square test was used for the categorical variables

Discussion

The human skin hosts a wide variety of microorganisms, many of which play a crucial role in defending against harmful pathogens through a phenomenon known as bacterial interference. These microorganisms, constituting the skin's flora, can be categorized as either resident or transient. Resident bacteria refer to the naturally occurring microorganisms that inhabit an individual's skin. These bacteria make their home on visible skin areas and within the skin's accessory structures. Transient bacteria are acquired when individuals come into contact with others or are exposed to surfaces teeming with bacterial presence. Among the diverse array of bacteria present on human skin, notable species include *Staphylococcus, Micrococcus, Peptococcus, Corynebacterium, Brevibacterium, Propionibacterium, Streptococcus, Neisseria,* and *Acinetobacter* species. Additionally, *Candida* spp. and the mites also take up residence on the skin. The quantity of bacteria within the stratum corneum is regulated to a certain extent by the continuous shedding of squames from the uppermost skin layer. The research findings highlighted that a significant portion of wound infections are caused by microorganisms commonly found in the body's natural flora and were seen in hospitalized patients. The skin's microbial community can generate biofilm, potentially leading to colonization and subsequent infection [6-11]. Similarly, in our study, the majority of the patients (>85%) were hospitalized patients. In our study, gram-negative bacteria isolation was detected in 60% of patients with infectious wounds, and gram-positive bacteria in 71.4% of patients with colonization. This data suggested that Gram-negative bacterial wound infections were more frequent in our hospital.

The colonized wounds' progress into infections is determined by several crucial factors. These factors encompass the concentration of bacteria per Gram of tissue and the host's immune system. In cases with appropriate wound care and management, the infection can escalate into septicemia, potentially leading to fatal outcomes. Wounds that have not progressed through the normal healing process and are open for ≥1 month are classified as chronic wounds. The most common risk factors of chronic wound infections were reported as metabolic disruptions (e.g., diabetes), vascular deficits (e.g., venous or arterial insufficiency), or mechanical impacts. A breach in the skin integrity heals uneventfully with time and is defined as acute wounds. Acute wounds are injuries that occur suddenly and typically heal within a predictable time frame. They are often caused by external trauma, such as cuts, burns, abrasions, or surgical incisions. Advanced age, inadequate nutrition, obesity, diabetes, prolonged use of steroids, and compromised immune function were the factors for wound infections [7, 8]. In a retrospective study from China, 815 patients were analyzed. Microbial culture positivity was most pronounced in the wound tissue of ulcers resulting from infections (87.6%), with pressure-related ulcers following closely at (77.1%), followed by diabetes-related ulcers at (68.3%), and venous diseases at (67.7%). Within this patient group, (63.9%) of the tested samples exhibited microbial growth, comprising (13.4%) polymicrobial infections and (86.6%) monomicrobial infections. [9]. The surgery, presence of prosthesis, and diabetes mellitus were the most common risk factors for wound infections. Similarly, in our study, monomicrobial isolation was frequent in wound infections. We found that the patients with surgery, prosthesis, diabetes mellitus, advanced age, and, immunosuppression were at risk for the development of wound infections. Immunsupression is very common in our study group due to 54.6% of the patients had cancer.

Within acute care settings, surgical wounds constitute the most prevalent wound type and they can cause potential complications like bleeding and wound reopening. SSI primarily manifest at the location of the surgical procedure, encompassing both the deep regions within the surgical zone contiguous to the operated organ (such as the hip, colon, pelvis, or brain) and the point of incision (the fascia, subcutaneous tissue, or skin). In conditions where a surgical site infection develops following a joint replacement procedure, the source of the infectious agent may be the nearby skin or the operating room. In an international study, the incidence of surgical site infections was estimated to occur in 1.9% to 40% of surgical procedures [6, 10]. In our study, among 119 patients evaluated as infected, 32.8% were surgical site infections. It was showed that surgical site infections were problematic in our hospital. We suggested

avoiding improper decontamination procedures (inappropriate antibiotic selection, compromised sterility practices) to decrease the incidence of post-surgical complications.

When evaluated clinically, infection in both acute and chronic wounds is typically characterized by an exaggerated inflammatory response surrounding the wound, elevated body temperature, pain, cellulitis, wound dehiscence, foul-smelling discharge, presence of pus, swelling, and warmth. Infection involves the infiltration of bacteria into tissue, while colonization is generally limited to the surface of the wound [7]. Our study indicated that, among the clinical findings, fever (21.8%), local signs of infection (10.9%), serous discharge (18.5%), and purulent discharge (19.3%) rates were higher in patients with infectious wounds than patients with colonization, although not statistically significant. We recommended evaluation of local and systemic singns, Gram-staining and culture results together for the diagnosis of the infection and colonization findings.

In a study conducted with 249 patients who had cesarean delivery, serum PCT, CRP levels, and WBC counts were measured at the postoperative 6th, 12th, and 24th hours. SSI assessments were conducted on the patients on the 2nd, 4th, and 7th days postoperatively. The study reported that 6% of the patients developed surgical site infections. The area under the curve (AUC) for PCT in predicting the SSI was 0.912 (95% CI: 0.79-1) with a sensitivity of 93.3% and specificity of 92.3% (p<0.001). The AUC for CRP was 0.854 and with a sensitivity of 80%, and specificity of 82.4%. Serum procalcitonin levels proved to be a more sensitive and specific indicator for the early diagnosis of SSIs following cesarean operation compared to others [12]. In our study, laboratory findings including elevated levels of CRP (82.3%), procalcitonin (15.9%), and higher numbers of leukocytes (34.4%) were seen in patients with infectious wounds. Although these results were not statistically significant, we recommended evaluating clinal and laboratory findings together in the diagnosis and following of wound infections. On the other hand, due to the majority of our patients having comorbidity and immunosuppression, there might be no statistically significant difference between infection and colonization.

Antibiotic resistance is a significant public health problem. In a study evaluating wound cultures, 600 isolates were analyzed, with 46.2% identified as Gram-positive bacteria, 51.3% as Gram-negative bacteria, and 2.5% as Candida spp. The most common isolates included S. aureus (29.2%), E. coli (11.5%), P. aeruginosa (11%), Proteus mirabilis (8%), and Klebsiella pneumoniae (5.8%). In a study evaluating wound cultures, 600 isolates were analyzed, with 46.2% identified as gram-positive bacteria, 51.3% as gram-negative bacteria, and 2.5% as *Candida* spp. The most common isolates were *S. aureus* (29.2%), *E. coli* (11.5%), *P. aeruginosa* (11%), *Proteus mirabilis* (8%), and *Klebsiella pneumoniae* (5.8%). Susceptibility tests revealed that 116 of the cultured bacteria exhibited resistance to multiple drugs, indicating the presence of multidrug-resistant strains. The resistance rates of *S. aureus* were >50% to methicillin, 92% to penicillin, 58.3% to erythromycin, and 50.9% to clindamycin. The resistance rates of *E. coli* were 68.1% to ampicillin, 68.1% to ciprofloxacin, 60.9% to levofloxacin, 3.9% to tigecycline, and 3.6% to amikacin [9]. In a study conducted with 5409 wound swabs in Saudi Arabia, a total of 14 different bacterial species were isolated and 9 of them were determined to be Gram negative bacteria. The most common isolates were *Klebsiella pneumoniae*, followed by *Pseudomonas aeruginosa*, *Escherichia coli*, *Acinetobacter baumannii*, methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *Enterococci* (VRE), and vancomycin-resistant *S. aureus* (VRSA). Multidrug resistant strains were determined as follows: *A. baumannii*, 97%; *K. pneumoniae*, 81%; *E. coli*, 71%; MRSA, 60%; *P. aeruginosa*, 33%; VRE, 22%; and VRSA, 2% [13]. In our study, the most common infection/colonization wound culture isolates were CoNS (19.4%), *E. coli* (14.8%), and *S. aureus* (13.1%). However, the Gram-negative isolation rate was higher in patients with infectious wounds than in patients with colonization (60% vs 16.6%). The rate of methicillin resistance was >50% in both CoNS and *S. aureus*. Within enteric bacilli, the resistance rate for 3rd generation cephalosporin was 55.1% and carbapenem 21.7%. In nonfermenter Gram-negative bacteria, resistance for ceftazidime was 68% and for carbapenem 48%. Notably, ceftazidime-avibactam was assessed in 42 Gram-negative

isolates with a resistance rate of 22%. In our study, 75.6% of patients with infectious wounds and 66.6% of patients with colonization received empirical treatment. Narrowed post-culture antimicrobial therapy was applied for 11.8%, and extended post-culture antimicrobial therapy for 36.1% of the patients with infectious wounds. Additionally, 13.4% of the patients with infectious wounds received antimicrobials for the first time after culture. Our study data suggested that every hospital should know the pathogenic agents and their antibiotic susceptibility patterns. The culture and antibiogram results had an important role in the management of wound infections and infection control. When choosing an empirical antimicrobial treatment option by clinicians, it should be kept in mind that Gram-negative bacterial wound infections are at the forefront in our hospital.

Our presented study, literature data [4, 5] indicated that the presence of microorganisms in Gram staining was not a good evaluating criteria for diagnosis of wound infection. The Q score for 136 samples (85.5%) was assessed as Q3. It was shown that Q scoring which assigns positive values to the count of PMNL cells and negative values to the count of squamous epithelial cells was a powerful marker for the determination of sample quality. In our study, it was determined that 76.3% of the wound samples were swab samples. It was reported that samples should be taken with at least two swabs for culture and Gram staining. The swab should be placed in 1-2 ml physiological saline or liquid medium, vortexed, and then inoculated into the medium, then the preparation is prepared for Gram staining [14]. We suggested that for an accurate diagnosis, appropriate and timely collection of swab samples and the application of laboratory sending criteria were necessary. If the samples dry out, the probability of bacterial isolation decreases. Given that clinical samples are not typically submitted to the laboratory in sets of two swabs, the reliability of our study Gram staining process becomes a concern.

In conclusion, wound infection rates, especially SSIs were common in our hospital among oncological patients. The most commonly isolated organisms from wound cultures were CoNS, *E. coli* and *S. aureus*. Gram negative isolation rate was higher in patients with infectious wounds than patients with colonization. Gram positive isolation rate was higher in colonized patients than patients with infectious wounds. The patients with surgery, prothesis, diabetes mellitus, and old age, immunsupression were prone wound infection. Among the clinical findings, the presence of fever, local signs of infection, serous discharge, purulent discharge, elevated levels of CRP, procalcitonin, and higher numbers of leukocyte contributed to the diagnosis of wound infection. We recommended to evaluate clinal and laboratory findings together in the diagnose of wound infections. The culture and antibiogram results had an important role for the management of wound infections and infection control. When choosing an empirical antimicrobial treatment option by clinicians, it should be kept in mind that Gram-negative pathogen rates isolated from wound infections are common in our hospital. Q scoring was a powerful marker for diagnosis of wound infection and exclude of colonization. The appropriate and timely collection of swab samples were necessary. Avoiding inproper decontamination procedures (inappropriate antibiotic selection, compromised sterility practices) will decrease the incidence of post-surgical complications.

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

References

1. Cerrahi Alan Enfeksiyonu Sürveyansı. Available at: https://hsgm.saglik.gov.tr/depo/birimler/bulasici-hastaliklar-ve-erken-uyari-db/Dokumanlar/Rehberler/CERRAHI_ALAN_ENFEKSIYONU_SURVEYANSI.pdf. Accessed December 14, 2023
2. Li S, Renick P, Senkowsky J, Nair A, Tang L. Diagnostics for wound infections. Adv Wound Care (New Rochelle) 2021;10:317-327. https://doi.org/10.1089/wound.2019.1103
3. Reeves N, Torkington J. Prevention of surgical site infections. Surgery (Oxford) 2021;40:20-24. https://doi.org/10.1016/j.mpsur.2021.11.008
4. Matkoski C, Sharp SE, Kiska DL. Evaluation of the Q score and Q234 systems for cost-effective and clinically relevant interpretation of wound cultures. J Clin Microbiol 2006;44:1869-1872. https://doi.org/10.1128/JCM.44.5.1869-1872.2006
5. McCarter YS, Sharp SE. Best laboratory practices for respiratory cultures. Clinical Microbiology Newsletter 2013;35:35-43. https://doi.org/10.1016/j.clinmicnews.2013.02.001

6. Alverdy JC, Hyman N, Gilbert J. Re-examining causes of surgical site infections following elective surgery in the era of asepsis. Lancet Infect Dis 2020;20:38-43. https://doi.org/10.1016/S1473-3099(19)30756-X

7. Wysocki AB. Evaluating and managing open skin wounds: colonization versus infection. AACN Clin Issues 2002;13:382-397. https://doi.org/10.1097/00044067-200208000-00005

8. Sen CK. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. Advances in Wound Care 2021;10:281-292. https://doi.org/10.1089/wound.2021.0026

9. Guan H, Dong W, Lu Y, et al. Distribution and antibiotic resistance patterns of pathogenic bacteria in patients with chronic cutaneous wounds in China. Front Med 2021;8:609584. https://doi.org/10.3389/fmed.2021.609584

10. Li T, Zhang H, Chan PK, Fung WC, Fu H, Chiu KY. Risk factors associated with surgical site infections following joint replacement surgery: a narrative review. Arthroplasty (London, England) 2022;4:11(e1-8). https://doi.org/10.1186/s42836-022-00113-y

11. Percival SL, Emanuel C, Cutting KF, Williams DW. Microbiology of the skin and the role of biofilms in infection. Int Wound J 2012;9:14-32. https://doi.org/10.1111/j.1742-481X.2011.00836.x

12. Kanza Gül D. Procalcitonin and C-reactive protein measurements in the early diagnosis of surgical site infections after cesarean section. CBUi SBED 2021;8:232-240. https://doi.org/10.34087/cbusbed.794037

13. Al Said HM, Alghamdi A, Ashgar SS, et al. Isolation and Detection of Drug-Resistant Bacterial Pathogens in Postoperative Wound Infections at a Tertiary Care Hospital in Saudi Arabia. Saudi J Med Med Sci 2023;11:229-234. https://doi:10.4103/sjmms.sjmms_405_22

14. Gizzie N, Adukwu E. Evaluation of Liquid-Based Swab Transport Systems against the New Approved CLSI M40-A2 Standard. J Clin Microbiol 2016;54:1152-1156. https://doi.org/10.1128/JCM.03337-15

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Authors' contributions to the article

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

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Comparison between mortality scoring systems in pediatric intensive care unit reliability and effectiveness

Çocuk yoğun bakım ünitesinde mortalite skorlama sistemlerinin güvenilirliği ve etkinliğinin karşılaştırılması

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Abstract

Purpose: In pediatric intensive care unit (PICU), high mortality risk is a significant issue. Risk adjustment tools are in place for early estimation of mortality risk. Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM), Pediatric Logistic Organ Dysfunction (PELOD) and Pediatric Sequential Organ Failure Assessment (PSOFA) are commonly used. The aim of this study was to evaluate the predictive performance of mortality using PRISM III, PIM3, PELOD-2, and PSOFA.

Materials and methods: This retrospective single-center study analysed patients aged between 1 month-18 years who were treated in PICU for various diseases between April and December 2021. Their electronic records were retrospectively examined for demographic characteristics, medical and clinical expectations, and morbidity/mortality.

Results: The study included 300 patients with a hospitalization period of 56.73±105.95 days. At the end of the study, 56 (18.7%) patients had died. All scoring systems and mortality correlations were statistically significant (p<0.0001). The predictive success rates for mortality, ranked from best to worst, were PRISM III, PELOD-2, PSOFA, and PIM 3, respectively, in terms of sensitivity and specificity.

Conclusion: The absence of any studies comparing these four mortality scoring systems adds to their importance for early recognition and rapid intervention in critically ill children. Based on our study, PRISM III data has been found to be more reliable in this heterogeneous population.

Key words: Mortality, pediatric, intensive care, reliability, effectiveness.

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Öz

Amaç: Çocuk yoğun bakım ünitesinde (ÇYBÜ) yüksek mortalite riski önemli bir sorundur. Mortalite riskinin erken ön görülmesi için çeşitli risk skorlama sistemleri vardır. Pediatric Risk of Mortality (PRISM), Pediatric Index of Mortality (PIM), Pediatric Logistic Organ Dysfunction (PELOD) ve Pediatric Sequential Organ Failure Assessment (PSOFA) yaygın olarak kullanılmaktadır. Çalışmamızın amacı, PRISM III, PIM3, PELOD-2 ve PSOFA' nın mortaliteyi öngörmedeki gücünün ve etkinliğinin değerlendirilmesidir.

Gereç ve yöntem: Tek merkezli retrospektif çalışmada Nisan-Aralık 2021 tarihleri arasında ÇYBÜ'de yatan 1 ay-18 yaş arası tüm hastalar incelendi. Elektronik kayıtlarından demografik özellikleri, klinik öyküleri ve morbidite/mortalite durumu araştırıldı.

Bulgular: Çalışmaya ÇYBÜ yatış süresi 56,73±105,95 gün olan 300 hasta dahil edildi. Çalışma sonunda 56 (%18,7) hasta vefat etmişti. Tüm skorlama sistemleri ve mortalite korelasyonları istatistiksel olarak anlamlı bulundu (p<0,0001). Mortaliteyi öngörmede başarı oranları, duyarlılık ve özgüllük açısından incelendiğinde başarılı olma oranı sırasıyla PRISM III, PELOD-2, PSOFA ve PIM 3 idi.

Sonuç: Dört mortalite skorlama sistemini karşılaştıran herhangi bir çalışmanın bulunmaması, kritik hastalığı olan çocuklarda erken tanı ve hızlı müdahale için skorlama sistemleri önemini artırmaktadır. Çalışmamıza dayanarak, PRISM III verilerinin heterojen hasta popülasyonumuzda mortalite ön gördürme için daha güvenilir olduğu bulunmuştur.

Anahtar kelimeler: Mortalite, pediatri, yoğun bakım, güvenilirlik, etkililik.

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Introduction

In the pediatric intensive care unit (PICU), high mortality rates are a significant concern. Risk adjustment tools are currently in use at admission for the estimation of mortality risk [1]. The Pediatric Risk of Mortality (PRISM) score, Pediatric Index of Mortality (PIM), Pediatric Logistic Organ Dysfunction (PELOD), and Pediatric Sequential Organ Failure Assessment (PSOFA) scores are commonly used in pediatric intensive care units worldwide. All of these scoring systems give a measure of severity of illness. Depending on these systems, critically ill patients are identified at an earlier stage in the PICU and their treatment is managed with the aim of reducing the mortality rate [2]. The scoring systems were designed not only to assess the risk of individual patients, but also to evaluate the performance of PICUs in comparison to others, to measure outcomes, and/or to report mortality rates in clinical studies. PRISM III, PELOD ve PIM scores are frequently used for mortality prediction in pediatrics [3, 4]. PSOFA was developed, because of PELOD due to not covering a large population and not including heterogenous diseases [5]. Although it is difficult to clearly demonstrate the superiority of one scoring system over another, many studies are currently being conducted on them. The aim is to identify critical patients early and to determine the best system through comparisons, using a common criterion in national and international pediatric intensive care units. This will support both scientific studies and patient care.

The PRISM III, which is one of the most commonly used scoring systems of mortality in PICUs, was used when examining patient data. While calculating PRISM III, seventeen different parameters including mental status, vital signs, blood gas measurements, pupillary reflex, and biochemical values in the first day are used. High scores indicate there is a high risk of mortality [6].

PELOD scoring was developed in intensive care to detect multiple organ failures. PELOD includes six organ dysfunctions and twelve variables, each recorded daily for five days [7]. The PELOD-2 that included changes add mean arterial pressure and lactate elevation to cardiovascular dysfunction and subtract hepatic dysfunction [8].

Using data from first hour of PICU admission, the PIM score was adjusted using eight physiological changes [9]. The advantage of the PIM 3 score is that it eliminates the limitations of the treatment received before admission to the intensive care unit. In addition, patients were divided into not only low-risk but also low and high-risk, unlike PIM 2 [10].

PSOFA; PELODS and PELOD-2 are one of the scoring systems that show organ dysfunction in pediatric patients, and were developed because of their inadequacy in terms of inclusiveness and scaling [5]. The difference of PSOFA from PELOD-2 is that in addition to the paO2/fiO2 ratio, the saO2/fiO2 ratio is also used [11]. While creating the scoring system, the score obtained in the PELOD score was accepted as 1 point; Scores between 2 and 4 are adapted to adult SOFA criteria.

The study aimed to evaluate the performance and predictive ability of the PRISM III, PIM 3, PELOD-2, and PSOFA scores for mortality. Additionally, we investigated the relationship between observed mortality-survivor outcomes and the accuracy of the scoring systems. We also conducted a statistical comparison of the reliability and effectiveness of all four scoring systems.

Material and methods

A retrospective single-center study was conducted, including patients aged 1 month to 18 years who were treated in the PICU between April and December 2021. The hospital is a third-level facility with a 52-bed Pediatric Intensive Care Unit that admits approximately 400 patients every six months. This diverse population of admissions includes cases of sepsis, respiratory failure, trauma, status epilepticus, genetic disorders, metabolic diseases, post-cardiac arrest, drowning and more during their stay in the PICU. This study included patients who were treated for any diseases, but excluded those who had no PRISM III recorded in electronic data. Patients whose age was not between 1 month and 18 years were also excluded.

Demographics, medical history, co-morbidity, length of stay, use of mechanical ventilation, Glasgow Coma Scale (GCS), labs, history of arrest, use of catheter, enteral nutrition, organ failure and/or need for dialysis, morbidity, development of sequelae, and mortality are examined. In addition, need for ventilatory and/or nutritional support at discharge from PICUs was assessed. In addition, the study recorded the patients' PRISIM III, PELOD-2, PIM 3, and PSOFA scores.

In this study, the PRISM III was recorded in the patient's electronic file according to our hospital's quality standards. The study team recorded the PELOD-2, PIM 3, and PSOFA scores on data forms using the same scoring calculator.

During the examination of our patients' complete blood count, we evaluated the values of hemoglobin, leukocytes, lymphocytes, and thrombocytes based on Z scores according to age. The study investigated transaminases for hepatic involvement, serum urea and creatinine for renal involvement, and prothrombin time and activated thromboplastin time for bleeding disorders. Significant deterioration was defined as an increase of 2 times or more from the normal value for age. The patients' radiological imaging was interpreted according to widely accepted diagnostic criteria outlined in relevant guidelines.

The data collected was recorded as patient data. For the study, the ethics committee approval was obtained from the Harran University Clinical Research Ethics Committee prior to the study's commencement. Family consent was not obtained for the patients included, as this was a retrospective study.

Statistical analysis

Statistical analyses were conducted using IBM® SPSS® 26 (SPSS Inc., Chicago, IL, USA) software. The normal distribution of variables was assessed using analytical methods (Kolmogorov-Smirnov test). Descriptive analyses were presented as mean±standard deviation for continuous data. The study presented descriptive statistics by providing frequency and percentage values for categorical variables related to sociodemographic and clinical information. To compare the scores of risk assessment parameters between the mortality/survival groups Mann Whitney U test was used for nonparametric parameters. For comparing categorical variables, either Pearson's Chi Square or Fisher's Exact Chi Square test was used. The study evaluated the effectiveness of four risk assessment parameters (PRISM, PELOD-2, PSOFA, and PIM 3) in determining mortality through Receiver Operating Characteristics (ROC) analysis, and determined cut-off value with youden index. For each parameter, the area under the curve (AUC) and cut-off values were calculated. Only results with a *p*-value below 0.05 were considered statistically significant.

Results

This study included 300 patients over a period of 6 months, of whom 174 (58%) were male and 126 (42%) were female, with a mean age of 48.60±67.21 months and a mean hospital stay of 56.73±105.95 days. Pneumonia was the most frequent diagnosis among hospitalized patients, accounting for 30% (n=90) of cases. Of the 300 patients studied, 156 (52%) had comorbidities. At the time of hospitalization, 144 (48%) patients had a Glasgow Coma Scale (GCS) score of less than 8, and 58 (19.3%) had a history of cardiac arrest before admission. Upon admission, 46.3% (n=139) of these patients required intubation and respiratory support via mechanical ventilation. Among our patients, 56 (18.7%) died. Table 1 shows the descriptive analysis of the patients enrolled in our study.

The laboratory test results of the patients revealed the following: 137 (45.7%) had leukocytosis, 39 (13%) had leukopenia, 72 (24%) had anemia, 18 (6%) had thrombocytopenia, 104 (34.7%) had respiratory acidosis, and 60 (20%) had metabolic acidosis. Transaminase elevation was observed in 39 (13%) patients, renal dysfunction in 33 (11%), and bleeding disorders in 13 (4.3%) patients. Upon examination of the posteroanterior chest radiographs, 119 (39.7%) cases of pneumonic infiltration, 19 (6.3%) cases of pulmonary edema, 16 (5.3%) cases of increased aeration consistent with acute bronchiolitis, and 4 (1.3%) cases of pneumothorax were observed.

Table 1. Characteristics of 300 critically Ill children admitted to PIC

Characteristics	Patients
Age (mean (±SD))	48.60±67.21 months
Gender (patient/%)	Male (174/58%) Female (126/42%)
Lenght of PICU days	56.73±105.95
Diagnosis of Hospitalization (patient/%)	Pneumonia (90/30%) Respiratory Failure (45/15%) Trauma (35/11.7%) Sepsis (25/8.3%) Acute Bronchiolitis (22/7.3%) Status Epilepticus (14/4.7%) Heart Failure (13/4.3%) Chronic Renal Failure (11/3.7%) Postoperative Surgery (10/3.3%) Drowning (10/3.3%) Congenital Metabolic Diseases (6/2%) Supraventricular Tachycardia (5/1.7%) Insect Bite (3/1%) Hemolytic Uremic Syndrome (3/1%) Encephalitis (2/0.7%) Gastrointestinal System Bleeding (2/0.7%) Diabetic Ketoacidosis (2/0.7%) Hanging (2/0.7%)
Comobidities (patient/%)	Yes (156/52%) No (144/48%)
Glascow Coma Scale (patient/%)	<8 (144/48%) >8 (156/52%)
Cardiac Arrest History (patient/%)	Yes (58/19.3%) No (242/80.7%)
First Admission Center (patient/%)	Emergency Department (200/66.7%) General Pediatrics Clinic (64/21.3%) Other Hospitals (30/10%) Postoperatively (6/2%)
First Respiratory Support (patient/%)	Intubation (139/46.3%) Bilevel Positive Pressure (73/24.3%) Oxygen Mask Support (38/12.7%) High Flow Nasal Cannulas (34/11.3%) Room Air (16/5.3%)
Current Status of Patients (patient/%)	Transferred to Clinics (148/49.3%) Still in PICU (29/9.7%) Transferred to Other Clinics/Home (67/22.3%) Exitus (56/18.7%)
Mortality (patient/%)	Alive (244/81.3%) Exitus (56/18.7%)

*PICU: Pediatric intensive care unit

In 45.6% of all patients, a central venous catheter was used for treatment, with the jugular vein being the most common insertion site (86.8%), followed by the femoral vein (9.5%) and subclavian vein (3.6%). Throughout the study period, 106 (35.3%) patients did not exhibit any secondary organ involvement. Of those who did, 88 (29.3%) had renal involvement, 29 (9.7%) had pulmonary involvement, 15 (5%) had cardiac involvement, and 10 (3.3%) had liver involvement. Furthermore, 18 (6%) patients had multiple affected organs. As a result, 16 (5.3%) underwent hemodialysis and 9 (3%) underwent peritoneal dialysis. Upon re-examination of patients transferred from the PICU after treatment, sequelae were evaluated. Of the patients, 29% were fed through a nasogastric tube and 0.7% through a gastrostomy. Additionally, 17% had a tracheostomy, 23% required oxygen support through a basic oxygen mask, and 9% showed clinical neurological involvement in the central nervous system.

The results of our study demonstrated a statistically significant relationship between all four scoring systems and mortality (Table 2). We also determined the most sensitive scoring system. The susceptibility levels and success rates of demonstrating mortality were listed, and the ROC analysis was used to evaluate the predictive success rate of mortality scoring systems in terms of sensitivity and specificity. The best to worst systems were PRISM III, PELOD-2, PSOFA, and PIM 3, as determined by the area under the curve (AUC) of the ROC curve. Figure 1 shows the ROC curve and area under the curve. Table 3 provides a detailed summary of the effectiveness of mortality scoring systems in terms of specificity and sensitivity.

Table 2. The relationship between all four scoring systems and mortality

Variables	General	Alive	Exitus	*p* value	*Z* values
PRISM III (median (IQR))	20 (20)	16 (15.2)	35 (17)	**<0.0001**	-9.042
PELOD-2 (median (IQR))	6 (10)	3 (9)	12 (14)	**<0.0001**	-6.925
PSOFA (median (IQR))	6 (10)	5 (10)	12 (14)	**<0.0001**	-6.160
PIM 3 (median (IQR))	3 (3)	3 (2)	5 (2)	**<0.0001**	-6.099

*PRISM III: The Pediatric Risk of Mortality Score III, PELOD-2: Pediatric Logistic Organ Dysfunction 2, IQR: Interquartil Range
PSOFA: Pediatric Sequential Organ Failure Assessment, *Mann Whitney U analysis was used to compare the groups
PIM 3: Pediatric Index of Mortality 3

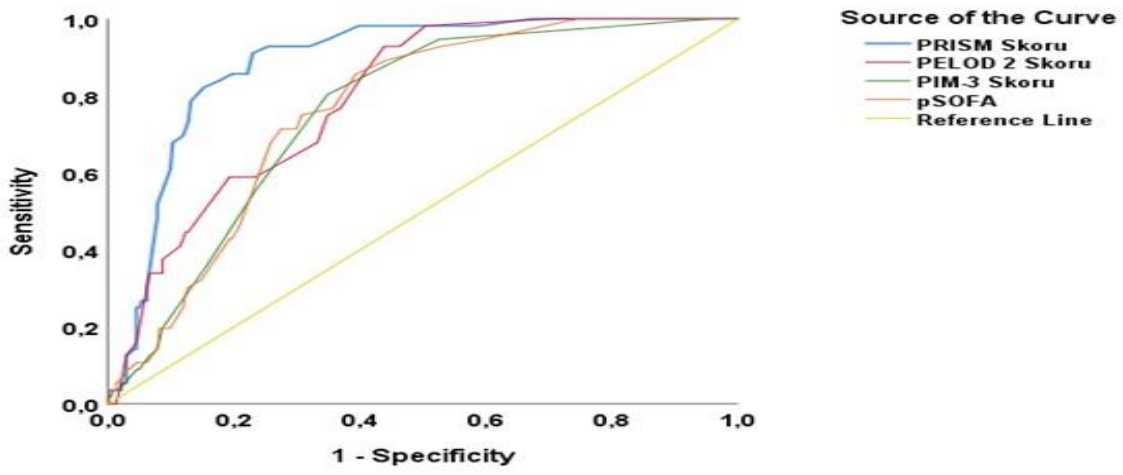

Figure 1. PICU scoring systems: evaluating their effectiveness with ROC analysis
(PRISM III: The Pediatric Risk of Mortality Score III; PELOD-2: Pediatric Logistic Organ Dysfunction 2; PSOFA: Pediatric Sequential Organ Failure Assessment; PIM 3: Pediatric Index of Mortality 3). The area under the curve values were evaluated based on the ROC analysis and compared to the reference line. Figure 1 shows the predictive success rate of mortality scoring systems in terms of sensitivity and specificity

Table 3. PICU scoring systems and their effectiveness evaluation

Variables	AUC	Standard error	*p* value	95% CI		Sensitivity (%)	Spesifity (%)	Cut-Off value	Predicted success order number*
				Lower limit	Upper limit				
PRISM III	0.887	0.020	**<0.0001**	0.847	0.927	83.9	82.4	27.5	1
PELOD-2	0.795	0.028	**<0.0001**	0.741	0.850	67.9	66.8	9.5	2
PSOFA	0.763	0.029	**<0.0001**	0.706	0.821	71.4	72.5	10.5	3
PIM 3	0.758	0.031	**<0.0001**	0.698	0.818	80.4	65.2	3.5	4

ROC analysis was performed and $p<0.05$ was statistically significant, AUC: Area Under Curve, PIM 3: Pediatric Index of Mortality 3
*Mortality Prediction Success Ranking by AUC Value, *PRISM III: The Pediatric Risk of Mortality Score III, CI: Confidence Interval
PELOD-2: Pediatric Logistic Organ Dysfunction 2, PSOFA: Pediatric Sequential Organ Failure Assessment

No statistical difference was found between mortality and age, length of stay in the PICU, or comorbidity, or first admission center ($p>0.05$). However, a significant relationship was found between mortality and lower GCS, type of diagnosis, first respiratory support, and cardiac arrest history ($p<0.0001$). In laboratories, there was no association between complete blood count, urea/creatinine, and coagulopathy ($p>0.05$). However, we did detect a significant association between blood gas samples and transaminases ($p<0.0001$). Although our study found no relationship between the use of central venous catheters, dialysis, and mortality ($p>0.05$), a statistically significant relationship was observed between organ failure ($p<0.0001$) and mortality. The statistical relationship between mortality and clinical and laboratory data, along with the corresponding point *p*-values, are presented in Table 4.

Table 4. The statistical relationship and distributions for mortality

		Alive	Exitus	*p* values	*Z/X²* values
Clinical/ laboratory data	**Age (month) (median (IQR))**	14 (68)	23 (84)	0.336	-0.420 z
	Length of stay in the PICU (day) (median (IQR))	19 (54.5)	14 (27)	0.462	-1.589 z
	Presence of comorbidity (n/%)	122 (49.8)	34 (61.8)	0.148	2.095 X^2
	First admission center (n/%)	142 (65.7)	38 (76)	0.462	2.577 X^2
	GCS < 8 (n/%)	79 (36.6)	42 (84)	**<0.0001**	35.609 X^2
	Respiratory support (n/%)	83 (38.4)	41 (82)	**<0.0001**	34.376 X^2
	Cardiac arrest history (n/%)	19 (8.8)	23 (46)	**<0.0001**	30.601 X^2
	Complete blood count abnormality n/%)	216 (88.5)	50 (89.2)	0.379	3.082 X^2
	Anormal urea/creatinine (n/%)	24 (11.1)	9 (18)	0.207	1.595 X^2
	Coagulopathy (n/%)	9 (4.2)	4 (8)	0.276	1.186 X^2
	Anormal blood gas tests (n/%)	123 (56.9)	41 (82)	**<0.0001**	24.078 X^2
	High transaminases (n/%)	26 (12)	13 (26)	**0.015**	5.913 X^2
	Central venous catheter using (n/%)	108 (50)	29 (58)	0.114	5.948 X^2
	Dialysis using (n/%)	20 (9.3)	5 (10)	0.444	1.625 X^2
	Organ failure (n/%)	121 (56)	38 (76)	**<0.0001**	79.831 X^2

*PICU: Pediatric Intensive Care Unit, z: Mann Whitney U analysis and X^2 : *Chi Square test* was used to compare the groups
GCS: Glasgow Coma Scale, IQR: Interquartil Range

Discussion

The PICU is capable of treating many critical and dynamic diseases. During this period, children may experience additional problems in addition to their serious illness. During this crucial period, it is important for paediatric intensive care physicians to maintain treatment that minimises pain, anxiety, and complications for their patients. Additionally, establishing healthy communication with the patient's family is essential [12, 13]. The factors that affect mortalities and morbidities include the number of patients, the number of intensive care specialists and nurses per patient, the criteria for admission to the intensive care unit, the diagnosis, underlying diseases, and invasive procedures applied. It is important to consider all of these factors when evaluating patient outcomes [14]. The hospital is a third-level facility with a 52-bed PICU that admits approximately 400 patients every six months. The patients admitted to the PICU have a variety of conditions, including sepsis, respiratory failure, trauma, status epilepticus, genetic disorders, metabolic diseases, post-cardiac arrests, and drownings. During their stay in the PICU, patients receive specialised care. This study includes patients who were treated for any disease. The hospital is located in the southeastern region of Türkiye, where the local population has lower sociocultural and socioeconomic status. These factors contribute to higher patient mortality rates. Multi-parameter studies are essential for evaluating a large number of patients and determining the feasibility and effectiveness of mortality predictive scoring systems. Early recognition of critical and high-risk patients can decrease mortality rates, and identifying the most effective system is crucial for some PICUs, including ours.

In a study carried out in our country, it was found that among patients admitted to the PICU, respiratory diseases were the most common reason for having to go to the PICU [15-19]. In our study, pneumonia was found to be the most common reason for hospitalization, affecting 90 patients (30%). This was followed by respiratory failure, which affected 45 patients (15%). The patient group that most frequently requires PICU care consists of those with chronic diseases and ongoing care needs. With the advancement of medicine, it is now possible to treat and save many children who are born prematurely and have underlying neurological, genetic, metabolic, and cardiological issues. In studies conducted in our country, Konca et al. [18] reported comorbidities in 25.5% of cases, Oz et al. [16] in 41.8%, and Tekerek et al. [12] in 47.2%. Contrary to the literature, 156 (52%) of the patients included in our study had comorbidities. This situation is linked to the sociocultural and socioeconomic status of our hospital's region, which has a high rate of consanguineous marriage and malnutrition. Studies conducted in our country have reported rates of intubation need and mechanical ventilation support in the PICU ranging from 24.1% to 41.9% Khilnani et al. [20] reported that 20.68% of their patients required mechanical ventilators, while Goncalves et al. [21] reported 68.5% [12, 15-17]. It is suggested that the patient population in need of a PICU is related to the clinic. Out of the total patients, 200 (66.7%) were admitted to PICU from our hospital's emergency service. Of these patients, 139 (46.3%) required intubation and respiratory support with a mechanical ventilator upon admission.

It is widely accepted that higher mortality scores are associated with longer PICU stays and higher mortality rates. According to this hypothesis, a review of the literature reveals that in a 24-month study of 556 critically ill patients in the PICU from 2011-2012, 29 (5.2%) died, and a length of stay ranging from 0 to 155 days was reported [21]. In our country, PICU mortality rates range from 2.4 to 27.6% [12, 15-19]. The study detected a mortality rate of 18.7% and an average length of stay of 56.73±105.95 days. The study included 300 pediatric patients with diverse and complex diseases, which may have influenced mortality and hospitalization rates. Therefore, the results reflect the actual progression of critically ill patients in the PICU.

In a study conducted by Gonzalez Luis et al. [22], the mean PRISM score for deceased patients in the PICU was 26.6, with a 54% probability of death. Surviving patients in the PICU without neurological dysfunction had a mean PRISM of 10.8 and a mean probability of death of 9.1%. At PICU admission, the average PRISM III score of our patients was 22.13±16.87, regardless of neurologic dysfunction. 52% of the included patients had comorbidities. However, our study found a lower average PRISM III score.

The study conducted by van Keulen et al. [2] on the reliability of PRISM and PIM scoring revealed that despite having fewer variables, the inter-observer variability in PIM scoring was higher than that of PRISM scoring. In a 2009 study evaluating prognosis and prognostic research in clinical practice, it was found that the PELOD-2 scoring system was less reliable than PRISM III in detecting mortality. PRISM III is a predictive mortality scoring system that has been shown to be more sensitive in certain populations. There is no universally accepted scoring system, therefore, it is necessary to conduct population validation studies before applying it in a different setting [23]. Currently, mortality scoring systems are widely studied, examining both commonalities and differences. Some groups attempt to adapt and enhance adult scoring systems for use with pediatric patients. PSOFA was developed to address the inadequate scaling of PELODS and PELOD-2 for children [5]. The main difference between PSOFA and PELOD-2 is that, in addition to the paO2/fiO2 ratio, the saO2/fiO2 ratio is also used. This allows for a more sensitive understanding of the pathology of pediatric pulmonary systems [11]. When creating the scoring system, we accepted the score obtained in the PELOD score as 1 point. Scores between 2 and 4 are adapted to adult SOFA criteria. The parameters are calculated every 24 hours, and the worst values are used as a basis. PSOFA, PRISM, and PIM 2 were found to be reliable for mortality based on the ROC curve. In the Egypt study conducted in the PICU, it was found that SOFA score was significantly higher in nonsurvivors [24]. In our heterogeneous population, we aimed to examine which scoring system is the most sensitive for predicting mortality based on these studies. Additionally, susceptibility levels were listed and mortality was demonstrated successfully through ROC analysis. In ROC curve analysis based on AUC, the predictive success rates of mortality scoring systems in terms of sensitivity and specificity were ranked from best to worst as follows: PRISM III, PELOD-2, PSOFA and PIM 3.

The study was retrospective and did not include patients with haematological oncology, patients with immunodeficiency or patients who had undergone surgery for congenital heart disease due to physical and equipment deficiencies in our hospital. These patient groups have a high risk of mortality, so they score highly. In contrast, it is noted that the facility accommodated a diverse group of 300 patients within a brief six-month period, and serves as an indicator of a tertiary hospital that houses the sole pediatric intensive care unit in a densely populated city with socio-economic challenges. The importance of these four scoring systems in comparison to other mortality scoring systems is further highlighted by the lack of studies that have compared them. Based on this study, multicenter prospective studies in which diseases are classified separately for the type of the disease are evaluated instead of heterogeneous groups can be planned in the future to investigate scoring systems.

In the management of critically ill patients with a high risk of mortality, it is essential to be able to predict the risk of death on admission and to act with caution. The aim is generally to reduce mortality by using a scoring system that is more suitable for the patient population. There is no universally accepted standard for the mortality scoring system. Therefore, it is necessary to conduct population validation and review studies before applying it in a different setting. In our study of a large and diverse pediatric population, we evaluated the predictive success rates of various mortality scoring systems in terms of sensitivity and specificity. The results showed that PRISM III had the highest success rate, followed by PELOD-2, PSOFA, and PIM 3 in descending order.

Based on our study, we conclude that the PRISM III scoring system is primarily successful and suitable for predicting PICU mortality. However, further multicenter, prospective studies are needed for clearer data as there is no gold standard among mortality predictive systems according to current studies.

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References

1. Brady AR, Harrison D, Black S, et al. Assessment and optimization of mortality prediction tools for admissions to pediatric intensive care in the United Kingdom. Pediatrics 2006;117:733-742. https://doi.org/10.1542/peds.2005-1853

2. Van Keulen JG, Polderman KH, Gemke RJBJ. Reliability of PRISM and PIM scores in paediatric intensive care. Arch Dis Child 2005;90:211-214. https://doi.org/10.1136/adc.2003.046722
3. Qureshi AU, Ali AS, Ahmad TM. Comparison of three prognostic scores (PRISM, PELOD and PIM 2) at pediatric intensive care unit under Pakistani circumstances. J Ayub Med Coll Abbottabad 2007;19:49-53.
4. Wang JN, Wu JM, Chen YJ. Validity of the updated pediatric risk of mortality score (PRISM III) in predicting the probability of mortality in a pediatric intensive care unit. Acta Paediatr Taiwan 2001;42:333-337.
5. Singer M, Deutschman CS, Seymour CW, et al. The third ınternational consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-810. https://doi.org/10.1001/jama.2016.0287
6. Pollack MM, Patel KM, Ruttimann UE. PRISM III: An updated pediatric risk of mortality score. Crit Care Med 1996;24:743-752. https://doi.org/10.1097/00003246-199605000-00004
7. Leteurtre S, Martinot A, Duhamel A, et al. Development of a pediatric multiple organ dysfunctionscore: use of two strategies. Med Decis Making 1999;19:399-410. https://doi.org/10.1177/0272989X9901900408
8. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logisticorgan dysfunction score. Crit Care Med 2013;41:1761-1773. https://doi.org/10.1097/CCM.0b013e31828a2bbd
9. Dragsted L, Jorgensen J, Jensen NH, et al. Interhospital comparisons of patient outcome from intensive care: importance of lead-time bias. Crit Care Med 1989;17:418-422. https://doi.org/10.1097/00003246-198905000-00008
10. Slater A, Shann F, Pearson G; Paediatric Index of Mortality (PIM) Study Group. PIM2: a revised version of the paediatric index of mortality. Intensive Care Med 2003;29:278-285. https://doi.org/10.1007/s00134-002-1601-2
11. Matics TJ, Sanchez Pinto LN. Adaptation and validation of a pediatric sequential organ failure assessment score and evaluation of the sepsis-3 definitions in critically Ill children. JAMA Pediatr 2017;171:172-352. https://doi.org/10.1001/jamapediatrics.2017.2352
12. Tekerek NU, Akyildiz BN. Prognosis of patients in a pediatric ıntensive care unit of a tertiary care center. Turkish J Pediatr Dis 2017;11:221-225. https://doi.org/10.12956/tjpd.2017.269
13. Demirkol D, Karabocuoglu M. Criteria of admission and discharge in pediatric care units. Turk Arch Pediatr 2010;45:82-84. https://doi.org/10.4274/tpa.45.82
14. Koroglu TF, Bayrakci B, Dursun O, Kendirli T, Yıldızdas D, Karabocuoglu M. A guide for pediatric intensive care units: propositions from pediatric emergency medicine and intensive care society. Turk Arch Pediatr 2006;41:139-145.
15. Asilioglu N, Kot H. Çocuk yoğun bakım ünitesine yatan olguların değerlendirilmesi ve sonuçları. Turkiye Klinikleri J Pediatr 2011;20:10-15.
16. Oz O, Bayraktar S, Elevli M, et al. Bir eğitim ve araştırma hastanesi çocuk yoğun bakım ünitesine yatan hastaların değerlendirilimesi. CAYD 2015;2:65-70.
17. Orhan MF, Yakut HI, Ikiz MA. Çocuk yoğun bakım ünitesinde 2 yıl içinde yatan 938 olgumuzun değerlendirilmesi. Türkiye Çocuk Hast Derg 2012;6:228-231.
18. Konca C, Tekin M, Karakoc F, Turgut M. Çocuk yoğun bakım ünitesinde yatan 770 hastanın değerlendirilmesi: tek merkez deneyimi. Türkiye Çocuk Hast Derg 2015;2:90-95. https://doi.org/10.12956/tjpd.2015.120
19. Poyrazoglu H, Dursun I, Gunes T, et al. Çocuk yoğun bakım ünitesine yatan olguların değerlendirimesi ve sonuçları. Erciyes Tıp Dergisi 2008;30:232-237.
20. Khilnani P, Sarma D, Singh R, et al. Demographic profile and outcome analysis of a tertiary level pediatric intensive care unit. Indian J Pediatr 2004;71:587-591. https://doi.org/10.1007/BF02724117
21. Goncalves JP, Severo M, Rocha C, Jardim J, Mota T, Ribeiro A. Performance of PRISM III and PELOD-2 scores in a pediatric intensive care unit. Eur J Pediatr 2015;174:1305-1310. https://doi.org/10.1007/s00431-015-2533-5
22. Gonzalez Luis G, Pons M, Cambra FJ, Martin JM, Palomeque A. Use of the Pediatric Risk of Mortality Score as predictor of death and serious neurologic damage in children after submersion. Pediatr Emerg Care 2001;17:405-409. https://doi.org/10.1097/00006565-200112000-00002
23. Moons KGM, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2009;338:b606. https://doi.org/10.1136/bmj.b606
24. El Mashad GM, El Mekkawy MS, Zayan MH. Paediatric sequential organ failure assessment (pSOFA) score: a new mortality prediction score in the paediatric intensive care unit. An Pediatr 2020;92:277-285. https://doi.org/10.1016/j.anpedi.2019.05.018

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Authors' contributions to the article

H.F.A. conceived the idea. H.F.A., S.R., M.C.S. and M.A.T. were involved in clinical care/following of the patients. S.R., M.A.T., and H.F.A. collected data. M.C.S. performed statistical analyzes of the data. H.F.A. wrote the first draft of the manuscript which was critically revised by all the authors. All authors read and approved the final version of the manuscript.

Research Article

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Effects of hepatic artery type and number on bile complications in right lobe living donor liver transplant recipients: single center experience without hepatic artery thrombosis

Sağ lob canlı verici karaciğer nakli alıcılarında hepatik arter çeşidi ve sayısının safra komplikasyonları üzerine etkileri: hepatik arter trombozu olmaksızın tek merkez deneyimi

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Abstract

Purpose: Hepatic artery provides blood supply to the biliary tract of the graft, one of the causes of the biliary complications that may occur in the post-transplant period may be the problems of the recipient's hepatic artery. We examined the effect of post-transplant biliary complications according to the type and number of recipient hepatic arteries.

Materials and methods: One hundred eighty-five patients older than 18 years of age who underwent right lobe living donor liver transplant (LDLT) for end-stage liver cirrhosis were included in the study. The recipient's right hepatic artery (RHA), left hepatic artery (LHA), propria hepatic artery (PHA) and common hepatic artery (CHA), which were anastomosed to the graft artery and double hepatic artery anastomoses formed of the right and left hepatic arteries, were examined. Biliary complications were analyzed statistically in terms of single or double artery anastomosis and anastomoses with the right or the other hepatic arteries.

Results: There was no statistically significant difference between single and dual artery anastomoses in terms of bile duct stricture or leakage (p=0.767). No statistically significant difference was observed between RHA, LHA, PHA, CHA, and between single and dual arteries in the evaluation of artery selection between those with and without biliary tract complications (p=0.445)

Conclusion: Hepatic artery type selection and number of the recipient does not change the biliary tract complication.

Keywords: Hepatic artery, liver, transplantation, bile, complication.

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Öz

Amaç: Hepatik arter, grefte ait safra yollarının kanlanmasını sağlar. Nakil sonrası dönemde oluşabilecek safra komplikasyonlarının nedenlerinden biri de alıcının hepatik arterindeki sorunlar olabilir. Alıcı hepatik arterin tipine ve sayısına göre nakil sonrası safra komplikasyonlarının etkisini inceledik.

Gereç ve yöntem: Çalışmaya, son dönem karaciğer sirozu nedeniyle sağ lob canlı vericili karaciğer nakli (CVKN) uygulanan 18 yaş üstü 185 hasta dahil edildi. Alıcının greft arterine anastomoz yapılan sağ hepatik arter (SağHA), sol hepatik arter (SolHA), propria hepatik arter (PHA) ve kommon hepatik arter (KHA) ve sağ ve sol hepatik arterlerden oluşan çift hepatik arter anastomozları incelendi. Biliyer komplikasyonlar tek veya çift arter anastomozu ve sağ veya diğer hepatik arterlerle anastomoz yapılması açısından istatistiksel olarak analiz edildi.

Bulgular: Tek ve çift arter anastomozları arasında safra kanalı darlığı veya sızıntısı açısından istatistiksel olarak anlamlı fark yoktu (p=0,767). Safra yolu komplikasyonu olan ve olmayanlar arasında arter seçiminin değerlendirilmesinde SağHA, SolHA, PHA, KHA ile tek ve çift arterler arasında istatistiksel olarak anlamlı fark gözlenmedi (p=0,445).

Sonuç: Alıcılarda anastomozda kullanılan hepatik arter tipi ve sayısı sayısı safra yolu komplikasyon oranını değiştirmemektedir.

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Anahtar kelimeler: Hepatik arter, karaciğer, transplantasyon, safra, komplikasyon.

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Introduction

Living donor liver transplantation (LDLT) stands as the most preferred surgical procedure for patients with end-stage liver cirrhosis and hepatocellular cancer who meet the criteria; often, right lobe donors are the preferred choice. Anatomical variations in the biliary tract and vessels in the donor graft, the condition of the recipient's portal vein, and the adequacy of arterial flow are factors that can affect the success of transplantation in terms of surgical technique. Among these factors, the hepatic artery (HA) plays a crucial role. The type, number, and diameter compatibility of the recipient's hepatic artery, as well as the presence of atherosclerotic diseases and intimal dissection that may occur in the artery, are significant considerations for ensuring proper graft vascularization [1, 2]. As the hepatic artery supplies blood to the biliary tract of the graft, complications in the recipient's hepatic artery can contribute to post-transplant biliary issues [3, 4]. In our study, we investigated the impact of post-transplant biliary complications based on the type and number of recipient hepatic arteries.

Materials and methods

A retrospective review was conducted on the liver transplantation (LT) database. The study encompassed 185 patients, aged 18 years and above, who underwent right lobe LDLT for end-stage liver cirrhosis between July 2021 and July 2023. Demographic data were calculated and stated in the study. Gender, age, MELD, Child-Pugh score, and etiology rates were analyzed. Whether the hepatic artery was left-or right-sided, and how many arteries there were analyzed. The recipient's right hepatic artery (RHA), left hepatic artery (LHA), propria hepatic artery (PHA) and common hepatic artery (CHA), which were anastomosed to the graft artery, were examined. Double hepatic artery anastomoses formed in the right and left hepatic arteries. Statistical analysis was conducted to assess biliary complications based on whether single or double artery anastomosis was performed and whether anastomoses involved the right hepatic artery or other hepatic arteries. The donor hepatic artery variations were classified according to Michel's classification, and bile variations were categorized following the classification [5, 6]. Those with single bile anastomosis and those with multiple biliary anastomosis were statistically analyzed separately for the right hepatic artery. In addition, which artery was used more in patients without biliary complications was statistically analyzed. As the study was designed retrospectively, patients were not provided with a written informed consent form. However, all procedures adhered to the ethical standards established by the committees overseeing human experimentation, both at the institutional and national levels, and were in the 1964 Declaration of Helsinki and its subsequent editions. The Human Experiments Ethics Committee granted approval for this study under the ethics committee.

Surgical technique

The anastomoses were performed by a single surgeon. Arterial anastomosis was done one by one with 8-0 polypropylene sutures. Biliary anastomoses were done one by one with 7-0 pds sutures, with the mucosal margin channel evolving from channel to channel or channel to plate. In addition, a 5 F-feeding catheter was placed on the biliary anastomosis proximally.

Postoperative hepatic artery evaluation

The hepatic artery flows were checked with Doppler ultrasonography (USG) in the first 3 days postoperatively. Results were confirmed by dynamic multiphase abdominal computed tomography (CT) in patients with suspected flow insufficiency. In addition, all patients underwent control thorax and dynamic multiphase abdominal CT on the 7th postoperative day.

Statistical analysis

Nominal and ordinal parameters were defined through frequency analysis, while scale parameters were characterized using means and standard deviations. Differences between

categorical parameters were assessed using the Chi-Square Test and Chi-Square Likelihood Tests. The normality of scale parameters was evaluated with the Kolmogorov-Smirnov test. The statistical software SPSS 17.0 for Windows was utilized with a 95% Confidence Interval.

Results

The average age was 54.4 years (ranging from 18 to 78), with a gender distribution of 44% female and 56% male. In terms of Child-Pugh classification, 25% of patients were classified as Child A, 38% as Child B, and the 37% as Child C. The mean MELD score for adult patients was 16.2 (Table 1).

Table 1. Demographic and etiology findings in LDLT recipients

n/%	LDLT Recipients (n:185)
Age (average)	54.4 (18-78)
Gender	
Famale	81 (44%)
Male	104 (56%)
Child Score	
Child A	46 (25%)
Child B	70 (38%)
Child C	69 (37%)
MELD Score	16.1
Anhepatic phase [Mean (minute)] (SD)/(min/max)	66.5 (±33.2)/(58-75.1)
Cold ischemia time [Mean (minute)] (SD)/(min/max)	72.2 (±20.4)/(65.4-92.3)
Operation time [Mean (minute)] (SD)/(min/max)	470 (±60.7)/(460-496)
G.R.W.R. [Mean (grams)] (SD)/(min./max.)	1.08 (±0.31)/(0.75-1.16)
ICU stay (Mean day) (SD)/(min./max.)	2.3 (±1.1)/(1.9-2.5)
Hospital stay (Mean day) (SD)/(min./max.)	15 (±7.1)/(14.7-17.2)
Etiology	
HBV	42 (22%)
HBV+HDV	10 (4%)
HCC	33 (18%)
NASH	29 (15%)
Autoimmune	12 (6%)
Alcohol	11 (5%)
Budd Chiari Syndrome	5 (2%)
Familial Cholestasis	2 (1%)
Primary Hyperoxaluria	2 (1%)
Hemachromatosis	2 (1%)
Wilson Disease	2 (1%)
HCV	2 (1%)
Cryptogenic	43 (23%)

LDLT: Living donor liver transplantation, HBV: Hepatitis B Virus, HCV: Hepatitis C virüs, HDV: Hepatitis D virüs, NASH: Nonalcoholicsteatohepatitis
SD: standart deviation

Upon examining etiological factors, the most prevalent factor among adults was Hepatitis B virus (HBV), accounting for 22%, followed by hepatocellular carcinoma (HCC) at 18%, and nonalcoholic-steatohepatitis (NASH) at 15%. The autoimmune etiology had a rate of 6%, while alcohol-induced cirrhosis and HBV+ Hepatitis D Virus (HDV) were at rates of 5% and 4%, respectively. Budd-Chiari syndrome had a 2% rate. Additional identified etiological factors comprised familial cholestasis, primary hyperoxaluria, hemochromatosis, Wilson's disease, and Hepatitis C Virus (HCV), each accounting for 1%. Cryptogenic cirrhosis was noted in 23% of the patients (Table 1).

The average cold ischemia time was 72 minutes, while the anhepatic phase duration averaged 66.5 minutes. The mean operative time was 470 minutes. Following surgery, patients stayed in the intensive care unit (ICU) for an average of 2.3 days, with a hospital stay averaging 15 days. (Table 1).

Graft artery anatomic variation was 60% type 1, 20% type 2, 16% type 3, and a total of 4% type 4, 5, 6 and 9. The anatomical variation of the graft bile duct on the donor preoperative dynamic multiphase CT scan and Magnetic Resonance Cholangio-Pancreatography (MRCP) imaging was type 1 (66%), type 2 (24%), and type 3 (10%).

In living-donor liver transplants, 96% (n:178) utilized living liver grafts with a single hepatic artery, while 4% (n:7) employed grafts with double hepatic artery branches. Among recipients, the anastomosis rate for the right hepatic artery was 88% (n:162), the rate for the left hepatic artery was 4% (n:8), the utilization rate for propria hepatic artery was 2% (n:4), and the utilization rate for the common hepatic artery was 2% (n:4). Double hepatic artery branches in the graft were anastomosed with the recipient's right and left hepatic artery. There was no statistically significant difference in biliary tract stricture or leakage between the patients in whom graft artery anastomosis was made to the recipient's RHA and those in which it was performed to the LHA and others (Table 2). Also, in the statistical analysis between RHA and all other artery anastomoses, no significant difference was observed in terms of bile duct complications (p>0.05). Again, no significant difference was observed between RHA, LHA, PHA, and CHA in terms of biliary complications (Table 3). There was no statistically significant difference between single and dual artery anastomoses in terms of bile duct stricture or leakage (p=0.767) (Table 2). No statistically significant difference was observed between RHA, LHA, PHA, CHA, and between single and dual arteries in the evaluation of artery selection between those with and without biliary tract complications (p=0.445) (Table 3). Furthermore, according to the Mitchell classification, 78% of the recipient arteries were Type 1, 19% were Type 2, and 3% were Type 3 (Table 4).

