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okarabay@sakarya.edu.tr
GSM: +90 5422431670
Sakarya Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları Anabilim Dalı, Sakarya, Türkiye

Prof. Dr. Süleyman KALELİ
skaleli@sakarya.edu.tr
GSM: +90 536 549 11 61
Sakarya Üniversitesi Tıp Fakültesi, Sakarya, Türkiye

Doç. Dr. Nevin İNCE
drnevince@gmail.com
GSM: +90 505 350 58 39
Düzce Üniversitesi Tıp Fakültesi, Düzce, Türkiye

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):103-110 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):103-110.*

Evaluating the Validity and Reliability of the Feeding to Manage Child Behavior Questionnaire (FMCBQ) among Turkish Parents

Çocuk Davranışlarını Yönetmek için Besleme Anketi'nin (ÇDYBA) Türk Ebeveynlerde Geçerlik ve Güvenirliğinin Değerlendirilmesi

[1,2]Murat YÜCEL, [3]Ümüş ÖZBEY YÜCEL

[1]Program of Medical Documentation and Secretariat, Sabuncuoğlu Şerefeddin Health Services Vocational School, Amasya University, Amasya, Türkiye
[2]Institute of Health Sciences, Department of Biostatistics, Eskişehir Osmangazi University, Eskişehir, Türkiye
[3]Department of Nutrition and Diet, Faculty of Health Sciences, Amasya University. Amasya, Türkiye

Murat Yücel: https://orcid.org/0000-0002-4506-8143
Ümüş Özbey Yücel: https://orcid.org/0000-0002-1438-0791

ABSTRACT

Objective: This study aimed to evaluate the validity and reliability of the Turkish version of the Food to Manage Child Behavior Questionnaire (FMCBQ-T).

Materials and Methods: A total of 256 parents participated in the study, and the data were collected through a survey. Content validity was evaluated using the Content Validity Ratio (CVR) and the Content Validity Index (CVI). Construct validity was performed with Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA).

Results: The majority of parents were between the ages of 31-40 (56.3%) and female (83.9%). The CVR was 1 for each item, and the CVI was 1 for the scale. The Turkish version of the scale was determined to have three factors and nine items, with factor loadings ranging from 0.63-0.90. Cronbach's alpha coefficient was 0.84 for the total scale. CFA fit indices were found to be χ^2/df=1.63, RMSEA=0.06, TLI=0.97, CFI=0.98, GFI=0.96, AGFI=0.92.

Conclusion: FMCBQ-T is a valid and reliable tool for Turkish parents. Since it is known that the feeding style in childhood affects later years of life, FMCBQ-T is necessary to evaluate how parents use food to manage their children.

Keywords: Child feeding, child behavior, food to soothe, food as reward

ÖZ

Amaç: Çocuk Davranışlarını Yönetmek İçin Besleme Anketi'nin (ÇDYBA-T) Türkçe geçerliğini ve güvenirliğini değerlendirmek amaçlanmıştır.

Materyal ve Metot: Çalışmaya toplam 256 ebeveyn katılmış ve veriler anket yoluyla toplanmıştır. Kapsam geçerliği, kapsam geçerlik indeksi (KGİ) ve içerik geçerlik oranı (KGO) ile değerlendirilmiştir. Yapı geçerliliği, açıklayıcı faktör analizi (AFA) ve doğrulayıcı faktör analizi (DFA) ile gerçekleştirilmiştir.

Bulgular: Ebeveynlerin çoğunluğu 31-40 yaş aralığında (%56,3) ve kadın (%83,9)'dı. KGO'nun her bir madde için 1, KGİ ise tüm ölçek için 1 olarak bulunmuştur. Ölçeğin Türkçe versiyonunun 3 faktör ve 9 maddeden oluştuğu belirlenmiştir. Faktör yükleri 0,63 ile 0,90 arasındadır. Cronbach' a katsayısının toplam ölçek için 0,84 olduğu bulunmuştur. DFA uyum indeksleri χ^2/sd =1,63, RMSEA=0,06, TLI=0,97, CFI=0,98, GFI=0,96 ve AGFI=0,92 olarak bulunmuştur.

Sonuç: ÇDYBA-T, Türk ebeveynler için geçerli ve güvenilir bir araçtır. Çocukluktaki beslenme tarzının yaşamın sonraki yıllarını etkilediği bilindiğinden, ÇDYBA-T ebeveynlerin çocuklarını yönetmek için yiyecekleri nasıl kullandıklarını değerlendirmede oldukça gereklidir.

Anahtar Kelimeler: Çocuk beslenmesi, çocuk davranışı, ödül olarak yiyecek, yatıştırıcı yiyecek

Sorumlu Yazar / Corresponding Author:
Murat Yücel
Sabuncuoğlu Şerefeddin Health Services Vocational School, Program of Medical Documentation and Secretariat, Amasya University, Amasya, Türkiye
Tel: +90242 618 63 35
E-mail: murat.yucel@amasya.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 23/10/2024
Kabul Tarihi/ Accepted: 11/05/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Yücel M and Özbey Yücel Ü. Evaluating the Validity and Reliability of the Feeding to Manage Child Behavior Questionnaire (FMCBQ) among Turkish Parents. Online Türk Sağlık Bilimleri Dergisi 2025;10(2):**103-110**. doi: 10.26453/otjhs.1570284

INTRODUCTION

Nutritional behaviors that begin in the family, especially through imitation of the mother, significantly shape the future nutritional behavior of children.[1] As these behaviors are known to be passed down to subsequent generations, teaching children proper nutritional behaviors is crucial.[2]

During childhood, when mood changes are frequent, food is often used as a tool to achieve the desired behavior. Different foods may be offered to children in order to correct the child's negative behavior or to reward correct behavior.[3] Such interventions, which parents may also use to save time, are very effective in the emotional control of children.[4]

Food, snacks, or drinks can be offered to calm the child who becomes angry when the parent is busy or in public places.[5] In particular, food-mediated reward practices, based on the parents' perceptions or expectations can facilitate the management of a child's behavior. However, it is not easy to determine in which situations these rewards, which do not have a direct nutritional purpose, are preferred.[2,4,5]

In relation to the information given above, a tool titled "The Feeding to Manage Child Behavior Questionnaire (FMCBQ)" was developed by Savage et al. to determine situations in which child behavior is managed through feeding reward.[6] In this study, it was aimed to adapt the FMCBQ in the Turkish language and to determine its validity and reliability among Turkish parents.

MATERIALS AND METHODS

Ethical Considerations: The study was conducted in accordance with the Declaration of Helsinki, and all procedures were approved by the Akdeniz University Faculty of Medicine Ethics Committee (Date: 20.07.2022, decision no: KAEK-482). Informed consent was obtained from all subjects.

Research Design and Sampling: This study was conducted in public kindergartens in Antalya, Türkiye, between April to August 2022. The sample consisted of parents with children aged between 2-6 years who volunteered to participate in the study. Parents whose children used medications that affect appetite or had any chronic disease were excluded (Figure 1). In adaptation studies, it is recommended that the approximate sample size be at least 5-10 times the number of scale items (between 9*5=45 and 9*10=90).[7] However, if the number of items in the scale is low, a minimum sample of 200 participants is considered more appropriate.[8,9] This study was completed with a total of 256 parents, meeting the sample requirements in the literature.

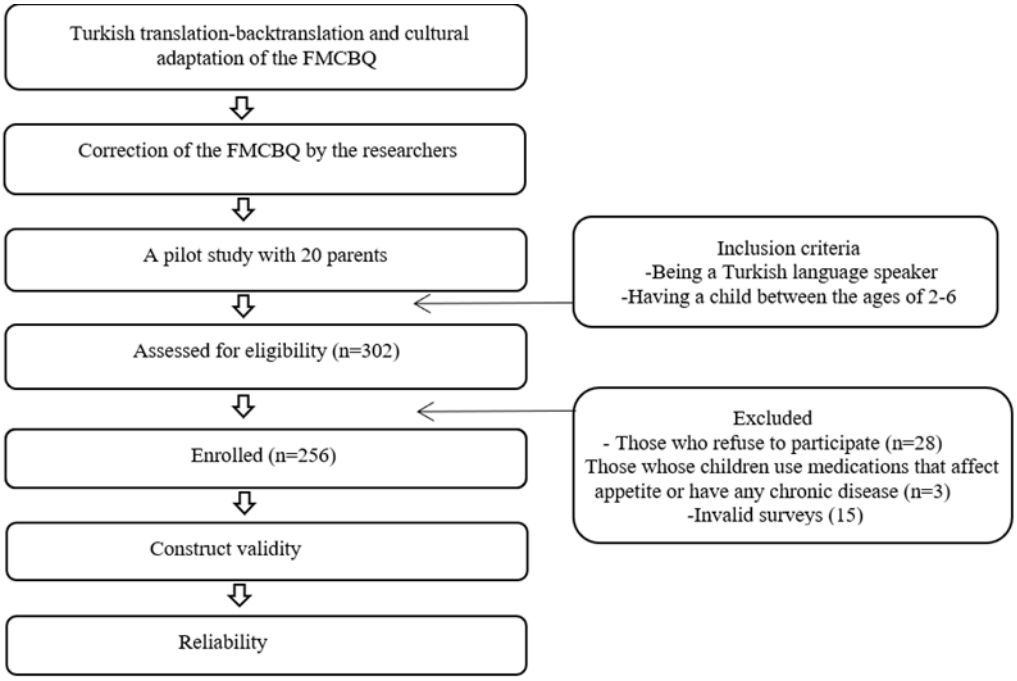

Figure 1. Flowchart of the study.

Data Collection: Study data were collected by contacting parents through kindergarten teachers. Before the study began, parents were provided with necessary information and a survey form. The first part of the form included socio-demographic information, while the second part consisted of FMCBQ items.

Body weight and height were measured using a scale and a non-stretchable tape, following standard procedures. Parents' BMI was calculated by dividing body weight by the square of height in meters (kg/m²) (WHO).[10] Children's BMI-for-ages were calculated using the WHO Anthro-Plus program.[11] All BMI values were classified based on WHO criteria.[10,11]

Original Version of the Feeding to Manage Child Behavior Questionnaire (FMCBQ): Before the study, the necessary permission was obtained via e-mail from the developers of the questionnaire. The FMCBQ originally comprises two factors and nine items (5-point Likert scale). Each item is scored from 0 to 4 points (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Always). The average score of each factor is calculated by dividing the total score by the number of items, ranging from 0 to 4 points. Unanswered items are excluded from scoring.[6]

The Food to Soothe (FTS) factor assesses the frequency of using food to prevent negative reactions or to keep children calm. It includes five items (1, 4, 5, 8, 9). The Food as Reward (FAR) factor evaluates the frequency of using food to reward children's behavior or food consumption and includes four items (2, 3, 6, 7).[6]

Turkish Translation and Adaptation Procedure: The translation-back-translation method was used for the Turkish adaptation process. In the first stage, the scale was translated from English to Turkish by individuals fluent in both languages, including two experts in English Language and Literature and five experts in Nutrition and Dietetics. The resulting draft was reviewed by five Nutrition and Dietetics experts for semantic integrity, consistency, and grammatical accuracy. After the evaluation, necessary corrections were made, and a pilot test was conducted with a sample of 20 parents. Based on the pilot test results, it was determined that each item was understandable, appropriate, and the total response time was approximately five minutes.

Content Validity and Construct Validity: Content validity calculations were made using the Lawshe Technique.[12] Content Validity Ratio (CVR) and Content Validity Index (CVI) were calculated based on the opinions of five experts. Before conducting Exploratory Factor Analysis (EFA), the adequacy of the sample size was evaluated using the Kaiser-Meyer-Olkin (KMO) test. Bartlett's test of sphericity was applied to assess the multivariate normal distribution assumption.[13]

To determine the theoretical structure, the Varimax rotation method was used to maximize the factor loadings of the items as much as possible.[14] The theoretical structure was tested using CFA. Fit indices, including χ^2/sd, RMSEA, TLI, CFI, GFI, and AGFI, were calculated using the maximum likelihood method.[15]

Reliability analysis was evaluated using the split-half method, Cronbach's alpha coefficient, Hotelling's T^2 test, and Tukey's test. In the split-half method, the scale was randomly divided into two parts, and the relationship between them was evaluated using the Spearman-Brown test.[16]

Statistical Analysis: SPSS and AMOS software were used for data analysis. During the validity assessment, EFA was conducted to determine the theoretical structure, with the varimax rotation method applied to maximize item factor loadings. The verification of the theoretical structure was tested with CFA. In the CFA, the fit of the model was evaluated with the χ^2/df, RMSEA, AGFI, GFI, CFI, and TLI.[15] During the reliability assessment, the internal consistency of the scale was tested with Cronbach's alpha coefficient and the split-half method. The scale's unbiasedness was assessed with Hotelling's T^2 test, and its additivity was examined using Tukey's test. The statistical significance level for the analyses was set at $p < 0.05$.

RESULTS

A total of 256 parents participated in the study. The majority were aged 31-40 years (56.3%), female (83.9%) and university graduates (48.8%). Approximately 97.6% of the participants were married, and 46.1% had one child. According to BMI classification, 59.0% of parents and 50% of children were classified as normal (Table 1).

The FMCBQ originally comprises nine items and two factors. However, as a result of the factor analysis, a three-factor structure with eigenvalues greater than one was determined, and the scree plot confirmed the existence of the factors. The cumulative variance value was calculated as 70.9% for the three factors. The FTS factor included five items (1, 4, 5, 8, 9), consistent with the original scale. However, the FAR factor is split into two separate factors, each comprising two items. The new factors were submitted for evaluation to five academicians for naming. Based on their consensus, the second factor was named "Food as a behavior reward (FBR)" (items 2 and 3), and the third factor was named "Food as an eating reward (FER)" (items 6 and 7). Factor loadings ranged from 0.63 to 0.90, with no overlapping items. In its final form, the scale was confirmed to have nine items and three factors. Each factor exhibited summability.

Cronbach's alpha coefficient was found to be 0.84 for all items, 0.88 for the FTS factor, 0.68 for the FBR factor, and 0.86 for the FER factor. CVR and CVI were calculated using the Lawshe Technique. The CVR was found to be 1.0 for each item, while the CVI was found to be 1.0 for the entire scale. The KMO test for sampling adequacy yielded a value of 0.88. Bartlett's test of sphericity was statistically significant ($p<0.05$) (Table 2).

Table 1. Demographic information.

		n (%)
Age	18-30	78 (30.4)
	31-40	144 (56.3)
	41 +	34 (13.3)
Gender	Woman	215 (83.9)
	Man	41 (16.1)
Education	Primary school	10 (3.9)
	High school	41 (16.1)
	University	125 (48.8)
	Master+	80 (31.2)
Marital status	Married	250 (97.6)
	Single	6 (2.4)
Number of children	1	118 (46.1)
	2	112 (43.8)
	3 +	26 (10.1)
BMI (kg/m2)	Underweight	5 (2.0)
	Normal	151 (59.0)
	Overweight	81 (31.5)
	Obese	19 (7.5)

Table 2. Explanatory factor and internal consistency analysis results of the FMCBQ-T.

Items	**Food to soothe**	**Food as behavior reward**	**Food as eating reward**	**Total scale**
(1) I give snacks or drinks as a way to distract and keep my child quiet when my child is acting out (ex: throwing a tantrum, whining, etc.)	0.70			0.57
(2) I give snacks or drinks as a way to distract and keep my child quiet when my child is sad or upset	0.76			0.67
(3) I give snacks or drinks as a way to distract and keep my child quiet when we are in public settings (ex, church/mosque, shopping, doctor's office, theatre, etc.)	0.70			0.64
(4) I give snacks or drinks to distract or keep my child quiet when I am feeling frustrated, stressed, or tired	0.70			0.71
(5) I give snacks or drinks to distract or keep my child busy when I am trying to get something done at home (example: on the phone, cleaning the house, preparing dinner, getting dressed, etc.)	0.81			0.66
(6) I offer my child his/her favorite foods as a reward for good behavior		0.63		0.62
(8) I withhold sweets/desserts from my child in response to bad behavior		0.90		0.82
(7) I offer my child a "treat" or "dessert" to get my child to eat his/her vegetables			0.88	0.85
(9) I offer my child a "treat" or "dessert" for eating everything on his/her plate			0.90	0.85
Eigenvalue	4.18	1.19	1.00	
Variance explanation (%)	46.44	13.26	11.20	70.90
Cronbach's *a* coefficient	0.88	0.68	0.86	0.84
CVI (entire scale)				1.0
CVR (each item)	1.0	1.0	1.0	
KMO				0.88
Bartlett's test of sphericity				<0.05

The fit index (χ^2/df) was found to be 1.63, and the RMSEA value was 0.06. Other CFA fit indices were found to be TLI = 0.97, CFI = 0.98, GFI = 0.96, AGFI = 0.92. Using the split-half method, the scale was divided into two parts, and the correlation between them was 0.76. The scale was found to be unbiased by Hotelling's T^2 test ($p < 0.05$). The Tukey test result for the scale was found to be significant ($p<0.05$) (Table 3).

Factor loadings of the scale items vary between 0.44 and 0.93. All standardized path coefficients of this model were found to be more than 0.4. The items with the lowest and highest factor loadings were identified within the FBR factor (Figure 2).

DISCUSSION AND CONCLUSION

Parents, who play a primary role in their child's nutrition, may use food as a reward to save time or encourage specific behaviors. Foods can also be used as a calming tool to ease children's challenging hospital experiences.[2,5] FMCBQ, developed by Savage et al.[6] is a valuable tool for identifying how and

Table 3. The fit statistics of the FMCBQ-T according to confirmatory factor analysis.

Fit statistic	Value	Criteria[15]
χ^2/df	1.63	<5
RMSEA	0.06	<0.08
TLI	0.97	>0.90
CFI	0.98	>0·90
GFI	0.96	>0.90
AGFI	0.92	>0.90
Split-half correlation coefficient	0.76	
Hotelling's T^2 test	$p < 0.05$	
Tukey test	$p < 0.05$	

RMSEA: root mean square error of approximation; TLI: Tucker-Lewis index; CFI: comparative fit index; GFI: goodness of fit index; AGFI: adjusted goodness of fit index.

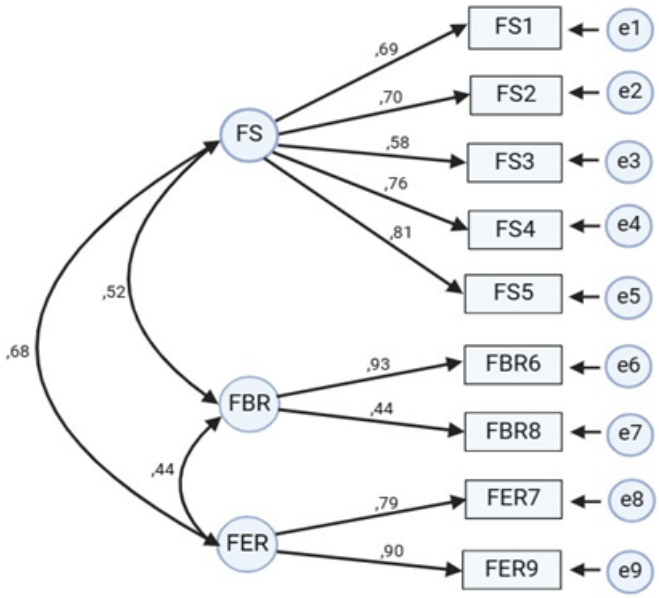

Figure 2. Confirmatory factor analysis diagram of the FMCBQ-T. FS: Food to soothe; FBR: Food as behavior reward; FER: Food as eating reward.

in which situations child behaviors are managed through food. Therefore, adapting FMCBQ into Turkish will meet an important need. This study was conducted with parents to test the Turkish version of FMCBQ and to evaluate its validity and reliability of FMCBQ-T.

CVR and CVI values were found to be 1, and the construct validity of FMCBQ-T was evaluated by five experts in the field of Nutrition and Dietetics.[13] Accordingly, experts confirmed that the scale accurately reflected its intended content. In this study, the KMO value was 0.88, and Bartlett's test of sphericity was found to be statistically significant ($p<0.05$). Therefore, the multivariate normal distribution assumption and factor analysis criteria were met.[17] The sample size was determined based on the guidelines outlined in the methods section, ensuring a sufficient number of parents were included.[7,8] FMCBQ-T was administered to a total of 256 parents.

EFA was performed to create the theoretical structure of the tool.[14] The original FMCBQ includes nine items and two factors, consisting of FTS and FAR.[6] However, in this study, factor analysis resulted in the nine items loading onto three distinct factors. The item loadings for the FTS factor were consistent with the original scale. In contrast, the four items of the FAR factor split into two separate factors, each with two items, rather than loading onto a single factor as in the original scale. The increase in the number of factors was reviewed by five experts, who determined that the FAR factor items assess rewards for specific behaviors or eating. Consequently, the three-factor structure was deemed more appropriate for the model.

Examination of the FAR factor items reveals that rewards are given for specific behaviors or eating. Thus, it is expected that this factor might split during the adaptation process. The outcome may also stem from cultural differences. In Turkish culture, it is a common practice from early childhood to use food as a reward for certain behaviors or adequate food intake, both among healthy children and children with autism, in whom eating behavior problems are frequently observed.[18-20] Additionally, semantic differences during the adaptation process and characteristics of the sample may also contribute to factor changes. In adaptation studies, equivalents in the target language can evoke different associations. Consequently, the FAR factor was divided into two factors, FBR and FER.

All factor loadings exceeded 0.40, the reference value in the literature.[17] According to EFA, the factors explain 70.9% of the total structure, and this value was above the minimum reference value of 50.0%.[21] Consequently, the three-factor structure of the FMCBQ-T effectively explained the theoretical model.[17,21] Similar to this study, other studies assessing parents' attitudes toward child feeding and obesity risk used scales that separately evaluate behavioral and nutritional factors. [22-24]

In adaptation studies, it is recommended to verify the theoretical model derived from EFA using CFA. Path coefficients in CFA should exceed 0.4.[15] In this study, the path coefficients for the items ranged from 0.44 to 0.93, indicating highly satisfactory results.[7] All CFA fit indices ($\chi 2/df= 1$, RMSEA=0.06, TLI=0.97, CFI=0.98, GFI=0.96 and AGFI=0.92) met the required criteria.[15] The adapted scale's fit indices outperformed those of the original version (RMSEA =0.12, GFI =0.90, CFI =0.88).[6]

The internal consistency of the FMCBQ-T was assessed using Cronbach's alpha coefficients. Cronbach's alpha coefficient between 0.60 and 0.80 indicates that the scale is reliable.[25] In this study, the Cronbach's alpha coefficients for the FTS, FBR and FER factors were 0.88, 0.68, and 0.86, respectively, and the coefficient for the entire scale was 0.84. In the original version, Cronbach's alpha coefficients were 0.84 for the FTS factor and 0.70 for the FAR factor.[6] In another study evaluating parents' feeding behaviors using the FMCBQ, Cronbach's alpha coefficients were 0.87 for the FTS factor and 0.72 for the FAR factor.[26]

A significant positive relationship was found between the FTS factor and child BMI ($p<0.05$). Given that increased BMI is associated with higher food consumption, it is expected that children given more food for soothing purposes may have a higher BMI. Several studies have indicated that the frequent use of food to soothe children in early childhood is associated with obesogenic eating behaviors in later childhood and exerts long-term effects on dietary habits and weight status.[27-30] Although parents use foods to soothe children for various reasons, this practice represents a major risk factor for childhood obesity.

This study has some limitations. Most participants were women, which was anticipated given that women tend to be more involved in child feeding than men. To minimize participation bias, the survey was distributed to both mothers and fathers, however, mothers provided the majority of responses. This may reflect mothers' primary role in child feeding within families or fathers' relative disengagement from these responsibilities. Future studies could address this limitation by implementing strategies to enhance father participation, such as targeted sampling through father-focused groups or social media platforms appealing to male parents. Additionally, the study was conducted in a single city, so the results may not be representative of the broader population. Future research should include more diverse geographic areas, a more balanced gender distribu-

tion, and larger sample sizes to improve generalizability.

In conclusion, this study demonstrated that the FMCBQ-T is a valid and reliable tool for Turkish parents. Due to cultural differences and feeding practices, the original two-factor scale was loaded onto three factors during the adaptation process. The adapted version, which distinguishes between behavioral and eating components, is better suited for the Turkish population. Given that childhood feeding practices influence later life, FMCBQ-T is an essential tool for assessing how parents use food to manage their children's behavior. Future studies should involve larger and more diverse regions and include greater father participation to evaluate further the use of food in managing children's behavior.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, and all procedures were approved by the Akdeniz University Faculty of Medicine Ethics Committee (Date: 20.07.2022, decision no: KAEK-482).

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

Author Contributions: Concept; MY, Supervision; MY-UOY; Materials; MY-OUY; Data Collection; MY-OUY; Analysis and/or Interpretation; MY-UOY, Writing: MY-UOY.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):111-117 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):111-117.*

Food Insecurity in Relation to Sustainable and Healthy Eating Behaviors and Obesity in Türkiye

Türkiye'de Besin Güvencesizliğinin Sürdürülebilir ve Sağlıklı Beslenme Davranışları ve Obezite ile İlişkisi

[1]Gökçe ÜNAL

[1]Ondokuz Mayıs University, Faculty of Health Sciences, Department of Nutrition and Dietetics, Samsun, Türkiye

Gökçe Ünal: http://orcid.org/0000-0002-9657-2358

ABSTRACT

Objective: This study aims to determine food insecurity (FI) in relation to sustainable and healthy eating behaviors and obesity in Türkiye.

Materials and Methods: The study was conducted between March and May 2023 in Samsun, Türkiye and included 461 people (67.0% women; aged 19 years and over). Data were collected via the online survey method. Using self-reported body weight (kg) and height (m), obesity was determined based on BMI ≥30 kg/m^2. The Food Insecurity Experience Scale (FIES) and Sustainable and Healthy Eating Behaviors Scale (SHEBS) were administered.

Results: The rate of FI was 42.5% and was higher in individuals aged 19–34 years (50.9%) than in individuals aged 35–49 years (36.4%) and 65+ years (34.0%) (p=0.03). FI was associated with a lower risk of obesity in the unadjusted model (p=0.005). After adjusting for gender, age, marital status and education degree, FI was no longer significantly associated with obesity (p=0.07) and was not associated with SHEBS score (p=0.61).

Conclusions: This study suggests that FI is not related to sustainable and healthy eating behaviors and obesity in this population. More studies investigating FI at the individual level in larger populations in Türkiye and the environmental and health impacts of FI are needed.

Keywords: Diet, environmental health, food insecurity, hunger, sustainable development

ÖZ

Amaç: Bu çalışma, Türkiye'de besin güvencesizliğinin (BG) sürdürülebilir ve sağlıklı beslenme davranışları ve obezite ile ilişkisini belirlemeyi amaçlamaktadır.

Materyal ve Metot: Çalışma Mart-Mayıs 2023 tarihleri arasında Samsun'da (Türkiye) gerçekleştirilmiş ve 461 bireyi (%67,0 kadın; 19 yaş ve üzeri) kapsamıştır. Veriler çevrimiçi anket yöntemiyle toplanmıştır. Bireylerin kendi bildirdikleri vücut ağırlığı (kg) ve boy uzunluğu (m) bilgileri kullanılarak, obezite BKİ ≥30 kg/m^2 olarak belirlenmiştir. Gıda Güvencesizliği Deneyim Ölçeği (GGDÖ) ve Sürdürülebilir ve Sağlıklı Beslenme Davranışları Ölçeği (SSBDÖ) uygulanmıştır.

Bulgular: BG oranı %42,5'tir ve 19-34 yaş arası bireylerde (%50,9), 35-49 yaş arası (%36,4) ve 65 yaş üstü (% 34,0) bireylere göre daha yüksektir (p=0,03). BG, düzeltilmemiş modelde daha düşük obezite riski ile ilişkilendirilmiştir (p=0,005). Cinsiyet, yaş, medeni durum ve eğitim derecesi için düzeltme yapıldıktan sonra, BG ile obezite (p=0,07) ve SSBDÖ puanı arasında anlamlı bir ilişki bulunmamıştır (p=0,61).

Sonuç: Bu çalışma, BG'nin bu popülasyonda sürdürülebilir ve sağlıklı beslenme davranışları ve obezite ile ilişkili olmadığını göstermektedir. Türkiye'de daha geniş popülasyonlarda bireysel düzeyde BG'yi ve BG'nin çevresel ve sağlık etkilerini araştıran daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Açlık, besin güvencesizliği, çevre sağlığı, diyet, sürdürülebilir kalkınma

Sorumlu Yazar / Corresponding Author:
Gökçe Ünal
Ondokuz Mayıs University, Kurupelit Campus, Faculty of Health Sciences, 55200, Atakum, Samsun, Türkiye
Tel.: +90(362) 312-1919 / 6392
E-mail: gokce.unal@omu.edu.tr, gokce_unal@yahoo.com.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 03/12/2024
Kabul Tarihi/ Accepted: 24/04/2025
Online Yayın Tarihi/ Published:30/06/2025

Atıf / Cited: Ünal G. Food Insecurity in Relation to Sustainable and Healthy Eating Behaviors and Obesity in Türkiye. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):111-117. doi: 10.26453/otjhs.1595684

INTRODUCTION

Food insecurity (FI) is a growing public health problem, especially in low- and middle-income countries, where a rapid transition in dietary habits, characterized by increased access to fast-food foods, is taking place.[1] One of the reasons for the dietary transition is the limited access to healthy foods that provide the nutrients necessary for a healthy life.[2] FI refers to inadequate access to food as well as low-quality nutrition. Around 41 per cent of the world's population is estimated to have suffered from FI in 2021.[3] This has implications for increasing rates of non-communicable diseases, particularly obesity and obesity-related hypertension, diabetes and cardiovascular diseases.[4] The global prevalence of obesity has been increasing,[5] and according to the most recent report, Türkiye, a middle-income Eastern Mediterranean country, has the highest prevalence of overweight and obese individuals in the European region.[6] The relationship between FI and obesity is mediated by many factors, including diet. Households experiencing FI were reported to have unhealthier diets than food-secure households, with higher consumption of fast food and sugary drinks and lower consumption of vegetables and fruits.[7] As FI increases, the consumption of nutrient-rich milk, vegetables and fruits decreases while the consumption of foods with high energy density and low nutrient content increases.[8]

Sustainable nutrition refers to the ability to meet the nutritional needs of current populations without reducing the ability of future generations to meet their needs and without harming the environment and natural assets. Sustainable diets are nutritionally adequate, safe, healthy, culturally acceptable, accessible, economically fair and affordable, while also maximizing human and natural resources. They are also protective and respectful of ecosystems and biodiversity.[9] Accordingly, sustainable dietary options that take into account the economic, health and sustainable aspects of food consumption are expected to alleviate FI and the health burden that it causes.[10] Unsustainable food systems often fail to provide the amount or type of food needed to maintain population health, leading to FI and obesity as a result of unhealthy diets.[11] Unsustainable and unhealthy diets can lead to overweight, obesity and obesity-related health problems, jeopardize food resources for current and future generations and cause irreversible environmental problems.[12,13]

This study aims to define FI, sustainable and healthy eating behaviors and obesity among individuals over 19 years of age in Türkiye and to determine FI in relation to sustainable healthy eating behaviors and obesity.

MATERIALS AND METHODS

Ethics Committee Approval: Ethics committee approval was received from the Ondokuz Mayıs University Ethics Committee (Date: 11/01/2023, decision no: 2022/584). The study was planned under the Helsinki Principles.

Study Design and Participants: This is a descriptive, cross-sectional study. The study sample was determined using a convenience sampling method. The study was conducted between March 2023 and May 2023 at Ondokuz Mayıs University in Samsun, Türkiye. Data were collected via the online survey method. The study was based on volunteers, and the subjects were included after having given their informed consent. Following the announcement of the survey via social media and messaging applications, individuals who consented to participate were included. Individuals under the age of 19 (children and adolescents) and pregnant women were excluded from the study. A sample size calculation was performed by calculating the effect size based on the data from the study, which found a significant difference between the diet quality scores of individuals with high and very low levels of FI.[14] The sample size was calculated using G*Power software: employing a one-tailed analysis with a 0.33 effect size and applying a power of 0.95 and a significance level of 0.05. This resulted in a sample size of 394.

Measures: Participants′ characteristics (i.e., gender, age, marital status, education degree, smoking status, income/expenditure balance) were noted. The participants were grouped into four categories: 19–34 years, being young adults; 35–49 years, being early middle-aged adults; 50–64 years, being late middle-aged adults; 65+, being old age. These age cut-off points have been chosen so they represent the life phases of the adult life span based on a previous study by Franssen et al. and the United Nations' definition of old age.[15,16] Self-reported body weight (kg) and height (cm) values of the participants were recorded, and body mass index (BMI) was calculated by dividing body weight (kg) by height squared (m^2). According to the World Health Organization classification, underweight was defined as <18.50 kg/m2, normal weight as 18.50-24.99 kg/m2, overweight as 25.00-29.99 kg/m2 and obesity as ≥30.00 kg/m2.[17]

The Food Insecurity Experience Scale (FIES), which was developed by the Food and Agriculture Organization of the United Nations[18] to measure FI at the individual level, was used to measure FI in this study. The scale has been translated into many languages, including Turkish,[1,19] and used in Turkey Nutrition and Health and Health Survey (TNHS) 2017.[20] The measurement is based on the circumstances and behaviors that respondents to an 8-item

questionnaire reported, which resulted from their inability to access food due to a lack of money or other resources. Responses are coded as 1 for "yes" or 0 for "no".[1] Those who answered no to all 8 items were defined as food-secure, while those who answered yes to at least one item were identified as food-insecure. While defining groups based on food security, this study focused on the dichotomous variable: being food-secure versus being food-insecure, based on a previous study.[21]

The Sustainable and Healthy Eating Behaviors Scale (SHEBS) was applied to evaluate sustainable and healthy eating behaviors. The scale was created based on the LiveWell method, the FAO definition of a sustainable diet, and the essentials of sustainable and healthful eating practices.[22] The scale's Turkish version's validity was assessed by Koksal et al.[23] The scale consists of 32 items in total, with responses on a seven-point Likert scale ranging from never to always. The items are divided into the following seven components: considering quality labels and choosing regional and organic foods, consuming seasonal food and avoiding food waste, reckoning with animal welfare, reduction of meat consumption, choosing healthy foods and aiming for a balanced diet, favoring local food, and choosing low-fat foods. Higher scores on this scale indicate higher numbers of sustainable and healthy eating behaviors. Cronbach's alpha coefficient was reported as 0.90 for the whole scale and 0.61-0.82 for the subscales.