Table 2. Bile complication rates and statistical result according to recipient artery type and number

Recipient Artery (n/rate)	No Bile Complication	Bile Leakage	Bile Stricture	Total (n/rate)	*p value **X^2 value
RHA	130 (80.2%)	14 (8.6%)	18 (11.2%)	162 (100%)	
LHA	7 (87.5%)	-	1 (12.5%)	8 (100%)	
PHA	4 (100%)	-	-	4 (100%)	*0.767
CHA	2 (50%)	1 (25%)	1 (25%)	4 (100%)	**4.911
RHA+LHA (dual artery anastomosis)	6 (85.7%)	-	1 (14.3%)	7 (100%)	
Total	149 (81%)	15 (8%)	21 (11%)	185 (100%)	

RHA: Right Hepatic Artery, LHA: Left Hepatic Artery, PHA: Propria Hepatic Artery, CHA: Common Hepatic Artery, N: Number
*p value; Chi-Square Test, **X^2 value

Table 3. Statistical evaluation of whether there is a difference in the type and number of arteries between those with and without biliary complications

Recipient Artery (n/rate)	Bile Complication (-)	Bile Complication (+)	Total (n/rate)	*p value **X^2 value
RHA	130 (80.2%)	32 (19.8%)	162 (100%)	
LHA	7 (87.5%)	1 (25%)	8 (100%)	
PHA	4 (100%)	-	4 (100%)	*0.445 **3.723
CHA	2 (50%)	2 (50%)	4 (100%)	
RHA+LHA (dual artery anastomosis)	6 (85.7%)	1 (14.3%)	7 (100%)	

RHA: Right Hepatic Artery, LHA: Left Hepatic Artery, PHA: Propria Hepatic Artery, CHA: Common Hepatic Artery, N: Number
*p value; Chi-Square Test, **X^2 value

Table 4. Recipient artery types according to the Mitchell classification

(n/%)	Type 1	Type 2	Type 3	Type 4
RHA				
LHA	145/ 78%	35/ 19%	5/ 3%	0/ 0%
PHA				
CHA				

RHA: Right Hepatic Artery, LHA: Left Hepatic Artery, PHA: Propria Hepatic Artery, CHA: Common Hepatic Artery, N: Number

Discussion

During the post-transplant period, there may be complication rates of up to 25% in the hepatic artery, potentially resulting in graft loss of up to 50% in the recipient. Early or late ischemic bile duct problems may also arise due to flow insufficiency. These complications play a significant role in contributing to morbidity and mortality in the recipient [1, 2, 4, 7].

Among biliary complications after liver transplantation, strictures and leaks hold a crucial place [8-10]. While the liver can withstand ischemia due to its rich vascular network, the biliary system is highly vulnerable to ischemia, primarily relying on the hepatic artery for its blood supply. Insufficiency in hepatic artery flow, leading to ischemia, plays a significant role at both the anastomosis level and in the etiology of hilar or intrahepatic bile duct strictures [2, 3, 7, 11].

Hepatic artery thrombosis significantly increases graft loss and early postoperative mortality; however, non-thrombotic hepatic artery flow insufficiency may necessitate long-term interventional and surgical interventions due to bile complications in recipients [12]. Furthermore, the risk of early hepatic thrombosis increases with the selection of the recipient artery towards its distal portion and an increase in artery length [13].

Despite the seemingly better outcomes of using the right hepatic artery for hepatic artery reconstruction in right lobe LDLT [14], the impact of different artery selections on biliary tract complications has been explored in various studies. It has been noted that the biliary stricture rate is higher in recipients where the right hepatic artery is used compared to the left artery, and this rate decreases in propria hepatic artery anastomoses [14-16]. While the use of the left hepatic artery correlates with a decrease in the biliary stricture rate, it is crucial not to overlook the findings indicating that the overall biliary complication rates remain unchanged regardless of whether the right or left hepatic artery is utilized [17]. Nevertheless, studies have also shown no significant difference in

terms of biliary complications between patients who underwent dual artery anastomosis (for example, a preference for both the right and left hepatic arteries) and those who underwent single artery anastomosis [18, 19]. In our study, no significant difference was observed between right, left, propria, and common hepatic artery choices in terms of bile duct complications. Similarly, no difference was observed between single and dual artery anastomoses in altering the biliary tract complication rates. There was no significant difference in hepatic artery selection between patients with strictures and leaks in the bile ducts and those without complications.

The study's limitations include the lack of information on recipient body mass index (BMI) values, chronic comorbidities, and preoperative nutritional status.

While the recipient's selection of the hepatic artery type does not alter the biliary tract complication rates, factors such as sufficient blood flow, the length of the chosen artery, the absence of intimal damage, and the absence of atherosclerosis should not be overlooked.

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References

1. Balci D, Ahn CS. Hepatic artery reconstruction in living donor liver transplantation. Curr Opin Organ Transplant 2019;24:631-636. https://doi.org/10.1097/MOT.0000000000000697
2. Oberkofler CE, Reese T, Raptis DA, et al. Hepatic artery occlusion in liver transplantation: What counts more, the type of reconstruction or the severity of the recipient's disease? Liver Transpl 2018;24:790-802. https://doi.org/10.1002/lt.25044
3. Koneru B, Sterling MJ, Bahramipour PF. Bile duct strictures after liver transplantation: a changing landscape of the Achilles' heel. Liver Transpl 2006;12:702-704. https://doi.org/10.1002/lt.20753
4. Seo CH, Ahn J, You YK, Choi HJ. Single-center experience with hepatic artery reconstruction during living donor liver transplantation: microscope versus surgical loupe. Ann Transplant 2021;26:e933371-933377. https://doi.org/10.12659/AOT.933371
5. Noussios G, Dimitriou I, Chatzis I, Katsourakisb A. The main anatomic variations of the hepatic artery and their importance in surgical practice: review of the literature. J Clin Med Res 2017;9:248-252. https://doi.org/10.14740/jocmr2902w
6. Eleazar Chaib E, Kanas AF, Galvão FHF, Carneiro D'Albuquerque LA. Bile duct confluence: anatomic variations and its classification. Surg Radiol Anat 2014;36:105-109. https://doi.org/10.1007/s00276-013-1157-6
7. Hann A, Seth R, Mergental H, Hartog H, Alzoubi M, Stangou A. Biliary strictures are associated with both early and late hepatic artery stenosis. Transplant Direct 2021;7:e643. https://doi.org/10.1097/TXD.0000000000001092
8. Kochhar G, Parungao JM, Hanouneh IA, Parsi MA. Biliary complications following liver transplantation. World J Gastroenterol 2013;19:2841-2846. https://doi.org/10.3748/wjg.v19.i19.2841
9. Robert C Verdonk RC, Buis CI, Porte RJ, et al. Anastomotic biliary strictures after liver transplantation: causes and consequences. Liver Transpl 2006;12:726-735. https://doi.org/10.1002/lt.20714
10. Matsuda H, Yagi T, Sadamori H, et al. Complications of arterial reconstruction in living donor liver transplantation: a single-center experience. Surg Today 2006;36:245-251. https://doi.org/10.1007/s00595-005-3131-3
11. Ng SW. Hepatic artery anastomosis in liver transplantation. Ann Acad Med Singap 2021;20:666-668. https://doi.org/10.47102/annals-acadmedsg.2021332
12. Piskin T, Demirbas T, Yalcin L, et al. Recipient splenic artery utilization for arterial re-anastomosis in living donor liver transplantation: single-center experience. Hepatogastroenterology 2012;59:1263-1264. https://doi.org/10.5754/hge11642
13. Herrero A, Souche R, Joly E, et al. Early hepatic artery thrombosis after liver transplantation: what is the impact of the arterial reconstruction type? World J Surg 2017;41:2101-2110. https://doi.org/10.1007/s00268-017-3989-4
14. Uchiyama H, Ikegami T, Soejima Y, et al. Use of recipient's left hepatic artery for artery reconstruction in right lobe living donor liver transplantation with duct-to-duct anastomosis. Transplantation 2010;89:1016-1021. https://doi.org/10.1097/tp.0b013e3181ce77c4
15. Zhao JC, Yan LN, Li B, et al. Hepatic arterial reconstruction and complications management in adult-to-adult living donor liver transplantation. Zhonghua Wai Ke Za Zhi 2008;46:166-169.
16. Fan ST, Lo CM, Liu CL, et al. Biliary reconstruction and complications of right lobe live donor liver transplantation. Ann Surg 2002;236:676-683. https://doi.org/10.1097/00000658-200211000-00019
17. Chikkala BR, Rahul R, Agarwal S, et al. Outcomes of right and left hepatic arterial anastomosis in right lobe living donor liver transplant. Exp Clin Transplant 2022;20:157-163. https://doi.org/10.6002/ect.2020.0309

18. Cakir T, Sabuncuoglu MZ, Soyer V, et al. Use of the Right Lobe Graft With Double Hepatic Arteries in Living-Donor Liver Transplant. Exp Clin Transplant 2022;20:495-499. https://doi.org/10.6002/ect.2015.0108

19. Lee KW, Sanghoon Lee S, Jeungmin Huh J, et al. Outcome of living donor liver transplantation using right liver allografts with multiple arterial supply. Liver Transpl 2016;22:1649-1655. https://doi.org/10.1002/lt.24600

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Authors' contributions to the article

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

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

Research Article

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Evaluating the efficacy of percutaneous nephrostomy in managing hematuria following antegrade double J ureteral stent placement

Perkütan antegrad çift J üreteral stent yerleştirilmesinin ardından gelişen hematürinin yönetiminde perkütan nefrostominin etkinliğinin değerlendirilmesi

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Abstract

Purpose: This study aims to evaluate the clinical outcomes of percutaneous nephrostomy in patients who develop hematuria during percutaneous antegrade double j stent placement.

Materials and methods: We conducted a multicenter retrospective cross-sectional study, reviewing medical records from January 2016 to June 2024, to identify patients who underwent percutaneous antegrade double j stent placement and developed hematuria. Percutaneous antegrade double j stent and nephrostomy procedures were performed under ultrasound and fluoroscopic guidance.

Results: The study included 151 patients with a mean age of 65.9±15.3 years; 46 (30.5%) were female, and 105 (69.5%) were male. Hematuria was observed in 20 (8.9%) of the 225 antegrade double j stent procedures. Hematuria was significantly more common in patients with benign conditions (35%) compared patients with malignant tumors (9.2%) (p=0.003). Postoperative nephrostomy was performed in 118 (52.4%) of the procedures. Among patients who developed hematuria, 11 (55%) received a nephrostomy, compared to 9 (45%) without hematuria, though this difference was not statistically significant (p=0.811).

Conclusion: Percutaneous nephrostomy appears to be an effective intervention for managing hematuria in patients undergoing antegrade double j stent placement. However, the study did not find a statistically significant difference in hematuria incidence with nephrostomy placement, indicating the need for further research with larger sample sizes to confirm these findings and optimize postoperative management strategies.

Keywords: Percutaneous, nephrostomy, stents, hematuria.

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Öz

Amaç: Bu çalışmada perkütan antegrad double j stent yerleştirilmesi sırasında hematüri gelişen hastalarda perkütan nefrostominin klinik sonuçlarının değerlendirilmesi amaçlandı.

Gereç ve yöntem: Perkütanöz antegrad double j stent yerleştirilen ve hematüri gelişen hastaları belirlemek için Ocak 2016'dan Haziran 2024'e kadar tıbbi kayıtları gözden geçiren, çok merkezli, retrospektif, kesitsel bir çalışma gerçekleştirdik. Perkütan antegrad double j stent ve nefrostomi işlemleri ultrason ve floroskopi rehberliğinde gerçekleştirildi.

Bulgular: Çalışmaya yaş ortalaması 65,9±15,3 yıl olan 151 hasta dahil edildi; 46'sı (%30,5) kadın, 105'i (%69,5) erkekti. Yapılan 225 antegrad double j stent işleminin 20'sinde (%8,9) hematüri görüldü. Hematüri malignitesi olmayan hastalarda (%35) malign tümörlü olanlara (%9,2) göre anlamlı olarak daha fazla görüldü (p=0,003). İşlemlerin 118'ine (%52,4) postoperatif nefrostomi uygulandı. Hematüri gelişen hastaların 11'ine (%55) nefrostomi uygulanırken, hematürisi olmayan 9 hastaya (%45) rağmen bu fark istatistiksel olarak anlamlı değildi (p=0,811).

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Sonuç: Perkütan nefrostomi, antegrad double j stent yerleştirilen hastalarda hematürinin tedavisinde etkili bir girişim gibi görülmektedir. Ancak bu çalışma, nefrostomi yerleştirilmesiyle hematüri insidansında istatistiksel olarak anlamlı bir fark bulamadı. Bu da, bulguları doğrulamak ve perioperatif yönetim stratejilerini optimize etmek için daha büyük örneklem boyutlarıyla daha fazla araştırmaya ihtiyaç olduğunu gösteriyor.

Anahtar kelimeler: Perkütan, nefrostomi, stent, hematüri.

Arslan M, Aslan HS, Kurnaz B, Han Alver K, Demirci M, Alpua M, Çelen S. Perkütan antegrad çift J üreteral stent yerleştirilmesinin ardından gelişen hematürinin yönetiminde perkütan nefrostominin etkinliğinin değerlendirilmesi. Pam Tıp Derg 2024;17:682-688.

Introduction

Percutaneous antegrade double J ureteral stent (ADJS) placement is a medical procedure performed to ensure the flow of urine from the kidney to the bladder. This procedure is typically used to treat obstructions or strictures in the ureter and involves placing a stent within the ureter to facilitate urine flow from the kidney to the bladder [1]. However, hematuria (the presence of blood in the urine) can occur in some patients during percutaneous ADJS placement [2].

In this context, percutaneous nephrostomy is considered a potential treatment option for managing hematuria. Percutaneous nephrostomy provides direct drainage of urine from the kidney, allowing the ureter and bladder to rest and aiding in the control of hematuria [3]. Additionally, nephrostomy offers a route for further intervention if complications such as ADJS migration or occlusion arise. However, further research is needed to determine the effectiveness and benefits of percutaneous nephrostomy in patients who develop hematuria.

The aim of this study is to evaluate the clinical outcomes of percutaneous nephrostomy in patients who develop hematuria during percutaneous ADJS placement. By examining hematuria and its impact on the overall health status of patients, we seek to determine whether percutaneous nephrostomy is a suitable treatment option for these patients. The findings are expected to contribute to clinical decision-making processes regarding the management of hematuria in ADJS practices.

Materials and methods

Study design and patient selection

This article presents a multicenter retrospective cross-sectional study aimed at investigating the clinical outcomes of percutaneous nephrostomy in patients who develop hematuria during percutaneous ADJS placement. Ethical approval was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee prior to the commencement of the study.

Medical records from January 2016 to June 2024 were reviewed to identify patients who underwent percutaneous ADJS placement and subsequently developed hematuria. The inclusion and exclusion criteria are demonstrated in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age 18 years or older **Underwent ADJS placement**	Patients with pre-existing coagulopathies
	Patients who underwent ureteral balloon angioplasty
	Patients who had undergone prior interventions affecting the urinary tract
	Incomplete medical records

ADJS: Antegrade double J ureteral stent

Percutaneous nephrostomy procedure

Percutaneous ADJS and nephrostomy were performed under ultrasound and fluoroscopic guidance. The procedures involve the insertion of a percutaneous ADJS to ensure direct urine drainage from the kidney, with or without a nephrostomy tube (Figure 1, 2). The indication for nephrostomy placement was persistent or worsening hematuria despite conservative management.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the study population. Continuous variables were expressed as mean ± standard deviation (SD) or median, while categorical variables were presented as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. The effectiveness of percutaneous nephrostomy was assessed using chi-square tests for categorical variables. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

Results

In this study, we evaluated the relationship between postoperative nephrostomy and the presence of hematuria in patients who underwent antegrade double J stent (ADJS) placement. The descriptive statistics and comparisons based on the presence of hematuria are presented in Table 2.

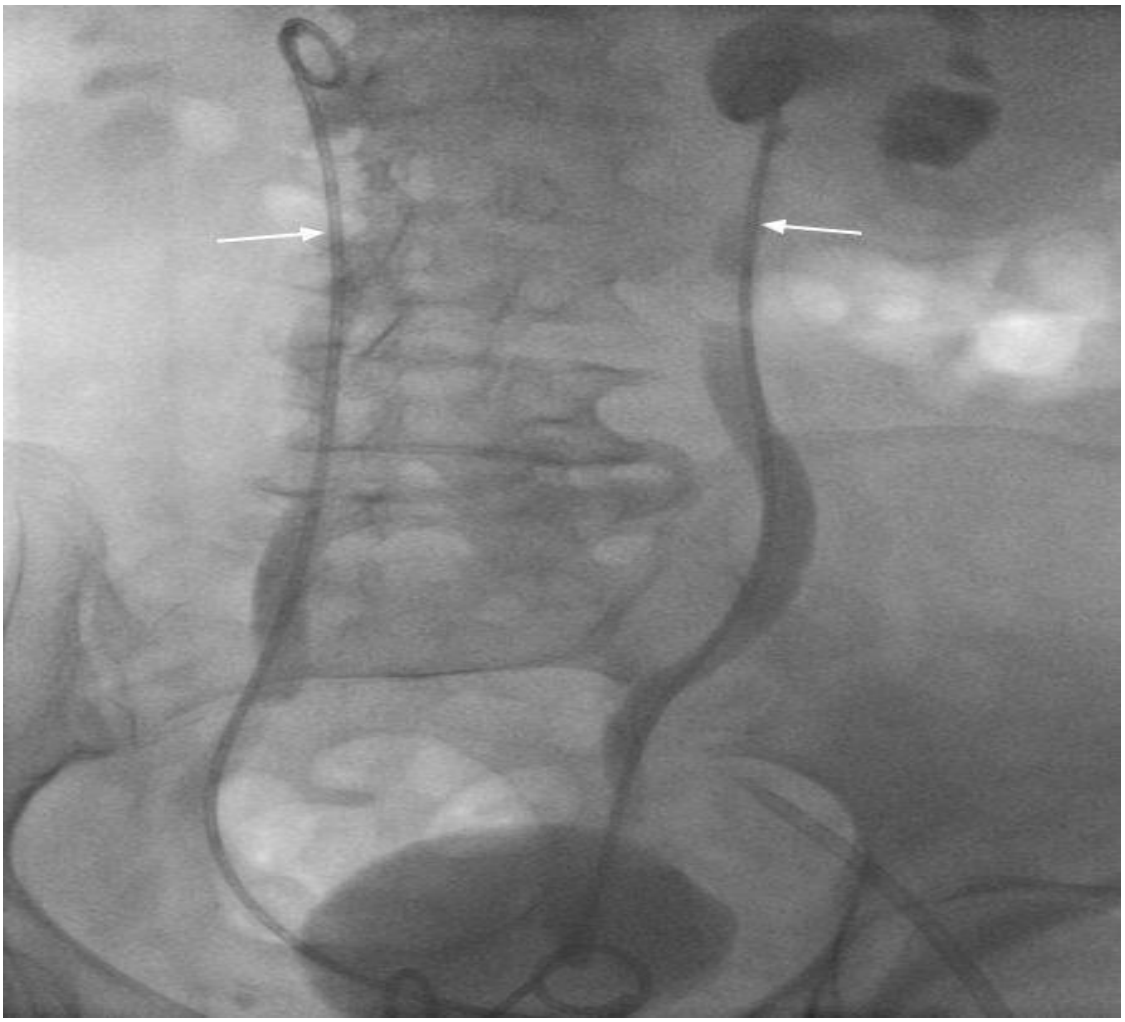

Figure 1. Antegrade double J stent placement (white arrow) into the ureter without a nephrostomy catheter

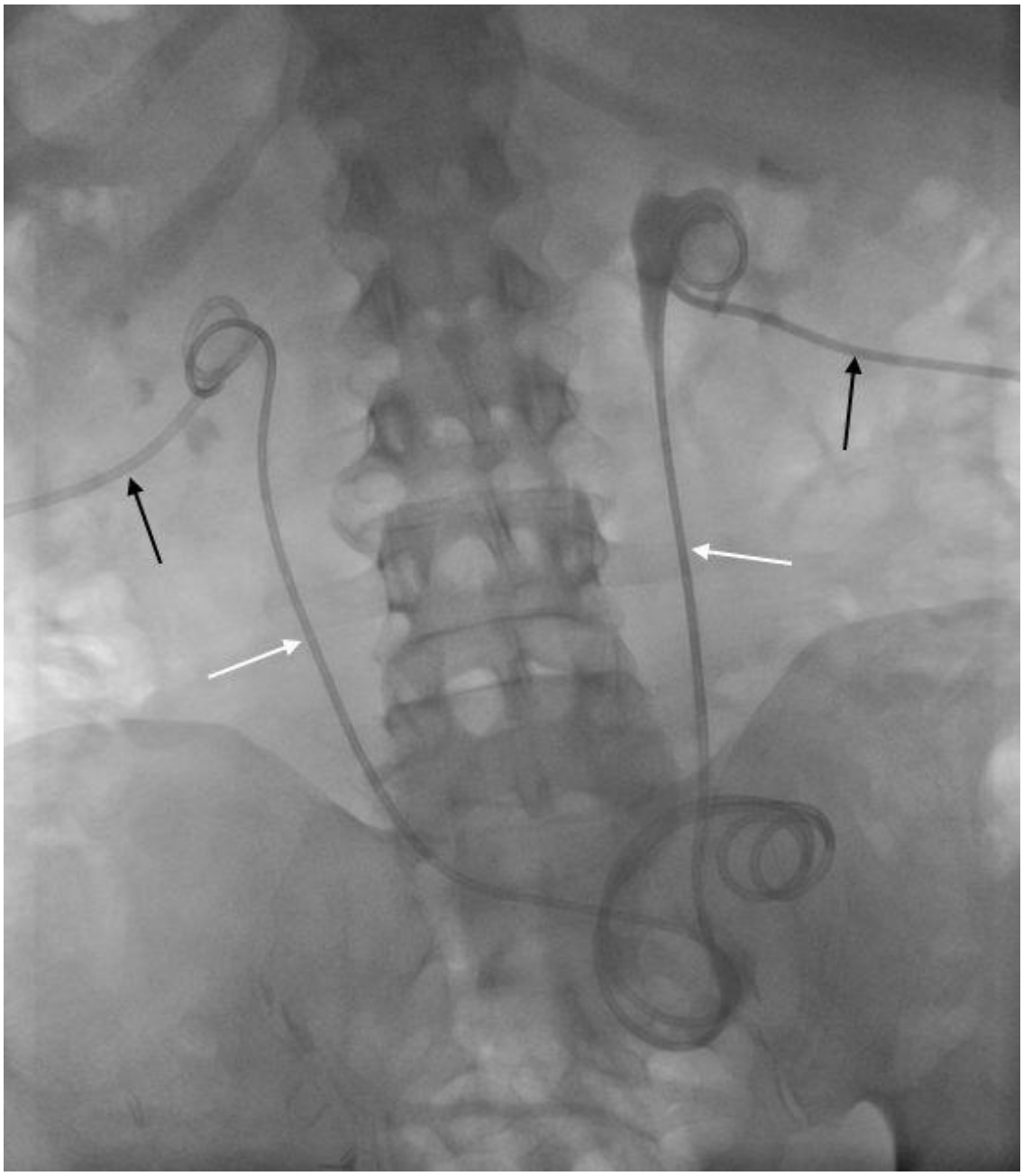

Figure 2. Antegrade double J stent placement (white arrow) into the ureter with a nephrostomy catheter (black arrow)

Table 2. Descriptive statistics of patients with a Double J catheter and comparisons based on the presence of hematuria

	Overall (n=151) **a**				
Age †	65.9±15.3				
Gender ‡					
Female	46 (30.5)				
Male	105 (69.5)				
	Overall (n=225) **b**	**Hematuria**		***p***	**Chi-square Test**
		(+) (n=20)	**(-)** (n=205)		
Tumor Type ‡					
Benign	25 (11.1)	7 (35)	18 (9.2)	**0.003***	x^2=12.684
Malignant	200 (88.9)	13 (65)	187 (90.8)		
Side ‡					
Right	114 (46.6)	11 (55)	103 (50.2)		
Left	110 (52.6)	9 (45)	101 (49.3)	0.884*	x^2=0.247
Transplant	1 (0.9)	0 (0.0)	1 (0.5)		
Post-procedure Nephrostomy, *yes* ‡	118 (52.4)	13 (65)	7 (35)	0.273*	x^2=1.200
Entry from Which Calyx ‡					
Lower	152 (67.5)	11 (55)	141 (75.0)		
Middle	60 (26.6)	9 (45)	51 (22.7)	0.103*	x^2=4.547
Upper	13 (5.7)	0 (0.0)	13 (2.3)		
Method ‡					
First hand approach	114 (50.7)	11 (55)	103 (50.2)	0.434*	x^2=0.612
Nephrostomy route approach	111 (49.3)	9 (45)	102 (49.8)		

†: Mean ± Standard Deviation, ‡: n (%), a: Patient number, b: Antegrade double J procedure number, *: Pearson Chi-Square
Fisher's Exact or Fisher Freeman Halton test

Patient demographics

The study included 151 patients with a mean age of 65.9±15.3 years. Among them, 46 (30.5%) were female, and 105 (69.5%) were male.

Hematuria and tumor type

Of the 225 ADJS procedures performed, hematuria was observed in 20 cases (8.9%), while 205 cases (91.1%) did not exhibit hematuria. Hematuria was significantly more common in patients with benign tumors (35%) compared to those with malignant tumors (9.2%) (*p*=0.003).

Laterality and transplant status

The distribution of hematuria did not significantly differ based on the side of the procedure, with 55% occurring on the right side and 45% on the left (*p*=0.884). Only one patient in the study had undergone a kidney transplant, and this patient did not develop hematuria.

Post-procedure nephrostomy

Postoperative nephrostomy was performed in 118 (52.4%) of the procedures. Among the patients who developed hematuria, 11 (55%) received a nephrostomy, compared to 9 (45%) of those who did not develop hematuria. However, this difference was not statistically significant (*p*=0.811).

Entry calyx and procedural method

The entry calyx for the nephrostomy was predominantly the lower calyx (67.5%), followed by the middle (26.6%) and upper calyx (5.7%). There was no significant difference in the incidence of hematuria based on the entry calyx (p=0.103). Additionally, the method of approach (first hand versus nephrostomy route) did not show a significant association with hematuria (p=0.434).

Discussion

This study aimed to evaluate the efficacy of percutaneous nephrostomy in managing hematuria following ADJS placement. Hematuria following ADJS placement is a relatively common complication, often resulting from microtraumas that occur during the procedure [4]. The decision to place a nephrostomy catheter post-ADJS remains controversial [5]. While nephrostomy can be inserted as a safety measure for managing hematuria following ADJS placement, there is currently insufficient data to support its necessity unequivocally.

The most common complication is bleeding, though it typically manifests as mild hematuria [3, 5]. In our study, hematuria developed in 20 out of 225 procedures (8.9%), and the majority of these cases (65%) required nephrostomy catheters. van der Meer et al. [4] reported mild hematuria in only 6 out of 130 patients following JJ stent insertion. In the presence of hematuria, it is recommended to monitor bleeding from the nephrostomy catheter for 2-3 days [6]. If the urine color does not change within this period, further investigation into the source of the bleeding may be necessary. Causes of persistent bleeding may include pseudoaneurysm, arteriovenous fistula, or arterio-calyceal fistula [6]. In this study, the only patient who required hospitalization due to hematuria was the one who had a pseudoaneurysm and was treated endovascularly. Consistent with the current study, Tlili et al. [7] observed that two patients were hospitalized for hematuria out of 188 stent insertion attempts.

Most practitioners leave a ‘covering nephrostomy’ in place for 24-48 hours after stent insertion [3, 7, 8]. This practice allows for the nephrostomy to be clamped to ensure adequate urine output through the stent (via the bladder) before the nephrostomy is removed and access is lost [9]. This approach provides a safeguard, ensuring the functionality of the stent and allowing for immediate intervention if complications arise. The results of our study indicate that postoperative nephrostomy was performed in approximately half of the procedures (52.4%). When examining the association between nephrostomy placement and the development of hematuria post-ADJS, our findings revealed that among patients who experienced hematuria, a slightly higher proportion received a nephrostomy (55%) compared to those who did not develop hematuria (45%). However, it’s crucial to note that this observed difference was not statistically significant (p=0.811). While the absence of statistical significance suggests that nephrostomy placement may not significantly affect the incidence of hematuria post-ADJS, further investigation with larger sample sizes is warranted to confirm these findings conclusively. Additionally, exploring other potential contributing factors to hematuria development and considering individual patient characteristics may provide further insights into optimal postoperative management strategies for ADJS procedures.

Interestingly, our results demonstrate a significant difference in the incidence of hematuria between patients with benign conditions and malignant tumors. Hematuria was significantly more common among patients with benign conditions, occurring in 35% of these cases, compared to only 9.2% in patients with malignant tumors (p=0.003). This suggests that the nature of the benign condition, such as stones or cystitis, may play a role in the likelihood of experiencing hematuria post-procedure.

One of the strengths of our study is the multicenter design, which enhances the generalizability of the findings. Additionally, the comprehensive review of medical records ensured a thorough assessment of patient outcomes. However, the retrospective nature of the study presents inherent limitations, such as potential selection bias and reliance on accurate record-keeping. Future prospective studies with larger sample sizes are needed to validate our findings and provide more robust evidence. Additionally, randomized controlled trials comparing nephrostomy with other interventions, such as conservative

management or alternative surgical techniques, would provide more definitive evidence on the optimal management strategies for this complication.

In conclusion, our study provides valuable insights into the management of hematuria following percutaneous ADJS placement. While percutaneous nephrostomy appears to be a feasible option for managing hematuria in these patients, our findings did not show a statistically significant difference in the incidence of hematuria between those who received nephrostomy and those who did not. This suggests that while nephrostomy may help in certain cases, its routine use solely for the prevention of hematuria may not be justified without further evidence. The significant difference in hematuria incidence between patients with benign and malignant conditions highlights the need for tailored management strategies based on individual patient characteristics. The multicenter design of our study enhances the generalizability of the results, yet the retrospective nature imposes limitations such as potential selection bias. Future research should focus on prospective studies with larger sample sizes and randomized controlled trials to validate these findings and optimize postoperative management strategies for ADJS procedures. These studies should also explore additional factors contributing to hematuria development to provide a more comprehensive understanding and improve patient outcomes.

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

References

1. Okeke Z, Okhunov Z, Smith A. Smith's textbook of endourology. 3rd ed. West Sussex: John Wiley&Sons, 2012;725-734.
2. Kim HJ, Yoon CJ, Lee S, Lee JH, Choi WS, Lee CH. Comparison between antegrade versus retrograde ureteral stent placement for malignant ureteral obstruction. J Vasc Interv Radiol 2022;33:1199-1206. https://doi.org/10.1016/j.jvir.2022.06.024
3. Yoo MJ, Bridwell RE, Inman BL, Henderson JD, Long B. Approach to nephrostomy tubes in the emergency department. Am J Emerg Med 2021;50:592-596. https://doi.org/10.1016/j.ajem.2021.09.034
4. van der Meer RW, Weltings S, van Erkel AR, et al. Antegrade ureteral stenting is a good alternative for the retrograde approach. Curr Urol 2017;10:87-91. https://doi.org/10.1159/000447157
5. Tibana TK, Grubert RM, Santos RFT, et al. Percutaneous nephrostomy versus antegrade double-J stent placement in the treatment of malignant obstructive uropathy: a cost-effectiveness analysis from the perspective of the Brazilian public health care system. Radiol Bras 2019;52:305-311. https://doi.org/10.1590/0100-3984.2018.0127
6. Hausegger KA, Portugaller HR. Percutaneous nephrostomy and antegrade ureteral stenting: technique-indications-complications. Eur Radiol 2006;16:2016-2030. https://doi.org/10.1007/s00330-005-0136-7
7. Tlili G, Ammar H, Dziri S, et al. Antegrade double-J stent placement for the treatment of malignant obstructive uropathy: a retrospective cohort study. Ann Med Surg 2021;69:102726. https://doi.org/10.1016/j.amsu.2021.102726
8. Chitale S, Raja V, Hussain N, et al. One-stage tubeless antegrade ureteric stenting: a safe and cost-effective option? Ann R Coll Surg Engl 2010;92:218-224. https://doi.org/10.1308/003588410X12518836439128
9. Dagli M, Ramchandani P. Percutaneous nephrostomy: technical aspects and indications. Semin Intervent Radiol. 2011;28:424-437. https://doi.org/10.1055/s-0031-1296085

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Authors' contributions to the article

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

Research Article

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Gender-specific effects of alternate-day fasting on body weight, oxidative stress, and metabolic health in middle-aged rats

Orta yaş sıçanlarda gün aşırı açlık protokolünün vücut ağırlığı, oksidatif stres ve metabolik sağlık üzerine cinsiyete özgü etkileri

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Abstract

Purpose: The purpose of this study was to assess the effect of alternate-day fasting (ADF) concerning sex as well as its function in systemic and tissue-level oxidative stress alterations associated with aging.

Materials and methods: Forty-two female (n=21) and male (n=21) Wistar rats (aged 16 months) were separated into six groups (n=7 each): Group-1 (control-male), Group-2 (1-month, ADF-male), Group-3 (2-month, ADF-male), Group-4 (control-female), Group-5 (1-month, ADF-female), and Group-6 (2-month, ADF-female). The ADF protocol was applied every other day for 24-h of fasting (three days/week). Serum samples were analyzed via ELISA to measure total oxidant-antioxidant status (TOS-TAS), and the oxidative stress index (OSI) was calculated.

Results: 2-months of ADF treatment reduced body weight (BW) compared compliance control groups (p<0.001). All groups' cumulative food intake and retroperitoneal fat weight decreased with ADF (p<0.05). Both 1-month and 2-month ADF interventions had positive effects on reducing TOS and OSI in both liver and serum, with a significant decrease observed in both groups compared to their respective controls (p<0.001). The liver TAS significantly increased in female rats (p<0.05), but this increase did not reach a significant level in male rats. The difference in the serum TAS between the groups was not significant.

Conclusions: This study evaluated the effects of ADF on BW, food consumption, and oxidative stress parameters in male and female rats. The findings highlight ADF's potential benefits in weight management and reducing oxidative stress. This study represents an important step in understanding the effects of ADF on metabolic health and in identifying potential clinical applications.

Keywords: Aging, alternate-day fasting, food intake, gender, oxidative stress.

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Öz

Amaç: Bu çalışmada, gün aşırı açlık protokolünün (ADF) cinsiyete özgü etkisinin ve yaşlanma ile ilişkili oksidatif stres değişimlerindeki işlevlerinin değerlendirilmesi amaçlandı.

Gereç ve yöntem: Kırk iki dişi (n=21) ve erkek (n=21) 16 aylık Wistar sıçanları altı gruba (n=7) ayrıldı: Grup-1 (kontrol-erkek), Grup-2 (1 ay, ADF-erkek), Grup-3 (2 ay, ADF-erkek), Grup-4 (kontrol-dişi), Grup-5 (1 ay, ADF-dişi) ve Grup-6 (2 ay, ADF-dişi). ADF protokolü günaşırı 24 saatlik oruç tutma şeklinde uygulandı (haftada üç gün). Serum örnekleri, ELISA yöntemiyle toplam oksidan-antioksidan seviyelerini (TOS-TAS) ölçmek için alındı ve oksidatif stres indeksi (OSI) hesaplandı.

Bulgular: İki aylık-ADF tedavisinin kümültatif kontrol gruplarıyla karşılaştırıldığında vücut ağırlığında (VA) anlamlı azalma tespit edildi (p<0,001). Tüm gruplarda kümülatif gıda alımının ve retroperitoneal yağ ağırlığının ADF ile azaldığı görüldü (p<0,05). Hem 1 aylık hem de 2 aylık ADF uygulanması karaciğer ve serumda TOS seviyesi ve OSI'yi azaltmada olumlu etkiler gösterdi ve her iki grup da kendi kontrollerine göre anlamlı bir azalma gözlemlendi (p<0,001). Karaciğer TAS seviyesi dişi sıçanlarda anlamlı olarak arttı (p<0,05), ancak erkek sıçanlarda bu artış anlamlı bir seviyeye ulaşmadı. Gruplar arasındaki serum TAS seviyesinde anlamlı fark saptanmadı.

Sonuç: Bu çalışma, erkek ve dişi sıçanlarda ADF'nin VA, gıda tüketimi ve oksidatif stres parametreleri üzerindeki etkilerini değerlendirdi. Bulgular, ADF'nin kilo yönetimi ve oksidatif stresi azaltmada potansiyel faydalarını vurgulamaktadır. Sonuç olarak, ADF'nin metabolik sağlık üzerindeki etkilerini anlamada ve olası klinik uygulamaları belirlemede önemli bir adımı temsil etmektedir.

Anahtar kelimeler: Yaşlanma, alternatif günlerde açlık, gıda alımı, cinsiyet, oksidatif stres.

Kılıç Erkek Ö, Gündoğdu G. Orta yaş sıçanlarda gün aşırı açlık protokolünün vücut ağırlığı, oksidatif stres ve metabolik sağlık üzerine cinsiyete özgü etkileri. Pam Tıp Derg 2024;17:690-701.

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Introduction

A progressive decline in all physiological activities is a hallmark of aging [1]. Substantial structural and functional changes occur in our organs and systems as we age. Free radicals, reactive oxygen species (ROS), and reactive nitrogen species (RNS) are highly reactive molecules with unpaired electrons [2]. The damage caused by ROS is called oxidative stress, which results from an imbalance between ROS production and antioxidant defenses. This imbalance plays a key role in aging [3].

The free radical theory of aging states that a a gradual rise in ROS and subsequent oxidative damage are pivotal in the aging process. In the absence of endogenous antioxidant defenses, free radicals damage cellular components like DNA, lipids, and proteins, contributing to aging and related disorders [4]. Overexpression of antioxidant enzymes can reduce ROS production and protect DNA, extending lifespan in mice [5]. Furthermore, long-lived mouse strains exhibit increased levels of antioxidant enzyme levels and decreased oxidative damage to proteins and lipids [6].

Rat liver mitochondria undergo oxidative stress and lose enzymatic activity during aging [7]. During aging, ROS overproduction leads to oxidative damage at both the liver and systemic levels. Luceri et al. [8] reported increased oxidative DNA damage in the livers of middle-aged rats (15 months), along with reduced DNA damage repair capacity. Many studies have shown that the aging liver exhibits signs of oxidative damage, and ROS levels in liver tissue significantly impact liver function and are linked to most age-related diseases [9].

Aging increases susceptibility to obesity due to declines in the basal metabolic rate and activity, although individual variations exist. Intermittent fasting (IF) has shown various health benefits in animal models [10, 11] and clinical trials [12, 13]. IF involves periods of eating and fasting, with different protocols such as time-restricted feeding, alternate-day fasting (ADF), or modified fasting with reduced daily food consumption [14].

Individuals aiming to lose weight often follow IF protocols, which include daily fasting periods of up to 16 hours or fasting intervals of up to 24 hours alternating with regular eating days. IF is a method to cause weight loss that has some beneficial effects. Despite the observed weight loss [13, 15] more studies are needed to evaluate whether ADF promotes health benefits or could cause undesired effects in the long term. Although ADF can reduce body weight and fat [16, 17], results vary due to differences in age, sex, and BMI among participants [18, 19]. Thus, a consensus on IF recommendations or preferred protocols is lacking, reflecting diverse study designs and divergent results [20].

The sex-dependent factors responsible for variations in oxidized macromolecule levels are largely unknown and controversial. Preliminary reports on sex-dependent variations in oxidative stress parameters in the plasma of aged subjects have been ambiguous. However, previous studies could not meaningfully correlate the relationships between sex and these oxidized macromolecules [21, 22]. We hope the present study will provide insight that clarifies this complex issue.

Considering the pivotal role of sex in feeding and aging, the question arises whether oxidative stress is influenced synchronously during prolonged food restriction followed by refeeding. Oxidative stress is known to be effective in the development of aging. However, there are no data in the literature examining the effects of age and ADF on oxidative stress parameters in different sexes. In light of this information, this study aimed to evaluate the role of ADF in aging-related oxidative stress changes at both the systemic and tissue levels and its effectiveness compared to that of sex.

Material and methods

Animal Experiments were approved by the Medical Ethics Committee of Pamukkale University.

Animals and experimental design

In this study, forty-two male and female Wistar rats (16 month old) were obtained from the Pamukkale University Medical Experimental Research and Practice Center. The animals were housed in a room with controlled temperature (23±2°C) and relative humidity (60±5%). The animals were kept under adequate light conditions (7.00 AM to 7.00 PM light/dark). The rats were randomly assigned to six equivalent groups (n=7) as follows:

Group 1 (Control group, n=7): Male rats were fed ad libitum

Group 2 (1-month ADF, n=7): Male rats fasted for three days and fed ad libitum for four days per week

Group 3 (2-month ADF, n=7): Male rats fasted for three days and fed ad libitum for four days per week

Group 4 (control group, n=7): Female rats were fed ad libitum

Group 5 (1-month ADF, n=7): Female rats fasted for three days and fed ad libitum for four days per week

Group 6 (2-month ADF, n=7): Female rats fasted for three days and fed ad libitum for four days per week

Study design and ADF protocol

The ADF protocol was applied for eight weeks at a ratio of 4:3 (4 ad libitum days per week and 3 days of total fasting) [23] (Table 1). ADF rats were subjected to 24-hour fasting, and involving 24 hours of free access to the same chow [24].

Table 1. Arrangement of feeding and fasting windows over the entire week

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Before 7.00 AM	Food Ad libitum period	Fasting period	Food Ad libitum period	Fasting period	Food Ad libitum period	Fasting period	Food Ad libitum period
After 7.00 AM	Food Ad libitum period	Fasting period	Food Ad libitum period	Fasting period	Food Ad libitum period	Fasting period	Food Ad libitum period

Food consumption and body weight measurements

Food consumption was calculated by deducting the amount of food left in the box (g) from the total amount of food given. As previously described, the percentage was determined three times a week till the ADF protocols concluded [25]. Feed efficiency was determined by calculating the quotient over the 8 week of experimentation as weekly food consumption per rat. Body weight (BW) was measured at initial, 4^{th} and 8^{th} week of the experiment procedure. In the last week of treatment (4^{th} and 8^{th} weeks), both groups were subjected to a 12-hour overnight fast.

Blood and tissue sampling

The rats were anesthetized by intraperitoneal injection of xylazine (10 mg/kg) and ketamine (90 mg/kg) following a fasting period of 12-hour. Serum samples were collected from the abdominal aorta of the animals in plain tubes without any anticoagulant for Enzyme-Linked Immunosorbent Assay (ELISA). Liver tissues were removed and quickly frozen using liquid nitrogen. The samples were stored at 2-8°C and homogenized. After centrifugation for 20 minutes at 2000 rpm, the supernatant was extracted. After the samples were centrifuged 15 min at 3500 rpm, the blood serum was obtained from the tubes without EDTA.

Oxidative stress parameters

The total oxidant status (TOS) of the serum and tissue samples was determined via an automated colorimetric method [26]. Using this technique, the sample's ferrous ion chelator complex is changed into a ferric ion, increasing absorbance when it reacts with the chromogen in an acidic environment. The concentration of oxidant molecules in the sample is proportional to the rise in absorbance observed using spectrophotometry. The Lowry method was used to measure the tissue protein level. The solid-phase sandwich ELISA principle was applied to the assessment of the serum and tissue sample using ready-to-use measurement kits in accordance with the manufacturer's instructions. The results are reported as μmol H_2O_2Eq/L and μmol H_2O_2Eq/mg protein, respectively.

Similarly, total antioxidant status (TAS) in the serum and tissue samples was also determined using an automated colorimetric method [27]. Serum TAS was determined using the following principle: every antioxidant in the sample reduces the blue-green 2,2'-azinobis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) radical to a colorless reduced form. The amount of antioxidants in the sample is exactly proportionate to the increase in absorbance that is detected spectrophotometrically. The solid-phase sandwich ELISA principle was applied to the assessment of the serum and tissue sample using ready-to-use measurement kits in accordance with the manufacturer's instructions. The results are reported as mmol Trolox Eq/L and mmol Trolox Eq/mg protein, respectively.

The oxidative stability index (OSI) is defined as the ratio of TOS to TAS, calculated using the following formula: OSI= TOS (μmol H2O2 equiv. /L)⁄TAS (μmol Trolox equiv. /L) × 100.

Statistical analysis

A power analysis was conducted using the GPower 3.1 program available online. The effect size reported in the reference study is large (d=1.22). The power analysis (f=0.9) indicated that a minimum of 42 rats (at least seven rats per group) would be required to achieve a power of 80% with a 95% confidence interval. The study used a total of 42 rats. IBM SPSS Statistics 25 program (Armonk, NY: IBM Corp.) version 23.0 was used for all statistical analyses. The standard deviation (SD) of the mean was used to define continuous variables. The normal distribution was determined using the Shapiro-Wilk tests. We employed One-way Anova analysis of variance (post hoc: Tukey method) for independent group comparisons. For statistical significance, $p<0.05$ was the threshold.

Results

Examination of body weight gain and food intake

BW (measured at the initial, 4th week and 8th week of the experiment) is shown in Figure 1A-C. The initial BW of male rats was significantly greater than that of concordant female rats (Group 1 vs Group 4, Group 2 vs Group 5, Group 3 vs Group 6, $p<0.001$), and the BW was not significantly different within the same sex groups ($p>0.05$). After 1 month of the experiment, the BW of the female rats was still significantly lower than that of the concordant male rats (Group 1 vs Group 4, Group 2 vs Group 5, Group 3 vs Group 6, $p<0.001$), and ADF did not significantly lower BW in any of the groups ($p>0.05$). At the end of the experiment, the BW of male rats was significantly greater than that of concordant female rats (Group 1 vs Group 4, Group 3 vs Group 6, $p<0.001$), and 2-months of ADF decreased the BW in both genders (Group 1 vs Group 3, Group 4 vs Group 6, $p<0.001$).

The weekly food consumption amount per rat is shown in Figure 2. The food consumption of male rats was significantly greater than that of concordant female rats (Group 1 vs Group 4, Group 2 vs Group 5, Group 3 vs Group 6; $p<0.001$, $p<0.001$, $p<0.05$, respectively). Additionally, rats in the 1-month and 2-month ADF groups consumed significantly less chow than did those in the control group ($p<0.001$). In addition, in the 2-month ADF group compared to the 1-month group, food consumption decreased significantly in males ($p<0.05$), while this decrease did not reach a significant level in females ($p>0.05$).

Investigation of retroperitoneal fat weight in the experimental groups

The retroperitoneal adipose tissue weights (g) of the rats in the experimental groups are shown in Figure 3. Although initial measurements of retroperitoneal fat weight in male rats was significantly lower than female rats (group 1 vs group 4, $p<0.01$), this decrease did not reach a significant level in 1-month and 2-month ADF applied male rats compared with concordance female rats (group 2 vs group 5, group 3 vs group 6; $p>0.05$). The 1-month ADF intervention significantly reduced the fat pad in female rats ($p<0.001$), whereas the reduction in male rats did not reach significance ($p>0.05$). At the end of the experiment, 2-month of ADF treatment significantly decreased the fat pad weight in both groups (Group 1 vs Group 3, Group 4 vs Group 6, $p<0.001$).

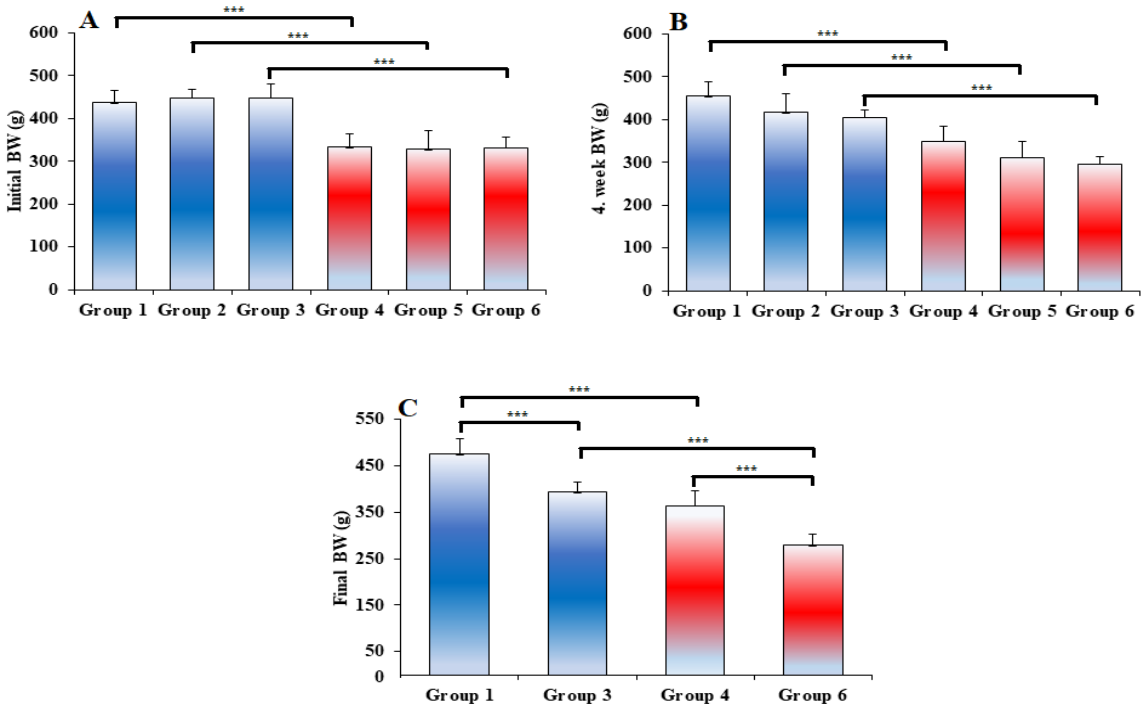

Figure 1. Changes in body weight over time across experimental groups

A. Initial body weight measurements. B. Body weight measurements at the 4th week of the experiment. C. Body weight measurements at the 8th week of the experiment
Data are shown as the mean ± standard deviation; n=7, ***: $p<0.001$
Group 1: male control, Group 2: male 1-month ADF, Group 3: male 2-month ADF, Group 4: female control, Group 5: female 1-month ADF
Group 6: female 2-month ADF

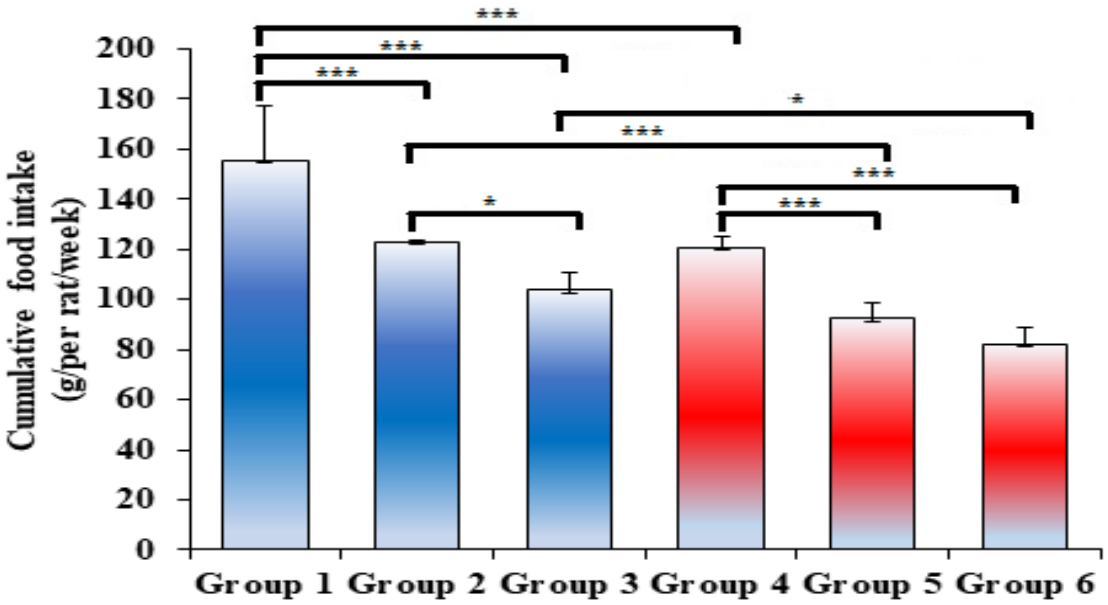

Figure 2. Cumulative food intake of the experimental groups

Data are shown as the mean ± standard deviation; n=7, *: $p<0.05$, ***: $p<0.001$
Group 1: male control, Group 2: male 1-month ADF, Group 3: male 2-month ADF, Group 4: female control, Group 5: female 1-month ADF
Group 6: female 2-month ADF

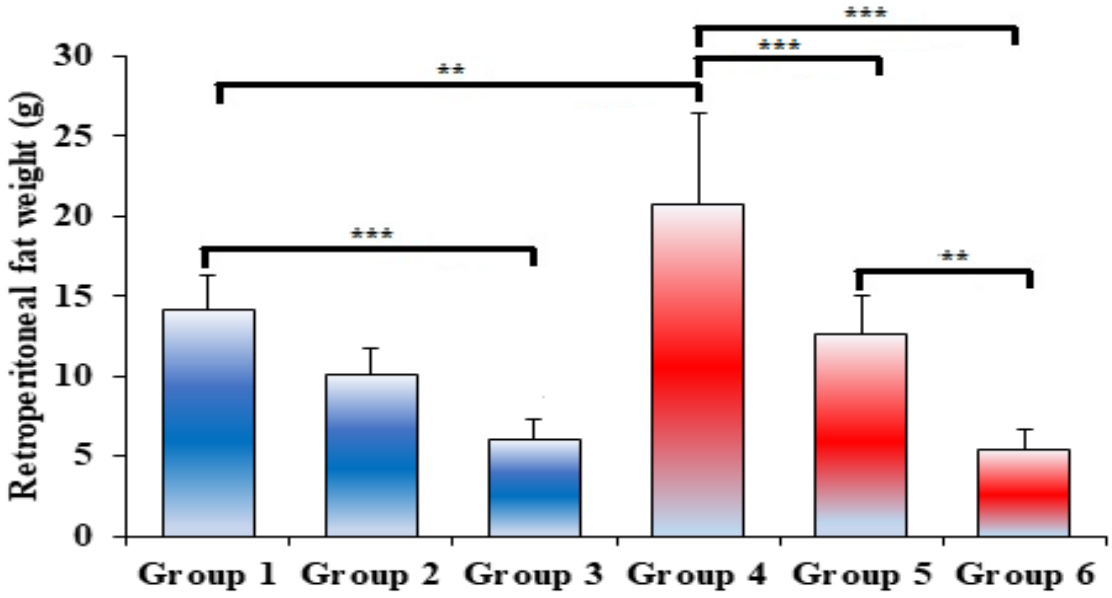

Figure 3. Retroperitoneal adipose tissue weight (g) of the experimental groups

Data are shown as the mean ± standard deviation; n=7, Statistically significant at, **: $p<0.01$, ***: $p<0.001$
Group 1: male control, Group 2: male 1-month ADF, Group 3: male 2-month ADF, Group 4: female control, Group 5: female 1-month ADF
Group 6: female 2-month ADF

Evaluation of serum and liver TOS, TAS, and OSI levels

The liver TOS, TAS, and OSI of the experimental groups are shown in Figure 4. Although the TOS and OSI of initial male rats were significantly greater than those of female rats (group 1 vs group 4, $p<0.01$), this decrease did not reach a significant difference between 1-month and 2-month ADF male rats and concordant female rats (group 2 vs group 5, group 3 vs group 6; $p>0.05$). The liver TOS and OSI were significantly lower in Group 2 and Group 3 than in Group 1 ($p<0.001$). Similar results were observed in female rats, as the TOS and OSI were significantly lower in Group 5 and Group 6 than in Group 4 ($p<0.05$ and $p<0.001$, respectively). The 1-month and 2-month ADF interventions had a positive effect on lowering liver TOS and OSI, but this decrease was much more significant in males. The liver TAS was significantly greater in Group 6 than in Group 4 and Group 5 ($p<0.001$ and $p<0.05$, respectively), but this increase did not reach a significant level in male rats.

The serum TOS, TAS, and OSI of the experimental groups are shown in Figure 5. The serum TOS and OSI were significantly lower in Group 2 and Group 3 than in Group 1 ($p<0.001$). Similar results were observed in female rats, as the TOS and OSI were significantly lower in Group 5 and Group 6 than in Group 4 ($p<0.001$). The 1-month and 2-month ADF interventions had a positive effect on lowering the serum TOS and OSI. However, the difference in the serum TAS between the groups was not significant ($p>0.05$).

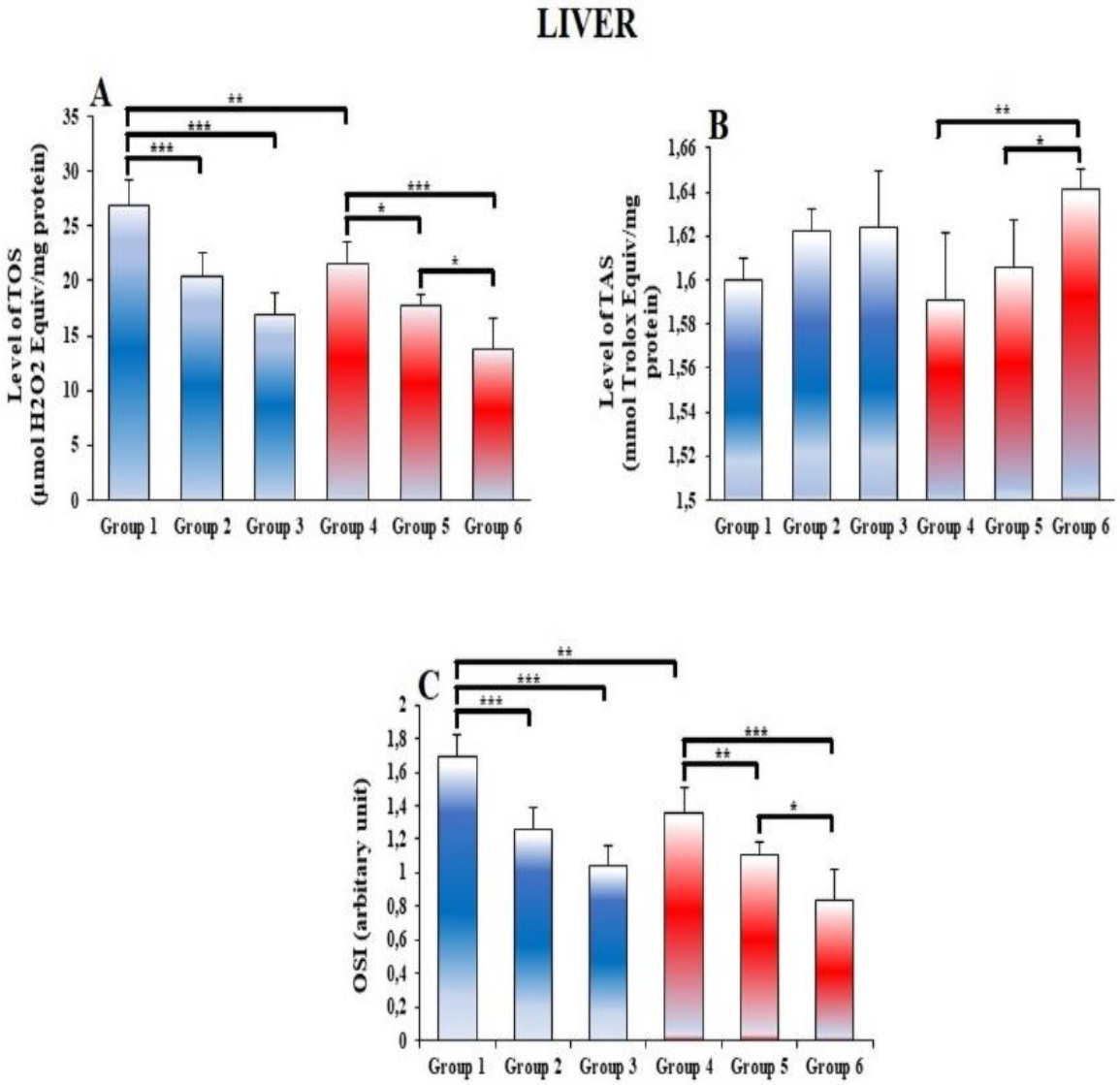

Figure 4. Levels of liver TOS, TAS, and OSI across experimental groups

A. Total Oxidant Status (TOS), B. Total Antioxidant Status (TAS), and C. Oxidative Stress Index (OSI). Data are shown as the mean ± standard deviation; n=7, Statistically significant at, *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$
Group 1: male control, Group 2: male 1-month ADF, Group 3: male 2-month ADF, Group 4: female control, Group 5: female 1-month ADF Group 6: female 2-month ADF

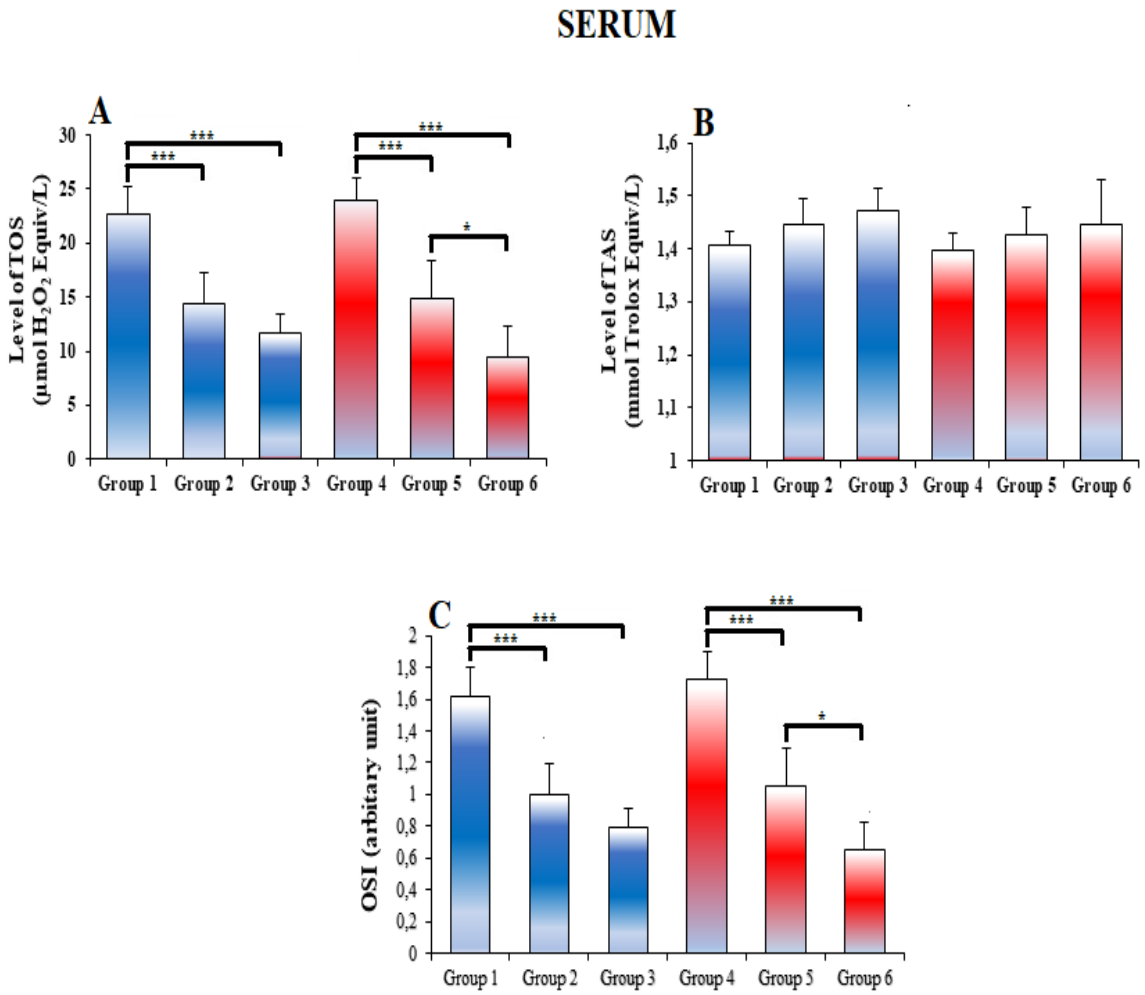

Figure 5. A. Levels of serum TOS, TAS, and OSI across experimental groups

A. Total Oxidant Status (TOS), B. Total Antioxidant Status (TAS), and C. Oxidative Stress Index (OSI). Data are shown as the mean ± standard deviation; n=7, Statistically significant at, *: $p<0.05$; ***: $p<0.001$

Group 1: male control, Group 2: male 1-month ADF, Group 3: male 2-month ADF, Group 4: female control, Group 5: female 1-month ADF Group 6: female 2-month ADF

Discussion

We conducted chronic fasting protocol experiments involving a healthy lifespan using middle-aged male and female rats to clarify the effects of ADF on age-associated changes in BW, body fat, and ROS levels. In the present study, we demonstrated that ADF positively affects BW at 2 months and that 1 month was insufficient to decrease BW in all ADF-treated rats. On the other hand, female rats had the highest retroperitoneal fat weight, which decreased with 1 month of ADF, while 2 months of ADF reduced fat weight regardless of sex. Although ADF lowered the OSI in both timelines with decreased TOS, the favorable effect of ADF was on increased TAS in 2-month-old ADF-treated female rats.

Previous studies have reported the beneficial effects of IF on BW and plasma glucose levels in obese individuals or obese rodent models [28, 29]. However, there is a lack of literature on the application of different IF types to increase healthspan in middle-aged rats. It has been found that IF protocols like ADF can successfully lower BW. In a research with overweight and obese participants, ADF decreased BW by 3% to 7% [18]. However, the reduction in BW induced by IF seems to vary on factors including age, the length of time spent consuming food, and the kind of diet [30]. For example, in male rats, TRF application was unable to stop the rise in BW induced by HFD in older animals as opposed to younger ones [25]. Conversely, ADF induced hyperphagia, hyperinsulinemia, and increased adiposity in juvenile female rats

[24]. These consequences could result from extreme or sudden energy restriction, leading to overeating and other undesirable behaviors. These behaviors can trigger “storage signals,” which promote the growth of adipose tissue [31]. It is significant to remember that in animal models, restricting access to chow or “tasty” items causes an increase in food intake [32, 33]. In this study, the effect of ADF on BW in middle-aged rats of both sexes was examined. Although 1-month of ADF treatment did not significantly affect BW in either sex, a significant decrease in weight loss was observed after 2-months of ADF treatment (Figure 1).

Adipose tissue regulates the cycling of triglycerides by controlling the uptake, esterification, and release of fatty acids, which are alternative fuel sources for the metabolically active organs [34]. During fasting periods, energy is obtained from glycogen which is followed by lipolysis of adipose tissue. This causes release of triacylglycerols and production of glucose from glycerol. Studies have also demonstrated fat loss accompanied with weight loss in ADF protocols [16, 35]. 4 weeks of ADF resulted in decrement of visceral fat, and improvement of lipid profiles in C57BL/6 mice [36]. We still do not understand why various regions of visceral fat respond differently to the dietary protocols between genders. However, we have observed that female rats in the same age group had higher BW, and implementing ADF for 2-months reduced retroperitoneal fat tissue regardless of gender (Figure 3).

ROS can oxidatively modify many biological macromolecules, including proteins, lipids, and nucleic acids, potentially causing genetic mutations and cellular aging. The aging process has been shown to affect the redox balance of plasma proteins, lipids, DNA, and antioxidants in both rats [2, 37] and humans with age-related diseases [38, 39].

Research employing IF protocols in animal models, often utilizing adult male rats, indicates favorable outcomes in diminishing indicators of oxidative stress and inflammation [19]. These benefits are attributed to physiological adaptations triggered by periods of food deprivation. Experimental studies indicate that oxidative damage resulting from ROS plays a role in the aging process. For different animals, tissues, and cell types, the amount to which oxidative stress accelerates aging may differ [3]. Luceri et al. [8] demonstrated an increase in oxidative DNA damage in the liver with age, particularly reaching very high levels in middle-aged animals. Notably, there was a significant correlation between systemic oxidative damage and liver oxidative damage in the same animal. These findings suggest an overall disruption in the balance between pro-oxidant and antioxidant status during aging. Navarro et al. [7] reported an increase in oxidative stress markers and a decrease in antioxidant enzymes in the brain and liver during the aging process in 60-week-old and 92-week-old rats compared to 28-week-old rats. According to Cakatay et al. [2], elevated levels of malondialdehyde (MDA) and 8-Hidroksi-2-deoksiguanozin (8-OHdG) found in elderly male rats may be a risk factor for plasma oxidation, while elevated total sulfhydryl (T-SH) levels in female rats may represent an adaptive response to oxidative damage.

Studies have extensively shown that levels of ROS in liver mitochondria notably rise following 36 and 72 hours of fasting in rats [40, 41], resulting in lipid peroxidation of cell membranes and oxidative stress in the liver. In contrast, ADF has been observed to mitigate oxidative stress. Interestingly, research suggests that while MDA levels in the liver significantly increase after 4 weeks of ADF treatment, prolonged ADF treatment spanning 8 to 16 weeks reduces MDA levels in visceral tissue of rats experiencing oxidative stress induced by conditions such as diabetes or spontaneous tumors [42, 43].

This phenomenon may be due to hormesis, a biological process where low doses of a harmful agent trigger a beneficial response. While higher doses can be toxic or lethal, low doses can enhance resilience and extend lifespan. Research shows that ADF, as a mild stressor, can increase stress resistance and prolong the lifespan of various organisms [44].

The liver mitochondria of rats fed freely leak fewer electrons per unit of O2 consumed at complex III compared to rats fed normally for 72 hours. This indicates that severe food deprivation, like fasting, can increase oxidative stress in the rat liver. The increase in oxidative stress is due to factors like higher mitochondrial free radical production and greater sensitivity of liver membranes to oxidative damage. This suggests that fasting and caloric restriction

may affect liver mitochondrial oxidative stress differently [41]. It is conceivable that ADF applied for different durations can modulate oxidative stress responses; short durations may activate cellular resistance with low-intensity oxidative stress, while longer durations may enhance antioxidant effects, balance the amount of ROS generated by mild stress, and thus reduce oxidative stress. In this study, in middle-aged rats, both male and female rats showed high levels of liver and serum TOS and OSI. Both 1-month and 2-month ADF interventions had positive effects in reducing both liver and serum TOS and OSI, and both groups showed a significant decrease compared to their controls. Liver TAS significantly increased with the 2-month ADF intervention in female rats, but this increase did not reach a significant level in male rats. Although there was an increase in serum TAS, it did not reach a significant level between the groups (Figure 4, 5)

There are some limitations in this study. Firstly, oxidative stress was only investigated using the TAS and TOS ELISA methods; changes in the levels of oxidative stress markers (such as MDA, glutathione, CAT, SOD, etc.) at the gene or protein levels could have been revealed. Finally, conducting analyses such as ROS analysis to examine the effects on reactive oxygen species could have further strengthened our study.

In conclusion, this study examined the effects of ADF on BW, food intake, and markers of oxidative stress in male and female middle-aged rats. Initially, male rats exhibited higher BW and food intake, but these differences decreased with ADF application. Prolonged ADF resulted in a significant decrease in retroperitoneal fat weight in both sexes. In addition, ADF significantly lowered oxidative stress markers at both tissue and systemic levels in both sexes, and particularly improved antioxidant levels in the liver of female rats. These observed differences may be due to aging processes and sex-specific homeostatic mechanisms. These findings highlight the potential benefits of ADF for weight management and mitigation of oxidative stress. Future investigations should address the molecular mechanisms and long-term effects of ADF.

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

References

1. López Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194-1217. https://doi.org/10.1016%2Fj.cell.2013.05.039
2. Çakatay U, Aydin S, Yanar K, Uzun H. Gender-dependent variations in systemic biomarkers of oxidative protein, DNA, and lipid damage in aged rats. Aging Male 2010;13:51-58. https://doi.org/10.3109/13685530903236470
3. Maldonado E, Morales Pison S, Urbina F, Solari A. Aging hallmarks and the role of oxidative stress. Antioxidants 2023;12:651. https://doi.org/10.3390/antiox12030651
4. Sharifi Rad M, Anil Kumar NV, Zucca P, et al. Lifestyle, oxidative stress, and antioxidants: back and forth in the pathophysiology of chronic diseases. Front Physiology 2020;11:694. https://doi.org/10.3389/fphys.2020.00694
5. Schriner SE, Linford NJ, Martin GM, et al. Extension of murine life span by overexpression of catalase targeted to mitochondria. Science 2005;308:1909-1911. https://doi.org/10.1126/science.1106653
6. Shields HJ, Traa A, Van Raamsdonk JM. Beneficial and detrimental effects of reactive oxygen species on lifespan: a comprehensive review of comparative and experimental studies. Front Cell Dev Biology 2021;9:628157. https://doi.org/10.3389/fcell.2021.628157
7. Navarro A, Boveris A. Rat brain and liver mitochondria develop oxidative stress and lose enzymatic activities on aging. Am J Physiol Regul Integr Comp Physiol 2004;287:1244-1249. https://doi.org/10.1152/ajpregu.00226.2004
8. Luceri C, Bigagli E, Femia AP, Caderni G, Giovannelli L, Lodovici M. Aging related changes in circulating reactive oxygen species (ROS) and protein carbonyls are indicative of liver oxidative injury. Toxicology Reports 2018;5:141-145. https://doi.org/10.1016/j.toxrep.2017.12.017
9. Lebel M, de Souza Pinto NC, Bohr VA. Metabolism, genomics, and DNA repair in the mouse aging liver. Current gerontology and geriatrics research 2011;2011:859415. https://doi.org/10.1155%2F2011%2F859415
10. Soares NL, Dorand VAM, Cavalcante HC, et al. Does intermittent fasting associated with aerobic training influence parameters related to the gut-brain axis of Wistar rats? Journal of Affective Disorders 2021;293:176-185. https://doi.org/10.1016/j.jad.2021.06.028
11. Badreh F, Joukar S, Badavi M, Rashno M, Dehesh T. The effects of age and fasting models on blood pressure, insulin/glucose profile, and expression of longevity proteins in male rats. Rejuvenation Research 2020;23:224-236. https://doi.org/10.1089/rej.2019.2205

12. Carvajal V, Marín A, Gihardo D, Maluenda F, Carrasco F, Chamorro R. Intermittent fasting and human metabolic health. Rev Med Chile 2023;151:81-100. https://doi.org/10.4067/s0034-98872023000100081
13. Gabel K, Hoddy KK, Haggerty N, et al. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study. Nutrition and Healthy Aging 2018;4:345-353. https://doi.org/10.3233/nha-170036
14. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing Research Reviews 2017;39:46-58. https://doi.org/10.1016/j.arr.2016.10.005
15. Harris L, Hamilton S, Azevedo LB, et al. Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis. JBI Evidence Synthesis 2018;16:507-547. https://doi.org/10.11124/jbisrir-2016-003248
16. Park J, Seo YG, Paek YJ, Song HJ, Park KH, Noh HM. Effect of alternate-day fasting on obesity and cardiometabolic risk: a systematic review and meta-analysis. Metabolism 2020;111:154336. https://doi.org/10.1016/j.metabol.2020.154336
17. Moon S, Kang J, Kim SH, et al. Beneficial effects of time-restricted eating on metabolic diseases: a systemic review and meta-analysis. Nutrients 2020;12:1267. https://doi.org/10.3390/nu12051267
18. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. Nutrition Reviews 2015;73:661-674. https://doi.org/10.1093/nutrit/nuv041
19. Lee JH, Verma N, Thakkar N, Yeung C, Sung HK. Intermittent fasting: physiological implications on outcomes in mice and men. Physiology 2020;35:185-195. https://doi.org/10.1152/physiol.00030.2019
20. Catterson JH, Khericha M, Dyson MC, et al. Short-term, intermittent fasting induces long-lasting gut health and TOR-independent lifespan extension. Current Biology 2018;28:1714-1724. https://doi.org/10.1016/j.cub.2018.04.015
21. Vassalle C, Novembrino C, Maffei S, et al. Determinants of oxidative stress related to gender: relevance of age and smoking habit. Clin Chem Lab Med 2011;49:1509-1513. https://doi.org/10.1515/CCLM.2011.622
22. Takahashi M, Miyashita M, Park JH, et al. The association between physical activity and sex-specific oxidative stress in older adults. J Sports Sci Med 2013;12:571-578.
23. Bilibio BLE, Dos Reis WR, Compagnon L, et al. Effects of alternate-day fasting and time-restricted feeding in obese middle-aged female rats. Nutrition 2023;116:112198. https://doi.org/10.1016/j.nut.2023.112198
24. Munhoz AC, Vilas Boas EA, Panveloski Costa AC, et al. Intermittent fasting for twelve weeks leads to increases in fat mass and hyperinsulinemia in young female Wistar rats. Nutrients 2020;12:1029. https://doi.org/10.3390/nu12041029
25. Olsen MK, Choi MH, Kulseng B, Zhao CM, Chen D. Time-restricted feeding on weekdays restricts weight gain: a study using rat models of high-fat diet-induced obesity. Physiology Behavior 2017;173:298-304. https://doi.org/10.1016/j.physbeh.2017.02.032
26. Erel O. A new automated colorimetric method for measuring total oxidant status. Clinical Biochemistry 2005;38:1103-1011. https://doi.org/10.1016/j.clinbiochem.2005.08.008
27. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. Clinical Biochemistry 2004;37:277-285. https://doi.org/10.1016/j.clinbiochem.2003.11.015
28. Mattson MP, Allison DB, Fontana L, et al. Meal frequency and timing in health and disease. PNAS 2014;111:16647-16653. https://doi.org/10.1073/pnas.1413965111
29. Baumeier C, Kaiser D, Heeren J, et al. Caloric restriction and intermittent fasting alter hepatic lipid droplet proteome and diacylglycerol species and prevent diabetes in NZO mice. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids 2015;1851:566-576. https://doi.org/10.1016/j.bbalip.2015.01.013
30. Sherman H, Genzer Y, Cohen R, Chapnik N, Madar Z, Froy O. Timed high-fat diet resets circadian metabolism and prevents obesity. FASEB J 2012;26:3493-3502. https://doi.org/10.1096/fj.12-208868
31. Cottone P, Sabino V, Steardo L, Zorrilla EP. Consummatory, anxiety-related and metabolic adaptations in female rats with alternating access to preferred food. Psychoneuroendocrinology 2009;34:38-49. https://doi.org/10.1016/j.psyneuen.2008.08.010
32. Wang L, Suyama S, Lee SA, et al. Fasting inhibits excitatory synaptic input on paraventricular oxytocin neurons via neuropeptide Y and Y1 receptor, inducing rebound hyperphagia, and weight gain. Front Nutr 2022;9:994827. https://doi.org/10.3389/fnut.2022.994827
33. Park S, Yoo KM, Hyun JS, Kang S. Intermittent fasting reduces body fat but exacerbates hepatic insulin resistance in young rats regardless of high protein and fat diets. The Journal of Nutritional Biochemistry 2017;40:14-22. https://doi.org/10.1016/j.jnutbio.2016.10.003
34. Carpentier AC. 100th anniversary of the discovery of insulin perspective: insulin and adipose tissue fatty acid metabolism. Am J Physiol Endocrinol Metab 2021;320:653-670. https://doi.org/10.1152/ajpendo.00620.2020

35. Stockman MC, Thomas D, Burke J, Apovian CM. Intermittent fasting: is the wait worth the weight? Curr Obes Rep 2018;7:172-185. https://doi.org/10.1007/s13679-018-0308-9

36. Varady KA, Hudak CS, Hellerstein MK. Modified alternate-day fasting and cardioprotection: relation to adipose tissue dynamics and dietary fat intake. Metabolism 2009;58:803-811. https://doi.org/10.1016/j.metabol.2009.01.018

37. Kayali R, Çakatay U, Tekeli F. Male rats exhibit higher oxidative protein damage than females of the same chronological age. Mechanisms of Ageing and Development 2007;128:365-369. https://doi.org/10.1016/j.mad.2007.03.003

38. Höhn A, König J, Grune T. Protein oxidation in aging and the removal of oxidized proteins. Journal of Proteomics 2013;92:132-159. https://doi.org/10.1016/j.jprot.2013.01.004

39. Pandey KB, Mehdi MM, Maurya PK, Rizvi SI. Plasma protein oxidation and its correlation with antioxidant potential during human aging. Disease Markers 2010;29:31-36. https://doi.org/10.3233/dma-2010-0723

40. Marczuk Krynickaabcdef D, Hryniewieckibe T, Piątekbf J, Paluszak J. The effect of brief food withdrawal on the level of free radicals and other parameters of oxidative status in the liver. Med Sci Monit 2003;9:131-135.

41. Sorensen M, Sanz A, Gomez J, et al. Effects of fasting on oxidative stress in rat liver mitochondria. Free Radical Research 2006;40:339-347. https://doi.org/10.1080/10715760500250182

42. Bhutani S, Klempel MC, Berger RA, Varady KA. Improvements in coronary heart disease risk indicators by alternat-day fasting involve adipose tissue modulations. Obesity 2010;18:2152-2159. https://doi.org/10.1038/oby.2010.54

43. Descamps O, Riondel J, Ducros V, Roussel AM. Mitochondrial production of reactive oxygen species and incidence of age-associated lymphoma in OF1 mice: effect of alternate-day fasting. Mechanisms of Ageing and Development 2005;126:1185-1191. https://doi.org/10.1016/j.mad.2005.06.007

44. Le Bourg E. Hormesis, aging and longevity. Biochimica et Biophysica Acta (BBA)-General Subjects 2009;1790:1030-1039. https://doi.org/10.1016/j.bbagen.2009.01.004

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Authors' contributions

G.G.: Methodology, data curation, investigation, resources, writing, review, and editing; O.K.E.: Conceptualization, methodology, data curation, investigation, resources, project administration, writing, review, and editing. The final manuscript has been read and approved by all of the authors.

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Herpes zoster awareness: a pilot centre analysis

Herpes zoster farkındalığı: bir pilot merkez analizi

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Abstract

Purpose: Herpes zoster (HZ), or shingles, is caused by the reactivation of the varicella-zoster virus (VZV), typically occurring years after a primary VZV infection (chickenpox). This study aims to assess the awareness of HZ and its vaccine among adults in Izmir, Türkiye, to inform future public health strategies and improve vaccination rates.

Materials and methods: A survey was conducted in April 2024 among adults aged 18-69 years in Izmir, Türkiye, using a random sampling method in urban and suburban communities. The survey, administered by healthcare professionals in public, consisted of dichotomous questions to determine demographic characteristics and measure knowledge about HZ and its vaccine.

Results: A total of 71 participants were included, with a mean age of 42.28±15.83 years. The gender distribution was nearly equal (50.3% male, 49.7% female). Overall, 59.2% of respondents were aware of HZ, but only 18.3% knew about the HZ vaccine. Women were significantly more likely to be aware of HZ than men (OR=2.79, 95% CI:1.02-4.19, p=0.04). Age did not significantly correlate with disease or vaccine awareness. There were no significant differences in disease awareness (χ^2=0.58, p=0.75) or vaccine awareness (χ^2=0.21, p=0.90) between different age groups.

Conclusion: The study highlights a moderate level of awareness about HZ but a low awareness of the HZ vaccine among adults in Izmir, Türkiye. Women were more likely to be aware of HZ, suggesting a gender disparity in disease awareness. Public health initiatives should focus on increasing awareness of the HZ vaccine, particularly older adults. Further research is needed to explore the reasons behind low vaccine awareness and develop strategies to improve vaccination rates.

Keywords: Herpes zoster, shingles vaccine, herpes zoster awareness.

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Öz

Amaç: Herpes zoster (HZ) veya zona, varisella-zoster virüsünün (VZV) reaktivasyonundan kaynaklanır ve tipik olarak birincil VZV enfeksiyonundan (suçiçeği) yıllar sonra ortaya çıkar. Çalışma, gelecekteki halk sağlığı stratejilerini oluşturmak ve aşılama konusunda nosyon kazandırmak amacıyla İzmir, Türkiye'deki yetişkinler arasında HZ ve aşısı hakkındaki farkındalığı değerlendirmek üzerine yürütülmüştür.

Gereç ve yöntem: Nisan 2024'te İzmir, Türkiye'de 18-69 yaş arası yetişkinler arasında, kentsel ve banliyö topluluklarında rastgele örnekleme yöntemi kullanılarak bir anket yapılmıştır. Sağlık çalışanları tarafından halka açık olarak uygulanan anket, demografik özellikleri belirlemek ve HZ ve aşısı hakkındaki bilgileri ölçmek için dikotomik sorulardan oluşmuştur.

Bulgular: Yaş ortalaması 42,28±15,83 yıl olan toplam 71 katılımcı çalışmaya dahil edilmiştir. Cinsiyet dağılımı neredeyse eşitti (%50,3 erkek, %49,7 kadın). Genel olarak, katılımcıların %59,2'si HZ'den haberdardı, ancak sadece %18,3'ü HZ aşısını biliyordu. Kadınların HZ'den haberdar olma olasılığı erkeklere göre anlamlı derecede daha yüksekti (OR=2,79, %95 GA:1,02-4,19, p=0,04). Yaş ile hastalık veya aşı farkındalığı arasında anlamlı bir ilişki bulunmamıştır. Farklı yaş grupları arasında hastalık farkındalığı (χ^2=0,58, p=0,75) veya aşı farkındalığı (χ^2=0,21, p=0,90) açısından anlamlı bir fark saptanmamıştır.

Sonuç: Çalışma, İzmir, Türkiye'deki yetişkinler arasında HZ hakkında orta düzeyde bir farkındalık olduğunu ancak HZ aşısı konusunda farkındalığın düşük olduğunu vurgulamaktadır. Kadınların HZ'den haberdar olma olasılığının daha yüksek olması, hastalık farkındalığında cinsiyet farklılığı olduğunu düşündürmektedir. Halk sağlığı girişimleri, özellikle yaşlı yetişkinler olmak üzere HZ aşısı konusunda farkındalığı artırmaya odaklanmalıdır. Düşük aşı farkındalığının arkasındaki nedenleri araştırmak ve aşılama oranlarını iyileştirmek için stratejiler geliştirmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: Zona, zona aşısı, zona farkındalığı.

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Introduction

Herpes zoster (HZ) is a clinical syndrome associated with reactivation of latent varicella zoster virus (VZV), typically occurring years after VZV infection. HZ is characterized by a painful, unilateral, vesicular skin rash that usually occurs in a single dermatome (sometimes in adjacent dermatomes).

Commonly involved sites include the thoracic, lumbar, cervical and trigeminal dermatomes. Skin rashes usually begin with a prodrome of pain or paresthesia that occurs 1-5 days before rash onset [1]. HZ usually lasts for 2-4 weeks and can have a very morbid course in the elderly and immuncompromised patients, where the risk of disease development is high [2]. It usually remains latent after VZV infection in childhood and manifests itself in adulthood. Although it can cause permanent neurological disorders such as cranial nerve palsy, hearing and visual deficits; post herpathic neuralgia (PHN) is the most common complication. PHN is severe pain that can last up to 3 months after the spontaneous remission phase of the disease. The incidence can reach 30%, especially in patients over 65 years of age and immunocompromised patients [3]. Moreover, the age-related increase in incidence rates is higher in complicated HZ than in uncomplicated HZ. After experiencing a first relapse, patients have higher risk for a second relapse [4].

With the aging of the population, it is thought that herpes zoster infection will be encountered more frequently, especially in developing countries in the future. According to the US Centers for Disease Prevention (CDC), 30% of people are expected to get Herpes Zoster at some point in their lives. Reactivation of the Varicella zoster virus occurs in 1 in 5 people worldwide [2]. The overall incidence of herpes zoster in Europe is about 3 per 1000 people per year and more than 10 per 1000 people per year in people over 80 years of age. The trend of increasing incidence continues in the world: The incidence of HZ has increased 4-fold in the last 6 decades [2, 5, 6]. Although there is no general epidemiological data for our country, prevalence data based on single clinic admissions show that one out of every 100 people has had shingles at some point in their lives; an Istanbul-based event-time cross-sectional study showed that the incidence of HZ increased from 182 per 100,000 people in 2011 to 285 per 100,000 people in 2019 [5-7].

Acyclovir and Brivudine are commonly used systemic antiviral therapies that may shorten the healing process of acute herpes zoster, but only if started within the first 48 hours of rash development. Indeed, there is no convincing evidence that acyclovir affects the incidence or duration of PHN, however, early treatment with acyclovir reduces the incidence of serious eye disorders in ophthalmic HZ patients. Nevertheless acyclovir-related serious adverse effects such as acute kidney injury caused by crystalopathy needs to be taken into account. Corticosteroids generally relieve acute pain but therapeutic benefit is limited [8]. The gold standard for laboratory diagnosis is PCR and direct identification of VZV in cell cultures. Detection of IgM- and IgG-anti-VZV antibodies is less sensitive and may be helpful in immunocompromised individuals.

Association with VZV

In childhood usually VZV-infected T cells circulate during Varizella Zoster infection. It evades the host response through down-regulation of major histocompatibility complex (MHC) class I expression and inhibition of interferon response genes. After the eruptive period, it may migrate retrogradely to the nerve ganglia via sensory neuron endings and remain latent. The primary factor determining the latency of the virus here is the T cell-mediated immune response, as protection against reinfection has been demonstrated in agammaglobulinemic individuals who do not produce VZV-specific antibodies but develop T cell-specific immunity after varicella infection [9, 10].

Varicella Zoster vaccination is part of routine in 36 countries, including Türkiye, the USA and Australia, and was added to the childhood vaccination schedule in Türkiye in 2013. Although the two-dose vaccination strategy, especially the booster dose, reduces VZV complications and hospitalizations in childhood, its population-based effectiveness on Herpes Zoster is debated. 50-year modeling predicts that the incidence of HZ can be reduced [10].

The Hope Simpson [11] hypothesis, first proposed in 1965, suggested that immunity acquired through VZV vaccination or

transmission would protect against Herpes Zoster infection in adulthood VZV vaccination has not been introduced in the UK, for example, due to the disappearance of herd immunity and lack of evidence of cost-effectiveness. In addition, although the incidence of HZ has continued to increase over the 20-year period since the introduction of VZV vaccination, similar incidence is found in countries and regions where the vaccine is and is not widely practiced, making this approach controversial [12]. A controlled prospective study published in 2019 also demonstrated the inability of VZV vaccine to provide protection against Herpes Zoster infection in immunosuppressed groups (hematologic malignancy) [13].

HZV vaccine and its features

The increasing average population and age of HZ infection and the severe course of complications suggest that especially elderly patients may benefit from HZ vaccination [14, 15].

Two types of herpes zoster vaccine are currently available. One is a single-dose vaccine (LZV) containing the same live attenuated virus used in the varicella vaccine; it has 14 times more attenuated virus plaque-forming units per dose. The other is recombinant zoster vaccine (RZV), which instead of live attenuated virus contains a small fraction of the virus that does not replicate but can increase immunogenicity. In a meta-analysis of 12 prospective studies in 2018, the recombinant form (RZV) was found to have higher protection compared to live attenuated vaccine, although local side effects at the vaccination site were found to be higher in patients over 50 years of age [16].

Further clinical trials and research to assess RZV are ongoing. The randomized controlled trial of 1736 healthy people over 60 years of age found that both vaccines had similar results to the placebo arm in terms of serious adverse events and mortality, but not in terms of efficacy; it showed that 50 healthy older adults needed to be vaccinated with LVZ to prevent one shingles attack, while 33 healthy older adults needed to be vaccinated with RZV to prevent one shingles attack.

In immunocompromised patients, where live vaccine (LZV) contrandicated, RZV found effective. A study based on model simulation groups shows that to prevent one case of HZ, the number needed to vaccinate was 9, 8 and 10, for hematopoietic stem cell transplantation, breast cancer and Hodgkin's lymphoma [17, 18]. However, given the heterogeneity of the immunocompromised population and the fact that timing and conditions of vaccine administration are important in this group, more studies and real-world data are needed over time.

Awareness

Adult immunization as a topic had been introduced to medical community and society almost three decades ago but despite clear benefits for reducing morbidity and mortality vaccine coverage is low even in developed countries and evolving slower [19]. While it depends on health service offers and resources, reimbursement or physicians attitude; SARS-CoV-2 has its effect on paradigms as well.

In terms of awareness of HZ as a disease and its vaccine in Türkiye, there is little data which varies widely [20, 21]. Overall, these analyses showed that very few Turkish individuals were aware of the vaccine and that the Turkish population had inadequate knowledge about the symptoms, causes and risks of HZ [7].

In a study, which included 200-300 people based on face-to-face and telephone communication and generally based on the urban population, Türkiye, together with Chile and India, was included in the group where disease awareness was in the 15-20% band, at the lowest level. It can be argued that the grammatical and cultural expressions related to the disease in the method of preparation of the questionnaire will differ from country to country. But in general, it shows that a successful vaccine initiative will require a community-wide effort to raise global awareness of HZ [22]. In general, although the awareness of Herpes Zoster infection is over 50% in the world, the awareness is quite low in terms of the same virus causing it as varicella, its complications and the presence-effects of the vaccine [23, 24].

Despite the fact that, new recombinant HZ vaccine on its way to be introduced, we hypotesized if there is a knowledge gap, that should be highlighted. We aim to determine

the perception of HZ and its vaccines in a city, where its senior and old community relatively big and continuing to grow.

Materials and methods

We designed a survey in adults aged 18–69 years in Izmir, Türkiye, in april 2024. A convenience sampling strategy was applied to recruit respondents in a total of 3 urban and suburban communities. Survey has been conducted face-to-face by three healthcare professionals mostly in bus and subway stations. They were held in two different time interval which includes one weekday (tuesday), weekend(sunday) and over the course of day to make out a heterogeneous group.

After the literature review, the questionnaire was prepared and applied by the researchers. The purpose of the questionnaire is to determine demographic characteristic and to measure their knowledge on existence of HZ and its vaccines. To be more direct and objective, the questionnaire consists of dichotomous questions except for demographics.

According to the results obtained from the preliminary study to calculate the sample size, 50-75 participants were needed for the study based on β=80 power, α=0.05 margin of error and d=0.2 effect size (G*Power version 3.1). People aged 18 years and older were randomly selected and included in the study. Patients who were too clinically demented to participate in a face-to-face survey and patients who refused to participate in the study were excluded.

Statistical analysis

The statistical analysis was carried out using the program SPSS version 24.0. The descriptive data were given as number, percentage, mean and standard deviation. Frequency distributions were given for categorical variables. Normality distribution of continuous variables is tested with Shapiro wilk. Continuous variables are assessed and compared with Mann whitney U, if not normal distributed. The chi-square test was used for group comparisons. Logistic regression analysis was employed to determine the factors associated with awareness of disease and vaccine. A *p*-value of <0.05 was considered statistically significant.

The study was approved by the Dokuz Eylul University Medical Faculty Ethics Committee.

Results

A total of 71 participants were enrolled in the study, with a mean age of 42.28±15.83 years (range: 19 to 72 years). The gender distribution was nearly equal, with 50.3% male and 49.7% female participants. The sociodemographic characteristics and response distributions are summarized in Tables 1 and 2.

Table 1 and 2 show the sociodemographic breakdown and the levels of awareness of HZ and its vaccine. The significant findings (*p*<0.05) are highlighted to emphasize key differences .

Awareness of herpes zoster and its vaccine

Overall, 59.2% of respondents were aware of Herpes Zoster (HZ) as a disease, but only 18.3% knew about the existence of the HZ vaccine.

Table 1. Responders according disease knowledge

	Number answered	Responders know the disease	Responders do not know the disease	*p* value	Test value
Female	35	25 (71.4%)	10 (28.6%)	0.038*	χ^2:4.304
Male	36	17 (46.3%)	19 (53.7%)		
Age (Mean±S.D**)**		41.24 (15.1)	43.79 (16.8)	0.8	z:-0.503

*p<0.05 statistically significant, S.D: Standard Deviation, z: Mann Whitney U test; χ^2: Chi Square test

Table 2. Responders according vaccine knowledge

	Number answered	Responders know the vaccine	Responders do not know the vaccine	*p* value	Test value
Female	35	8 (23%)	27 (77%)	0.329	χ^2:4.304
Male	36	5 (13%)	31 (87%)		
Age (Mean±S.D)		38.31 (16.3)	43.17 (15.6)	0.330	z:-0.975

S.D: Standard Deviation, z: Mann Whitney U test, χ^2: Chi Square test

The data presented in Table 1 and 2 includes number, percentage, mean, and standard deviation for various sociodemographic variables. Figure 1 displays the awareness levels of HZ and its vaccine across different age groups, providing a visual representation of how awareness varies among age demographics.

There was no significant difference in disease awareness (χ^2=0.58, *p*=0.75) or vaccine awareness between age groups (χ^2=0.21, *p*=0.90).

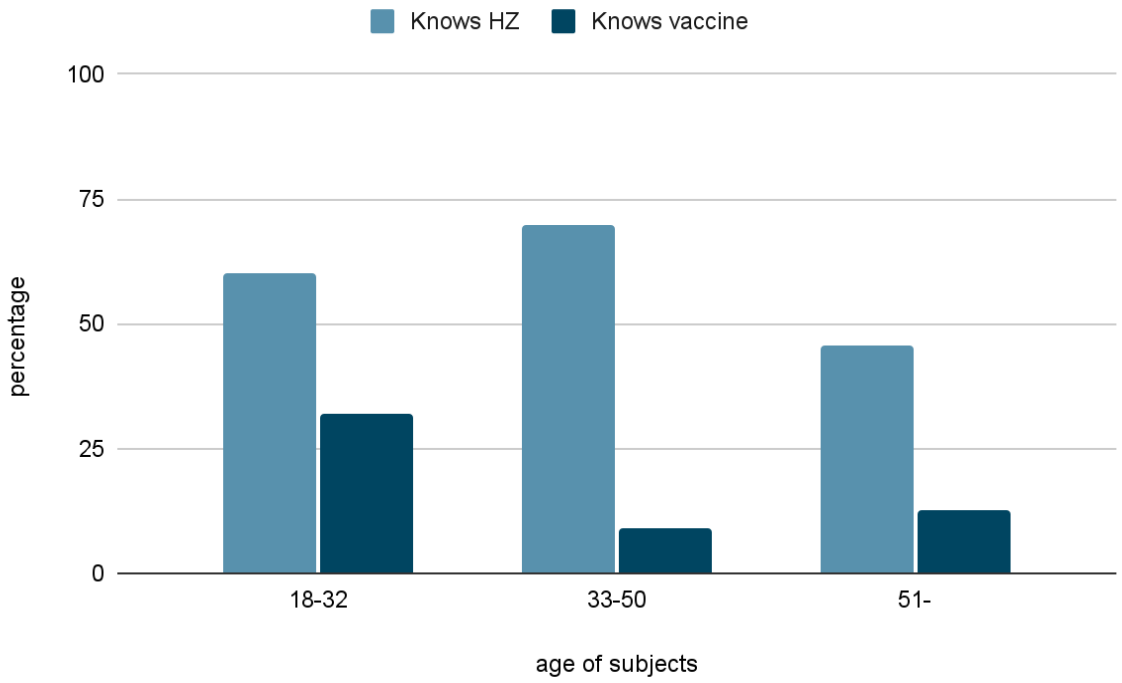

Figure 1. Age of subjects

Age and gender correlation

In the logistic regression analysis, women were significantly more likely to be aware of HZ than men, with an odds ratio (OR) of 2.79 (95% CI: 1.02-4.19, *p*=0.04). However, age did not show a significant correlation with disease awareness (*p*=0.87). Neither age nor gender showed a significant correlation with awareness of the HZ vaccine (Table 3).

Table 3. Logistic regressions

	Disease knowledge		Vaccine Knowledge	
	OR (CI 95%)	***p* value**	**OR (CI 95%)**	***p* value**
Female	2.79 (1.9-3.2)	0.04*	1.90 (1.24-2.5)	0.31
Age	1.010 (0.97-1.032)	0.87	1.023 (0.98-1.103)	0.29

*$p<0.05$ statistically significant, OR: Odds Ratio, CI: Confidence Interval

Discussion

Determination requirement of awareness of HZ as disease and vaccine in Türkiye has been adressed in the field [7]. The aging of the population will be associated with the morbidity of HZ and its complications over time. In addition, given that the risk of developing HZ is increased not only by malignancies but also by chronic conditions or comorbidities such as asthma, chronic heart disease, chronic obstructive pulmonary disorder, depression and rheumatoid arthritis, it will be necessary to raise awareness among a large population and the health professionals who treat them [4].

Although Türkiye currently has a relatively young demographic structure (median age of citizens is 34 years), in the last 15 years, the percentage of the population over the age of 65 has increased from 7.1 to 10.2. And the number of people over 65, currently 10.2 million, is estimated to be 16.3 in 2040 [25].

Most data, including a meta analysis of 8-countries reflecting younger age, female gender, higher income and education level were associated with increased willingness to vaccinate [26, 27]. This is another indicator of the importance of raising awareness of the HZ vaccine, especially among older, at-risk populations. Our data do not show any age discrepancy but show a knowledge dominance of women over men, which is consistent with previous data [26, 28]. Regarding the direct relationship between disease knowledge and vaccination willingness is debatable and this existence of disease awareness difference could convey itself in the vaccination rate is argumentative, but this is gender gap reflected in the HZ vaccination rate, as shown by a Canadian study [29]. In the awareness analysis study with the questionnaire applied in the United Arab Emirates, the awareness of the disease was 64.3% and the awareness of the presence of vaccine was 15%, which is similar to our data and most of those who had information about vaccination were women and those with chronic diseases [27].

Insufficient knowledge of HZ of the Turkish population may be attributable to insufficient information from vaccination clinics or other health care providers. While reliability and validity of studies in Türkiye regarding HZ is limited since most of them conducted in or outpatient clinics; we were able to measure information of public awareness by conducting it in public [7].

In a Chinese study, greater knowledge and awareness in participants did not contribute to higher willingness, but regarding difference, it can be hypothesized due to lack of HZ vaccine reimbursement [30]. And also physician attitudes play a large role, this needs to be hypothesised in further studies. Although vaccine orientation and its implementation in risk groups are also subject to factors such as reimbursement and health chain/system, studies have shown that one of the most determinant factors is physician-patient information flow and recommendation [31]. It is thought that healthy and sick individuals who are undecided or reluctant about vaccination and who are in risk groups will tend to be vaccinated with the recommendation of health professionals [27]. As with the HPV vaccine, acceptance by doctors and the public is at least as influential as the level of scientific evidence in real life, and to some extent determines reimbursement and inclusion in the routine vaccination schedule. As a vaccine topic, HZ has a newly introduced recombinant vaccine and it can be foreseen that knowledge will increase as it is administered over time.

Patient demand had a profound impact on physicians' decisions; 84.9% (73/86) of physicians who said they did not recommend HZ

vaccination reported that they would vaccinate upon patient request. This points to the health awareness of not only physicians but also individuals [31]. The study's strength include the fact that the opinion can be clearly assessed thanks to the small number of sequential questions and that it is not-time consuming, which has eliminated selection and survey bias to some extent. It is also considered to reflect the general population base in terms of public realisation.

There are a few limitations. The study is conducted in a single city with a different average age and education level than the country as a whole. And although some of the participants had heard of HZ or vaccine, this did not reflect how knowledgeable they were about them, so the measure of awareness did not assess the depth of knowledge about HZ and its vaccine.

The lack of knowledge about HZ in Türkiye must be taken seriously and steps must be taken to address it. The role of healthcare providers is crucial. Physicians and other healthcare professionals should actively engage in educating their patients about the benefits of the HZ vaccine, especially for high-risk groups. There is a need for comprehensive public health campaigns to raise awareness about the HZ vaccine, particularly focusing on older adults and men who demonstrated lower levels of awareness.

The study suggests the necessity of further research to explore the reasons behind the low awareness of the HZ vaccine and to develop strategies to improve vaccination rates.

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References

1. Schmader K. Herpes Zoster. Ann Intern Med 2018;169:897. https://doi.org/10.7326/L18-0558
2. Harpaz R, Ortega Sanchez IR, Seward JF, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008;57:1-30.
3. Weitzman D, Shavit O, Stein M, Cohen R, Chodick G, Shalev V. A population based study of the epidemiology of Herpes Zoster and its complications. J Infect 2013;67:463-469. https://doi.org/10.1016/j.jinf.2013.06.016
4. Batram M, Witte J, Schwarz M, et al. Burden of herpes zoster in adult patients with underlying conditions: analysis of german claims data, 2007-2018. Dermatol Ther 2021;11:1009-1026. https://doi.org/10.1007/s13555-021-00535-7
5. Soysal A, Gönüllü E, Yıldız İ, Karaböcüoğlu M. Incidence of varicella and herpes zoster after inclusion of varicella vaccine in national immunization schedule in Turkey: time trend study. Hum Vaccin Immunother 2021;17:731-737. https://doi.org/10.1080/21645515.2020.1788861
6. Kawai K, Yawn BP, Wollan P, Harpaz R. Increasing Incidence of Herpes Zoster Over a 60-year period from a population-based study. Clin Infect Dis 2016;63:221-226. https://doi.org/10.1093/cid/ciw296
7. Badur S, Senol E, Azap A, et al. Herpes zoster burden of disease and clinical management in Turkey: a comprehensive literature review. Infect Dis Ther 2023;12:1937-1954. https://doi.org/10.1007/s40121-023-00849-3
8. Gross G, Schöfer H, Wassilew S, et al. Herpes zoster guideline of the German Dermatology Society (DDG). J Clin Virol 2003;26:277-289. https://doi.org/10.1016/s1386-6532(03)00005-2
9. Ku CC, Besser J, Abendroth A, Grose C, Arvin AM. Varicella-Zoster virus pathogenesis and immunobiology: new concepts emerging from investigations with the SCIDhu mouse model. J Virol 2005;79:2651-2658. https://doi.org/10.1128/JVI.79.5.2651-2658.2005
10. Varela FH, Pinto LA, Scotta MC. Global impact of varicella vaccination programs. Hum Vaccin Immunother 2019;15:645-657. https://doi.org/10.1080/21645515.2018.1546525
11. Hope Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. J Proc R Soc Med 1965;58:9-20. https://doi.org/10.1177/003591576505800106
12. Whitley RJ. Changing dynamics of varicella-zoster virus infections in the 21st century: the impact of vaccination. J Infect Dis 2005;191:1999-2001. https://doi.org/10.1086/430328
13. Mullane KM, Morrison VA, Camacho LH, et al. Safety and efficacy of inactivated varicella zoster virus vaccine in immunocompromised patients with malignancies: a two-arm, randomised, double-blind, phase 3 trial. Lancet Infect Dis 2019;19:1001-1012. https://doi.org/10.1016/S1473-3099(19)30310-X
14. Schwarz TF, Volpe S, Catteau G, et al. Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults. Hum Vaccin Immunother 2018;14:1370-1377. https://doi.org/10.1080/21645515.2018.1442162
15. Hillebrand K, Bricout H, Schulze Rath R, Schink T, Garbe E. Incidence of herpes zoster and its complications in Germany, 2005-2009. J Infect 2015;70:178-186. https://doi.org/10.1016/j.jinf.2014.08.018

16. Tricco AC, Zarin W, Cardoso R, et al. Efficacy, effectiveness, and safety of herpes zoster vaccines in adults aged 50 and older: systematic review and network meta-analysis. BMJ 2018;363:k4029. https://doi.org/10.1136/bmj.k4029
17. Curran D, Patterson BJ, Carrico J, et al. Public health impact of recombinant zoster vaccine for prevention of herpes zoster in US adults immunocompromised due to cancer. Hum Vaccin Immunother 2023;19:2167907. https://doi.org/10.1080/21645515.2023.2167907
18. de Oliveira Gomes J, Gagliardi AM, Andriolo BN, et al. Vaccines for preventing herpes zoster in older adults. Cochrane Database Syst Rev 2023;10:CD008858. https://doi.org/10.1002/14651858.CD008858.pub5
19. Greenberg GM, Koshy PA, Hanson MJS. Adult vaccination. Am Fam Physician 2022;106:534-542.
20. Erdoğdu Hİ. Influenza, pneumococcal and herpes zoster vaccination rates amongst people aged 65 years and older and related factors. Turkish Journal of Geriatrics 2018;21:498-506. https://doi.org/10.31086/tjgeri.2018.54
21. Revanli RA, Yuceer C, Senol E, et al. Awareness and attitude of family physicians about human papilloma virus and herpes zoster vaccines. Klimik Dergisi 2016;29:15-20. https://doi.org/10.5152/kd.2016.04
22. Paek E, Johnson R. Public awareness and knowledge of herpes zoster: results of a global survey. Gerontology 2010;56:20-31. https://doi.org/10.1159/000240046
23. Volpi A, Gross G, Hercogova J, Johnson RW. Current management of herpes zoster: the European view. Am J Clin Dermatol 2005;6:317-325. https://doi.org/10.2165/00128071-200506050-00005
24. Yang TU, Cheong HJ, Song JY, Noh JY, Kim WJ. Survey on public awareness, attitudes, and barriers for herpes zoster vaccination in South Korea. Hum Vaccin Immunother 2015;11:719-726. https://doi.org/10.1080/21645515.2015.1008885
25. Turkish Statistics Institute's data on age prediction of Turkish society. Available at: https://data.tuik.gov.tr/Bulten/Index?p=The-Results-of-Address-Based-Population-Registration-System-2023-49684&dil=2. Accessed February 06, 2024
26. Wang Q, Yang L, Li L, Liu C, Jin H, Lin L. Willingness to vaccinate against herpes zoster and its associated factors across who regions: global systematic review and meta-analysis. JMIR Public Health Surveill 2023;9:e43893. https://doi.org/10.2196/43893
27. Al Khalidi T, Genidy R, Almutawa M, et al. Knowledge, attitudes, and practices of the United Arab Emirates population towards Herpes Zoster vaccination: a cross-sectional study. Hum Vaccin Immunother 2022;18:2073752. https://doi.org/10.1080/21645515.2022.2073752
28. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: uptake of the first new vaccine to target seniors. Vaccine 2009;27:882-887. https://doi.org/10.1016/j.vaccine.2008.11.077
29. Liu XC, Simmonds KA, Russell ML, Svenson LW. Herpes zoster vaccine (HZV): utilization and coverage 2009 - 2013, Alberta, Canada. BMC Public Health 2014;14:1098. https://doi.org/10.1186/1471-2458-14-1098
30. Lu X, Lu J, Zhang F, et al. Low willingness to vaccinate against herpes zoster in a Chinese metropolis. Hum Vaccin Immunother 2021;17:4163-4170. https://doi.org/10.1080/21645515.2021.1960137
31. Yang TU, Cheong HJ, Choi WS, Song JY, Noh JY, Kim WJ. Physician attitudes toward the herpes zoster vaccination in south Korea. Infect Chemother 2014;46:194-198. https://doi.org/10.3947/ic.2014.46.3.194

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Authors' contributions to the article

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

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Controlling nutritional (CONUT) score for nutritional screening in kidney transplant recipients

Böbrek transplantli bireylerde beslenme takibi için CONUT skoru

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Abstract

Purpose: Nutrition is severely impaired in individuals with renal impairment, and transplant often ameliorates this condition. In this study, we aimed to evaluate the controlling nutritional status (CONUT) score of kidney transplant (KT) recipients.

Materials and methods: Using the data from the nephrology transplant unit, we analyzed 188 patients whose data on the constituents of the CONUT score were available. We included KT individuals with at least one lymphocyte count and total cholesterol and albumin concentrations. This data has been used to calculate the CONUT score. The decrease of lymphocyte counts, and total cholesterol was determined with 0, 1, 2, and 3 points, and the reduction of albumin was assigned with 0, 2, 4, and 6 points in agreement with disease severity. Patients were classified according to this score: normal, light, moderate, and severe.

Results: There were 130 patients in normal, 54 in light, and three in moderate and one in severe group. The CONUT score was good for regular-weight patients both before and after transplantation. All laboratory findings revealed significant differences between CONUT groups (p<0.05).

Conclusion: After transplantation, the number of patients in the underweight group decreased when normal weight and obesity increased. However, some patients' nutrition was not ameliorated. The CONUT score may be a useful tool for monitoring transplant patients' nutritional status.

Keywords: Kidney transplantation, nutrition process, clinical laboratory test, risk scores.

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Öz

Amaç: Kronik böbrek hastalığı hastanın nutrisyonel durumunu bozmaktadır. Nakil bu tabloyu sıklıkla düzeltir. Çalışmamızda böbrek transplantı olan bireylerde nutrisyonel durumu değerlendirmek için kontrol beslenme durumu (CONUT) skorunu değerlendirmeyi amaçladık.

Gereç ve yöntem: Böbrek nakli olan bireyleri takip eden Nefroloji bilim dalından gelen verileri kullanarak, 188 bireyin CONUT skorunu hesaplamayı amaçladık. Laboratuvar bilgi sisteminde en az bir kez ölçülmüş, lenfosit sayısı, total kolesterol ve albümin düzeyleri olan nakilli bireylerini dahil ettik. Lenfosit sayısı ve toplam kolesteroldeki azalma 0, 1, 2 ve 3 puanla, albümin azalması ise hastalığın şiddetine göre 0, 2, 4 ve 6 puanla belirlendi. Hastalar bu skora göre normal, hafif, orta ve ağır olarak sınıflandırıldı.

Bulgular: Normal grupta 130, hafif grupta 54, orta grupta 3 ve ağır grupta bir hasta vardı. CONUT skoru normal kilolu hastalar için hem nakil öncesinde hem de sonrasında iyiydi. Tüm laboratuvar bulguları CONUT grupları arasında anlamlı fark olduğunu ortaya koydu (p<0,05).

Sonuç: Transplantasyon sonrası normal kilolu ve obez birey sayısı artarken, az kilolu hasta sayısı azaldı. CONUT skoru transplante hastaların beslenme durumunu izlemede etkin bir araç olarak öne sürülebilir.

Anahtar kelimeler: Böbrek nakli, nutrisyonel durum, klinik laboratuvar testleri, risk skorlama.

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Introduction

Chronic kidney disease (CKD) is characterized with loss of kidney function or structural alterations that have been determined more than three months and have health implications [1]. In CKD, irreversible abnormalities in kidney structure are due to ischemic, toxic, or metabolic damage. Inflammation and malnutrition may cause severe complications and increase the mortality rate in CKD patients [2, 3].

Recently, dialysis and kidney transplantation (KT) have been the applicable treatment modalities. KT is the best proper treatment for individuals with end-stage renal disease [4]. Nutritional status of patients is important after KT. The patient's nutrition after kidney transplantation is affected by many factors, such as the period after transplantation, the stage of deterioration in kidney function (chronic kidney disease stages 1-5), side effects of immunosuppressants and other drugs, interactions of drugs with foods, and the immune- regulating effects of some food additives. The patient's metabolic homeostasis after transplant surgery is affected by many factors, for example time after surgery, renal function, side effects of drugs, possible food-drug interferences, especially side effects of immune-suppressive [4, 5].

About 25% of transplanted patients are overweight/obese with hypertension, hyperglycaemia, and more extended hospitalization periods [6]. On the other hand, malnutrition is usually related to an increased morbidity ratio after organ transplantation [7].

Therefore, predicting prognosis using pre-treatment clinical variables is important to ensure recovery and offer an optimal monitoring strategy. In the literature, hs-CRP, IL-6 and TNF-α are the most known inflammation markers and they have potential role in the prognosis of chronic diseases. Many nutritional scores have been used to monitor the prognosis of this clinical situation. The CONtrolling NUTritional status (CONUT) score is widely used to control nutritional status in chronic diseases and malignancies [8]. This index has so many advantages for monitoring nutritional status in inflammatory diseases because it is cost-effective, simple to calculate, and non-invasive [9, 10]. However, the usefulness of CONUT in assessing patients who underwent KT has not been determined yet. We initiate to evaluate the CONUT score to determine whether protein-energy metabolism is valuable for monitoring nutritional situations in kidney transplant patients in present study.

Materials and methods

We included 188 kidney transplant recipients who underwent KT surgery and followed up at Pamukkale University Nephrology Department. We collected gender, age, etiology of CKD, hypertension, immune suppressive agent, donor relationship, diabetes mellitus status, weight and height findings before-after transplantation, transplantation date, and laboratory results from the Hospital Information System (HIS) between February 2018 and February 2019. The study was done with the approval of the ethical board of the Pamukkale University Medicine Faculty, Denizli, Türkiye (16.01.2018/02).

We used serum total cholesterol and albumin levels, and total lymphocyte counts for this nutritional score. We showed calculating this score in detail in Table 1 [10].