Statistical Analyses: Data analysis was performed in the IBM Statistical Package for the Social Sciences (SPSS), Version 24. The study variables were described using percentages, frequencies, means, and standard deviations. The independent samples t-test and the one-way analysis of variance (One-Way ANOVA) test, followed by the Bonferroni post hoc test, were conducted to identify differences in SHEBS scores based on participant characteristics. Chi-square tests were applied to report differences in rates of FI and obesity according to the characteristics of the participants. Linear regression models were evaluated to determine associations between FI (independent variable) and sustainable and healthy eating behaviors (total and component scores of SHEBS) as dependent variables. Binary logistic regression models were administered to investigate the associations between FI (independent variable) and obesity as the dependent variable. Models adjusted for gender, age, marital status, and education degree. The results were evaluated at the 95% confidence interval and the significance level of $p < 0.05$.

RESULTS

A total of 461 individuals, mostly women (67.0%) and the majority of whom were between the ages of 19-34 (37.5%), participated in the study. The participants were mainly married (54.7%), graduates of high school and above (67.9%) and non-smokers (73.5%). They mostly (80.5%) had an income that was equal to or more than their expenditure. Most individuals (39.0%) had a normal weight, while the overweight rate was 33.6% (Table 1).

Table 1. Demographic information.

Characteristics		Data n (%)
Gender	Women	309 (67.0)
	Men	152 (33.0)
Age	19-34 years	173 (37.5)
	35-49 years	99 (21.5)
	50-64 years	95 (20.6)
	65+ years	94 (20.4)
Marital status	Single	209 (45.3)
	Married	252 (54.7)
Education degree	Middle school and below	148 (32.1)
	High school and above	313 (67.9)
Smoking status	Yes	122 (26.5)
	No	339 (73.5)
Income/expenditure balance	More	113 (24.5)
	Equal	258 (56.0)
	Less	90 (19.5)
BMI categories	Underweight	24 (5.3)
	Normal weight	180 (39.0)
	Overweight	155 (33.6)
	Obesity	102 (22.1)

BMI: Body Mass Index.

Table 2 shows that 42.5% of the participants were food-insecure and that the rate of participants with obesity was 22.1%. The SHEBS score differed according to gender (higher among women), age (higher among older ages), marital status (higher among married people) and education degree (higher among middle-school graduates and below) (p<0.001). The obesity rate differed according to age (higher among older ages), marital status (higher among married people) and education degree (higher among middle-school graduates and below) (p<0.001). Moreover, food-insecure participants had lower rates of obesity than those who were food-secure (15.8% vs. 26.8%; p=0.005). The FI rate differed significantly by age. Accordingly, the rate of FI was higher in individuals aged 19–34 years (50.9%) than in individuals aged 35–49 years (36.4%) and 65 years and over (34.0%) (p=0.03).

The two models (unadjusted and adjusted) for linear regression indicated associations between FI (independent variable) and SHEBS (total and component scores). There were no significant associations between FI and SHEBS total scores in the unadjusted (B= –1.133, SE: 2.396, β= –0.026, p=0.58) and the adjusted model (B=1.144, SE: 2.249, β=0.022, p=0.61). Furthermore, there were no significant associations between FI and SHEBS component scores (Table 3).

Table 2. SHEBS scores, food insecurity and obesity rates by characteristics.

Characteristics		**SHEBS score[1]**		**Obese[2]**		**Food-insecure[2]**	
		Mean±SD	**p-value**	**n (%)**	**p-value**	**n (%)**	**p-value**
Total		131.7±25.4		102 (22.1)		196 (42.5)	
Gender	Women	134.8±23.4	**0.001**	68 (22.0)	0.93	134 (43.4)	0.60
	Men	125.4±28.1		34 (22.4)		62 (40.8)	
Age	19-34 years	122.7±26.7[a]	**0.001**	7 (4.0)[a]	**0.001**	88 (50.9)[a]	**0.03**
	35-49 years	132.0±21.7[b]		21 (21.2)[b]		36 (36.4)[b]	
	50-64 years	138.3±23.6[bc]		37 (38.9)[c]		40 (42.1)	
	65+ years	141.3±23.0[cd]		37 (39.4)[c]		32 (34.0)[b]	
Marital status	Single	124.8±26.7	**0.001**	23 (11.0)	**0.001**	106 (50.7)	**0.001**
	Married	137.5±22.8		79 (31.3)		90 (35.7)	
Education degree	Middle school and below	141.9±21.8	**0.001**	62 (41.9)	**0.001**	53 (35.8)	**0.05**
	High school and above	126.9±25.6		40 (12.8)		143 (45.7)	
Smoking status	Yes	127.9±27.9	**0.05**	20 (16.4)	0.08	52 (42.6)	0.98
	No	133.1±24.4		82 (24.2)		144 (42.5)	
Food security	Food-insecure	130.9 ± 24.1	0.58	31 (15.8)	**0.005**		
	Food-secure	132.3 ± 26.4		71 (26.8)			

SHEBS: Sustainable and Healthy Eating Behaviors Scale; Score range for SHEBS is 32–224; SD: Standard Deviation; [1]Independent samples t-test results are displayed except for the age variable. One-way analysis of variance followed by Bonferroni post hoc test used for age. Different letters indicate differences between groups after post hoc tests (Bonferroni test results); [2]Chi-square test results; [a,b,c,d]: Different letters indicate differences between groups.

Table 3. Linear regression results of associations between food insecurity (independent variable) and Sustainable and Healthy Eating Behaviors Scale (SHEBS) total and component scores as dependent variables.

Dependent variables		**Independent variable: Food security (ref. food-secure)**					
		Model 1 (Unadjusted)			**Model 2 (Adjusted)**		
		B (SE)	**β**	**p-value**	**B (SE)**	**β**	**p-value**
SHEBS total score		–1.333 (2.396)	–0.026	0.58	1.144 (2.249)	0.022	0.61
SHEBS components	Quality labels (regional and organic)	–0.438 (0.700)	–0.029	0.53	–0.035 (0.679)	–0.002	0.96
	Seasonal food and avoiding food waste	–1.181 (0.660)	–0.083	0.07	–0.334 (0.606)	–0.024	0.58
	Animal welfare	0.267 (0.497)	0.025	0.59	0.628 (0.492)	0.059	0.20
	Meat reduction	0.197 (0.353)	0.026	0.58	0.445 (0.342)	0.059	0.19
	Healthy and balanced diet	0.030 (0.398)	0.003	0.94	0.192 (0.398)	0.023	0.63
	Local food	–0.621 (0.407)	–0.071	0.13	–0.291 (0.388)	–0.033	0.45
	Low fat	0.413 (0.303)	0.063	0.17	0.538 (0.305)	0.083	0.08

SHEBS: Sustainable and Healthy Eating Behaviors Scale.; Model 1: Unadjusted model.; Model 2: Model adjusted for gender, age, marital status, and education degree.

As displayed in Table 4, FI was associated with a lower risk of obesity in the unadjusted model (OR=0.513, 95%CI:0.321–0.822, p=0.005). However, after adjusting for gender, age, marital status and education degree, the regression analyses indicated that FI was no longer associated with obesity (OR=0.625, 95%CI:0.376–1.039, p=0.07).

Table 4. Binary logistic regression results of associations between food insecurity (independent variable) and obesity as dependent variable.

Dependent variable	Independent variable: Food security (ref. food-secure)					
	Model 1 (Unadjusted)			Model 2 (Adjusted)		
	B	OR (CI 95%)	p-value	B	OR (CI 95%)	p-value
Obesity (ref. non-obese)	–0.667	0.513 (0.321–0.822)	**0.005**	–0.469	0.625 (0.376–1.039)	0.07

Model 1: Unadjusted model; Model 2: Model adjusted for gender, age, marital status, and education degree. Note: The OR lower than 1 indicates the independent variable (being food-insecure) is associated with a lower risk of the dependent variable (being obese).

DISCUSSION AND CONCLUSION

FI causes unsustainable dietary behaviors, such as insufficient consumption of fruits and vegetables and increased consumption of ultra-processed foods, leading to increasing rates of obesity and obesity-related non-communicable diseases.[2,4,8] Global food affordability has been negatively affected by the COVID-19 epidemic and rising international conflicts, which have worsened FI.[3] All these factors suggest that the rates of FI and its nutritional consequences (e.g. unsustainable dietary behaviors and obesity) should be analyzed in Türkiye. The present study revealed a high rate of FI (42.5%). After adjusting for gender, age, marital status and education degree, FI was not significantly associated with obesity. Additionally, FI was not associated with sustainable and healthy eating behaviors in the present study.

By 2024, the FAO had reported a global prevalence of FI of 28.9%.[18] In a recent study from Türkiye, the household FI rate was found to be 24.4 per cent,[24] which is considerably lower than that found in the present study, in which FI at the individual level was 42.5%. In the previous study,[24] the education level of individuals (approximately 80 per cent had a university education) was much higher than that in the current study (67.9% had high school and above education). Considering the adverse association between a lower education level and FI,[25] this may explain the higher level of FI in the current study than in the previous study. The rate of obesity in this study (22.1%) was lower than that in the most recent TNHS 2017 study (34.1%).[20] This may be due to the participation of a large proportion (37.7%) of young people. The SHEBS scores of the individuals who participated in the study (131.7 ± 25.4) were found to be at a moderate level (score range: 32–224) and were similar to those reported by previous studies conducted in Türkiye.[26,27]

The increase in consumption of unsustainable diets with highly processed food due to convenience, cost and taste is leading the world's population towards a more processed, easier and less varied, low-quality diet, resulting in a large proportion of the world's population being undernourished in terms of nutrients.[9] Sustainable nutrition emphasizes a healthy and balanced diet rich in nutrients, while limiting sugar and artificial ingredients.[22] Studies have shown the negative effect of FI on overall diet quality. A study highlighted that food-insecure women eat less healthy foods, such as vegetables, fruits, while eating higher unhealthy foods such as processed meat and sweets. Therefore, this unsustainable, low-quality diet has been linked to FI.[28] Another research identified a significant association between FI and poor diet quality in low-income adults.[8] The results of the studies on the relationship between FI and dietary environmental impact vary. Unlike the similar study conducted in Türkiye, which found a negative relationship between FI and sustainable eating behaviors with low environmental impact,[24] this study found no relationship between FI and these behaviors. Similar to the present study, research conducted among French adults did not find a relationship between FI and sustainable diets.[29] In this study, individuals' knowledge about sustainable nutrition and access to a sustainable diet were not investigated. Sustainable nutrition and sustainable diets are relatively new concepts–and knowledge of the subject and accessibility of sustainable foods are necessary to implement these behaviors. These and other factors that may affect adherence to sustainable dietary behaviors should be investigated in future studies while assessing the relationship with FI.

In this study, no association was found between FI and obesity. FI is predicted to cause weight gain by increasing the consumption of unhealthy foods and leading to obesity and related health consequenc-

es.[28,4] However, previous studies have not shown a constant relationship between FI and obesity. A past study on women did not find an association between FI and BMI and other anthropometric measurements (waist circumference, fat mass) indicative of obesity.[28] Another study reported that the relationship between FI and obesity is particularly evident in women living in high-income countries.[3] Here, FI levels of the food-insecure individuals may also be contributing factors. To explain, while obesity is an expected outcome for individuals who are mildly food-insecure and have access to unhealthy, high-calorie, high-fat foods, it may not be an expected outcome in the short term for individuals who are severely food-insecure (at the hunger level). In the current study, it is difficult to make an inference as FI levels were not determined. In a study conducted among university students in Türkiye, no relationship was found between food security level and body weight.[30] The relationship between FI and obesity has been shown in children and young people but has not yet been determined in young adults and the elderly, but it has been pointed out that more research is needed.[3] Lastly, food-insecure individuals have a high risk of poor mental health, such as stress, anxiety and depression, which may possibly mediate the association of FI to obesity through increased consumption of high-calorie, high-fat, unhealthy foods.[3,25]

There are limitations to be mentioned regarding this study. First, the cross-sectional design of the study could not demonstrate causation. Second, the individuals participating in the study were not homogeneously distributed according to age groups. Finally, it relied on self-reporting, so participants' responses might have been subject to social-desirability bias.

In conclusion, this study reported a high level of FI in the Turkish population. However, sustainable and healthy eating behaviors and obesity did not vary according to FI. It is anticipated that the negative effects of FI will be clearer in the coming years. Obesity is a condition that requires a process, and the effects of FI will become evident, particularly among the currently young population. Longitudinal studies showing the effects of FI on obesity and health, especially in children and young people, are needed. Sustainable diets have been proposed as low-budget and affordable diets to tackle FI. Therefore, efforts to make sustainable diets economically advantageous and to increase accessibility to these diets may be useful for reducing FI and its negative consequences in Türkiye and other countries.

Ethics Committee Approval: Ethics committee approval was received from the Ondokuz Mayıs University Ethics Committee (Date: 11/01/2023, decision no: 2022/584). The study was planned under the Helsinki Principles.

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

Author Contributions: Concept – GÜ; Supervision – GÜ; Materials – GÜ; Data Collection and/or Processing – GÜ; Analysis and/or Interpretation – GÜ; Writing – GÜ.

Peer-review: Externally peer-reviewed.

Acknowledgements: The author thanks the Nutrition and Dietetics students of Ondokuz Mayıs University Faculty of Health Sciences for their assistance in collecting the study data.

Other Information: A part of the study was presented as a poster paper at the 31st European Congress on Obesity 2024 (ECO2024).

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):118-123 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):118-123*

COVID-19 Deteriorates Thyroid Function Tests During the Acute Phase

Covıd-19 Akut Dönemde Tiroid Fonksiyon Testlerini Bozuyor

[1]Hayrullah YAZAR, [2]Mehmet ÖZDIN, [3]Tayfur DEMIRAY

[1]Sakarya University Faculty of Medicine, Department of Medical Biochemistry, Sakarya, Türkiye
[2]Sakarya University Training and Research Hospital, Clinical Biochemistry Laboratory, Sakarya, Türkiye
[3]Sakarya University Faculty of Medicine, Department of Medical Microbiology, Sakarya, Türkiye

Hayrullah Yazar: https://orcid.org/0000-0001-9447-6322
Mehmet Özdin: https://orcid.org/0000-0003-3077-7171
Tayfur Demiray: https://orcid.org/0000-0003-1161-4684

ABSTRACT

Objective: This study aims to evaluate thyroid function tests in patients diagnosed with COVID-19, who had normal thyroid function in the past.

Materials and Methods: This research was conducted using the data of patients who visited COVID-19 outpatient clinics for the first time and had normal thyroid function in their medical history. All patients were divided into two groups based on their age and gender. Group I consisted of patients whose PCR test was positive for the first time, while Group II (control group) consisted of patients whose test was negative. The study examined the TSH (thyroid-stimulating hormone), fT3 (free triiodothyronine), fT4 (free thyroxine), albumin, and total protein (TP) test parameters of all patients in both groups and compared the results between them. Statistical significance was assessed using SPSS 20.0, and a *p*-value of less than 0.05 was considered significant.

Results: The study included 1360 patients, with 356 in Group I and 1004 in Group II. In Group I, TSH levels were low, but fT3 and fT4 levels were significantly high. Additionally, albumin and TP values were significantly lower in Group I. A moderate positive correlation was found between albumin and fT3 levels, as well as between albumin and TP levels, in Group I. The age and gender characteristics of the patients were similar in both groups.

Conclusions: There is a significant increase in thyroid function tests when COVID-19 infection is first diagnosed. However, detailed pathophysiological studies are needed to reveal the underlying reasons for this increase.

Keywords: Albumin, COVID-19, thyroid-stimulating hormone, thyroxine, total protein, triiodothyronine

ÖZ

Amaç: Bu çalışmada, geçmişte tiroid fonksiyonu normal olan COVID-19 tanısı almış hastalarda tiroid fonksiyon testlerinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Bu araştırma, COVID-19 polikliniklerine ilk kez başvuran ve tıbbi geçmişinde normal tiroid fonksiyonu olan hastaların verileri kullanılarak yürütülmüştür. Tüm hastalar yaş ve cinsiyetlerine göre iki gruba ayrılmıştır. Grup I, PCR testi ilk kez pozitif çıkan hastalardan oluşurken, Grup II (kontrol grubu) testi negatif çıkan hastalardan oluşmuştur. Çalışmada, her iki gruptaki tüm hastaların TSH (tiroid uyarıcı hormon), sT3 (serbest triiyodotironin), sT4 (serbest tiroksin), albumin ve toplam protein (TP) test parametreleri incelenmiş ve sonuçlar aralarında karşılaştırılmıştır. İstatistiksel anlamlılık SPSS 20.0 kullanılarak değerlendirilmiş ve 0,05'ten küçük p değeri anlamlı kabul edilmiştir.

Bulgular: Çalışmaya 1360 hasta dahil edilmiş olup, Grup I'de 356 ve Grup II'de 1004 hasta yer almıştır. Grup I'de TSH düzeyleri düşüktü, ancak sT3 ve sT4 düzeyleri anlamlı derecede yüksekti. Ek olarak, albümin ve TP değerleri Grup I'de anlamlı derecede düşüktü. Grup I'de albümin ve sT3 düzeyleri arasında ve albümin ve TP düzeyleri arasında orta düzeyde pozitif korelasyon bulundu. Hastaların yaş ve cinsiyet özellikleri her iki grupta da benzerdi.

Sonuç: COVID-19 enfeksiyonu ilk teşhis edildiğinde tiroid fonksiyon testlerinde anlamlı bir artış vardır. Ancak, bu artışın altında yatan nedenleri ortaya çıkarmak için ayrıntılı patofizyolojik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Albümin, COVID-19, tiroid stimüle edici hormon, tiroksin, total protein, triiyodotironin

Sorumlu Yazar / Corresponding Author:
Tayfur Demiray
Sakarya Üniversitesi Tıp Fakültesi, Korucuk Kampüsü, Tıbbi Mikrobiyoloji ABD, Sakarya, Türkiye.
Tel.: +90 530 466 27 00
E-mail: tayfurdemiray@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 04/02/2025
Kabul Tarihi/ Accepted: 19/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Yazar H and et al. COVID-19 Deteriorates Thyroid Function Tests During the Acute Phase. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):118-123. doi: 10.26453/otjhs.1633422

INTRODUCTION

The COVID-19 infection, caused by the highly contagious SARS-CoV-2 virus, first emerged in Wuhan, China, in 2019, leading to a global pandemic in 2020.[1] It has been reported that the increase in mortality among COVID-19 patients is associated with various disorders triggered by the infection.[2] In fact, some researchers have described COVID-19 as "the most significant public health threat worldwide this century".[3] Studies indicate that long-term COVID-19 can affect multiple organs and cause over 200 symptoms. It is estimated that at least 65 million people worldwide suffer from this condition.[4] However, the lack of a complete consensus on its treatment and the numerous mysteries surrounding its pathogenesis raise critical questions about COVID-19. Many scientific studies have been conducted on COVID-19; further detailed research is needed to investigate the relationship between COVID-19 infection and thyroid function. The SARS-CoV-2 virus penetrates the cells using the angiotensin-converting enzyme 2 (ACE 2) receptor, including cells in the thyroid gland. Consequently, there is a link between SARS-CoV-2 infection and various thyroid disorders, as reported.[5]

Thyroid hormones are among the most important hormones involved in regulating metabolism and significantly affect all cells in the body. The thyroid gland produces, stores, and releases T3 and T4 hormones into the bloodstream as needed. Hypothyroidism occurs due to insufficient thyroid hormone secretion, whereas hyperthyroidism is marked by high T3 and T4 levels along with low serum TSH levels.[6] Increased thyroid hormone synthesis can occur due to excessive secretion of pre-synthesized thyroid hormones or extreme thyroid hormone concentration in tissues caused by endogenous or exogenous extrathyroidal sources.[7] Commonly used tests for thyroid function include TSH, fT3, and fT4. Additionally, albumin and total protein (TP) levels, which play a role in thyroid hormone transport, should not be overlooked.

This study aimed to investigate differences in thyroid tests during the acute phase of COVID-19 in patients admitted to outpatient clinics. The study examined the relationship between COVID-19 and thyroid hormones during the acute period, taking into account albumin, total protein (TP), age, and gender. The findings are expected to provide new insights for clinicians.

MATERIALS AND METHODS

Ethics Committee Approval: This study was conducted upon approval from the Sakarya University Faculty of Medicine Ethics Committee (Date: 04.03.2022, decision no: 112789). All authors declare to follow and obey the Helsinki Declaration criteria.

Study Design: In addition, this study was carried out with the permission and approval of the Ministry of Health of the Republic of Türkiye and in accordance with the scientific research criteria of the ministry. The research was conducted between March 11, 2020, and February 28, 2022, using the automation system of a training and research hospital. Participants included individuals who applied to COVID-19 outpatient clinics for the first time and had normal thyroid function in their medical history. Patients under the age of 18, patients with a history of thyroid disease, those under treatment that could affect thyroid hormone levels, and patients on steroid therapy were excluded. The patients were divided into two distinct groups: the patient group (Group I) consisted of those with a positive PCR test, and the control group (Group II) consisted of those with a negative PCR test. The study examined TSH (thyroid-stimulating hormone), fT3 (free triiodothyronine), fT4 (free thyroxine), albumin, and TP test parameters for all individuals in both groups. Age and gender were also recorded, and all data were compared between the groups.

Molecular Testing for SARS-CoV-2: Both nasopharynx and oropharynx swab samples were collected from patients using a Dacron swab. Immediately after collection, the samples were retained in a viral transport medium, stored at 2-8°C, and delivered to the molecular microbiology laboratory for analysis. The samples were transported in compliance with cold chain protocols and infection control measures. Upon arrival at the microbiology laboratory, the samples were processed in a level 3 bio-safe negative pressure room. Total nucleic acid isolation was performed using the Bio-Speedy® Viral Nucleic Acid Isolation Kit (Bioeksen, Türkiye). The Bio-Speedy® COVID-19 RT-qPCR Detection Kit (Bioeksen, Türkiye) was used for RT-PCR analysis. PCR amplification data and the test results were evaluated consistently with the manufacturer's recommendations.

Biochemical Analysis: Hormone tests were performed using the Architect i2000 SR (Abbott, USA) device. Albumin and TP tests were conducted on Beckman Coulter AU 5800 (Koto-Ku, Tokyo, Japan) fully automated analyzers. The normal range for Thyroid Stimulating Hormone (TSH) is 0.35-5.5 mIU/L, with a precision of ≤2.4% CV and a sensitivity of ≤0.0025 µIU/mL. Free T3 (fT3) falls within a normal range of 2.3-4.2 ng/L, has a precision of ≤5.3% CV, and a sensitivity of ≤1.0 pg/mL. Free T4 (fT4) has a reference range of 0.89-1.76 ng/L, a precision of ≤4.6% CV, and a sensitivity of ≤0.4 ng/dL. Total Protein (TP) is typically within 66-83 g/L,

with a precision of ≤0.5% CV and a sensitivity of 0.77 g/L. Albumin levels normally range from 35-52 g/L, with a precision of ≤0.58% CV and a sensitivity of 0.07 g/L.

Statistical Analysis: SPSS 20.0 was used for all analyses. A power analysis was carried out using G*Power 3.1 software to determine whether the sample size was adequate to detect statistically significant differences between the two independent groups (Group I/study group, Group II/control group) in thyroid function parameters. As a result of the literature review, studies that were suitable for our study were taken into consideration, and the information required for sample calculation was obtained from these studies. Since the smallest effect size between the two groups was obtained as d = 0.26, the study hypothesised that there would be a small effect size between the two groups with d = 0.26, and it was determined that a total of at least 624 people should be studied, with at least 312 people in each group at a power of 90% and a 5% error level. However, since this study has a cross-sectional design, the minimum value calculated was taken into account in order to increase the generalizability of the study and the maximum number that could be reached in the relevant data range was aimed for. Thus, 1360 people were included in the study. The distribution of continuous variables was assessed using visual and statistical methods. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are shown as median and interquartile range (1st and 3rd quartiles). Categorical variables are expressed as percentages and numbers. The chi-square test was used to compare categorical variables between the case and control groups. The Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. Spearman correlation analysis was performed for continuous variables, and box plots were used for visual representation. A p-value of <0.05 was considered statistically significant.

RESULTS

In Group I, TSH levels were low, while fT3 and fT4 levels were high (Figure 1).

The mean values of the thyroid function tests were presented in Table 1, and the comparative results among these hormones were statistically significant (p<0.001 for TSH, p=0.007 for fT3, and p<0.001 for fT4). Additionally, albumin and TP values were significantly lower in Group I (p<0.001 for both). In Group I, a low negative correlation was detected between fT3, TP levels, and age.

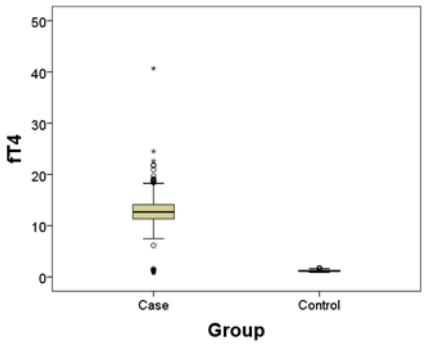

Figure 1. Box plot graph of fT4 levels in the case and control groups.

Table 1. Comparison of TSH, fT3, fT4, TP, and albumin levels for Group I and Group II.

Parameters		Group I (*n*=356)	Group II n(*n*=1004)	p
Sex	Male	206 (57.9)	529 (52.7)	0.092[a]
	Female	150 (42.1)	475 (47.3)	
Age, Average ± SD		64.12±17.07	59.28 ± 11.67	0.061[b]
TSH, Median (1st Q-3rd Q)		0.82 (0.35-1.50)	1.65 (1.09-2.59)	**0.001**[c]
fT3, Median (1st Q-3rd Q)		3.27 (2.42-4.29)	3.12 (2.86-3.40)	**0.007** [c]
fT4, Median (1st Q-3rd Q)		12.68 (11.32-14.13)	1.18 (1.07-1.29)	**0.001** [c]
Albumin, Median (1st Q-3rd Q)		32.70 (28.15-37.15)	42.50 (40.20-44.70)	**0.001** [c]
Total Protein, Median (1st Q-3rd Q)		63.00 (57.90-68.00)	71.80 (69.20-76.70)	**0.001** [c]

[a]: Pearson Ki kare test; [b]: Student t test; [c]: Mann-Whitney U test; SD: Standard Deviation; Q: Quartile.

Conversely, a moderate positive correlation was found between albumin levels and both fT3 and TP levels (Table 2). There was also a weak negative correlation between albumin and age, as well as between fT3 and age. A low positive correlation was observed between albumin and both fT3 and TP levels.

In Group II, a high positive correlation was found between albumin levels and both fT3 (r=0.308, p<0.001) and TP levels (r=0.473, p<0.001), as shown in Table 3.

Table 2. Correlations of age, TSH, fT3, fT4, Albumin, and TP in Group I.

Parameters	Tests	Age	TSH	fT3	fT4	Albumin	TP
Age	***r***	1	0.023	-0.358 [a]	-0.075	-0.491 [a]	-0.281 [a]
	p		0.668	**0.001**	0.156	**0.001**	**0.001**
TSH	***r***	0.023	1	0.060	-0.153**	0.052	0.036
	p	0.668		0.256	0.004	0.325	0.506
fT3	***r***	-.358**	0.060	1	0.392**	0.539 [a]	-0.347 [a]
	p	**0.001**	0.256		**0.001**	**0.001**	**0.001**
fT4	***r***	-0.075	-0.153**	0.392 [a]	1	0.049	0.121
	p	0.156	**0.004**	**0.001**		0.363	0.023
Albumin	***r***	-.491**	0.052	0.539 [a]	0.049	1	-0.701 [a]
	p	**0.001**	0.325	**0.001**	0.363		**0.001**
Total Protein	***r***	-.281**	0.036	0.347 [a]	0.121	0.701 [a]	1
	p	**0.001**	0.506	**0.001**	0.023	**0.001**	

[a]: p<0.001.

Table 3. Correlation of age, TSH, fT3, fT4, Albumin, and TP in Group II.

Parameters	Tests	Age	TSH	fT3	fT4	Albumin	TP
Age	***r***	1	0.004	-0.382[a]	-0.014	-0.367 [a]	-0.193 [a]
	p		0.908	**0.001**	0.661	**0.001**	**0.001**
TSH	***r***	0.004	1	-0.040	-0.120 [a]	-0.055	0.035
	p	0.908		0.210	**0.001**	0.079	0.272
fT3	***r***	-0.382 [a]	-0.040	1	0.144 [a]	0.308 [a]	0.058
	p	**0.001**	0.210		**0.001**	**0.001**	0.067
fT4	***r***	-0.014	-0.120 [a]	0.144 [a]	1	0.119 [a]	0.105 [a]
	p	0.661	**0.001**	**0.001**		**0.001**	**0.001**
Albumin	***r***	-0.367 [a]	-0.055	0.308 [a]	0.119 [a]	1	0.473 [a]
	p	**0.001**	0.079	**0.001**	**0.001**		**0.001**
Total Protein	***r***	-0.193 [a]	0.035	0.058	0.105 [a]	0.473 [a]	1
	p	**0.001**	0.272	0.067	**0.001**	**0.001**	

[a]: p<0.001.

DISCUSSION AND CONCLUSION

It is well-known that COVID-19 primarily affects the lungs.[8] However, ongoing research is exploring how the virus impacts other medical conditions, including thyroid function. Thyroid hormones possess a highly vital role in regulating essential bodily functions such as growth, development, metabolism, and energy supply.[9] Therefore, routine checks for TSH, fT3, and fT4 levels are essential when assessing thyroid gland function. Additionally, albumin and total protein measurements should be considered when studying thyroid hormones. This research suggests that these measurements are necessary to evaluate thyroid function accurately.

COVID-19 can cause transient or permanent changes in thyroid function, and non-thyroidal illness syndrome has been frequently reported. After the acute infection period, some patients have suffered subacute thyroiditis and thyroid hormone imbalances, which in turn cause long-term complications. Immune system responses and ongoing inflammation are blamed for such complications.[4]

A study of 146 COVID-19 patients in the intensive care unit with normal thyroid levels found that thyroid hormone levels decreased slightly in those who recovered, but the decrease was more significant in those who died.[10] The study suggested that a severe decrease in thyroid hormones could serve as a prognostic parameter for COVID-19 patients. However, other studies indicate that hypothyroidism is observed in COVID-19 patients in later stages. In contrast, our findings suggest that hormone levels tend to

increase during the acute phase of COVID-19, possibly due to systemic and metabolic processes. We believe this represents a temporary period of thyrotoxicosis. If the patient does not respond to treatment and progresses to a severe stage, thyroid tissue damage may occur, leading to a noteworthy decline in hormone levels. In another study involving 48 SARS patients, significant decreases in serum T3, T4, and TSH levels were observed. Specifically, serum T3 and T4 levels decreased by 94% and 46%, respectively. During recovery, T3 and T4 levels were 90% and 38%, respectively. The decrease in T3 levels was particularly correlated with disease severity.[11,12]

A retrospective analysis of 274 COVID-19 patients in intermediate and critical conditions found that 113 patients died, while 161 recovered. T3 serum levels were significantly lower in those who died compared to those who recovered (0.7 mIU/mL vs. 2.8 pmol/L, respectively). However, the difference in T4 levels between the two groups (15.8 pmol/L for those who died and 18.3 pmol/L for those who recovered) was not significant.[13] Another retrospective study of hospitalized SARS-CoV-2-infected patients with previously unknown thyroid diseases found that 56% (28/50) of patients had significantly lower TSH levels.[14] Additionally, serum T3, T4, and TSH levels in SARS patients were considerably lower compared to controls during both the progression and recovery periods of the disease.[15] However, in COVID-19 patients, T4 and T3 levels increase while TSH levels decrease.[16] Our study found that COVID-19 patients had low TSH levels, while fT3 and fT4 levels were elevated.

Studies have shown that low serum albumin levels are associated with poor prognosis in COVID-19 patients and are among the specific biomarkers of severe infection.[17] Low serum albumin levels were also observed in COVID-19 patients in another study.[18] Serum albumin levels are among the test parameters examined in COVID-19 studies. Our study, along with others, revealed that albumin levels are low in COVID-19 patients. For example, a study on the C-reactive protein to albumin ratio in severe COVID-19 patients suggested that this ratio could be an essential biomarker for risk stratification and clinical follow-up.[19] These findings support the idea that albumin levels are low in COVID-19 patients.