Table 1. Scoring system for the CONUT

Parameter	Undernutrition degree			
	None	Light	Moderate	Severe
Serum albumin (g/dL)	≥3.50	3.00-3.49	2.50-2.99	<2.50
Score	0	2	4	6
Total lymphocyte count (K/uL)	≥1600	1200-1599	800-1199	<800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3

CONUT score= Serum albumin score + Total lymphocyte count score + Total cholesterol score
The risk of malnutrition is classified as normal (score 0-1), light (2-4), moderate (5-8) and severe

All analyses were performed by a IBM SPSS Statistics 25 software. Continuous variables were indicated as mean ± standard deviation; qualitative variables were meant as counts. Shapiro–Wilk and Kolmogorov Smirnov tests revealed test normality. We used the independent samples t-test when parametric test hypotheses were for independent groups' comparisons. The Mann-Whitney U test was used when parametric test hypotheses were not provided. Spearman correlation analysis were used to analyse the relationships between continuous variables. Statistical significance was determined as $p<0.05$.

Results

The sample consisted of 71 males and 117 females, with a mean age of 45.68±13.02 years, ranging from 19 to 72 years old. One hundred forty-four subjects had received their kidneys from living donors (76.5%), and 44 from cadaver donors (23.5%). The causes of CKD were as follows: diabetic nephropathy (n=84, 45%), chronic glomerulonephritis (n=73, 39%), genetic disorders (n=11, 6%), hypertensive nephrosclerosis (n=8, 4%) and idiopathic (n=12, 6%). A total of 26 out of all subjects were given cyclosporine, and 162 were tacrolimus therapy. The average time after transplantation was 84 months (24-120 months). According to CONUT score calculation; there were 130 patients in the normal group; 54 were in light, three were in moderate, and one was in severe. There was one KT recipient in the severe group, so we merged moderate and severe under one heading as "moderate". By taking into consideration CONUT, we compared patients body mass index (BMI) before and after transplant. The results revealed CONUT was well related to normal weight patients in both periods. Most patients were included in the overweight group after the transplant.

The moderate group was not included in the comparisons due to an insufficient number of subjects. We only compared normal and light groups; there is a statistical difference between two groups on behalf of routine laboratory analytes (Table 2). Spearmean's correlation coefficients between indices patients' characteristics are shown in Table 3. Our data revealed strong negative correlation between total cholesterol and CONUT score (r=-0.75). All other coefficients were <0.7 could be accepted as moderate relations, all the statistical significance.

Table 2. All rotuine parameters of individuals and the comparison of normal and light groups

	Normal (n=130)	Light (n=54)	Moderate (n=4)	*p*
White blood cell(K/uL)	8.47 (4.99-21.15)	6.72 (1.69-13.65)	4.38 (3.01-9.11)	0.0001* (z=-3.722)
Red blood cell(M/uL)	4.74±0.78	4.4±0.8	3.02±0.4	0.01* (t=2.602)
Hemoglobin (g/dL)	13.23±1.98	12.49±2.13	9.18±1.63	0.028* (t=2.214)
Hematocrit (%)	40.54±5.88	38.24±6.62	26.98±4.81	0.023* (t=2.285)
Platelet(K/uL)	245.5 (14.2-514)	220.5 (110-415)	183.5 (37-216)	0.024* (z=-2.262)
Lymphocyte (K/uL)	2.37 (1.12-54.6)	1.47 (0.61-3.33)	0.83 (0.57-2.14)	0.0001* (z=-5.758)
Monocyte(K/uL)	0.62 (0.32-2.95)	0.51 (0.25-1.14)	0.5 (0.24-1.05)	0.004* (z=-2.854)
Basophile(K/uL)	0.03 (0.01-0.7)	0.03 (0-0.6)	0.02 (0.01-0.03)	0.007* (z=-2.688)
Neutrophil(K/uL)	4.98 (0.04-15.16)	4.32 (0.47-11.43)	2.98 (1.63-5.71)	0.043* (z=-2.02)
Urea (mg/dl)	39 (18-153)	48.5 (20-162)	62.5 (54-136)	0.041* (z=-2.041)
BUN (mg/dl)	18 (8-71)	22.5 (9-76)	29 (25-64)	0.037* (z=-2.09)
Creatinine (mg/dl)	1.26 (0.58-9.87)	1.6 (0.7-9.86)	3.18 (0.6-13.16)	0.009* (z=-2.627)
Calcium (mg/dl)	9.66 (7.69-11.92)	9.32 (7.61-10.3)	9.12 (7.78-12.8)	0.0001* (z=-3.966)
Phosphorus (mg/dl)	3.27 (1.98-7.04)	3.57 (2.4-5.67)	4.07 (1.86-5.25)	0.013* (z=-2.495)
ALT (IU/L)	16 (5.8-88)	12 (4-90)	17 (12-37)	0.002* (z=-3.116)
AST (IU/L)	17 (8-37)	15 (8-86)	28 (9-57)	0.035* (z=-2.109)

Table 2. All rotuine parameters of individuals and the comparison of normal and light groups (contunied)

Triglyceride (mg/dl)	148.5 (53-464)	117 (40-218)	138 (83-213)	0.0001* (z=-3.816)
Cholesterol (mg/dl)	197 (141-295)	137.5 (86-230)	142 (131-161)	0.0001* (z=-7.994)
HDL cholesterol(mg/dl)	49.5 (22-108)	43.5 (21-113)	33 (20-50)	0.001* (z=-3.457)
LDL cholesterol (mg/dl)	114 (61-206)	73 (37-152)	86.5 (51-101)	0.0001* (z=-6.944)
VLDL (mg/dl)	30 (11-73)	23.5 (8-44)	27.5 (17-43)	0.0001* (z=-3.867)
GFR_CKD_EPI (ml/dk)	63.8±23.44	52.88±31.81	10±5.66	0.048* (t=2.027)

*p<0.05 statistically significant; t: Independent Samples t test; z: Mann Whitney U test; Descriptive statistics are shown as Mean ± Standart Deviation; Moderate group was not included in the comparisons due to insufficient number of subjects

Table 3. Relations between CONUT, laboratory parameters, and clinical findings

	CONUT	
	r	***p***
BMI (After Tx)	-0.276	0.0001*
BMI (Before Tx)	-0.201	0.006*
White Blood Cell	-0.363	0.0001*
Red Blood Cell	-0.276	0.0001*
Hemoglobin	-0.197	0.006*
Hematocrit	-0.208	0.004*
Mean corpuscular volume	0.153	0.034*
Mean corpuscular hemoglobin	0.153	0.035*
Platelet	-0.244	0.001*
Lymphocyte	-0.508	0.0001*
Monocyte	-0.287	0.0001*
Basophile	-0.329	0.0001*
Urea	0.163	0.024*
Creatinine	0.174	0.016*
Calcium	-0.26	0.0001*
Phosphorus	0.167	0.021*
ALT	-0.209	0.004*
Triglyceride	-0.348	0.0001*
Cholesterol	-0.75	0.0001*
HDL cholesterol	-0.235	0.001*
LDL cholesterol	-0.651	0.0001*
VLDL cholesterol	-0.34	0.0001*
Creatinine clearance	-0.167	0.025*

*statistically significant correlation; r: Spearman Correlation Coefficient

Discussion

Our study suggested that CONUT is a rapid and quick-to-use screening tool for kidney transplant patients, requiring only three laboratory parameters for estimation. Our study showed that the transplant ameliorated patients' nutrition. After transplantation, the number of patients in the underweight group decreased when normal weight and obesity increased.

When we classified KT patients into three groups with reference to CONUT estimation, some hemogram parameters, calcium, phosphorus, cholesterol panel tests, and liver and kidney function tests were better in the normal group.

CONUT was first validated by De Ulibarri et al. [11] in a sample of 53 individuals from different service hospitals in Spain. The authors computed a nutritional formula estimated with albumin, lymphocyte, and cholesterol and revealed that CONUT seemed to be an efficient tool for early detection and continuous control of hospital under nutrition. After this validation, the CONUT score was managed in many studies to evaluate nutritional situations and clinical outcomes. Literature revealed that in both cancers and chronic situations, CONUT can be an independent predictor of all-cause mortality.

Liu et al. [12] and his friends set up a study with 9764 participants, this score may serve as a valuable biomarker in foreseeing clinical consequences in patients with gastric cancer. Di Vincenzo et al. [13] revealed CONUT is an independent prognostic score by evaluating 15 studies including 16 929 stroke patients, and it is not also related with nutrition but also could be independent risk factor for infections and major disabilities authors suggested.

Fukushima et al. [14] revealed that CONUT helps predict the long-term prognosis of 58 patients with end-stage liver diseases. By assessing five models, the authors revealed the patient had a higher risk factor for mortality with high CONUT scores. Narumi et al. [15], patients with high CONUT score with chronic heart failure. Harimoto et al. [16] estimated the CONUT score in hepatocellular carcinoma patients, and Toyokawa et al. [9] established CONUT in patients with resectable thoracic esophageal squamous cell carcinoma.

In our study, CONUT score was not only well correlated with nutritional parameters in transplant but also related to the 24-hour creatinine clearance test (-0.167, p=0.025), which was a gold standard test showing CKD stage. An increased CONUT score was related to low creatinine clearance, high creatinine, and urea levels.

Lower GFR_CKD_EPI is a lousy indicator not only of all-cause morbidity/mortality but also of worsening nutrition. Takagi et al. [17] evaluated CONUT in 311 end stage CKD patients who stably initiated dialysis. During the following period, 100 patients died because of some complications and the patients with higher CONUT scores. Likely Takagi et al. [17], Huo et al. [18] studied this score in diabetic kidney disease and showed CONUT was an independent risk factor for development of end stage renal disease. Zhou et al. [19] assessed the CONUT score, in total of 252 patients with ESRD initially undergoing peritoneal dialysis. In the 1.9-year period, 35 patients died who had a high score of CONUT.

In our study, our kidney transplant patients have low CONUT scores, and there weren't any deaths, so we showed that we can use this score, an independent indicator of death in chronic diseases, to monitor well-being. As life expectancy with a transplanted kidney increase, the nutritional score also improves.

This study has some limitations because it is a retrospective study and a single hospital experience. On the other hand, one patient is in the severe group and four patients are in the moderate group; so, we can only compare two groups, light and normal. By increasing the number of patients monitored and extending the period, the relationship between high CONUT values and mortality can be evaluated by including more patients in these groups. This point showed us that CONUT is more valuable for monitoring kidney transplant recipients before and after surgery. A prospective study by Zarifi et al. [20], conducted among 40 kidney transplant recipients and 40 healthy adults, revealed that transplantation improved clinical and nutritional status. They showed that the malnutrition index percentage gradually decreased in the following period.

This study aimed to evaluate kidney transplant patients' nutrition with CONUT score. Our study will shed light on other studies conducted on kidney transplant patients.

In conclusion, nutritional status has been shown to be a relevant clinical factor in patients with kidney transplant patients. This comprehensive analysis showed that the CONUT score is a valuable monitoring tool for kidney transplant patients, which is an objective and non-invasive approach.

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

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:4. https://doi.org/10.1038/kisup.2012.76
2. Çiçek EA, Rota S, Dursun B, Kavalci E. Evaluation of serum NGAL and hepcidin levels in chronic kidney disease patients. Ren Fail 2016;38:35-39. https://doi.org/10.3109/0886022X.2015.1107823
3. Munib S, Ahmed T, Ahmed R, Din NU. Renal allograft biopsy findings in live-related renal transplant recipients. J Coll Physicians Surg Pak 2021;31:197-201. https://doi.org/10.29271/jcpsp.2021.02.197
4. Allawi AAD. Malnutrition, inflamation and atherosclerosis (MIA syndrome) in patients with end stage renal disease on maintenance hemodialysis (a single centre experience). Diabetes Metab Syndr 2017;12:91-97. https://doi.org/10.1016/j.dsx.2017.09.003
5. Keshavarz Shahbaz S, Pourrezagholi F, Nafar M, et al. Dynamic variation of kidney injury molecule-1 mRNA and protein expression in blood and urine of renal transplant recipients: a cohort study. Clin Exp Nephrol 2019;23:1235-1249. https://doi.org/10.1007/s10157-019-01765-y
6. Veroux M, Corona D, Sinagra N, et al. Nutrition in kidney transplantation. Int J Artif Organs 2013;36:677-686. https://doi.org/10.5301/ijao.5000234
7. Marino LV, Romão EA, Chiarello PG. Nutritional status, energy expenditure, and protein oxidative stress after kidney transplantation. Redox Rep. 2017;22:439-444. https://doi.org/10.1080/13510002.2017.1325572
8. Hwang JH, Ryu J, An JN, et al. Pretransplant malnutrition, inflammation, and atherosclerosis affect cardiovascular outcomes after kidney transplantation. BMC Nephrol 2015;16:1-12. https://doi.org/10.1186/s12882-015-0108-3
9. Toyokawa T, Kubo N, Tamura T, et al. The pretreatment Controlling Nutritional Status (CONUT) score is an independent prognostic factor in patients with resectable thoracic esophageal squamous cell carcinoma: results from a retrospective study. BMC Cancer 2016;16:1-4. https://doi.org/10.1186/s12885-016-2696-0
10. Yoshihisa A, Kanno Y, Watanabe S, et al. Impact of nutritional indices on mortality in patients with heart failure. Open Heart 2018;5:1-8. https://doi.org/10.1136/openhrt-2017-000730
11. De Ulíbarri JI, Gonzalez Madrono A, De Villar NGP, et al. CONUT: a tool for controlling nutritional status. Nutr Hosp 2005;20:38-45.
12. Liu H, Yang XC, Liu DC, Tong C, Wen W, Chen RH. Clinical significance of the controlling nutritional status (CONUT) score in gastric cancer patients: a meta-analysis of 9,764 participants. Front Nutr 2023;10:1156006(e1-11). https://doi.org/10.3389/fnut.2023.1156006
13. Di Vincenzo O, D'Elia L, Ballarin G, Pasanisi F, Scalfi L. Controlling Nutritional Status (CONUT) score and the risk of mortality or impaired physical function in stroke patients: a systematic review and meta-analysis. Nutr Metab Cardiovasc Dis 2023;33:1501-1510. https://doi.org/10.1016/j.numecd.2023.05.012
14. Fukushima K, Ueno Y, Kawagishi N, et al. The nutritional index 'CONUT' is useful for predicting long-term prognosis of patients with end-stage liver diseases. Tohoku J Exp Med 2011;224:215-219. https://doi.org/10.1620/tjem.224.215
15. Narumi T, Arimoto T, Funayama A, et al. Prognostic importance of objective nutritional indexes in patients with chronic heart failure. J Cardiol 2013;62:307-313. https://doi.org/10.1016/j.jjcc.2013.05.007
16. Harimoto N, Yoshizumi T, Sakata K, et al. Prognostic significance of preoperative Controlling Nutritional Status (CONUT) score in patients undergoing hepatic resection for hepatocellular carcinoma. World J Surg 2017;41:2805-2812. https://doi.org/10.1007/s00268-017-4097-1
17. Takagi K, Takahashi H, Miura T, et al. Prognostic value of the Controlling Nutritional Status (CONUT) score in patients at dialysis initiation. Nutrients 202231;14:2317(e1-11). https://doi.org/10.3390/nu14112317
18. Huo Q, He T, Xiong J, Zhao J. Controlling nutritional status score is associated with renal progression, cardiovascular events, and all-cause mortality in biopsy-proved diabetic kidney disease. Front Physiol 2023;14:1231448(e1-10). https://doi.org/10.3389/fphys.2023.1231448

19. Zhou H, Chao W, Cui L, Li M, Zou Y, Yang M. Controlling Nutritional Status (CONUT) score as immune-nutritional predictor of outcomes in patients undergoing peritoneal dialysis. Clin Nutr 2020;39:2564-2570. https://doi.org/10.1016/j.clnu.2019.11.018

20. Zarifi SH, Shadnoush M, Pahlavani N, et al. Nutritional status in kidney transplant patients before and 6-month after transplantation: result of PNSI study. Clin Nutr ESPEN 2021;41:268-274. https://doi.org/10.1016/j.clnesp.2020.11.024

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Authors' contributions to the article

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

Research Article

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Risk factors and biomarkers for interstitial lung disease and pulmonary arterial hypertension in systemic sclerosis: experience of two tertiary centers in Türkiye

Sistemik sklerozda interstisyel akciğer hastalığı ve pulmoner arteriyel hipertansiyon için risk faktörleri ve biyobelirteçler: Türkiye'de iki tersiyer merkezin deneyimi

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Abstract

Purpose: To define the clinical and laboratory characteristics of patients with systemic sclerosis (SSc), and to investigate the risk factors affecting the prevalence of interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), which are important causes of morbidity and mortality.

Materials and methods: 88 patients with SSc were compared according to the presence of ILD and PAH. ILD was confirmed by chest high-resolution computed tomography, and PAH was suspected and considered probable PAH when right ventricular systolic pressure was >40 mmHg according to echocardiography during rest.

Results: Of the 88 patients, 44.3% had diffuse-type and 55.7% had limited-type SSc. Diffuse type, percentages of positive anti-scleroderma-70 (anti-Scl70) antibody and anti-centromere antibody, white blood cell (WBC), platelet, erythrocyte sedimentation rate (ESR), smoking, and presence of the sclerodactyly and telangiectasia differed significantly in SSc with ILD group. The positive titer of anti-Scl70 antibody (odds ratio (OR)=6.124, *p*=0.004), platelet count (OR=0.138, *p*=0.002), ESR (OR=1.042, *p*=0.035) and presence of telangiectasia (OR=10.571, *p*=0.001) were associated with ILD in patients with SSc. Also, while diffuse-type (OR=0.223, *p*=0.010), the presence of sclerodactyly (OR=11.112, *p*=0.028) and telangiectasia (OR=3.861, *p*=0.020) were risk factors for the development of ILD in nonspecific interstitial pneumonia pattern, anti-Scl-70 antibody positivity (OR=12.921, *p*=0.019) and high ESR (OR=1.034, *p*=0.030) were found to be risk factors for the development of usual interstitial pneumonia pattern. When evaluated in terms of PAH, the only risk factor was found to be advanced age (OR=1.073, 95% CI:1.012-1.139, *p*=0.019).

Conclusion: Positive titer of the anti-Scl70 antibody, diffuse type, presence of telangiectasia, and high ESR were independently associated with ILD in SSc patients.

Keywords: Interstitial lung disease, NSIP, pulmonary arterial hypertension, systemic sclerosis, UIP.

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Öz

Amaç: Sistemik skleroz (SSk) hastalarının klinik ve laboratuvar özelliklerini tanımlamak, önemli morbidite ve mortalite nedenleri olan interstisyel akciğer hastalığı (İAH) ve pulmoner arteriyel hipertansiyon (PAH) prevalansını etkileyen risk faktörlerini araştırmak.

Gereç ve yöntem: Sistemik skleroz tanısı olan 88 hasta İAH ve PAH varlığına göre karşılaştırıldı. Akciğerin yüksek rezolüsyonlu bilgisayarlı tomografisi ile İAH doğrulandı ve istirahatte uygulanan ekokardiyografiye göre sağ ventriküler sistolik basınç >40 mmHg olduğunda olası PAH olarak değerlendirildi ve kaydedildi.

Bulgular: 88 hastanın %44,3'ünde yaygın tipte ve %55,7'sinde sınırlı tipte SSk vardı. Diffüz tip, pozitif anti-skleroderma-70 (anti-Scl70) antikoru ve anti-sentromer antikor yüzdeleri, beyaz kan hücresi, trombosit sayısı, eritrosit sedimantasyon hızı (ESH), sigara içme ve sklerodaktili ve telanjiektazi varlığı İAH olan grupta anlamlı farklı saptandı. Anti-Scl70 antikorunun pozitif titresi (odds oranı (OR)=6,124, *p*=0,004), trombosit sayısı (OR=0,138, *p*=0,002), ESH (OR=1,042, *p*=0,035) ve talenjiektazi varlığı (OR=10,571, *p*=0,001), SSk'li hastalarda İAH ile ilişkili bulundu. Ayrıca diffüz tip (OR=0,223, *p*=0,010), sklerodaktili (OR=11,112, *p*=0,028) ve talenjiektazi (OR=3,861, *p*=0,020) varlığı nonspesifik interstisyel pnömoni paterninde İAH gelişimi için risk faktörleri iken, anti Scl-70 antikor pozitifliği (OR=12,921, *p*=0,019) ve yüksek ESH'nın (OR=1,034, *p*=0,030) usual interstisyel pnömoni paterni gelişimi için risk faktörleri olduğu saptandı. PAH açısından değerlendirildiğinde ise tek risk faktörünün ileri yaş olduğu görüldü (OR=1,073, %95 GA:1,012-1,139, *p*=0,019).

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Sonuç: Anti Scl-70 antikorunun pozitif titresi, yaygın tip, talenjiektazi varlığı ve yüksek ESH, SSk hastalarında İAH'nın varlığı ile bağımsız olarak ilişkilendirildi.

Anahtar kelimeler: İnterstisyel akciğer hastalığı, NSIP, pulmoner arteriyel hipertansiyon, sistemik skleroz, UIP.

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Introduction

Systemic sclerosis (SSc) is a chronic multisystem disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs [1]. SSc occurs as a result of triggering by environmental factors in genetically susceptible individuals [2]. SSc is associated with autoantibody positivity; antinuclear antibodies (ANA) may be present in more than 90% of SSc cases, and at least one of the more specific autoantibodies (anti-centromere antibody, anti-Scleroderma 70 (Scl70) antibody and anti-RNA polymerase III antibody) is present in up to 70% [3]. SSc affects the internal organs and musculoskeletal system and has a significant impact on morbidity, mortality, and quality of life [4, 5]. Interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) associated with SSc are the most important causes of mortality and morbidity in the course of this disease [6].

Pulmonary arterial hypertension occurs due to loss of pulmonary microvascularity as a result of vasculopathy and progressive pulmonary fibrosis [3]. Although it is a mortal complication, early intervention and treatment optimization provides a better prognosis [7]. Recently, the definition of PAH has been revised by the 6th World Symposium on Pulmonary Hypertension (WSPH). According to the updated definition, PAH is characterized by pulmonary artery wedge pressure (PAWP) ≤15 mmHg, pulmonary vascular resistance (PVR) ≥3 Wood units, and mean pulmonary artery pressure (mPAP) >20 mmHg as determined by right heart catheterization [8]. Classically, doppler echocardiography (DE) has served as the main screening tool for PAH, but can cause misleading overestimation of pulmonary artery pressures [9]. Although right-heart catheterization is mandatory for a definitive diagnosis, echocardiography (resting and exercise) represents a key noninvasive imaging test on the diagnostic-prognostic-therapeutic PAH algorithm [10]. It has been reported that the presence of PAH can be mentioned if the pulmonary artery systolic pressure (PASP) is >40 mmHg in DE [11]. While the incidence of PAH in SSc on echocardiography is reported to be 10-15% [12, 13] in the PHAROS study conducted with SSc patients, PAH was found in 69% of the patients, and in the DETECT study, this rate was 60% [14, 15].

Interstitial lung disease is characterized by chronic inflammation and fibrosis that progresses to respiratory failure and death [16]. Risk factors associated with the development and progression of ILD include older age at disease onset, presence of diffuse cutaneous SSc, African-American ethnicity, presence of anti-Scl-70/anti-topoisomerase I antibodies and/or absence of anticentromere antibodies [17, 18]. The most common pulmonary involvement in SSc is non-specific interstitial pneumonia (NSIP) and the second most common is usual interstitial pneumonia (UIP), which has a worse prognosis [3]. Evidence of ILD has been observed in 40-75% of SSc patients based on lung function changes and in more than 90% in autopsy series [19, 20].

It is estimated that the prevalence has increased significantly recently due to advances in imaging and evaluation methods. The purpose of this study; to describe the clinical and laboratory characteristics of SSc patients and to investigate the prevalence of ILD and PAH, which are important causes of morbidity and mortality, and the risk factors affecting them.

Materials and methods

A total of 88 patients (9 males, 79 females, mean age 53.35±13.92 years) who applied between January 2016 and January 2021, were over 18 years old, and met the classification criteria for Systemic Sclerosis (SSc) by the American College of Rheumatology

[21] were retrospectively examined for this study. From data obtained from medical records, demographic information, disease subset (diffuse or limited skin involvement), clinical findings (sclerodactyly, talingiectasia, Raynaud's phenomenon, digital ulcer, arthralgia, dysphagia, presence of lung, heart and kidney involvement), disease duration, concomitant Comorbidities and medications used were recorded. Laboratory data included complete blood cell counts [hemoglobin, white blood cell (WBC), platelet (PLT)], including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The presence and titers of autoantibodies, including ANA, anti-Scl70 antibody, anti-centromere antibody, anti-SSA antibodies, and anti-SSB antibodies, were collected.

Specific investigations including two-dimensional ECHO, pulmonary function tests, X-ray chest and high-resolution computed tomography (HRCT) chest were conducted to evaluate cardiopulmonary involvement. By examining the HRCT reports evaluated by the radiologist, the presence of ILD in patients with ground-glass opacities, reticular pattern or honeycomb findings and the presence of probable PAH in those with pulmonary artery systolic pressure (PASP) >40 mmHg on echocardiography during rest were accepted and recorded [11].

This study was conducted in accordance with the Helsinki Declaration. All participants were informed and their consent was obtained. The study was approved by the local ethics committee.

Statistical analysis

The Statistical Package for Social Sciences version 22.0 software was used to evaluate the data. Descriptive statistical data are expressed as frequency (percentage), number and mean±standard deviation, or median (min-max). The distribution properties of the numeric variables were evaluated by Kolmogorov–Smirnov test. Independent-samples t-test was used for inter group comparisons of numeric variables with normal distribution, and Mann–Whitney's U test was used for variables without normal distribution. We conducted a logistic regression analysis to identify factors independently associate parameters of ILD and the estimates of the strengths of associations were demonstrated by the odds ratio (OR) with a 95% confidence interval (CI). Categorical data were evaluated using chi-square test. A *p*-value of <0.05 was considered statistically significant.

Results

The mean age of patients was 53.35±13.92 years and the median duration of disease was 4 (0.5-38) years. Out of 88 patients, 79 were females and 9 patients were males; female/male ratio was 8.7/1. Based on the extent of skin involvement, patients were classified as diffuse cutaneous systemic sclerosis 39 (44.3%) and limited cutaneous systemic sclerosis 49 (55.7%). 86 (97.7%) were ANA-positive, 39 patients (44.3%) had positive titers of anti-Scl70 antibody, and 37 patients (42%) had positive titers of anti-centromere antibody (Table 1). While only PAH detected in 3 patients, both ILD and PAH were detected in 7 (8%) patients.

Patients with SSc who had PAH were older than patients without a diagnosis of PAH (62.91±8.72 vs. 51.99±14.03, p=0.014). In SSc patients with ILD, more patients had positive titers of anti-Scl70 antibody (68.4% vs. 26%, p<0.001) and less patients had positive titers of anti-centromere antibody (21.1% vs. 58%, p=0.001) compared to those without ILD. SSc patients with ILD had significantly higher ESR, WBC and PLT levels (Table 2). While ILD was detected in 11 (22.4%) patients with limited cutaneous type, ILD was detected in 27 (69.2%) patients with diffuse cutaneous type (p<0.001).

Considering the subtypes of ILD, 25 patients had NSIP (65.8%), while 12 patients had UIP (31.6%) and 1 patient had cryptogenic organizing pneumonia (2.6%). Diffuse involvement, presence of telangiectasia, anti scl-70 antibody positivity and high ESR were found to be risk factors for ILD. While diffuse involvement, presence of sclerodactyly and telangiectasia were risk factors for the development of ILD in NSIP pattern, anti Scl-70 antibody positivity and high ESR were found to be risk factors for the development of UIP pattern. Univariate and multivariate logistic regression analysis showing associate parameters of ILD in Table 3, NSIP and UIP in Table 4. When evaluated in terms of PAH, the only risk factor was found to be advanced age (OR=1.073, 95% CI:1.012-1.139, p=0.019).

Table 1. Characteristics of patients with systemic sclerosis (n=88)

Parameters		**Patients group (n=88)**
Age, years (mean±SD)		53.35±13.92
Gender, F/M (n)		79/9
Disease duration, years, median (min-max)		4 (0.5-38)
Limited/Diffuse type, n		49/39
Smoker, n (%)		9 (10.2%)
Raynaud's Syndrome, n (%)		76 (86.4%)
Digital ulcer, n (%)		15 (17%)
Abnormal nailfold capillaroscopy finding, n (%)		65 (73.9%)
Sclerodactyly, n (%)		60 (68.2%)
Telangiectasia, n (%)		31 (35.2%)
Arthralgia, n (%)		23 (26.1%)
Dysphagia, n (%)		21 (23.9%)
PAP, mmHg, (mean±SD)		26.11±11.41
Pulmonary Arterial Hypertension, n (%)		11 (12.5%)
Interstitial Lung Disease, n (%)		38 (43.2%)
Rheumatoid factor, n (%)		20 (22.7%)
Anti Nuclear Antibody, n (%)	**Negative**	2 (2.3%)
	1/160	11 (12.5%)
	1/320	19 (21.6%)
	1/1000	46 (52.3%)
	1/3200	10 (11.4%)
Anti-Scl70, n (%)		39 (44.3%)
Anti Centromer, n (%)		37 (42%)
Anti SS-A, n (%)		11 (12.5%)
Anti SS-B, n (%)		2 (2.3%)
ESR, mm/h, (mean±SD)		24.39±19.68
CRP, mg/L, (mean±SD)		6.87±8.08

Data are presented as the (mean±SD), median (min-max) or n (%)
Anti-Scl70: Anti-Scleroderma70, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate
PAP: Pulmonary Arterial Pressure

Table 2. Comparison of systemic sclerosis patients according to interstitial lung disease **(IAH)** and pulmonary arterial hypertension (PAH)

Parameters	SSc-ILD (n=38)		Test Value	*p*	SSc-PAH (n=11)		Test Value	*p*
	Presence	Absence			Presence	Absence		
Age, years, (mean±SD)	56.11±12.5	51.26±14.7	-1.632*	0.106	62.91±8.72	51.99±14.03	-2.505*	**0.014**
Female, n (%)	36 (94.7%)	43 (86%)	1.795$^{\Phi}$	0.180	10 (90.9%)	69 (89.6%)	0.018$^{\Phi}$	0.894
Disease duration, years, median (min-max)	5 (0.5-38)	4 (0.5-21)	-0.965^	0.334	9 (2-20)	4 (1-38)	-1.636^	0.102
Diffuse type, n (%)	23 (71.1%)	12 (24%)	19.371$^{\Phi}$	**<0.001**	2 (18.2%)	37 (48.1%)	3.480$^{\Phi}$	0.062
Smoker, n (%)	7 (18.4%)	2 (4%)	4.819$^{\Phi}$	**0.027**	1 (9.1%)	8 (10.4%)	0.018$^{\Phi}$	0.894
Raynaud's Syndrome, n (%)	35 (92.1%)	41 (82%)	1.872$^{\Phi}$	0.171	9 (81.8%)	67 (87%)	0.221$^{\Phi}$	0.639
Digital ulcer, n (%)	5 (13.2%)	10 (20%)	0.715$^{\Phi}$	0.398	2 (18.2%)	13 (16.9%)	0.011$^{\Phi}$	0.915
Abnormal nailfold capillaroscopy finding, n (%)	29 (76.3%)	36 (72%)	0.208$^{\Phi}$	0.648	9 (81.8%)	56 (72.7%)	0.412$^{\Phi}$	0.521
Sclerodactyly, n (%)	33 (86.8%)	27 (54%)	10.735$^{\Phi}$	**0.001**	7 (63.6%)	53 (68.8%)	0.120$^{\Phi}$	0.729
Telangiectasia, n (%)	21 (55.3%)	10 (20%)	11.766$^{\Phi}$	**0.001**	5 (45.5%)	26 (33.8%)	0.576$^{\Phi}$	0.448
Arthralgia, n (%)	11 (28.9%)	12 (24%)	0.274$^{\Phi}$	0.601	-	23 (100%)	4.448$^{\Phi}$	**0.035**
Dysphagia, n (%)	10 (26.3%)	11 (22%)	0.221$^{\Phi}$	0.638	4 (36.4%)	17 (22.1%)	1.018$^{\Phi}$	0.298
PAB, mmHg, (mean±SD)	28.64±13.22	24.26±9.47	-1.623^	0.105	47.63±13.32	23.08±6.98	-5.377^	**<0.001**
Rheumatoid factor, n (%)	10 (26.3%)	10 (20%)	0.490$^{\Phi}$	0.484	13 (65%)	7 (35%)	3.697$^{\Phi}$	0.620
Anti-Scl70, n (%)	26 (68.4%)	13 (26%)	15.745$^{\Phi}$	**<0.001**	5 (45.5%)	34 (44.2%)	0.007$^{\Phi}$	0.935
Anti Centromer, n (%)	8 (21.1%)	29 (58%)	12.096$^{\Phi}$	**0.001**	2 (18.2%)	35 (45.5%)	2.938$^{\Phi}$	0.110
Anti SS-A, n (%)	5 (45.5%)	6 (54.5%)	0.026$^{\Phi}$	0.871	1 (9.1%)	10 (13%)	0.134$^{\Phi}$	0.715
ESR, mm/h, (mean±SD)	33.08±24.6	17.78±11.30	-2.891^	**0.004**	21.45±13.28	24.81±20.46	-0.114^	0.910
CRP, mg/L (mean±SD)	8.43±10.33	5.69±5.67	-1.118^	0.264	5.12±3.95	7.12±8.50	-0.588^	0.557
WBC, K/uL, (mean±SD)	7.56±1.98	7.36±2.09	-0.729^	**0.046**	8.23±1.37	7.34±2.09	-1.773^	0,076
PLT, K/uL, (mean±SD)	309.39±90.91	275.10±94.61	-2.157^	**0.031**	281.36±51.32	291.12±98.84	-0.227^	0.820

Categorical data were evaluated using chi-square test, ^z: Mann–Whitney's U test were used, *t: Independent-samples t-test was used, $^{\Phi}$cs: chi-square, Anti-Scl70: Anti-Scleroderma 70, CRP: C-reactive protein WBC: White blood cell, PAB: Pulmonary Arterial Pressure, ESR: Erythrocyte sedimentation rate, PLT: Platelet

Table 3. Univariate and multivariate logistic regression analysis showing associate parameters of ILD

	Univariate analysis			Multivariate regression analysis		
	OR	**CI**	***p***	**OR**	**CI**	***p***
Diffuse type	0.129	0.049-0.334	**<0.001**	0.138	0.040-0.474	**0.002**
Smoker	0.185	0.036-0.947	**0.043**			
Presence of Sclerodactyly	5.622	1.885-16.767	**0.002**			
Presence of Telangiectasia	4.941	1.925-12.686	**0.001**	10.571	2.750-40.644	**0.001**
Anti-Scl70 antibody	6.167	2.430-15.649	**<0.001**	6.124	1.757-21.348	**0.004**
Anti Centromer antibody	0.193	0.074-0.505	**0.001**			
ESR	1.050	1.019-1.081	**0.001**	1.042	1.003-1.083	**0.035**

Logistic regression analysis were used, Anti-Scl70: Anti-Scleroderma 70, ESR: Erythrocyte sedimentation rate, OR: Odds Ratio
CI: Confidence Interval

Table 4. Univariate and multivariate logistic regression analysis showing associate parameters of NSIP and UIP

	Univariate analysis			Multivariate regression analysis		
	OR	**CI**	***p***	**OR**	**CI**	***p***
NSIP						
Diffuse type	0.253	0.094-0.678	**0.006**	0.223	0.072-0.695	**0.010**
Presence of Sclerodactyly	18.000	2.290-141.464	**0.006**	11.112	1.299-95.064	**0.028**
Presence of Telangiectasia	5.689	2.090-15.488	**0.001**	3.861	1.235-12.073	**0.020**
UIP						
Diffuse type	0.217	0.054-0.217	**0.031**			
Anti-Scl70 antibody	18.857	2.310-153.914	**0.006**	12.921	1.513-110.370	**0.019**
ESR	1.047	1.017-1.078	**0.002**	1.034	1.003-1.065	**0.030**
CRP	1.070	1.007-1.137	**0.029**			

Logistic regression analysis were used, Anti-Scl70: Anti-Scleroderma 70, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate
NSIP: Nonspecific interstitial pneumonia, UIP: Usual interstitial pneumonia, OR: Odds Ratio, CI: Confidence Interval

Discussion

Systemic sclerosis is a rare autoimmune connective tissue disease and the presence of cardiopulmonary involvement is associated with poor prognosis; It increases mortality and morbidity. Therefore, it is important to quickly diagnose ILD or PAH and start early treatment. However, diagnosis is often delayed as disease findings can develop gradually without symptoms such as dyspnea or cough and typical findings on PFT or chest radiography [22]. Therefore, in this study, to define the clinical and laboratory characteristics of SSc patients, the risk factors affecting ILD and PAH, which are important causes of morbidity and mortality, and the prevalence of PAH and ILD were investigated. Diffuse cutaneous type, smoking, presence of sclerodactyly, presence of telangiectasia, anti-scl70 positivity and anti-centromere negativity were found to be significantly higher in the ILD group. Diffuse cutaneous type, presence of

telangiectasia, anti-scl70 antibody positivity and high ESR at the time of diagnosis were found to be important risk factors for the development of ILD. Regarding ILD involvement patterns, diffuse involvement type, presence of sclerodactyly and thalangiectasia were determined as risk factors for NSIP pattern, presence of anti scl-70 antibody and high ESR at the time of diagnosis were determined as risk factors for development of UIP pattern.

In this study, the most common features detected in SSc patients were ANA positivity, Raynaud's syndrome and abnormal capillaroscopic findings, respectively. Similarly, in the update published by The European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) group, the most prominent features of the disease are Raynaud's phenomenon (96.3%), antinuclear antibodies (93.4%) and a typical capillaroscopic pattern (90%) has been reported [23].

The incidence of ILD, an important involvement pattern of SSc, is higher in patients with the diffuse cutaneous type than in those with the limited type of SSc. The European Scleroderma Trials and Research group reported that in 3,656 SSc patients, the incidence of ILD was 53% in patients with diffuse type SSc and 35% in patients with limited type [24]. Although our results for the incidence of ILD were not the same according to subtype, according to the findings in this study, the prevalence of ILD was found to be higher in patients with diffuse type SSc.

Lung involvement has been reported to be associated with specific ethnic, socioeconomic and behavioral factors in SSc [25]. It has been reported that significant abnormalities are frequently detected in nail videocapillaroscopy in patients with SSc with concomitant cardiopulmonary disease, and it has been stated that pulmonary involvement should be suspected if there are abnormal nail videocapillaroscopy patterns or digital ulcers in a patient with SSc [26, 27]. However, in our study, no significant difference was found in patients with ILD and/or PAH in terms of the presence of either digital ulcer or abnormal capillaroscopy.

Risk factors associated with progressive ILD in patients with SSc include diffuse cutaneous type, male gender, African American race, presence of anti-Scl70 antibodies, absence of anti-centromere antibodies [28-30]. Although a number of potential biomarkers have been identified that may be indicative of lung involvement in patients with SSc [31], autoantibodies are currently the only blood markers available in routine clinical practice. In line with other studies showing a strong relationship between anti-Scl70 antibody and ILD, in this study, SSc patients with ILD had higher anti-Scl70 antibody positivity and lower anti-centromere antibodies than those without ILD [27, 32]. Additionally, anti-Scl70 antibody positivity was found to be an independent risk factor for ILD in SSc patients.

Blood cell counts and inflammatory marker levels of SSc patients with ILD were found to be different from those of patients without ILD. There were no secondary infections such as pneumonia in our patients, but WBC and ESR were significantly higher in SSc patients with ILD compared to those without ILD. Therefore, it is thought that increased WBC and ESR may represent a non-infective chronic inflammatory state in the pulmonary tissue. It should be kept in mind that it may be necessary to be careful in terms of the development of ILD in patients with increased ESR and WBC despite the absence of an infective focus during follow-up. A large cohort showed that baseline CRP was associated with shorter survival and decreased forced vital capacity in SSc patients with ILD [33]. Similar to our findings, in a study conducted in Korea, WBC and ESR were found to be significantly higher in SSc patients with ILD; it has been noted that WBC is widely used as other inflammatory markers, including ESR and CRP, and such data may represent circulating markers that may predict inflammation in the lung interstitium [27]. In this study, CRP levels were found to be high in ILD patients, although it did not have statistical power.

The common HRCT pattern seen in SSc-associated ILD is NSIP, with a greater proportion of ground-glass opacities and a lower degree of reticulation [27]. up to two-thirds of patients, ground-glass opacities progress to fibrosis, even with treatment. Honeycomb cysts, a marker for UIP and pulmonary fibrosis, can be seen in up to one-third of patients with ILD and are more common in patients with limited cutaneous SSc. The pattern of HRCT findings correlates well with

histology. Ground glass opacities/consolidation correlate with active inflammation, and reticular opacities/honeycombing are associated with fibrotic lesions [34]. In this study, the NSIP pattern was present in 65.8% of the 25 patients, while the UIP pattern was present in 31.6% of the 12 patients, which was similar to the study conducted by Mulkoju et al. [34]. In addition, in our study, the type of diffuse involvement, the presence of sclerodactyly and telangiectasia were found to be independent risk factors for the development of the NSIP pattern, and the presence of anti-scl-70 antibodies and high ESR at the time of diagnosis were found to be independent risk factors for the development of the UIP pattern.

The reported prevalence of pulmonary hypertension in systemic sclerosis varies between 5% [35, 36] and 30% [37] depending on the definition and exclusion criteria used in previous studies. It has been previously reported that organ involvement may be more frequent and begin earlier in SSc patients with diffuse involvement [38]. The only exception is that PAH can occur equally frequently in both diffuse and limited skin involvement [39], although some studies have reported it to be more common in limited skin involvement [34]. In our study, although the prevalence of PAH was not equal in the groups with limited and diffuse skin involvement, no significant difference was found. Pulmonary hypertension caused by SSc usually occurs after 10 to 15 years. However, PAH can occur at any stage in patients with limited or diffuse disease [34]. In our study, no significant effect of disease duration on the development of PAH was found, but the only risk factor for PAH was found to be advanced age. It has been reported in various studies that advanced age is a risk factor together with anti-centromere antibodies and limited cutaneous SSc [40, 41].

Limitations of this study include its retrospective nature, a small number of recorded patients, incomplete data on the progression or survival of Systemic Sclerosis (SSc), and the absence of right heart catheterization data for evaluating PAH. Additionally, the threshold value of PASP >40 mmHg for PAH may be considered high, and therefore, the prevalence of PAH may be underestimated compared to the actual value.

Consequently, the characteristics of patients with SSc, a rare disease, were analyzed and it was found that the positive value of anti-Scl70 antibody was more frequent in patients with SSc with ILD, the positive value of anti-centromere antibody was less frequent, and the WBC, ESR and platelet count were higher. In addition, while diffuse involvement type, presence of telangiectasia, anti-Scl70 positivity and high ESR at diagnosis were found to be independent risk factors for ILD, the risk factor for PAH was determined to be advanced age. It should be kept in mind that ILD may develop in patients who develop elevated WBC, ESR and PLT during their follow-up.

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References

1. Barsotti S, Orlandi M, Codullo V, et al. One year in review 2019: systemic sclerosis. Clin Exp Rheumatol 2019;119:3-14.
2. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res 2019;20:13. https://doi.org/10.1186/s12931-019-0980-7
3. Adigun R, Goyal A, Hariz A. Systemic Sclerosis. [Updated 2022 May 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430875/. Accessed March 14, 2024
4. Kowal Bielecka O, Fransen J, Avouac J, et al. EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327-1339. https://doi.org/10.1136/annrheumdis-2016-209909
5. Elhai M, Meune C, Boubaya M, et al. EUSTAR group. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897-1905. https://doi.org/10.1136/annrheumdis-2017-211448
6. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685-1699. https://doi.org/10.1016/S0140-6736(17)30933-9
7. Sobanski V, Launay D, Hachulla E, Humbert M. Current Approaches to the treatment of Systemic-Sclerosis-Associated Pulmonary Arterial Hypertension (SSc-PAH). Curr Rheumatol Rep 2016;18:10. https://doi.org/10.1007/s11926-015-0560-x
8. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913. https://doi.org/10.1183/13993003.01913-2018

9. Vachiéry JL, Brimioulle S, Crasset V, Naeije R. False-positive diagnosis of pulmonary hypertension by Doppler echocardiography. Eur Respir J 1998;12:1476-1478. https://doi.org/10.1183/09031936.98.12061476
10. Ferrara, F, Zhou X, Gargani L, et al. Echocardiography in pulmonary arterial hypertension. Curr Cardiol Rep 2019;21:22. https://doi.org/10.1007/s11886-019-1109-9
11. Meune C, Avouac J, Wahbi K, et al. Cardiac involvement in systemic sclerosis assessed by tissue-doppler echocardiography during routine care: a controlled study of 100 consecutive patients. Arthritis Rheum 2008;58:1803-1809. https://doi.org/10.1002/art.23463
12. Yang X, Mardekian J, Sanders KN, Mychaskiw MA, Thomas J 3rd. Prevalence of pulmonary arterial hypertension in patients with connective tissue diseases: a systematic review of the literature. Clin Rheumatol 2013;32:1519-1531. https://doi.org/10.1007/s10067-013-2307-2
13. Hachulla E, Gressin V, Guillevin L, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792-3800. https://doi.org/10.1002/art.21433
14. Hinchcliff M, Fischer A, Schiopu E, Steen VD, PHAROS Investigators. Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. J Rheumatol 2011;38:2172-2179. https://doi.org/10.3899/jrheum.101243
15. Coghlan JG, Denton CP, Grünig E, et al. DETECT study group. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340-1349. https://doi.org/10.1136/annrheumdis-2013-203301
16. Kalchiem Dekel O, Galvin JR, Burke AP, Atamas SP, Todd NW. Interstitial lung disease and pulmonary fibrosis: a practical approach for general medicine physicians with focus on the medical history. J Clin Med 2018;7:476. https://doi.org/10.3390/jcm7120476
17. Jaeger VK, Wirz EG, Allanore Y, et al. EUSTAR co-authors. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR Study. PLoS One 2016;11:e0163894. https://doi.org/10.1371/journal.pone.0163894
18. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA Jr. A clinical and serologic comparison of African American and Caucasian patients with systemic sclerosis. Arthritis Rheum 2012;64:2986-2994. https://doi.org/10.1002/art.34482
19. Varga J. Systemic sclerosis: an update. Bull NYU Hosp Jt Dis 2008;66:198-202.
20. Bussone G, Mouthon L. Interstitial lung disease in systemic sclerosis. Autoimmun Rev 2011;10:248-255. https://doi.org/10.1016/j.autrev.2010.09.012
21. Masi AT, Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581-590. https://doi.org/10.1002/art.1780230510
22. Giacomelli R, Liakouli V, Berardicurti O, et al. Interstitial lung disease in systemic sclerosis: current and future treatment. Rheumatol Int 2017;37:853-863. https://doi.org/10.1007/s00296-016-3636-7
23. Meier FM, Frommer KW, Dinser R, et al. EUSTAR Co-authors. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71:1355-1360. https://doi.org/10.1136/annrheumdis-2011-200742
24. Walker UA, Tyndall A, Czirják L, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754-763. https://doi.org/10.1136/ard.2006.062901
25. McNearney TA, Reveille JD, Fischbach M, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum 2007;57:318-326. https://doi.org/10.1002/art.22532
26. Markusse IM, Meijs J, de Boer B, et al. Predicting cardiopulmonary involvement in patients with systemic sclerosis: complementary value of nailfold videocapillaroscopy patterns and disease-specific autoantibodies. Rheumatology (Oxford) 2017;56:1081-1088. https://doi.org/10.1093/rheumatology/kew402
27. Jung E, Suh CH, Kim HA, Jung JY. Clinical characteristics of systemic sclerosis with ınterstitial lung disease. Arch Rheumatol 2018;33:322-327. https://doi.org/10.5606/ArchRheumatol.2018.6630
28. Ashmore P, Tikly M, Wong M, Ickinger C. Interstitial lung disease in South Africans with systemic sclerosis. Rheumatol Int 2018;38:657-662. https://doi.org/10.1007/s00296-017-3893-0
29. Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N, Louthrenoo W. Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: inception cohort study. Mod Rheumatol 2016;26:588-593. https://doi.org/10.3109/14397595.2015.1115455
30. Ho KT, Reveille JD. The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther 2003;5:80-93. https://doi.org/10.1186/ar628
31. Kennedy B, Branagan P, Moloney F, et al. Biomarkers to identify ILD and predict lung function decline in scleroderma lung disease or idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2015;32:228-236.

32. Liaskos C, Marou E, Simopoulou T, et al. Disease-related autoantibody profile in patients with systemic sclerosis. Autoimmunity 2017;50:414-421. https://doi.org/10.1080/08916934.2017.1357699

33. Liu X, Mayes MD, Pedroza C, et al. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res (Hoboken) 2013;65:1375-1380. https://doi.org/10.1002/acr.21968

34. Mulkoju R, Saka VK, Rajaram M, et al. Pulmonary manifestations in systemic sclerosis: hospital-based descriptive study. Cureus 2020;12:e8649. https://doi.org/10.7759/cureus.8649

35. Avouac J, Airò P, Meune C, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290-2998. https://doi.org/10.3899/jrheum.100245

36. Erken Pamukcu H, Tunca Ç, Özişler C, et al. Pulmonary hypertension screening in patients with systemic sclerosis, in a tertiary center, in Turkey; a cross-sectional original study. TJCL 2020;11:146-155. https://doi.org/10.18663/tjcl.630633

37. McGoon MD, Benza RL, Escribano Subias P, et al. Pulmonary arterial hypertension: epidemiology and registries. J Am Coll Cardiol 2013;62:51-59. https://doi.org/10.1016/j.jacc.2013.10.023

38. Hachulla E, Launay D. Diagnosis and classification of systemic sclerosis. Clin Rev Allergy Immunol 2011;40:78-83. https://doi.org/10.1007/s12016-010-8198-y

39. Hachulla E, de Groote P, Gressin V, et al. Itinér AIR-Sclérodermie Study Group. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009;60:1831-1839. https://doi.org/10.1002/art.24525

40. Jiang Y, Turk MA, Pope JE. Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). Autoimmun Rev 2020;19:102602. https://doi.org/10.1016/j.autrev.2020.102602

41. Morrisroe K, Huq M, Stevens W, Rabusa C, Proudman SM, Nikpour M; Australian Scleroderma Interest Group (ASIG). Risk factors for development of pulmonary arterial hypertension in Australian systemic sclerosis patients: results from a large multicenter cohort study. BMC Pulm Med 2016;16:134. https://doi.org/10.1186/s12890-016-0296-z

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Authors' contributions to the article

M.P., T.I.D., and H.U. contributed to the study conception and design. Material preparation and data collection were performed by M.P. and H.U., and analysis by T.I.D. The first draft of the manuscript was written by M.P. and T.I.D. All authors commented on previous versions of the manuscript and read and approved the final manuscript. All co-authors take full responsibility for the integrity of the study and the final version of the manuscript.

Research Article

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Choroidal and retinal changes in patients with allergic rhinoconjunctivitis

Alerjik rinokonjonktivitli hastalarda koroid ve retina değişiklikleri

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Abstract

Purpose: Allergic rhinoconjunctivitis (ARC) is an allergic upper respiratory tract disease characterized by sneezing, runny nose, nasal congestion and ocular and nasal itching due to inflammation of the nasal and conjunctival mucosa. There are no studies evaluating both the choroidal and retinal areas in ARC patients. Our objective was to evaluate patients with ARC at the time of diagnosis and before initiating treatment using Optical Coherence Tomography (OCT).

Material and methods: This prospective cross-sectional study included 30 patients with ARC who presented to the Pediatric Allergy & Immunology Outpatient Clinic and 30 healthy control individuals. OCT scans were captured with Cirrus HD OCT-5000 (Carl Zeiss, Jena, Germany) in the enhanced depth imaging (EDI) mode.

Results: Of the study population, 66.7% (n=20) of patient group and 56.6% (n=17) of control group were female. The mean age was 13±2.3 and 13.9±1.8 years in the patient and control groups, respectively. The temporal subfoveal choroidal thickness was statistically significantly thinner in ARC patients with asthma (p=0.032). A robust negative correlation was found between minimum ganglion cell-inner plexiform layer (GCIPL) thickness and absolute eosinophil count (AEC) in patients with ARC (r:-0.551, p<0.0001).

Conclusion: In our study, the GCIPL thickness was lower in ARC patients. Similarly, although it did not reach statistical significance, the minimum GCIPL thickness was lower in our patient group with asthma compared to those without asthma. Our results suggest that multiple allergen sensitization and elevated eosinophils may influence GCIP thickness. However, both choroidal and retinal tissue might be impacted during chronic follow-up. Further studies are needed to support these findings.

Keywords: Retina, allergy, rinitis, choroid.

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Öz

Amaç: Alerjik rinokonjonktivit (ARK), burun ve konjonktival mukozanın iltihaplanmasına bağlı olarak hapşırma, burun akıntısı, burun tıkanıklığı ve gözde ve burunda kaşıntı ile karakterize alerjik bir üst solunum yolu hastalığıdır. ARK hastalarında hem koroid hem de retina bölgelerini değerlendiren çalışma bulunmamaktadır. Amacımız ARK'lı hastaları tanı anında ve tedaviye başlamadan önce Optik Koherens Tomografi (OKT) kullanarak değerlendirmektir.

Gereç ve yöntem: Bu prospektif kesitsel çalışmaya Çocuk Alerji ve İmmünoloji Polikliniği'ne başvuran 30 ARK hastası ve 30 sağlıklı kontrol dahil edildi. OKT taramaları, gelişmiş derinlik görüntüleme (EDI) modunda Cirrus HD OCT-5000 (Carl Zeiss, Jena, Almanya) ile ölçüldü.

Bulgular: Çalışma popülasyonunun hasta grubunun %66,7'si (n=20), kontrol grubunun %56,6'sı (n=17) kadındı. Ortalama yaş hasta ve kontrol gruplarında sırasıyla 13±2,3 ve 13,9±1,8 yıldı. Astımlı ARK hastalarında temporal subfoveal koroid kalınlığı istatistiksel olarak anlamlı derecede daha inceydi (p=0,032). ARK'lı hastalarda minimum ganglion hücre-iç pleksiform tabaka (GCIPL) kalınlığı ile mutlak eozinofil sayısı arasında güçlü bir negatif korelasyon bulundu (r:-0,551, p<0,0001).

Sonuç: Çalışmamızda ARK hastalarında GCIPL kalınlığı daha düşüktü. Benzer şekilde astımlı hasta grubumuzda da minimum GCIPL kalınlığı istatistiksel anlamlı bulunmasa da astımı olmayanlara göre daha düşüktü. Sonuçlarımız çoklu alerjen duyarlılığının ve yüksek eozinofillerin GCIPL kalınlığını etkileyebileceğini göstermektedir. Ancak kronik takip sırasında hem koroid hem de retina dokusu etkilenebilir. Bu bulguları desteklemek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Retina, alerji, rinit, koroid.

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Introduction

Allergic rhinitis (AR) is an upper respiratory system disorder associated with inflammation of nasal mucosa, and characterized by sneezing, nasal itching, runny nose and nasal congestion. It is a chronic allergic disease commonly seen in both children and adults [1]. It develops on the basis of type 1 hypersensitivity reaction in an early phase where mediators released upon mast cell degranulation, including histamine, prostaglandins, leukotrienes, quinines, and platelet-activating factor, play a major role. In the late phase, eosinophil-mediated inflammation is predominant in the nasal mucosa [2]. Inflammation leads to increased vascular permeability, mucosal edema and impaired mucociliary clearance [1]. It predisposes to respiratory problems such as severe nasal congestion, impaired sleep quality and sinusitis [3]. Recent studies suggest an estimated prevalence of 10% to 40% for AR [1, 2]. Clinical manifestation accompanied by ocular involvement with symptoms such as ocular itching, watering and redness are called allergic rhinoconjunctivitis (ARC) [4]. ARC can be triggered by many external factors such as air pollution, seasonal change, cigarette smoke, and viral infections. However, the most common triggering agents are aeroallergens such as tree or grass pollens, mold fungi, house dust mites and animal dander [2, 5]. These allergens are also involved in the etiology of allergic asthma (AA) in addition to AR and ARC [6].

The choroid is a posterior eye tissue with a dense vascular network that nourishes the outer layers of the retina. Figure 1 schematically illustrates layers of the retina and the choroid [7]. Clinical studies have shown that both the stromal and vascular structures of the choroid are impacted by various systemic diseases [8-11]. New imaging methods that measure choroidal thickness (ChT) and choroidal vascularity index (CVI) have spurred research on the correlation between the choroid and numerous diseases. In the literature, there are studies investigating choroidal parameters in diseases involving the respiratory tract such as asthma bronchiale, chronic obstructive lung disease, and sleep apnea syndrome [12-15]. The Ganglion Cell-Inner Plexiform Layer (GCIPL) complex comprises ganglion cell nuclei and dendrites in the retina. GCIPL thickness has been evaluated in various autoimmune and autoinflammatory disease groups [16]. Moreover, noteworthy findings have been shown in different systemic conditions including sleep apnea syndrome, Parkinson's disease, and Alzheimer's disease [17-19]. However, there has been no evaluation of both the choroid and retinal ganglion area in patients with ARC. In our study, we aimed

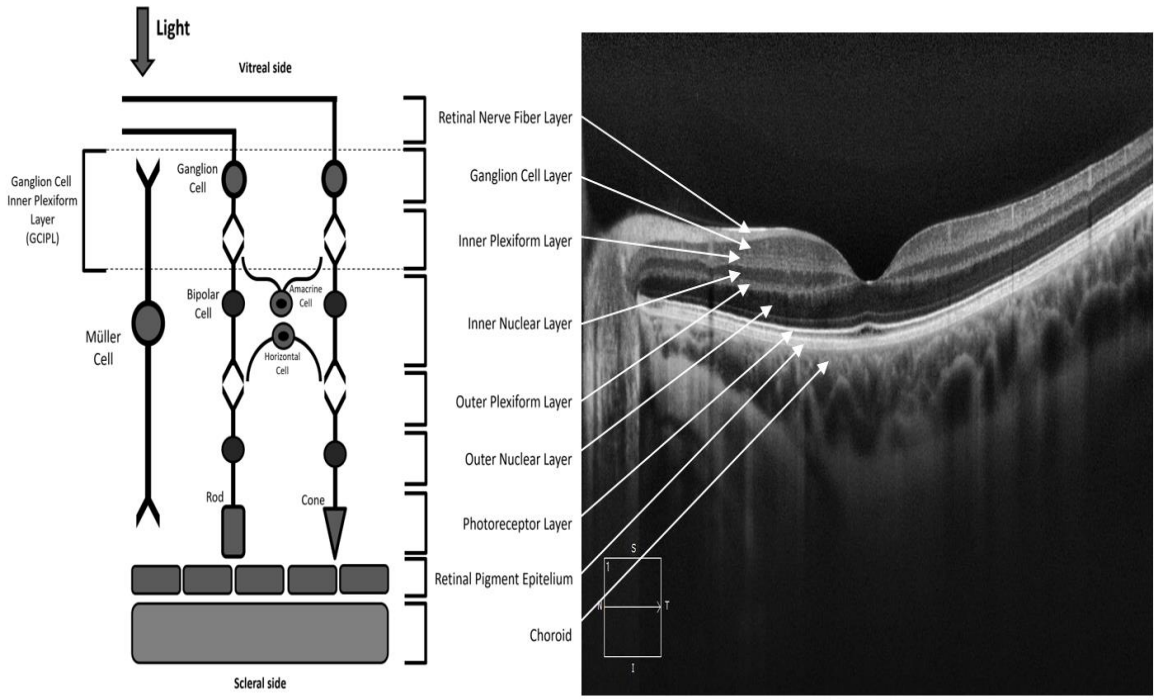

Figure 1. Layers of retina and choroid

to evaluate patients with ARC at the time of diagnosis and before initiating treatment using *Optical Coherence Tomography (*OCT).

Material and methods

This prospective cross-sectional study included 30 patients with ARC who presented to the pediatric allergy & immunology outpatient clinic and 30 healthy control individuals. The study was approved by the local Ethics Committee and conducted according to the Declaration of Helsinki Ethical Principles.

Power analysis

The sample size was determined based on previous studies with similar designs and objectives. Although there is limited literature evaluating both choroidal and retinal changes in patients with allergic rhinoconjunctivitis (ARC), an estimated effect size (Cohen's d ≈ 0.75) was used to calculate the required sample size. Using a significance level (alpha) of 0.05 and a desired statistical power of 80% (beta = 0.20), it was determined that a minimum of 30 patients and 30 controls would provide adequate power to detect meaningful differences between groups. This sample size is consistent with other ophthalmologic and immunologic studies that employed Optical Coherence Tomography (OCT) to assess retinal and choroidal parameters.

Patient group

The study included patients with newly diagnosed and treatment-naive ARC who presented to our hospital between July 2022 and September 2023. Patients who received any prior treatment, who were previously diagnosed with ARC and under follow-up and who had concomitant infections were excluded. A skin prick test (SPT) was performed to determine aeroallergen sensitization in patients with ARC. Following a thorough assessment involving detailed medical history, physical examination and allergy tests to confirm the diagnosis, the patients were referred to our ophthalmology outpatient clinic and they underwent OCT. Thirty patients with ARC included in the study.

Control group

Thirty healthy children of equivalent age and gender were selected as the control group. They were not receiving any medical treatment and had no chronic disease. They also underwent OCT in our ophthalmology outpatient clinic. Afterwards, the same parameters were compared between the patient and control groups.

Skin prick test

SPT was applied to the volar aspect or dorsum of the forearm. Patients were instructed to refrain from any antihistaminic agents at least one week prior to test. Histamine served as the positive control, and physiologic saline was the negative control during SPT. Reactions were assessed 15 minutes after administration. Allergens that produced an induration at least 3 mm greater than that of the negative control (excluding erythema) were deemed positive, while those producing a reaction less than 3 mm were considered negative.

Choroidal measurements

OCT scans were performed in Enhanced Depth Imaging (EDI) mode using a Cirrus HD OCT-5000 device (Carl Zeiss, Jena, Germany). Measurements were performed early in the morning to avoid interference with the diurnal rhythm. The fovea was evaluated through a single 30° horizontal Spectral Domain EDI OCT scan comprising an average of 100 images. ChT and CVI were also quantified. CVI was assessed using the open-source software ImageJ Fiji (//fiji.sc./Fiji) as described by Agrawal et al. [20]. The images transferred to ImageJ were rescaled by set scaling. The choroidal area to be measured was marked using polygon selection tool. Choroidal boundaries were marked as the outer border of the retinal pigment epithelium/ Bruch's membrane complex anteriorly and the inner border of the sclera posteriorly. For each of the subfoveal 1500 µm, temporal 1500 µm and nasal 1500 µm choroidal areas, CVI was calculated using the following steps. After selecting the region of interest, it was added to the ROI manager tool to calculate its total area. The image was converted to 8 bits and binarized using autolocal threshold (Niblack). Then the image was converted back to red-green-blue (RGB) and added to the ROI manager tool using color threshold. The two images in the ROI manager were merged and the resulting image was saved and the marked area was calculated. The first measurement indicated the total choroidal area (TCA), and the last

measurement provided stromal area (SA). The luminal area (LA) was obtained by subtracting the stromal area from the total choroidal area. CVI was computed by expressing the ratio of LA to TCA as a percentage (CVI=[LA/TCA]X100). Subfoveal ChT was measured manually from the outer edge of the retinal pigment epithelium at the fovea to the sclerochoroidal interface. Figure 2 illustrates the measured areas of the retina and choroidal tissue.

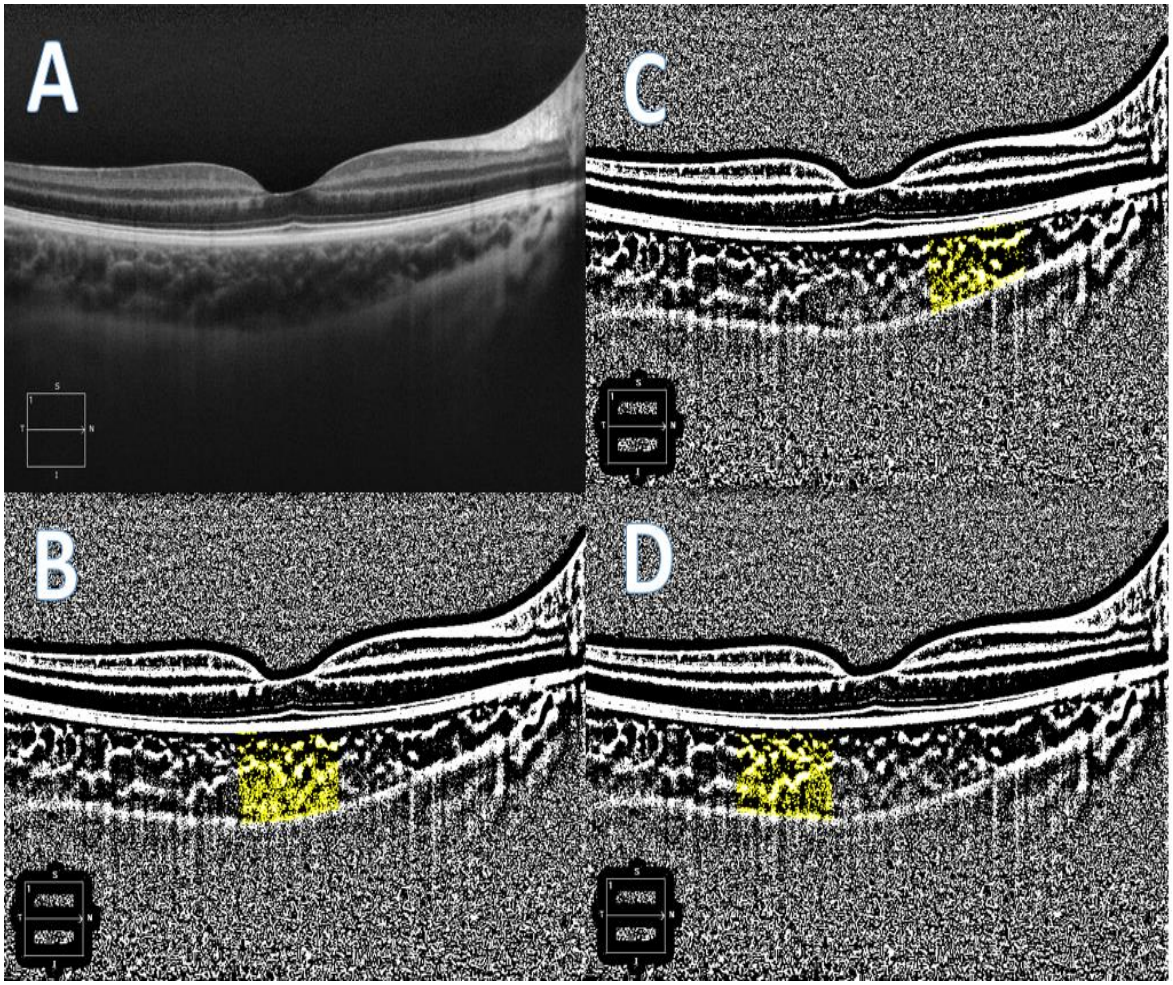

Figure 2. OCT images and binarized images taken in enhanced depth of imaging (EDI) mode of a 15-year-old allergic rhinitis patient; Black pixels in the marked area in the choroid indicate stroma, and white pixels indicate vascular lumen areas

Original OCT image (A), subfoveal 1500 µm (B), nasal 1500 µm (C), temporal 1500 µm (D)

Retinal measurements

The minimum and mean thickness of the GCIPL layers, macular volume (MV) and central subfield thickness (CST) were measured automatically using the Cirrus HD OCT-5000 device during OCT scans of patient and control groups. Cirrus HD OCT-5000 measures GCIPL thickness within annulus area of the fovea with an inner ring vertical diameter of 1 mm, and outer ring vertical diameter of 4 mm. Horizontal diameters are 20% wider. In this elliptical annulus area, the minimum and mean value of GCIPL thickness are automatically measured and reported [21]. CST is reported as the mean thickness of the retina within a 1 mm diameter circle centered at the fovea. Macular volume refers to the retinal volume within a 6x6 mm cube centered at the fovea [22].

Data evaluation

Demographic data, patient gender, patient age, blood tests, total IgE levels, skin prick test results and presence of concomitant asthma were analyzed from the patient files. OCT outcomes obtained in the opthtalmologic outpatient clinic in both the patient and control groups were evaluated. Based on the SPT results, the patients were divided into three groups as “those without allergen sensitization”, “those with single allergen sensitization”, and “those with multiple allergen sensitization”. The patient group was divided into two subgroups as those with and without concomitant asthma. Thus, the patient group was compared both with the control group and within the subgroups.

Statistical analysis

Data were analyzed using SPSS statistical software, version 22 (SPSS Inc, Chicago, IL). Continuous variables were expressed as mean ± SD and categorical variables as number (%). Normality testing was conducted to determine if the data followed a normal distribution. For this purpose, histograms and Q-Q plots were generated in SPSS to visually inspect the shape of the distribution. The Shapiro-Wilk test was used due to the sample size of 30, which is considered suitable for this test. A p-value greater than 0.05 from the Shapiro-Wilk test indicated that the data were normally distributed. Additionally, skewness and kurtosis values were calculated to assess the normality of the data further. For comparing continuous variables, independent t-tests and One-Way ANOVA were used for normally distributed data. In contrast, Mann-Whitney U test was employed for data not meeting the normality assumption.Categorical variables were analyzed using Chi-square tests. This comprehensive approach ensured the appropriate use of statistical methods and the reliability of the results.

Results

Of the study population, 66.7% (n=20) of patient group and 56.6% (n=17) of control group were female. The mean age was 13±2.3 and 13.9±1.8 years in the patient and control groups, respectively. There was no significant difference in age and gender between the two groups. A comparison of demographic data and parameters measured by OCT are shown in Table 1. No significant difference was found in choroidal tissue measurements between the patient and control groups. An evaluation of the patient group by allergen sensitization showed that absolute eosinophil count (AEC) was statistically significantly higher in patients with multiple allergen sensitization (p=0.002). Similarly, GCIPL thickness was lower in this group compared to those with monoallergen sensitization and non-sensitization, but the difference did not reach statistical significance (p=0.054). Table 2 shows a detailed comparison between the patient groups according their allergen sensitization status. The comorbidity rate in ARC cases was as follows: 36.6% (n=11) had asthma, 10% (n=3) had atopic dermatitis, and 10% (n=3) had food allergy to which tolerance developed. The patient group was also evaluated as those with and without asthma (Table 3). The temporal SA value of ARC patients with asthma was statistically significantly thinner (p=0.032).

We found a strong negative correlation between GCIPL thickness and AEC in patients with ARC (r:-0.551, p<0.0001).

Table 1. Comparison of study groups

		Patients (n=30)	Control (n=30)	*p* value	t or z value
Gender					
Female (n, %)		10 (33.3%)	13 (43.4%)	0.426	0.635[k]
Male (n, %)		20 (66.7%)	17 (56.6%)		
Age (years, mean±SD)		13±2.3	13.9±1.8	0.085	1.752[z]
ChT (µm, mean±SD)		353.9±61.6	353.5±74.5	0.985	-0.019[z]
Total TCA (µm, mean±SD)		1255306.2±2.3	1243306.4±2.3	0.844	-0.197[t]
Total SA (µm, mean±SD)		414441.1±85493.9	416809.4±85250.1	0.915	0.107[t]
Total LA (µm, mean±SD)		840871.1±1.5	826493.1±1.5	0.723	-0.356[t]
Total CVI (%, mean±SD)		67.02±2.1	66.5±1.9	0.346	-0.951[t]
Subfoveal TCA 1500 (µm, mean±SD)		439510.3±80467.7	446803±86456.9	0.736	0.338[t]
Subfoveal SA 1500 (µm, mean±SD)		142171.4±30948.4	146658±33018.5	0.589	0.543[t]
Subfoveal LA 1500 (µm, mean±SD)		297338.9±52224.2	300144.6±55820.4	0.841	0.201[t]
Subfoveal CVI 1500 (%, mean±SD)		67.7±2.5	67.3±2.5	0.483	-0.706[t]
Temporal TCA 1500 (µm, mean±SD)		441002.3±73861.9	424704.8±77193.8	0.407	-0.836[t]
Temporal SA 1500 (µm, mean±SD)		146785.8±27013.7	144597.6±27933.1	0.759	-0.308[t]
Temporal LA 1500 (µm, mean±SD)		294216.5±49806.7	280107.2±50593.7	0.281	-1.089[t]
Temporal CVI 1500 (%, mean±SD)		66.7±2.3	65.9±1.7	0.163	-1.412[t]
Nasal TCA 1500 (µm, mean±SD)		374799.6±114201	371794.7±94319.,4	0.907	-0.117[t]
Nasal SA 1500 (µm, mean±SD)		125483.9±37295.2	125553.4±31683.3	0.994	-0.212[t]
Nasal LA 1500 (µm, mean±SD)		249315.6±69300.2	246241.3±66084.1	0.861	-0.176[t]
Nasal CVI 1500 (%, mean±SD)		66.4±3.2	66.05±3.2	0.596	-0.533[t]
GCIPL	**Mean** (µm, mean±SD)	83.7±4.7	84.8±4.8	0.405	0.838[t]
	Minimum (µm, mean±SD)	78.6±14.5	83.7±4.2	0.068	1.858[t]
CST (µm, mean±SD)		249.8±19.4	249.6±18.6	0.962	1.858[t]
MV (µm, mean±SD)		10.2±0.4	10.2±0.3	0.975	-0.031[t]

ChT: choroidal thicknes, TCA: total choroidal area, SA: stromal area, LA: luminal area, CVI: choroid vascularity index, MV: macular volume GCIPL: ganglion cell inner plexiform layer, CST: central subfield thickness, SD: standart deviation, k: chi-square; t: t value ; z: z value

Table 2. Comparison of patient groups according to allergen sensitization

		Non-sensitized patients (n=12)	Monosensitized patients (n=13)	Multiple sensitization patients (n=5)	*p* value	f value
Age (years, mean±SD)		12.3±2.5	13.5±2.1	13.2±2.3	0.455	0.812
Eosinophil (count /mm^3, mean±SD)		245.5±252.1	424.4±361.2	1206.1±496.4	**0.002**	9.217
Total IgE (kU/l, mean±SD)		145.3±122.5	418.6±753.9	1277.5±392.4	0.100	2.6
ChT (µm, mean±SD)		344.1±70.5	350±33.6	392±88.7	0.310	1.225
Total TCA (µm, mean±SD)		1199806±2191985	1247716±1791845	1409806±3716325	0.253	1.447
Total SA (µm, mean±SD)		393243.6±71582.7	409972.7±72417.1	476933±1298985	0.181	1.82
Total LA (µm, mean±SD)		806595.3±1555125	837120.7±1139695	932883.8±2451975	0.330	1.154
Total CVI (%, mean±SD)		67.1±2.5	67.2±2.1	66.2±1.36	0.673	0.402
Subfoveal TCA 1500 (µm, mean±SD)		415916±78886.9	446137.3±66550.1	478906.4±1130975	0.325	1.173
Subfoveal SA 1500 (µm, mean±SD)		132496±28028.6	145548.3±28570.1	156612.4±41908.8	0.309	1.227
Subfoveal LA 1500 (µm, mean±SD)		283420±55404.1	300589.1±39664.4	322294±52224.2	0.373	1.024
Subfoveal CVI 1500 (%, mean±SD)		68.1±3.3	67.5±2	67.5±1.7	0.839	0.176
Temporal TCA 1500 (µm, mean±SD)		447090±64014.7	414709±50808.1	494754.4±1207050	0.110	2.4
Temporal SA 1500 (µm, mean±SD)		148491±23678.1	136798.3±18826.4	168660.8±41886.5	0.073	2.883
Temporal LA 1500 (µm, mean±SD)		298599±43646.3	277910.7±36778.2	326093.6±80601.1	0.173	1.874
Temporal CVI 1500 (%, mean±SD)		66.7±2.3	67±2.5	65.8±1.6	0.666	0.412
Nasal TCA 1500 (µm, mean±SD)		336833±94515.3	386247±89539.7	436156±1436820	0.178	1.843
Nasal SA 1500 (µm, mean±SD)		112256.6±29500.4	127626.1±36201	151659.8±48613.1	0.134	2.17
Nasal LA 1500 (µm, mean±SD)		224576.3±67144.5	258620.9±56059.2	284496.2±96579.9	0.223	1.588
Nasal CVI 1500 (%, mean±SD)		66.3±3.4	67.1±3.4	65±2.1	0.473	0.77
GCIPL	**Mean** (µm, mean±SD)	83.2±4	84.9±5.3	82.6±4.8	0.637	0.459
	Minimum (µm, mean±SD)	81±4.1	82±5.5	64.6±33	0.054	3.251
CST (µm, mean±SD)		242.8±13.8	252.3±21.2	257±26.4	0.260	1.416
MV (µm, mean±SD)		10±0.3	10.3±0.5	10.2±0.2	0.209	1.662

ChT: choroidal thicknes, TCA: total choroidal area, SA: stromal area, LA: luminal area, CVI: choroid vascularity index, GCIPL: ganglion cell inner plexiform layer, CMT: central subfield thickness, MV: macular volume
SD: standart deviation, One-way ANOVA test: f value
*Post Hoc analized with tukey test: For eosinophil: non-sensitized versus multiple sensitization p=0.001, monosensitized versus multiple sensitization p=0.007; non-sensitized versus monosensitized p=0.511

Table 3. Comparison of patients with and without asthma

		With asthma (n=11)	Without asthma (n=19)	*p* value	t or z value
Gender					
Female (n, %)		4 (36.4%)	6 (31.5%)	0.789	0.072[k]
Male (n, %)		7 (63.6%)	13 (68.5%)		
Age (years, mean±SD)		12.6±2.6	13.2±2.2	0.533	0.631[z]
Eosinophil (count /mm^3, mean±SD)		587.5±518.8	363.3±396.4	0.275	-1.125[z]
Total IgE (kU/l, mean±SD)		401.2±499.3	363.3±396.4	0.904	0.122[z]
ChT (µm, mean±SD)		347.5±45.9	357.5±70.1	0.675	0.423[z]
Total TCA (µm, mean±SD)		1166306±1063905	1306800.6±2761490.5	0.119	1.61[t]
Total SA (µm, mean±SD)		376668.7±45357.7	436309.4±96209.6	0.064	1.925[t]
Total LA (µm, mean±SD)		789643.8±73639.9	870529±1854690.5	0.180	1.377[t]
Total CVI (%, mean±SD)		67.7±2.1	66.6±2.1	0.186	-1.356[t]
Subfoveal TCA 1500 (µm, mean±SD)		416949.8±40127.3	452571.6±95112.3	0.249	1.176[t]
Subfoveal SA 1500 (µm, mean±SD)		131843.1±16541.8	148150.9±35891.2	0.168	1.415[t]
Subfoveal LA 1500 (µm, mean±SD)		285106.7±26765.7	304420.7±62062.2	0.338	0.975[t]
Subfoveal CVI 1500 (%, mean±SD)		68.4±1.8	67.3±2.8	0.301	-1.504[t]
Temporal TCA 1500 (µm, mean±SD)		406804.3±51763.1	460801.1±78565.5	0.052	2.031[t]
Temporal SA 1500 (µm, mean±SD)		133059.8±19075.4	154732.4±28138.1	**0.032**	2.263[t]
Temporal LA 1500 (µm, mean±SD)		273744.5±37498.1	306068.7±53020.1	0.087	1.775[t]
Temporal CVI 1500 (%, mean±SD)		67.2±2.5	66.4±2.1	0.328	-0.995[t]
Nasal TCA 1500 (µm, mean±SD)		342558.3±42826.9	393465.5±1243830	0.203	1.305[t]
Nasal SA 1500 (µm, mean±SD)		111765.8±21393.3	133426.1±42486.5	0.127	1.571[t]
Nasal LA 1500 (µm, mean±SD)		230792.5±27723.1	260039.5±83542.4	0.273	1.119[t]
Nasal CVI 1500 (%, mean±SD)		67.4±3.6	65.9±2.9	0.219	-1.257[t]
GCIPL	**Mean** (µm, mean±SD)	84±5.4	83.6±4.3	0.841	-0.203[t]
	Minimum (µm, mean±SD)	74.8±23.4	80.8±4.3	0.281	1.809[t]
CST (µm, mean±SD)		251.4±25.2	248.9±15.8	0.740	-0.336[t]
MV (µm, mean±SD)		10.3±0.4	10.1±0.4	0.429	-0.803[t]

ChT: choroidal thicknes, TCA: total choroidal area, SA: stromal area, LA: luminal area, CVI: choroid vascularity index, MV: macular volume GCIPL: ganglion cell inner plexiform layer, CST: central subfield thickness, SD: standart deviation, k: chi-square; t: t value ; z: z value

Discussion

The choroid is one of the vascular tissues with the highest blood supply. Its blood supply is affected by local or systemic inflammatory factors. Recently, the choroid has become a focal point of research in numerous systemic diseases, with promising findings indicating its potential as a biomarker. Various studies across diverse disease groups with systemic inflammation have demonstrated significant reductions in CVI and ChT [23].

Studies related with diseases involving the upper and lower respiratory tract are gaining momentum in the literature. A study in patients with nasal septal deviation showed no significant differences in subfoveal, temporal and nasal ChT measurements compared to a control group [24]. Another study by Savran Elibol et al. [25] evaluated patients with nasal polyps using OCT and suggested that increased inflammation in the nasal region might contribute to an increase in choroidal blood supply in the anatomically adjacent area. Inflammation and obstruction in the upper respiratory system may influence the sympathetic and parasympathetic balance, potentially resulting in changes in the choroidal tissue thickness. However, both studies found no significant differences compared to the control group. In our study, we observed no significant difference in choroidal measurements among patients with ARC (Table 1). Decreased CVI and ChT levels have been reported in various clinical studies, particularly in respiratory conditions such as sarcoidosis, asthma and sleep apnea syndrome [26-28]. We also examined patients with and without asthma. Many studies have shown an increased prevalence of allergic conditions such as atopic dermatitis (AD), food allergy (FA), AR, and AA within specific age groups, following a sequential pattern with increasing age. AD and FA are more prevalent in infancy while AR and AA commonly manifest in childhood [29]. This progressive nature of allergic conditions is referred to as “atopic march”. Accordingly, there is a risk of development of AA in cases with AR. Atopic inflammation in nasal mucosa may induce changes in the lower respiratory tract through three fundamental mechanisms: nasal-tracheal reflex, cytokines and secretions [29]. A study by Yılmaz et al. [12] reported statistically significant reductions in CVI and subfoveal ChT in asthma patients. In our study, when comparing our ARC patients with and without asthma, we observed a lower ChT in asthmatic patients, although the difference was not statistically significant. Across all three areas (subfoveal 1500μm, temporal 1500μm, and nasal 1500μm), TCA, SA and LA were lower in ACR patients with asthma than those without asthma. Notably, the decrease in temporal 1500μm SA was statistically significant. On the other hand, CVI ratio was higher, albeit not statistically significant, in ARC patients with asthma. We attribute this finding to the fact that the decrease in SA was more pronounced compared to LA.

It could be proposed that CVI and ChT ratios of ACR patients may be influenced by the subsequent development of AA in the context of atopic march in the coming years. Considering that we conducted the measurements in our ARC patients prior to the initiation of treatment, we have shown that choroidal tissue was not significantly affected in allergic patients with upper respiratory tract involvement. However, in the light of recent studies, it has been substantiated that alterations in choroidal tissue occur in conditions associated with lower respiratory tract such as asthma [12, 26, 27].

Chen et al. [30] reported a thinner retinal nerve fiber layer (RNFL) in patients with allergic conjunctivitis (AC). The same study showed no significant difference in macular thickness measurements among AC patients compared to the control group. Similarly, in our study, we observed no statistically significant differences in macular measurements between the patient and control groups. Nevertheless, there is no study evaluating the GCIPL thickness in patients with ARC. Although the minimum GCIPL thickness in our patient group was lower compared to the control group, the difference did not reach statistical significance. Notably, in the group with multiple sensitizations, the minimum GICPL thickness was significantly lower compared to the other two groups (monoallergen sensitization group and non-sensitization group) (Table 2). The macular thickness was similar in these groups. Additionally, the minimum GCIPL thickness was lower in our patient group with asthma than those without asthma (Table 3). In the literature, there are studies evaluating both retina and choroid in various autoimmune and autoinflammatory disease groups, revealing

that inflammation may lead to thinning, especially in the choroid and retina [16]. Clinical studies suggest that assessing choroidal measurements provide more informative insights than retinal measurements. Despite the abundance of clinical studies evaluating ChT and CVI measurements, research on GCIPL is very limited. Notably, some findings suggest the potential benefit of retinal measurements in conditions such as psoriasis, metabolic syndrome and Behcet's disease, offering promise for future studies [16]. Our study also emphasized the significance of choroidal and retinal measurements in chronic respiratory allergies such as AR, ARC and AA as we observed a robust negative correlation between the minimum GCIPL thickness and AEC. Patients with predominant eosinophil exhibited multiple sensitizations, and AEC was statistically significantly higher in ARC patients with multiple allergen sensitization. Our results suggest that multiple allergen sensitization and elevated eosinophil levels contribute to GCIPL thickness. The findings also suggest choroidal and retinal tissue measurements are promising indicators in ARC patients with multiple sensitization and elevated AEC, possibly serving as biomarkers in the future. However, further evidence-based studies are required to support these findings.

In conclusion, our study did not find any significant impact on choroidal tissue in patients with ARC. However, we observed that ChT was thinner in patients with concomitant asthma. On the other hand, GCIPL thickness was lower in patients with ARC. Although not reaching statistical significance, the minimum GCIPL thickness was also lower in our asthmatic patients compared to those without asthma. These findings suggest that both choroidal and retinal tissues may be affected in the chronic follow-up. Additional studies are necessary to provide robust support for these observations.

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

References

1. Eifan AO, Durham SR. Pathogenesis of rhinitis. Clin Exp Allergy 2016;46:1139-1151. https://doi.org/10.1111/cea.12780
2. Okano M, Fujieda S, Gotoh M, et al. Executive summary: Japanese guidelines for allergic rhinitis 2020. Allergol Int 2023;72:41-53. https://doi.org/10.1016/j.alit.2022.11.003
3. Blaiss MS. Pediatric allergic rhinitis: physical and mental complications. Allergy Asthma Proc 2008;29:1-6. https://doi.org/10.2500/aap2008.29.3072
4. Phipatanakul W. Allergic rhinoconjunctivitis: epidemiology. Immunol Allergy Clin North Am 2005;25:263-281. https://doi.org/10.1016/j.iac.2005.03.001
5. Yorgancıoğlu AA, Gemicioğlu B, Cingi C, et al. ARIA 2019, Allerjik rinite tedavi yaklaşımı-Türkiye. Turk Thorac J 2020;21:122-133. https://doi.org/10.5152/TurkThoracJ.2019.19084
6. Tsuge M, Ikeda M, Matsumoto N, Yorifuji T, Tsukahara H. Current ınsights into atopic march. Children (Basel) 2021;8:1067. https://doi.org/10.3390/children8111067
7. Joyce C, Le PH, Sadiq NM. Histology, Retina. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan
8. Nickla DL, Wallman J. The multifunctional choroid. Prog Retin Eye Res 2010;29:144-168. https://doi.org/10.1016/j.preteyeres.2009.12.002
9. Wei WB, Xu L, Jonas JB, et al. Subfoveal choroidal thickness: the Beijing Eye Study. Ophthalmology 2013;120:175-180. https://doi.org/10.1016/j.ophtha.2012.07.048
10. Aksoy M, Asena L, Tekindal MA, Ayvazoğlu Soy EH, Yılmaz G, Haberal M. Choroidal vascularity ındex and choroidal thickness changes following renal transplantation. Turk J Ophthalmol 2023;53:97-104. https://doi.org/10.4274/tjo.galenos.2022.02489
11. Seo WW, Yoo HS, Kim YD, Park SP, Kim YK. Choroidal vascularity index of patients with coronary artery disease. Sci Rep 2022;12:3036. https://doi.org/10.1038/s41598-022-07120-8
12. Yılmaz M, Polat OA, Karayiğit DZ, Ayyıldız T. Choroidal vascularity index and choroidal thickness changes in patients with allergic asthma. Photodiagnosis Photodyn Ther 2021;36:102494. https://doi.org/10.1016/j.pdpdt.2021.102494
13. Kocamış O, Zorlu D. Choroid and retinal nerve fiber layer thickness in patients with chronic obstructive pulmonary disease exacerbation. J Ophthalmol 2018;2018:1201976. https://doi.org/10.1155/2018/1201976
14. Xin C, Wang J, Zhang W, Wang L, Peng X. Retinal and choroidal thickness evaluation by SDOCT in adults with obstructive sleep apnea-hypopnea syndrome (OSAS). Eye (Lond) 2014;28:415-421. https://doi.org/10.1038/eye.2013.307
15. Yakut ZI, Karadag R, Ozol D, Senturk A. Evaluation of arterial blood flow changes by orbital Doppler in chronic obstructive pulmonary disease and asthma. J Investig Med 2015;63:12-16. https://doi.org/10.1097/jim.0000000000000118

16. Steiner M, Esteban Ortega MDM, Muñoz Fernández S. Choroidal and retinal thickness in systemic autoimmune and inflammatory diseases: a review. Surv Ophthalmol 2019;64:757-769. https://doi.org/10.1016/j.survophthal.2019.04.007
17. Sundaram V, Haridas S, Dhar M, Harikrishnan CP. Evaluation of retinal nerve fiber layer, ganglion cell layer, and optic nerve head morphological parameters in patients with obstructive sleep apnea and comparison with normal population. Indian J Ophthalmol 2022;70:453-457. https://doi.org/10.4103/ijo.IJO_985_21
18. Živković M, Dayanir V, Stamenović J, et al. Retinal ganglion cell/inner plexiform layer thickness in patients with Parkinson›s disease. Folia Neuropathol 2017;55:168-173. https://doi.org/10.5114/fn.2017.68584
19. López de Eguileta A, Cerveró A, Ruiz de Sabando AR, Sánchez Juan P, Casado A. Ganglion cell layer thinning in alzheimer's disease. Medicina (Kaunas) 2020;56:553. https://doi.org/10.3390/medicina56100553
20. Agrawal R, Salman M, Tan KA, et al. Choroidal vascularity index (CVI)–a novel optical coherence tomography parameter for monitoring patients with panuveitis? PLoS One 2016;11:e0146344 https://doi.org/10.1371/journal.pone.0146344
21. Mwanza JC, Durbin MK, Budenz DL, et al. Cirrus OCT Normative Database Study Group. Profile and predictors of normal ganglion cell–ınner plexiform layer thickness measured with frequency-domain optical coherence tomography. Invest Ophthalmol Vis Sci 2011;52:7872-7879. https://doi.org/10.1167/iovs.11-7896
22. Saxena S, Caprnda M, Ruia S, et al. Spectral domain optical coherence tomography based imaging biomarkers for diabetic retinopathy. Endocrine 2019;66:509-516. https://doi.org/10.1007/s12020-019-02093-7
23. Ataş F, Kaya M, Ayhan Z, Ozkan O, Birlik M. Evaluation of choroidal vascularity index in systemic sclerosis patients. Photodiagnosis Photodyn Ther 2023;41:103297. https://doi.org/10.1016/j.pdpdt.2023.103297
24. Üstün Bezgin S, Çakabay T, Bayramoğlu SE, Sayın N, Koçyiğit M. Evaluation of choroidal thickness measurements in patients with marked nasal septal deviation. Braz J Otorhinolaryngol 2020;86:242-246. https://doi.org/10.1016/j.bjorl.2018.11.009
25. Savran Elibol E, Doğan R, Elbay A, Cırık AA, Aykut V, Yenigün A. Evaluation of coroid thickness of patients with nazal polype. J Ear Nose Throat and Head Neck Surgery 2020;28:216-221. https://doi.org/10.24179/kbbbbc.2020-75404
26. Ugurlu E, Pekel G, Akbulut S, Cetin N, Durmus S, Altinisik G. Choroidal vascularity index and thickness in sarcoidosis. Medicine (Baltimore) 2022;101:e28519. https://doi.org/10.1097/MD.0000000000028519
27. Özcan G, Temel E, Örnek K, et al. Choroidal vascularity index in obstructive sleep apnea syndrome. Sleep Breath 2022;26:1655-1659. https://doi.org/10.1007/s11325-021-02538-2
28. Yang L, Fu J, Zhou Y. Research progress in atopic march. Front Immunol 2020;11:1907. https://doi.org/10.3389/fimmu.2020.01907
29. Leynaert B, Neukirch C, Kony S, et al. Association between asthma and rhinitis according to atopic sensitization in a population-based study. J Allergy Clin Immunol 2004;113:86-93. https://doi.org/10.1016/j.jaci.2003.10.010
30. Chen D, Li R, Huang D, et al. Altered retinal nerve fiber layer thickness in children with allergic conjunctivitis: the Nanjing eye study. BMC Ophthalmol 2022;22:183. https://doi.org/10.1186/s12886-022-02399-7

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Author contributions

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Research Article

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Evaluation of Ema, Töllner and Rodwell scores in the diagnosis of neonatal sepsis

Yenidoğan sepsis tanısında Ema, Töllner ve Rodwell skorlarının değerlendirilmesi

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Abstract

Purpose: There are no specific signs, symptoms and rapid laboratory tests to definitively diagnose sepsis in the neonatal period. Therefore, in this study, we planned to investigate the clinical adequacy and reliability of EMA (European Medicines Agency), Töllner and Rodwell hematological scoring in the early diagnosis of neonatal sepsis.

Materials and methods: EMA, Töllner and Rodwell hematological scoring was performed on each patient. Complete blood count, peripheral smear, C-reactive protein, procalcitonin, blood gas and blood sugar values of newborn babies with suspected sepsis were recorded, blood culture, urine culture and cerebrospinal fluid examination and cultures taken when necessary were evaluated. Using statistical analysis, the 'Positive Expected Value and Negative Expected Values' ratios of the scores were obtained, and the performance results were examined.

Results: 95 newborns with a preliminary clinical diagnosis of sepsis were included in the study. These babies were divided into two groups: clinical (n:71) and proven sepsis (n:24) according to blood culture results. Positive and negative predictive values of scoring systems in definitive sepsis diagnosis; for EMA respectively; 21.5%, 56.3% for Töllner; It was determined as 31.3%, 77.8%, and 100%, 77.8% for Rodwell.

Conclusion: Our study showed that clinician opinion and standard laboratory tests are limited in the diagnosis of neonatal sepsis, and Rodwell hematological scoring is more prominent in recognizing proven sepsis compared to the other two scores.

Keywords: Sepsis, newborn, EMA, Töllner, Rodwell.

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Öz

Amaç: Yenidoğan döneminde sepsis tanısını kesin olarak saptayacak özgün belirti, bulgu ve hızlı laboratuvar testleri bulunmamaktadır. Bu nedenle bu çalışmada yenidoğan sepsisinin erken tanısında EMA (European Medicines Agency), Töllner ve Rodwell hematolojik skorlamalarının klinik yeterlilik ve güvenirliğini araştırmayı planladık.

Yöntem: Her hastaya EMA, Töllner ve Rodwell hematolojik skorlaması yapıldı. Sepsis düşünülen yenidoğan bebeklerin tam kan sayımı, periferik yayma, C-reaktif protein, prokalsitonin, kan gazı ve kan şekeri değerleri kaydedildi, bebeklerden alınan kan kültürü, idrar kültürü ve gerekli hallerde alınmış beyin omurilik sıvı incelemesi ve kültürleri değerlendirildi. İstatistiksel analizler kullanılarak skorlamaların 'Pozitif Beklenen Değer ve Negatif Beklenen Değerler' oranları elde edildi, performans sonuçları incelendi.

Bulgular: Klinik sepsis ön tanısı alan 95 yenidoğan çalışmaya alındı. Bu bebekler kan kültürü sonuçlarına göre klinik (n:71) ve kanıtlanmış sepsis (n:24) olmak üzere iki gruba ayrıldı. Kesin sepsis tanısında skorlama sistemlerinin pozitif ve negatif prediktif değerleri; sırasıyla EMA için; %21,5, %56,3, Töllner için; %31,3, %77,8, Rodwell için ise %100, %77,8 saptandı.

Sonuç: Çalışmamız, yenidoğan sepsis tanısında klinisyen görüşünün ve standart laboratuvar testlerin sınırlı olduğunu, Rodwell hematolojik skorlamasının diğer iki skorlamaya göre kanıtlanmış sepsisi tanımada daha ön planda olduğunu göstermiştir.

Anahtar kelimeler: Sepsis, yenidoğan, EMA, Töllner, Rodwell.

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Introduction

Neonatal sepsis is a clinical syndrome in which systemic findings and signs of infection are seen in the first month of life and a specific pathogen is grown in blood culture [1-3]. Despite advances in maternal and neonatal care, neonatal sepsis continues to be a major factor in morbidity and mortality [4-6].

Signs and symptoms in the neonatal sepsis are generally non-specific. In early-onset neonatal sepsis, findings related to multiple organs or systems may occur, whereas in late and very late-onset neonatal sepsis, infection findings may be multisystemic or focal (such as meningitis, pneumonia, omphalitis, osteomyelitis, septic arthritis) [7]. Neonatal sepsis may affect many systems and present with many different findings such as moaning, withdrawal of auxiliary respiratory muscles, nasal wing respiration, apnea, cyanosis, tachypnea in the respiratory system; bradycardia/ tachycardia, peripheral circulatory disorder, hypotension, increased capillary filling time in the cardiovascular system; feeding intolerance, failure to suck, vomiting, diarrhoea, abdominal distension, hepato-splenomegaly, jaundice in the digestive system; sclera, cutis marmaratus, pustules, abscesses, petechiae, pupura in the skin; and lethargy, hypotonicity, tendency to sleep, poor or high pitched crying, puffy fontanelle, irritability, convulsion, hypoactivity, temperature irregularities and failure to suck in the central nervous system [7-10].

Isolation of the specific pathogenic agent from the blood, which should be absolutely sterile, is the gold standart for definitly diagnosis of the neonatal sepsis [11]. In a blood culture taken with the correct methods, the growth time of the agent is within the first 48 hours in 90% of patients. While waiting for the culture result, there is no test with high sensitivity and specificity that can help to define the diagnosis of sepsis in a shorter time. Diagnosis is aided by the use of several inflammatory markers together [8].

In addition to the lack of specific signs, symptoms, findings and rapid laboratory tests for the diagnosis of neonatal sepsis, the possibility that findings suggestive of sepsis may be related to non-infectious causes that are common in the neonatal period makes the diagnosis of neonatal sepsis difficult. This situation makes timely diagnosis and initiation of treatment difficult in babies without sepsis or leads to unnecessary treatment [2].

Various combinations of inflammatory response factors, laboratory analysis, and physical examination findings have been used in the literature to create sepsis scores. In 1982, Töllner developed the first known scoring system for neonatal sepsis to define sepsis on the basis of both clinical and basic laboratory assessment [12]. Rodwell developed hematological sepsis scoring in 1988 [13]. The Pediatric Committee (PDCO) of the European Medicines Agency (EMA) proposed the EMA sepsis criteria for the standardisation of the diagnosis of neonatal sepsis in 2010 [14]. However, a specific scoring method with high sensitivity and reliability in recognizing neonatal sepsis has not yet been developed. Also, there are no reports evaluating EMA, Töllner and Rodwell scores together in the literature. Therefore, in this study, EMA, Töllner, and Rodwell scores were compared in proven and clinical sepsis cases and their predictive values in the early diagnosis of the neonatal sepsis were evaluated.

Materials and methods

A total of 95 neonates who were admitted to the neonatal intensive care unit of Pamukkale University Hospital between July 2021 and July 2023, who were diagnosed with clinical or proven sepsis, and for whom parental consent was obtained, were enrolled in this study.

Newborns who had significant congenital abnormalities, proven intrauterine infection, metabolic disease, history of chorioamnionitis, preterm rupture of membranes (>18 hours), history of maternal antibiotic use in the last

week of pregnancy (except for the last 4 hours prenatally), and antibiotic use in the last 1 week with a clinical diagnosis of sepsis were not included in the study.

Complete blood count, peripheral smear, C-reactive protein (CRP), procalcitonin, blood gas and blood glucose values routinely obtained from newborn babies with sepsis were recorded. Blood culture, urine culture and cerebrospinal fluid (CSF) examination and culture obtained when necessary were recorded.

EMA scoring, Rodwell hematological scoring, and Töllner scoring were performed in each patient included in the study.

All data were evaluated with SPSS 25.0 (IBM SPSS Statistics 25, IBM Corporation, Armonk, New York, United States). Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as numbers and percentages.

Spearman or Pearson correlation analyses were used to analyse relationships between continuous variables. When the assumptions for parametric tests were met, the significance test for the difference between two means and one-way analysis of variance were used to analyse differences between groups; when the assumptions for parametric tests were not met, Kruskal-Wallis analysis of variance and the Mann-Whitney U test were used.

Variations between categorical parameters were assessed by Chi-square analysis. ROC analysis method was used for analysing the performance and validity of the scores.

Youden Index value was used in determining the most appropriate cut-off point as a result of ROC analysis. As a result of the examinations made with the most appropriate cut-off points obtained from Youden Index values, the performance results were analysed by obtaining the ratio of 'Positive Expected Value and Negative Expected Value' of the scoring.

This study was approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee.

Results

A total of 95 neonates with clinical or proven sepsis admitted to the neonatal intensive care unit of Pamukkale University Hospital were involved in our study. Demographic and clinical data of these infants according to clinical sepsis and proven sepsis are presented in Table 1. Table 2' EMA, Table 3' Töllner and Table 4' Rodwell scores parameters are shown. Table 5, show the positive and negative predictive values of EMA, Töllner and Rodwell scores in proven sepsis, respectively.

When comparing the demographic and clinical data between both groups, a statistically significant difference was found in birth weight, Apgar scores, age at onset of infection, early (<3 days), late (3-30 days), very late (>30 days) sepsis and length of hospital stay, while there was no other statistically important difference. Significant differences were observed between both groups in terms of respiratory evaluation, metabolic acidosis and apnea data in the Töllner score, and degenerative changes in neutrophils in the Rodwell score, which are among the parameters of the EMA score.

The positive and negative predictive values of the scoring methods for the definite diagnosis of sepsis were 21.5%, 56.3%; 31.3%, 77.8% and 100%, 77.8% for EMA, Töllner, and Rodwell scoring, respectively.

Table 1. Comparison of demographic and clinical data between two groups

	Clinical sepsis	Proven sepsis	*p* value	z – x^2
Total Count (n)	71	24		
Birth weight				
Mean ± SD, (gram)	2570.18±934.24	1395.20±774.45	0.001*	z:4.715
Weight according to birth week				
AGA	55 (77.5%)	17 (70.8%)		
SGA	10 (14%)	5 (20.8%)	0.733	x^2:0.622
LGA	6 (8.5%)	2 (8.4%)		
Mean birth week ± SD	35.08±5.58	30.02±4.73	0.063	z:4.506
Gender				
Girl (percentage)	27 (38.0%)	7 (29.2%)	0.434	x^2:0.613
Boy (percentage)	44 (62.0%)	17 (70.8%)		
Birth type				
C/S	65 (91.5%)	24 (100%)	0.332	x^2:2.165
SVD	6 (8.5%)	-		
Apgar Score (median, min-max)				
1th minute	8 (4-9)	9 (6-10)	0.005*	z:3.415
5th minute	9 (5-9)	8 (1-10)		z:3.307
Age at onset of infection (day)	7	17	0.001*	z:3.871
Respiratory support (percentage)	48 (67.6%)	18 (75.0%)	0.496	x^2:0.462
Respiratory support type (percentage)				
O_2 in newborn incubator	4 (8.3%)	1 (5.6%)		
nCPAP	27 (56.3)	4 (22.2%)	0.062	x^2:7.346
nIPPV	11 (22.9%)	9 (50%)		
Intubated PTV	6 (12.5)	4 (22.2%)		
Inotrope support	4 (5.6%)	0 (44.4%)	0.569	x^2:1.412
RDS	31 (43.7%)	15 (62.5%)	0.110	x^2:2.549
PDA	8 (28.6%)	7 (38.9%)	0.304	x^2:6.022
GM-IVH	4 (10.5%)	5 (23.8%)	0.206	x^2:4.573
Sepsis				
Early	41 (57.7%)	2 (8.3%)	0.001*	x^2:21.83
Late	29 (40.8%)	18 (75%)	0.027*	
Hospital stay ± SD, days	30.33±25.22	55.50±36.30	0.001*	z:4.736

SD: standard deviation, AGA: appropriate for gestational age, SGA: small of gestational age, LGA: large of gestational age
C/S: caesarean section, SVD: spontaneous vaginal delivery, nCPAP: nasal continuous positive airway pressure
nIPPV: nasal intermittent positive pressure ventilation, PTV: patient triggered ventilation, RDS: respiratory distress syndrome
PDA: patent ductus arteriosus, GM-IVH: germinal matrix intraventricular hemorrhage, z: mann whitney u, x^2: Chi-squared test
* $p<0.05$ statistically significant

Table 2. Evaluation of EMA score parameters

	Clinical sepsis	Proven sepsis	*p* value	x^2
Body temperature				
normal	58 (81.6%)	22 (91.6%)		
>38.5	12 (16.9%)	2 (8.3%)	0.486	x^2:1.444
<36.0	1 (1.40%)	0		
Cardiovascular system				
normal	50 (70.4%)	13 (54.1%)		
arrhythmia	16 (22.5%)	10 (41.6%)		
urine <1 ml/kg/h	3 (4.2%)	0	0.101	x^2:7.762
hypotension	2 (2.8%)	0		
impaired peripheral perfusion	0	1 (4.1%)		
Skin and subcutaneous lesions				
none	70 (98.5%)	24 (100%)	1.000	x^2:0.342
sclerem	1 (1.40%)	0		
Respiratory				
normal	21 (29.5%)	6 (25%)		
apnea	7 (9.8%)	10 (41.6%)	0.002*	x^2:14.563
tachypnea	29 (40.8%)	3 (12.5%)		
increased oxygen/ventilation support	14 (19.7%)	5 (20.8%)		
Gastrointestinal				
no findings	21 (29.5%)	6 (25%)		
feeding intolerance	17 (23.9%)	10 (41.6%)	0.165	x^2:5.094
decreased absorption	26 (36.6%)	4 (16.6%)		
abdominal distension	7 (9.8%)	4 (16.6%)		
Non-specific findings				
none	50 (70.4%)	16 (66.6%)		
irritability	8 (11.2%)	3 (12.5%)	0.429	x^2:2.768
lethargy	8 (11.2%)	1 (4.1%)		
hypotonicity	5 (7%)	4 (16.6%)		
Leukocyte count				
normal	60 (84.5%)	20 (83.3%)		
<4000	1 (1.40%)	1 (4.1%)	0.710	x^2:0.684
>20000	10 (14%)	3 (12.5%)		
Immature/Total neutrophil ratio				
<0.2	18 (25.3%)	4 (16.6%)	0.576	x^2:0.760
>0.2	53 (74.6%)	20 (83.3%)		
Platelet count				
>100000	64 (90.1%)	22 (91.6%)	1.000	x^2:0.490
<100000	7 (9.8%)	2 (8.3%)		
CRP				
<15 mg/dL	48 (67.6%)	20 (83.3%)	0.192	x^2:2.181
>15 mg/dL	23 (32.3%)	4 (16.6%)		
Base deficit				
<10 mEq/L	69 (97.1%)	21 (87.5%)	0.101	x^2:3.373
>10 mEq/L	2 (2.8%)	3 (12.5%)		
Serum lactate				
<2 mMol/L	17 (23.9%)	10 (41.6%)	0.119	x^2:2.769
>2 mMol/L	54 (76.1%)	14 (58.3%)		

CRP: c-reactive protein, x2: Chi-squared test; * $p<0.05$ statistically significant

Table 3. Evaluation of Töllner score parameters

	Clinical Sepsis	Proven Sepsis	*p* value	x^2
Change in skin color				
none	64 (90.1%)	20 (83.3%)		
middle	4 (5.6%)	3 (12.5%)	0.500	x^2:1.386
evident	2 (2.8%)	1 (4.1%)		
Peripheral circulatory disorder				
none	69 (97.1%)	23 (95.8%)	1.000	x^2:0.107
damaged	2 (2.8%)	1 (4.1%)		
Hypotonia				
none	66 (92.9%)	19 (78.2%)		
middle	4 (5.6%)	5 (20.8%)	0.078	x^2:5.093
evident	1 (1.40%)	0		
Bradycardia				
none	71 (100%)	24 (100%)	-	-
Apnea				
none	54 (76%)	10 (41.6%)	0.005*	x^2:9.650
yes	17 (23.9%)	14 (58.3%)		
RDS				
none	35 (49.2%)	13 (54.1%)	0.814	x^2:0.170
yes	36 (50.7%)	11 (45.8%)		
Hepatomegaly				
none	71 (100%)	23 (95.8%)	0.253	x^2:2.990
yes	-	1 (4.1%)		
GIS finding				
none	23 (32.3%)	6 (25%)	0.612	x^2:0.462
yes	48 (67.6%)	18 (75%)		
Leukocyte				
normal	50 (70.4%)	18 (75%)		
leukocytosis	20 (28.1%)	5 (20.8%)	0.586	x^2:1.067
leukopenia	1 (1.40%)	1 (4.1%)		
Shift left				
none	56 (78.8%)	16 (66.6%)	0.273	x^2:1.457
yes	15 (21.1%)	8 (33.3%)		
Thrombocytopenia				
none	60 (84.5%)	21(87.5%)	1.000	x^2:0.128
yes	11 (15.4%)	3 (12.5%)		
Metabolic acidosis				
none	28 (39.4%)	17 (70.8%)		
pH>7.2	42 (59.1%)	5 (20.8%)	0.003*	x^2:11.78
pH<7.2	1 (1.40%)	2 (8.3%)		

RDS: respiratory distress syndrome, GIS: gastrointestinal system, x^2: Chi-squared test; * $p<0.05$ statistically significant

Table 4. Evaluation of Rodwell score parameters

	Clinical sepsis	Proven sepsis	*p* value	x^2
Total leukocyte count				
normal <5000	67 (94.3%)	20 (83.3%)		
>25 000 at birth, 12-24	1 (1.4%)	1 (4.1%)	0.243	x^2:2.831
>30000 per hour, >21000 after 2nd day	3 (4.2%)	3 (12.5%)		
Total neutrophil count				
normal	47 (66.1%)	16 (75%)	1.000	x^2:0.002
neutrophil count increased or decreased	24 (33.8%)	8 (25%)		
Immature Neutrophil count				
normal	17 (23.9%)	4 (16.6%)	0.576	x^2:0.552
increased	54 (76%)	20 (83.3%)		
I/T				
normal	18 (25.3%)	4 (16.6%)	0.576	x^2:0.760
increased	53 (74.6%)	20 (83.3%)		
I/M				
<0.3	18 (25.3%)	4 (16.6%)	0.090	x^2:3.712
>0.3	53 (74.6%)	20 (83.3%)		
Degenerative changes in neutrophils				
normal	68 (95.7%)	19 (79.1%)	0.023*	x^2:6.415
toxic granulation	3 (4.2%)	5 (20.8%)		
Platelet count				
<150 000	13 (18.3%)	3 (12.5%)	0.753	x^2:0.432
>150 000	58 (81.6%)	21 (87.5%)		

I/T: immature/total neutrophil ratio, I/M: immature/maturity neutrophil ratio, x^2: Chi-squared test; * $p<0.05$ statistically significant

Table 5. Sensitivity, specificity, positive and negative predictive values of the EMA, Töllner and Rodwell score

		Clinical sepsis (n)	Proven sepsis (n)	Sensitivity	Specificity	PPV	NPV
EMA scoring	**Positive**	62	17	70.8%	12.7%	21.5%	56.3%
	Negative	9	7				
Töllner scoring	**≥5 (possible sepsis)**	22	10	41.7%	69%	31.3%	77.8%
	<5 (no sepsis)	49	14				
Rodwell scoring	**≥5 (sepsis)**	0	5	29.4%	100%	100%	77.8%
	<3 (no sepsis)	42	12				

Discussion

In this presented study, we found the positive and negative predictive values of the scoring methods in the diagnosis of proven sepsis to be 21.5%, 56.3%, 31.3%, 77.8%, and 100%, 77.8% for EMA, Töllner, and Rodwell, respectively. As can be seen from this study, Rodwell hematological scoring appears to be the most effective scoring method in definitive sepsis detection.

To demonstrate the importance of the Rodwell hematological scoring method in the detection of neonatal sepsis, a study was conducted in India in 2009 in which 12 patients with proven sepsis, 26 patients with clinical sepsis and 12 healthy infants were included. It was found that immature/total neutrophil ratio (I:T) and immature/maturity neutrophil ratio (I:M) were the highest sensitive parameters in defining neonates with sepsis [15]. A study was conducted in India in April-July 2011 to evaluate and emphasise the importance of the Rodwell hematological scoring method in the rapid detection of neonatal sepsis. A total of 110 infants with proven sepsis (n=42), clinical sepsis (n=22) and control group (n=46) were included in the study. Immature polymorphonuclear neutrophil (PMN) count was found to be the highest sensitive (96.87%) and I:M PMN ratio the most specific (97.22%) indicator. It has been shown that hematological sepsis scoring has a much higher sensitivity and specificity in premature than in term newborns [16]. In our study, we did not detect any differences in ratio of I:M and I:T and did not divide the groups into term and premature infants however, we noticed that the change in the direction of toxic granulation in neutrophils in the Rodwell hematological scoring method could be evaluated in favour of proven sepsis.

A multicentre prospective methodological study was conducted in Türkiye between October 2015 and November 2018 to evaluate the adequacy of EMA sepsis criteria in the definition of neonatal sepsis. A total of 245 infants over 34 weeks of age who met the EMA criteria or suspected sepsis were accepted into the trial. In 97 infants, EMA criteria were found to be positive, and 113 patients were diagnosed with proven sepsis. The sensitivity, specificity, and accuracy of the EMA criteria for proven sepsis were 44.2%, 64.4%, and 55.1%, respectively [17]. In our study, we found the positive and negative predictive values of EMA scoring method in the diagnosis of definite sepsis to be 21.5% and 56.3%.

In a study published in Indonesia in 2022, which included forty-seven newborns, the positive predictive value of Töllner score in the diagnosis of neonatal sepsis was 91.7% and the negative predictive value was 87.5% [18]. In contrast to the high positive and negative predictive value according to Indonesia study, we found a positive predictive value of 31.3% and a negative predictive value of 77.8% for the Töllner score in our study.

To our knowledge, there is no any publication included a comparison of all three sepsis scoring methods including EMA, Töllner, and Rodwell used to diagnosis for the neonatal sepsis. Therefore, our study is the first study to comperison all three sepsis scoring methods. The primary limit of this research was the restricted number of patients and the lack of a healthy control group.

In conclusion, our study showed that clinical assessment and routine laboratory tests are limited in the definition of neonatal sepsis and that the Rodwell hematological score is more accurate in detecting proven sepsis than the other two scoring methods. It is urgently needed to find more sensitive and more specific scoring methods or biological parameters for earlier recognition of neonatal sepsis, which is an important cause of morbidity and mortality. For this, additional large-scale randomised controlled trials with long-term results are needed.

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Referrences

1. Satar M, Engin Arısoy A, Çelik İH. Turkish neonatal society guideline on neonatal infections-diagnosis and treatment. Turk Pediatri Ars 2018;53:88-100. https://doi.org/10.5152/TurkPediatriArs.2018.01809
2. Haslam BD. Epidemiology of infection. In: Kliegman RM, Blum NJ, Shah SS, eds. Nelson textbook of pediatrics. 21st ed. Philadelphia: Elsevier 2020:996-1005.