In conclusion, there is a significant increase in thyroid function tests in patients who are admitted to outpatient clinics with suspected COVID-19 and test positive on PCR. This increase may be due to a sudden metabolic response, but more detailed studies are needed to uncover the underlying pathophysiological mechanisms. The findings of this study were derived from data collected exclusively from patients at a single hospital. More significant and comprehensive conclusions could be achieved through a meta-analysis that synthesizes data from this and similar studies.

Ethics Committee Approval: This study was conducted upon approval from the Sakarya University Faculty of Medicine Ethics Committee (Date: 04.03.2022, decision no: 112789). All authors declare to follow and obey the Helsinki Declaration criteria.

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

Author Contributions: Concept – MO, HY, TD; Supervision – MO, HY, TD; Materials – MO, HY, TD; Data Collection and/or Processing – MO, HY, TD; Analysis and/or Interpretation – MO, HY, TD; MO, HY, TD, Writing – MO, HY, TD.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):124-130 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):124-130*

Non-Thyroidal Illness Syndrome in Neonatal Intensive Care Units

Yenidoğan Yoğun Bakım Ünitesinde Tiroid Dışı Hastalık Sendromu

[1]Kübra BOYDAĞ GÜVENÇ, [2]Esra Deniz PAPATYA ÇAKIR, [3]Özgül SALİHOĞLU

[1]Department of Pediatric Intensive Care, University of Health Sciences Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, Istanbul, Türkiye
[2]Department of Pediatric Endocrinology,University of Health Sciences, Bakırköy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Türkiye
[3]Department of Neonatal Intensive Care, University of Health Sciences, Bakırköy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Türkiye

Kübra Boydağ Güvenç: https://orcid.org/0000-0003-3881-6980
Esra Deniz Papatya Çakır: https://orcid.org/0000-0003-4664-7435
Özgül Salihoğlu: https://orcid.org/0000/0002/2132/1888

ABSTRACT

Objective: This study aims to establish the incidence of non-thyroidal illness syndrome (NTIS) in newborns and investigate its potential impact on neonatal outcomes. Additionally, by identifying the risk factors associated with the development of NTIS, this study aims to deepen the understanding of the condition.

Materials and Methods: A total of 337 patients in the neonatal intensive care unit were studied retrospectively. Data on demographic and clinical characteristics, including gestational age, birth weight, head circumference, height, Apgar score, SNAPPE score, presence of congenital anomalies, mode of delivery, respiratory support, and duration of hospitalization, were collected. All patients underwent measurement of TSH and free T4 levels.

Results: The study found that 4.5% of patients were diagnosed with NTIS. Patients with NTIS had higher rates of preterm delivery. NTIS patients exhibited lower gestational age, birth weight, head circumference, height, and Apgar scores than non-NTIS patients. NTIS patients had significantly more extended hospital stays, but no differences in mechanical ventilation duration or SNAPPE scores were obtained.

Conclusions: This study indicates that thyroid dysfunction can occur in critically ill newborns, highlighting the necessity of evaluating thyroid function in this demographic.

Keywords: Euthyroid sick syndrome, neonatal intensive care unit, non-thyroidal illness syndrome, thyroid function tests, thyroid screening

ÖZ

Amaç: Bu çalışmanın amacı yenidoğanlarda tiroid dışı hastalık sendromunun (TDHS) yaygınlığını belirlemek ve yenidoğan sonuçları üzerindeki potansiyel etkilerini araştırmaktır. Ayrıca, TDHS gelişimi ile ilişkili risk faktörlerini belirleyerek, sendromun daha iyi anlaşılmasına katkıda bulunmak amaçlanmaktadır.

Materyal ve Metot: Yenidoğan yoğun bakım ünitesinde yatan 337 hastanın verileri retrospektif olarak toplandı. Gebelik yaşı, doğum ağırlığı, Apgar skoru, SNAPPE skoru, doğum şekli, konjenital anomaliler, solunum desteği ve hastanede yatış süresi gibi demografik ve klinik veriler toplanmıştır. Tüm hastalarda tiroid uyarıcı hormon (TSH) ve serbest tiroksin (sT4) düzeyleri ölçülmüştür.

Bulgular: Çalışmaya alınan hastaların %4,5'inde TDHS saptanmıştır. TDHS tanısı alan hastalar, daha düşük gebelik haftası, doğum ağırlığı, baş çevresi, boy, ve Apgar skorlarına sahipti. TDHS hastalarının hastane yatış süreleri anlamlı şekilde daha uzun bulunmuş, ancak mekanik ventilasyon süresi ve SNAPPE skorlarında fark gözlenmemiştir.

Sonuç: Bu çalışma, kritik hastalık geçiren yenidoğanlarda tiroid fonksiyon bozukluklarının görülebileceğini ve bu grubun tiroid fonksiyonlarının değerlendirilmesinin önemli olduğunu göstermektedir.

Anahtar Kelimeler: Tiroid dışı hastalık sendromu, tiroid fonksiyon testleri, tiroid taraması, ötiroid hasta sendromu, yenidoğan yoğun bakım ünitesi

Sorumlu Yazar / Corresponding Author:
Kübra Boydağ Güvenç
Department of Pediatric Intensive Care, University of Health Sciences Sancaktepe Sehit Prof. Dr. Ilhan Varank Training and Research Hospital, İstanbul, Türkiye
Tel.: +905058681926
E-mail: kubrabydg@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 04/02/2025
Kabul Tarihi/ Accepted: 04/05/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Boydağ Güvenç K and et al. Non-Thyroidal Illness Syndrome in Neonatal Intensive Care Units. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):124-130. doi: 10.26453/otjhs.1633458

INTRODUCTION

Thyroid hormones play a vital role in brain development throughout the postpartum period. After birth, serum levels of thyroxine (T4) and triiodothyronine (T3) rise significantly, supporting the somatic growth and maturation of the newborn. Low thyroid hormone levels during early life can negatively affect growth and development, potentially resulting in irreversible cognitive impairment due to brain injury.[1,2]

Endocrine disorders caused by underlying diseases, stress, or medications are frequently observed in critically ill patients.[3] Particularly in premature infants, the immaturity of the thyroid axis, maternal and fetal medications, and prematurity-related morbidities all increase the likelihood of abnormalities in thyroid function tests (TFT).[4]

Altered thyroid hormone phenomenon, known as non-thyroidal illness syndrome (NTIS), refers to a distinct pattern of hormonal changes in the pituitary –thyroid axis in patients without primary thyroid disease.[5,6] There is ongoing debate about whether this hormonal alteration represents an adaptive protective response or a maladaptive process that may warrant therapeutic intervention.[7,8]

Several studies have reported associations between TFT abnormalities and the development of severe illness and poor clinical outcomes.[9] Therefore, early screening for thyroid dysfunction and appropriate clinical evaluation are essential in neonates admitted to neonatal intensive care units (NICU).

The goal of this study is to establish the prevalence of NTIS in newborns and to investigate its potential impact on neonatal outcomes. In addition, by identifying risk factors that are linked to the onset of NTIS, this study seeks to improve the understanding of the disorder.

MATERIALS AND METHODS

Ethics Committee Approval: The study was performed in compliance with the Declaration of Helsinki. The study methodology was approved by the Ethics Committee of Bakirkoy Sadi Konuk Training and Research Hospital (Date: 29.05.2017, decision no: 2017-04-22), and all anonymized data linked to the study are accessible upon reasonable request.

The study enrolled 337 patients aged 0 to 1 month at Bakirkoy Sadi Konuk Training and Research Hospital NICU. Clinical and demographic data were retrospectively acquired from the hospital's computerized information management system and patient records. Gestational weeks, birth weights, diagnoses, Apgar score[10], Score for Neonatal Acute Physiology with Perinatal Extension (SNAPPE),[11] genders, mode of delivery, presence of congenital anomalies, the requirement of respiratory support, inotropic agents or phototherapy, duration of hospitalization, the requirement for inotropes or transfusions prior to evaluation and outcomes was recorded. The SNAPPE score is a scale calculated within the first 24 hours using physiological and perinatal data to predict the risk of mortality in neonates.[11] The incidence of postpartum surgical procedures and the mother's chronic illness were also noted. Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) values were obtained for all hospitalized patients. Patients were classified into three groups according to the timing of thyroid function tests: 0-7 days, 8-15 days, and 16-30 days. The diagnosis of NTIS was made when patients with abnormal thyroid function test values showed improvement in control values. Control values were obtained after 15 days for all patients. The control TFT values for 21 deceased patients could not be collected due to their poor clinical status, resulting in their exclusion from the research.

The last menstrual period (LMP) reported by the mother or the modified Ballard score was used to ascertain the gestational age of all preterm neonates.[12] Infants below 37 weeks of gestation were classified as premature, while those at 42 weeks or above were considered post-term. The evaluation of growth was conducted by employing Lubchenko's growth curves, and infants with height, weight, and head circumference values below the 10th percentile for their respective gestational ages were categorized as small for gestational age (SGA). In contrast, newborns with measurements exceeding the 90th percentile were categorized as large for gestational age (LGA) relative to their gestational age.

The analysis of hormone levels for free triiodothyronine (fT3), fT4, and TSH was conducted using the electrochemiluminescence immunoassay (ECLIA) method from patient serum, with a Roche Elecsys E170 device employed for this purpose. The reference range of thyroid tests was 0.43-16.1 mIU/L and 0.83-3.09 ng/dL for TSH and fT4, respectively.

Statistical Analysis: The data collected in this research were analyzed utilizing the SPSS 20.0 software program for Windows. Continuous variables adhering to a normal distribution were represented as mean±standard deviation, whilst non-normally distributed data were conveyed as median (minimum -maximum) values. The distribution's normality was assessed by using histograms and the Kolmogorov-Smirnov test. Categorical variables were represented as counts (percentages). The importance of the disparities between the two group means in independent samples was evaluated utilizing the Mann-Whitney U test for non-normally distributed data and the Student's t-test for regularly distributed data. In instances of repeated measurements, the Wilcox-

on test was utilized for non-normally distributed data in pair-wise group comparisons, and the Friedman test was utilized for multiple groups exceeding two. Results were deemed statistically significant if their p-values were below 0.05.

RESULTS

The study recruited a total of 337 patients. Of these, 60.2% (n=203) were male. Cesarean section was conducted in 59.3% (n=200) of these cases. Among the patients, 86.3% were classified as appropriate for gestational age (AGA), 6,2% as SGA, and 7,7% as LGA. Furthermore, 43% (n=145) of the patients were preterm, while 56.9 % (n=192) were term infants. The median birth weight was 2880 grams (690 -4670 g), and the median length of hospitalization was 9 days (1-273). The average SNAPPE score was found to be 15 (1-59), and the median length of mechanical ventilation was determined to be 5 (1-76) days (Table 1).

Out of the fifteen patients (4.5%) diagnosed with NTIS, all of them were AGA. When the relationship between NTIS and prematurity was examined, the prevalence of NTIS was found to be 1.6% in term infants and 8.3% in preterm infants. NTIS was significantly more common in preterm infants compared to term infants (p = 0.007). This finding suggests that prematurity may be associated with an increased risk of developing NTIS (Table 2).

The study's findings indicated that patients diagnosed with NTIS exhibited lower gestational week, head circumference, birth weight, and height ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$ consecutively). In NTIS patients, A lower Apgar score was observed at 1 and 5 minutes ($p=0.005$, $p=0.007$). Furthermore, patients with NTIS had considerably longer hospital stays and needed oxygen support, as demonstrated in Table 2 ($p=0.001$, $p=0.001$). The two groups did not demonstrate any substantial disparities in terms of lactate levels, SNAPPE scores, or the duration of mechanical ventilation. NTIS was more prevalent in patients diagnosed with sepsis (p = 0.033). Gender, mode of delivery, presence of chronic maternal disease, and frequency of postpartum surgical procedures were similar between groups. Patients with and without NTIS exhibited similar features regarding the presence of congenital anomalies, transfusion prior to the evaluation, use of inotropic agents, and requirement of phototherapy (Table 3).

Table 1. Clinical features of patients.

Gender, male, n (%)		203 (60.2)
Birth weight (gr), median (min-max)		2880 (690-4670)
Birth height (cm), median (min-max)		48 (26-56)
Birth head circumference (cm), median (min-max)		34 (20-39)
Gestation Week, median (min-max)		37 (21-42)
Cesarean section n, (%)		200 (59.3)
Prematurity (≤36 gestational week), n (%)		145 (43.0)
Birth weight for gestational age, n (%)	AGA	290 (86.0)
	SGA	26 (7.71)
	LGA	21 (6.23)
Apgar at 1 minute, median (min-max)		8 (0-9)
Apgar at 5 minutes, median (min-max)		9 (1-10)
SNAPPE score, median (min-max)		15 (1-59)
Duration of mechanical ventilation (day), median (min-max)		5 (1-76)
Length of hospitalization at NICU (day), median (min-max)		9 (1-273)

AGA: Appropriate for gestational age; SGA: Small for Gestational Age; LGA: Large for Gestational Age; SNAPPE score: Score for neonatal acute physiology with perinatal extension; NICU: Neonatal intensive care unit

Table 2. Association between gestational age and the presence of non-thyroidal illness syndrome.

		No NTIS	NTIS	p
Gestational week, n (%)	**≤36**	133 (91.7)	12 (8.3)	**0.007**
	>36	189 (98.4)	3 (1.6)	

NTIS: Non-thyroidal illness syndrome.

Table 3. Clinical features of patients with and without non-thyroidal illness syndrome.

Clinical features		No NTIS	NTIS	p
Gestation week, median (min-max)		37 (23-42)	28 (25-38)	**0.001**
Birth weight (gr), median (min-max)		2900 (690-4670)	1080 (750-3520)	**0.001**
Birth height (cm), median (min-max)		48 (25-56)	36 (32.5-50)	**0.001**
Birth head circumference (cm), median (min-max)		34 (20-39)	27 (24-35)	**0.001**
Gender, n (%)	**Female**	131 (%97.8)	3 (%2.2)	0.110
	Male	191 (%94.1)	12 (%5.9)	
Mode of delivery, n (%)	**NVD**	132 (%96.4)	5 (%3.6)	0.555
	C/S	190 (%95.0)	10 (%5.0)	
Apgar at 1 minute, median (min-max)		8 (0-9)	5 (1-9)	**0.005**
Apgar at 5 minute, median (min-max)		9 (3-10)	8 (2-10)	**0.007**
SNAPPE score, median (min-max)		14.5 (1-59)	18 (12-32)	0.561
Duration of mechanical ventilation (day), median (min-max)		5 (1-76)	11 (1-48)	0.235
Requirement of supplemental oxygen (L/Min), median (min-max)		3 (1-19)	16 (2-24)	**0.001**
Length of hospitalization at NICU (day), median (min-max)		10 (2-273)	62 (2-136)	**0.001**
Lactic acid on admission (mmol/L), median (min-max)		1 (0.9-6.1)	1 (0.9-1.7)	0.255
Requirement of inotropic agents, n (%)		16 (88.9)	2 (11.1)	0.123
Presence of congenital anomaly, n (%)		19 (100)	0	0.411
Requirement of transfusion prior to evaluation, n (%)		16 (88.9)	2 (11.1)	0.188
Requirement of phototherapy, n (%)		77 (92.8)	6 (7.2)	0.167
Requirement of postpartum surgical procedure, n (%)		13 (86.7)	2 (13.3)	0.139
Presence of sepsis		14 (82.4)	3 (17.6)	**0.033**

NTIS: Non-thyroidal illness syndrome; NVD: Normal vaginal delivery; C/S: Cesarean section; SNAPPE score: Score for neonatal acute physiology with perinatal extension; NICU: Neonatal intensive care unit

During the first week of life, both fT4 and TSH levels were significantly lower in preterm infants compared to term infants (p = 0.024 and p = 0.016, respectively). This suggests that thyroid hormone suppression is more prominent in preterm neonates during the early neonatal period. However, no statistically significant differences were observed between the two groups in fT4 and TSH levels during the 8–15 and 16–30 day intervals (p >0.05 for all comparisons), indicating that the divergence in thyroid function is most marked during the first week after birth (Table 4).

Table 4. Comparison of thyroid function test values between preterm and term infants by sampling day.

Parameters		Prematurity (≤36 gestational weeks	Term (>36gestational weeks)	p
0-7 days, median (min-max)	fT4 (ng/dL)	1.295 (0.64-2.08)	1.38 (0.46-2.74)	**0.024**
	TSH (µIU/mL)	3.425 (0.65-45.28)	4.545 (0.22-38.34)	**0.016**
8-15 days, median (min-max)	fT4 (ng/dL)	1.295 (0.3-2.07)	1.37 (0.77-9.0)	0.071
	TSH (µIU/mL)	3.190 (0.64-19.69)	3.35 (0.55-68.11)	0.954
16-30 days, median (min-max)	fT4 (ng/dL)	1.154 (0.62-2.07)	1.19 (0.77-1.66)	0.768
	TSH (µIU/mL)	3.46 (0.91-22.97)	3.51 (0.73-22.5)	0.948

fT4: free thyroxine; TSH: Thyroid-stimulating hormone.

Thyroid function test results of all patients included in the study are presented in Table 5 according to the timing of sample collection (days 0–7, 8–15, and 16 –30). For each time interval, median values and corresponding minimum–maximum ranges of fT4 and TSH levels are reported (Table 5).

Table 5. Thyroid function test values by sampling time in all patients.

Parameters		Median (min-max)
0-7 days, median (min-max)	fT4 (ng/dL)	1.34 (0.46-2.74)
	TSH (μIU/mL)	3.87 (0.22-45.28)
8-15 days, median (min-max)	fT4 (ng/dL)	1.33 (0.3-9)
	TSH (μIU/mL)	3.32 (0.55-68.11)
16-30 days, median (min-max)	fT4 (ng/dL)	1.19 (0.62-2.07)
	TSH (μIU/mL)	3.46 (0.73-22.97)

fT4: free thyroxine; TSH: Thyroid-stimulating hormon

DISCUSSION AND CONCLUSION

TFTs are significant biomarkers linked to disease severity and therapy efficacy in both adult and pediatric populations. Studies indicate that thyroid hormone levels serve as a predictive marker for certain serious disorders. Specifically, alterations in TSH, fT4, and fT3 concentrations may be important for forecasting disease advancement and therapeutic response.[13,14]A study by Goldsmith et al. found that lower T3 and T4 levels in sick term newborns were linked to prolonged mechanical ventilation, elevated lactate levels, and higher SNAPPE scores. The study also demonstrated that the group with combined low T3, T4, and TSH levels had the highest fatality rate, highlighting that impaired thyroid function may significantly influence prognosis and outcomes in sick neonates.[9] Hammati et al.'s study revealed a significant decrease in fT3 levels during critical illness, although no notable changes were observed in fT4 and TSH levels. This study found no significant link among the length of mechanical ventilation, the existence of congenital heart disease (CHD), and the levels of fT3 and fT4.[15] Another study found that fT4 levels were not associated with mortality but were correlated with a prolonged hospital stay. Additionally, male gender, vaginal delivery, hypoxic-ischemic encephalopathy, and the need for mechanical ventilation exceeding 24 hours were recognized as risk factors.[16] Collectively, these studies underscore the importance of evaluating thyroid function in sick-term newborns, as abnormalities in thyroid hormone levels correlate with negative clinical outcomes, prolonged hospital stays, increased need for interventions, and elevated mortality rates. The present study reinforces these observations by showing that NTIS was associated with significantly lower Apgar scores, birth weight, and gestational age, along with increased oxygen demand and longer hospitalization.

Hypothyroxinemia is prevalent among preterm newborns.[17,18] The significance of thyroid hormones in brain development is well-documented. Nonetheless, the consequences of hypothyroxinemia in preterm infants are not fully understood. There is ongoing discourse surrounding the necessity of levothyroxine treatment for premature infants with hypothyroxinemia.[19,20] A study specifically investigating hypothyroxinemia in premature infants concluded that 14.5% of preterm births exhibited hypothyroxinemia. Additionally, 92% of these cases were observed in preterm infants born prior to 32 weeks of gestation and weighing under 1500 grams. Consequently, the recommendation was made for the implementation of early screening for hypothyroxinemia in this specific group of preterm infants.[21] According to the Yoon et al. study, transient hypothyroxinemia in newborns with extremely low birth weight is linked to higher composite morbidities and mortality. Furthermore, the initially measured T4 level was identified as a more effective predictor of outcomes in these patients.[22] In accordance with extant literature, the present study disclosed that 80% of patients with the condition were preterm infants. Furthermore, patients diagnosed with NTIS exhibited a lower gestational age and reduced birth weight, which were statistically significant.

Perinatal asphyxia has been shown to impair cellular function across multiple organs, leading to reduced oxidative phosphorylation and ATP production. Hence, it is essential to acknowledge the critical influence of prenatal hypoxia on thyroid function.[23] Thyroid dysfunction has been observed in asphyxic neonates in previous studies. A study investigating the effects of birth asphyxia on thyroid hormones demonstrated a notable decline in TSH levels post-asphyxia, with the magnitude of the reduction corresponding with the severity of asphyxia.[24] A separate investigation revealed a decline in TFT levels in asphyxiated newborns at 18 and 24 hours after birth.[25] Our investigation revealed that the Apgar score of NTIS patients was significantly lower compared to those without NTIS. In our opinion, thyroid

hormone levels should be closely monitored in asphyxia patients.

The incidence of NTIS is increased in sepsis. The study by El-Nawawy et al. underscores the high prevalence of NTIS among pediatric patients with shock and illustrates the relationship between thyroid hormone dysfunction and disease severity.[26] Likewise, research conducted by Xu et al. indicates a significant frequency of NTIS in pediatric patients with sepsis. This study observed a negative correlation between interleukin-6 (IL-6) levels and T3 and T4 levels, highlighting the impact of inflammatory cytokines on thyroid hormone regulation.[27] Consistent with the previous literature, our investigation also identified a greater prevalence of sepsis in patients with NTIS. Taken together, these findings suggest that NTIS is not only a biochemical phenomenon but also a potential indicator of systemic disease severity in neonates. This reinforces the need to assess thyroid function not solely as routine screening, but as an integrated part of neonatal critical care evaluation.

The study's limitations can be attributed to two factors: firstly, the small number of patients included, and secondly, the retrospective natures of the research design. The inability to assess fT3 levels in certain NTIS patients, along with the exclusion of those who died before a thyroid evaluation could be performed, represents additional limitations of the study. These variables may have led to the underrepresentation of NTIS cases and limited the examination of the correlation between NTIS and mortality.

In conclusion, our study highlights the importance of timely and comprehensive thyroid function evaluation in neonates, particularly those who are preterm or critically ill. Identifying and understanding the early hormonal patterns associated with NTIS may contribute to improved risk stratification and clinical outcomes. Further prospective studies are warranted to clarify whether thyroid hormone abnormalities in this population are simply markers of illness severity or modifiable therapeutic targets.

Ethics Committee Approval: The study was approved by the Ethics Committee. (Date: 29.05.2017, decision no: 2017-04-22).

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

Author Contributions: Concept-KB, EDPÇ ÖS; Supervision- EDPÇ, ÖS; Materials- KB, ÖS; Data Collection and/or Processing- KB; Analysis and/or Interpretation- KB, EDPÇ, ÖS; Writing KB.

Peer-review: Externally peer-reviewed.

Other information: This study was derived from a thesis titled Retrospective Examination of Thyroid Functions in the Neonatal Intensive Care Unit..

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):131-138 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):131-138*

Impact of Mydriatic Drops and Pain on Systemic Responses During Retinopathy of Prematurity Screening

Prematüre Retinopatisi Taraması Sırasında Midriatik Damlaların ve Ağrının Sistemik Yanıtlar Üzerindeki Etkisi

[1]Gulay BILGIN,[2]Demet TEKCAN, [3]Mustafa Gurkan ERDOGAN, [4]Sirin GUVEN

[1]Eskisehir City Hospital, Department of Pediatric, Division of Pediatric Pulmonology, Eskisehir, Türkiye
[2]Selcuk University, Faculty of Medicine, Department of Pediatric, Division of Pediatric Allergy and Immunology, Konya, Türkiye
[3]Istanbul University, Faculty of Medicine, Division of Ophthalmology, Istanbul, Türkiye
[4]University of Health Science, Prof Dr Ilhan Varank Sancaktepe Training and Research Hospital, Department of Pediatric, Istanbul, Türkiye

Gulay Bilgin: https://orcid.org/0000-0001-6207-3748
Demet Tekcan: https://orcid.org/0000-0003-1864-5651
Mustafa Gurkan Erdogan: https://orcid.org/0000-0003-4155-0407
Sirin Guven: https://orcid.org/0000-0001-8727-5805

ABSTRACT

Objective: Retinopathy of Prematurity (ROP) presents a significant challenge for neonatal intensive care units (NICUs). Therefore, the study aims to investigate the impact of neonatal pain on the systemic and procedural side effects of ROP examinations and mydriatic drops, with the aim of enhancing screening safety.

Materials And Methods: This study, designed as a prospective descriptive investigation, included 70 preterm infants admitted to the NICU between August and November 2012. Patients were monitored during the examination and for 48 hours afterwards, focusing on vital signs and any side effects. The Neonatal Infant Pain Scale was applied to all patients. Statistical analysis was conducted using SPSS version 15.

Results: Adverse effects were absent in 41.4% of the infants. Flushing was observed in 22.9%, gastric residuals were noted in 10%, vomiting occurred in 8.6%, and a combination of flushing, apnea, and gastric residuals was seen in 2.9% of the infants. The pain group exhibited temporary increases in heart rate and body temperature, most notably within the first hour after the examination. There were no significant relationships between pain and blood pressure, oxygen saturation levels, or respiratory rates ($p>0.05$).

Conclusions: A comprehensive understanding of the adverse effects associated with mydriatic drops and the examination procedure is essential. During ROP screenings, infants should be closely monitored in standardized clinical settings, appropriate pain management strategies should be implemented, and caregivers must receive thorough education upon discharge.

Keywords: Mydriatic drops, neonatal intensive care units, neonatal pain, preterm infants, retinopathy of prematurity

ÖZ

Amaç: Prematüre retinopatisi (ROP), yenidoğan yoğun bakım üniteleri (YYBÜ) için önemli bir klinik sorundur. Bu çalışmada, ROP taramaları sırasında uygulanan midriyatik damlaların ve yenidoğanda oluşan ağrının, sistemik ve işlemle ilişkili bulgular üzerindeki etkileri değerlendirilmiş; böylece tarama güvenliğinin artırılması hedeflenmiştir.

Materyal ve Metot: Prospektif tanımlayıcı nitelikteki bu çalışmaya, Ağustos–Kasım 2012 tarihleri arasında YYBÜ'ye yatırılan 70 prematüre bebek dahil edildi. Tüm hastalar, ROP muayenesi sırasında ve sonrasındaki 48 saat boyunca, yaşamsal bulgular ve gelişebilecek yan etkiler açısından takip edildi. Ağrı değerlendirmesi için tüm bebeklere Yenidoğan Bebek Ağrı Ölçeği (NIPS) uygulandı. İstatistiksel analizler SPSS 15.0 programı ile gerçekleştirildi.

Bulgular: Bebeklerin %41,4'ünde herhangi bir yan etki gözlenmedi. %22,9'unda ciltte kızarıklık, %10'unda mide içeriği artışı, %8,6'sında kusma ve %2,9'unda ciltte kızarıklık, apne ve mide içeriği artışının birlikte görüldüğü belirlendi. Ağrı hisseden grupta, özellikle muayeneden sonraki ilk saatte kalp hızı ve vücut sıcaklığında geçici artış izlendi. Ağrı ile kan basıncı, oksijen satürasyonu ve solunum hızı arasında anlamlı bir ilişki saptanmadı ($p>0,05$).

Sonuç: ROP taramaları sırasında uygulanan midriyatik damlalar ve muayene işlemiyle ilişkili olumsuz etkilerin iyi anlaşılması büyük önem taşımaktadır. Bu süreçte bebeklerin standart klinik koşullarda yakından izlenmesi, etkili ağrı yönetimi sağlanması ve taburculuk öncesinde bakım veren kişilere yeterli eğitim verilmesi gereklidir.

Anahtar Kelimeler: Midriyatik damlalar, prematüre bebekler, prematüre retinopatisi, yenidoğan ağrısı, yenidoğan yoğun bakım üniteleri

Sorumlu Yazar / Corresponding Author:
Gulay Bilgin
Department of Pediatrics, Division of Pediatric Pulmonology, Eskisehir City Hospital, 71 Evler, Çevreyolu, 26080, Odunpazarı/ Eskisehir, Türkiye
Tel.: +905432280879
E-mail: gulaybas1010@yahoo.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 07/02/2025
Kabul Tarihi/ Accepted: 12/04/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Bilgin G and et al. Impact of Mydriatic Drops and Pain on Systemic Responses During Retinopathy of Prematurity Screening. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):131-138. doi: 10.26453/otjhs.1635603

INTRODUCTION

Retinopathy of Prematurity (ROP) poses a major concern in neonatal intensive care units (NICU) due to its potential to cause severe visual impairment or even permanent blindness if not detected and managed in time.[1] Despite the serious implications of this condition, appropriate screening and timely treatment can effectively prevent its progression. The initial screening for ROP typically begins between four to six weeks after birth, offering a critical window for early intervention.[2]

To facilitate the examination, pupil dilation is achieved using topical phenylephrine 2.5% and tropicamide 1%. While these drops are essential for ensuring a thorough evaluation, they pose potential risks. Documented side effects include tachycardia, bradycardia, apnea, hypertension, oxygen desaturation, cyanosis, vomiting, and increased gastric residual volumes.[3,4] However, despite several studies in the literature, it is still uncertain whether these effects stem from the systemic action of the mydriatic drops or the stress and discomfort associated with the examination itself.[4-6]

Neonates, especially preterm infants, have an immature nervous system, which affects their pain perception and response to external stimuli.[7,8] Studies suggest that ROP examination is a potentially painful procedure, and despite the use of local anesthetics, neonates exhibit physiological responses indicating pain and discomfort.[8,9] In particular, pain-related stress may contribute to systemic changes (e.g., instability in heart rate, blood pressure, and oxygen saturation levels), all of which have also been documented as potential side effects of mydriatic drops.[7,8,10]

This investigation aims to explore the systemic and procedural side effects associated with ROP examinations and the mydriatic drops used, with an emphasis on how neonatal pain influences these outcomes.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Umraniye Training and Research Hospital. (Date: 16.08.2012, decision no:2012-4). It was carried out in accordance with the Helsinki Declaration. Written informed consent was collected from the parents of babies.

Study Design and Setting: This prospective descriptive study was conducted between August 2012 and December 2012 at Umraniye Training and Research Hospital, involving 70 preterm infants who were monitored during follow-up in the clinic.

Inclusion and Exclusion Criteria: The study involved preterm infants born before 31 weeks or weighing under 1500 g at birth. Additionally, infants between 1500-2000 g with a gestational age above 31 weeks were included if they required respiratory or circulatory support.[2] Gestational age was determined using the modified Ballard score. Exclusion criteria included major congenital heart anomalies, sepsis, and dependence on mechanical ventilation.

Ophthalmologic Examination Procedure: ROP screening began at 4 to 6 weeks postnatally. Pupil dilation was induced by administering one drop of phenylephrine 2.5% and tropicamide 1% three times at 5-minute intervals. Pressure was applied to the lacrimal ducts during administration. Topical anesthesia was provided with proparacaine hydrochloride 0.5%. Examinations were performed using a binocular indirect ophthalmoscope with 20- and 28-diopter lenses. Following the use of a neonatal lid speculum, the anterior segment and fundus were examined. Findings were documented based on the International Classification of Retinopathy of Prematurity (ICROP) criteria.[11] A single retinal specialist performed all evaluations. Follow-ups occurred every 2 –4 weeks for infants without ROP and 1–2 weeks for stage 1–2 ROP.

Monitoring of Vital Signs and Side Effects: Vital signs, including temperature, blood pressure (BP), respiratory rate, oxygen saturation (sPO_2), and heart rate (HR), assessed at baseline, 1-, 24-, and 48-hours post-examination. In addition to vital signs, side effects (flushing, restlessness, gastric residuals, vomiting, apnea, and abdominal distension) were documented. Pain was assessed immediately after the examination with the Neonatal Infant Pain Scale (NIPS).[7,10,12] These scales evaluate behavioral and physiological indicators of pain (facial expression, crying, breathing pattern, limb movement, and autonomic responses). The NIPS score ranges from 0 to 7, with scores above 3 indicating the presence of pain.

Statistical Analysis: Data analysis was performed using SPSS (Statistical Package for Social Sciences for Windows) 15.0. The Kolmogorov-Smirnov test assessed normality. Descriptive statistics were presented as means, standard deviations, and frequencies. Student's t-test compared two independent groups, while paired-sample t-tests evaluated changes over time. Chi-square tests assessed categorical variables. A p-value <0.05 was considered significant.

RESULTS

Table 1 presents the demographic and baseline clinical characteristics of the study population. A total of 70 preterm infants were included, with 41 (58.6%) being male and 29 (41.4%) females. The mean gestational age was 31.44±2.64 weeks (range:24–34 weeks), and the mean age was 39.77±12.39 days

(range:27–75 days). The mean birth weight was 1851.76±512.88 g (range: 660–2720 g), and the mean current weight at the time of examination was 2357.10±708.87 g (range: 940–4500 g). The number of ROP examinations ranged from one or more, with 38 infants (54.3%) undergoing a single examination and 32 infants (45.7%) undergoing multiple examinations. The mean NIPS score one hour after the examination was 3.47±1.15 (range:2–6), with a median score of 4 (Table 1).