3. Stovall SH, Hoffman MA. Bacteremia, Sepsis, and Septic Shock. In: Kline MW, Blaney SM, Giardino Ap, eds. Rudolph's pediatrics. 23rd ed. McGraw-Hill Education 2018:3295-3304.
4. Embree JE, Alfattoh NI. Infections in the newborn. In: MacDonald MG, Seshia MMK, eds. Avery's neonatology pathophysiology and management of the newborn. 7th ed. Philadelphia: Wolters Kluwer 2016:930-982.
5. Weinberg GA. Infections of Organ Systems. In: Chess PR, ed. Avery's neonatology board review certification and clinical refresher. 1st ed. Philadelphia: Elsevier 2019:273-281.
6. Clinical features, evaluation, and diagnosis of sepsis in term and late preterm infants. Available at: https://www.uptodate.com/contents/clinical-features-evaluation-and-diagnosis-of-sepsis-in-term-and-late-preterm-neonates. Accessed March 04, 2022
7. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet 2017;390:1770-1780. https://doi.org/10.1016/S0140-6736(17)31002-4
8. Satar M, Arısoy AE, Çelik İH. Türk neonatoloji derneği yenidoğan enfeksiyonları tanı ve tedavi rehberi 2023 güncellemesi. Available at: https://neonatology.org.tr/tani-tedavi-protokolleri. Accessed December 9, 2023
9. Edwards MS, Baker CJ. Sepsis in the newborn. In: Gershon AA, Hotez PJ, Katz SL, eds. Krugman's infectious diseases of children. 11th ed. Philadelphia:Mosby 2004:545-561.
10. Gerdes JS. Diagnosis and management of bacterial infections in the neonate. Pediatr Clin North Am 2004;51:939-959. https://doi.org/10.1016/j.pcl.2004.03.009
11. Embree JE, Alfattoh NI. Infections in the newborn. In: MacDonald MG, Seshia MMK, eds. Avery's neonatology pathophysiology and management of the newborn. 7th ed. Philadelphia: Wolters Kluwer 2016:930-982.
12. Saldir M, Tunc T, Cekmez F, et al. Endocan and soluble triggering receptor expressed on myeloid cells-1 as novel markers for neonatal sepsis. Pediatr Neonatol 2015;56:415-421. https://doi.org/10.1016/j.pedneo.2015.03.006
13. Rodwell RL, Leslie AL, Tudehope DI. Early diagnosis of neonatal sepsis using a hematologic scoring system. J Pediatr 1988;112:761-767. https://doi.org/10.1016/s0022-3476(88)80699-1
14. European Medicines Agency (EMA). Report on the Expert Meeting on Neonatal and Paediatric Sepsis. London: 2010. Available at: https://www.ema.europa.eu/en/documents/report/reportexpert-meeting-neonatal-paediatric-sepsis_en.pdf. Accessed April 13, 2020
15. Narasimha A, Harendra Kumar ML. Significance of hematological scoring system (HSS) in early diagnosis of neonatal sepsis. Indian J Hematol Blood Transfus 2011;27:14-17. https://doi.org/10.1007/s12288-010-0050-2
16. Makkar M, Gupta C, Pathak R, Garg S, Mahajan NC. Performance evaluation of hematologic scoring system in early diagnosis of neonatal sepsis. J Clin Neonatol 2013;2:25-29. https://doi.org/10.4103/2249-4847.109243
17. Tuzun F, Ozkan H, Cetinkaya M, et al. Is European Medicines Agency (EMA) sepsis criteria accurate for neonatal sepsis diagnosis or do we need new criteria? PLoS One 2019;14:e0218002. https://doi.org/10.1371/journal.pone.0218002
18. Putri VR, Lubis BM, Lubis IND. Effectiveness of Tollner's score and procalcitonin for diagnosing neonatal sepsis. IJISRT 2022;7:947-950. https://doi.org/10.5281/zenodo.6974466

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Authors' contributions to the article

O.M.A.O. and B.E. constructed the main idea and hypothesis of the study. Discussion section of the article written by M.T. O.M.A.O. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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Artificial intelligence meets medical expertise: evaluating GPT-4's proficiency in generating medical article abstracts

Yapay zeka tıbbi uzmanlıkla buluşuyor: GPT-4'ün tıbbi makale özetleri oluşturmadaki yeterliliğinin değerlendirilmesi

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Abstract

Purpose: The advent of large language models like GPT-4 has opened new possibilities in natural language processing, with potential applications in medical literature. This study assesses GPT-4's ability to generate medical abstracts. It compares their quality to original abstracts written by human authors, aiming to understand the effectiveness of artificial intelligence in replicating complex, professional writing tasks.

Materials and methods: A total of 250 original research articles from five prominent radiology journals published between 2021 and 2023 were selected. The body of these articles, excluding the abstracts, was fed into GPT-4, which then generated new abstracts. Three experienced radiologists blindly and independently evaluated all 500 abstracts using a five-point Likert scale for quality and understandability. Statistical analysis included mean score comparison inter-rater reliability using Fleiss' Kappa and Bland-Altman plots to assess agreement levels between raters.

Results: Analysis revealed no significant difference in the mean scores between original and GPT-4 generated abstracts. The inter-rater reliability yielded kappa values indicating moderate to substantial agreement: 0.497 between Observers 1 and 2, 0.753 between Observers 1 and 3, and 0.645 between Observers 2 and 3. Bland-Altman analysis showed a slight systematic bias but was within acceptable limits of agreement.

Conclusion: The study demonstrates that GPT-4 can generate medical abstracts with a quality comparable to those written by human experts. This suggests a promising role for artificial intelligence in facilitating the abstract writing process and improving its quality.

Key words: Artificial intelligence, ChatGPT, radiology, diagnosis, abstracts.

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Öz

Amaç: GPT-4 gibi büyük dil modellerinin ortaya çıkışı, tıbbi literatürdeki potansiyel uygulamalarla birlikte doğal dil işlemede yeni olanaklar sağlamıştır. Bu çalışma GPT-4'ün tıbbi makale özetleri oluşturma yeteneğini değerlendirmektedir. Çalışma yapay zekanın karmaşık, profesyonel yazma görevlerini kopyalamadaki etkinliğini anlamayı amaçlamakta ve kalitelerini insan yazarlar tarafından yazılan orijinal özetlerle karşılaştırmaktadır.

Gereç ve yöntem: 2021-2023 yılları arasında yayınlanan beş önde gelen radyoloji dergisinden toplam 250 orijinal araştırma makalesi seçildi. Bu makalelerin tamamı, özetler hariç, GPT-4'e yüklendi ve daha sonra GPT-4 tarafından yeni özetler oluşturuldu. Üç deneyimli radyolog, kalite ve anlaşılabilirlik açısından beşli Likert ölçeği kullanarak 500 özetin tamamını kör ve bağımsız bir şekilde değerlendirdi. İstatistiksel analizde, değerlendiriciler arasındaki güvenilirliği ölçmek için Fleiss' Kappa testi ve değerlendiriciler arasındaki uyum düzeylerini değerlendirmek için Bland-Altman grafikleri kullanıldı.

Bulgular: Analiz, orijinal ve GPT-4 ile oluşturulan özetler arasında ortalama puanlar açısından anlamlı bir fark olmadığını ortaya koymuştur. Değerlendiriciler arası güvenilirlik açısından, orta ile önemli düzeyde uyuma işaret eden kappa değerleri bulunmuştur; değerler Gözlemci 1 ve 2 arasında 0.497, Gözlemci 1 ve 3 arasında 0.753 ve Gözlemci 2 ve 3 arasında 0.645 idi. Bland-Altman analizi hafif bir sistematik sapma göstermiş ancak kabul edilebilir uyum sınırları içinde kalmıştır.

Sonuç: Çalışma, GPT-4'ün insan uzmanlar tarafından yazılanlarla karşılaştırılabilir kalitede tıbbi özetler oluşturabildiğini göstermektedir. Yapay zeka kullanımı özet yazma sürecini kolaylaştırma ve kalitesini artırma konusunda önemli katkılar sağlayabilir.

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Anahtar kelimeler: Yapay zeka, ChatGPT, radyoloji, tanı, özet.

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Introduction

Recent advancements in natural language processing have culminated in the creation of sophisticated large language models (LLMs) like GPT-4, which have demonstrated proficiency in producing high-quality text. GPT-4, in particular, has garnered significant interest for its capacity to generate text that is both coherent and richly informative across a diverse array of subjects [1-4]. LLMs offer educational support to medical students by enhancing their understanding with insightful explanations and demonstrating deductive reasoning [5, 6]. Patients also benefit from LLMs as they provide accurate information on various health conditions and offer emotional support, empowering patients and caregivers to navigate health challenges more effectively [7]. Moreover, LLMs can be used as a writing assistant in medical articles [8-10].

Abstracts in medical articles hold paramount importance as they serve as concise summaries that encapsulate the essential elements of a study, such as the objectives, methodology, results, and conclusions [11]. They function as a pivotal reference, enabling readers, including healthcare professionals and researchers, to swiftly discern the relevance and applicability of the study to their respective interests or fields. Abstracts facilitate quick decision-making by providing an accessible overview, which is especially crucial in the fast-paced medical environment where timely information is essential. They also enhance the visibility and accessibility of research by acting as a screening tool, allowing for efficient navigation through databases and journals and helping identify the most pertinent articles without delving into the full texts [11, 12]. Additionally, they play a crucial role in academic gatherings such as conferences, where they serve as a brief synopsis of the research, aiding participants in identifying sessions of interest. Thus, abstracts are instrumental in disseminating knowledge, fostering scientific communication, and facilitating informed decisions in medical practice and research [13]. GPT-4 can generate abstracts of medical articles, and the quality of the generated abstracts depends on various factors, such as the complexity of the content and the quality of the input provided. While GPT-4 is a valuable tool in assisting human authors, the ability and quality of abstract generation in radiology articles of GPT-4 have not been investigated yet. Herein, we aimed to assess the effectiveness of GPT-4 in generating research article abstracts and examine the quality of these abstracts.

Materials and methods

A reviewer (H.P.) collected a total of 250 research articles that were published between 2021 and 2023 in the five radiology journals (*Radiology, European Radiology, American Journal of Roentgenology, Japanese Journal of Radiology and Diagnostic and Interventional Radiology*). Fifty consecutive articles from each journal and sub-specialty (Abdominal, Breast, Cardiothoracic, Neuro, and Musculoskeletal radiology) were collected. The reviewer uploaded the text of the 250 articles to GPT-4, excluding the abstract section, and the abstracts were regenerated by GPT-4. The prompt fed to the GPT-4 were as follows:

1. *For articles in Radiology:* Generate an abstract for this article with a maximum word count of 300, using these subheadings: Background, Purpose, Materials and Methods, Results, and Conclusion.

2. *For articles in European Radiology:* Generate an abstract for this article with a maximum word count of 250, using these subheadings: Objective, Materials and methods, Results, Conclusions.

3. *For articles in American Journal of Roentgenology:* Generate an abstract for this article with a maximum word count of 350, using these subheadings: Background, Objective, Methods, Results, Conclusion, and Clinical Impact.

4. *For articles in Diagnostic and Interventional Radiology:* Generate an abstract for this article with a maximum word count of 400, using these subheadings: Purpose, Methods, Results, and Conclusion.

5. *For articles in Japanese Journal of Radiology:* Generate an abstract for this article with a maximum word count of 300, using these subheadings: Purpose, Materials and Methods, Results, and Conclusion.

Then the reviewer (H.P.) created a document including 250 original abstracts and 250 abstracts generated by GPT-4 in random order.

Three experienced academic radiologists with 8 (F.U.), 21 (E.S.), and 22 (A.B.Y.) years of experience in radiology independently evaluated the 500 abstracts using a five-point Likert scale about the quality and understandability of the abstract. The scoring in this Likert scale ranges from “Very poor” to “Very good”. A score of 1 represents a “Very poor” quality, indicating the lowest level of quality in the evaluation. A score of 2 corresponds to “Poor” quality, showing a level slightly better but still below average. A neutral or average quality is represented by a score of 3, labeled as “Fair”, indicating a middle ground in the quality assessment. A score of 4 corresponds to “Good” quality, indicating an above-average level of quality. Finally, the highest quality level is signified by a score of 5, labeled as “Very good”, representing the optimum level of quality in this scale. The observers conducted their evaluations without knowledge of whether the abstracts were originals or generated by GPT-4, ensuring that they were blind to the origin of each abstract to maintain objectivity in the assessment process.

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

Descriptive statistics including mean, median, standard deviation, and variance were calculated to summarize and describe the main aspects of the dataset and to give a comprehensive overview of the ratings. The Shapiro-Wilk Test was used to ascertain whether the dataset followed a normal distribution, guiding the selection between parametric and non-parametric tests. Independent samples t test (depending on the normality of the data) was conducted to compare the scores of the original abstracts against those generated by GPT-4, helping to identify if there were significant differences in quality perceptions. The Fleiss’ Kappa test, utilized to evaluate inter-rater reliability among the three experienced radiologists, yielded values that indicated the extent of agreement, with kappa (K) ranges typically interpreted as follows: below 0.20 signifying poor agreement, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial, and 0.81-1.00 indicating almost perfect agreement [14]. To assess the concordance between the quality scores assigned to the original and GPT-4 generated abstracts, a Bland-Altman plot analysis was conducted, providing a visual representation of the agreement between observers and highlighting any systematic differences or anomalies. Statistical analyses were executed utilizing MedCalc version 20 (MedCalc Software) and SPSS version 23 (IBM), with a p value of less than 0.05 designated as the threshold for statistical significance.

Results

Three observers, in a blind and independent assessment, evaluated a total of 500 abstracts from 250 research articles, with 250 being the original versions and the remaining 250 re-generated using GPT-4. The analysis revealed no significant differences in the mean scores between the original and the GPT-4 generated abstracts across all observers, as detailed in Table 1. Furthermore, when comparing scores based on the journal and subspecialty, no significant differences were found. The p-values, according to the journal, were 0.384, 0.368, and 0.446 for Observers 1, 2, and 3, respectively. Regarding subspecialty, the P-values were 0.929, 0.610, and 0.871 for Observers 1, 2, and 3, correspondingly.

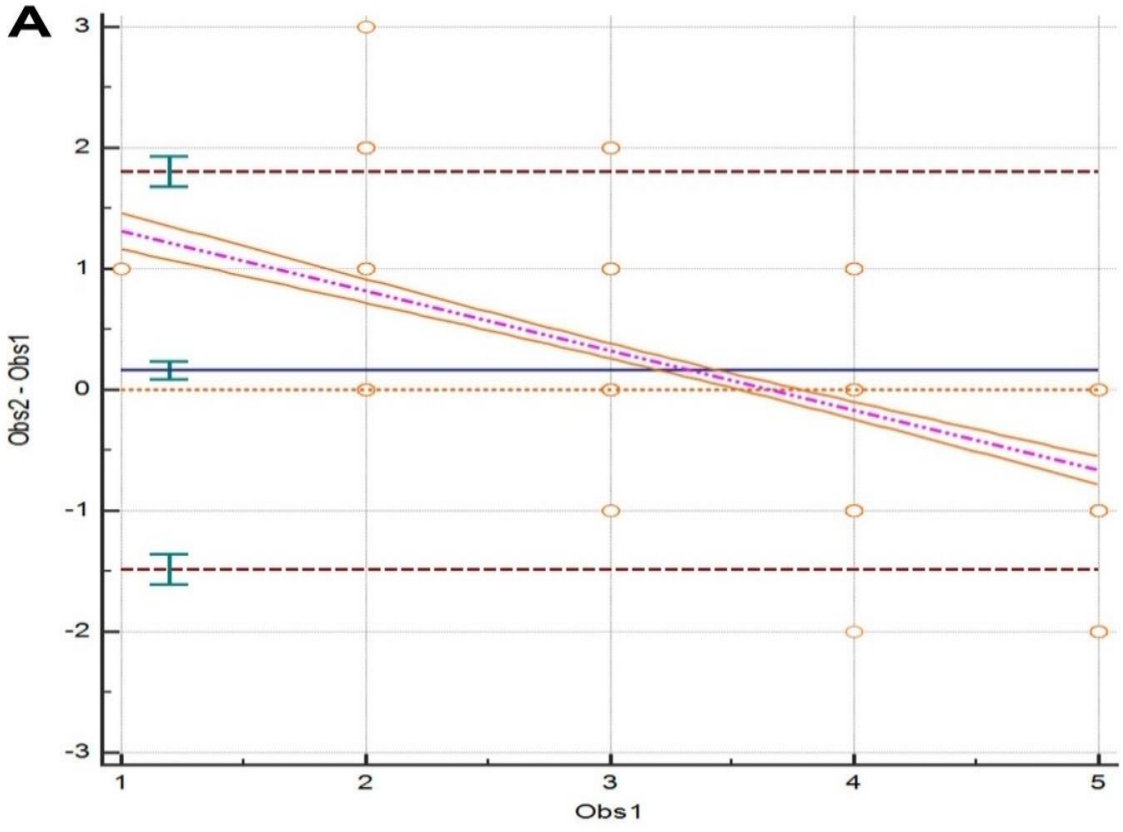
The assessments between Observer 1 and Observer 2 exhibited moderate agreement (κ=0.497) with a 95% confidence interval (CI) ranging from 0.442 to 0.552. Between Observer 1 and Observer 3, there was a substantial agreement (κ=0.753) with a 95% CI of 0.708 to 0.798. Similarly, a substantial agreement was noted between Observer 2 and Observer 3 (κ=0.645), with the 95% CI extending from 0.592 to 0.699.

Table 1. Comparative evaluation of abstract quality scores

Reference		Number of abstracts	Score (Mean±SD)	*p* value	t value
Observer 1	***Original***	250	3.32±0.98	0.989	-0.11
	GPT-4	250	3.33±1.03		
Observer 2	***Original***	250	3.36±0.85	0.107	-2.76
	GPT-4	250	3.57±0.85		
Observer 3	***Original***	250	3.4±0.91	0.867	-0.12
	GPT-4	250	3.41±1		

The p-values and t-values presented in the table represent the results of independent samples t-tests conducted to compare the means between the Original and GPT-4 groups

The Bland-Altman analysis was conducted to assess the agreement between the evaluations made by Observers 1, 2, and 3 (Figure 1). Systematic differences indicated by the mean differences were 0.1617 (95% CI: 0.08804 to 0.2353) for Observer 2 and 0.07984 (95% CI: 0.02648 to 0.1332) for Observer 3, respectively. These values suggest a small bias between Observer 1 and the other two observers. Limits of agreement, which define the range in which 95% of differences between observations by Observer 1 and the other observers lie, were calculated. For Observer 2, the limits of agreement ranged from -1.4826 (95% CI: -1.6086 to -1.3567) to 1.8060 (95% CI: 1.6801 to 1.9319), while for Observer 3, the range was -1.1118 (95% CI: -1.2030 to -1.0205) to 1.2714 (95% CI: 1.1802 to 1.3627).



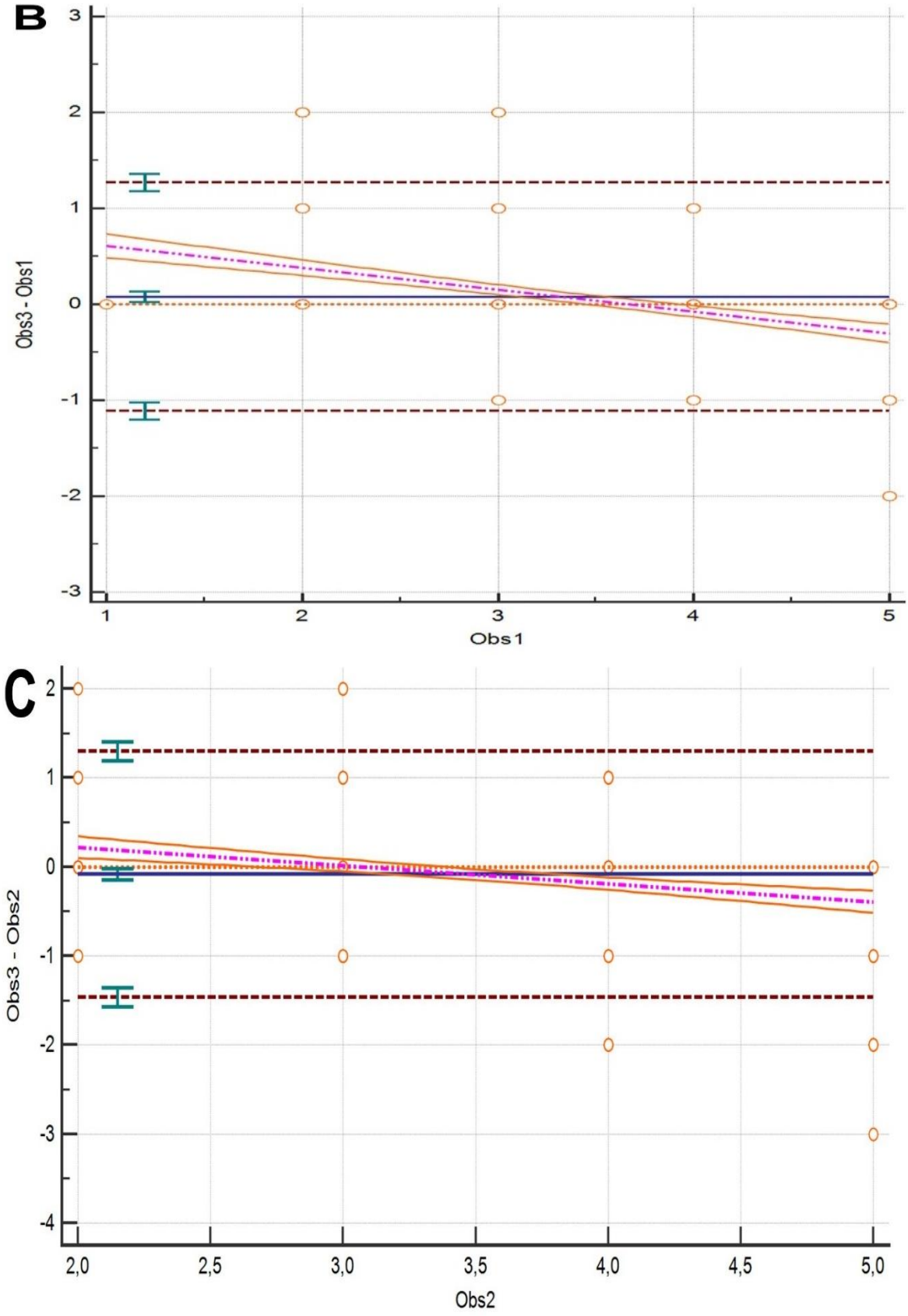


Figure 1. Bland-Altman plots for inter-observer agreement. A) Observer 1 and 2, B) Observer 1 and 3, C) Observer 2 and 3

Discussion

This study demonstrates that GPT-4 can create abstracts comparable in quality to their original counterparts, a finding reinforced by the negligible differences in mean scores assigned by three observers to both the original and the GPT-4-generated abstracts. It reveals that GPT-4 can adeptly undertake tasks typically reserved for skilled professionals, such as creating research article abstracts. Incorporating GPT-4 into the abstract writing process could positively influence the quality.

Recently, Jeblick et al. [15] and Li et al. [16] investigated the effectiveness of ChatGPT in simplifying radiology reports for better understanding and showed that ChatGPT regenerated reports in a way that was easily understood. In these studies, the authors showed that although the data were generally considered accurate and safe when evaluated by radiologists in terms of accuracy, completeness and safety, there were some errors and omissions that could mislead patients [15, 16]. While the present study found high-quality output indistinguishable from human-generated abstracts, the previous studies highlight a need for caution due to inaccuracies that could lead to patient harm. These results emphasize the necessity for further development and human oversight of LLMs within clinical practice.

There are only a few studies in the literature that evaluated the capabilities of LLMs, including GPT-4. In the present study on GPT-4's performance in abstract generation, GPT-4 produced work on par with human experts regarding quality, suggesting a high level of linguistic competence and understanding. Similarly, Ueda et al. [17] found GPT-4 capable of formulating differential and final diagnoses, highlighting its potential utility as a diagnostic aid. This is in line with the present study, where GPT-4 demonstrated the ability to synthesize and communicate complex medical information accurately. Fink et al. [18] also observed GPT-4's superior performance over ChatGPT in extracting and labeling data from oncologic CT reports. This suggests that GPT-4 has advanced text-processing abilities that can be precisely tuned to the subtleties of medical information extraction. Sun et al. [19] further extend the conversation by examining how GPT-4's generated impressions compare with human radiologists' work. While radiologists were favored for their detailed and accurate reports, non-radiologist physicians found GPT-4's outputs more straightforward and less likely to contribute to clinical missteps [19]. Comparing these studies reveals both the promise and the nuanced performance of GPT-4. While GPT-4 can replicate professional-level writing and data interpretation, it may not yet match the deep clinical understanding that comes with human expertise, as noted in Sun et al. [19] study. These findings collectively highlight the potential of GPT-4 as a supportive tool rather than a replacement for human professionals in medical settings.

This study has several limitations. Firstly, the assessment of abstract quality is inherently subjective, and despite the use of experienced radiologists as evaluators, their judgments may not fully represent the broader academic or clinical community. Secondly, the choice of articles and the prompts provided to GPT-4 could also influence the quality of the generated abstracts, potentially limiting the applicability of the findings to scenarios where such careful selection and prompting are not feasible. Lastly, the study only evaluated the abstracts based on quality and understandability without assessing other critical aspects such as accuracy of content, relevance, and the inclusion of key findings. Despite these limitations, this study boasts several notable strengths, including its methodologically sound approach, characterized by a rigorous blind and independent review process conducted by experienced radiologists using a well-established evaluation scale. Additionally, the study is pioneering in its exploration of AI's role in medical writing, aligning with contemporary technological trends and providing relevant insights for the application of LLMs in medical research and education.

In conclusion, the results reveal that LLMs can produce abstracts of a quality that is statistically indistinguishable from those written by human authors, as judged by experienced radiologists. The moderate to substantial agreement between observers and the slight systematic differences suggest that while GPT-4's capabilities are promising, there is a discernible variance in human evaluations of abstract quality. The negligible biases and

proportional differences in scores emphasize the potential of LLMs for assisting with medical writing tasks.

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References

1. Elkassem AA, Smith AD. Potential Use Cases for ChatGPT in Radiology. AJR 2023;221:373-376. https://doi.org/10.2214/AJR.23.29198
2. Shen Y, Heacock L, Elias J, et al. ChatGPT and other large language models are double-edged swords. Radiology 2023;307:e230163. https://doi.org/10.1148/radiol.230163
3. Ufuk F. The role and limitations of large language models such as ChatGPT in clinical settings and medical journalism. Radiology 2023;307:e230276. https://doi.org/10.1148/radiol.230276
4. Sevgi UT, Erol G, Doğruel Y, Sönmez OF, Tubbs RS, Güngor A. The role of an open artificial intelligence platform in modern neurosurgical education: a preliminary study. Neurosurg Rev 2023;46:86(e1-11). https://doi.org/10.1007/s10143-023-01998-2
5. Bhayana R, Krishna S, Bleakney RR. Performance of ChatGPT on a radiology board-style examination: insights into current strengths and limitations. Radiology 2023;307:e230582. https://doi.org/10.1148/radiol.230582
6. Akinci D'Antonoli T, Stanzione A, Bluethgen C, et al. Large language models in radiology: fundamentals, applications, ethical considerations, risks, and future directions. Diagn Interv Radiol 2023;30:80-90. https://doi.org/10.4274/dir.2023.232417
7. Amin K, Khosla P, Doshi R, Chheang S, Forman HP. Artificial intelligence to improve patient understanding of radiology reports. Yale J Biol Med 2023;96:407-417. https://doi.org/10.59249/NKOY5498
8. Ghim JL, Ahn S. Transforming clinical trials: the emerging roles of large language models. Transl Clin Pharmacol 2023;31:131-138. https://doi.org/10.12793/tcp.2023.31.e16
9. Tippareddy C, Jiang S, Bera K, Ramaiya N. Radiology reading room for the future: harnessing the power of large language models like ChatGPT. Curr Probl Diagn Radiol 2023;1-6. https://doi.org/10.1067/j.cpradiol.2023.08.018
10. Currie GM. Academic integrity and artificial intelligence: is ChatGPT hype, hero or heresy?. Semin Nucl Med 2023;53:719-730. https://doi.org/10.1053/j.semnuclmed.2023.04.008
11. Gastel B, Day RA. How to write and publish a scientific paper. 9th ed. Greenwood, USA: Bloomsbury Publishing, 2022.
12. Atzen SL, Bluemke DA. How to write the perfect abstract for radiology. Radiology 2022;305:498-501. https://doi.org/10.1148/radiol.229012
13. Woolston C. Words matter: jargon alienates readers. Nature 2020;579:309. https://doi.org/10.1038/d41586-020-00580-w
14. Gisev N, Bell JS, Chen TF. Interrater agreement and interrater reliability: key concepts, approaches, and applications. Res Social Adm Pharm 2013;9:330-338. https://doi.org/10.1016/j.sapharm.2012.04.004
15. Jeblick K, Schachtner B, Dexl J, et al. ChatGPT makes medicine easy to swallow: an exploratory case study on simplified radiology reports. Eur Radiol 2023:(e1-9). https://doi.org/10.1007/s00330-023-10213-1
16. Li H, Moon JT, Iyer D, et al. Decoding radiology reports: Potential application of OpenAI ChatGPT to enhance patient understanding of diagnostic reports. Clin Imaging 2023;101:137-141. https://doi.org/10.1016/j.clinimag.2023.06.008
17. Ueda D, Mitsuyama Y, Takita H, et al. ChatGPT's Diagnostic performance from patient history and imaging findings on the diagnosis please quizzes. Radiology 2023;308:e231040. https://doi.org/10.1148/radiol.231040
18. Fink MA, Bischoff A, Fink CA, et al. Potential of ChatGPT and GPT-4 for data mining of free-text CT reports on lung cancer. Radiology 2023;308:e231362. https://doi.org/10.1148/radiol.231362
19. Sun Z, Ong H, Kennedy P, et al. Evaluating GPT4 on impressions generation in radiology reports. Radiology 2023;307:e231259(e1-4). https://doi.org/10.1148/radiol.231259

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Authors' contributions to the article

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

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An effective treatment for progressive keratoconus with two-year outcomes: accelerated epithelium-on corneal cross-linking

Progresif keratokonus için etkili bir tedavinin iki yıllık sonuçları: hızlandırılmış epi-on korneal çapraz bağlama

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Abstract

Purpose: Corneal collagen cross-linking (CXL) is a surgical technique for progressive keratoconus. There are several technical modifications with varying clinical outcomes. This study aimed to evaluate the long-term outcomes of the accelerated epithelium-on CXL.

Materials and methods: A retrospective study was performed on progressive keratoconus patients treated via the accelerated epithelium-on CXL who completed the 24th-month follow-up. We included 111 eyes of 77 patients. Clinical variables, including visual acuity, aberrometry, topographic measurements, and refractive outcomes, were evaluated at the postoperative 12th and 24th months.

Results: There was a significant improvement in postoperative visual acuity in 50.4% of patients (p<0.001). Baiocchi Calossi Versaci total index and lower low-order aberration values determined at the 12th-month and 24th-month follow-up visits were significantly higher than the baseline values (p=0.044 and p=0.033). The depths of the anterior chapter and its aqueous part, the anterior chamber volume, front apical keratometry, and the mean power of the pupil were significantly lower in the 12th and 24th-month evaluations than the baseline values (p<0.05). For the 12th-month evaluation, significant increments in the central corneal thickness (p=0.043) and back apical keratometry (p=0.034) were detected than the baseline values. The horizontal anterior chamber diameter (p=0.005) and the keratoconus area (p=0.001) were significantly different in the 24th-month evaluation than in the preoperative period.

Conclusion: The study findings indicated that accelerated epithelium-on CXL stabilized disease progression and significantly improved visual acuity. Therefore, accelerated epithelium-on CXL stands out as one of the better options among the modified CXL techniques to treat progressive keratoconus surgically.

Keywords: Aberrometry, corneal topography, epithelium-on corneal cross-linking, keratoconus, visual acuity.

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Öz

Amaç: Korneal kollajen çapraz bağlama (CXL), progresif keratokonus için cerrahi bir tekniktir. Farklı klinik sonuçlara sahip çeşitli teknik modifikasyonları vardır. Bu çalışmada, hızlandırılmış epitelyum-on CXL'nin uzun vadeli sonuçlarını değerlendirmeyi amaçladık.

Gereç ve yöntem: Hızlandırılmış epitelyum-on CXL ile tedavi edilen ve 24. ay takibini tamamlayan progresif keratokonus hastaları üzerinde retrospektif bir çalışma yaptık. 77 hastanın 111 gözünü dahil ettik. Görme keskinliği, aberrometri, topografik ölçümler ve kırma kusurları gibi klinik değişkenleri cerrahi sonrası 12. ve 24. aylarda değerlendirdik.

Bulgular: Hastaların %50,4'ünde ameliyat sonrası görme keskinliğinde anlamlı artış görüldü (p<0,001). 12. ay ve 24. ay takiplerinde belirlenen Baiocchi Calossi Versaci total indeksi ve alt düşük dereceli aberasyon değerleri, başlangıç değerlerinden anlamlı derecede yüksekti (p=0,044 ve p=0,033). Ön kamara derinliği, ön kamara hacmi, ön apikal keratometri ve gözbebeğinin ortalama gücü, 12. ve 24. ay değerlendirmelerinde başlangıç değerlerine göre anlamlı derecede düşüktü (p<0,05). 12. ay değerlendirmesinde santral kornea kalınlığında (p=0,043) ve arka apikal keratometride (p=0,034) başlangıç değerlerine göre anlamlı artışlar tespit edildi. Horizontal ön kamara çapı (p=0,005) ve keratokonus alanı (p=0,001) 24. ay değerlendirmesinde ameliyat öncesine göre anlamlı olarak farklıydı.

Sonuç: Çalışma bulguları, hızlandırılmış epitelyum-on CXL'in görme keskinliğini önemli ölçüde artırdığını ve hastalığın progresyonunu durdurduğunu gösterdi. Böylece, hızlandırılmış epitelyum-on CXL'in, progresif keratokonusun cerrahi tedavisinde modifiye CXL yöntemleri arasında iyi bir seçenek olduğu ortaya konuldu.

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Anahtar kelimeler: Aberometri, görme keskinliği, Epi-on korneal çapraz bağlama, keratokonus, korneal topografi.

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Introduction

Keratoconus is a bilateral progressive, noninflammatory degenerative ectasia of the cornea characterized by the conical protrusion, progressive thinning, and changes in biomechanical properties [1-3]. Although spectacles can be used in the early stages of the disease, hard corneal lenses are often needed to achieve good visual acuity due to increased myopia and irregular astigmatism in the later stages [1]. On the other hand, some patients with progressive keratoconus might require corneal collagen cross-linking (CXL) [2]. Several studies have addressed the long-term effectiveness of various technically modified versions of CXL in overcoming keratectasia in patients with keratoconus [1].

Among the technically modified versions of CXL, the epithelium-on (epi-on CXL, transepithelial) and the epithelium-off (epi-off CXL) stand out as the most common CXL techniques [1, 4, 5]. The difference between the two methods is whether the corneal epithelium is removed in the final state. Among these two techniques, the epi-off CXL technique has been associated with a higher risk of postoperative morbidity in some studies [6] but not in others [4, 7]. It has been accepted that the epi-on CXL technique is as effective as the epi-off CXL and, at the same time, a less invasive alternative to the epi-off CXL technique [8, 9]. The standard or accelerated CXL technique has been developed, taking into consideration that the irradiation time is part of the operation [2, 5, 10, 11]. It is widely believed that accelerated protocols are associated with a shorter duration of surgery and lower complication rates [12]. However, the data on which CXL method is the most effective in terms of postoperative visual results remain controversial.

There are a number of studies on the postoperative changes in tomographic, densitometric, visual, and aberrometry parameters, including maximum keratometry, central corneal thickness, visual acuity, spherical equivalent, and corneal biomechanical properties in the eyes with keratoconus after CXL [2]. However, the number of studies evaluating the long-term outcomes of accelerated epi-on CXL is limited.

In this context, this study was carried out to investigate the long-term outcomes of the accelerated epi-on CXL on patients with keratoconus.

Material and methods

Study design

The material of this retrospective study consisted of the eyes of all consecutive patients with progressive keratoconus who were treated with the accelerated epithelium-on CXL technique and followed up for 24 months at the eye diseases department of our hospital between January 2013 and July 2016. Patients with biomicroscopic, retinoscopic, and tomographic findings suggestive of keratoconus, Krumeich keratoconus stages of 1 to 3, absence of deep scar formation in the central cornea, and the thinnest pachymetric measurements of ≥400 μm were deemed to have keratoconus [13]. Patients with a central corneal thickness thinner than 400 μm at the thinnest point, pregnancy or lactation, systemic autoimmune or collagen tissue disorders, neurodermatitis, sequelae of hydrops fetalis, recurrent corneal erosion, dystrophia of the cornea, lacrimal gland dysfunction, history of herpes virus keratitis, deep corneal scarring visible on the slit-lamp examination, and untreated eyelid disorders were excluded from the study. In the end, 111 eyes of 77 patients were included in the study sample.

The study was approved by the Recep Tayyip Erdogan University Non-Interventional Clinical Research Ethics. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. The written informed consent could not be taken from the patients due to the retrospective design of the study and the unanimity of data.

Data collection process

A standardized diagnostic, therapeutic, and follow-up protocol was applied to all patients. All data were prospectively recorded into a predesigned worksheet.

All patients underwent a complete ocular assessment with slit-lamp biomicroscopy and ocular fundus examinations prior to CXL. The visual acuity measurements were performed based on a logarithm of the minimum angle of resolution (LogMAR) Snellen chart [14]. The Bailey-Lovie (logMAR) chart was used to measure visual acuity from a testing distance of six meters under standardized lighting conditions.

The anterior segment examination was performed using biomicroscopy. Corneal topography was performed using Placido disc topography (Sirius 1.2, CSO, Florence, Italy, combined with Scheimpflug camera) under standardized lighting conditions. The average of three consecutive measurements was recorded.

Corneal densitometry was obtained using Sirius 1.2, CSO, Florence, Italy. The grayscale units of backscattered light were used to express densitometry that was calculated automatically by the respective software. A scale ranging from 0 (completely transparent) to 100 (completely opaque) was used in all measurements.

All measurements were performed without pupil dilatation during the daytime between 1.00 PM and 5.00 PM [14].

Surgical procedure

Patients who have been using contact lenses were asked to stop to do so at least one month before the clinical examination and the CXL procedure. The same experienced surgeon performed all procedures.

Under sterile conditions, the eye was anesthetized with 0.5% proparacaine hydrochloride (Alcaine, Alcon Laboratories, Puurs, Belgium). A speculum was placed between the eyelids. The corneal epithelium was left intact. Riboflavin solution was applied to the corneal surface for ten minutes at one-minute intervals without removing the cornea. The first four of these ten applications were performed using the Paracel solution (ParaCel™, Avedro Inc., Massachusetts, USA) containing 0.25% riboflavin, hydroxypropyl methylcellulose, and benzalkonium chloride, and the subsequent six applications were performed using the VibeX Xtra solution (VibeX Xtra™, Avedro Inc., Massachusetts, USA) containing 0.22% riboflavin and NaCl.

Ultraviolet A was applied with the Avedro KXL system (Avedro Inc., Waltham, MS, USA). The parameters for accelerated CXL are an ultraviolet power of 45mW/cm², a UV irradiation time of 2 minutes, pulsed illumination of 40 seconds (45mW/cm^2, 1 sec on/1 sec off), and a surface dose of 7.20 J/cm² [15]. Subsequently, the cornea and conjunctiva were washed with Ringer's lactate, and the eye was closed.

Follow-up procedure

Patients were recommended to close their eyes with EYE PATCH for one day and then use sodium hyaluronate drops (Eyestil 0.15% eye drops, four times a day) for one week.

All patients were examined postoperatively at the 1st, 12th, and 24th months.

Outcomes of the study

Based on the patients' medical records and the data entered into the predesigned worksheets, the following data were determined as the primary outcomes of the study:

i. visual acuity data,

ii. aberrometry measurement data (low-order, high-order, longitudinal, total, longitudinal spherical aberrations, Baiocchi Calossi Versaci front, back, and total indexes, Root Mean Square Front and Back Areas (RMSf A and RMSb A),

iii. topographic measurement data (anterior chamber aqueous and total depths, anterior chamber volume, horizontal anterior chamber diameter, iridocorneal angle, central corneal thickness, corneal volume, thickness of the thinnest part of the cornea, curvature asymmetry-front value, curvature asymmetry-back value, apical keratometry front and back values, keratoconus vertex front and back values, keratoconus area, keratoconus volume), and

iv. refractive outcomes (cylindrical dioptric power and cylindrical value axis).

Statistical analysis

SPSS 20.0 (Statistical Product and Service Solutions for Windows, Version 20.0, IBM Corp., Armonk, NY, U.S., 2011) software package was used to analyze the collected data statistically. Descriptive statistics obtained from the collected data were expressed as numbers (n), and percentage (%) values in the case of categorical variables and as mean and standard deviation values in the case of normally distributed numerical variables. Kolmogorov-Smirnov test and graphics were used to determine whether the numerical variables conformed to the normal distribution. The paired t-test were used to compare dependent groups featuring normally-distributed. Probability (*p*) values of <0.05 were deemed to indicate statistical significance.

Results

Visual acuity

The preoperative and postoperative 24th-month visual acuity of 111 eyes were 0.33±0.33 and 0.26±0.30 logMAR, respectively. Accordingly, there was a significant difference in the visual acuity between the preoperative and postoperative measurements (p<0.001). There was a significant improvement in 56 (50.4%) eyes, whereas there was no significant change in 32 (28.9%) eyes. On the other hand, there was a significant decrease in visual acuity in 23 (20.7%) eyes.

Aberrometric measurements

The results of the preoperative and postoperative aberrometry measurements are given in Table 1. There were no significant differences between the baseline, 12th, and 24th-month measurements except for Baiocchi Calossi Versaci total index and low-order aberration (p<0.05). The Baiocchi Calossi Versaci total index values measured at the 12th-month follow-up visit were significantly higher than the baseline values (p=0.044). Additionally, the low-order aberration values measured at the 24th-month follow-up visit were significantly lower than the baseline values (p=0.033).

Table 1. Comparison of preoperative and postoperative 24th-month aberrometric measurements

	Preoperative	Postoperative 12th month	*t*	*p*	Postoperative 24th month	*t*	*p*
Low-order aberration	2.16±1.22	2.26±1.23	-1.89	0.060[a]	2.28±1.16	-2.04	0.043[a]
High-order aberration	2.22±0.93	2.22±0.92	-0.65	0.948[a]	2.21±0.95	0.46	0.644[a]
Total aberration	3.21±1.29	3.53±2.90	-1.24	0.216[a]	3.52±2.85	-1.19	0.235[a]
Longitudinal spheric aberration	-0.59±2.65	-0.72±2.34	1.05	0.296[a]	-0.53±2.42	-0.21	0.834[a]
Baiocchi Calossi Versaci front index	3.33±1.43	3.42±1.50	-1.92	0.057[a]	3.39±1.46	-1.26	0.210[a]
Baiocchi Calossi Versaci back index	3.50±1.30	3.58±1.36	-1.818	0.720[a]	3.58±1.37	-1.89	0.061[a]
Baiocchi Calossi Versaci total index	3.38±1.31	3.49±1.39	-2.70	0.008[a]	3.45±1.37	-1.91	0.059[a]
Root mean square front area (mm^2)	0.221±0.083	0.318±0.948	-1.054	0.294[a]	0.368±1.43	-1.04	0.300[a]
Root mean square back area (mm^2)	0.482±0.144	0.491±0.151	-1.725	0.087[a]	0.489±0.151	-1.83	0.069[a]

All values were given as mean ± standard deviation, [a]: Paired sample t test

Corneal topography

The baseline depths of the anterior chapter and its aqueous part, the anterior chamber volume, front apical keratometry, and the mean power of the pupil were significantly higher than the respective values measured at the 12th- and 24th-month follow-up visits ($p<0.05$) (Table 2). The central corneal thickness and back apical keratometry values determined at the 12th-month follow-up visit were significantly higher than the baseline values ($p=0.043$ and $p=0.034$, respectively). In addition, the horizontal anterior chamber diameter and the keratoconus area values determined at the 24th-month follow-up visit were significantly different than the baseline values ($p=0.005$ and $p=0.001$, respectively). There was no significant difference between the baseline and postoperative measurements in other corneal topographic measurements ($p>0.05$).

Table 2. Preoperative and postoperative 24th-month corneal topographic measurements

	Preoperative	Postoperative 12th month	*t*	*p*	Postoperative 24th month	*t*	*p*
Anterior chamber aqueous depth (µm)	3.366±0.282	3.352±0.280	2.490	0.014[a]	3.350±0.289	3.061	0.003[a]
Anterior chamber depth (µm)	3.835±0.278	3.817±0.275	3.720	<0.001[a]	3.815±0.285	4.47	<0.001[a]
Anterior chamber volume (mm^3)	184.3±33.876	181.75±32.812	3.788	<0.001[a]	181.48±34.117	3.567	<0.001[a]
Horizontal anterior chamber diameter (µm)	12.34±0.57	12.51±2.52	-.896	0.372[a]	12.077±1.33	2.061	0.042[a]
Iridocorneal angle (°)	46.3±7.3	45.5±5.6	1.408	0.162[a]	45.64±5.64	1.431	0.155[a]
Central corneal thickness (µm)	463±38	466±39	-2.247	0.027[a]	464.7±38.9	-0.484	0.629[a]
Corneal volume (mm^3)	54.87±3.45	55.10±3.32	-1.553	0.27[a]	59.71±3.30	-1.046	0.298[a]
Corneal thinnest point	444.8±55.83	444.8±56.43	.012	0.990[a]	448.2±37.5	-0.827	0.410[a]
Curvature asymmetry-front	6.53±2.99	6.71±3.06	-1.493	0.138[a]	6.69±3.09	-1.351	0.180[a]
Curvature asymmetry-back	1.76±0.63	1.81±0.68	-1.861	0.065[a]	1.79±0.68	-1.382	0.170[a]
Apical keratometry front	56±4.27	55.64±3.99	2.842	0.005[a]	55.53±4.05	2.488	0.014[a]
Apical keratometry back	-9.70±1.07	-9.13±1.08	-9.709	<0.001[a]	-9.12±1.06	-1.812	0.73[a]
Mean power of the pupil	46.18±2.19	46.02±2.01	2.090	0.039[a]	45.99±1.94	2.625	0.01[a]
Keratoconus vertex front	32.12±12.15	32.64±12.337	-1.476	0.143[a]	32.60±12.49	-0.991	0.324[a]
Keratoconus vertex back	75.29±24.92	76.40±24.81	-1.720	0.088[a]	76.62±25.626	-1.720	0.088[a]
Keratoconus area (mm^2)	5.82±1.49	6.24±5.86	-0.777	0.439[a]	5.94±1.44	-2.253	0.026[a]
Keratoconus volume (mm^3)	0.105±0.0407	0.1125±0.0977	-0.863	0.390[a]	0.1072±0.0452	-0.883	0.379[a]

All values were given as mean ± standard deviation, [a]: Paired sample t test

Dioptric power measurements

Although the cylindrical dioptric power values increased in the postoperative 12th and 24th-month evaluations compared to baseline values, the differences were insignificant (p=0.113 and p=0.053, respectively) (Table 3).

There were no intra- or postoperative complications or adverse reactions in the study group during and after the CXL procedure.

Table 3. Preoperative and postoperative cylindrical dioptric power measurements.

	Preoperative	Postoperative 12th month	*t*	*p*	Postoperative 24th month	*t*	*p*
Cylindrical dioptric power	-3.43±1.34	-2.42±1.42	-0.94	0.347[a]	-2.46±1.29	-0.90	0.367[a]

All values were given as mean ± standard deviation, [a]: Paired sample t test

Discussion

The findings of this study suggest that the accelerated epithelium-on corneal collagen cross-linking (CXL) technique may have the potential to prevent the progression of keratoconus. This is based on the observed significant improvement in visual acuity at the 24th-month evaluation, as well as the absence of significant changes in the topographic parameters over the same time period.

The epi-off CXL is generally considered a superior treatment modality for halting progressive keratoconus [16, 17]. On the other hand, the transepithelial CXL approaches have also been proposed in the context of reduced postoperative complication risks [9, 15, 18-22]. Several authors recommended that a thin cornea, poor corneal endothelial function, and slowly progressing keratoconus might indicate the epi-on CXL [17]. Faster visual recovery and decreased postoperative pain were cited among the other advantages of the epi-on CXL. Nevertheless, compared to epi-off CXL, a higher degree of pain was reported in patients who underwent epi-on CXL [15, 23]. In comparison, no acute or chronic complications were observed in this study that could be attributed directly related to the surgical technique used. Then again, the time required for visual recovery and postoperative pain were not evaluated within the scope of this study. Additionally, the epi-on CXL's efficacy in terms of not leading to any morbidity and stopping the progression of keratoconus could not be evaluated since there was no control group. Yet, the findings have been deemed sufficient to conclude that the epi-on CXL is a viable surgical alternative to epi-off CXL in stopping the progression of keratoconus.

The original CXL procedure, as described by Wollensak et al. [24] in 2003, used UVA light at 3 mW/cm^2 intensity for 30 minutes leading to a total radiant exposure of 5.4 J/cm^2 [15]. Accordingly, since then, a total UVA energy of 5.4 J/cm^2 has been deemed sufficient and non-toxic for the epi-off CXL [23, 25]. However, the upper limit of total energy dose for epi-on CXL has been questioned on multiple occasions. In this context, several authors suggested a total UVA energy of 7.2 J/cm^2 for the UVA energy needed in epi-on CXL [23]. The relatively long duration of surgery, which can be as long as one hour, has been deemed the main disadvantage of epi-on CXL [15]. Several authors tried to develop new approaches using high-intensity UVA irradiation to shorten the duration of epi-on CXL surgery. Although all these approaches utilized different high-intensity protocols with various intensities and employed different cutoff values of duration of surgery [11, 12, 26-28], the outcomes were favorable.[15] Among these approaches, the approach developed by Kır et al. [15], who proposed using UVA irradiation at 45 mW/cm^2 for 2 minutes and 40 seconds, was utilized in this study. Consequently, significant differences were recorded in the measurements related to the anterior chamber, central corneal thickness, the corneal thinnest point, and front and back apical keratometry performed throughout the follow-up period. Although these measurements did not provide sufficient data indicative of the cessation of disease progression by the epi-on CXL technique, they provided sufficient data suggestive of the stabilization effect of the epi-

on CXL technique on the pathological process in the cornea in these patients.

The surgical outcomes of the epi-on CXL technique in patients with keratoconus remain controversial. Based on the corrected distance visual acuity (CDVA) measurements and topographic parameters, some studies reported improvement, whereas others reported worsening or stabilization with the use of the epi-on CXL. The assessment of the efficacy of CXL procedures was commonly based on visual acuity data. Nevertheless, it was speculated that the keratometry scores might be more sensitive in assessing progressive keratoconus compared to visual acuity data [12]. In addition, disturbances in the visual acuity caused by the transparency of the refractive media and retinal and optic nerve conditions might act as late effects. In sum, the cylindrical dioptric power measurements did not indicate a significant improvement.

Topographic parameters have also been used to quantify the changes following CXL procedures in patients with keratoconus. The mean corneal thickness at the thinnest point might indicate the corneal stroma's degree of lamellar remodeling [15]. There are contradictory findings on postoperative corneal thickness following CXL procedures in the literature. In comparison, no change was detected in the corneal thickness between the baseline measurements and those performed at the 12th and 24th-month follow-up visits. The mean and maximum keratometry values are among the other topographic parameters used to quantify the changes following CXL procedures in patients with keratoconus [16]. Significant reductions were observed in both mean and maximum keratometry values measured at 12 and 18 months after the epi-on and epi-off CXL procedures [11, 23, 25]. These reductions were attributed to decreased corneal curvature and distortion [25]. Similarly, in this study, a significant decrease was observed in the apical keratometry values. However, prospective large-scale studies are needed to establish an optimum topographic parameter indicating the efficacy of the CXL procedures.

Changes in the central cornea and corneal thickness at the thinnest point are among the other parameters used to assess the efficacy of CXL procedures. The thinning of the cornea is generally considered an early event, followed by an increase in the thickness of the cornea. Nevertheless, no significant thinning in the cornea was reported after the epi-on CXL procedure [8]. In contrast, significant reductions in the thickness of the central cornea and corneal thickness at the thinnest point were reported in other studies featuring follow-up periods of up to 24 months. A significant increase was reported in the central corneal thickness at the 12th-month measurement, and a significant difference between the baselines and 24th-month measurements [11, 12]. Given the conflicting results, several authors concluded that corneal pachymetry might not be considered a reliable assessment tool for predicting the progression of the disease after CXL [25].

High-order aberration was another parameter indicating disturbed visual function and contrast sensitivity. Post-CXL changes in the high-order aberrations might be used to evaluate keratoconus's progression. Previous studies reported increases in this type of refraction error in the early phases, followed by decreases up to the baseline values in the following period [2]. Other studies revealed a close relationship between the baseline values and the postoperative changes [29]. In contrast, improvements were detected in high-order aberrations for up to one year after the accelerated epi-off CXL [30]. However, no significant changes were detected in this study in the low-order or high-order aberrations after CXL. Methodological differences between the studies might be implicated in the differences in the quality of postoperative visual functions.

Several technical modifications related to the type of epi-on approach, riboflavin solutions, and adjunctive agents were reported in the literature [15]. Some authors recommended using benzalkonium chloride, ethylenediaminetetraacetic acid-Tris, iontophoresis, sodium chloride, and proxymetacaine hydrochloride 0.5% to increase the transepithelial absorption of riboflavin [15, 23]. For this purpose, a chemical solution containing hydroxypropyl methylcellulose and benzalkonium chloride was used in this study, as in other studies [15]. Oxygen supplementation was another maneuver used to increase the riboflavin permeability of the corneal epithelium [3, 19]. The variable outcomes of

the epi-on CXL procedure might be attributed to such differences between the methodologies employed in different studies.

Limitations of the study

Apart from its strengths, such as its relatively larger sample size and extended follow-up duration, there were also some limitations to this study, the primary ones being its retrospective design and lack of a control group. Secondly, the fact that different CXL methods were not addressed in this study might be deemed another limitation as a comparison between these methods could not be made.

In conclusion, the study findings indicated that accelerated epithelium-on CXL stabilized disease progression and significantly improved visual acuity. Therefore, accelerated epithelium-on CXL stands out as one of the best options among the modified CXL techniques to treat progressive keratoconus surgically. However, prospective controlled studies are needed to corroborate the findings of this study based on patients with better clinical outcomes.

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose.

References

1. Knutsson KA, Genovese PN, Paganoni G, et al. Evaluation of a post-operative therapy protocol after epithelium-off corneal cross-linking in patients affected by keratoconus. J Clin Med 2022;11:7093. https://doi.org/10.3390/jcm11237093
2. Mohebbi M, Samavat B, Mohammadi A. One-year non-comparative observational study to evaluate corneal tomographic, densitometric, and aberrometric features following accelerated corneal cross-linking in progressive keratoconus. Int Ophthalmol 2023;43:1721-1735. https://doi.org/10.1007/s10792-022-02572-3
3. Borchert GA, Watson SL, Kandel H. Oxygen in corneal collagen crosslinking to treat keratoconus: A systematic review and meta-analysis. Asia Pac J Ophthalmol 2022;11:453-459. https://doi.org/10.1097/APO.0000000000000555
4. Ang MJ, Darbinian JA, Hoskins EN, Holsclaw DS, Sudesh S, Chandra NS. The safety profile of fda-approved epithelium-off corneal cross-linking in a us community-based healthcare system. Clin Ophthalmol 2022;16:1117-1125. https://doi.org/10.2147/OPTH.S359224
5. Wajnsztajn D, Shmueli O, Zur K, Frucht Pery J, Solomon A. Predicting factors for the efficacy of cross-linking for keratoconus. PLoS One 2022;17:e0263528. https://doi.org/10.1371/journal.pone.0263528
6. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009;35:1358-1362. https://doi.org/10.1016/j.jcrs.2009.03.035
7. Ferdi AC, Kandel H, Nguyen V, et al. Five-year corneal cross-linking outcomes: a save sight keratoconus registry study. Clin Exp Ophthalmol 2023;51:9-18. https://doi.org/10.1111/ceo.14177
8. Vaidya NS, Daneshmand A, Epstein RJ, et al. Pachymetric assessment after EpiSmart® epithelium-on cross-linking for keratoconus and post-surgical ectasia. Clin Ophthalmol 2022;16:1829-1835. https://doi.org/10.2147/OPTH.S359710
9. D'Oria F, Palazón A, Alio JL. Corneal collagen cross-linking epithelium-on vs. epithelium-off: a systematic review and meta-analysis. Eye Vis 2021;8:34. https://doi.org/10.1186/s40662-021-00256-0
10. Li Y, Lu Y, Du K, et al. Comparison of efficacy and safety between standard, accelerated epithelium-off and transepithelial corneal collagen crosslinking in pediatric keratoconus: a meta-analysis. Front Med 2022;9:787167. https://doi.org/10.3389/fmed.2022.787167
11. Stock RA, Brustollin G, Mergener RA, Bonamigo EL. Efficacy of standard and accelerated (10 minutes) corneal crosslinking in keratoconus stabilization. Clin Ophthalmol 2020;14:1735-1740. https://doi.org/10.2147/OPTH.S258205
12. Kandel H, Nguyen V, Ferdi AC, et al. Comparative efficacy and safety of standard versus accelerated corneal crosslinking for keratoconus: 1-year outcomes from the save sight keratoconus registry study. Cornea. 2021;40:1581-1589. https://doi.org/10.1097/ICO.000000000000274
13. Atalay E, Najjar RP, Tun TA, Özalp O, Bilgeç MD, Yıldırım N. Corneal elevation changes after forced eyelid closure in healthy participants and in patients with keratoconus. Clin Exp Optom 2019;102:590-595. https://doi.org/10.1111/cxo.12891
14. Ziaei M, Gokul A, Vellara H, Patel D, McGhee CNJ. Prospective two year study of changes in corneal density following transepithelial pulsed, epithelium-off continuous and epithelium-off pulsed, corneal crosslinking for keratoconus. Cont Lens Anterior Eye 2020;43:458-464. https://doi.org/10.1016/j.clae.2020.03.004
15. Kır MB, Türkyılmaz K, Öner V. Transepithelial high-intensity cross-linking for the treatment of progressive keratoconus: 2-year outcomes. Curr Eye Res 2017;42:28-31. https://doi.org/10.3109/02713683.2016.1148742

16. Arance Gil Á, Villa Collar C, Pérez Sanchez B, Carracedo G, Gutiérrez Ortega R. Epithelium-off vs. transepithelial corneal collagen crosslinking in progressive keratoconus: 3 years of follow-up. J Optom 2021;14:189-198. https://doi.org/10.1016/j.optom.2020.07.005
17. Ouyang BW, Ding H, Wang H, et al. Comparison of corneal biological parameters between transepithelial and epithelium-off corneal cross-linking in keratoconus. Int J Ophthalmol 2021;14:998-1005. https://doi.org/10.18240/ijo.2021.07.06
18. Nawaz S, Gupta S, Gogia V, Sasikala NK, Panda A. Trans-epithelial versus conventional corneal collagen crosslinking: a randomized trial in keratoconus. Oman J Ophthalmol 2015;8:9-13. https://doi.org/10.4103/0974-620X.149855
19. Kamiya K, Kanayama S, Takahashi M, Shoji N. Visual and topographic improvement with epithelium-on, oxygen-supplemented, customized corneal cross-linking for progressive keratoconus. J Clin Med 2020;9:3222. https://doi.org/10.3390/jcm9103222
20. Nath S, Shen C, Koziarz A, et al. Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia: a systematic review and meta-analysis. Ophthalmology 2021;128:1150-1160. https://doi.org/10.1016/j.ophtha.2020.12.023
21. Ng SM, Ren M, Lindsley KB, Hawkins BS, Kuo IC. Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus. Cochrane Database Syst Rev 2021;3:CD013512. https://doi.org/10.1002/14651858.CD013512.pub2
22. Ng SM, Hawkins BS, Kuo IC. Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus: Findings from a cochrane systematic review. Am J Ophthalmol 2021;229:274-287. https://doi.org/10.1016/j.ajo.2021.05.009
23. Yuksel E, Cubuk MO, Yalcin NG. Accelerated epithelium-on or accelerated epithelium-off corneal collagen cross-linking: contralateral comparison study. Taiwan J Ophthalmol 2020;10:37-44. https://doi.org/10.4103/tjo.tjo_11_19
24. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:620-627. https://doi.org/10.1016/s0002-9394(02)02220-1
25. Farhat R, Ghannam MK, Azar G, et al. Safety, efficacy, and predictive factors of conventional epithelium-off corneal crosslinking in the treatment of progressive keratoconus. J Ophthalmol 2020;2020:7487186. https://doi.org/10.1155/2020/7487186
26. Latif K, Iqbal MS. Visual and topographical outcomes following accelerated trans-epithelial corneal crosslinking in progressive keratoconus. J Coll Physicians Surg Pak 2017;27:552-555.
27. Aldairi W, AlQahtani R, Alzaid S, Mousa A, Khandekar R, Al Swailem SA. Accelerated versus conventional corneal collagen crosslinking: short-term clinical outcomes in stabilizing keratoconus. Saudi J Ophthalmol 2022;36:47-52. https://doi.org/10.4103/sjopt.sjopt_49_22
28. Salman A, Ghabra M, Darwish TR, Kailani O, Ibrahim H, Ghabra H. Corneal higher-order aberration changes after accelerated cross-linking for keratoconus. BMC Ophthalmol 2022;22:225. https://doi.org/10.1186/s12886-022-02457-0
29. Naderan M, Jahanrad A. Higher-order aberration 4 years after corneal collagen cross-linking. Indian J Ophthalmol 2017;65:808-812. https://doi.org/10.4103/ijo.IJO_21_17
30. De Bernardo M, Capasso L, Tortori A, Lanza M, Caliendo L, Rosa N. Trans epithelial corneal collagen crosslinking for progressive keratoconus: 6 months follow up. Cont Lens Anterior Eye 2014;37:438-441. https://doi.org/10.1016/j.clae.2014.07.007

Ethics committee approval: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the local ethics committee that Recep Tayyip Erdogan University Non-Interventional Clinical Research Ethics Committee (approval date 12.12.2018, and number: 2018/186).