Table 2 illustrates the distribution of pain and adverse effects in the study population. Pain was present in 52.9% (n=37) of infants, while 47.1% (n=33) had no pain. Adverse effects included flushing (23.5%), gastric residuals (10.3%), restlessness (8.8%), vomiting (3.0%), and apnea (1.4%). Additionally, 42.5% of infants had no adverse effects. Some infants exhibited multiple adverse effects, with 2.9% experiencing a combination of flushing, apnea, and gastric residuals, 2.9% having both flushing and residuals, 2.9% showing flushing and apnea, 2.9% presenting gastric residuals and vomiting, and 2.9% having flushing with restlessness (Table 2).

Table 1. Demographic data and baseline clinical characteristics of the patients.

		Min-Max	Mean±SD (%)
Age (day)		27-75	39.77±12.39
Gestational age (week)		24-34	31.44±2.64
The number of examinations		1-5	1.70±0.95
Birth weight (g)		660-2720	1851.76±512.88
Current weight (g)		940-4500	2357.10±708.87
NIPS score (number)		2–6	3.47±1.15
			n (%)
Gender	Male		41 (58.6)
	Female		29 (41.4)
The number of examinations	1 time		38 (54.3)
	≥2 times		32 (45.7)

NIPS: Neonatal Infant Pain Scale

Table 2. NIPS and adverse effects distribution.

Category		n (%)
NIPS	Pain (+)	37 (52.9)
	Pain (-)	33 (47.1)
Adverse Effects	No adverse effects	29 (41.4)
	Flushing	16 (22.9)
	Gastric Residuals	7 (10.0)
	Restlessness	1 (1.4)
	Vomiting	6 (8.6)
	Apnea	1 (1.4)
	Flushing + Apnea + Residuals	2 (2.9)
	Flushing + Residuals	2 (2.9)
	Flushing + Apnea	2 (2.9)
	Residuals + Vomiting	2 (2.9)
	Flushing + Restlessness	2 (2.9)

NIPS: Neonatal Infant Pain Scale

Baseline body temperature showed no significant differences between infants undergoing single (36.79±0.43°C) or multiple examinations (36.90±0.59°C, p=0.369). In both groups, body temperature increased significantly at the 1st hour post-examination compared to baseline (single-examination:37.21±0.70°C, p=0.001; multiple-examinations:37.25±0.72°C, p=0.009); however, levels reverted to baseline by the 24th hour (single examination:36.71±0.42; multiple examination:36.81±0.53, p=0.398 and p=0.514). At the 48th hour, a meaningful decline was examined relative to the baseline in both groups (single examination:36.59±0.12; multiple examination:36.56±0.14, p=0.007 and p=0.004). Infants with pain exhibited markedly elevated body temperatures at the 1st (37.50±0.71°C versus 36.93±0.56°C, p=0.001) and 24th hour (39.93±0.58°C versus 36.56±0.15°C, p=0.001) than those without pain. No difference was found at the 48th hour (36.58±0.12 versus 36.57±0.14, p=0.861) (Table 3).

Table 3. Body Temperature variations based on number of examinations and presence of pain.

Time Point	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	36.79±0.43	36.90±0.59	0.369
ROP Post 1st Hour	37.21±0.70	37.25±0.72	0.827
ROP Post 24th Hour	36.71±0.42	36.81±0.53	0.372
ROP Post 48th Hour	36.59±0.12	36.56±0.14	0.351
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.001**	0.009**	
Pre vs Post 24th Hour	0.398	0.514	
Pre vs Post 48th Hour	0.007**	0.004**	
Time Point	**Pain Present (Mean ±SD)**	**Pain Absent (Mean ±SD)**	**$^{+}$p**
ROP Post 1st Hour	37.50±0.71	36.93±0.56	0.001**
ROP Post 24th Hour	39.93±0.58	36.56±0.15	0.001**
ROP Post 48th Hour	36.58±0.12	36.57±0.14	0.861

ROP: Retinopathy of Prematurity; $^{+}$: Student t-test; $^{++}$: Paired sample t-test; **: p<0.01

The analysis of SAP showed no significant baseline variation between the groups based on examination numbers. Similarly, SAP at the first hour post-examination did not differ significantly (86.42±18.06 mmHg vs 85.59±11.72 mmHg, p=0.825). However, at the 24th hour, a significant increase in SAP was noted in the multiple-examinations group (81.06±8.05 mmHg vs. 76.05±10.52 mmHg, p=0.031). There were no constant differences at the 48th hour (76.31±9.59 mmHg vs. 78.25±7.72 mmHg, p=0.362). Within-group comparisons revealed that there was no meaningful alteration at the 1st hour in the single-examination group (p=0.470), but significant decreases were evaluated at the 24th and 48th hours (p=0.002). In the multiple-examinations group, SAP showed a notable rise at the first hour (p=0.018), while no notable changes were determined at the 24th (p=0.696) or 48th hours (p=0.267). Table 4 demonstrates the variations in SAP and HR following ROP examination based on the number of examinations and the presence of the pain. SAP fluctuations appeared dependent on examination frequency and time after the procedure. No significant differences were examined in the mean SAP between infants with pain and the non-pain group at the 1st hour (87.94±18.69 vs.83.91±10.42), 24th hour (77.94±10.89 vs. 78.78±8.41), and 48th hour of post-examination (76.43±9.25 vs.78.06±8.28) (p=0.263, p=0.721, p=0.443, respectively). HR showed a noticeable increase in the multiple examination group compared to the single examination group at baseline (148.50±17.03 bpm vs. 138.92±16.20 bpm, p=0.019) and at the 24th hour post-examination (146.15±11.16 bpm vs. 134.97±9.71 bpm, p=0.001). Similarly, at the 48th hour post-examination, HR remained significantly elevated in the multiple-examination group (137.12±13.66 bpm vs 130.18±11.65 bpm, p=0.025). However, no significant difference was examined at the 1st-hour post-examination (152.02±15.63 bpm vs 159.37±17.01 bpm, p=0.064). Within-group comparisons revealed a meaningful increase in HR at the 1st hour post-examination over baseline in both groups (p=0.001; p=0.002, respectively). HR significantly decreased at the 48th hour relative to baseline in both groups (p=0.002 for both). There were no important changes at the 24th hour post-examination in either group (p=0.121; p=0.420, respectively). These findings indicated that ROP examinations induced transient changes in HR, with more pronounced effects in infants who underwent multiple examinations. Table 4 also summarizes the HR variations with and without pain at different time points of post-examination. HR was substantially higher in infants with pain instead of those without pain at 1st hour post-examination (p=0.001), and no noticeable variations in HR were determined between the groups at 24th- or 48th-hours post-examination (p=0.196; p=0.989, respectively). Within-group comparisons revealed a significant decrease in HR from 1st hour to 24th hours post-examination and from 24th hours to 48th hours post-examination (p=0.001 for both). Thus, pain during the ROP examination was associated with transient elevations in HR, primarily evident within the 1st hour post-examination (Table 4).

Table 5 presents the SpO_2 and respiratory rate changes based on the number of examinations conducted. SpO_2 levels showed no significant differences between infants who underwent single or multiple examinations at any time (p=0.444, p=0.127, p=0.072, p=0.099, respectively). In the single-examination group, SpO_2 significantly increased at both the 24th hour (p=0.002) and the 48th hour (p=0.005) compared to baseline. In contrast, no significant changes were observed in the multiple-examinations group at these time points (p=0.248, p=0.941, p=0.088, respectively). The respiratory rate significantly increased at the 1st hour post-examination (p=0.001) and approached baseline

levels by the 48th hour in the single-examination group (p=0.210). In the multiple-examinations group, there was a substantial increase in respiratory rate at the 1st hour (p=0.043), but no notable changes at the other time points (p=0.630, p=0.539, respectively) (Table 5).

Table 4. Systolic arterial pressure & heart rate variations based on number of examination and presence of pain.

Systolic Arterial Pressure	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	84.13±19.57	80.31±11.88	0.320
ROP Post 1st Hour	86.42±18.06	85.59±11.72	0.825
ROP Post 24th Hour	76.05±10.52	81.06±8.05	0.031*
ROP Post 48th Hour	76.31±9.59	78.25±7.72	0.362
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.470	0.018	
Pre vs Post 24th Hour	0.002**	0.696	
Pre vs Post 48th Hour	0.002**	0.267	
Systolic Arterial Pressure	**Pain Present (Mean ±SD)**	**Pain Absent (Mean ±SD)**	**$^{+}$p**
ROP Post 1st Hour	87.94±18.69	83.91±10.42	0.263
ROP Post 24th Hour	77.94±10.89	78.78±8.41	0.721
ROP Post 48th Hour	76.43±9.25	78.06±8.28	0.443
Heart Rate	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	138.92±16.20	148.50±17.03	0.019*
ROP Post 1st Hour	152.02±15.63	159.37±17.01	0.064
ROP Post 24th Hour	134.97±9.71	146.15±11.16	0.001**
ROP Post 48th Hour	130.18±11.65	137.12±13.66	0.025*
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.001	0.002	
Pre vs Post 24th Hour	0.121	0.420	
Pre vs Post 48th Hour	0.002**	0.002**	
Heart Rate	**Pain Present (Mean±SD)**	**Pain Absent (Mean ±SD)**	**$^{+}$p**
ROP Post 1st Hour	162.13±14.29	147.82±15.82	0.001**
ROP Post 24th Hour	141.81±11.74	138.15±11.64	0.196
ROP Post 48th Hour	133.38±11.76	133.33±14.43	0.989
Comparison	**$^{++}$p**	**$^{++}$p**	
Post 1st Hour vs Post 24th Hour	0.001**	0.001**	
Post 24th Hour vs Post 48th Hour	0.001**	0.001**	

ROP: Retinopathy of Prematurity; $^{+}$: Student t-test; $^{++}$: Paired sample t-test; **: p<0.01

Table 5. Oxygen saturation and respiratory rate changes based on number of examinations.

Oxygen Saturation (SpO_2, %)	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	98.45 ± 1.88	97.94 ± 3.53	0.444
ROP Post 1st Hour	98.47 ± 1.81	97.40 ± 3.51	0.127
ROP Post 24th Hour	99.39 ± 1.32	97.97 ± 4.17	0.072
ROP Post 48th Hour	99.98 ± 0.75	98.43 ± 2.81	0.099
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.941	0.248	
Pre vs Post 24th Hour	0.002**	0.941	
Pre vs Post 48th Hour	0.005**	0.088	
Respiratory Rate (bpm)	**Single Examination (Mean±SD)**	**Multiple Examinations (Mean±SD)**	**$^{+}$p**
ROP Pre-Examination	38.31 ± 6.37	41.75 ± 6.29	0.027
ROP Post 1st Hour	44.31 ± 7.43	43.62 ± 6.65	0.686
ROP Post 24th Hour	40.34 ± 6.15	42.09 ± 5.65	0.222
ROP Post 48th Hour	39.13 ± 6.12	42.09 ± 5.91	0.045
Comparison	**$^{++}$p (Single Examination)**	**$^{++}$p (Multiple Examinations)**	
Pre vs Post 1st Hour	0.001**	0.043*	
Pre vs Post 24th Hour	0.005**	0.630	
Pre vs Post 48th Hour	0.210	0.539	

ROP: Retinopathy of Prematurity; $^{+}$: Student t-test; $^{++}$: Paired sample t-test; **: p<0.01

DISCUSSION AND CONCLUSION

Consistent evaluation and monitoring of preterm infants are crucial for mitigating the advancement of ROP. The adverse effects during ROP examinations may result from both mydriatic drops and procedural stress. Studies suggest that mydriatic drops may contribute to cardiovascular, respiratory, and gastrointestinal side effects due to systemic absorption.[3,6,13] However, distinguishing these pharmacological effects from procedural pain and stress remains a challenge.

In the study, ROP examinations led to temporary changes in body temperature, HR, respiratory rate, SAP, and sPO_2. Although generally mild, these changes resolved within 24 to 48 hours. Notably, 52.9% of infants experienced pain, which was associated with transient HR and temperature increases, particularly within the first hour. This finding aligns with previous research indicating pain-related activation of the sympathetic nervous system.[10] Similarly, Tasdemir et al. have shown that multisensory stimulation effectively reduces procedural pain and improves physiological stability in preterm infants undergoing ROP examinations. This approach has been associated with lower pain scores, reduced heart rate, and improved oxygen saturation levels.[14] However, the absence of meaningful differences in sPO_2 and respiratory rate between infants with and without pain suggested that these parameters were less influenced by pain during ROP examinations. The role of procedural stress, such as the use of speculums and scleral pressure, was highlighted in previous research as contributors to pain.[14],[15] This emphasizes the need for effective pain management and optimization of the fundoscopic examination strategies.

Previous studies revealed no meaningful changes in body temperature during ROP examinations.[16] However, a recent study identified flushing and fever as the most common side effects, occurring in 68% and 46% of cases, respectively.[17] In our study, flushing was predominantly observed with a ratio of 23.5%. On the other hand, a transient increase in body temperature was detected within the first hour post-examination. Among infants experiencing pain, temperature elevations persisted at 24 hours, suggesting a role of stress-induced thermoregulation changes.

The literature presents conflicting results regarding BP changes during ROP examinations.[3] While some studies have reported a decrease in BP, others have observed an increase, potentially due to variations in mydriatic drop regimens. However, other recent studies detected no significant change in blood pressure.[4,6,18] In our study, SAP increased significantly at 24 hours in infants undergoing multiple examinations. Kremer et al. found no significant difference in BP when comparing low-dose and very low-dose regimens.[19] However, a review published in 2020 highlighted the superior safety profile of microdrop administration.[9] These findings suggest that techniques like nasolacrimal pressure application may reduce systemic absorption.

Jiang et al. reported a transient increase in HR during ROP examinations, which peaked during the procedure and approached to near-baseline levels after 60 minutes.[16] Similarly, in the study, an important increase in HR was examined within the first hour post-examination, particularly in infants experiencing pain. By the 48th hour, HRs had normalized. These results reinforce the importance of observing infants for at least 24 to 48 hours post-examination. On the other hand, a recent study revealed that while mydriatic drops may influence HR and regional cerebral oxygenation, they do not appear to significantly impact cerebral blood flow velocities or the metabolic rate of oxygen consumption, indicating their general safety.[18]

Unlike HR and respiratory rates, sPO_2 levels showed minimal fluctuation in the study across groups, contrasting with studies reporting significant oxygen desaturation during ROP screening, presumably due to variances in study design, like the application of supplemental oxygen or variations in procedure duration.[3,6,19] Similarly, Alpay et al. also found a temporary decrease in sPO2 after mydriatic drop administration, but not statistically significant. Since the desaturation coincided with the examination, they blamed procedural stress.[4]

Apnea was observed in five infants, all of whom recovered with tactile stimulation without further intervention. While apnea following ROP screening is commonly reported within 24 to 48 hours, no significant changes were seen at 12 hours in some studies.[6] Publications suggest that apnea may result from procedural pain, stress, stimulation of the oculocardiac reflex, or the anticholinergic effects of mydriatic drops.[3,4,6,10] These findings emphasize the need for immediate post-examination monitoring rather than during the procedure itself.

The results of this study underscore the importance of performing ROP examinations under controlled clinical conditions with appropriate monitoring and pain management strategies. Infants should be closely observed for at least 24 to 48 hours following the examination, particularly in outpatient settings where immediate medical intervention may not be readily available. Additionally, the adoption of micro-drop techniques and other strategies to reduce systemic absorption of mydriatic drops should be prioritized.

This study has a few limitations. Being a single-center study is one of them. Meanwhile, the sample size was constrained, which may limit the extent to which the results can be generalized to larger popu-

lations. Furthermore, pain was assessed using the NIPS, a subjective scale that may introduce variability. The absence of a control group further limits our ability to distinguish the effects of mydriatic drops from procedural stress. Finally, we did not measure biochemical markers or assess long-term outcomes related to the systemic effects of the procedure. Future multicenter studies with larger cohorts and advanced monitoring techniques are needed to validate and expand upon these findings.

In conclusion, ROP examinations transiently affect physiological parameters in preterm infants due to both procedural pain and systemic drug effects. While most side effects are mild and self-limiting, careful monitoring, pain control, and protocol optimization are crucial. Educating caregivers about potential adverse effects may reduce parental anxiety and enhance infant safety.

Ethics Committee Approval: This study was designed in accordance with the Helsinki Principles and received ethical approval from the Ethics Committee of Umraniye Training and Research Hospital. (Date: 16.08.2012, decision no:2012-4). The permissions of the parents of the babies included in the study were obtained via written consent.

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

Author Contributions: Concept – GB, DT, MGE, ŞG; Supervision – MGE, ŞG; Materials – GB, MGE, ŞG; Data Collection and/or Processing – GB, DT, MGE; Analysis and/or Interpretation – GB, DT, ŞG; Writing –GB, DT, MGE, ŞG.

Peer-review: Externally peer-reviewed.

Other Information: This study was produced from the specialization thesis entitled "Systemic Effects of Mydriatic Drops and Physical Examination During Screening for Retinopathy of Prematurity". This study was presented as a poster at 27th International Pediatric Association (IPA) Congress of Pediatrics in 2013.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):139-144 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):139-144*

Evaluation of the Use of Leftover Graft Materials in Dentistry Procedures

Diş Hekimliği İşlemlerinde Kalan Greft Materyallerinin Kullanımının Değerlendirilmesi

[1]İsmail TAŞDEMİR, [2]Veysel İÇEN, [3]Mücahid Faik ŞAHİN

[1]Karamanoğlu Mehmetbey University Faculty of Dentistry Department of Periodontology, Karaman, Türkiye
[2]Karamanoğlu Mehmetbey University Faculty of Dentistry Department of Oral and Maxillofacial Surgery, Karaman, Türkiye
[3]Private Clinic, Bursa, Türkiye

İsmail Taşdemir: https://orcid.org/0000-0003-0110-1412
Veysel İçen: https://orcid.org/0000-0003-3112-8528
Mücahid Faik Şahin: https://orcid.org/0000-0001-6953-026X

ABSTRACT

Objective: We evaluated the use of leftover graft materials in dental procedures, the sterilisation methods used, and the storage conditions and durations under which leftover graft materials **(**LGMs) were stored.

Materials and Methods: An online survey of 200 Turkish dentists was conducted. The survey consisted of 14 open-ended and multiple-choice questions. Information was sought about the types of grafts the dentists used, their frequency of use, the use of LGMs, whether such LGMs were sterilized before use, and their preferences regarding storage conditions before use.

Results: Overall, 81.3% of dentists stated that they used LGMs. Of them, 69.6% did not sterilise the material before use. Also, 59.9% of the dentists thought that LGMs could be used after the package had been opened. When the branch distribution and years of practice of the dentists who answered the question "What do they do with the remaining graft materials after the first use?" were evaluated, no statistically significant difference was found between the groups. When the distribution of dentists who answered the question "Do you re-sterilize the graft before use?" was examined according to their branches, no statistically significant difference was found between the groups.

Conclusions: LGMs are frequently used by Turkish dentists after the package has been opened. Future studies should determine the risk of cross-infections and the bioactivity of LGMs.

Keywords: Allograft, autogenous graft, bone graft, xenograft

ÖZ

Amaç: Bu çalışmada diş hekimliğinde ilk kullanımdan sonra arta kalan greft materyallerinin kullanımı, kullanılan sterilizasyon yöntemleri, arta kalan greft materyallerinin (AGM) saklanma koşulları ve sürelerinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: 200 Türk diş hekimine yönelik çevrimiçi bir anket yapıldı. Anket 14 açık uçlu ve çoktan seçmeli sorudan oluşuyordu. Diş hekimlerinin kullandığı greft türleri, kullanım sıklıkları, AGM' lerinin kullanımı, bu AGM' lerinin kullanımdan önce sterilize edilip edilmediği ve kullanımdan önce saklama koşullarıyla ilgili tercihleri hakkında bilgi istendi.

Bulgular: Genel olarak diş hekimlerinin %81,3'ü AGM' lerini kullandığını belirtti. Bunların %69,6'sı materyali kullanmadan önce sterilize etmediğini belirtti. Ayrıca diş hekimlerinin %59,9'u AGM' lerinin paket açıldıktan sonra yeniden kullanılabileceğini düşündüğünü belirtti. İlk kullanımdan sonra kalan greft materyallerini ne yapıyorsunuz sorusuna cevap veren diş hekimlerinin branş dağılımı ve tecrübe yılı değerlendirildiğinde gruplar arasında istatistiksel olarak anlamlı bir fark bulunamamıştır. Grefti kullanmadan önce tekrar sterilize ediyor musunuz? sorusuna cevap veren diş hekimlerinin branşlara göre dağılımı incelendiğinde gruplar arasında istatistiksel olarak anlamlı bir fark bulunamamıştır.

Sonuç: Çalışmanın sonuçlarına göre greft materyalleri ilk kullanımdan sonra diş hekimleri tarafından sıklıkla kullanılmaktadır. Bu nedenle ileriki zamanlarda çapraz enfeksiyon riskini ve greftlerin tekrar kullanımdan sonraki biyoaktivitesini belirlemek için çalışmalar yapılmasına ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Allogreft, kemik grefti, ksenogreft, otojen greft

Sorumlu Yazar / Corresponding Author:
İsmail Taşdemir
Üniversite mahallesi. 2055 sok. No:5 Merkez/Karaman, Türkiye
Tel.: +90545 569 45 73
E-mail: drismailtasdemir@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 04/03/2025
Kabul Tarihi/ Accepted: 21/04/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Taşdemir İ and et al. Evaluation of the Use of Leftover Graft Materials in Dentistry Procedures. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):139-144. doi: 10.26453/otjhs.1651071

INTRODUCTION

In dentistry, bone grafts are used in many areas, such as the treatment of trauma, periodontal defects, and bone defects after tooth extraction, to increase the amount of adequate bone before dental implant surgery, and to repair various types of defects during dental implants.[1,2] Bone-grafting procedures are valid and reliable treatments for replacing missing bone and bone augmentation.[3,4] Although autogenous bone grafts are still considered the gold standard, their use is limited due to several disadvantages, such as requiring a second surgical site to harvest the graft and the need to harvest a minimal amount of tissue, often resulting in an insufficient amount of material.[4-6] Because of these limitations, dentists frequently prefer allografts, xenografts and synthetic grafts when appropriate.[7-9] Allografts and xenografts undergo processing to remove organic materials and are sterilised to eliminate antigens, bacteria, and viruses.[10,11] Common sterilisation techniques include exposure to gamma radiation, treatment with ethylene oxide, and other chemical processing methods to prevent cross-infection risks from donor organisms.[12,13] After sterilisation, these products undergo stringent safety tests before being commercially available.[14] Bone grafts are typically sold in sterile packaging, and manufacturer guidelines dictate that each package should be used for a single patient. Once opened, any remaining graft material should be discarded to prevent contamination and cross-infection.[15] Therefore, it is important to investigate the current use of such materials and the conditions under which they are used.

This study aimed to evaluate the frequency of LGM use in dental procedures, dentists' awareness of the associated risks, the storage practices employed, and the length of storage (after opening the original package) before use.

MATERIALS AND METHODS

Ethics Committee Approval: Ethical approval was received from Karamanoglu Mehmetbey University, Faculty of Medicine Local Scientific Medical Research Ethics Committee (Date: 30.05.2024, decision no: 06-2024/09). The study adhered to the ethical guidelines of the Declaration of Helsinki.

Data collection: A self-administered and online (14 questions in three parts; Table I), prepared using Google Forms (Google, Inc., 2017, California, USA) and was randomly sent to 200 dentists via email and text. To develop the survey, we first conducted a literature review and prepared 14 questions about LGM use in routine medical practice; this was emailed to three experts for verification of the content and assessed using a five-point Likert scale. Each question was evaluated and deemed appropriate for use.

The first 6 questions in the survey consisted of the following questions: age, gender, the institution they work for, how many years they have been a dentist, areas of expertise and whether they use graft material.

The questions in the second part consisted of questions about how many packages of grafts dentists use annually, what type of graft material they use, and whether they reuse the graft after the first use. The questions in the third section consisted of questions measuring whether the graft was re-sterilized before use, if so, what method they used for sterilization, under what storage conditions they stored leftover graft material before using, how long the package was used from the date it was first opened, and questions about using leftover graft.

The survey consisted of open-ended and multiple-choice questions. Participants who answered "I want to participate" on the consent form in the first part proceeded to the second part and participated in the study by answering the questions. The first part of the survey stated that participation was voluntary, and dentists who chose not to participate could refrain from completing it. The survey was sent to a total of 200 dentists, and the answers of 187 dentists who accepted and participated in the survey were used in the study.

Statistical Analysis: All data were analyzed using SPSS Statistics Version 21.0 (IBM Corp., New York). Chi-square analysis was used to evaluate the relationships between categorical variables. The threshold for statistical significance was set at $p<0.05$.

RESULTS

The results are given in Table 1. In the study, 57.8% of the participants identified as male, 41.7% as female, and 0.5% chose not to disclose their gender. Most were 25-35 years old and worked at universities. Most of the participants (43.9 %) were periodontology specialists and had about 10 years or more of professional experience. Most of the participants (39.6 %) had 0-5 years of experience using grafts, and 11.2 % had never used grafts. Among graft users, 41.6 % used 0-10 packages of graft material each year, 25.9 % used 10-20 packs, and 33.5 % used more than 20. The participants used xenografts at the highest rate (42.8 %), followed by allogeneous grafts (24.7 %) and other grafts. After opening a package and using graft material the majority of participants (81.3 %) reported using it again; only 18.7 % stated that they do not use LGMs. While the majority of reusers, 69.6 %, stated that they did not sterilize the graft again before use, 30.4 % stated that they sterilized the graft before

use. The majority of those who sterilize before reuse (70.7 %) sterilize by autoclave but less frequently use other sterilization methods. The vast majority (62.2 %) stored LGM in a cupboard at room temperature, about 37 % kept it in a refrigerator and only 0.7 % stored it in a deep freezer. Nearly all participants used leftover material within 1-6 months, with only about 5.2 % of dentists using it after more than 6 months of storage. Most participants (59.9 %) felt that LGM could be used later, 25.7 % felt that it should not be used again, and 14.4 % had no opinion.

Table 1. Responses of the participants to the questions.

Variables	Subcategory	n (%)
1. Gender	Female	78 (41.7)
	Male	108 (57.8)
	I don't want to specify	1 (0.5)
2. Age	25-35	102 (54.5)
	36-45	77 (41.2)
	46 and above	8 (4.3)
3. Which institution do you work for?	University	81 (43.3)
	Private outpatient clinic	43 (23.0)
	Own Clinic	40 (21.4)
	Oral and Dental Health Center	23 (12.3)
4. Branch	Oral and Maxillofacial Surgery	47 (25.1)
	Dentist	58 (31.0)
	Periodontology	82 (43.9)
5. Years of practice	0-5 years	45 (24.1)
	5-10 years	56 (29.9)
	More than 10 years	86 (46.0)
6. How many years have you been using graft material?	I don’t use	21 (11.2)
	0-5 years	74 (39.6)
	5-10 years	48 (25.7)
	More than 10 years	44 (23.5)
7. How many packages of grafts do you use annually?	0-10	69 (41.6)
	10-20	43 (25.9)
	More than 20	54 (32.5)
8. What type of graft material do you use?	Autogenous Graft	16 (9.6)
	Allogeneous Graft	41 (24.7)
	Xenograft	71 (42.8)
	Synthetic Graft	3 (1.8)
	Autogenous Graft, Allogeneous Graft	1 (0.6)
	Autogenous Graft, Xenograft	3 (1.8)
	Allogenous Graft, Xenograft	8 (4.8)
	Autogenous Graft, Allogeneous Graft, Xenograft	13 (7.8)
	Autogeneous Graft, Allogeneous Graft, Xenograft, Synthetic Graft	10 (6.0)
9. What do you do with the remaining graft materials after the first use?	I don’t use it again	31 (18.7)
	I use it again	135 (81.3)
10. Do you re-sterilize the graft before use?	Yes	41 (30.4)
	No	94 (69.6)
11. By what method do you sterilize before use?	Dry Hot Air Sterilization	8 (19.5)
	Autoclave	29 (70.7)
	Gamma Sterilization	4 (9.8)
12. Where do you store the graft until reuse?	In The Cupboard At Room Temperature	84 (62.2)
	Refrigerator	50 (37.0)
	In The Deep Freezer	1 (0.7)
13. How many months do you use the graft from the date the package is first opened?	0-1 Months	43 (31.9)
	1-3 Months	52 (38.5)
	3-6 Months	33 (24.4)
	More than 6 months	7 (5.2)
14. What do you think about the reuse of graft materials after the original package of graft materials is opened?	Should Not Be Used Again	48 (25.7)
	Reusable	112 (59.9)
	I Don't Know	27 (14.4)

When the distribution of branches of dentists ' responded to the question of what do you do with the remaining graft materials after the first use? was examined, no significant difference was found between branches (p>0.05) (Table 2).

When the distribution of years of practice of dentists who responded to the question of what do you do with the remaining graft materials after the first use? was examined, no significant difference was found between the years of practice and their responses to the use of the leftover graft (p>0.05) (Table 3).

When the distribution of the branches of dentists who answered the question of do you re-sterilize the graft before use was examined, no significant difference was found between the branches (p>0.05) (Table 4).

DISCUSSION AND CONCLUSION

In dentistry, grafting procedures are usually performed in local operating rooms. Today, many precautions are taken to minimize the number of microorganisms in these types of local operating rooms. However, these places can never be completely sterilized due to independent risk factors such as the type of surgery, the place of the procedure, and the number of personnel.[16] In addition, the use of tools such as rotary handpieces and ultrasonic handpieces in the process can result in the release of a lot of aerosol into the environment.[17] These aerosols formed during surgical procedures may increase the risk of cross-infection between patients, as well as infect dental implants and biomaterials such as graft materials and membranes used.[18-20] Infection of graft

Table 2. Distribution of branches of dentists who responded to the question of what do you do with the remaining graft materials after the first use.

		Branch			p-value
		Oral and Maxillofacial Surgery	Dentist	Periodontology	
I don't use it again	n	10	6	15	0.37
	% within branch	25.0	13.0	18.8	
I use it again	n	30	40	65	
	% within branch	75.0	87.0	81.2	
Total	n	40	46	80	
	% within branch	100.0	100.0	100.0	

Table 3. Distribution of years of practice of dentists who responded to the question of what do you do with the remaining graft materials after the first use.

		Years of practice			p-value
		0-5 years	5-10 years	More than 10 years	
I don't use it again	n	6	12	13	0.58
	% within years of practice	18.8	23.1	15.9	
I use it again	n	26	40	69	
	% within years of practice	81.2	76.9	84.1	
Total	n	32	52	82	
	% within years of practice	100.0	100.0	100.0	

Table 4. Distribution of the branches of dentists who answered the question of do you re-sterilize the graft before use.

		Branch			p-value
		Oral and Maxillofacial Surgery	Dentist	Periodontology	
Yes	n	8	12	15	0.73
	% within branch	26.7	30.0	23.1	
No	n	22	28	50	
	% within branch	73.3	70.0	76.9	
Total	n	30	40	65	
	% within branch	100.0	100.0	100.0	

materials, implants and membranes used during procedures for various reasons may cause the applied treatment to fail, resulting in additional treatment applications and additional costs for patients and dentists.[17,21]

For these reasons, manufacturers do not recommend using commercially produced graft materials after they have been opened.[15] However, 81.3% of the dentists who participated in our study and stated that they used graft materials stated that they used the remaining graft material. In addition, when the reuse of dentists was evaluated according to the branches and years of practice, no significant difference was found in our study. This situation showed that there was a tendency towards the reuse of graft materials, regardless of the content and quality of the education received and the experience of the dentists over the years.

There are very few studies on the use of LGMs. Only one study evaluated bacterial contamination of such materials after 1 minute, 10 minutes and 1 hour on the operating table and did not document any contamination.[15] However, there have been no studies on the risk of contamination of an opened package over a longer period. In our study, 68 % of dentists used LGM after more than a month of storage. This situation has highlighted the need for studies examining the risk of infection in graft materials that have been stored for long periods.

About 70% of dentists did not re-sterilize the material before using it. Among those who did re-sterilize, the vast majority did so using an autoclave, and the rest used gamma sterilisation or dry hot air methods. However, the bioactivity and Ca/P ratios of graft materials may change when stored under different conditions and different sterilisation methods.[22] As it is well known, graft materials are sterilized by gamma radiation, treatment with ethylene oxide, and other chemical processing methods to prevent the risk of cross-infection from donor organisms during production.[12,13] However, in our study, the autoclave and dry heat sterilization methods, which dentists often use to re-sterilize the grafts, expose the grafts to high temperatures for long periods. In this case, the biological activities and biological structures of the graft materials may change, which may negatively affect their effectiveness and intended use.

Most participating dentists stored LGM in a cupboard at room temperature, and nearly all others put it in a refrigerator. Manufacturers generally recommend storing graft materials at room temperature, but 37.7% of study participants reported storing remaining grafts in refrigerators and deep freezers.[23] However, no studies have examined the effects of either of these storage conditions on the structure and bioactivity of graft materials in general, much less LGM.

In conclusion, although the use of LGM is not recommended, the vast majority of surviving dentists frequently do so. Therefore, studies should investigate the effects of storage conditions, sterilisation methods, and storage durations after first use on the risk of cross-infection and bioactivity of LGMs. The limitation of this study is that it was conducted only with dentists in Türkiye.

Ethics Committee Approval: Our study was approved by the Karamanoglu Mehmetbey University Faculty of Medicine Local Scientific Medical Research Ethics Committee (Date: 30.05.2024, decision no: 06-2024/09). The study adhered to the ethical guidelines of the Declaration of Helsinki.

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

Author Contributions: Concept – İT, Vİ; Supervision – İT, Vİ; Materials – İT, Vİ, MFŞ; Data Collection and/or Processing – İT, Vİ, MFŞ; Analysis and/or Interpretation – İT, Vİ, MFŞ; Writing –İT, MFŞ.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):145-152 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):145-152*

Technology in Physiotherapy: A Bibliometric Analysis of Artificial Intelligence in Physiotherapy and Rehabilitation

Fizyoterapide Teknoloji: Fizyoterapi ve Rehabilitasyonda Yapay Zekâya Dair Bibliyometrik Bir Analiz

[1]Güzin Kaya AYTUTULDU, [2]İlhan AYTUTULDU, [3]Tansu Birinci OLGUN, [2]Yusuf Sinan AKGÜL

[1]Biruni University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation (English), İstanbul, Türkiye
[2]Gebze Technical University, Faculty of Engineering, Department of Computer Engineering, Kocaeli, Türkiye
[3]Istanbul Medeniyet University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, İstanbul, Türkiye

Güzin Kaya Aytutuldu: https://orcid.org/0000-0002-0192-9861
İlhan Aytutuldu: https://orcid.org/0000-0003-4237-8442
Tansu Birinci Olgun: https://orcid.org/0000-0002-7993-3254
Yusuf Sinan Akgül: https://orcid.org/0000-0001-8501-4812

ABSTRACT

Objective: This study aimed to perform quantitative and qualitative evaluations of the state of artificial intelligence (AI) for physiotherapy and rehabilitation.

Materials and Methods: The bibliometric data have been collected using title and abstract keyword searches from the Web of Science database for AI applications in the physiotherapy field. A total of 187 articles were identified using keywords such as machine learning, deep learning, artificial neural network, artificial intelligence, natural language processing, and physiotherapy.

Results: A total of 187 articles published between 2001 and 2024 were analyzed. The year 2023 had the highest publication volume (47 articles). "Engineering Electrical Electronic" was the most productive research field. Frequently occurring terms included "Machine Learning," "Rehabilitation," and "Artificial Intelligence."

Conclusions: Publications on artificial intelligence and physiotherapy have significantly increased in recent years. These findings underscore the increasing relevance of AI-driven technologies for clinical practice, therapeutic decision-making, and rehabilitation research. For physiotherapists, healthcare professionals, and interdisciplinary researchers, this study provides valuable insight into emerging trends and areas of concentration. Future work can benefit from bibliometric analyses across different databases to support multidisciplinary research.

Keywords: Artificial intelligence (AI), deep learning, machine learning, physiotherapy and rehabilitation, Web of Science (WoS)

ÖZ

Amaç: Bu çalışma, fizyoterapi ve rehabilitasyon alanında yapay zekânın mevcut durumunu nicel ve nitel olarak değerlendirmeyi amaçlamaktadır.

Materyal ve Metot: Bibliyometrik veriler, Web of Science veri tabanında başlık ve özet anahtar kelime aramaları yapılarak toplanmıştır. "Makine öğrenimi," "derin öğrenme," "yapay sinir ağı," "yapay zekâ," "doğal dil işleme" ve "fizyoterapi" gibi anahtar kelimeler kullanılarak toplam 187 makaleye ulaşılmıştır.

Bulgular: 2001–2024 yılları arasında yayımlanan toplam 187 makale analiz edilmiştir. En fazla yayının yapıldığı yıl 2023 olup, bu yıl içinde 47 makale yayımlanmıştır. En üretken araştırma alanı "Elektrik Elektronik Mühendisliği" olarak belirlenmiştir. En sık karşılaşılan terimler arasında "Makine Öğrenimi," "Rehabilitasyon" ve "Yapay Zekâ" yer almaktadır.

Sonuç: Yapay zekâ ve fizyoterapi üzerine yapılan yayınlar son yıllarda önemli ölçüde artmıştır. Bu bulgular, klinik uygulamalar, tedaviye yönelik karar verme süreçleri ve rehabilitasyon araştırmaları açısından yapay zekâ destekli teknolojilerin artan önemini vurgulamaktadır. Fizyoterapistler, sağlık profesyonelleri ve disiplinler arası araştırmacılar için bu çalışma, yükselen eğilimler ve odaklanılan alanlar hakkında değerli içgörüler sunmaktadır. Multidisipliner çalışma yapan araştırmacılar için Scopus ve PubMed gibi farklı veri tabanlarından çıkarılacak bibliyometrik analizler gelecekteki çalışmalara yön verebilir.

Anahtar Kelimeler: Derin öğrenme, fizyoterapi ve rehabilitasyon, makine öğrenimi, yapay zekâ, Web of Science (WoS)

Sorumlu Yazar / Corresponding Author:
Güzin Kaya Aytutuldu
Biruni University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation (English), İstanbul, Türkiye
Tel.: +905366265884
E-mail: gaytutuldu@biruni.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 16/03/2025
Kabul Tarihi/ Accepted: 16/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Aytutuldu GK and et al. Technology in Physiotherapy: A Bibliometric Analysis of Artificial Intelligence in Physiotherapy and Rehabilitation. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):145-152. doi: 10.26453/otjhs.1659222

INTRODUCTION

Machine learning (ML) and deep learning (DL) are subsets of artificial intelligence (AI).[1] ML is the study of computer algorithms that automatically improve through experience by applying mathematical approaches, and DL refers to an algorithm that learns by processing input data through artificial neural networks (ANN) that mimic neurons in the biological brain.[1] Both are fast-growing, interdisciplinary fields with remarkable applications in clinical practice in healthcare.[2-4] The interdisciplinary nature of these fields, spanning computer science, mathematics, and healthcare, is a testament to the breadth of recent developments in AI technologies leading to innovative healthcare.[5]

AI usually assists healthcare professionals in clinical decision-making, such as diagnosing diseases, planning treatments, and predicting outcomes.[6,7] Integrating AI technology in healthcare is critical for developing novel approaches to addressing healthcare challenges and discovering new opportunities.[8] During the coronavirus disease 2019 (COVID-19), healthcare services had to limit outpatient services. This crisis also highlighted the significant contribution of AI in enhancing telemedicine and telerehabilitation worldwide, paving the way for new possibilities in healthcare.[9] In addition, previous studies have highlighted the potential of ML and DL in physiotherapy and rehabilitation, an essential branch of the healthcare field, to improve quality of life.[10,11]

AI-based systems, such as virtual reality-based rehabilitation platforms and motion-sensing devices, are being developed to activate clinical evaluation areas such as balance, walking, daily living activities, and upper and lower extremity skills.[12-14] These systems can provide real-time feedback, track progress, and predict clinical outcomes, thereby enhancing the quality of care and patient outcomes.[13-15] AI and ML have been used to record exercises, provide personalized advice, and detect joint angles.[16] ANN has also been used for gait classification and monitoring according to the lower extremity joint angle.[17] Some studies further pointed out the application of ML in musculoskeletal physiotherapy by proposing a digitalized system for physiotherapy and developing a smart sensor-based rehabilitation exercise recognition system.[14,16] Current literature underscores the potential of AI technologies to improve the accuracy, efficiency, and personalization of physiotherapy practices.[10,11,13-16] A few reviews in the literature investigate physiotherapy and rehabilitation practices supported by AI technology. [16-19]

However, there has yet to be a bibliometric analysis that scans research and journals to guide researchers in publishing their work in this common field. This study aimed to perform quantitative and qualitative evaluations of the state of AI in physiotherapy and rehabilitation.

MATERIALS AND METHODS

***Ethical Approval*:** The bibliometric data have been collected using the title and abstract keyword search from the Web of Science database for terms belonging to AI in the physiotherapy field. Ethics committee approval of this study is not required.

Data Collection: The bibliometric data have been collected using the title and abstract keyword search from the Web of Science (WoS) database for terms belonging to AI in the physiotherapy field. The study used the keywords "Physiotherapy" OR "Physical Therapy" AND "Machine Learning," "Deep Learning," "Artificial Intelligence," "Artificial Neural Network," OR "Natural Language Processing." These keywords were selected based on a preliminary review of the literature and common terminology found in prior studies intersecting artificial intelligence and physiotherapy. The aim was to capture a comprehensive range of relevant articles covering core AI methodologies (e.g., machine learning, deep learning) as well as broader AI-related terminology (e.g., artificial intelligence, neural networks, NLP).

The publication periods are from 2001 to 2024 (data accessed: 29 May 2024), and the articles, reviews, conference proceedings, and book chapters published in the English language were included in the research. The comprehensive search has yielded a substantial corpus of 187 documents (Figure 1).

Bibliometric Analysis: Bibliometric analysis was conducted following the guide developed by Donthu and his colleagues.[20] The subsequent step involved the bibliometric analysis of these selected documents, focusing on identifying key patterns and trends in the research field. The bibliometric study helps in understanding research trends and guides researchers and funding agencies in making informed decisions about publication strategies, promotions, research priorities, collaborations, and funding allocations.

This study uses bibliometric analysis to provide an overview of AI trends in the field of physiotherapy and rehabilitation. Initially, the analysis was performed using an advanced WoS search. The WOS was selected due to its comprehensive coverage of multidisciplinary and high-impact journals, as well as its robust citation indexing features, which are highly compatible with bibliometric mapping tools such as VOSviewer and Biblioshiny. Specifically, the advanced search capabilities of WoS provide access to detailed bibliometric indicators, including top source titles, publication counts by quartile, an-

nual publication trends, citation metrics, document type classifications, WoS category distributions, and citation topic clusters. These characteristics made WoS particularly suitable for conducting rigorous quantitative and qualitative analysis. Nevertheless, it is acknowledged that the inclusion of additional databases such as Scopus or PubMed in future studies could further enrich the scope and comprehensiveness of bibliometric evaluations.

We used the bibliometrix application, specifically biblioshiny 4.1, which is an R tool (R 4.4.0 version used in this study) for comprehensive science mapping analysis. The biblioshiny application, a web interface for bibliometrics, is Java software, and it was used to observe affiliations of published articles.[21] Authors tagged publications according to subbranches of physiotherapy. Publication numbers and citation numbers are shown according to these fields. VOSviewer is a user-friendly tool known for its simplicity, flexibility, and responsiveness to user demands. It offers high-quality graphics but limits alternatives to its pre-programmed functions and requires repeated analysis due to its inability to combine data from different sources. Finally, the documents most comprehensively analysed with VOSviewer were subjected to Network Visualisation, enabling the creation of a visual map that displays the interrelationships between various author keywords. This methodological approach ensures a structured and rigorous literature analysis, offering valuable insights into the convergence of technologies and methodologies within rehabilitation technology.

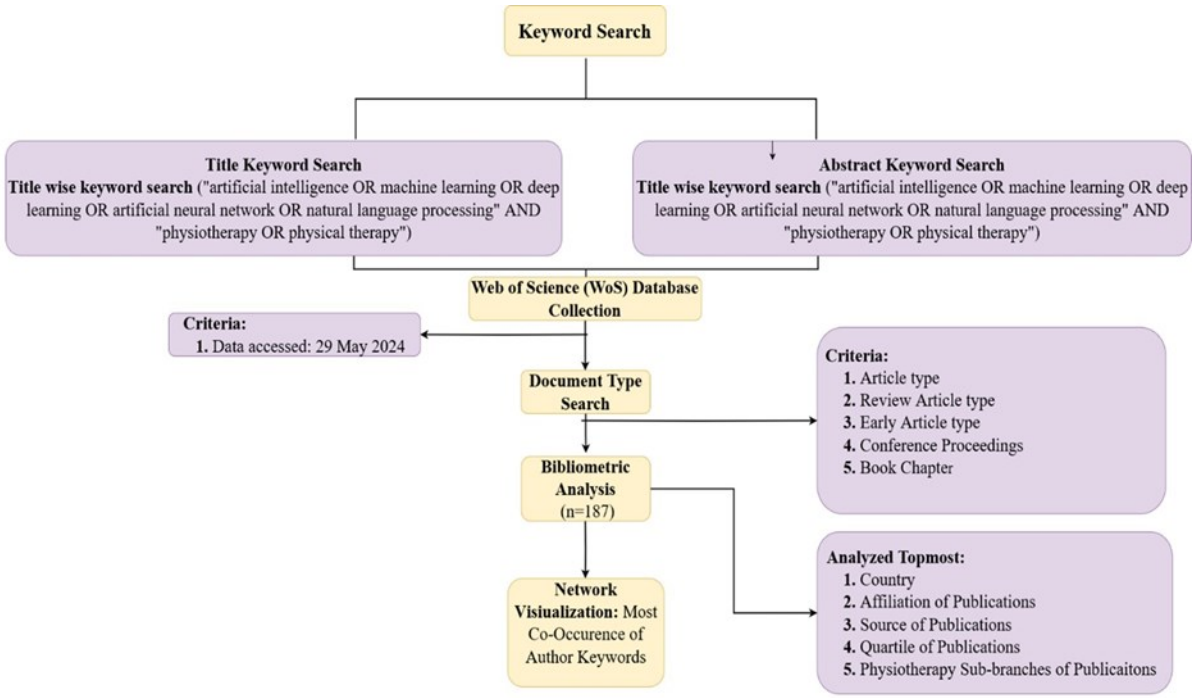

Figure 1. Workflow diagram.

RESULTS

A total of 187 articles published between 2001 and 2024 were included. The number of published articles remained low until 2016, followed by a steady rise, peaking at 47 publications in 2023. This trend highlights the growing research interest in the application of computational methods in physiotherapy. Publications rose from 18 in 2020 to 37 in 2022, reaching a peak of 47 in 2023. Category-specific growth followed a similar pattern. Notably, 38 articles indexed in the Science Citation Index Expanded were published in 2023, indicating rising academic interest in the field. This reflects increasing academic recognition and dissemination of computational approaches in physiotherapy across high-impact venues. The notable rise in publications after 2020 likely reflects the increased attention toward remote rehabilitation and AI-driven healthcare solutions prompted by the COVID-19 pandemic. Most documents were original research articles (126), followed by proceeding papers (47) and review articles (11). Other types, such as editorials, book chapters, and data papers, were rare, underscoring a strong focus on peer-reviewed research. Between 2001 and 2015, the number of publications was limited. Over time, however, research expanded across various subfields, with significant contributions in neural systems and rehabilitation engineering. Although the article count was low (3 and 1, respectively), highly cited journals included *IEEE Transactions on Neural Systems and Rehabilitation Engineering*. *Sensors* was the most prolific journal, contributing 15 articles. *IEEE Access* and *Applied Sciences-Basel* followed with six and five articles, respectively. Most papers were published in Q2 of 2023 (Table 1). Specifically, we note that Sensors is an open-access journal with a strong focus on applied technologies in healthcare, which may attract a higher volume of submissions in emerging interdisciplinary areas like AI in physiotherapy.

The most frequently cited sources reflect the interdisciplinary nature of the field, with *Sensors* (107 citations), *npj Digital Medicine* (100), and *JMIR mHealth and uHealth* (85) leading in impact. Other prominent journals include *IEEE Transactions on Neural Systems and Rehabilitation Engineering* and *Composites Part A*, each with 72 citations, followed by *IEEE Access* (69). These highly cited publications span domains such as biomedical signal processing, rehabilitation, digital health, and applied sciences, indicating a broad and growing academic interest. Institution-wise, the University of Toronto led with 22 publications, followed by Harvard University (12), Harvard Medical School (8), and the University of California System (8). Additional contributions came from institutions such as Radboud University Nijmegen and Shanghai Jiao Tong University, each with 6 articles. Citation patterns varied by sub-branch. While musculoskeletal rehabilitation had the most articles, neurological and orthopedic topics had relatively higher citation rates, suggesting greater scholarly influence (Figure 2).

Table 1. Publication count by quartile and proceedings per year.

Publication Year	BOOK	ESCI	PROCEEDING	Q1	Q2	Q3	Q4	Rehabilitation: Q1 Engineering: Q2
2001	0	0	0	1	0	0	0	0
2007	0	0	0	0	0	1	0	0
2009	0	0	0	0	1	0	0	0
2010	0	0	1	0	0	0	0	0
2011	0	0	0	1	0	0	0	0
2013	0	0	1	1	2	1	0	0
2014	0	0	0	0	0	0	0	1
2015	0	0	4	0	1	0	0	0
2016	0	0	2	1	0	1	1	0
2017	1	0	2	0	0	0	1	0
2018	0	0	4	0	1	1	0	0
2019	0	0	6	1	3	3	3	1
2020	0	0	7	1	6	2	2	0
2021	0	1	4	1	11	2	3	0
2022	0	0	8	5	17	2	5	0
2023	0	0	4	6	26	8	2	1
2024	0	0	0	3	8	3	1	0

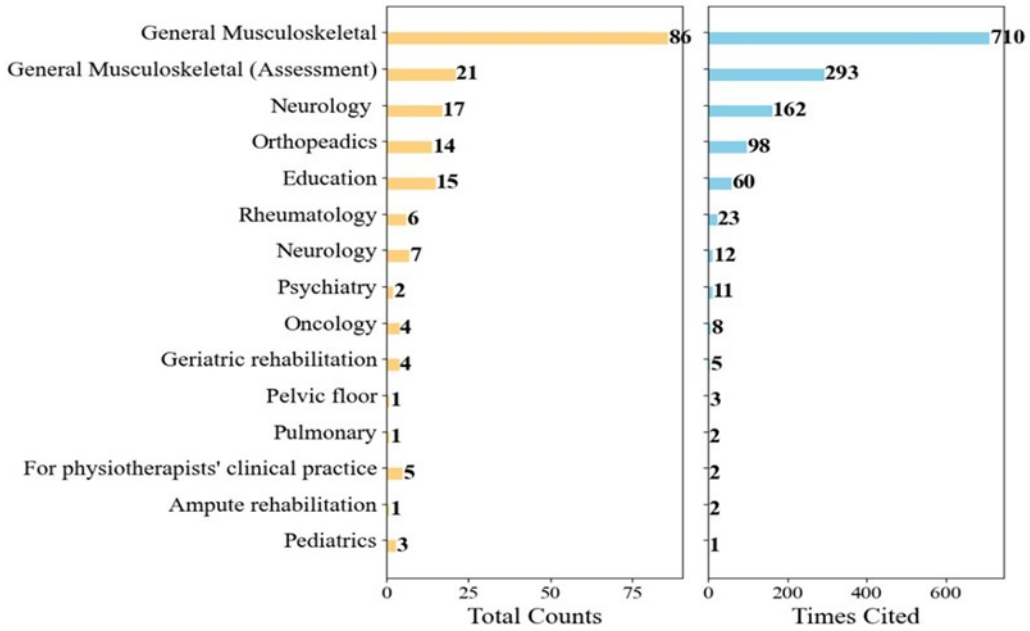

Figure 2. Times cited and total counts across physiotherapy sub-branches.

Other significant fields include AI-related computer sciences and rehabilitation. At the meso level (Figure 3a), “Gait and Posture” led (47.7%), while “Rehabilitation Robotics” was most prominent at the micro level (34.7%), followed by “Falls” (18.9%) (Figure 3b). As depicted in Figure 3c, “Engineering Electrical Electronic” was the dominant category (22.8%), followed by “Instruments Instrumentation” and “Engineering Biomedical” (both 12.6%).

Finally, the co-occurrence network (Figure 4) shows frequent keyword pairings. "Machine Learning" was central, closely associated with "Physiotherapy," "Natural Language Processing," and "Wearable Sensors." Other relevant terms like "Artificial Intelligence," "Virtual Reality," and "Pose Estimation" highlight the field’s interdisciplinary scope and technological integration.

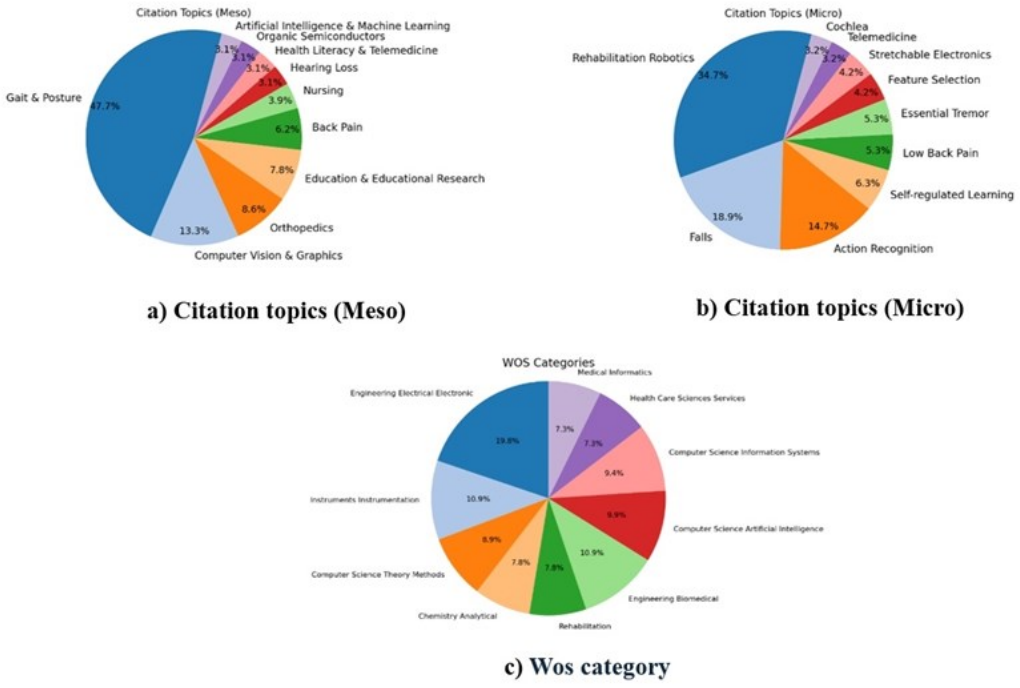

Figure 3. Distribution of Web of Science categories.

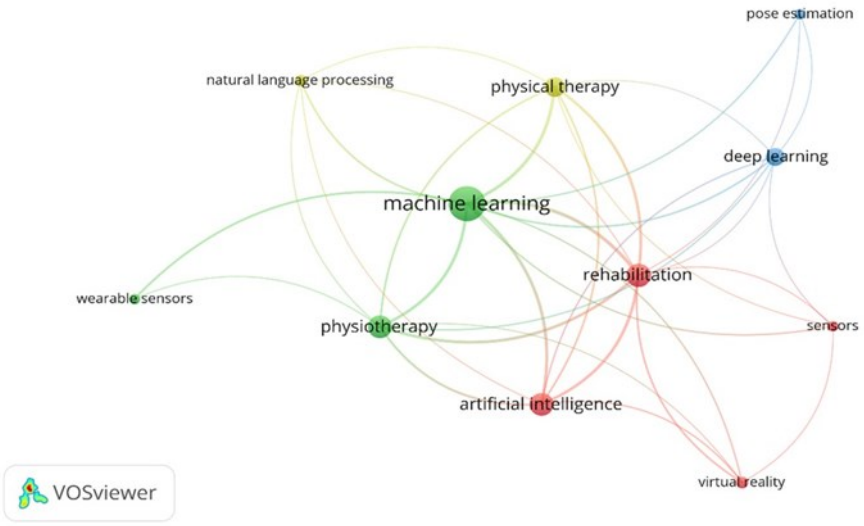

Figure 4. Co-occurrence network visualization of author keywords in rehabilitation technology research.

DISCUSSION AND CONCLUSION

The findings show that articles on AI in physiotherapy and rehabilitation are relevant studies that have started to be published in recent years. The fact that 47 articles were published in 2023, the year with the most publications, shows that the field has been open to development in recent years. These findings are concurrent with the significant contribution of AI in enhancing telerehabilitation during the COVID-19 pandemic.[9] The increasing trend in recent years suggests that telerehabilitation, which gained momentum during the pandemic, is likely to remain a mainstream component of healthcare delivery going forward.[22] According to the WoS categories, "Electrical, Electronic Engineering" is the most published research field. It was observed that the journal “Sensors" stands out in this field, especially as the journal that publishes the most and receives the most citations. It was seen that gait assessment and motion analysis issues are prominent in using AI in physiotherapy and rehabilitation. When the WoS citation topics were considered, "Gait and Posture" was the most studied area, followed by "Computer Vision and Graphics" at the meso level. The systematic review presented in 2024 showed the use of DL techniques in physiotherapy and rehabilitation with an emphasis on exercise and movement analysis.[23] The hybrid models, such as CNN + LSTM (Convolutional Neural Network + Long Short-Term Memory), CNN + GRU (Convolutional Neural Network + Gated Recurrent Unit), and MLP + SVM (MultiLayer Perceptron + Support Vector Machine), were explained in usage for the rehabilitation field.

The most cited article was about wearable biometric monitoring devices (BMDs) and artificial intelligence (AI), enabling patient data to be measured and analyzed remotely. The authors emphasized that considering patients' perspectives ensures that technology is utilized effectively without compromising the human aspects of care, causing undue burden, or intruding on patients' lives in their study. The second most cited article was about a home care system using a commercial smartwatch and ML model that could facilitate participation in home education and be used for home care therapy in the treatment of chronic stroke patients.

Co-occurrence analysis, which identifies high-frequency keywords appearing in various studies, can assist researchers in quickly grasping the key points of a relevant topic. In this study, the most frequently used keywords were "Machine Learning," "Artificial Intelligence," "Rehabilitation," "Physiotherapy," and "Deep Learning." Additionally, the keywords "Sensors," "Wearable Sensors," and "Virtual Reality" were found to form the same cluster.

In addition, the area most researched at the micro level in our study was rehabilitation robotics, which probably accounted for the most significant proportion due to its emerging potential to improve patient recovery and quality of life. "Rehabilitation Robotics" was followed by "Falls" in our study. "Falls"

was the second most common topic, highlighting the critical need for effective fall prevention and management strategies, especially in the aging population. Numerous scoping and systematic reviews exist in the literature on the prevention and detection of falls in older adults using AI applications.[24,25] A bibliometric analysis like our study was also found on AI and falls in older adults.[26]

The literature systematically maps the use of machine learning in neurorehabilitation, which includes diseases such as stroke and spinal cord injury, neurodegenerative disease, Parkinson's disease, and quadriplegia.[27] It has been concluded that ML is a field of computational intelligence research that examines the development of methods that can extract concepts (knowledge) from data samples, and is most used in stroke patients. Recent studies have further demonstrated the feasibility of AI integration in clinical and telerehabilitation settings, particularly through wearable sensors, VR systems, and intelligent robotic devices.[28,29,30] These findings support the notion that real-world adoption of AI is accelerating, especially for gait analysis, post-stroke rehabilitation, and motion tracking.

The integration of AI and machine learning into physiotherapy is reshaping clinical practice by enabling personalized, data-driven interventions. Tools such as wearable sensors and predictive models not only enhance assessment and treatment but also lay the groundwork for standardized, technology-informed clinical guidelines. These developments point toward a future where hybrid care models and AI-assisted evaluations become integral to rehabilitation protocols.

In conclusion, to our knowledge, this is the first study in which bibliometric analysis has been conducted on AI-related physiotherapy and rehabilitation subjects, which have recently gained attention worldwide. This study provides a comprehensive bibliometric analysis of AI applications in physiotherapy and rehabilitation, highlighting a sharp rise in publications, particularly following the COVID-19 pandemic. While the overall number of publications remains modest, the increasing trend underscores growing interest in areas such as gait analysis, rehabilitation robotics, and telerehabilitation. It also highlights the need for a multidisciplinary approach involving clinicians, engineers, and data scientists to advance rehabilitation technologies. One of the limitations of this study is the exclusive use of the Web of Science (WoS) database for bibliometric analysis. Future studies could benefit from incorporating data from multiple scientific databases, such as Scopus and PubMed, to provide a more comprehensive understanding and support researchers working in multidisciplinary fields. To guide future work, researchers should focus on developing explainable AI models that can be integrated into clinical workflows, particularly for personalized therapy, remote monitoring, and outcome prediction. Promising areas include adaptive exercise systems, intelligent prosthetics, and AI-assisted movement analysis. Practitioners may benefit from AI tools for motion tracking, progress monitoring, and patient adherence, especially in telehealth settings.

Ethics Committee Approval: The bibliometric data have been collected using the title and abstract keyword search from the Web of Science (WoS) database for terms belonging to AI in the physiotherapy field.

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

Author Contributions: Concept- GKA, TBO, IA; Materials – IA, GKA, YSA; Data Collection and/or Processing – TBO, IA, GKA; Analysis and/or Interpretation – TBO, IA, GKA, YSA; Writing – TBO, IA, GKA, YSA.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):153-161 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):153-161*

Predictive Role of Halp Score, LCR Value and CRP-Albumin Ratio for Survival and Recurrence in Gastric Cancer

Mide Kanserinde Halp Skoru, LCR Değeri ve CRP-Albumin Oranının Sağkalım ve Nüks için Öngörücü Rolü

[1]Adem SENTURK, [2]Ahmet Tarik HARMANTEPE, [2]Emre GÖNÜLLÜ, [3]Alp Omer CANTURK, [4]Fuldem MUTLU, [1]Metin ERCAN

[1]Sakarya University Training and Research Hospital - Department of Surgical Oncology, Sakarya, Türkiye
[2]Sakarya University Training and Research Hospital - Department of Gastrointestinal Surgery, Sakarya, Türkiye
[3]Sakarya University Training and Research Hospital - Department of General Surgery, Sakarya, Türkiye
[4]Sakarya University Faculty of Medicine - Department of Radiology, Sakarya, Türkiye

Adem Senturk: http://orcid.org/0000-0002-7626-4649
Alp Omer Canturk: http://orcid.org/0000-0003-3641-7628
Ahmet Tarik Harmantepe: https://orcid.org/0000-0003-2888-7646
Fuldem Mutlu: http://orcid.org/0000-0001-7761-2417
Metin Ercan: http://orcid.org/0000-0001-8294-0239

ABSTRACT

Objective: To investigate whether the ratios of biochemical markers such as hemoglobin, albumin, lymphocyte and platelet (HALP) score, lymphocyte-C-reactive protein ratio (LCR) and CRP/Albumin ratio can predict the survival and recurrence of the disease in gastric cancer patients.

Materials and Methods: Adult patients who were operated for gastric cancer in our clinic between January 2014 and December 2023 (n: 85) were included in this retrospective study. HALP and CRP/Albumin scores and LCR ratios were calculated from the preoperative biochemical data of the patients.

Results: Overall survival of patients with a low HALP score was significantly shorter than that of patients with a high HALP score (30.6 vs 35.5 months) ($p<0.05$). In addition, overall survival of patients with low LCR rate was significantly shorter than that of patients with high LCR score (27.9 vs 35.6 months, $p<0.05$), and similarly, the overall survival of patients with low CRP/Albumin value was significantly shorter than that of patients with high CRP/Albumin value (29.9 months vs 32.4 months) ($p<0.05$). There was a strong correlation between HALP, LCR, and CRP/Albumin scores and recurrence (for each $p<0.05$). According to the results of multivariate Cox regression analysis, HALP score, LCR score and CRP/albumin ratio were found to be independent and positive factors for overall survival ($p<0.05$).

Conclusions: Low scores in any of the HALP, LCR, and CRP/Albumin scores were associated with poor postoperative overall survival and recurrence in patients with gastric cancer.

Keywords: Biomarkers, gastric cancer, prognosis, recurrence

ÖZ

Amaç: Hemoglobin, albumin, lenfosit ve trombosit (HALP) skoru, lenfosit-C-reaktif protein oranı (LCR) ve CRP/Albumin oranı gibi biyokimyasal belirteçlerin oranlarının mide kanseri hastalarında hastalığın sağ kalımını ve tekrarını tahmin edip edemeyeceğini araştırmak.

Materyal ve Metot: Ocak 2014 ile Aralık 2023 tarihleri arasında kliniğimizde mide kanseri nedeniyle opere edilen yetişkin hastalar (n: 85) bu retrospektif çalışmaya dahil edildi. Hastaların preoperatif biyokimyasal verilerinden HALP ve CRP/Albumin skorları ve LCR oranları hesaplandı.

Bulgular: Düşük HALP skorlu hastaların genel sağ kalım süresi, yüksek HALP skorlu hastalara göre anlamlı derecede daha kısaydı (30.6'ya karşı 35.5 ay) ($p<0,05$). Ayrıca, düşük LCR oranına sahip hastaların genel sağ kalım süresi, yüksek LCR skorlu hastalara göre anlamlı derecede daha kısaydı (27.9'a karşı 35.6 ay, $p<0,05$) ve benzer şekilde, düşük CRP/Albumin değerine sahip hastaların genel sağ kalımı, yüksek CRP/Albumin değerine sahip hastalara göre anlamlı derecede daha kısaydı (29.9'a karşı 32.4 ay) ($p<0,05$). HALP, LCR ve CRP/Albumin skorları ile tekrarlama arasında güçlü bir korelasyon vardı (her biri için $p<0,05$). Çok değişkenli Cox regresyon analizinin sonuçlarına göre, HALP skoru, LCR skoru ve CRP/albumin oranının genel sağ kalım için bağımsız ve pozitif faktörler olduğu bulundu ($p<0,05$).