Authors' contributions to the article

M.K. formulated the primary concept and hypothesis for the research. M.K. conceptualized the theory and organized the materials and methods section. M.K. conducted the data analysis for the results section. M.K authored the discussion section of the article. M.O, H.F. and F.U. reviewed, revised, and provided approval. Additionally, all authors engaged in comprehensive discussions regarding the study and endorsed the final version.

Research Article

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Relationship between duration of undiagnosed illness, clinical features and cognitive impairment in bipolar disorder

Bipolar bozuklukta tanısız geçen hastalık süresinin klinik özelikler ve bilişsel bozulmayla ilişkisi

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Abstract

Purpose: It is believed that a delay in the diagnosis of bipolar disorder may adversely affect the clinical course and outcome. This study aimed to investigate the relationship between diagnostic delay and clinical variables, as well as neurocognitive and social cognitive disorders.

Materials and methods: Eighty-four patients with bipolar disorder in remission were included in the study. Participants were evaluated using a neuropsychological battery that assessed verbal memory and learning, visual memory and learning, verbal fluency, attention, processing speed, executive functions, working memory, and social cognition.

Results: The duration of undiagnosed illness was longer in patients with bipolar II disorder, those without psychotic features, those with at least one suicide attempt, those whose first episode was depressive, and those currently on antidepressants. A significant positive correlation was found between the duration of undiagnosed illness and scores on the Controlled Oral Word Association Test, total number of episodes, hypomanic episodes, depressive episodes, and their respective durations. Conversely, a significant negative correlation was found between the duration of undiagnosed illness and both the number and duration of manic episodes.

Conclusion: We found that a delay in diagnosis and treatment was associated with more recurrences in bipolar disorder, an increased number of depressive episodes, and at least one lifetime suicide attempt. However, the association between extended periods of untreated illness and poor clinical and functional outcomes did not align with cognitive impairment.

Keywords: Bipolar disorder, delayed diagnosis, neurocognitive disorders, social intelligence.

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Öz

Amaç: Bipolar bozuklukta tanıda gecikmenin klinik seyir ve sonlanım üzerine olumsuz etkileri olabileceği düşünülmektedir. Çalışmamızda tanıda gecikme ile klinik değişkenler ve nöro/sosyal bilişsel bozukluklar arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve yöntem: Bipolar bozukluk tanılı remisyonda 84 hasta çalışmaya alındı. Katılımcılar sözel bellek/öğrenme, görsel bellek/öğrenme, sözel akıcılık, dikkat, işlem hızı, yürütücü işlevler, çalışma belleği ve sosyal biliş alanlarında değerlendirme imkanı veren nöropsikolojik bir batarya ile değerlendirildi.

Bulgular: Tanısız geçen sürenin bipolar- II bozukluk tanılı hastalarda, yaşam boyu psikotik özellik göstermemiş hastalarda, yaşam boyu en az bir defa intihar girişiminde bulunmuş hastalarda, ilk epizodu depresif epizod olan hastalarda ve halihazırda tedavilerinde antidepresan bulunan hastalarda daha uzun olduğu bulundu. Tanısız geçen hastalık süresi ile Kontrollü Kelime Akıcılık Testi, toplam epizod sayısı, hipomanik epizod sayısı, depresif epizod sayısı, toplam epizod süresi, hipomanik epizod süresi ve depresif epizod süresi arasında anlamlı düzeyde pozitif yönde ilişki; manik epizod sayısı ve manik epizod süresi arasında ise anlamlı düzeyde negatif yönde ilişki saptanmıştır.

Sonuç: Tanıda ve tedavide gecikmenin bipolar bozuklukta daha sık nüksle, daha sık depresif epizodla ve yaşamı boyunca en az bir defa intihar girişiminde bulunmuş olmakla ilişkili olduğunu bulduk. Tanısız geçen sürenin uzunluğu ile klinik seyir ve işlevsellik açısından kötü sonlanım arasındaki ilişkiye bilişsel bozulma eşlik etmemektedir.

Anahtar kelimeler: Bipolar bozukluk, gecikmeli tanı, nörobilişsel bozukluklar, sosyal zeka.

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Introduction

Bipolar disorder (BD) is a recurrent, chronic illness that typically begins at a young age and significantly impairs an individual's social and occupational functioning [1]. The World Health Organization's World Mental Health Surveys have identified BD as the second leading cause of lost workdays [2]. Despite causing significant functional impairment, there is a considerable delay between the onset of BD and the start of appropriate treatment. Most patients diagnosed with BD receive their diagnosis approximately 6-10 years after first presenting with symptoms to a clinician [3].

One of the most significant factors contributing to the delay in diagnosis is that the first episode in BD is often a depressive episode, during which it is difficult to clearly distinguish between unipolar and bipolar disorders based on diagnostic criteria [4, 5]. Other reasons for the delayed diagnosis during psychiatric assessment include the inability to differentiate mood episodes with psychotic features from psychotic disorders and the misdiagnosis due to mild mood symptoms being mistaken for personality traits [6, 7].

The delay in diagnosis and treatment is not only a result of certain adverse clinical features but also believed to have negative impacts on functional and clinical outcomes [8, 9]. A delay in diagnosis and treatment has been associated with a diagnosis of bipolar II disorder, depressive onset, and a higher number of depressive episodes [10, 11]. Buoli et al. [10] found a relationship between the duration of untreated illness (DUI) and factors such as hospitalization in the past year, suicide attempts in the past year, absence of lifetime psychotic symptoms, and fewer manic episodes. Di Salvo et al. [11] identified early onset, long illness duration, a higher number of mood episodes, lifetime suicide attempts, and current medical comorbidity as clinical features associated with delay in treatment. Delay in diagnosis has also been linked to poor response to lithium [12] and cognitive impairment [13].

Although there are studies in the literature that associate the prolonged duration of untreated BD with adverse clinical outcomes, there is a limited number of studies investigating its relationship with cognitive impairment. Our study aims to explore the relationship between the delay in diagnosing BD and clinical variables as well as neuro/social cognitive impairments. We hypothesized that as the duration of undiagnosed illness lengthens, treatment would become more difficult, resulting in more frequent and prolonged episodes, which in turn would lead to a greater severity of cognitive impairment.

Materials and methods

The ethics committee approved the study, and all participants signed an informed consent form. The study sample included 84 patients diagnosed with BD in remission, who were consecutively chosen from volunteers meeting the inclusion and exclusion criteria. These patients were being followed at the psychiatry outpatient clinic of Manisa Celal Bayar University Hafsa Sultan Hospital between December 2020 and October 2022.

The inclusion criteria for the patients were as follows: meeting the diagnostic criteria for bipolar I disorder or bipolar II disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5); being between the ages of 18-65, literacy in Turkish, and being in remission for the past 2 months (i.e., a Young Mania Rating Scale [YMRS] score <6 and a Hamilton Depression Rating Scale [HDRS] score<8).

The exclusion criteria were as follows: (i) having a prior diagnosis of schizophrenia spectrum, other psychotic disorders, or substance-induced disorders according to DSM-5 criteria; (ii) having intellectual disability or neurological diseases affecting the central nervous system; (iii) having been diagnosed with a substance or alcohol use disorder within the last 6 months; (iv) having hearing or vision impairments that interfere with the administration of cognitive tests and performance during testing; (v) having a history of electroconvulsive therapy or transcranial magnetic stimulation treatment within the last three months; and (vi) having been treated with benzodiazepines or psychostimulants within the last 6 months.

The Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5/CV) was used to verify all current and past psychiatric diagnoses of the patients [14, 15]. The Vocabulary Subtest of the Wechsler Adult

Intelligence Scale-Revised (WAIS-R) was administered to assess premorbid intelligence [16]. The HDRS, Hamilton Anxiety Rating Scale (HARS), and YMRS were used to assess the current mood state [17-19].

The sociodemographic and clinical data form collected personal characteristics such as age, gender, marital status, education level, occupation, and place of residence, in addition to clinical features such as age of illness onset; polarity of the first episode; DUI ; total number, duration, and characteristics of episodes; number and duration of hospitalizations; subtype of BD; presence of episodes with psychotic features; history of suicide attempts; current treatment; duration of remission; history of comorbid psychiatric disorders; family history of psychiatric illness; and smoking status.

A neuropsychological battery, individually administered to all participants, provided an opportunity to assess verbal memory/learning, visual memory/learning, verbal fluency, attention, processing speed, executive functions, working memory, and social cognition.

The Rey Auditory Verbal Learning Test (RAVLT) was used to assess verbal learning and memory. Scores for the RAVLT included total scores for trials 1-5, delayed recall (Trial 7), and correct recall [20]. Visual learning and memory were assessed using immediate and delayed recall scores from the Visual Reproduction Subtest of the Wechsler Memory Scale [20]. To evaluate verbal fluency, the Controlled Oral Word Association Test (COWAT) was administered, utilizing the letters K, A, and S [20]. Processing speed and executive functions were assessed using the Stroop Test-Çapa Form (ST) [21] and the Trail Making Test (TMT) [22]. Working memory was evaluated with the Auditory Consonant Trigrams Test (ACT) [20, 23]. The Reading the Mind in the Eyes Test (RMET) [24] and the Hinting Test [25] were used to assess the visual and verbal aspects of the Theory of Mind (ToM) in the domain of social cognition.

Statistical analysis

Descriptive analyses of the total sample were performed. The Shapiro-Wilk test was used to assess the normality of the data. Due to the non-normal distribution of the DUI, the Mann-Whitney U test was used to compare groups defined by categorical variables such as gender, occupation, marital status, place of residence, smoking status, bipolar subtype, presence of psychotic features, history of suicide attempts, polarity of the first episode, presence of BD or major depressive disorder in first- or second-degree relatives, and the use of lithium, valproate, lamotrigine, and antidepressants.

Spearman correlation analysis was used to examine the relationship between cognitive performance and non-categorical numerical sociodemographic and clinical characteristics with the DUI. For analyzing the number of episodes, episode durations, illness duration, DUI, TMT, and ST results, which did not follow a normal distribution, log10 normalization was applied to transform them into a normal distribution [26]. Partial correlation analysis was conducted for the relationship between the number of episodes and hospitalizations, by controlling the illness duration. A p-value below 0.05 was deemed statistically significant for all analyses. Statistical analyses were performed using IBM SPSS Statistics 20.0.

Results

The total sample included 84 bipolar patients in remission: 41 women (48.8%) and 43 men (51.2%). The mean age of illness onset in the sample was 22.7±7.6 years, with a median DUI of 11.0 months and an interquartile range (IQR) of 2.0-33.0 months. Descriptive analyses, correlation analysis results, and DUI values by category for sociodemographic and clinical characteristics are shown in Tables 1 and 2.

The DUI showed significant differences based on BD subtype ($Z=2.56$, $p=0.010$), the presence or absence of lifetime psychotic features ($Z=2.08$, $p=0.038$), the presence or absence of lifetime suicide attempts ($Z=2.46$, $p=0.014$), the polarity of the first episode ($Z=5.5$, $p<0.001$), and whether antidepressants were included in the current treatment ($Z=2.33$, $p=0.020$).

The DUI was found to be longer in patients diagnosed with bipolar II disorder, in those who had not exhibited lifetime psychotic features, in those who had made at least one lifetime suicide attempt, in those with a depressive onset, and in those currently receiving antidepressant treatment.

Table 1. Socio-demographic variables of the total sample and values of DUI/Spearman correlation according to these variables

Variables		Total Sample (n=84)	DUI, months, median (IQR)	Z	*p*
Gender, n (%)	Female	41 (48.8)	12.0 (1.75-48.0)	0.01	0.989
	Male	43 (51.2)	10.0 (2.0-23.0)		
Occupation, n (%)	Unemployed	30 (35.7)	10.5 (2.0-30.0)	0.07	0.948
	Other	54 (64.3)	11.5 (2.0-39.0)		
Marital Status, n (%)	Married	39 (46.4)	11.0 (2.0-48.0)	0.52	0.605
	Not married	45 (53.6)	10.0 (1.75-20.5)		
Place of residence, n (%)	Urban	77 (91.7)	11.0 (2.0-48.0)	0.45	0.650
	Rural	7 (8.3)	9.0 (2.0-22.0)		
Smoking status, n (%)	Present	51 (60.7)	12.0 (2.0-24.0)	0.40	0.693
	Absent	33 (39.3)	8.0 (1.5-54.0)		
Variables		**Total Sample (n=84)**	***Spearman rho, p***		***p***
Age, years, M±SD		40.5±12.1	0.07		0.525
Education, years, M±SD		11.2±4.1	0.14		0.189
Vocabulary Raw Score, M±SD		40.9±11.8	0.11		0.341

Note DUI=duration of untreated illness, M=mean, SD=standard deviation, n=number of sample, IQR=Inter Quantile Range

Table 2. Clinical variables of the total sample and values of DUI /Spearman correlation according to these variables

Variables		Total Sample (n=84)	DUI, months, median (IQR)	Z	*p*
Bipolar Subtype, n (%)	Bipolar I Disorder	66 (78.6)	8.0 (1.50-22.25)	2.56	**0.010**
	Bipolar II Disorder	18 (21.4)	16.0 (12.0-63.0)		
Psychotic Features, n (%)	Present	34 (40.5)	4.25 (1.0-14.0)	2.08	**0.038**
	Absent	50 (59.5)	12.0 (3.5-51.0)		
Suicide Attempt, n (%)	Present	23 (27.4)	12.0 (8.0-72.0)	2.46	**0.014**
	Absent	61 (72.6)	8.0 (1.25-22.5)		
First Episode Polarity, n (%)	Mania	34 (40.5)	1.5 (0.5-6.25)	5.5	**<0.001**
	Depression	49 (58.3)	14.0 (9.5-60.0)		
	Undetermined	1 (1.2)	-		
Bipolar Disorder in 1st or 2nd Degree Relatives, n (%)	Present	26 (31)	11.0 (2.0-60.0)	0.58	0.564
	Absent	58 (69)	11.0 (2.0-23.25)		
Major Depressive Disorder in 1st or 2nd Degree Relatives, n (%)	Present	36 (42.9)	11.5 (2.0-60.0)	0.77	0.444
	Absent	48 (57.1)	10.5 (1.63-23.5)		
Lithium (Current Treatment)	Present	40 (47.6)	10.5 (2.0-23.75)	0.14	0.889
	Absent	44 (52.4)	11.5 (1.63-45.0)		
Valproate (Current Treatment)	Present	42 (50.0)	8.5 (1.38-22.5)	1.42	0.157
	Absent	42 (50.0)	12.0 (3.5-60.0)		
Lamotrigine (Current Treatment)	Present	13 (15.5)	12.0 (5.0-78.0)	1.24	0.215
	Absent	71 (84.5)	11.0 (2.0-24.0)		
Antidepressants (Current Treatment)	Present	18 (21.4)	14.5 (11.25-120.0)	2.33	**0.020**
	Absent	66 (78.6)	8.0 (1.88-23.25)		

Table 2. Clinical variables of the total sample and values of DUI /Spearman correlation according to these variables (continued)

Variables	Total Sample (n=84)	*Spearman rho, p*	*p*
Age at Onset, years, M±SD	22.7±7.6	0.03	0.761
Duration of Illness, years, median (IQR)	16.6 (7.33-27.4)	0.07	0.537
Total Number of Episodes, median (IQR)	6.0 (4.0-9.0)	0.26	**0.017**
Manic Episodes, median (IQR)	2.0 (1.0-3.0)	-0.37	**0.001**
Hypomanic Episodes, median (IQR)	1.0 (0.0-2.0)	0.27	**0.014**
Depressive Episodes, median (IQR)	2.5 (1.0-5.0)	0.51	**<0.001**
Mixed Episodes, median (IQR)	0.0 (0.0-0.0)	-0.08	0.469
Total Episode Duration, months, median (IQR)	12.0 (7.12-16.75)	0.27	**0.014**
Mania Duration, months, median (IQR)	2.0 (0.81-6.0)	-0.38	**<0.001**
Hypomania Duration, months, median (IQR)	1.0 (0.0-2.0)	0.25	**0.022**
Depression Duration, months, median (IQR)	6.0 (3.0-11.0)	0.49	**<0.001**
Mixed Episode Duration, months, median (IQR)	0.0 (0.0-0.0)	-0.08	0.450
Total Number of Hospitalizations, median (IQR)	1.0 (1.0-3.0)	-0.21	0.052

Note DUI=duration of untreated illness, M=mean, SD=standard deviation, n=number of sample, IQR= Inter Quantile Range

Gender, employment status, marital status, residence in rural or urban areas, smoking habits, family history of mood disorders, and the use of lithium, valproate, or lamotrigine in current treatment did not exhibit significant differences in the DUI.

A significant positive correlation was found between the DUI and the total number of episodes (p=0.26, p=0.017), number of hypomanic episodes (p=0.27, p=0.014), number of depressive episodes (p=0.51, p<0.001), total episode duration (p=0.27, p=0.014), duration of hypomanic episodes (p=0.25, p=0.022), and duration of depressive episodes (p=0.49, p<0.001). In contrast, a significant negative correlation was found between the DUI and the number of manic episodes (p=-0.37, p=0.001) and the duration of manic episodes (p=-0.38, p<0.001).

The correlation between cognitive tests and the DUI is shown in Table 3. No significant correlation was found between the DUI and variables such as age, education level, vocabulary test score, age of illness onset, illness duration, total number of hospitalizations, cognitive tests, or the number and duration of mixed episodes.

Table 4 presents the correlation between the DUI and various variables, after controlling for illness duration and normalizing variables such as the number of episodes, episode durations, illness duration, and the DUI.

When controlled for illness duration, the DUI showed a significant positive correlation with the COWAT (r=0.22, p=0.045), total number of episodes (r=0.27, p=0.013), number of hypomanic episodes (r=0.27, p=0.012), number of depressive episodes (r=0.48, p<0.001), total episode duration (r=0.28, p=0.011), duration of hypomanic episodes (r=0.25, p=0.024), and duration of depressive episodes (r=0.45, p<0.001). A significant negative correlation was found between the DUI and the number of manic episodes (r=-0.37, p=0.001) and the duration of manic episodes (r=-0.40, p<0.001).

Table 3. The correlation between cognitive tests and the DUI

Neuro/Social Cognitive Tests, M ± SD	Total Sample (n=84)	Spearman rho, *p*	*p*
Trail Making Test A Duration, s	46.2±25.7	0.09	0.382
Trail Making Test B Duration, s	154.9±102.6	0.00	0.997
Trail Making Test B-A Duration, s	108.8±83.9	-0.04	0.708
Stroop C Duration, s	99.7±36.5	-0.01	0.944
Stroop Interference, s	66.4±30.6	0.03	0.811
Rey 1-5 Recall Number	44.6±8.3	0.10	0.352
Rey 7 Recall Number	8.3±2.6	0.01	0.924
Rey Correct Recall	11.7±2.5	-0.11	0.306
Auditory Consonant Trigrams	47.6±8.5	0.11	0.335
COWAT	30.9±13.4	0.13	0.237
WMS-R VR immediate recall	29.1±8.2	0.07	0.544
WMS-R VR delayed recall	23.7±9.9	0.05	0.672
RMET	20.5±5.2	0.13	0.257
Hinting Test	15.3±3.3	0.20	0.068

Note DUI=duration of untreated illness, COWAT= Controlled Oral Word Association Test, RMET= Reading the Mind in the Eyes Test WMS-R VR= Wechsler Memory Scale—visual reproduction subtest, s= second, M=mean, SD=standard deviation, n=number of sample

Table 4. Correlation between dui and various variables, controlling for illness duration and normalized variables

Variables/Cognitive Tests	Partial Correlation (r)	*p*
Trail Making Test A Duration, s	0.04	0.683
Trail Making Test B Duration, s	-0.04	0.683
Trail Making Test B-A Duration, s	-0.08	0.455
Stroop C Duration, s	-0.06	0.595
Stroop Interference, s	-0.07	0.519
Rey 1-5 Recall Number	0.12	0.289
Rey 7 Recall Number	0.01	0.934
Rey Correct Recall	-0.09	0.382
Auditory Consonant Trigrams	0.19	0.083
COWAT	0.22	**0.045**
WMS-R VR immediate recall	0.08	0.432
WMS-R VR delayed recall	0.08	0.497
RMET	0.19	0.078
Hinting Test	0.21	0.057
Age of illness onset	0.01	0.933
Total number of episodes	0.27	**0.013**
Number of manic episodes	-0.37	**0.001**
Number of hypomanic episodes	0.27	**0.012**
Number of depressive episodes	0.48	**<0.001**
Number of mixed episodes	-0.15	0.177

Table 4. Correlation between dui and various variables, controlling for illness duration and normalized variables (continued)

Variables/Cognitive Tests	Partial Correlation (r)	*p*
Total Duration of Episodes	0.28	**0.011**
Mania Duration	-0.40	**<0.001**
Hypomania Duration	0.25	**0.024**
Depression Duration	0.45	**<0.001**
Mixed Episode Duration	-0.15	0.177
Total Number of Hospitalizations	-0.21	0.056

Note DUI=duration of untreated illness, COWAT= Controlled Oral Word Association Test, RMET= Reading the Mind in the Eyes Test WMS-R VR= Wechsler Memory Scale—visual reproduction subtest, n=number of sample

Discussion

In our study, we investigated the relationship between delays in diagnosing BD, clinical variables, and neuro/social cognitive impairments. Although the duration of undiagnosed illness was not found to be associated with cognitive impairment, it was observed that as the duration of undiagnosed illness increased, the total number and duration of episodes, particularly depressive episodes, also increased. These findings are consistent with the literature suggesting that patients who do not receive appropriate treatment in the early phase of the illness, experience more frequent recurrences over time [9, 11].

In line with the literature, our study found that delays in the diagnosis and appropriate treatment of BD were associated with not having experienced a psychotic episode, exhibiting a clinical presentation of bipolar II disorder, having the first mood episode as a depressive episode, being on antidepressant treatment, and having attempted suicide at least once in a lifetime [10, 11]. Consistent with the association between bipolar II disorder and DUI, our findings showed that the number of hypomanic episodes increased with longer undiagnosed periods, while the number of manic episodes decreased [10, 11].

When controlling for the duration of the illness, it was found that as the undiagnosed duration increased, the COWAT scores also increased. This finding contradicts our initial assumption and may not appropriately be considered as a positive effect of the delay in diagnosis. Instead, it could be due to certain clinical characteristics that lead to a longer undiagnosed period and are associated with a better cognitive profile [27, 28].

In our study, the mean duration of the undiagnosed illness was found to be 35.6±7.9 months, with a median of 11 months and an IQR of 2.0–33.0 months. This duration is significantly shorter than those reported in previous studies [3]. This difference may be attributed to the study sample, which consisted of patients who were being followed up at a university hospital located in a city center that includes a specialized mood disorders clinic.

To interpret the findings of this study, it is important to recognize its limitations. Firstly, the study was conducted at a single center, a specialized facility with a specific focus on BD, which limits the generalizability of the sample to the broader population. Additionally, the sample size was relatively small, and the cross-sectional design of the study allowed for the identification of associations only, rather than causal inferences. Another consequence of this being a cross-sectional study based on medical records and surveys is the potential for recall bias, particularly regarding the accuracy of information obtained about the early stages of the illness. Other than this, most longitudinal studies indicate that cognitive decline with age in people with bipolar disorder is similar to that of healthy individuals [29-31]. Cognitive functions diminish with age, regardless of contributing factors. Our study included participants aged 18 to 65, which may account for the variability in the severity of cognitive impairment observed. Moreover, participants were using various medications, which may have contributed to heterogeneity

in the assessment of cognitive functions. These patients were also fully recovered being followed up and treated in a specialized mood disorders clinic. This might have reduced the use of multiple medications or those that could impair cognitive functions during the disease while ensuring patients receive the best treatment through psychotherapeutic interventions when needed [32]. Therefore, symptom control and neurocognitive improvement were achieved in most patients. Finally, the study did not include certain sociodemographic characteristics, such as current income level, duration of employment, occupational changes, and changes in marital status, which could reflect functionality.

In conclusion, our study found that delays in diagnosis and treatment were associated with more frequent recurrences, a higher incidence of depressive episodes, and a history of at least one suicide attempt among patients diagnosed with BD. Our study has revealed that the association between extended periods of untreated illness and poor clinical and functional outcomes did not align with cognitive impairment. Future research should focus on identifying other factors that might mediate the relationship between poor outcomes and delays in treatment. To prevent the negative consequences of delayed treatment, clinicians are advised to be aware of the risk of missed diagnoses, especially in patients without a history of episodes with psychotic features or those presenting with depressive symptoms during their initial visit.

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

References

1. Grande I, Berk M, Birmaher B, Vieta E. Bipolar disorder. Lancet (London, England) 2016;387:1561-1572. https://doi.org/10.1016/S0140-6736(15)00241-X
2. Alonso J, Petukhova M, Vilagut G, et al. Days out of role due to common physical and mental conditions: results from the WHO World Mental Health surveys. Mol Psychiatry 2011;16:1234-1246. https://doi.org/10.1038/mp.2010.101
3. Dagani J, Signorini G, Nielssen O, et al. Meta-analysis of the Interval between the Onset and Management of Bipolar Disorder. Can J Psychiatry 2017;62:247-258. https://doi.org/10.1177/0706743716656607
4. Serafini G, Gonda X, Aguglia A, et al. Bipolar subtypes and their clinical correlates in a sample of 391 bipolar individuals. Psychiatry Res 2019;281:112528. https://doi.org/10.1016/j.psychres.2019.112528
5. O'Donovan C, Alda M. Depression preceding diagnosis of bipolar disorder. Front Psychiatry 2020;11:500. https://doi.org/10.3389/fpsyt.2020.00500
6. Altamura AC, Buoli M, Caldiroli A, et al. Misdiagnosis, duration of untreated illness (DUI) and outcome in bipolar patients with psychotic symptoms: a naturalistic study. J Affect Disord 2015;182:70-75. https://doi.org/10.1016/j.jad.2015.04.024
7. Faedda GL, Marangoni C, Serra G, et al. Precursors of bipolar disorders: a systematic literature review of prospective studies. J Clin Psychiatry 2015;76:614-624. https://doi.org/10.4088/JCP.13r08900
8. Altamura AC, Dell'Osso B, Berlin HA, Buoli M, Bassetti R, Mundo E. Duration of untreated illness and suicide in bipolar disorder: a naturalistic study. Eur Arch Psychiatry Clin Neurosci 2010;260:385-391. https://doi.org/10.1007/s00406-009-0085-2
9. Hong W, Zhang C, Xing MJ, et al. Contribution of long duration of undiagnosed bipolar disorder to high frequency of relapse: a naturalistic study in China. Compr Psychiatry 2016;70:77-81. https://doi.org/10.1016/j.comppsych.2016.06.013
10. Buoli M, Cesana BM, Fagiolini A, et al. Which factors delay treatment in bipolar disorder? A nationwide study focussed on duration of untreated illness. Early Interv Psychiatry 2021;15:1136-1145. https://doi.org/10.1111/eip.13051
11. Di Salvo G, Porceddu G, Albert U, Maina G, Rosso G. Correlates of long duration of untreated illness (DUI) in patients with bipolar disorder: results of an observational study. Ann Gen Psychiatry 2023;22:12. https://doi.org/10.1186/s12991-023-00442-5
12. Fico G, Anmella G, Gomez Ramiro M, et al. Duration of untreated illness and bipolar disorder: time for a new definition? Results from a cross-sectional study. J Affect Disord 2021;294:513-520. https://doi.org/10.1016/j.jad.2021.07.062
13. Galimberti C, Bosi MF, Volontè M, Giordano F, Dell'Osso B, Viganò CA. Duration of untreated illness and depression severity are associated with cognitive impairment in mood disorders. Int J Psychiatry Clin Pract 2020;24:227-235. https://doi.org/10.1080/13651501.2020.1757116
14. Elbir M, Alp Topbaş Ö, Bayad S, et al. Adaptation and reliability of the structured clinical interview for DSM-5-disorders - clinician version (SCID-5/CV) to the Turkish language. Turk Psikiyatri Derg 2019;30:51-56.
15. First MB. Structured Clinical Interview for the DSM (SCID). The Encyclopedia of Clin Psychology 2015:1-6. https://doi.org/10.1002/9781118625392.WBECP351

16. Torrent C, Martínez Arán A, Amann B, et al. Cognitive impairment in schizoaffective disorder: a comparison with non-psychotic bipolar and healthy subjects. Acta Psychiatr Scand 2007;116:453-460. https://doi.org/10.1111/J.1600-0447.2007.01072.X
17. Akdemir A, Türkçapar MH, Orsel SD, Demirergi N, Dag I, Ozbay MH. Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. Compr Psychiatry 2001;42:161-165. https://doi.org/10.1053/comp.2001.19756
18. Karadag F, Oral ET, Yalcın FA, Erten E. Young Mani Derecelendirme Ölçeğinin Türkiye'de geçerlilik ve güvenilirliği. Türk Psikiyatri Dergisi 2001;13:107-114.
19. Yazici MK, Demir B, Tanriverdi N, Karaağaoğlu E, Yolaç P. Hamilton Anksiyete Değerlendirme Ölçeği, değerlendiriciler arası güvenirlik ve geçerlik çalışması. Türk Psikiyatri Dergisi 1998;9:114-117.
20. Strauss E, Sherman E, Spreen O. A Compendium of Neuropsychological Tests, Third Edition 2006.
21. Emek Savaş DD, Yerlikaya D, Yener GG, Tanör ÖÖ. Validity, reliability and normative data of the Stroop test Çapa version. Turk Psikiyatri Derg 2020;31:9-21. https://doi.org/10.5080/U23549
22. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. Perceptual and Motor Skills 1958;8:271–276. https://doi.org/10.2466/pms.1958.8.3.271
23. Anil AE, Kivircik BB, Batur S, et al. The Turkish version of the Auditory Consonant Trigram Test as a measure of working memory: a normative study. Clin Neuropsychol 2003;17:159-169. https://doi.org/10.1076/CLIN.17.2.159.16510
24. Yildirim EA, Kasar M, Güdük M, Ateş E, Kucukparlak I, Ozalmete EO. Investigation of the reliability of the "reading the mind in the eyes test" in a Turkish population. Turk Psikiyatri Derg 2011;22:177-186.
25. Bora E, Eryavuz A, Kayahan B, Sungu G, Veznedaroglu B. Social functioning, theory of mind and neurocognition in outpatients with schizophrenia; mental state decoding may be a better predictor of social functioning than mental state reasoning. Psychiatry Res 2006;145:95-103. https://doi.org/10.1016/j.psychres.2005.11.003
26. Feng C, Wang H, Lu N, et al. Log-transformation and its implications for data analysis. Shanghai Arch Psychiatry 2014;26:105-109. https://doi.org/10.3969/j.issn.1002-0829.2014.02.009
27. Bora E. Neurocognitive features in clinical subgroups of bipolar disorder: a meta-analysis. J Affect Disord 20187;229:125-134. https://doi.org/10.1016/j.jad.2017.12.057
28. Keramatian K, Torres IJ, Yatham LN. Neurocognitive functioning in bipolar disorder: What we know and what we don't. Dialogues Clin Neurosci 2022;23:29-38. https://doi.org/10.1080/19585969.2022.2042164
29. Delaloye C, Moy G, de Bilbao F, et al. Longitudinal analysis of cognitive performances and structural brain changes in late-life bipolar disorder. Int J Geriatr Psychiatry 2011;26:1309-1318. https://doi.org/10.1002/gps.2683
30. Gildengers AG, Chisholm D, Butters MA, et al. Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychol Med 2013;43:801-811. https://doi.org/10.1017/S0033291712001614
31. Samamé C, Cattaneo BL, Richaud MC, Strejilevich S, Aprahamian I. The long-term course of cognition in bipolar disorder: a systematic review and meta-analysis of patient-control differences in test-score changes. Psychol Med 2022;52:217-228. https://doi.org/10.1017/S0033291721004517
32. Mather M. Aging and cognition. Wiley Interdiscip Rev Cogn Sci 2010;1:346-362. https://doi.org/10.1002/wcs.64

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Authors' contributions to the article

E.A., and O.A. designed the study. E.A. conducted data collection. E.A. and O.A. performed statistical analysis. Discussion section of the article written by E.A. and O.A. All authors discussed the entire study and approved the final version.

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Morphology in the last 10 years: a bibliometric analysis

Son 10 yılda morfoloji: bibliyometrik bir analiz

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Abstract

Purpose: Morphology is the science of structure, function and development. Many different disciplines work in this field of science.

Bibliometric analysis is a method that examines the productivity, efficiency and performance of factors such as author, country and university.

Materials and methods: In this study, the researches conducted in the field of morphology in the last 10 years were analyzed bibliometrically.

Results: It was analyzed that 83214 studies were conducted in the last 10 years, the most studies were conducted at the Temerty Faculty of Medicine of the University of Toronto, the United States of America as the country and SCI-Expanded index. Elsevier publishing house is the most used publishing house and neuroscience is the field of science with the highest number of publications.

Conclusion: Studies in the field of morphology, which has shed light on other branches of science throughout history, have been increasing in the last 10 years. In our study, it is aimed to guide scientists who will conduct research in the field of morphology in the future.

Keywords: Morphology, bibliometric analysis, medicine.

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Öz

Amaç: Morfoloji yapı, fonksiyon ve gelişme bilimidir. Bu bilim alanında pek çok farklı disiplin çalışmaktadır.

Bibliyometrik analiz yazar, ülke, üniversite gibi faktörlerin üretkenliğini, etkililiğini ve performansını inceleyen bir yöntemdir.

Gereç ve yöntem: Bu çalışmada son 10 yılda morfoloji alanında yapılan araştırmalar bibliyometrik olarak analiz edilmiştir.

Bulgular: Son 10 yılda 83214 çalışmanın yapıldığı, ülke olarak en fazla çalışmanın Amerika Birleşik Devletleri Toronto Üniversitesi Temerty Tıp Fakültesi'nde yapıldığı ve SCI-Expanded indeksi analiz edildi. Elsevier yayınevi en çok kullanılan yayınevi olup sinir bilimi ise en fazla yayına sahip bilim alanıdır.

Sonuç: Tarih boyunca diğer bilim dallarına ışık tutan morfoloji alanında yapılan çalışmalar son 10 yılda artış göstermektedir. Çalışmamızda gelecekte morfoloji alanında araştırma yapacak bilim insanlarına yol gösterilmesi amaçlanmaktadır.

Anahtar kelimeler: Morfoloji, bibliyometrik analiz, tıp.

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Introduction

Morphology is the branch of science that studies the structure and anatomical form of living things and investigates their physical properties. It examines the physiological forms of living organisms, such as organs and systems, as well as other structural features of living organisms. The Department of Morphology consists of various disciplines, including cell and developmental biology, genetics and molecular medicine [1]. The sentence 'Morphology is a good witness that does not lie' actually tells us in a good way that the structural features of the living creature are defined by morphology [2].

Morphology, which comes from the Greek word morph, which means shape and form, defines both the formal properties and physical activities of the living structure. It analyses and defines from the smallest physical structure to the whole body as a whole [3].

Bibliometrics is of Greek origin and means book and measurement [4]. Today, its use can be described as measuring, that is, analysing the publications resulting from the studies carried out. Bibliometric analyses provide cumulative information by analysing the publications made and indexed in a scientific field, their characteristics and literature status [5]. In these analyses, publications in the literature are examined quantitatively using statistical methods. Bibliometric study aims to determine which topics current research focuses on. In this way, it helps researchers to plan future research by using the information obtained from past research.

Bibliometric analysis provides a different perspective in reflecting developments in various fields of scientific research. This analysis is a useful method to objectively measure the current status and international scientific impact of a particular topic. At the same time, it provides researchers and readers with a concise and understandable overview of general trends in research areas [6].

Bibliometrics is a research approach used to measure and analyse the impact of scientific studies on a particular research. Bibliometrics is a meta-science study that makes science the object of study. Bibliometrics uses three elements of scientific activity as a basis: input, output and impact of a publication. These three elements can then be mapped and used to expand knowledge in a particular research area. This study clarifies the interrelationships between authors, publications, institutions and other characteristics of a given field [7]. It is also a systematic, transparent and reproducible review process based on a statistical approach to provide an overview of the current state of the literature in a given field through the analysis of published literature [8].

Bibliometric analysis is a method that shows the productivity and impact of research and the performance of authors. In particular, the number of citations is one of the indicators of the level of impact of an article in the relevant field. In this way, scientists and clinicians interested in the field of study can focus on the results of influential articles [9]. In addition, bibliometric studies also give an idea about the future vision of a journal. Although there are studies using bibliometric methods in various fields in the literature, there are very few bibliometric studies in the field of anatomy and there are no bibliometric studies on anatomy journals. Citation analysis is the most widely used form of bibliometrics and allows to measure the impact factor of journals [10]. The influence of an author and an article is often measured by the number of citations. The number of citations an article receives is one of the measures of its scientific value [11]. However, the scientific rigour of an article and its impact on clinical practice cannot be measured solely on the basis of the citations it receives [12].

Web of Science (WoS) database is one of the databases widely used in bibliometric research. The most valid measure of the quality of scientific publications and the productivity of researchers at the international level is the number of articles published in journals in the WoS database and the number of citations to these articles. All these criteria can be interpreted as a quality indicator and can be used to evaluate institutions, academics and even countries [13]. VOS viewer is a specially designed software tool that creates and visualises bibliometric maps, thus showing structural and dynamic aspects of scientific research fields. The popularity of bibliometric studies is steadily increasing. The progress, usability and accessibility of bibliometric software such as

VOS viewer, the interdisciplinary characteristics of bibliometric methodologies, its usefulness for large-scale processing of scientific data and its high research impact are directly linked to the popularity of bibliometric studies [7].

The aim of this study is to guide scientists doing research on this subject by determining which publications on morphology are most cited, who contributed to them, and what topics they deal with.

Materials and methods

Permission was received for the study from Pamukkale University Ethics Committee.

Data collection

The Web of Science online database was searched to identify the publications that mentioned 'Morphology' in their titles, abstracts or keywords. To systematically exclude irrelevant publications, the search strategy was designed as follows: TS= Morphology and PY=2013-2022. ((TS=(morphology)) or (QMTS=("Morphology")) and (PY=("2022" or "2021" or "2020" or "2019" or "2018" or "2017" or "2016" or "2015" or "2014" or "2013") and TASCA=("Physiology" or "Obstetrics Gynecology" or "Ophthalmology" or "Rehabilitation" or "Cell Biology" or "Neurosciences" or "Rheumatology" or "Tropical Medicine" or "Geriatrics Gerontology" or "Medicine Legal" or "Medical Informatics" or "Psychology" or "Critical Care Medicine" or "Emergency Medicine" or "Hematology" or "Anthropology" or "Chemistry Medicinal" or "Surgery" or "Microbiology" or "Anatomy Morphology" or "Anesthesiology" or "Dermatology" or "Nutrition Dietetics" or "Pediatrics" or "Genetics Heredity" or "Pathology" or "Dentistry Oral Surgery Medıcıne" or "Orthopedics" or "Psychiatry" or "Urology Nephrology" or "Clinical Neurology" or "Medicine General Internal") and Edn=("Wos. SCI" or "Wos.ESCI" or "Wos.SSCI" or "Wos. ISTP") and Py=("2022" or "2021" or "2020" or "2019" or "2018" or "2017" or "2016" or "2015" or "2014" or "2013")) Booleans: And, Or, Not Field Tags: TS=Topic, TI=Title, AB=Abstract, AU=Author, AI=Author Identifiers, AK=Author Keywords, PY=Year Published, WC=Web of Science Categories.

Data processing and analyzing

Publications related to morphology were identified, bibliometric data were extracted and evaluated. The selected parameters were the number of citations, study type, first author's name, university, year of publication and country.

The identified publications were ranked in descending order according to the number of citations. The VOS viewer software was used with default parameters to create a bubble map that analyses and visualises the words/ sentences used in the titles and abstracts of publications. Collaboration between countries was established with the VOS viewer software. VOS viewer is a software designed to visualise bibliometric data [14]. VOS viewer, is a software that gives special attention to the graphical representation of bibliometric maps [14].

Results

When the studies conducted in the last 10 years are examined, it is seen that there are a total of 83214 studies, 72446 of which are articles, 6115 review articles, 2903 meeting abstracts, 950 proceeding papers, 885 editorial materials, 362 early access (Figure 1).

When the studies were listed to evaluate them in terms of citations, it was seen that the most cited study was 'the third international consensus definitions for sepsis and septic shock' by Singer et al. [15], with 12596, and the following study was also a consensus conference study (Table 1). The 10 most cited studies were written in English and listed regardless of the years (Table 1).

When the university departments where the studies were conducted were evaluated, the top 5 universities were University Of Toronto Temerty Faculty Of Medicine with 425 publications, Stanfort Medicine with 412 publications, Stanford University school of Medicine with 412 publications, Washington University in St Louis School of Medicine with 387 studies and University College London School of Life and Medical Sciences with 362 studies (Table 2).

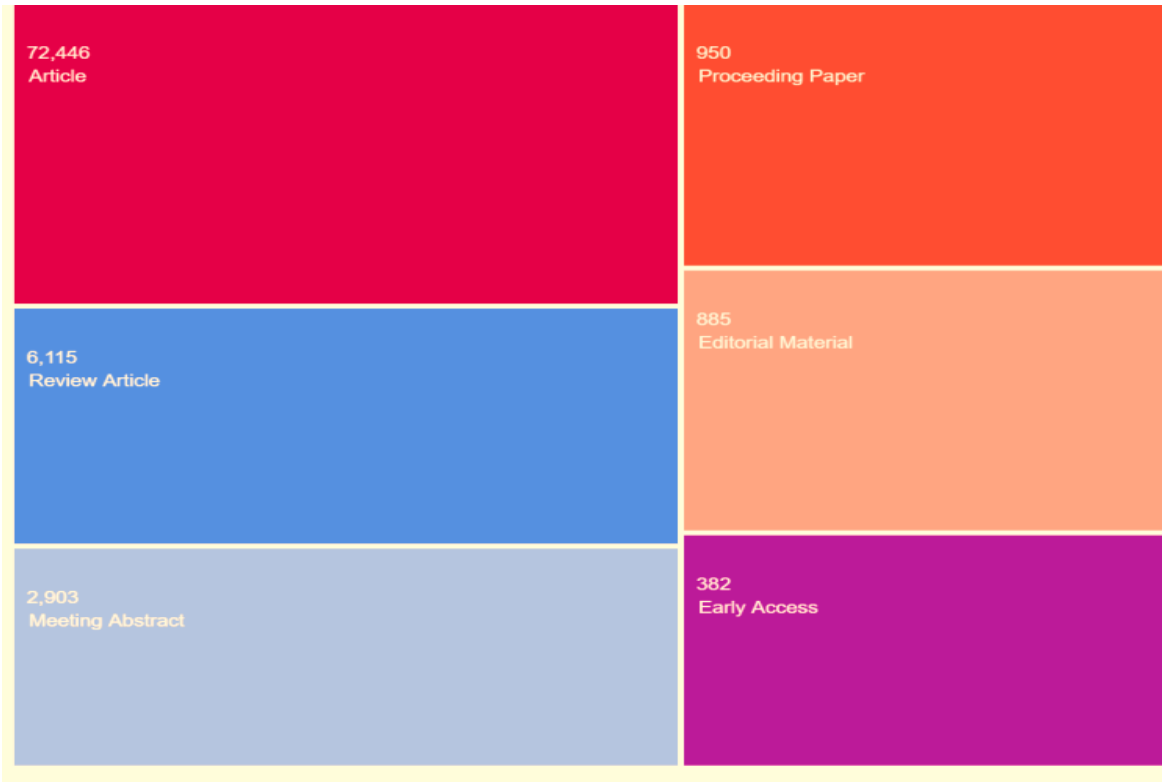

Figure 1. Document type visualization

Table 1. Top 10 most cited publications

	Article Title	Authors	Citation
1	The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)	Singer, M; Deutschman, CS; Seymour, CW	12596
2	The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma Definition of Grading Patterns and Proposal for a New Grading System	Epstein, JI; Egevad, L; Amin, MB	1896
3	The gut microbiota of insects - diversity in structure and function	Engel, P; Moran, NA	1380
4	The Chicago Classification of esophageal motility disorders, v3.0	Kahrilas, PJ; Bredenoord, AJ; Fox, M; Gyawali, CP; Roman, S; Smout, AJPM; Pandolfino, JE	1326
5	Neurotrophin regulation of neural circuit development and function	Park, H; Poo, MM	1302
6	Mechanisms of Plaque Formation and Rupture	Bentzon, JF; Otsuka, F; Virmani, R	1251
7	Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes	Steensma, DP; Bejar, R; Jaiswal, S	1226
8	Signaling mechanisms of the epithelial-mesenchymal transition	Gonzalez, DM; Medici, D	1127
9	Resting-state connectivity biomarkers define neurophysiological subtypes of depression	Drysdale, AT; Grosenick, L; Downar, J	1102
10	Effect of Essential Oils on Pathogenic Bacteria	Nazzaro, F; Fratianni, F; De Martino, L	1046

Table 2. University department visualization

Affiliation with Department	Count
Johns hopkıns unıversıty school of medıcıne	530
Shanghaı medıcal unıversıty 2	508
Stanford medıcıne	476
Stanford unıversıty school of medıcıne	470
Unıversıty college london school of lıfe and medıcal scıences	470
Johns hopkıns medıcıne	424
Unıversıty of calıfornıa san francısco school of medıcıne	418
Unıversıty of toronto temerty faculty of medıcıne	414
Unıversıty of pıttsburgh schools of the health scıences	409
Washıngton unıversıty ın st louıs school of medıcıne	383
Yale school of medıcıne	363
Uw medıcıne	362
Unıversıty of pıttsburgh school of medıcıne	361
Unıversıty of washıngton school of medıcıne	359
The unıversıty of melbourne faculty of medıcıne dentıstry and health scıences	358
Unıversıty of mıchıgan mıchıgan medıcıne	349
Harvard medıcal school	338
Unıversıty of mıchıgan school of medıcıne	336
West chına center of medıcal scıences	336
Perelman school of medıcıne	324

When the countries where broadcasts are made are examined, they are in the top 10 as USA, followed by China, Germany, England, Japan, Italy, Canada, Brazil, India and France (Figure 2).

When the publications are examined as index, 76162 publications are SCI-Expanded, 6172 publications are ESCI, 4621 publications are SSCI, 2827 publications are CPCI-S, 495 publications are A&HCI, 203 publications are BKCI-S, 127 publications are IC, 16 publications are CPCI-SSH.

Considering the publication language of the studies, it is seen that 82026 studies were published in English, 391 studies in German, 363 studies in Spanish, 102 studies in French, 97 studies in Russian, 64 studies in Turkish, 30 studies in Portuguese, 26 studies in Polish, 24 studies in Czech, and 19 studies in Korean (Figure 3).

Data taken from the web of science website with the WOS viewer program are shown according to years. This chart evaluates the 500 most cited studies in the last 10 years (Figure 4). A total of 34 authors in 6 clusters are associated with each other and shown in (Figure 4). In this figure, it can be seen that the authors refer to each other regardless of the years.

When Most published Authors are analysed, there is no author in the top 20 and the first 5 authors are Warren Alan, Antonescu Cristina R., Alfarraj Saleh, Agaimy Abbas, Khaled AL-Rasheid (Table 3).

Looking at the WOS Categories Cell Biology, Neurosciences, Surgery, Microbiology, Anatomy Morphology, Genetics Heredity, Pathology, Dentistry Oral Surgery Medicine, biochemistry Molecular Biology and Orthopedics are ranked as the top 10 (Table 4).

When looking at the publishing house information, it is seen that Elsevier is at the top with 17957 publications, followed by Wiley and Springer natural publishing houses (Table 5).

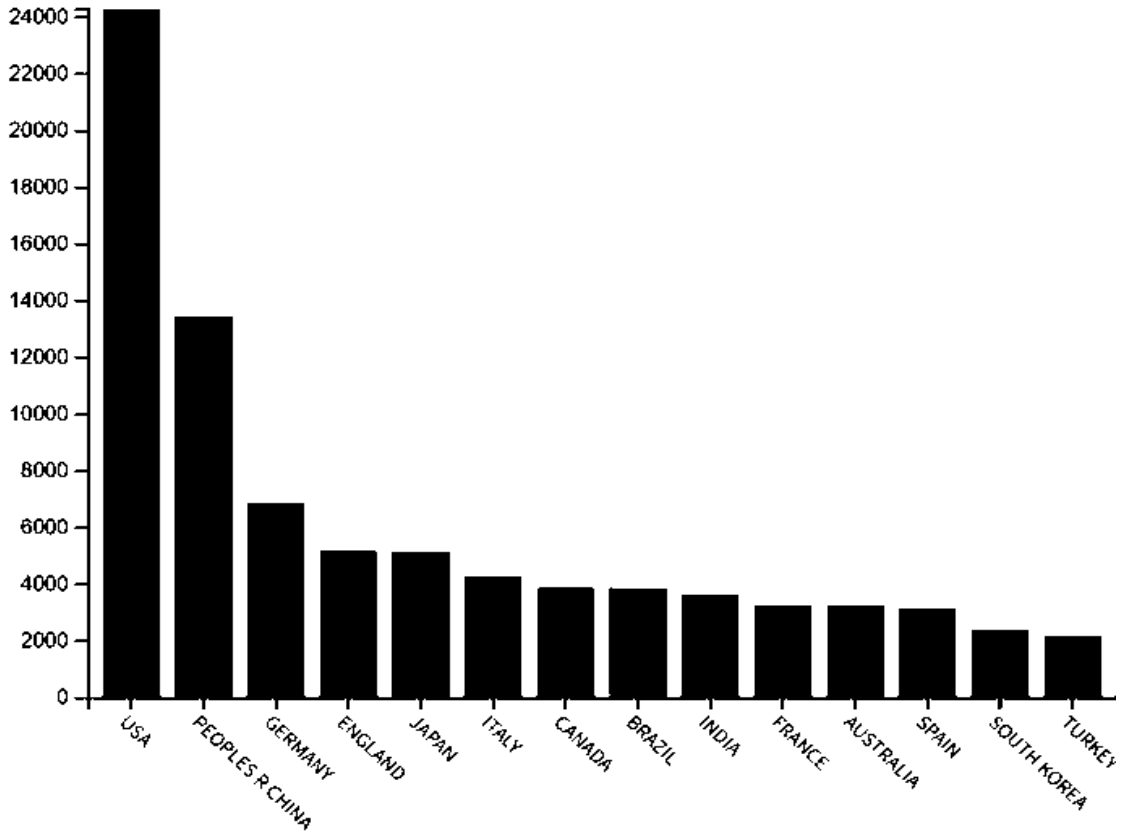

Figure 2. Country visualization

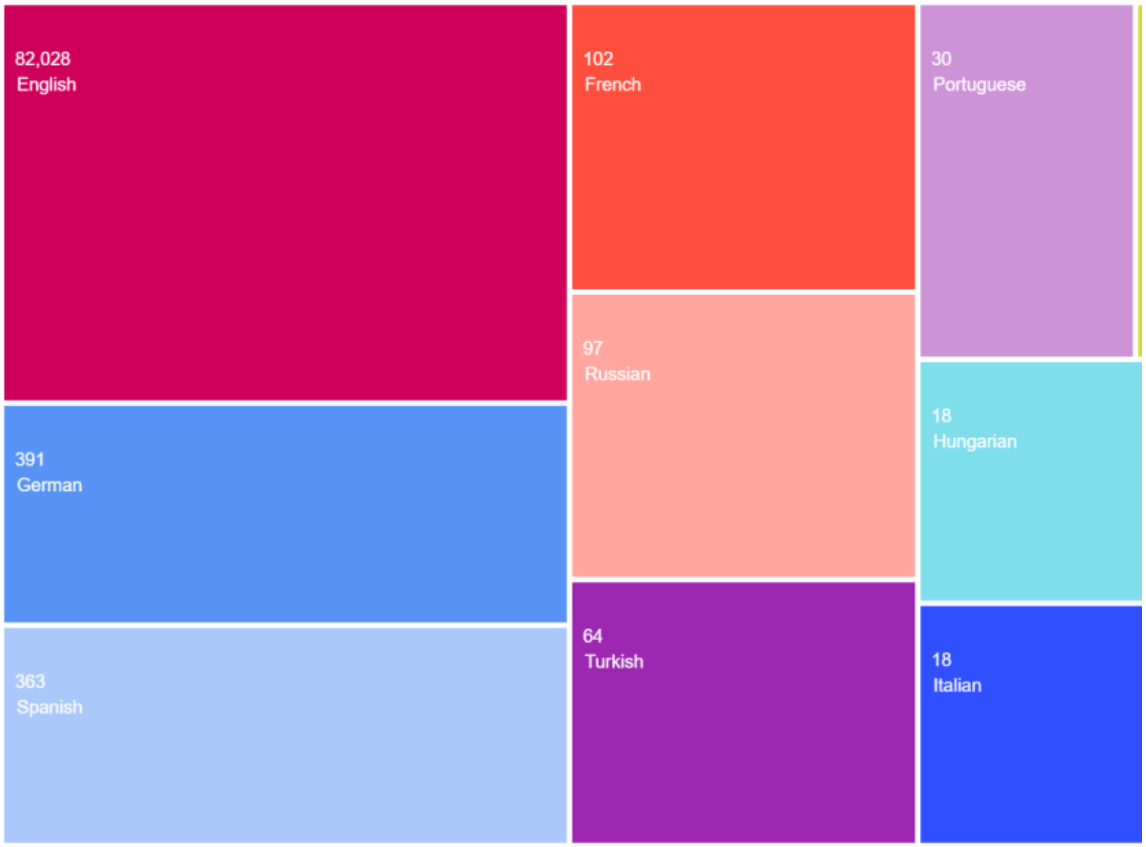

Figure 3. Language visualization

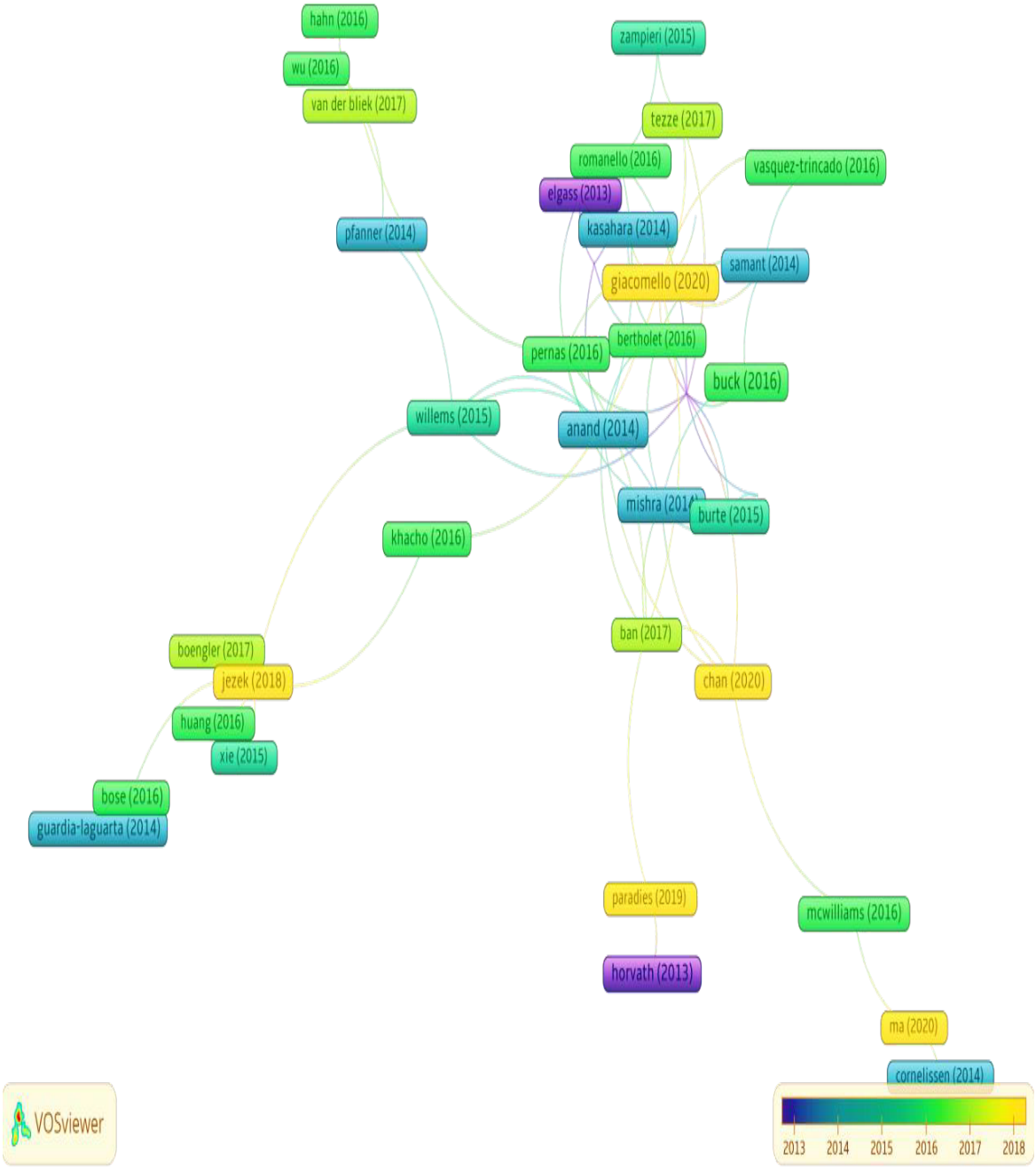

Figure 4. WOS viever graphic for years by citation

Table 3. Most published Authors

Researcher Profiles	Count
Warren, Alan	93
Antonescu, Cristina R.	80
Alfarraj, Saleh	56
Agaimy, Abbas	55
Khaled AL-Rasheid	54
Ahmad, Mushtaq	54
Zafar, Muhammad	53
Flores, Gonzalo	51
Sultana, Shazia	50
Tubbs, R. Shane	49
Zhang, Lei	49
Michal, Michael	47
Cheng, Liang	46
White, Tonya	46
Hes, Ondrej	46
Oliva-Poch, Ester	45
Epstein, Jonathan I.	45
Hu, Xiaozhong	44
Iwanaga, Joe	43
Ahmad, Prof. Dr. Mushtaq	42

Table 4. WOS Categories

Web of Science Categories	Count
Cell bıology	11039
Neurosclences	10231
Surgery	6910
Mıcrobıology	5958
Anatomy morphology	5816
Genetıcs heredıty	5466
Pathology	5259
Dentıstry oral surgery medıcıne	5207
Bıochemıstry molecular bıology	4875
Orthopedıcs	4558
Clınıcal neurology	4188
Medıcıne general ınternal	4095
Ophthalmology	3862
Obstetrıcs gynecology	3031
Physıology	2952
Evolutıonary bıology	2925
Chemıstry medıcınal	2173
Pharmacology pharmacy	2049
Bıotechnology applıed mıcrobıology	2030
Anthropology	2020

Table 5. Publisher

Publishers	Count
Elsevier	18071
Springer Nature	13503
Wiley	13471
Frontiers Media Sa	3466
Lippincott Williams & Wilkins	3460
Oxford Univ Press	2686
Mdpi	2314
Taylor & Francis	2036
Sage	1722
Assoc Research Vision Ophthalmology Inc	888
Karger	783
Amer Soc Microbiology	736
Mary Ann Liebert, Inc	734
Wolters Kluwer Medknow Publications	730
Hindawi Publishing Group	687
Amer Physiological Soc	618
Bmj Publishing Group	498
Soc Chilena Anatomia	489
Thieme Medical Publishers	466

Discussion

Morphology is an important and broad branch of science covering many branches of science, especially medicine [2]. When morphology in the field of medicine is analysed, it is revealed that neuroscience, cell biology and surgical sciences make a great contribution to morphology (Table 4). The place of the anatomy department in morphology is not at the top of the list as it may first come to mind, but it ranks 7th with 5816 publications (Table 4). In the study of Petekkaya et al. [16], it is seen that anatomy increased after 1997. When examined in more detail, it was seen that radiological anatomy was at the forefront [16]. The year with the most publications related to anatomical terminology obtained was in 2020 [7]. In the field of anatomy, especially in education, studies related to technology are also increasing. An example of this is virtual reality technologies. With the development of science and technology, VR will have a wider application in the field of anatomy and will also become a powerful modern teaching method in medical research institutions [17]. In the field of anatomy, Ankara University and Hacettepe University are ranked in the top 2 in Türkiye [4].

Morphology should not be considered only as a branch of basic sciences, on the contrary, it should not be forgotten that it examines all processes starting from gynaecology and obstetrics and foetus and continuing until death [18]. In addition, morphology is an important science for plastic surgery and surgery has always progressed in the light of morphology throughout history [19]. In the surgical fields of dentistry, morphology follows anatomy with 5207 studies. It is obvious that morphology is a valuable branch of science not only for medicine but also for dentistry. The number of studies concerning the diagnosis and treatment modalities of maxilla facial fractures has significantly increased over the years [20].

Bibliometric analysis is a scientific method that researchers can use to glance at prominent areas of medical research and obtain an overview of the landscape of published literature [21]. Bibliometric studies are widely used in the field of information science, and enable researchers to make quantitative analyses of the academic literature [22]. Bibliometric techniques have been used in a wide variety of program evoluations including tracing research advances in cancer and the development of the

oral contraceptive [23]. When we examine the current status of studies on morphology using the bibliometric analysis method, it is seen that there has been an increase in the number of studies conducted in this field in the last 10 years and citations to the past in the following years. Especially the fact that the current state of the morphology department before the 2000s has changed compared to the post-2000s has reflected positively on the studies. This increase is seen not only in basic sciences but also in some departments of internal sciences. The number of publications written in the field of rheumatology in Türkiye is shown to have increased remarkably up until 2006 [24]. This increase is also seen when we look at surgical sciences. A bibliometric analysis allows for the identification of the number and quality of publications from a specific country. In general, Türkiye ranked 14th out of 122 countries in terms of the number of publications in the field of orthopedics and traumatology [25]. One of the reasons for this increase over the years is the increase in the number of academicians. Bahşi et al. [4] stated that the increase in the number of academicians as well as the increase in the number of medical faculties were effective in this increase.

Studies on morphology are carried out by many countries, especially the United States, China and Germany, and mostly in English. English, as the language of science, continues its dominance in this field. More articles belong to the document type of article and were written in English [26]. The documents from SSCI and SCIE databases via Web of Science and more than 99% of the articles were written in English [27]. The fact that the publications made in Turkish are 64 and ranked 6th shows the situation of our country.

Bibliometric analyses of the data were performed using VOSviewer software. This program is a professional software used to analyse and visualise bibliometric networks that help to understand trends in scientific research [28]. The figures and tables in our article were created with this system.

Network visualisation maps were created to show how much journals cite each other and the co-use of keywords and terms. In network visualisation maps, the thickness of the line between two elements reflects the strength of the relationship depending on the number of lines between the two elements. In fact, bibliometric analysis involves the application of mathematical and statistical methods to scientific publications [29].

In the future it will be important for scholarly disciplines to examine closely the literature as it represents the behavior of the scholars. Bibliometric analysis presents some empirical evidence that can be used in such an examination [30].

In conclusion, the science of morphology contributes to more studies in every field every year, and studies are carried out increasingly in many countries and universities. Morphology, which has shed light on other branches of science throughout history, needs to be studied more in our country.

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

References

1. Czarnecki PG, Shah JV. The ciliary transition zone: from morphology and molecules to medicine. Trends in Cell Biology 2012:22:201-210. https://doi.org/10.1016/j.tcb.2012.02.001
2. Rees G. Medicine: “Morphology is a witness which doesn’t lie”: Diagnosis by similarity relation and analogical inference in clinical forensic medicine. Social Science & Medicin 2011:73:866-872. https://doi.org/10.1016/j.socscimed.2011.02.032
3. Musumeci G. Progress for journal of functional morphology and kinesiology in 2020. J Funct Morphol Kinesiol 2021;6:11(e1-4). https://doi.org/10.3390/jfmk6010011
4. Bahşi İ, Adanır SS, Kervancıoğlu P, Orhan M, Govsa F. Bibliometric analysis of Turkey’s research activity in the anatomy and morphology category from the web of science database. Eur J Ther 2021;27:268-280. https://doi.org/10.58600/eurjther-27-4-108
5. Horata E. Bibliometric analysis of the Top 100 most cited articles on the thalamus anatomy. MSD 2024;11:89-98. https://doi.org/10.36472/msd.v11i3.1141
6. Kundakcı YE, Atay E. Bibliometric and visualized analysis of global research on technology in anatomy education from 1987 to 2021. Eur J Anat 2023;27:517-528. https://doi.org/10.52083/HNNY3374
7. Iman AF, Handayani S, Munawaroh S, Wiyono N. Bibliometric review of anatomical terminology. Open Access Maced J Med Sci 2023;11:236-242. https://doi.org/10.3889/oamjms.2023.11259

8. Aria M, Cuccurullo C. bibliometrix: An R-tool for comprehensive science mapping analysis. Journal of Informetrics 2017;11:959-975. https://doi.org/10.1016/j.joi.2017.08.007
9. Adnan S, Ullah R. Top-cited articles in regenerative endodontics: a bibliometric analysis. J Endod 2018;44:1650-1664. https://doi.org/10.1016/j.joen.2018.07.015
10. Adanır SS, Bahşi İ, Kervancıoğlu P, Orhan M, Cihan ÖF. Bibliometric analysis of articles published in Anatomy, the official publication of the Turkish Society of Anatomy and Clinical Anatomy between 2007–2018. Anatomy 2020;14:39-43. https://doi.org/10.2399/ana.20.019
11. Eyre Walker A, Stoletzki N. The assessment of science: the relative merits of post-publication review, the impact factor, and the number of citations. PLOS Biolog 2013;11:e1001675. https://doi.org/10.1371/journal.pbio.1001675
12. Mishra L, Kim HC, Singh NR, Rath PP. The top 10 most-cited articles on the management of fractured instruments: a bibliometric analysis. Restor Dent Endod 2018;44:e2. https://doi.org/10.5395/rde.2019.44.e2
13. Thompson DF. Bibliometric analysis of pharmacology publications in the united states: a state-level evaluation. Journal of Scientometric Research 2018;7:167-172. https://doi.org/10.5530/jscires.7.3.27
14. Van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics 2010;84:523-538. https://doi.org/10.1007/s11192-009-0146-3
15. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAVA 2016;315:801-810. https://doi.org/10.1001/jama.2016.0287
16. Petekkaya E, Karadağ M, Dokur M. Bibliometric and altmetric analysis of publications examining education methods in realm of anatomy. 2021;7:391-408. Eur Res J https://doi.org/10.18621/eurj.776229
17. Li Z, Li Z, Peng C, Zhao M, He Q. A Bibliometric analysis of virtual reality in anatomy teaching between 1999 and 2022. Front Educ 2022;7:874406. https://doi.org/10.3389/feduc.2022.874406
18. Panigel M. Gynaecology: Anatomy and morphology. Clin Obst Gynaecology 1986;13:421-445. https://doi.org/10.1016/S0306-3356(21)00027-3
19. Macalister A. A text-book of human anatomy: systematic and topographical, including the embryology, histology and morphology of man, with special reference to the requirements of practical surgery and medicine/ by Alexander Macalister. London, Griffin, 1889.
20. Tekin AM, Bahşi I. Global research on maxillofacial fracture over the last 40 years: a bibliometric study. Brief Clinical Studies 2021;32:e568-e572. https://doi.org/10.1097/SCS.0000000000007627
21. Kumar M, George RJ, Anisha PS. Bibliometric analysis for medical research. Indian Journal of Psychological Medicine 2023;45:277-282. https://doi.org/10.1177/02537176221103617
22. Rueff Barroso CR, Sepulchro LCC, Delpupo FVB, et al. Profile analysis of the scientific articles published in the journal of morphological sciences between 2000 and 2017: a bibliometric study. JMS Bibliometric Study 2018;35:255-260. https://doi.org/10.1055/s-0038-1676541
23. Narin F. Policy P. Bibliometric techniques in the evaluation of research programs. Science and Public Policy 1987;14:99-106.
24. Bahşi A, Zengin O. A bibliometric analysis of Turkish research activity in the rheumatology category of the web of science database. 2021;27:299-310. https://doi.org/10.5152/eurjther.2021.21020
25. Gürbüz Y, Süğün TS, Özaksar K. A bibliometric analysis of orthopedic publications originating from Turkey. Acta Orthop Traumatol Turc 2015;49:57-66. https://doi.org/10.3944/AOTT.2015.14.0044
26. Li Y, Xu G, Long X, Ho YS. A bibliometric analysis of classic publications in web of science category of orthopedics. Journal of Orthopaedic Surgery and Research 2019;14:1-11. https://doi.org/10.1186/s13018-019-1247-1
27. Liao H, Tang M, Luo L, Li C, Chiclana F, Zeng XJ. A bibliometric analysis and visualization of medical big data research. Sustainability 2018;10:166. https://doi.org/10.3390/su10010166
28. Zeybek V, Karabağ G, Yavuz MS. Türkiye'den adli tip alaninda yapilmiş yayinlarin bibliyometrik analizi. Adli Tıp Bülteni 2022;27:218-224. https://doi.org/10.17986/blm.1587
29. Thompson DF, Walker CKJ. A descriptive and historical review of bibliometrics with applications to medical sciences. 2015;35:551-559. https://doi.org/10.1002/phar.1586
30. Budd JM. A bibliometric analysis of higher education literature. Research in Higher Education 1988;28:180-190. https://doi.org/10.1007/BF00992890

Ethics committee approval: Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study (permission date: May 13, 2024, and number: E-60116787-020-525231).

Authors' contributions to the article

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

Case Report

Pamukkale Medical Journal
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Calculi migration into the left renal vein during percutaneous nephrolithotomy: a rare complication and literature review

Perkütan nefrolitotomi esnasında sol renal vene kalkül migrasyonu: nadir bir komplikasyon ve literatür taraması

Eser Ördek, Fatih Gökalp, Bilal Kulak, Ferhat Uçurmak, Sadık Görür

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Abstract

Percutaneous nephrolithotomy (PCNL) has long been the standard treatment of choice for the management of large and complex renal calculi. PCNL is a safe and well-tolerated surgical procedure when performed systematically and correctly; however, as with any surgical intervention, although mild complications may occur in this surgery, serious complications may also occur. In this article, we report a rare case of migration of residual calculi into the renal vein during PCNL surgery and aim to present its presentation, treatment and management in a tertiary care center.

Keywords: Percutaneous nephrolithotomy, renal vein injury, thrombosis, anticoagulant therapy.

Ordek E, Gokalp F, Kulak B, Ucurmak F, Gorur S. Calculi migration into the left renal vein during percutaneous nephrolithotomy: a rare complication and literature review. Pam Med J 2024;17:796-802.

Öz

Üriner sistem taş hastalıklarının cerrahi tedavisinde perkütan nefrolitotomi (PCNL) ameliyatı, uzun yıllardır büyük hacimli ve kompleks böbrek taşlarının tedavisinde sık tercih edilen standart bir tedavi haline gelmiştir. PCNL sistematik ve doğru şekilde yapıldığında güvenilir ve iyi tolere edilebilen cerrahi bir prosedürdür; ancak herhangi bir cerrahi müdahalede olduğu gibi bu ameliyatta da basit olmakla beraber ciddi komplikasyonlar da gelişebilmektedir. Bu yazıda, PCNL ameliyatı sırasında rezidü kalkülün renal vene migrasyonu olan nadir bir olguyu sunarak bunun üçüncü basamak bir merkezde ortaya çıkışını, tedavisini ve nasıl yönetildiğini sunmayı amaçladık.

Anahtar kelimeler: Perkütan nefrolitotomi, renal ven yaralanması, trombozis, antikoagülan tedavi.

Ördek E, Gökalp F, Kulak B, Uçurmak F, Görür S. Perkütan nefrolitotomi esnasinda sol renal vene kalkül migrasyonu: nadir bir komplikasyon ve literatür taraması. Pam Tıp Derg 2024;17:796-802.

Introduction

Percutaneous nephrolithotomy (PCNL) in the surgical treatment of urinary tract stone diseases was first introduced by Fernström and Johansson [1] in 1976 and has become the most preferred treatment technique for large volume and complex renal stones. PCNL is typically a safe and well-tolerated surgical procedure when performed systematically and correctly; however, as with any surgical intervention, PCNL can also develop serious complications, although they are often simple [2]. Puncturing the renal system through the appropriate calyx and subsequent dilatation are the two most important critical steps in PCNL. The majority of complications in PCNL operations occur most frequently during these two steps.

Studies have reported complication rates for PCNL ranging from 20-83% [3]. Common complications are minor, and the Clavien grade I, II, III, IV and V complication rates in the literature are 11.1%, 5.3%, 3.6%, 0.5% and 0.03%, respectively [3]. The most common minor complications after percutaneous

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nephrolithotomy are drainage tube leakage (15%) and transient fever (10-30%) [4]. Less common but serious complications of PCNL (Clavien grades III, IV and V) are usually associated with percutaneous access to the renal collecting system and include adjacent organ injury, renal hilum injury, pleural injury, massive bleeding or urosepsis.

Bleeding that occurs during percutaneous nephrolithotomy procedures is mainly venous and usually mild. Most of the time, bleeding resolves by self-limiting or responds positively to correct and appropriate maneuvers such as placement of a large-caliber percutaneous nephrostomy drainage tube into the system [5]. In addition, although injury to the main renal vascular structures is rare with a rate of 0.5-2.4%, it is one of the complications that can be quite serious and its treatment is difficult [6].

In our literature review, calculi migration into the renal vein has not been reported before and our case will be the first reported case. In this article, we aimed to present the management of calculi migrated into the renal vein during PCNL surgery in an asymptomatic patient in the light of current literature.

Case presentation

A 45-year-old female patient with operation history for breast, ovarian, rectal cancer, thyroid cancer and chemo-radiotherapy treatments due to these comorbidities and Glanzman thrombocytopenia presented to our urology clinic with left flank pain. Investigations revealed a 2.8 cm stone extending from the lower pole of the left kidney to the renal pelvis and several millimetric calculi in the lower pole of the kidney (Figure 1). The patient was planned to be performed with PCNL. Written informed consent was obtained from the patient and the procedure was performed by experienced urologists under general anesthesia. After retrograde catheterization with a 6 Fr ureteral stent in the left ureteral orifice in the lithotomy position, a 14 Fr foley catheter was inserted and the patient was turned to the prone position. Contrast material was injected through the ureteral stent and the left renal pelvicalyceal system was visualized. Under C-arm fluoroscopy guidance, percutaneous access was made from the posterior lower pol calyx. Tract dilatation was performed using coaxial serial Teflon-coated renal dilators under coherent scope images. Finally, a 28 Fr amplatz sheath was placed and a 26 Fr nephroscope was used for the procedure. During nephroscopic examination of the lower pol calyx and renal pelvis, intense venous bleeding was observed from the irrigation fluid drain of the nephroscope. However, no intrapelvic hemorrhage or hematuria from the foley catheter was observed. Operation was continued and bleeding was controlled by placing an amplatz sheath over the bleeding pathway. Then, using the automatic pressure irrigation device (Figure 2) in the system, the pressure was kept slightly high and the stones in the lower pole and renal pelvis were rapidly and carefully fragmented with using pneumatic lithotripter and extracted with stone forceps. Meanwhile, mucosal injury was observed in the renal pelvis, but the procedure was continued because there was no evidence of extravasation or serious bleeding. The patient had slightly low blood pressure since the beginning of the procedure and was given one unit of erythrocyte suspension intraoperatively and fluid replacement according to anesthesia recommendations. However, considering the serious comorbidities of the patient, it was decided to terminate the procedure before complete stone-free status was achieved. A 16 Fr malecot catheter was placed and used as a nephrostomy tube at the end of the procedure. Contrast material was injected through the nephrostomy tube and it was observed that the pelvicalyceal system was compact and the contrast material passed from the renal pelvis to the ureter (Figure 3). The nephrostomy tube was fixed to the skin, the valve of the tube was closed and the renal area was compressed for approximately 15 minutes.

The patient followed in the intensive care unit for 24 hours. Urine from both the urethral foley catheter and nephrostomy tube was clear and the patient was hemodynamically stable. First postoperative day, the patient was transferred to the urology service, the foley catheter was removed and mobilization was provided. The patient's hemodynamics was stable and hemoglobin was not decreased. The nephrostomy tube valve was closed before the tube withdrawn.

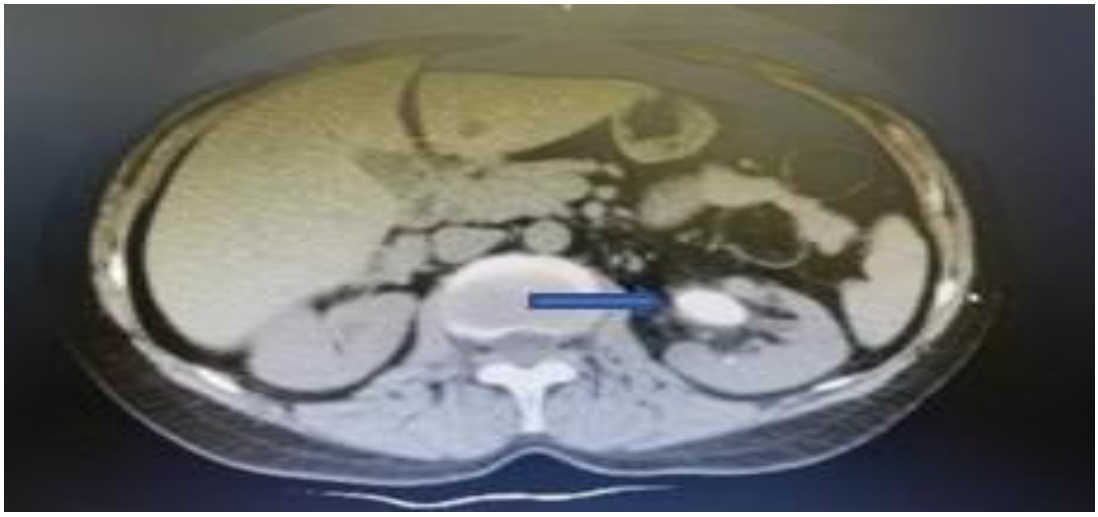

Figure 1. Stone in the renal pelvis, pre-operative CT image, (blue arrow)

Figure 2. Automatic pressure irrigation instrument

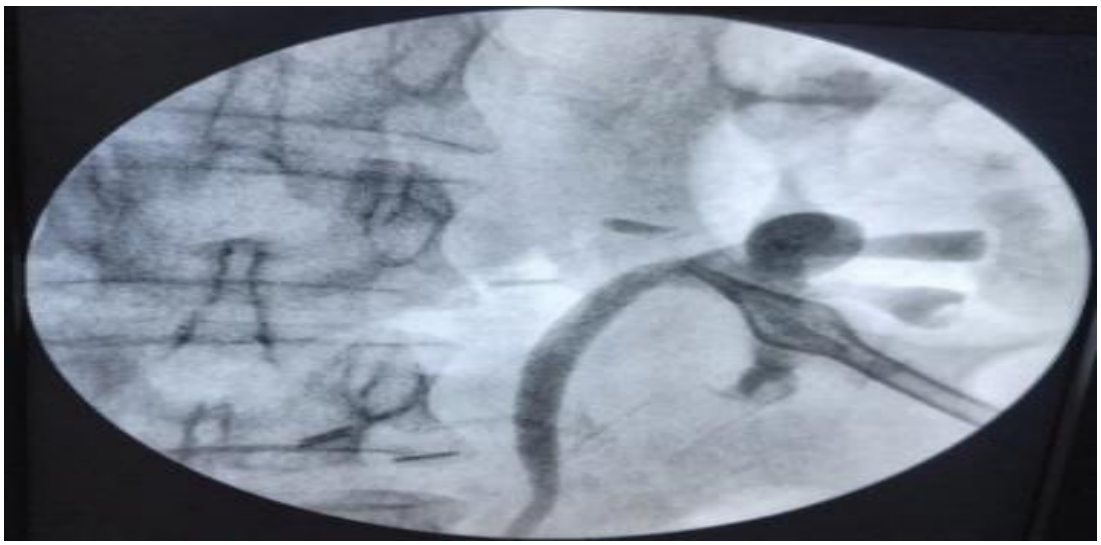

Figure 3. Percutaneous nephrostomy and antegrade pyelography image

On the second postoperative day, the patient had left renal colic and mild wetting near the tube entry site. The nephrostomy tube was opened and a non-contrast whole abdominal computed tomography (CT) was performed. CT scan showed several residual calculus near the nephrostomy tube in the renal pelvis and an opacity with a diameter of approximately 8 mm in the vascular structure thought to be the left renal vein (Figure 4). The patient was consulted with the radiology clinic. The patient was confirmed that she had Nutcracker syndrome and the presence of a stone in the dilated renal vein. Renal doppler ultrasonography was performed and renal artery-vein flow was normal. Since the patient had additional comorbidities such as malignancy, she was consulted to the specialists of Cardiovascular Surgery, Hematology and Interventional Radiology departments against the risk of thromboembolism. The patient also had Glanzman thrombocytopenia and it was decided to start enoxaparin treatment. The stone in the renal vein was considered unlikely to pass to the vena cava due to Nutcracker syndrome and the patient was asymptomatic; so invasive angiography or open surgical stone extraction was not considered primarly. The patient was managed conservatively with anticoagulation therapy. A double j (DJ) stent was placed under fluoroscopy and contrast dye guidance, and the nephrostomy tube was extracted (Figure 5). The extravasation into the renal vein or outside of the pelvis was not observed. The patient was kept under observation for a week after surgery and parenteral antibiotics and anticoagulant treatment were given. She was discharged with recommendations due to her general condition and clinical stability.

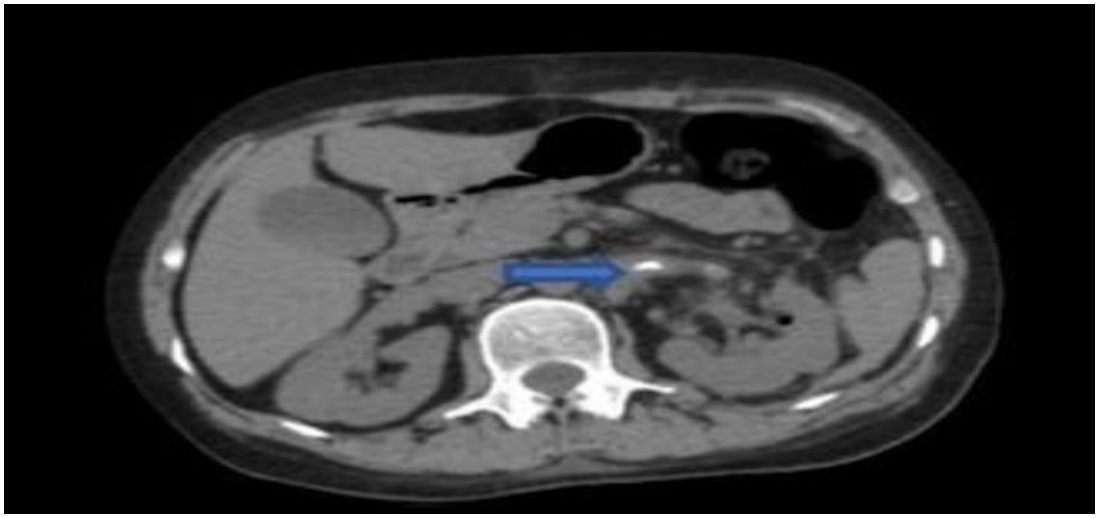

Figure 4. Calculus migrating into the renal vein, (blue arrow)

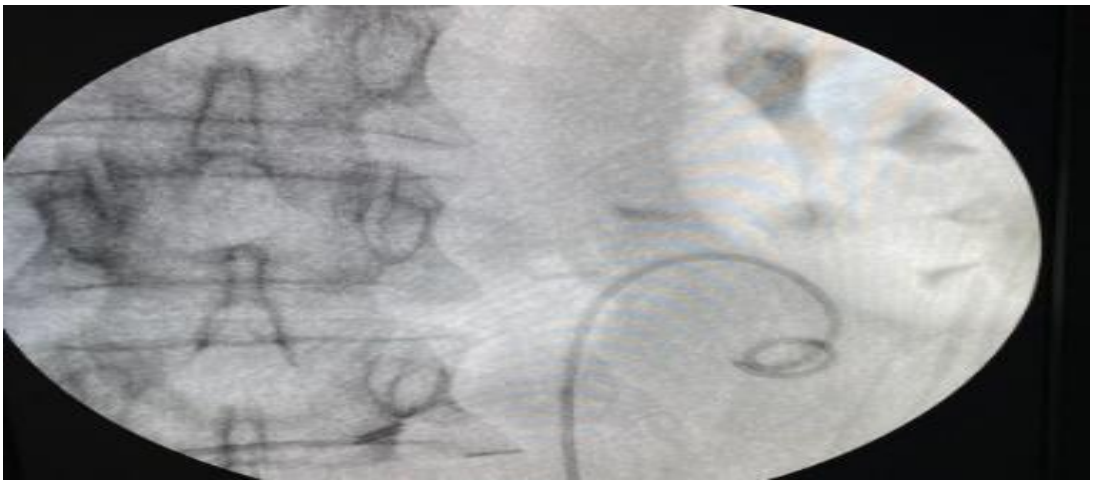

Figure 5. Removal of nephrostomy tube and insertion of DJ

The patient continued to receive anticoagulation and prophylactic antibiotics for three months after surgery. DJ was extracted in the 3rd postoperative month. During the follow-up period of approximately 4 months, the patient remained asymptomatic without developing any thrombotic events, hematuria, or signs of infection. In serial imaging, it was observed that the stone was stably positioned in the renal vein and impacted the endothelium. Additionally, anticoagulant therapy was well tolerated without any side effects.

Discussion

Percutaneous nephrolithotomy has an important place especially in renal stone surgery in our country, where the incidence of nephrolithiasis is high, and is now widely practiced. Ideally, it should be performed in centers with the support of a multidisciplinary team consisting of experienced anesthesiologists and radiologists, and with the possibility of an intensive care unit where patients can be followed up if necessary to ensure the best surgical success. Preoperative multidetector CT imaging helps in surgical planning and initial access to the kidney, especially in large and complex kidney stones. It may also help to predict stone-free rates [7]. Performing appropriate puncture in the appropriate calyx and correct calyceal dilatation are the most critical steps in achieving complete stone-free by fragmenting and extracting the stones appropriately.

Sometimes the puncture needle or axial dilators may injure the renal parenchyma and move towards the renal vein or even major vascular structures such as the vena cava. In addition, the risk of injury during PCNL becomes higher when the renal vein is closer to renal pelvis and posterior calyx [8]. Our patient had a millimetric stone in the lower pole and a 2.8 cm stone in the renal pelvis. This stone, which was known to have been present for a long time, and the associated inflammation may have made the renal pelvis wall and surrounding structures weaker. In addition, the patient's history of malignancy, chemotherapy and radiotherapy treatment may have made the renal parenchyma and surrounding vascular structures more fragile.

Bleeding is one of the most common clinical complications in PCNL surgery. Massive bleeding and related complications may accelerate organ damage or lose and may lead to mortality if managed unproperly [9]. Bleeding usually occurs commonly due to injury of the anterior or posterior segmental arteries; however, this complication can be prevented by performing renal puncture in the posterolateral plane along the avascular line known as the Brödel line [10].

The great vessels and the main renal vascular system injury usually occur during initial percutaneous access. One of the best ways to avoid large vessel injuries is to approach percutaneous renal access in a systematic manner and to carefully evaluate imaging of the renal parenchyma and vasculature prior to the procedure. Bleeding with initial percutaneous access and amplatz dilatation is usually venous in nature and may originate from the skin, muscle, renal capsule or renal parenchyma. Mild or moderate hemorrhages can often be controlled with tamponade and a large caliber nephrostomy tube. Nowadays, with further miniaturization of surgical equipment and novel techniques, blood transfusion rates were decreased significantly from 6.9% in the first series to less than 2% [4].

PCNL is actually an important kidney stone surgery and there is a consensus on what should be done in cases of vascular injuries that may disrupt the patient's hemodynamics. However, unfortunately, there is no clear literature information about complications such as stone migration into the vascular structure, which does not disrupt hemodynamics, as in our case example. PCNL causes controlled grade IV damage to the kidney according to the American Association for the Surgery of Trauma renal injury classification [11]. Grade IV injury also includes renal vein and artery injury. According to the trauma literature, even damage to the main vascular structures can often be treated with angioembolization without the need for open surgery. Renal vein injury during PCNL is a serious complication and should be timely diagnosed and treated correctly.

Actually, Aggarwal et al. [12] reported a patient in whom the nephrostomy tube pierced the renal parenchyma and injured the renal vein during PCNL in another center and nephrectomy was performed. Intraoperative or postoperative severe venous hemorrhage, profound hypotension or massive hematuria that disrupts vital signs should raise suspicion of possible injury to the main renal vascular structures.

Although the normal renal vein pressure is 12-15 cm H_2O, the pressure of the irrigation fluid in the renal collecting system should be kept under this value. The irrigation fluid is in an open system and flows freely both through the edge of the nephroscope and through the amplatz sheath. In our case, the fact that we used continuous irrigation fluid with automatic pressure and the patient had fragile tissue weakness due to additional comorbidities may have triggered renal vein mucosal damage. Therefore, the irrigation fluid should be adjusted minimal pressure in patients with comorbidities and especially in patients who have received chemotherapy-radiotherapy.

Patients should be given blood and fluid replacement according to the amount of bleeding, hemodynamic findings and low hemoglobin. Intravenous broad-spectrum antibiotic treatment should be given to prevent possible bacteremia or sepsis in the presence of foreign bodies such as stones or guidewire tips in the renal venous system. In our clinic, routine prophylactic and postop parenteral third-generation cephalosporin antibiotherapy is given in patients undergoing PCNL surgery. However, we did not observe any fever, hematuria, low hemoglobin or hemodynamic instability in our patient both intraoperatively and postoperatively, which ruled us out renal vascular system damage.

In our case, low, single-dose anticoagulant therapy was given in consultation with hematology and cardiovascular surgery specialists because the patient had platelet dysfunction and radiologic evidence of renal vein nutcracker syndrome. In addition, since the renal vein system is a high-flow but low-pressure system and the risk of thrombosis is relatively lower compared to other vessels, there is still no definitive literature information regarding anticoagulation treatment [13]. However, Zumrutbas et al. [14], in a case report published in 2016, stated that PCNL can be safely performed in patients with rare bleeding disorders. Additionally, surgical care of patients with congenital and rare bleeding disorders should only be performed in hospitals where a multidisciplinary team, including the surgeon and an experienced hematologist, collaborates.

As in our case, it can sometimes be difficult to recognize and diagnose renal vein injury intraoperatively. Short-term staining in vascular structures on antegrade pyelography performed by administering a contrast medium through the nephrostomy placed at the end of the operation may provide us with an idea. In addition, in a patient who is hemodynamically stable in terms of vital signs, complications such as arteriovenous fistula, aneurysm or pseudoaneurysm should come to mind in clinical situations such as persistent macroscopic hematuria or self-limited hematoma. Such complications can be successfully treated with angioembolization or other endovascular interventions along with conservative treatment and close follow-up [15].

To our knowledge, this is the first and only case of renal vein injury and stone migration to the renal vein during PCNL. In addition, despite the major vascular damage, the absence of clinical picture and the anatomical variation of the patient allowed the patient to be followed and treated with a conservative approach. The patient's multiple malignancies, platelet dysfunction, history of chemotherapy-radiotherapy and untreated renal pelvic calculi for many years made PCNL surgery high-risk. Also, the presence of radiologic Nutcracker syndrome increased the risk of possible vein damage by making the renal vein more dilated than normal, prevented the calculi migrating into the renal vein from migrating to the vena cava and impinged on the renal vein endothelium.

As a result, it is important to correctly determine the focus of bleeding and the cause of bleeding in percutaneous nephrolithotomy surgery. The presence of intraoperative venous bleeding or the absence of any serious clinical and vital sign disturbance during postoperative follow-up usually reduces the likelihood of major vascular injury. However, in suspected complicated cases and especially in patients with high comorbidities, prompt postoperative imaging, even in the absence of obvious

symptoms, will help in the early detection of possible vascular injury and complications. In addition, asymptomatic migration of the stone into the renal vein during PCNL causes diagnostic difficulties and treatment strategies require a balanced approach between surgical intervention and observation.

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

References

1. Fernström I, Johansson B. Percutaneous pyelolithotomy. A new extraction technique. Scand J Urol Nephrol 1976;10:257-259. https://doi.org/10.1080/21681805.1976.11882084
2. Rudnick DM, Stoller ML. Complications of percutaneous nephrostolithotomy. Can J Urol 1999;6:872-875.
3. de la Rosette J, Assimos D, Desai M, et al. The clinical research office of the endourological society percutaneous nephrolithotomy global study: indications, complications, and outcomes in 5803 patients. J Endourol 2011;25:11-17. https://doi.org/10.1089/end.2010.0424
4. Shin TS, Cho HJ, Hong SH, Lee JY, Kim SW, Hwang TK. Complications of percutaneous nephrolithotomy classified by the modified clavien grading system: a single center's experience over 16 years. Korean J Urol 2011;52:769-775. https://doi.org/10.4111/kju.2011.52.11.769
5. Galek L, Darewicz B, Werel T, Darewicz J. Haemorrhagic complications of percutaneous lithotripsy: original methods of treatment. Int Urol Nephrol 2000;32:231-233. https://doi.org/10.1023/a:1007126900772
6. Poudyal S. Current insights on haemorrhagic complications in percutaneous nephrolithotomy. Asian J Urol 2022;9:81-93. https://doi.org/10.1016/j.ajur.2021.05.007
7. Klein I, Gutiérrez Aceves J. Preoperative imaging in staghorn calculi, planning and decision making in management of staghorn calculi. Asian J Urol 2020;7:87-93. https://doi.org/10.1016/j.ajur.2019.07.002
8. Sampaio FJ. The dilemma of the crossing vessel at the ureteropelvic junction: precise anatomic study. J Endourol 1996;10:411-415. https://doi.org/10.1089/end.1996.10.411
9. Zhang LW, Fei X, Song Y. The clinical efficacy of novel vacuum suction ureteroscopic lithotripsy in the treatment of upper ureteral calculi. World J Urol 2021;39:4261-4265. https://doi.org/10.1007/s00345-021-03722-5
10. Nunes TF, Tibana TK, Santos RFT, Carramanho Junior JDC, Marchiori E. Percutaneous insertion of bilateral double J stent. Radiol Bras 2019;52:104-105. https://doi.org/10.1590/0100-3984.2017.0230
11. Coccolini F, Moore EE, Kluger Y, et al. Kidney and urotrauma: WSES-AAST guidelines. World J Emerg Surg 2019;14:54(e1-25). https://doi.org/10.1186/s13017-019-0274-x
12. Aggarwal A, Bhargava P, Bhirud DP. Renal vein injury during percutaneous nephrolithotomy: a surgical catastrophe - Management and lessons learned. Indian J Urol 2022;38:309-311. https://doi.org/10.4103/iju.iju_241_22
13. Ge G, Wang Z, Wang M, Li G, Xu Z, Wang Y, Wan S. Inadvertent insertion of nephrostomy tube into the renal vein following percutaneous nephrolithotomy: a case report and literature review. Asian J Urol 2020;7:64-67. https://doi.org/10.1016/j.ajur.2018.06.003
14. Zumrutbas AE, Toktas C, Baser A, Tuncay OL. Percutaneous nephrolithotomy in rare bleeding disorders: a case report and review of the literature. J Endourol Case Rep 2016;2:198-203. https://doi.org/10.1089/cren.2016.0105
15. Martin X, Murat FJ, Feitosa LC, et al. Severe bleeding after nephrolithotomy: results of hyperselective embolization. Eur Urol 2000;37:136-139. https://doi.org/10.1159/000020129

Informed consent: Written informed consent was obtained from the patient.

Authors' contributions to the article

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

Case Report

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1434678

Coexistence of anti-musk-positive bulbar myasthenia gravis and myotonic dystrophy Type 1: the first case report from Türkiye

Anti-musk pozitif bulbar myastenia gravis ve miyotonik distrofi Tip 1 birlikteliği: Türkiye'den ilk vaka sunumu

Esra Demir Ünal

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Abstract

Muscle-specific tyrosine kinase (MuSK) myasthenia gravis (MG) is an acute-onset subtype of MG that primarily affects the fasciobulbar muscles and begins with progressive velopharyngeal and respiratory symptoms such as early respiratory crises, swallowing, and speaking difficulties. Myotonic dystrophy Type 1 (DM1) is an autosomal dominantly inherited autoimmune neuromuscular disease characterized by distal-dominant muscle weakness, cardiovascular pathologies, and corneal disorders. In this case report, we discussed a 42-year-old female patient with a previous diagnosis of DM1 and diagnosed with MuSK-MG as a result of electroneuromyographic and antibody tests upon the development of bulbar symptoms and thymus hyperplasia. The patient underwent video-assisted thymectomy, and medical treatment was started with a combination of pyridostigmine and methylprednisolone. The coexistence of anti- MuSK positive MG with thymoid hyperplasia and DM 1 has not been reported so far, and it has been predicted that both diseases may trigger each other through neuroinflammatory mechanisms on an autoimmunergic basis.

Keywords: Autoimmunity, muscle-specific tyrosine kinase myasthenia gravis, myotonic dystrophy Type 1, neuroinflammation, thymus hyperplasia.

Demir Unal E. Coexistence of anti-musk-positive bulbar myasthenia gravis and myotonic dystrophy Type 1: the first case report from Türkiye. Pam Med J 2024;17:804-808.

Öz

Kas spesifik tirozin kinaz (MuSK) miyastenia gravis (MG), öncelikle fasyobulbar kasları etkileyen ve erken solunum krizleri, yutma ve konuşma güçlükleri gibi ilerleyici velofaringeal ve solunum semptomlarıyla başlayan, MG'nin akut başlangıçlı bir alt tipidir. Miyotonik distrofi Tip 1 (DM1), distal dominant kas zayıflığı, kardiyovasküler patolojiler ve kornea bozuklukları ile karakterize, otozomal dominant geçişli, otoimmün nöromüsküler bir hastalıktır. Bu olgu sunumunda, daha önce DM1 tanısı alan, bulber semptomları ve timus hiperplazisi gelişmesi üzerine elektronöromiyografik ve antikor testleri sonucunda MuSK-MG tanısı alan 42 yaşındaki kadın hastayı tartıştık. Hastaya video yardımlı timektomi uygulandı ve piridostigmin ve metilprednizolon kombinasyonu ile medikal tedaviye başlandı. Anti-MuSK pozitif MG ile timoid hiperplazi ve DM 1'in birlikteliği şu ana kadar bildirilmemiş olup, her iki hastalığın otoimmünerjik temelde nöroinflamatuar mekanizmalar yoluyla birbirini tetikleyebileceği öngörülmektedir.

Anahtar kelimeler: Otoimmünite, kas spesifik tirozin kinaz miyastenia gravis, miyotonik distrofi Tip 1, nöroinflamasyon, timus hiperplazisi.

Demir Ünal E. Anti-musk pozitif bulbar myastenia gravis ve miyotonik distrofi tip 1 birlikteliği: Türkiye'den ilk vaka sunumu. Pam Tıp Derg 2024;17:804-808.

Introduction

Muscle-specific tyrosine kinase (MuSK) Myasthenia Gaves (MG) is an autoimmune neuromuscular junction disease characterized by acute onset bulbar symptoms and respiratory deterioration. Diagnosis is made by MuSK-Ab testing, edrophonium/neostigmine test, and electroneurophysiological studies such as repetitive nerve stimulation (RNS), single-fiber electromyography (SFEMG), and needle EMG. In anti-MuSK-Ab positive patients, minimal follicular hyperplastic thymus (remnant) or thymoma can rarely be observed [1, 2]. Myotonic dystrophy 1 (DM1) is an autosomal dominant inherited neuromuscular systemic disease that occurs after the unstable trinucleotide (CTG) repeat expansion in dystrophia myotonia-protein kinase (DMPK) gene [3] and usually

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affects somatic and smooth muscles, as well as systemic organ disturbance. It is characterized by low amplitude in compound muscle activation potential (CMAP), especially in distal muscles in EMG tests, and early recruitment pattern and myotonic discharges inneedle EMG. In this case report, we evaluated DM1 and MG coexistence from neuroimmunologic and autoimmunergic perspectives in a patient diagnosed with DM1 who developed Anti- MuSK positive MG with thymic hyperplasia.

Case report

A 42-year-old female patient presented with difficulty in swallowing and lisping for a month. Her complaints were diurnal and tended to increase in the evening. In medical history, she had a diagnosis of Myotonic dystrophy type 1 (DM1) 10 years ago. The patient first applied to cardiology with complaints of fatigue, generalized weakness, and dyspnea, and transthoracic echocardiography revealed grade 1 atrioventricular block, mild mitral insufficiency, and grade 1 interatrial septal aneurysm. During the examination, generalized asymmetrical decreased muscle tone and loss of dominant muscle strength in the lower extremities were observed, and she was referred to Electromyography (EMG). EMG nerve conduction studies detected decreased CMAP in the right peroneal, bilateral tibial, and right ulnar motor nerves. Needle EMG showed myotonic discharges (from 1+to 4+scales) in the distal muscles, which were more prominently seen in the lower extremity (Tibialis anterior, peroneus longus, gastrocnemius medius) muscles (Figure 1). In muscle biopsy, basophilic regenerating fibers and splitting fibers varying in shape and diameter, dominated by fibrosis and adipose tissue, were observed (Figure 1). The molecular genetic analyses revealed the number of cytosine thymine- guanine (CTG) repeats to be over 100 (cytosine-CTG repeats of the ZNF9 gene was <30) in the myotonic dystrophy DM protein kinase (DMPK) fragment gene. Four years after the first diagnosis, the patient developed blurred vision and dry eyes, and the Optical coherence tomography revealed corneal thinning (285-402 microns (threshold value for average minimum corneal thickness is 492 microns)) in pachymetry mapping. The Schirmer test was evaluated as negative. The current findings were assessed as significant regarding the eye and cardiovascular involvement of DM1. In the neurologic examination, soft palate paresis with marked dysphagia and rhinolalia, along with widespread a decrease in deep tendon reflex and markedly strength loss in distal extremities in lower extremities (lower extremity distal 4/5, proximal +4/5) were detected. In the myasthenic antibody screening protocol, anti-acetylcholine receptor antibody (anti-AChR Ab) and anti-titin were evaluated as negative. The patient's anti- muscle-specific tyrosine kinase antibody (anti-MuSK Ab) was detected positive. Other autoimmune disease antibody tests were concluded as negative. Partial improvement in orofaciobulbar dysfunction (especially swallowing dysfunction) was observed with the Edrophonium test.

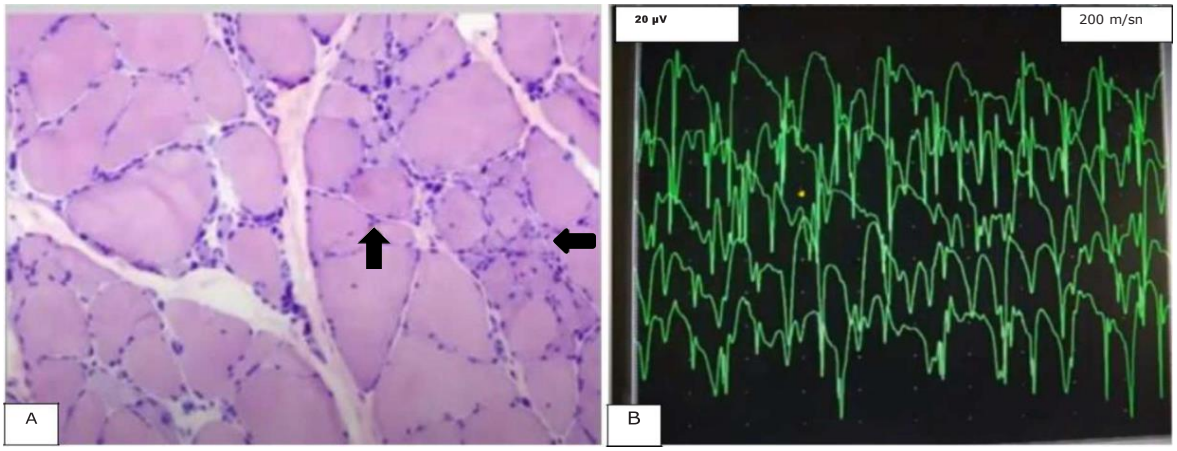

Figure 1. The histological features of muscle biopsy revealed a high number of central nuclei and a markedly increased variation in fiber diameter (black arrow) (A). Concentric needle electroneuromyography revealed myotonic discharges with variable amplitude and frequency induced by mechanical stimulation (Tibialis anterior) (B)

In the repetitive nerve stimulation test (RNS), the trapezius and orbicularis oculi muscles showed evident amplitude decrements (21% and 35%, respectively). Positron Emission Tomography computed tomography was applied after a suspicious nodular lesion in the anterior mediastinum in the thorax CT, and a low-level FDG uptake in reticular densities was observed (Figure 2). The findings were evaluated as a thymic remnant, and thymus type B2 thymoma was detected in pathological investigation (T1N0M0). The patientwas diagnosed with anti-MuSK-MG (MuSK antibody-positive seronegative MG) with thymus hyperplasia accompanying the systemic involvement (cardiac and eye) of DM. The treatment was applied with oral methylprednisolone (16 mg/day) and pyridostigmine tablet (720 mg/day). She was operated on with video-assisted thoracoscopic thymectomy, and following the operation, two courses of intravenous methylprednisolone (IVMP) (1000 mg/day) were provided progressive improvement in bulbar complaints after medical and operational treatment was observed.

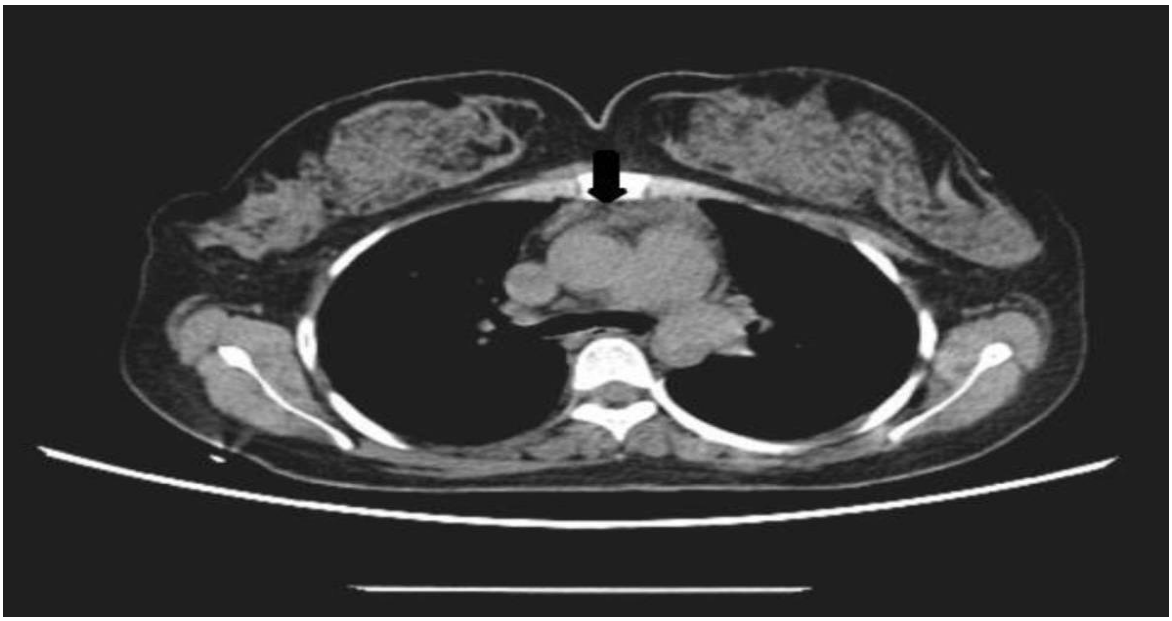

Figure 2. Thymic remnant causing low levels of FDG uptake was observed in reticular densities in the anterior mediastinum (black arrow)

Discussion

The neuromuscular junction is a particular synapse formed between motor neurons and muscle fibers, and its association with different muscular diseases has been reported in a few rare cases [4, 5]. Clinically, it is challenging to distinguish neuromuscular junction pathologies from myopathies from each other because their coexistence incidence is infrequent, and their symptoms/findings are similar. However, making a differential diagnosis, which may affect the entire treatment process, is essential in terms of diagnosis and treatment and understanding autoimmunergic and neuroinflammatory interaction mechanisms. MuSK protein is responsible for the differentiation and aggregation of AChR by triggering low-density lipoprotein receptors (LRP-4) at the neuromuscular junction [6]. MuSK antibodies consist of the HLA DR14 and DQ5-related IgG4 isotype and prevent AchR aggregation by inhibiting the MuSK-LRP4 complex [7]. DMs are genetically inherited neuromuscular diseases characterized by generalized muscle weakness and degeneration. Disease etiopathogenesis is thought to be related to the interaction of antigen-presenting cells and tool-like receptors, which increase in the extracellular matrix as a result of CTG repeat increase, and this precipitates the release of a series of Danger Associated Molecular Patterns from damaged fibers that cause aggravation of the inflammation, and muscular dystrophy [8, 9]. DM has been associated with tumors, including thymoma, but it is not clear whether this is a part of the syndrome or occurs incidentally [10]. Different studies have reported changes in the

expression of various immune mediators, such as CXCL10, CCL5, CXCL8, TNFAIP3, and TNFRSF9, in DM1-related glial cell lines [11]. Additionally, a significant increase in interferon-regulated genes (IRGs) and genes associated with the innate immune response was observed in DM1 patients compared to healthy controls [12]. These studies provide detailed information to understand different aspects of immune system dysregulation, particularly in adaptive immunity and, to a lesser degree, innate immunity in DM1. In the Observational Prolonged Trial In DM1 to Improve QoL standards (OPTIMISTIC) [13] study, the correlation between blood transcriptome and DM disease severity was examined using a number of complementary pathways, gene ontology, and upstream regulatory analyses. It has been determined that symptom severity in DM1 is associated with transcriptomic alterations in innate and adaptive immunity, specifically macrophage priming, mitochondrial protein import, and Th2-cell expansion. Based on current findings, there is an immunologic dysfunction at the root of both diseases and immunoglobulin (IVIG) treatment can be shown as evidence that immunological dysfunction can be seen after IVIG treatment in both [14, 15].

This case report presents a neuroimmunological perspective on an autoimmunergic basis to anti-MuSK-MG and DM1 coexistence. Immune mechanisms may trigger both diseases in genetically predisposed individuals, and any study that will elucidate the etiopathogenesis in this field will guide immunological treatments for both diseases.

Conflicts of interest: The authors have no potential conflicts of interest to disclose.

References

1. Poursadeghfard M, Abolhasani Foroughi A, Karamimagham S. Thymolipoma-associated myasthenia gravis with high titer of anti- muskab: a case report. Int J Mol Cell Med 2019;8:90-93. https://doi.org/10.22088/IJMCM.BUMS.8.1.90
2. Lauriola L, Ranelletti F, Maggiano N, et al. Thymus changes in anti-MuSK-positive and -negative myasthenia gravis. Neurology 2005;64:536-538. https://doi.org/10.1212/01.WNL.0000150587.71497.B6
3. Ashizawa T, Sarkar PS. Myotonic dystrophy types 1 and 2. Handb Clin Neurol 2011;101:193-237. https://doi.org/10.1016/B978-0-08-045031-5.00015-3
4. Elahi B, Laughlin RS, Litchy WJ, Milone M, Liewluck T. Neuromuscular transmission defects in myopathies: rare but worth searching for. Muscle Nerve 2019;59:475-478.
5. Rodriguez Cruz PM, Sewry C, Beeson D, et al. Congenital myopathies with secondary neuromuscular transmission defects; a case report and review of the literature. Neuromuscul Disord 2014;24:1103-1110. https://doi.org/10.1016/j.nmd.2014.07.005
6. Burden SJ, Yumoto N, Zhang W. The role of MuSK in synapse formation and neuromuscular disease. Cold Spring Harb Perspect Biol 2013;5:a009167(e1-13). https://doi.org/10.1101/cshperspect.a009167
7. Plomp JJ, Huijbers MG, van der Maarel SM, Verschuuren JJ. Pathogenic IgG4 subclass autoantibodies in MuSK myasthenia gravis. Ann N Y Acad Sci 2012;1275:114-122. https://doi.org/10.1111/j.1749- 6632.2012.06808.x
8. Tieleman AA, denBroeder AA, vande Logt AE, van Engelen BG. Strong association between myotonic dystrophy type 2 and autoimmune diseases. J Neurol Neurosurg Psychiatry 2009;80:1293-1295. https://doi.org/10.1136/jnnp.2008.156562
9. Junghans RP, Ebralidze A, Tiwari B. Does (CUG) Repeatin DMPK mRNA 'Paint' chromosome 19 to suppress distant genes to create the Diverse Phenotype of Myotonic Dystrophy?: a new hypothesis of long-range cis autosomal inactivation. Neurogenetics 2001;3:59-67. https://doi.org/10.1007/ s100480000103
10. Mueller CM, Hilbert JE, Martens W, Thornton CA, Moxley RT 3rd, Greene MH. Hypothesis: neoplasms in myotonic dystrophy. Cancer Causes Control 2009;20:2009-2020. https://doi.org/10.1007/s10552-009-9395-y
11. Azotla Vilchis CN, Sanchez Celis D, Agonizantes Juárez LE, et al. Transcriptome Analysis Reveals Altered Inflammatory Pathway in an Inducible Glial Cell Model of Myotonic Dystrophy Type 1. Biomolecules 2021;11:159(e1-22). https://doi.org/10.3390/biom11020159
12. Jeremy D, Rhodes JD, Lott MC, Russell SL, et al. Activation of the innate immune response and interferon signalling in myotonic dystrophy type 1 and type 2 cataracts, Human Molecular Genetics 2012;21:852-862. https://doi.org/10.1093/hmg/ddr515
13. Nieuwenhuis S, Widomska J, Blom P, et al. and on behalf of the Optimistic Consortium. Blood transcriptome profiling links immunity to disease severity in myotonic dystrophy Type 1 (DM1). Int J Mol Sci 2022;23:3081(e1-24). https://doi.org/10.3390/ijms23063081
14. Sasson SC, Corbett A, Mc Lachlan AJ, et al. Enhanced serum immunoglobulin g clearance in myotonic dystrophy-associated hypogammaglobulinemia: a case series and review of the literature. J Med Case Rep 2019;13:338(e1-7). https://doi.org/10.1186/s13256-019-2285-3

15. Takahashi H, Kawaguchi N, Nemoto Y, Hattori T. High-dose intravenous immunoglobulin for the treatment of MuSK antibody-positive seronegative myasthenia gravis. J Neurol Sci 2006;247:239-241. https://doi.org/10.1016/j.jns.2006.05.065

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The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Before starting the study, the corresponding author obtained written consent from the participant. The consent form, patient demographic, and clinical and imaging information of each patient included in the study were recorded and stored in the patient forms by the corresponding author.

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