Sonuç: HALP, LCR ve CRP/Albumin skorlarından herhangi birinde düşük skorlar, mide kanseri olan hastalarda düşük postoperatif genel sağ kalım ve nüks ile ilişkiliydi.

Anahtar Kelimeler: Biyobelirteçler, mide kanseri, prognoz, nüks

Sorumlu Yazar / Corresponding Author:
Ahmet Tarık Harmantepe
Şirinevler, Adnan Menderes Cd Sağlık Sk No:195, 54100 Adapazarı/Sakarya Turkey
Tel.: +905347810376
E-mail: tarikharmantepe@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 25/03/2025
Kabul Tarihi/ Accepted: 16/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Senturk A and et al. Predictive Role of Halp Score, LCR Value and CRP-Albumin Ratio for Survival and Recurrence in Gastric Cancer. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):153-161. doi: 10.26453/otjhs.1663269

INTRODUCTION

Gastric Cancer (GC) is a complex disease characterized as a primary epithelial malignancy that originates in the stomach. It develops through multiple stages and is influenced by various risk factors. In recent years, global efforts in prevention, screening, and treatment have led to a general decrease in the disease's incidence and mortality rates. Despite this, GC remains the fifth most common cancer worldwide and ranks fourth in cancer-related deaths.[1]

Precise pathological tumor staging plays a crucial role in assessing survival outcomes for these individuals. While the overall survival rate for GC is 45% at one year, it drops to 26% at five years, and further decreases to 7% in cases of metastatic GC.[2]

Recent research suggests a potential link between systemic inflammation and cancer development, invasion, proliferation, and metastasis.[3] Inflammation, regardless of its cause, contributes to cancer progression by promoting angiogenesis and enhancing apoptosis resistance around the tumor.[4] Elevated levels of neutrophils, leukocytes, platelets, and C-reactive protein (CRP), along with reduced lymphocyte and albumin values in the preoperative period, serve as indicators of systemic inflammatory response.[5] Various prognostic factors based on inflammatory response are derived by combining these biochemical parameters.[6] These factors are utilized not only in determining the prognosis of malignant diseases but also in autoimmune, inflammatory, and infectious conditions where the severity of inflammation is critical.[7]

C-reactive protein (CRP) is a protein produced during the body's response to various inflammatory conditions, including infection, cancer, ischemia, and trauma.[8,9] Other factors known to influence cancer patient prognosis include hemoglobin levels, as well as leukocyte and platelet counts.[10] Serum albumin, the most prevalent protein in human blood plasma, is liver-produced and serves as a crucial prognostic indicator in cancer patients, with low levels (hypoalbuminemia) suggesting a poor outlook.[10] The lymphocyte-to-CRP ratio (LCR) is utilized as a prognostic marker in diverse cancer types.[11] Similarly, a low HALP score, which combines albumin, hemoglobin, platelet, and lymphocyte counts, indicates an unfavourable prognosis in cancer.[10] Research has shown that the CRP/albumin ratio is an independent prognostic indicator for patients with infection, cancer, and comorbidities.[12]

This research aims to explore the connections between CRP/albumin ratio, HALP score, and LCR value and the survival and recurrence rates in GC patients who have undergone surgical treatment.

MATERIALS AND METHODS

Ethics Committee Approval: Our study was approved by the Sakarya University Ethics Committee (Date: 28.12.2023, decision no: E. 318701). The study was carried out following the Helsinki Declaration and international guidelines.

Sample and Study Design: This retrospective observational study included 85 patients who underwent surgery for GC at the Surgical Oncology Clinic of the Sakarya Education and Research Hospital between January 2014 and December 2023. Patient data were obtained from patient files and electronic hospital databases. All laboratory data, including hemogram, CRP, and albumin levels, were obtained from blood samples collected within one week prior to surgery. The same clinical laboratory and standardized protocols were used for all biochemical analyses to minimize measurement variability. As a routine clinical practice in our department, patients were followed up according to a standardized protocol until they died due to disease recurrence. During the follow-up of the patients, control imaging was performed at certain periods (ultrasonography, computed tomography, PET/CT).

Adult patients aged > 18 years who underwent surgery for pathologically confirmed GC were included in this study. Patients with incomplete clinicopathological and follow-up data, those who had been treated for another cancer before Chemoradiotherapy (CRT), those with any inflammatory disease, those who had not undergone surgery, and those with secondary malignancies were excluded.

Variables including chemotherapy regimens, comorbidities, surgical procedures, pathological diagnoses, types of lymph node dissection, tumor size, metastatic site, and patient survival time were recorded and analyzed. Overall survival was defined as the time from surgery to death or last follow-up visit. To calculate inflammation markers, the results of preoperative blood tests were recorded.

HALP Score Calculation: Hemoglobin (gr/dL) x Lymphocyte (count/µl) x Albumin (gr/dL) / Platelet (count/µl).

LCR Calculation: Lymphocyte (count/µl) / CRP (mg/L).

CRP/Albumin Score Calculation: CRP (mg/L)/ Albumin (gr/dL)

Statistical Analysis: Statistical analyses were conducted using SPSS version 27. Categorical variables were presented as frequencies and percentages, while continuous variables were expressed as means with standard deviations. The Kolmogorov-Smirnov test was used to assess the normality of continuous data. For comparisons, categorical variables were analyzed using the chi-square test or Fisher's exact

test, whereas independent samples t-tests were applied for continuous variables. The optimal cut-off points were determined based on the minimum P-value from the log-rank $\chi 2$ test and the highest sensitivity and specificity for overall survival. The prognostic significance of CRP/Albumin, LCR, and HALP was evaluated using Receiver Operating Characteristic (ROC) analysis. The area under the curve (AUC) was classified as follows: 0.9–1.0 (excellent), 0.8–0.9 (good), 0.7–0.8 (moderate), 0.6–0.7 (poor), and 0.5–0.6 (unsuccessful). The sensitivity and specificity of the cut-off values were assessed. The optimum cut-off value was calculated by minimizing the sum of the absolute values of the differences between AUC and sensitivity and AUC and specificity, provided that the difference between sensitivity and specificity is minimal. Kaplan-Meier survival curves were compared using the log-rank test, and independent prognostic factors for survival were determined through multivariate Cox regression analysis. A 95% confidence interval was used, with statistical significance defined as $p<0.05$.

RESULTS

In this study, the demographic and clinical characteristics of 85 patients with gastric cancer were evaluated. The mean age of the patients was 62.1±10.8 years, and 60% were male. The average survival time was 31.5±22.6 months. The mean hemoglobin level was 11.4±2.1 g/dL, albumin was 3.24±0.68 g/dL, and lymphocyte count was 1640.1±874.1/mm³. The mean tumor size was 6.1±2.9 cm, with a median lymph node count of 25 (18.5-32) and a median metastatic lymph node count of 6 (1.0-10.0). Lymphovascular invasion was detected in 76.5% of patients, while perineural invasion was present in 60%. Additionally, 30.6% of patients experienced relapse, and 68.2% were deceased. Adjuvant chemotherapy was administered to 90.6% of patients, while 31.8% received neoadjuvant chemotherapy. Among the biochemical markers, the CRP/Albumin ratio was 5.3±9.8, and the HALP score was 37.5±19.4. D2 lymph node dissection was performed in 51.7% of patients, and 27.1% had malignant 8a lymph nodes (Table 1).

Table 1. Demographic and clinical characteristics of patients with gastric cancer (n:85).

Variables	n (%)/Mean±SD/Median (25P, 75P)
Age (Years)	62.1±10.8
Sex (Male/ Female)	51 (60.0) / 34 (40.0)
Survival (Months)	31.5±22.6
Hemoglobin (gr/dL)	11.4±2.1
Albumin (gr/dL)	3.24±0.68
Lymphocyte (/mm^3)	1640.1±874.1
Platelet (µL)	25365.6±94204.4
CRP (mg/L)	20.1±32.7
Fibrinogen (mg/dL)	334.9±143.1
Neutrophil (/mm^3)	7.3±4.6
Monocyte (/mm^3)	0.6±0.3
CEA (ng/mL)	21.2±101.3
CA 19-9 (U/mL)	108.4±288.1
Tumor size (cm)	6.1±2.9
Lymph nodes (n)	25 (18.5. 32.0)
Metastatic lymph nodes (n)	6 (1.0.10.0)
HALP score	37.5±19.4
LCR score	2.8±2.6
CRP/Albumin score	5.3±9.8
LDN (D1 / D2 / D2+) (%)	1(1.2) / 40(47.1) / 44(51.7)
8a LN (benign/ malign)	62 (72.9) / 23 (27.1)
Lymphovascular invasion (Positive/Negative)	65 (76.5) / 20(23.5)
Perineural invasion (Pozitive/Negative)	51 (60.0) / 34(40.0)
Differentiation (Poor/Little/ Moderate/Well)	2 (2.4)/ 32 (37.6) / 35 (41.2)/ 16 (18.8)
Relapse (Yes/No)	26 (30.6) /59 (69.4)
Comorbidity (Yes/No)	44 (51.8) / 41(48.2)
Deceased (Yes/No)	58 (68.2) / 27 (31.8)
Adjuvant Chemotherapy (Yes/No/ Radiotherapy)	77 (90.6)/ 7 (8.2)/ 1 (1.2)
Neoadjuvant Chemotherapy (Yes/No)	27 (31.8) / 58 (68.2)

Descriptive data are given as n (%) or mean±standart deviation; CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; HALP score: Hemoglobin (gr/dL) x Albumin (gr/dL) x Lymphocyte (count/µl) / Platelet (count/µl); LCR score: Lymphocyte (count/µl) / CRP (mg/L); LDN: Lymphadenectomy; LN: Lymph nodes.

The predictive performance of HALP in assessing treatment response for GC patients was analyzed using ROC-derived cut-off values. The optimal cut-off thresholds were determined as follows: 28.61 for HALP, 1.97 for LCR, and 3.41 for CRP/Albumin. At these thresholds, classification performance was as follows: HALP demonstrated a sensitivity of 86.3% and specificity of 76.5%; LCR exhibited a sensitivity of 80.4% and specificity of 64.8%; and CRP/Albumin showed a sensitivity of 82.1% and specificity of 70.6% (respectively, p=0.018, p=0.023, p=0.044). An analysis of the association between clinicopathological parameters and HALP revealed statistically significant relationships with gender (p=0.045), survival duration(p=0.047), haemoglobin (p<0.001), albumin (p<0.001), lymphocyte (p<0.001), platelet (p=0.009), CRP (p=0.041), CEA (p=0.033), Ca19-9 (p=0.009), tumor size (p<0.001), lymphovascular invasion (p=0.029), perineural invasion (p=0.042), 8a lymph nodes involvement (p=0.041), as well as the administration of adjuvant and neoadjuvant therapies (Table 2).

Similarly, the evaluation of LCR in relation to clinicopathological variables showed significant correlations with metastatic lymph nodes, lymphovascular invasion, and perineural invasion, relapse with p-values of 0.035, 0.043, 0.015, 0.049, respectively (Table 3).

Table 2. HALP score and clinical correlations in gastric cancer.

Variables	HALP score [Mean±SD/ n (%)/Median (p25, p75)]			p-values
	Low (≤28.61//N:52)	**High (>28.61//N:33)**		
Age (Years)	63.9±11.5	59.4±8.8	t= 2.149	0.298
Sex (Female. n (%))	25(29.4)	9(10.6)	χ^2=13.641	**0.045**
Survival (Months)	28.9 (21.8-38.2)	32.4 (25.8-39.1)	t=7.231	**0.047**
Hemoglobin (gr/dL)	10.6±1.5	13.4±2.2	t=8.072	**0.001**
Albumin (gr/dL)	2.8±0.7	3.6±0.5	F=19.438	**0.001**
Lymphocyte (/mm^3)	1266.9±0.634	2282.3±0.8838	F=34.008	**0.001**
Platelet (µL)	274.513.5±89.680.9	219.756.3±90.807.4	F=8.192	**0.009**
CRP (mg/L)	18.4 (3.5. 55.7)	13.5(4.5. 67.4)	Z=2.514	**0.041**
Fibrinogen (mg/dL)	343.0±141.4	319.5±152.5	F=0.521	0.318
CEA (ng/mL)	32 (32.0. 57.5)	23.5(15.2. 71.7)	Z=2.359	**0.033**
CA 19-9 (U/mL)	97.0 (33.0. 322.5)	71.4 (42.2.286.3)	Z=3.102	**0.009**
Tumor size (cm)	6.8±3.1	4.7±2.2	F=11.969	**0.001**
Lymph nodes	29.1±10.2	25.3±12.0	F=1.449	0.232
Metastatic lymph nodes	6.0 (3.8-8.3)	6.2 (3.7-8.8)	F=0.114	0.906
T status (T1/T2/T3/T4)	4/5/17/26	3/6/15/9	χ^2=6.125	0.409
N status (N0/N1/N2/N3)	18/11/6/17	12/5/2/14	χ^2 =4.541	0.474
LDN (D1 / D2 / D2+)	1/23/28	0/17/16	χ^2=0.974	0.614
8a LN (Benign/ Malign)	38/14	24/9	t=2.856	**0.041**
Lymphovascular invasion (+)	41/11	24/9	χ^2=8.112	**0.029**
Perineural invasion (+)	34/18	17/16	χ^2=4.415	**0.042**
Differentiation (Poor/Little/ Moderate/Well)	1/22/21/8	1/10/14/8	χ^2=1.740	0.199
Relapse (Yes/No)	16/36	10/23	t =1.964	0.486
Comorbidity (Yes/No)	31/21	13/20	U=2.526	**0.044**
Deceased (Yes/No)	35/17	23/10	U=2.688	**0.042**
Adjuvant Chemotherapy (Yes/No/ Radiotherapy)	46/6	32/1	χ^2=10.993	**0.003**
Neoadjuvant Chemotherapy (Yes/No)	15/37	12/21	t=3.894	**0.031**

Descriptive data are given as n(%); Mean±standart deviation or median (25P,75P); Chi-square (χ^2,) One-way Anova test (F test); Independent sample t-test; Mann Whitney U test (Z test) and Kruskal-Wallis tests (U test); CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; LDN: Lymphadenectomy, LN: Lymph nodes.

Table 3. LCR score and clinical correlations in gastric cancer.

Variables	LCR score [Mean±SD/ n (%)/Median (p25, p75)]			p-values
	Low (≤1.97. n:46)	**High (>1.97. n:39)**		
Age (Years)	63.1±10.2	61.3±11.2	t= 1.172	0.782
Sex (Female. n (%))	25(29.4)	26(30.6)	χ^2 =2.559	0.176
Survival (Months)	27.1 (22.6-34.2)	34.8 (26.3-43.8)	t =6.723	**0.031**
Hemoglobin (gr/dL)	10.1±1.7	13.6±2.2	t=4.124	**0.038**
Albumin (gr/dL)	3.0±0.6	3.5±0.7	F=12.530	**0.003**
Lymphocyte (/mm^3)	1298.1±0.748	2043.5±0.846	F=19.812	**0.001**
Platelet (µL)	269246.1±85667.9	240140.1±98992.1	F=3.926	**0.048**
CRP (mg/L)	18.6 (8.5-38.4)	10.4 (3.1-51.9)	Z=1.429	**0.016**
Fibrinogen (mg/dL)	371.4±158.5	315.7±134.6	F=0.999	0.327
CEA (ng/mL)	29.5 (20.0-54.0)	16.0 (12.9-76.2)	Z=3.126	**0.003**
CA 19-9 (U/mL)	121.0 (43.0-288.0)	85.6 (27.5-319.7)	Z=2.829	**0.009**
Tumor size (cm)	6.3±3.0	4.8±2.8	F=1.277	0.211
Lymph nodes	28.6±11.2	24.5±10.8	F=0.765	0.165

Table 3. Continue.

Metastatic lymph nodes	8.2 (5.22-11.29)	4.3 (2.67-5.92)	F=5.845	**0.035**
T status (T1/T2/T3/T4)	4/5/15/22	3/6/17/13	χ^2 =4.766	0.713
N status (N0/N1/N2/N3)	14/15/4/13	16/1/4/18	χ^2=13.498	**0.021**
LDN (D1 / D2 / D2+)	0/21/25	1/19/19	χ^2 =1.891	0.421
8a LN (Benign/ Malign)	32/14	30/9	t=3.579	0.304
Lymphovascular invasion (+)	38/8	27/12	χ^2 =6.798	**0.043**
Perineural invasion (+)	28/18	23/16	χ^2 11.247	**0.015**
Differentiation (Poor/Little/ Moderate/Well)	1/20/19/6	1/12/16/10	χ^2 =1.063	0.137
Relapse (Yes/No)	12/34	14/25	t =2.104	**0.049**
Comorbidity (Yes/No)	23/23	21/18	U=2.526	0.407
Deceased (Yes/No)	29/16	28/11	U=2.714	**0.048**
Adjuvant Chemotherapy (Yes/No/ Radiotherapy)	41/5	37/2	χ^2 =1.921	0.291
Neoadjuvant Chemotherapy (Yes/No)	17/29	10/29	t =2.510	0.189

Chi-square (χ^2); One-way Anova test (F test); Independent sample t-test; Mann-Whitney U test (Z test) and Kruskal-Wallis tests (U test); CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; LDN: Lymphadenectomy.

A high CRP/Albumin ratio in gastric cancer patients was significantly associated with lower hemoglobin, albumin, and lymphocyte levels, as well as fewer metastatic lymph nodes. Patients with a low CRP/ Albumin ratio had higher rates of lymphovascular and perineural invasion, 8a lymph node malignancy, relapse, and mortality. Additionally, those with a high ratio were more likely to receive adjuvant and neoadjuvant chemotherapy (Table 4).

In the univariate analysis, several factors were identified as predictors of survival, including sex, Adjuvant Chemotherapy, Neoadjuvant Chemotherapy, Mortality, Lymph node, 8aLN, CRP, Hb, Albumin, Platelet, T stage, N stage, tm size, Metastatic LN station, Lymph Vascular Invasion, and recurrence. Univariate Cox regression analysis demonstrated a significant association between HALP, LCR, and CRP/Albumin levels and overall survival time.

Table 4. CRP/Albumin score and clinical correlations in gastric cancer.

Variables	CRP/Albumin ratio [Mean±SD/ n (%)/Median (p25, p75)]			p-values
	Low (≤3.41. n:56)	**High (>3.41. n:29)**		
Age (Years)	63.8±9.6	59.0±12.2	t=2.355	0.466
Sex (Female. n (%))	34(40)	17 (20)	χ^2 =13.035	**0.037**
Survival (Months)	28.7 (23.1-36.7)	31.5(25.4-39.3)	t=0.211	0.647
Hemoglobin (gr/dL)	10.1±2.2	11.6±1.9	t=3.487	**0.046**
Albumin (gr/dL)	2.8±0.6	3.5±0.7	F=17.157	**0.001**
Lymphocyte (/mm^3)	1478.8±0.865	1723.6±0.874	F=14.448	**0.003**
Platelet (µL)	265029.1±88898.9	232079.3±101.630	F=2.361	0.128
CRP (mg/L)	16.0 (3.14-76.0)	11.0 (5.1-58.7)	Z=2.677	**0.047**
Fibrinogen (mg/dL)	370.7±125.9	266.8±155.2	F=3.804	**0.042**
CEA (ng/mL)	38.5 (18.7-56.2)	13.5 (5.7-52.8)	Z=3.504	**0.001**
CA 19-9 (U/mL)	103.0 (55.0-312.5)	97.3 (57.0-272.0)	Z=0.541	0.614
Tumor size (cm)	5.9±2.7	6.2±3.2	F=0.805	0.652
Lymph nodes	27.3±11.2	26.1±10.6	F=1.018	0.641
Metastatic lymph nodes	6.3 (4.66-9.26)	4.2 (2.39-6.57)	F=2.996	**0.031**
T status (T1/T2/T3/T4)	5/7/21/7/23	2/4/11/12	χ^2=3.052	0.802
N status (N0/N1/N2/N3)	20/8/6/22	10/8/2/9	χ^2=2.621	0.758
LDN (D1 / D2 / D2+)	1/30/25	0/10/19	χ^2=11.606	0.149
8a LN (Benign/ Malign)	43/13	19/10	t=3.229	**0.038**
Lymphovascular invasion (+)	43/13	22/7	χ^2=5.674	**0.038**
Perineural invasion (+)	34/22	17/12	χ^2=4.411	**0.042**
Differentiation (Poor/Little/ Moderate/Well)	1/22/22/11	1/10/13/5	χ^2=3.573	0.258
Relapse (Yes/No)	18/38	8/21	t=3.398	**0.027**
Comorbidity (Yes/No)	29/26	14/15	U=1.897	0.437
Deceased (Yes/No)	37/18	20/9	U=2.963	**0.035**
Adjuvant Chemotherapy (Yes/No/ Radiotherapy)	52/4	26/3	χ^2=11.259	**0.016**
Neoadjuvant Chemotherapy (Yes/No)	15/41	12/17	t=2.877	**0.034**

Chi-square (χ^2); One-way Anova test (F test); Independent sample t-test; Mann Whitney U test (Z test) and Kruskal-Wallis tests (U test); CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; LDN: Lymphadenectomy; LN: Lymph nodes.

Multivariate Cox regression analysis identified the HALP score as an independent positive predictor of overall survival (HR = 2.49, 95% CI: 1.294–2.487, p< 0.001). Similarly, LCR was found to be an independent prognostic factor favorably associated with overall survival (HR = 1.298, 95% CI: 1.043–1.757, p = 0.027). The CRP/Albumin ratio was also determined to be an independent useful predictor of overall survival (HR = 2.886, 95% CI: 1.831–4.396, p=0.033) (Table 5).

Table 5. Univariate and multivariate Cox analysis for overall survival of gastric cancer patients in 85 patients.

	Univariate analysis		Multivariate analysis	
Variable	**HR (95%CI)**	**p-values**	**HR (95%CI)**	**p-values**
Age.	1.032 (1.008-1.282)	0.056	1.541 (0.841-3.647)	0.115
Sex: Female vs. Male	1.156 (1.075-1.526)	**0.015**	1.837 (0.953-2.741)	**0.024**
Adjuvant Chemotherapy	1.896 (1.202–3.921)	**0.025**	1.067 (1.012–1.783)	**0.031**
Neoadjuvant Chemotherapy	1.363 (1.132-6.478)	**0.040**	2.134 (1.274-3.416)	**0.047**
Mortality	2.015 (1.532–5.791)	**0.038**	2.711 (1.327-4.673)	**0.001**
Lymph nodes	1.054 (1.012-1.096)	**0.010**	1.819 (1.317-1.928)	**0.001**
8aLN	3.899 (1065-6.273)	**0.037**	2.011(1.231-3.722)	**0.017**
CRP	1.785 (1.465-2.278)	**0.013**	1.907(1.480-2.165)	**0.001**
Hb	1.776 (1.571-3.056)	**0.017**	2.115 (1.709-2.755)	**0.013**
Albumin	0.723(0.334-0.968)	**0.010**	0.944 (0.663-0.999)	**0.006**
Platelet	2.852(1.142-3.877)	**0.042**	2.942 (1.109-5.231)	**0.039**
Differentiation	0.964 (0.535–0.996)	0.171	1.479 (1.075-1.710)	0.124
T Status	2.847 (1.647-5.134)	**0.014**	2.588 (1.368-4.763)	**0.037**
N Status	1.029 (1.001-2.276)	**0.008**	1.632 (1.277-1.927)	**0.022**
HALP ((≤28.61/>28.61)	2.521 (1.583-5.911)	**0.001**	2.497 (1.294-2.487)	**0.001**
LCR (≤1.97/>1.97)	1.266 (1.136-1.701)	**0.037**	1.298 (1.043-1.757)	**0.027**
Crp/Albumin (≤3.41/ >3.41)	2.480 (1.243-2.295)	**0.026**	2.886 (1.831-4.396)	**0.033**
Recurrence	3.184 (1.733-6.911)	**0.001**	3.699 (1.911-6.429)	**0.001**
Metastatic lymph nodes	-1.224 (1.015-2.843)	**0.033**	-3.522 (2.271-4.326)	**0.001**
Tumor size	-0.983 (0.860-0.999)	**0.023**	-2.478(1.012-3.148)	**0.012**
Lymph Vascular Invasion	-2.342 (1.475-3.814)	**0.029**	-2.268 (1.517-2.833)	**0.047**
Perineural invasion	-1.713 (1.122-2.621)	**0.041**	-1.742 (1.245-2.683)	**0.038**

CRP: C-reactive protein; CEA: Carcinoembryonic antigen; CA 19-9: Carbohydrate antigen 19-9; HALP score: Hemoglobin (gr/dL) x Albumin (gr/dL) x Lymphocyte (count/µl) / Platelet (count/µl); LCR score: Lymphocyte (count/µl) / CRP (mg/L); LDN: Lymphadenectomy.

DISCUSSION AND CONCLUSION

The systemic inflammatory response has gained recognition as an influential predictor of cancer prognosis, and hematologic and biochemical markers have been increasingly integrated as prognostic indicators.[13]

In our study, we evaluated 85 patients with GC and demonstrated that the HALP (Hemoglobin, Albumin, Lymphocyte, Platelet) score, LCR (Lymphocyte-to-C-Reactive Protein ratio), and CRP/Albumin ratio can serve as novel prognostic markers for locally advanced GC. Models incorporating these markers effectively identified patients at higher risk of poor survival. We observed that the mean overall survival of the patients was 31.5±22.6 months, aligning well with values reported in the literature.[14]

The HALP score has recently emerged in the literature as a novel prognostic biomarker across various malignancies.[10,15,16] Anemia, often manifesting as a paraneoplastic syndrome in patients with upper gastrointestinal cancers such as gastric and esophageal cancers, is typically exacerbated by oral intake issues and chronic tumor bleeding.[16] Platelets, by secreting vascular endothelial growth factor (VEGF), play a significant role in promoting angiogenesis, which may facilitate tumor metastasis.[17] HALP has been linked to prognosis in various cancers, including pancreatic adenocarcinoma, colorectal, bladder, esophageal, kidney, and small-cell lung cancers.[18] In our study, we found a significant negative correlation between HALP scores and the number of metastatic lymph nodes as well as tumor size (p<0.05). Additionally, we observed significant associations between HALP scores and both lymphovascular invasion and perineural invasion (p<0.05). Numerous studies have underscored the prognostic importance of the HALP score; for instance, Sargın and Düşünceli reported that a low HALP score indicates a poorer prognosis in GC patients.[19]

The LCR, calculated by dividing the lymphocyte count by the CRP level, is significantly associated with prognosis in digestive system cancers.[20] As an inflammation marker, LCR is a reliable predictor of overall survival in GC, with low preoperative LCR values linked to worse survival outcomes and advanced cancer stages.[21] In addition, lymphovascular invasion, defined by the infiltration of tumor cells into lymphatic or blood vessels, is a critical route for tumor dissemination and serves as an independent

prognostic factor in resectable GC, particularly in stage N0 patients.[22] In our study, we observed significant associations between LCR values and lymphovascular invasion ($p<0.05$), as well as between mean LCR scores and survival, tumor size, metastatic lymph nodes count, N 0-1 stages, perineural invasion, mortality, and recurrence ($p<0.05$).

The CRP/Albumin ratio is employed in various prognostic scoring systems to assess survival and treatment efficacy among cancer patients.[23] In our study, we found that the CRP/Albumin ratio represents a promising prognostic marker for locally advanced GC. Toyokawa et al. previously reported that the CRP/Albumin ratio is an independent predictor of overall survival in stage III GC patients.[24] Moreover, Liu et al. observed that higher serum albumin levels reduce mortality among cachectic cancer patients, thus underscoring albumin as a valuable prognostic indicator.[25] Lymph node involvement and metastatic spread are among the most significant prognostic factors in GC.[26] Non-randomized studies conducted in Japan and other countries have indicated that high lymph node involvement (≥20%) is associated with poor prognosis; thus, extensive lymph node dissection could enhance survival by increasing the number of metastatic lymph nodes removed.[27] In our study, we noted that the mean number of lymph nodes removed was 26.9±11.1, with a mean of 6.2±7.7 metastatic nodes, consistent with literature findings that highlight the impact of lymph node positivity on survival.

Considering that CRP elevation is associated with the characteristics of cancer, the most important way to change the CRP/Albumin ratio is to change the albumin value. Low albumin levels due to malnutrition are common in GCs.

Systemic inflammatory responses associated with cancer are critical indicators of tumor progression. Inflammation plays a significant role not only within the local tumor microenvironment but also systemically, influencing tumor biology.[28] These responses often involve changes in the secretion of cytokines, hormones, growth factors, and acute-phase proteins.[29] Recent studies have highlighted that biomarkers such as CRP, complete blood count, albumin, and serum inflammation-based scores can reflect the systemic inflammatory state and predict prognosis in cancer patients.[28] All these molecular pathways support our study.

This study has some limitations. A major limitation is that it is a retrospective and single-center study. In addition, the relatively small sample size and incomplete follow-up records further limit the generalizability of our findings. Nonetheless, our study is significant in that it represents one of the few analyses evaluating the prognostic values of HALP, LCR, and CRP/Albumin inflammatory markers concurrently in relation to recurrence and survival among GC patients. Future prospective multicenter studies are warranted to elucidate better the relationship between these inflammatory markers, postoperative changes, and prognosis in GC.

In conclusion, our findings indicate that the preoperative inflammatory markers HALP, LCR, and Albumin ratios are effective adjunctive tools for predicting postoperative overall survival and recurrence in patients with GC. Integrating these markers with conventional diagnostic tools may enhance prognostic accuracy. Given their low cost, accessibility, and ease of use, these markers hold potential for broader clinical application. However, further prospective, multicenter studies are necessary to confirm their clinical utility and validate their role in routine practice.

Ethics Committee Approval: The study was approved by the Sakarya University Ethics Committee (Date: 28.12.2023, decision no: E. 318701). The study was carried out following the Helsinki Declaration and international guidelines. This study was conducted in accordance with the principles of the Declaration of Helsinki. Since it was a retrospective study, informed consent/consent form was not obtained from the patient/relatives.

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

Author Contributions: Concept – AŞ, ATH; Supervision – AŞ, ATH, AOC; Materials – AOC, FM; Data Collection and/or Processing – ME, ATH; Analysis and/or Interpretation – EG, ATH; Writing –AŞ, ATH.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):162-169 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):162-169*

The Effect of Lavender Inhalation on Sleep Quality in Individuals with Coronary Heart Disease: A Randomized Controlled Study

Koroner Kalp Hastalığına Sahip Bireylerde Kullanılan Lavanta İnhalasyonunun Uyku Kalitesi Üzerine Etkisi: Randomize Kontrollü Bir Çalışma

[1]Esma GÖKÇE, [2]Sevgi DENİZ DOĞAN, [3]Sevban ARSLAN

[1]Toros University, Vocational School of Health Services, Mersin, Türkiye
[2]Isparta University of Applied Sciences, Uluborlu Selahattin Karasoy Vocational School of Health Services, Isparta, Türkiye
[3]Çukurova University, Faculty of Health Sciences, Surgical Nursing Department, Adana, Türkiye

Esma Gökçe: https://orcid.org/0000-0001-9581-6958
Sevgi Deniz Doğan: https://orcid.org/0000-0003-0311-2123
Sevban Arslan: https://orcid.org/0000-0002-8893-9391

ABSTRACT

Objective: Sleep disorders frequently manifest in individuals with coronary heart disease (CHD). Evaluating sleep quality in these patients is crucial for devising effective healthcare interventions. This study aimed to assess the impact of long-term *home-based* lavender inhalation on sleep quality among individuals diagnosed with CHD.

Materials and Methods: A randomized controlled trial involving two groups was conducted in the cardiology clinics of a university hospital in 2023. Sixty-four patients (32 in the experimental group and 32 in the control group) were enrolled. Data collection utilized the Personal Information Form and the Pittsburgh Sleep Quality Index (PSQI). The experimental group received lavender oil inhalation for one month. The PSQI was administered to both groups at the study's commencement and conclusion (pre-test and post-test, respectively).

Results: A statistically significant difference was observed between the pretest and posttest PSQI scores in the experimental group (p=0.000). Furthermore, the posttest PSQI mean scores of the experimental group were found to be significantly lower than those of the control group (p=0.004).

Conclusions: Lavender inhalation demonstrated an enhancement in sleep quality among patients with CHD. To the best of our knowledge, this is the first randomized controlled study to evaluate sleep quality in CHD patients through a one-month lavender inhalation program conducted entirely at home. These findings contribute to the literature and are recommended for health practices. However, considering limitations such as its single-center design, it is important that the findings are supported by studies in broader populations and over longer durations.

Keywords: Aromatherapy, coronary heart diseases, lavender oil, sleep quality

ÖZ

Amaç: Uyku bozuklukları, koroner kalp hastalığı (KKH) olan bireylerde sıkça görülmektedir. Bu hastalarda uyku kalitesinin değerlendirilmesi, etkili sağlık müdahalelerinin geliştirilmesi açısından önemlidir. Bu çalışmanın amacı, KKH tanısı konmuş bireylerde uzun süreli *ev temelli* lavanta inhalasyonunun uyku kalitesi üzerindeki etkisini değerlendirmektir.

Materyal ve Metot: Bu çalışma 2023 yılında bir üniversite hastanesinin kardiyoloji kliniklerinde iki gruplu, randomize kontrollü olarak yürütülmüştür. Çalışmaya 64 hasta katılmıştır (32 deney grubu, 32 kontrol grubu). Veri toplama aracı olarak Kişisel Bilgi Formu ve Pittsburgh Uyku Kalitesi İndeksi (PUKİ) kullanılmıştır. Deney grubuna bir ay boyunca lavanta yağı inhalasyonu uygulanmıştır. PUKİ, her iki gruba da çalışmanın başlangıcında ve sonunda (sırasıyla ön test ve son test) uygulanmıştır.

Bulgular: Deney grubunda ön test ve son test PUKİ puanları arasında istatistiksel olarak anlamlı bir fark gözlenmiştir (p=0.000). Ayrıca, deney grubunun son test PUKİ ortalama puanları, kontrol grubu puanlarından anlamlı derecede düşük bulunmuştur (p=0.004).

Sonuç: Lavanta inhalasyonun, KKH olan bireylerde uyku kalitesinde iyileşme sağladığı tespit edilmiştir. Bildiğimiz kadarıyla bu çalışma, tamamen evde uygulanan bir aylık lavanta inhalasyon programı aracılığıyla KKH hastalarında uyku kalitesini değerlendiren ilk randomize kontrollü çalışmadır. Bu bulgular literatüre katkıda bulunmakta ve sağlık uygulamaları için önerilmektedir. Ancak, çalışmanın tek merkezli olması gibi sınırlılıklar göz önüne alındığında, bulguların daha geniş popülasyonlarda ve uzun süreli çalışmalarla desteklenmesi önemlidir.

Anahtar Kelimeler: Aromaterapi, koroner kalp hastalıkları, lavanta esansiyel yağı, uyku kalitesi

Sorumlu Yazar / Corresponding Author:
Esma Gökçe
Toros University, Vocational School of Health Services, Mersin, Türkiye.
Tel.: +905306376781
E-mail: esmagokce0@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 28/03/2025
Kabul Tarihi/ Accepted: 15/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Gökçe E and et al. The Effect of Lavender Inhalation on Sleep Quality in Individuals with Coronary Heart Disease: A Randomized Controlled Study. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):162-169. doi: 10.26453/otjhs.1667629

INTRODUCTION

It is estimated that approximately 17.9 million people in the world die each year due to coronary heart disease (CHD) and stroke, a figure anticipated to escalate to 23.3 million by 2030.[1] CHD significantly impacts quality of life, morbidity, and mortality. Sleep disorders frequently affect patients with CHD.[2]

Sleep, a complex biobehavioral phenomenon, profoundly affects psychological well-being, quality of life, morbidity, and mortality in chronic disease sufferers.[3] In individuals with sleep problems, the autonomic nervous system and hypothalamic-adrenocortical axis are activated, and immune functions are impaired. These issues also contribute to systemic inflammation, elevating the risk of metabolic syndrome, type 2 diabetes, hypertension, cardiovascular diseases, and premature mortality.[4] Sleep disruptions hinder tissue repair, cellular immunity, energy balance, endocrine, and metabolic functions vital for healing.[3,4]

Non-pharmacological methods, especially complementary alternative practices, are increasingly recommended.[5] In recent years, aromatherapy is one of the complementary therapies whose use has increased significantly due to its easy and effective use and cost savings.[5] Lavender, renowned for its anxiolytic, hypnotic, sedative, analgesic, and anticonvulsant properties, is a widely used aromatic herbal oil in aromatherapy.[6] It has also been reported to improve sleep quality and reduce pain and anxiety.[7,8]

Although various non-pharmacological methods have been studied to improve sleep in CHD patients,[9] to date there has been no randomized controlled trial evaluating the long-term effect of lavender inhalation performed entirely in the home environment. On the other hand, lavender oil inhalation studies, including a one-month home-based intervention, are available in the literature in different populations.[10]

However, this study addresses this gap by implementing a one-month home-based intervention that reflects a real and sustainable approach to self-care for individuals with CHD. Assessing sleep quality in these patients is crucial for planning effective healthcare interventions. Therefore, this study aimed to evaluate the impact of long-term home-based lavender inhalation on sleep quality among individuals diagnosed with CHD.

MATERIALS AND METHODS

Ethical Considerations: The study adhered to the principles outlined in the Helsinki Declaration. Approval was obtained from the Ethics Committee for Scientific Research and Publication of Isparta Applied Sciences University (Date: 12.01.2023, decision no: 131/07). Institutional approval to conduct the study was also obtained from the Chief Physician of Çukurova University Balcalı Hospital (E-59565534-010.01-679091). Prior to participation, all patients were duly informed about the study's objectives, emphasized the voluntary nature of their involvement, and assured of their right to withdraw at any point. Patients were explicitly notified that their participation or withdrawal would not influence their ongoing treatment and care. Informed consent was obtained from all of the participants. This study was registered in ClinicalTrials.gov under the registration number (ID: NCT05704946).

Trial Design: This investigation followed a randomized controlled interventional design, adhering to the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT).

Participants and Sample Size: The population of the study encompassed patients diagnosed with CHD receiving treatment at the cardiology clinic of a university hospital in 2023. The sample was constituted of individuals aged 85 and below, literate, not hearing impaired, not having coagulation disorder, migraine, and chronic headaches, not allergic to lavender (Lavandula angustifolia), not receiving any sleep-related medical treatment and who agreed to participate. Patients who experienced asthma problems or allergic reactions related to inhalation, such as respiratory distress, cough, and nausea, or expressed a desire to withdraw from the study, were planned to be excluded from the study. However, no patient withdrew from the study due to these reasons (n=0). In this study, based on the research conducted by McDonnell & Newcomb, the number of samples for each group was calculated as 26 for the independent sample t-test with an effect size of 0.8, 5% margin of error and 80% power using the G*Power 3.1.9.7 programme.[11] Considering the possibility of data loss, the number of samples for each group was increased by 20%, and it was planned to include 32 patients for each group. One patient in the experimental group was lost to follow-up due to failure to communicate, and two patients in the control group were lost to follow-up because they refused to be a voluntary participant in the study. The study was completed with a total of 61 patients, 31 of whom were in the education group and 30 in the control group (Figure 1). A post-hoc power analysis determined this study's power to be 84% with an effect size of 0.77 and a margin of error of 0.05.

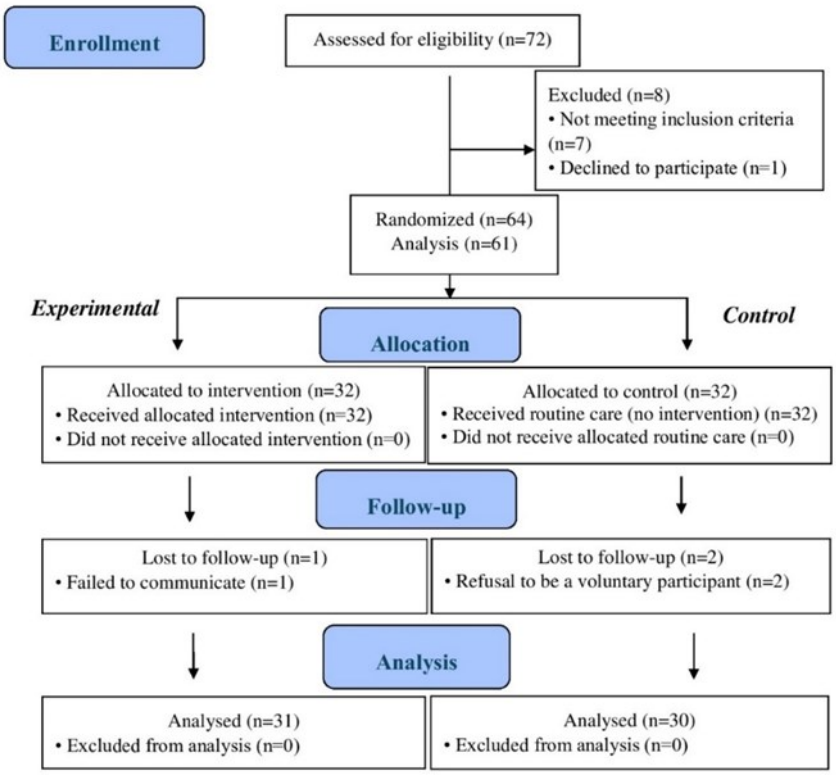

Figure 1. CONSORT flow diagram.

Outcome Measures: Data collection for this study involved the utilization of two instruments: the Personal Information Form and the Pittsburgh Sleep Quality Index (PSQI).

The Personal Information Form, developed by the researchers, encompassed 10 queries pertaining to sociodemographic characteristics, specific health attributes, and medication usage associated with CHD.

The PSQI is a self-report scale developed by Buysse et al. for the assessment of sleep quality and sleep disturbance over the past month.[12] The validity and reliability of the PSQI were subsequently investigated by Ağargün et al.[13] PSQI comprises 24 questions designed. The first 19 questions are self-administered by the participants and cover subjective sleep quality, sleep duration, sleep latency, sleep disorders, habitual sleep efficiency, sleep medication use, and daytime dysfunction, making up 7 components in the index. PSQI scores of ≤5 indicate good sleep quality, while scores exceeding 5 indicate poor sleep quality. However, in this study, the Cronbach's alpha coefficient for the scale was determined to be 0.85.

Data Collection: Data were collected in 2023. The study was carried out with two groups, control and experiment. Randomization occurred subsequent to interviews with willing participants who were informed about the study's objectives**.**

Randomization and Blinding: Participants were allocated to the experimental (n = 32) and control (n = 32) groups using block randomization with a block size of 4 through the website (https://www.randomizer.org/). The random allocation sequence was concealed using closed envelopes to ensure blinding. The sequence and allocation details were securely managed by an independent nurse who was not involved in data collection or analysis. Participants were enrolled by the primary researcher, who was unaware of the allocation sequence. Throughout the study, participants were blinded to their group assignments, and the researchers responsible for outcome assessments were also blinded to the group allocations.

Intervention: Participants were interviewed upon admission to the clinic, and written informed consent was obtained. They were then asked to complete the Personal Information Form and the PSQI questionnaire. Participants were instructed to use a chosen nickname when completing the questionnaire, which would be used for the final evaluation.

In this study, Rosense brand lavender oil (30 mL, Isparta lavender) produced from the Lavandula angustifolia species, which is the most widely utilized

and referenced species in the health field,[14] was used. In addition, lavender is known for its anxiolytic and sedative properties and has been shown to improve sleep quality.[6,7] It was preferred due to its potential positive effects on sleep problems commonly seen in CHD patients, its safe profile, and its potential to increase patient compliance.[8,11] Furthermore, a review of the literature indicates that it is frequently administered via the inhalation method.[9,10, 15,16] The selection and dosage of the oil were determined in consultation with a phytotherapy expert. The researcher provided detailed instructions on the lavender oil application technique. The patients were informed that they should apply two drops of lavender oil to the lower right side and two drops to the lower left side of their pillows approximately 20 to 30 minutes before going to sleep each night for one month following their discharge. For patients who utilized double pillows, they were specifically instructed to apply lavender oil to the pillow they slept on. In particular, lavender oil was applied to the underside of the pillow, thus preventing the patient from being disturbed by odor intensity or skin contact. Participants in the intervention group were encouraged to contact the researcher via a provided phone number if they had any questions or experienced any issues during the application period.

No intervention was applied to the control group, and they were instructed to maintain their normal sleep habits for one month. Both groups were contacted by the researcher every Friday to monitor progress. In the follow-up process for the experimental group, adherence to the lavender oil application was evaluated, and participants were encouraged to maintain compliance. The follow-up for the control group, on the other hand, aimed to confirm that participants sustained their existing sleep habits during the study period and ensured their continued participation. At the end of the fourth week, participants completed the PSQI questionnaire online using their chosen nicknames. Upon the completion of data collection, participants were thanked for their participation. To ensure ethical compliance, participants in the control group were provided with the same materials used in the experimental group after the study concluded, along with instructions on how to use the lavender oil in the same manner.

Statistical Analysis: Statistical analyses for the study were conducted using IBM SPSS Statistics 24. Data normality was confirmed via skewness and kurtosis values; thus, parametric tests were employed. Data interpretation involved frequency tables and descriptive statistics for participant characteristics; the independent samples t-test for between-group comparisons; and the Paired Samples t-test for within-group pre-post PSQI comparisons. Additionally, a $\chi 2$ test was applied to compare categorical baseline variables and to explore associations between qualitative variables. A p-value < 0.05 was considered statistically significant.

RESULTS

According to the descriptive characteristics of the groups, the mean age in the experimental group was 65.55 ± 10.54, while it was 67.07 ± 9.58 in the control group ($p = 0.559$). The duration of coronary heart disease was equal in both groups, with a mean of 7.00 years (experimental: ±6.31; control: ±6.70). In the experimental group, 15 patients (48.4%) were male and 16 (51.6%) were female, while in the control group, 18 patients (60.0%) were male and 12 (40.0%) were female ($p = 0.363$). Regarding education level, 12 patients in the experimental group had completed primary school, 12 had completed high school, and 7 had university degrees; in the control group, the corresponding numbers were 16, 10, and 4, respectively ($p = 0.459$). In terms of economic status, 24 patients in the experimental group and 26 in the control group reported having an income less than their expenses ($\chi^2 = 0.367$, $p = 0.544$). Concerning marital status, 19 patients in the experimental group were married, and 12 were single, whereas 22 patients in the control group were married, and 8 were single ($p = 0.316$). The presence of chronic diseases (excluding coronary heart disease) was reported by 23 patients in the experimental group and 27 in the control group ($p = 0.108$). Regarding smoking habits, 17 patients in the experimental group and 18 in the control group were non-smokers, while 10 patients in each group quit smoking ($p = 0.804$). As for exercise status, 9 patients in the experimental group and 10 in the control group reported engaging in regular physical activity ($p = 0.717$) (Table 1).

Regarding drug use, no statistically significant differences were found between the experimental and control groups in terms of anticoagulant use (80.6% vs 80.0%, p=0.949), beta-blocker uses (74.2% vs 66.7%, p=0.519), diuretic use (71.0% vs 63.3%, p=0.525), ACE inhibitor use (67.7% vs 56.7%, p=0.372), cardiac vasodilator use (61.3% vs. 56.7%, p=0.714), statin use (51.6% vs. 53.3%, p=0.893), and cardiac glycoside use (22.6% vs. 6.7%, p=0.80) (Table 2).

The pre-test and post-test PSQI scores within the control group showed no statistically significant difference (p=0.089). However, within the experimental group, there was a significant difference was observed between pre-test and post-test PSQI scores (p=0.000). Notably, the post-test mean scores for the experimental group were lower than their pre-test scores. During the pre-test, no statistically significant difference between groups was observed in mean scores (p=0.491). However, during the post-

Table 1. Comparison of descriptive characteristics of the patients.

		Experimental Group (n=31)	Control Group (n=30)	Test
Age, mean±SD [Min-Max]		65.55±10.54 [44-85]	67.07±9.58 [48-85]	t=-0.588[a] p=0.559
CHD duration (year), mean±SD [Min-Max]		7.00±6.31 [1-20]	7.00±6.70 [1-21]	t=-0.420[a] p=0.676
Sex, n (%)	Male	15 (48.4)	18 (60.0)	χ^2=0.828[b]
	Female	16 (51.6)	12 (40.0)	p=0.363
Education level, n (%)	Primary school	12 (38.7)	16 (53.3)	χ^2=1.555[b]
	High school	12 (38.7)	10 (33.3)	p=0.459
	University	7 (22.6)	4 (13.3)	
Economic situation, n (%)	Income less than expenses	24 (77.4)	26 (86.7)	χ^2=0.367[b]
	Income equal to expenses	7 (22.6)	4 (13.3)	p=0.544
Marital status, n (%)	Married	19 (61.3)	22 (73.3)	χ^2=1.003[b]
	Single	12 (38.7)	8 (26.7)	p=0.316
Chronic disease (excluding CHD), n (%)	Yes	23 (74.2)	27 (90.0)	χ^2=2.577[b]
	No	8 (25.8)	3 (10.0)	p=0.108
Smoking usage status, n (%)	Yes	4 (12.9)	2 (6.7)	χ^2=0.702[b]
	No	17 (54.8)	18 (60.0)	p=0.804
	Quit smoking	10 (32.3)	10 (33.3)	
Exercise status, n (%)	Yes	9 (29.0)	10 (33.3)	χ^2=0.132[b]
	No	22 (71.0)	20 (66.7)	p=0.717

CHD: Coronary Heart Disease; SD: Standard Deviation; a: Independent Sample-t; b: Pearson-χ^2

Table 2. Comparison of drugs used by patients for CHD.

		Experimental Group (n=31)	Control Group (n=30)	Test
Anticoagulant, n (%)	Yes	25 (80.6)	24 (80.0)	χ^2=0.004[a]
	No	6 (19.4)	6 (20.0)	p=0.949
Beta Blocker, n (%)	Yes	23 (74.2)	20 (66.7)	χ^2=0.415[a]
	No	8 (25.8)	10 (33.3)	p=0.519
Diuretic, n (%)	Yes	22 (71.0)	19 (63.3)	χ^2=0.403[a]
	No	9 (29.0)	11 (36.7)	p=0.525
ACE Inhibitor, n (%)	Yes	21 (67.7)	17 (56.7)	χ^2=0.796[a]
	No	10 (32.3)	13 (43.3)	p=0.372
Cardiac Vasodilator, n (%)	Yes	19 (61.3)	17 (56.7)	χ^2=0.135[a]
	No	12 (38.7)	13 (43.3)	p=0.714
Statins, n (%)	Yes	16 (51.6)	16 (53.3)	χ^2=0.018[a]
	No	15 (48.4)	14 (46.7)	p=0.893
Cardiac Glycoside, n (%)	Yes	7 (22.6)	2 (6.7)	χ^2=3.070[a]
	No	24 (77.4)	28 (93.3)	p=0.80

ACE: Angiotensin Converting Enzyme, [a]: Independent Sample-t; [b]: Pearson-χ^2.

test, a significant difference was observed in mean PSQI scores between the groups (p=0.004). Specifically, the experimental group exhibited a notably lower post-test mean score compared to the control group (Table 3).

Table 3. Comparison of the PSQI score averages of the groups.

PSQI	Experimental Group (n=31)	Control Group (n=30)	Test
Pre-test, mean±SD [Min-Max]	12.81±4.02 [6-19]	12.03±4.67 [5-21]	t=0.694[a] p=0.491
Post-test, mean±SD [Min-Max]	7.52±3.80 [3-17]	10.83±4.77 [3-20]	t=-3.008[a] **p=0.004**
Test	t=6.385[b] **p=0.000**	t=1.759[b] p=0.089	

PSQI: Pittsburgh Sleep Quality Index; SD: Standard Deviation; a: Independent Sample-t; b: Pearson-χ^2.

DISCUSSION AND CONCLUSION

Sleep disorders are addressed through a variety of approaches, encompassing both pharmacological and non-pharmacological methods. However, although pharmacologic treatments can significantly improve sleep quality, they may have side effects and may cause addiction.[15] Therefore, it is important that non-pharmacologic methods are safer.

The investigation aimed at exploring the impact of aromatherapy on the sleep quality of individuals with coronary heart disease revealed a notable enhancement in sleep quality among patients undergoing aromatherapy inhalation. Davari et al. reported findings congruent with the present study, noting an augmentation in sleep quality following aromatherapy among cardiac patients.[15] Likewise, Emami-Sigaroudi et al. observed the efficacy of aromatherapy involving lavender essential oil in averting sleep disorders.[8] Lavender essential oil operates on the limbic system, stimulating the production of γ-aminobutyric acid, particularly within the amygdala, thereby promoting sleep initiation. Moreover, its tranquilizing properties facilitate sleep by suppressing the release of acetylcholine.[16] Polonini et al. demonstrated that the daily intranasal administration of an essential oil blend comprising lavender and fennel prior to sleep resulted in a notable reduction in salivary cortisol levels and an improvement in sleep quality.[17] Her and Cho conducted a systematic review demonstrating that aromatherapy significantly improves sleep quality in adults and older individuals, with additional benefits such as reduced stress, pain, anxiety, depression, and fatigue.[18] In a clinical trial conducted by Mahdavikian et al., evaluating lavender aromatherapy's effectiveness over seven days in 105 cardiac care unit patients, significant positive effects on sleep quality were observed within the experimental group when compared to the control group.[19]

However, conflicting results exist regarding the effectiveness of aromatherapy in this context. Otaghi et al. conducted a clinical study among patients in a cardiac care unit, all of whom were candidates for angiography. They administered lavender essential oil four times (every 8 hours, starting 24 hours before angiography) but found no notable difference in sleep quality between the intervention and control groups.[20] Furthermore, another study involving 150 cardiac patients demonstrated that aromatherapy massage using lavender oil did not yield a significant difference in sleep quality compared to routine massage over 7 days.[21] These discrepancies in the efficacy of lavender oil in enhancing sleep among individuals with cardiovascular diseases might arise from variations in study duration and the specific interventions employed. While some studies did not observe significant effects of lavender inhalation,[20,21] this study demonstrated significant improvements in sleep quality with the extended one-month home-based intervention.

Overall, the comprehensive review by Luo and Jiang on aromatherapy studies provided encouraging evidence supporting the efficacy of lavender in addressing sleep disorders across diverse populations and medical conditions.[22] However, they underscored the necessity for additional clinical trials employing robust methodologies and extended intervention durations. Such trials are crucial for forming more evidence-based conclusions regarding the impact of lavender on sleep-related issues and for delving deeper into its mechanisms of action.

In conclusion, it can be said that lavender inhalation improves sleep quality in patients with CHD. Unlike previous studies limited to clinical or short-term applications,[9] this study uniquely implemented a monthly lavender inhalation protocol in the home environment of patients in this population. This design not only increases ecological validity but also provides insights into complementary therapies applicable in routine daily life. Lavender is one of the most commonly used herbs for patients with sleep disorders. There are various application techniques, with inhalation being the most preferred. The mechanisms likely involve lavender's known anxiolytic and sedative properties, potentially mediated through the central nervous system. Given its non-invasive, cost-effective, and easily applicable nature, alongside its suitability for cardiac patients, lavender essential oil serves as a promising, independent healthcare intervention. Healthcare professionals can consider incorporating lavender inhalation into patient education as a simple approach to improving sleep quality in CHD patients. However, the generalizability of these findings is limited by the study's sample, which included only patients discharged from a single clinic within a university hospital. Additionally, the assessment of patients' sleep quality was confined to the scale's items, representing a further limitation. Future studies should explore the effects of lavender inhalation over extended periods and its potential impact on long-term cardiovascular outcomes.

Ethics Committee Approval: The study adhered to the principles outlined in the Helsinki Declaration. Approval was obtained from the Ethics Committee for Scientific Research and Publication of Isparta Applied Sciences University (Date: 12.01.2023, decision no: 131/07). Institutional approval to conduct the study was also obtained from the Chief Physician of Çukurova University Balcalı Hospital (E-59565534-010.01-679091). Prior to participation, all patients were duly informed about the study's objectives, emphasized the voluntary nature of their invol-

vement, and assured of their right to withdraw at any point. Patients were explicitly notified that their participation or withdrawal would not influence their ongoing treatment and care. Informed consent was obtained from all of the participants. This study was registered in ClinicalTrials.gov under the registration number (ID: NCT05704946).

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

Author Contributions: Concept – EG, SDD, SA; Supervision – SA; Materials – EG; Data Collection and Processing – EG; Analysis and Interpretation – SDD; Writing – EG, SDD, SA.

Peer-review: Externally peer-reviewed.

Acknowledgement: The authors would like to thank all the patients for their time and for allowing us to collect this data.

Other Information: This study was presented at the International Health Services Congress. The congress took place on November 21-22, 2023, at Toros University in Mersin, Türkiye.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):170-177 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):170-177*

The Relationship Between Executive Functioning and Burnout, Depressive, Anxiety and Broad Autism Phenotype Symptoms in Parents of Children with Autism Spectrum Disorder

Otizm Spektrum Bozukluğu Olan Çocukların Ebeveynlerinde Yürütücü İşlevlerle Tükenmişlik, Depresif, Anksiyete ve Geniş Otizm Fenotip Belirtilerinin İlişkisi

[1]Mustafa Esad TEZCAN, [2]Şeyda Nur İspir ÇALTINER, [2]Hacer Reyyan DEMİREL, [1]Beyza Nur KORUCU, [3]Barış Şen, [2]Fatih EKİCİ

1Department of Child and Adolescent Psychiatry, Selçuk University Faculty of Medicine, Konya, Türkiye
2Department of Psychiatry, Selçuk University Faculty of Medicine, Konya, Türkiye
3Department of Psychiatry, Manavgat State Hospital, Antalya, Türkiye

Mustafa Esad Tezcan: https://orcid.org/0000-0001-8362-1934
Şeyda Nur İspir Çaltıner: https://orcid.org/0009-0003-5811-6727
Hacer Reyyan Demirel: https://orcid.org/0009-0004-6452-0790,
Beyza Nur Korucu: https://orcid.org/0009-0006-7092-1421
Barış Şen: https://orcid.org/0000-0002-3902-1816
Fatih Ekici: https://orcid.org/0000-0003-4000-7429

ABSTRACT

Objective: The aim of this study was to compare burnout, depression, anxiety and broad autism phenotype scores in parents of children diagnosed with autism spectrum disorder (ASD) with parents of typically developing (TD) healthy children and to investigate the relationship between these scores and executive functions.

Materials and Methods: This study included 43 parents of children diagnosed with ASD and 53 healthy controls aged 29-40 years. Participants were evaluated with Beck anxiety-depression inventory, Maslach burnout inventory and Autism-Spectrum Quotient (AQ) scores. Parents were assessed with the Structured Clinical Interview for Mental Disorders using the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders and the Stroop test was administered to assess executive functions in parents.

Results: Significantly higher anxiety, depression, burnout and AQ scores were observed in the ASD group compared to controls ($p< 0.001$). Compared to controls, the ASD group performed significantly worse on the Stroop test ($p< 0.05$). In addition, poor performance in the Stroop test was not significantly associated with anxiety, depression, burnout and AQ scores in the ASD group.

Conclusions: This study suggests that parents of children with ASD may have more anxiety, depression and burnout symptoms.

Keywords: Autism spectrum disorder, broad autism phenotype, burnout, executive functions, parents

ÖZ

Amaç: Bu çalışmanın amacı otizm spektrum bozukluğu (OSB) tanılı çocukların ebeveynlerinde tükenmişlik, depresyon, anksiyete ve geniş otizm fenotipi skorlarını tipik gelişen (TG) sağlıklı çocukların ebeveynleri ile karşılaştırmak ve bu skorların yürütücü işlevler ile ilişkilerini araştırmaktır.

Materyal ve Metot: Bu çalışmaya 29-40 yaşları arasında 43 OSB tanılı çocukların ebeveynleri ve 53 TG sağlıklı kontrol dahil edilmiştir. Katılımcılar Beck anksiyete-depresyon ölçeği, maslach burnout inventory ve Autism-Spectrum Quotient (AQ) skorları ile değerlendirilmiştir. Ebeveynler, Ruhsal Bozuklukların Tanısal ve İstatistiksel El Kitabının Beşinci Baskısı kullanılarak Ruhsal Bozukluklar için Yapılandırılmış Klinik Görüşme ile değerlendirilmiş ve ebeveynlerde yürütücü işlevleri değerlendirmek için Stroop testi uygulanmıştır.

Bulgular: ASD grubunda kontrollere göre anlamlı olarak daha yüksek anksiyete, depresyon, tükenmişlik ve AQ skorları gözlendi ($p< 0,001$). Kontrollerle karşılaştırıldığında, ASD grubunun Stroop testinde anlamlı olarak daha kötü performans sergilediği gözlenmiştir ($p<0,05$). Ayrıca ASD grubunda Stroop testindeki kötü performansın anksiyete, depresyon, tükenmişlik ve AQ skorları ile anlamlı düzeyde ilişkili olmadığı belirlenmiştir.

Sonuç: Bu çalışma ASD'li çocukların ebeveynlerinde daha fazla anksiyete, depresyon ve tükenmişlik belirtileri olabileceğini göstermektedir.

Anahtar Kelimeler: Ebeveynler, geniş otizm fenotipi, otizm spektrum bozukluğu, tükenmişlik, yürütücü işlevler

Sorumlu Yazar / Corresponding Author:
Mustafa Esad Tezcan
Department of Child and Adolescent Psychiatry, Present Address: Ardıçlı, Akademi, Celal Bayar St., No:313, 42250 Selçuklu/Konya/ Türkiye
Tel.: +905317903819
E-mail: esadaxe@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 11/04/2025
Kabul Tarihi/ Accepted: 16/05/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Tezcan ME and et al. Have The Relationship Between Executive Functioning and Burnout, Depressive, Anxiety and Broad Autism Phenotype Symptoms in Parents of Children with Autism Spectrum Disorder. Online Türk Sağlık Bilimleri Dergisi 2025;10(2):170-177. doi: 10.26453/otjhs.1672755

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that occurs in early childhood and is characterized by persistent deficits in social communication and interaction as well as restricted and repetitive behaviors.[1] Children with ASD need additional support throughout life, which creates extra challenges and difficulties for parents. Parents need to learn how to manage behavior, sleep and eating problems in children with ASD.[2] In this respect, parenting skill is an important factor in child development, and the effects of parenting stress on children's mental, emotional and behavioral health have received increasing attention.[3] Parents of children with ASD often experience emotional and informational gaps and face more social challenges, such as depression, anxiety and marital problems, than parents of typically developing (TD) children.[4] However, it has been reported that parents of children with ASD are more likely to experience parental burnout and show higher levels of parental burnout than parents of TD children.[5] In addition, a recent meta-analysis reported that anxiety and depressive disorders are the most common psychiatric disorders in parents of children with ASD.[6-7]

Executive functioning (EF) is vital for successful parenting because it enables parents to be understanding, sensitive and flexible with their children. Parents draw on these capacities when planning and modifying behavior, responding to cues, regulating emotions in the face of stress and challenging child behavior, solving problems and making decisions.[8] In a recent study, it was observed that there were significant differences between parents of children with ASD and parents of TD children in alert and executive control networks, and it was reported that parents of children with ASD had decreased EF functioning.[9] EF impairment is also common in ASD, and given the broad autism phenotype, family members may also have impaired EF, and such parental research may be important.[10]

The aim of this study was to understand the cognitive and emotional differences between parents of children diagnosed with ASD and parents of TD healthy children and to investigate whether the Stroop test is associated with emotional symptoms in parents of children with ASD using the Stroop test, Maslach burnout inventory, Beck anxiety and depression inventory and Autism-Spectrum Quotient. The hypothesis of the study is that parents of children with ASD may have more emotional symptoms and perform worse on tests of executive function than parents of TD children.

MATERIALS AND METHODS

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Selçuk University Faculty of Medicine (Date: 25.02.2025, decision no: 2025/04).

Study Design and Participants: Participants were recruited from the Child and Adolescent Psychiatry Outpatient Clinic of Selçuk University Faculty of Medicine. Exclusion criteria included children with organic brain injury and head trauma, history of hypoxia-ischemia, known genetic disorders, visual or hearing impairments, and chronic physical illnesses. Considering these criteria, participants diagnosed with ASD were included in the study. The TD control group consisted of healthy children who came to our clinic for consultation and were randomly selected according to the exclusion criteria. The parents of the children included in the study constitute the main sample of the study. Parents of children with ASD and TD healthy controls did not have chronic physical, neurological or psychiatric diseases. The clinical evaluation of the children was performed by an expert child psychiatrist, and the parental evaluation of both groups included in the study was performed by an expert psychiatrist. The sample size of the study consisted of the parents of children diagnosed with ASD who presented to the child psychiatry clinic, and the parents of TD children who were referred for consultation but were not diagnosed with any neurological or psychiatric disorder. Forty -three parents (of children with ASD) and 53 parents (of TD controls) were included. Written informed consent was obtained from the parents of children in both groups. The ages of the children ranged between 6 and 9 years, and the ages of the parents ranged between 29 and 40 years. After the examination, sociodemographic data forms for both groups were completed by the clinician and the EF test was measured by the clinician.

Clinical Assessment: The children in both groups were evaluated by a certificated interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (KSADS-PL) and diagnosed on the basis of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.[11] The validity and reliability of the K-SADS-PL for Turks were confirmed by Ünal et al.[12]

The Structured Clinical Interview for DSM-5 mental disorders (SCID-5) was used to systematically assess whether parent participants currently or previously met the criteria for psychiatric diagnoses specified in the DSM-5. It has been shown by Elbir et al. that the Turkish form of the SCID-5 can be used reliably both in clinical practice and research.[13]

The Beck Anxiety Inventory (BAI) is a self-assessment scale developed by Beck and colleagues and used to measure the severity of anxiety symptoms experienced by the individual. Scores obtained from the scale range from 0 to 63, and an increase in the score obtained from the test indicates an increase in the level of anxiety. The Turkish validity and reliability of the scale ($\alpha = 0.93$) was conducted by Ulusoy et al.[14-15]

Beck Depression Inventory (BDI), developed by Beck and colleagues, defines depressive symptomatology. An increase in scale score is interpreted as an increase in clinical severity. Turkish validity and reliability ($\alpha= 0.78$) study was conducted.[16-17]

The Maslach Burnout Inventory (MBI) is a 22-item Likert-type scale developed by Maslach and Jackson to assess self-reported burnout symptoms. The scale consists of three subscales (emotional exhaustion, depersonalization and personal accomplishment). Turkish validity and

reliability were conducted by Ergin et al. (α= 0.83 for Emotional Exhaustion, 0.72 for Personal Accomplishment, and 0.65 for Depersonalization).[18,19-20]

The Autism Spectrum Quotient (AQ) was developed by Baron-Cohen et al. The AQ aims to determine the degree to which any adult with normal intellectual capacity exhibits autistic traits or has a 'broad phenotype'. The ASQ originally consisted of five domains (social skills, attention switching, attention to detail, communication, and imagination). The validity and reliability (α= 0.63) study of the Turkish version of the scale was conducted by Köse et al.[21-22]

The Stroop Test was administered to participants by a clinician and assesses primarily complex attention and is available in several versions. Stroop Test TBAG was used in our study.[23] The Stroop test serves as a measure of inhibitory control and complex attention by requiring individuals to override an automatic and dominant response (e.g., reading the written word) in favor of a conflicting task (e.g., naming the color of the ink). It is also employed to examine the interference effect, reflecting the individual's capacity to manage competing cognitive demands simultaneously. Validity and reliability studies of the Stroop Test for the Turkish population were performed by Karakaş et al.[24]

Statistical Analyses: SPSS 29.0 statistical software (SPSS Inc., Chicago, IL) was used for statistical analysis. Age, Stroop test and clinical assessment scales were compared between the two groups using Student's t-test or Mann-Whitney U test according to their distributional characteristics, and sex was compared between both groups using the Chi-square test. Skewness and kurtosis values between -2 and +2 were used to determine the normal distribution. The significance value was accepted as $p < 0.05$ at the 95% confidence interval. Correlations between the Stroop test and clinical scales were also evaluated with Pearson (parametric values) and Spearman (non-parametric values). Since multiple comparisons were made, Bonferroni correction was applied to control for type I error. In this adjustment, the significance test for each comparison was set as p= 0.00045 and correlations with a p-value below this threshold were considered statistically significant. Effect sizes were estimated using Cohen's d for parametric and non-parametric comparisons and Cramér's V for categorical variables. Cohen's d effect sizes were considered large at ≥0.8, intermediate at 0.5–0.7, small at 0.2–0.4 and as having no effect at <0.2. Post-hoc power was calculated for each clinical scale and Stroop test by taking into account Cohen's d effect size, sample sizes, alpha level (α=0.05) and between-group sample ratio.

RESULTS

Forty-three parents of participants with ASD and 53 parents of TD healthy control participants, totaling 96 parents, were included in the study. The mean CARS scores of children with ASD were 31.60±5.79. There was no statistically significant difference between both groups in terms of age and sex. Regarding EF, Stroop whole episode durations were significantly longer in the ASD group than in TDs. Stroop second, third, fourth and fifth segment corrections were significantly higher in the ASD group compared to TDs. The number of errors in the fourth and fifth Stroop sections was significantly higher in the ASD group compared to TDs. Regarding clinical scales, Beck anxiety and depression inventory, Maslach Burnout Inventory and all subscores of autism-spectrum quotient were significantly higher in ASD group compared to TDs (Table 1). The post-hoc power results of the

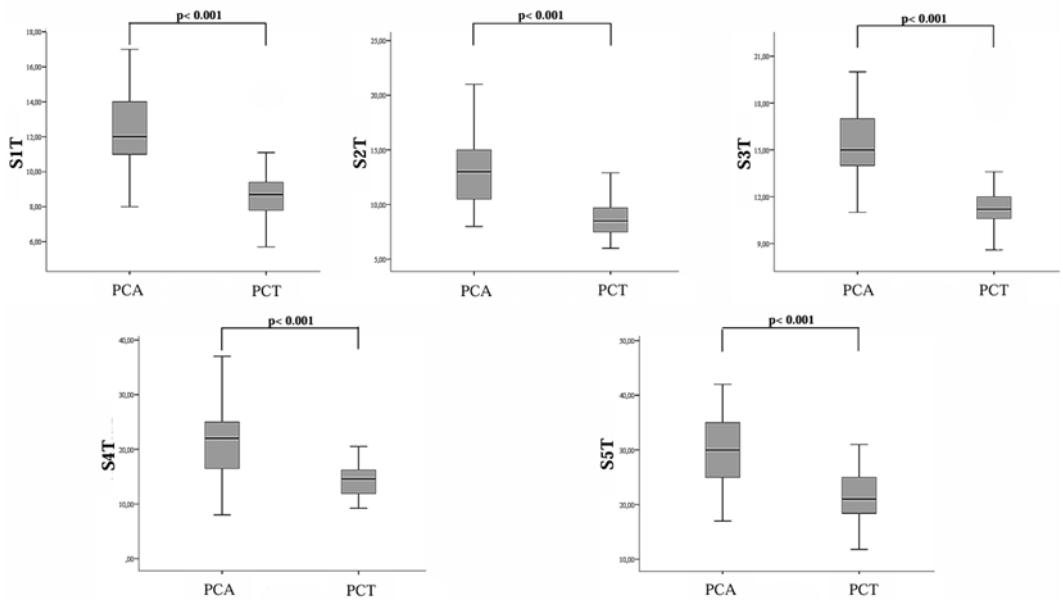

Figure 1. Box plots of Stroop test times (ST) in both groups. PCA: Parents of children with ASD; PCT: Parents of children with typically developing healthy controls.

questionnaires of clinical evaluations and Stroop test in both groups are given in Table 1. Demographic characteristics, Stroop test scores and scale data of the two groups are shown in Table 1.

Table 1. Data on the comparison of demographic characteristics, Stroop tests and scale scores of both groups.

		Parents of children with ASD (43)	Parents of children with TD (53)	p	$t/x^2/z$	d
Age[b]		35.53±3.42	35.19±4.57	0.319	-0.996	0.008
Sex, n	Male	15	25	0.225	1.474	0.124[a]
	Female	28	28			
S1T		12.18±2.35	8.91±1.71	**0.001**	7.861	3.740 0.99[c]
S1E		-	-	-	-	-
S1C		-	-	-	-	-
S2T[b]		13.24±3.45	8.84±1.78	**0.001**	-6.729	2.738 0.99[c]
S2E[b]		0.02±0.15	-	-	-	-
S2C[b]		0.30±0.46	0.05±0.30	**0.001**	-3.453	0.625 0.85[c]
S3T[b]		15.52±2.49	11.48±2.19	**0.001**	-6.982	0.171 0.99[c]
S3E[b]		-	0.01±0.13	-	-	-
S3C[b]		0.83±0.99	0.20±0.45	**0.001**	-3.620	0.811 0.97[c]
S4T[b]		20.71±6.95	14.72±3.85	**0.001**	-4.962	0.106 0.85[c]
S4E[b]		0.27±0.70	0.01±0.13	**0.022**	-2.298	0.514 0.69[c]
S4C		0.88±1.05	0.30±0.50	**0.001**	3.561	0.705 0.92[c]
S5T		29.53±6.29	22.07±5.07	**0.001**	6.430	0.130 0.96[c]
S5E[b]		0.65±1.04	0.20±0.59	**0.006**	-2.733	0.521 0.70[c]
S5C		1.76±1.49	0.77±0.89	**0.001**	4.041	0.808 0.97[c]
Beck-D		13.62±9.34	6.45±3.07	**0.001**	5.253	0.731 0.99[c]
Beck-A[b]		10.93±10.26	3.22±3.96	**0.001**	-4.123	0.736 0.99[c]
MBI emotional exhaustion[b]		11.27±8.50	4.35±3.31	**0.001**	-4.233	0.500 0.99[c]
MBI depersonalization		3.55±3.26	1.71±1.43	**0.001**	3.697	0.731 0.94[c]
MBI personal accomplishment[b]		24.67±5.31	14.09±3.02	**0.001**	-7.642	0.244 1.0[c]
AQ Social Skills[b]		3.20±1.79	1.41±0.92	**0.001**	-5.631	1.256 1.0[c]
AQ ability to shift attention[b]		4.41±1.63	2.58±0.71	**0.001**	-6.054	1.450 1.0[c]
AQ paying attention to details[b]		4.93±2.04	1.62±1.34	**0.001**	-7.237	1.913
AQ communication[b]		3.02±1.48	0.98±0.86	**0.001**	-6.425	1.677 1.0[c]
AQ imagination[b]		3.46±1.48	1.07±1.14	**0.001**	-7.034	1.804 1.0[c]

ASD: Autism spectrum disorder; TD: Typically developing healthy controls; Beck-D: Beck depression inventory; Beck-A: Beck anxiety inventory; AQ: Autism-spectrum quotient; MBI: Maslach burnout inventory; S1T: Stroop 1. Part Time; S1E: Stroop 1. Part Error; S1C: Stroop 1. Part Correction: S2T: Stroop 2. Part Time; S2E: Stroop 2. Part Error; S2C: Stroop 2. Part Correction: S3T: Stroop 3. Part Time; S3E: Stroop 3. Part Error; S3C: Stroop 3. Part Correction: S4T: Stroop 4. Part Time; S4E: Stroop 4. Part Error; S4C: Stroop 4. Part Correction: S5T: Stroop 5. Part Time; S5C: Stroop 5. Part Correction: S5E: Stroop 5. Part Error; d: Cohen's d effect size. [a]Cramer's V effect size; [b]Mann-Whitney U; [c]Post-hoc power analysis.

ox plots of Stroop test times in both groups are shown in Figure 1.

No significant correlation was observed between Bonferroni correction and the Stroop test and all other clinical variables (Table 2).

Table 2. Correlation coefficients between clinical scale scores and Stroop test subscores.

		Beck-D	Beck-A	MBI-EE	MBI-DP	MBI-PA	AQ-SS	AQ-ASA	AQ-PAD	AQ-Co	AQ-I
S1^{T}	p	0.235	0.972	0.022	0.054	0.879	0.004	0.626	0.648	0.012	0.008
	r	0.185	0.005	0.348	0.296	0.024	0.431	-0.076	-0.072	0.380	0.397
S2^{T}	p	0.065	0.225	0.022	0.084	0.782	0.005	0.935	0.653	0.072	0.105
	r	0.284	-0.189	0.348	0.267	0.044	0.417	0.013	-0.071	0.277	0.251
S2^{C}	p	0.019	0.323	0.007	0.001	0.149	0.056	0.361	0.431	0.015	0.273
	r	0.355	0.154	0.406	0.483	0.224	0.294	0.143	0.123	0.368	0.171
S3^{T}	p	0.009	0.956	0.293	0.978	0.900	0.006	0.917	0.805	0.038	0.010
	r	0.395	0.009	0.164	0.004	0.020	0.413	-0.016	0.039	0.317	0.390
S3^{C}	p	0.062	0.201	0.063	0.403	0.048	0.064	0.301	0.349	0.093	0.818
	r	0.287	0.199	0.286	0.131	0.304	0.285	-0.161	0.146	0.259	0.036
S4^{T}	p	0.542	0.725	0.125	0.094	0.191	0.123	0.172	0.625	0.167	0.014
	r	0.096	-0.055	0.238	0.258	0.203	0.239	-0.212	-0.077	0.215	0.372
S4^{E}	p	0.314	0.070	0.033	0.080	0.691	0.197	0.986	0.821	0.640	0.082
	r	0.157	0.279	0.325	0.270	0.062	0.201	0.003	0.036	0.073	0.269
S4^{C}	p	0.011	0.981	0.003	0.007	0.473	0.020	0.291	0.588	0.092	0.948
	r	0.386	0.004	0.438	0.408	0.112	0.354	-0.165	0.085	0.261	-0.010
S5^{T}	p	0.025	0.971	0.166	0.138	0.642	0.020	0.569	0.011	0.076	0.007
	r	0.340	0.006	0.215	0.230	-0.073	0.353	-0.089	-0.383	0.273	0.403
S5^{E}	p	0.219	0.121	0.022	0.120	0.741	0.003	0.809	0.351	0.010	0.138
	r	0.191	-0.240	0.349	0.240	0.052	0.447	-0.038	-0.146	0.389	0.230
S5^{C}	p	0.016	0.380	0.731	0.722	0.943	0.423	0.843	0.463	0.107	0.349
	r	0.365	0.137	0.054	-0.056	0.011	0.125	0.031	-0.115	0.249	0.146

Beck-D: Beck depression inventory; Beck-A: Beck anxiety inventory; MBI: Maslach burnout inventory; EE: Emotional exhaustion; DP: Depersonalization; PA: Personal accomplishment; AQ: Autism-spectrum quotient; SS: Social skills; Co: Communication; I: Imagination; ASA: Ability To Shift Attention; PAD: Paying Attention To Details; S1^{T}: Stroop 1. Part Time; S2^{T}: Stroop 2. Part Time; S2^{C}: Stroop 2. Part Correction: S3^{T}: Stroop 3. Part Time; S3^{C}: Stroop 3. Part Correction: S4^{T}: Stroop 4. Part Time; S4^{E}: Stroop 4. Part Error; S4^{C}: Stroop 4. Part Correction: S5^{T}: Stroop 5. Part Time; S5^{C}: Stroop 5. Part Correction: S5^{E}: Stroop 5. Part Error: After multiple comparisons with Bonferroni correction, corrected with a threshold value of p 0.00045.

DISCUSSION AND CONCLUSION

In this study, self-reported depression, anxiety, AQ and burnout levels and Stroop test performance of parents of children with ASD were compared with parents of TD healthy children and the relationship between Stroop test and self-reported depressive, anxiety and burnout symptoms in the ASD group was evaluated. To our knowledge, this is the first study to examine the relationship between the Stroop test and anxiety, depression, burnout symptoms and AQ scores in parents of children with ASD. Parents of children with ASD included in the study did not have any psychiatric disorder according to DSM-5. For this study, post-hoc power analysis showed that the sample size may be adequate for the Stroop test, AQ, burnout, depression and anxiety scales.

Stroop whole segment durations were significantly longer in the ASD group than in TDs. Stroop second, third, fourth and fifth segment corrections were significantly higher in the ASD group compared to TDs. The number of errors in the fourth and fifth Stroop sections was significantly higher in the ASD group compared to TDs. Regarding clinical scales, Beck anxiety and depression scores, Maslach Burnout Inventory and all sub-scores of autism-spectrum quotient were significantly higher in the ASD group compared to TDs.

As shown in a recent meta-analysis, burnout, anxiety and depression levels were significantly higher among parents of children with ASD compared to the control group.[5-25] It has been reported that parents with a child with ASD experience high levels of stress, stigmatization and hopelessness, which can lead to burnout.[26] Caring for children with ASD can be extremely challenging, as treatment and interventions for children with ASD are lengthy processes and children with ASD face more challenges in school and employment. Because of this, parents experience great stress and difficulties, and as a result, parenting stress turns into parental burnout.[27] The fact that parents of children with ASD experience more anxiety, depres-

sion and burnout symptoms than TDs may suggest that caring for children with ASD may be more difficult. It may also indicate that these parents should be supported with closer monitoring to enable more favorable living conditions when caring for children with ASD. Further follow-up studies are needed to understand this issue more clearly and to understand which psychiatric disorders may develop in these parents during clinical follow-up.

In various studies, it has been reported that parents of children with ASD have higher scores on AQ subscores than parents of TD children.[28] Sensory processing difficulties (labelled as a broad autism phenotype), like many autism-related traits and atypicalities, have been reported among unaffected relatives of individuals with ASD, including parents. A significantly higher proportion of parents of children with ASD compared to parents of TD children (21.1% vs. 7.5%) were members of the broad autism phenotype (BAP) group, suggesting that higher AQ scores in first-degree relatives of children with ASD compared to the TD group may be a reflection of the BAP.[29] Although the high AQ scores observed in parents of children with ASD suggest that these family members may be affected by the BAP, this was not clearly demonstrated in our study. Beyond subjective measurements to understand the BAP, supporting this phenotype with genetic studies may allow this to be more clearly demonstrated. In this respect, the fact that parents of children with ASD are affected by this phenotype may also affect their ability to care for these children. Therefore, there is a need for further studies, including genetic analyses with a larger sample size, when evaluating parents of children with ASD.

EFs are vital for successful parenting because they enable parents to be understanding, responsive and flexible. Parents draw on these capacities when planning and modifying behavior, responding to cues, regulating emotions in the face of stress and challenging child behavior, solving problems and making decisions. Mothers with low attentional control have been reported to exhibit harsher and more negative parenting.[30] In our study, parents of children with ASD had worse executive functioning skills compared to TD, which may refer to the BAP. Whether this finding is associated with a BAP has not been clearly demonstrated. Therefore, there is a need for more advanced EF tests and repeated EF measurements when evaluating executive functions in parents of children with ASD.

In our study, no significant correlation was observed between the Stroop test and other clinical variables. This finding may be related to the complexity of parental burnout and mental health. It may also suggest that the results are influenced by multiple factors beyond performance on a single executive function test. Additionally, the relatively small sample size may have affected the relationship between executive functions and clinical variables. Further research with a larger sample and the inclusion of more advanced executive function tests is needed to better understand the potential implications of these findings, particularly in terms of developing targeted support or interventions that consider both the psychological burden and possible executive function difficulties in these parents.

The strengths of our study include the inclusion of parents and children in both groups. To our knowledge, this is the first study to examine the relationship between the Stroop test and anxiety, depression, burnout, and broad autism phenotype symptoms in parents of children with ASD. However, this study also has limitations. In our study, ASD was DSM-5 and special assessment tools such as the autism diagnostic observation schedule and the autism diagnostic interview were not used. However, parental assessment was cross-sectional and psychiatric disorders that may occur in follow-up studies were not examined. In parental assessment, subjective questionnaires were used to determine clinical symptomatology, and blood and tissue examination and genetic analysis were not performed. In the parent assessment, only one parent of the child was assessed. Due to the limited number of participants, no sex-specific assessment was made for parents. In the evaluation of executive function, only the Stroop test was performed because it is performed in a shorter time in clinical practice, and other EF tests were not performed. We could not perform multiple correction in our study. We did not control for potential confounders such as age, sex, socioeconomic status and BMI, which could have influenced the results of the study. In our study, we could not evaluate child-parent interaction in further analysis. Future research could address this limitation by linking child-parent interaction in ASD etiopathogenesis with genetic analyses. In the assessment of family members in the context of the BAP, only parents were assessed; siblings and other relatives were not assessed.

In conclusion, parents of children with ASD performed significantly worse on the Stroop test than parents of TD children. Parents of children with ASD had higher anxiety, depression, burnout and AQ scores. In addition, the Stroop test was not significantly associated with anxiety, depression, burnout and AQ scores. These findings suggest that parents of children with ASD may show more internalizing symptoms and experience more burnout due to this. However, further studies are needed to understand the ability of EF deficits to predict clinical symptomatology in parents of children with ASD and their potential role in this regard.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Selçuk University Faculty of Medicine (Date: 25.02.2025, decision no: 2025/04).

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

Author Contributions: Concept – MET, FE, ŞİÇ; Supervision – MET, FE; Materials – MET, ŞİÇ, HRD, BNK, BŞ; Data Collection and/or Processing – MET, ŞİÇ, HRD, BNK, BŞ; Analysis and/or Interpretation – MET, FE, BNK; Writing – MET, FE.

Peer-review: Externally peer-reviewed.

Acknowledgement: The authors wish to thank the patients and families who participated in this study.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):178-184 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):178-184*

An Important Risk Factor for Nursing Students: Sharp Instrument Injuries

Hemşirelik Öğrencileri İçin Önemli Bir Risk Faktörü: Kesici-Delici Alet Yaralanmaları

[1]İbrahim KAVASLAR, [2]Ebru ÖZEN BEKAR, [3]Handan ALAN

[1]Nursing Management Doctorate Program, Istanbul University-Cerrahpaşa, Institute of Graduate Studies, Istanbul, Türkiye
[2]Department of Nursing, Faculty of Health Sciences, Duzce University, Duzce, Türkiye
[3]Department of Nursing Administration, Florence Nightingale Faculty of Nursing, Istanbul University-Cerrahpasa, Istanbul, Türkiye

İbrahim Kavaslar: https://orcid.org/0000-0001-6172-3067
Ebru Özen Bekar: https://orcid.org/0000-0002-6214-1541
Handan Alan: https://orcid.org/0000-0001-7414-2288

ABSTRACT

Objective: Sharp instrument injuries constitute a significant occupational risk for nursing students, exposing them to blood-borne pathogens. This study aimed to investigate the prevalence, causes, and outcomes of sharp instrument injuries among fourth-year nursing students during their clinical training.

Materials and Methods: This prospective and descriptive study was conducted with 190 fourth-year nursing students at a university in Türkiye during the 2022–2023 academic year. Students were divided into two groups, each completing a 14-week clinical placement in either the fall or spring semester. Data were collected using a structured case reporting form and analyzed with descriptive statistics.

Results: Sharp instrument injuries occurred in 14.7% of students. The most frequent procedures leading to injury were subcutaneous injections (32.1%) and recapping needles (50.0%). Injuries were most common in internal medicine departments (39.3%) and peaked between days 21 and 40 of clinical practice (42.9%). Primary contributing factors included carelessness (64.3%), insufficient supplies (50.0%), and lack of experience (32.1%). Emotional responses to injury included anxiety (64.3%) and fear (50.0%). All affected students received follow-up care, with no seroconversion for HIV, HBV, or HCV reported.

Conclusions: Sharp instrument injuries pose a notable occupational risk for nursing students, primarily due to inexperience, inadequate equipment, and unsafe practices. While simulation training may lower injury rates, increased confidence and speed during clinical placements can heighten risk. Strengthening curricula on safe practices, ensuring supervision, and offering emotional support are key to reducing injuries and enhancing clinical learning.

Keywords: Nursing education, nursing students, occupational exposure, sharps injuries, workplace safety

ÖZ

Amaç: Kesici-delici alet yaralanmaları, hemşirelik öğrencileri için önemli bir mesleki risk oluşturarak onları kan yoluyla bulaşan patojenlere maruz bırakmaktadır. Bu çalışmanın amacı, dördüncü sınıf hemşirelik öğrencilerinin klinik uygulamaları sırasında yaşadıkları kesici-delici alet yaralanmaları sıklığını, nedenlerini ve sonuçlarını araştırmaktır.

Materyal ve Metot: Bu prospektif ve tanımlayıcı çalışma, 2022-2023 akademik yılında Türkiye'deki bir üniversitede 190 dördüncü sınıf hemşirelik öğrencisi ile yürütülmüştür. Öğrenciler, her biri güz ya da bahar döneminde 14 haftalık bir klinik stajı tamamlayan iki gruba ayrılmıştır. Veriler yapılandırılmış bir vaka raporlama formu kullanılarak toplanmış ve tanımlayıcı istatistiklerle analiz edilmiştir.

Bulgular: Öğrencilerin %14,7'si kesici-delici alet yaralanmaları yaşamıştır. Yaralanmaya en sık neden olan işlemler subkutan enjeksiyonlar (%32,1) ve iğne kapatma işlemleri (%50,0) olmuştur. Yaralanmalar en fazla dâhiliye servislerinde (%39,3) görülmüş ve klinik uygulamanın 21–40. günleri arasında en yüksek seviyeye ulaşmıştır (%42,9). Başlıca nedenler dikkatsizlik (%64,3), yetersiz malzeme (%50,0) ve deneyimsizlik (%32,1) olarak belirlenmiştir. Yaralanmalara verilen duygusal tepkiler arasında kaygı (% 64,3) ve korku (%50,0) öne çıkmıştır. Yaralanan tüm öğrencilere takip bakımı sağlanmış olup, HIV, HBV veya HCV serokonversiyonu gözlenmemiştir.

Sonuç: Bulgular, hemşirelik öğrencilerinde görülen kesici -delici alet yaralanmalarının büyük ölçüde deneyimsizlik, yetersiz ekipman ve güvensiz uygulamalarla ilişkili olduğunu göstermektedir. Simülasyon temelli eğitim yaralanma oranlarını azaltabilirken, klinik uygulama sırasında artan güven ve işlem hızının riski artırabileceği belirtilmiştir. Klinik uygulamalarda güvenliğe odaklanan müfredatların geliştirilmesi, sıkı gözetim sağlanması ve duygusal destek sunulması hem yaralanma oranlarını azaltmak hem de öğrencilerin klinik öğrenme deneyimlerini ve mesleki gelişimlerini iyileştirmek açısından temel stratejiler olarak önerilmektedir.

Anahtar Kelimeler: Hemşirelik eğitimi, hemşirelik öğrencileri, iş yeri güvenliği, kesici-delici alet yaralanmaları, mesleki maruziyet

Sorumlu Yazar / Corresponding Author:
İbrahim Kavaslar
Nursing Management Doctorate Program, Istanbul University-Cerrahpaşa, Institute of Graduate Studies, Istanbul, Türkiye
Tel.: + 90 542 728 82 31
E-mail: ikavaslar@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 10/04/2025
Kabul Tarihi/ Accepted: 18/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Kavaslar İ and et al. An Important Risk Factor for Nursing Students: Sharp Instrument Injuries. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):178-184. doi: 10.26453/otjhs.1673479

INTRODUCTION

Sharp instrument injuries (SIIs) refer to injuries caused by tools such as needles and scalpels used in healthcare settings. These injuries are one of the major occupational risks and significantly contribute to the transmission of blood-borne infections. According to data provided by the WHO, SIIs account for 39% of Hepatitis C, 37% of Hepatitis B, and 4.4% of HIV infections among healthcare workers globally.[1,2]

Due to their active involvement in patient care during clinical training, nursing students have increased exposure to sharp instruments and injury risk.[3] Compared to experienced nurses, they often lack the clinical competence needed to handle these instruments safely. According to Benner's model, clinical competence develops through five stages: novice, advanced beginner, competent, proficient, and expert.[4] Therefore, nursing students are more vulnerable to sharp instrument injuries during early training.[5] Reported prevalence rates for SIIs among healthcare workers vary between 41.5% and 64.9%.[6–8] Among nursing students, findings in the literature show considerable variation, with prevalence ranging from 18.8% to 71%, depending on the country, study year, and methodology. Among nursing students, prevalence rates vary depending on country, study year, and methodology. Reported rates include 60.3% in China,[9] 19.4% in Türkiye,[10] 71% in Vietnam,[11] 49% in another study conducted in Türkiye,[12] 35% in a systematic review encompassing multiple countries,[13] and 18.8% in Taiwan.[14]

Despite their frequency, many SIIs remain unreported, with underreporting rates between 39.5% and 86.9%.[5,9,13,15] These injuries typically occur in clinical settings, training hospitals, and laboratories, often due to unsafe practices such as recapping needles[9-12] and improper disposal[9,11] during procedures. Studies underline the need for safe equipment, personal protective tools, and better training to prevent such incidents.[9,10,12,13,16]

Beyond physical effects, SIIs can lead to psychological consequences. Affected individuals may experience anxiety, fear, or panic[17-19] and elevated levels of stress and depression have been observed.[20] Among students, such injuries may reduce confidence in clinical practice, provoke fear, and negatively affect academic performance.[21,22]

These findings reveal the importance of sharps injuries in terms of both clinical and psychological effects. However, it is stated that the majority of students do not report injuries due to anxiety and fear.[23] This study aimed to investigate the prevalence, causes, and outcomes of SIIs among fourth-year nursing students during clinical training. Unlike previous studies that rely on retrospective recall, it uses a prospective design to document injuries in real time, providing more accurate data to support prevention and educational efforts.

MATERIALS AND METHODS

Ethics Committee Approval: For the implementation of the study, ethics committee approval was obtained from Duzce University Scientific Research and Publication Ethics Committee (Date: 20.10.2022, decision no: 22/417). Before starting data collection, institutional permissions and verbal and written consent were obtained from all student nurses participating in the study.

Type of Research: The study was conducted with a prospective design to examine sharp instrument injuries among nursing students and to determine their causes.

Range and Sample of the Research: The study was conducted between October 2022 and June 2023 with fourth-year nursing students (N=190) at a university in Türkiye. Before starting clinical practice, all students received 16 hours of occupational health and safety training, including approximately three hours on the prevention of sharp instrument injuries. The clinical practice was carried out four days a week in the inpatient clinics of the university hospital under nurse supervision and lasted a total of 56 days. During this period, students performed invasive procedures on real patients for the first time. The students were divided into two groups, with one group completing their training in the fall semester and the other in the spring semester. All internship participants were included in the study.

Data Collection Methods: Personal Information Form and Case Report Form were used in data collection. The Case Report Form was created by the researchers. This form consists of 12 questions and includes questions such as date, time, place, region, severity of the injury, how the injury occurred, and contamination status of the sharp object.

Data Collection: A total of 190 students were followed up by researchers during the internship period in the fall semester (95) and spring semester (95) for two 14-week academic terms. In the event of a contaminated SII, the student was given the necessary support by a researcher, and data was collected by meeting with the student face-to-face within 8 hours. Non-contaminated SII (such as glass stuck in the hand while breaking medicine ampoules) were determined as an exclusion criterion.

Statistical Analysis: The study consists of data from 190 participants. Analyses were conducted using the IBM SPSS Statistics 26 software. Frequencies (number, percentage) were calculated for categorical variables, while descriptive statistics (mean, standard deviation) were used for numerical variables.

RESULTS

The students were 21.8±1.8 years old on average, 75.3% female, 24.7% male. All students were tested for HIV, Hepatitis B and Hepatitis C before starting the internship, and no problems were detected. In addition, all students completed their Hepatitis B vaccinations before the internship. Of the students we followed, 85.3% were not injured, 13.7% (n=26) were injured once, 1% (n=2) were injured twice, and 14.7% (n=28) were injured with sharp objects (Table 1).

Of the students who experienced needlestick injuries, 32.1% experienced injuries while performing subcutaneous injections, 50% while closing the needle cap, and 39.3% in internal medicine clinics. Most of the students (64.3%) stated that they acted carelessly, and 50% experienced a problem with insufficient supplies. In addition, half of the students who experienced needlestick injuries stated that they felt fear after the incident (Table 2).

When we examine the distribution of injuries by day, it is seen that injuries begin from the third day and continue in the following days with experience. In addition, 42.9% of the students experienced injuries between the 21st and 40th days of their internship (Figure 1).

Table 1. Demographics and contaminated SII occurrence (n=190).

Information		**Data**
Age, Mean±SD		21.8±1.8
Sex, n (%)	Male	47 (24.7)
	Female	143 (75.3)
Injuries, n (%)	No injuries	162 (85.3)
	Injured once	26 (13.7)
	Injured twice	2 (1.0)

Table 2. SII: Characteristics, causes and emotional reactions (n=28).

Information		**Data**
Procedures in which SIIs occurred, n (%)	Subcutaneous injection	9 (32.1)
	Blood glucose measurement	7 (25)
	Intramuscular injection	5 (14.3)
	Withdrawing blood	3 (10.7)
	Intravenous catheterization	2 (7.1)
	Disposing of medical waste	2 (7.1)
Stage of the procedures where the SIIs occurred, n (%)	During the needle cap closing	14 (50)
	During the actual procedure	11 (39.3)
	While throwing away the waste	3 (10.7)
Clinics, n (%)	Internal clinic	11 (39.3)
	Surgical clinic	7 (25)
	Labour ward	6 (21.4)
	Emergency ward	3 (10.7)
	Paediatrics ward	1 (3.6)
Reasons Expressed, n (%)	Being careless	18 (64.3)
	Being in a rush	7 (25)
	Patients' sudden movements	3 (10.7)
	Insufficient supplies (such as no treatment tray)	14 (50)
Problems Experienced, n (%)	Inexperience	9 (32.1)
	Misdirection by nurse	5 (17.9)
***Post-injury Emotions,** n (%)	Worry	18 (64.3)
	Fear	14 (50)
	Sadness	6 (21.4)

*: More than one emotion was expressed.

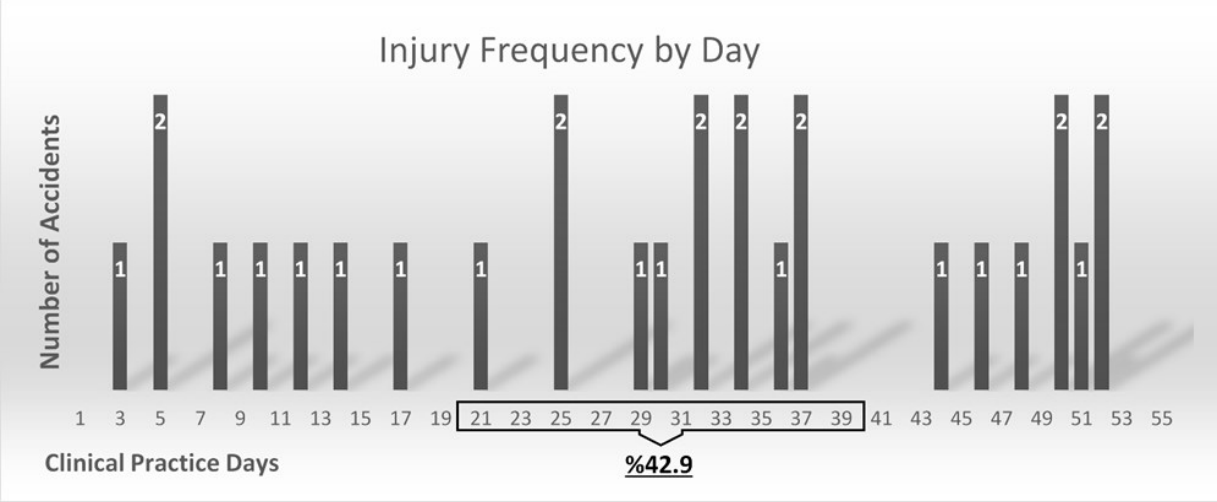

Figure 1. Injury frequency by day.

In the controls performed after the injury, it was determined that the needles to which 89.3% of the students were exposed were not contaminated with HIV, HBV or HCV. However, it was determined that the needles with which two students were injured were contaminated with HBV and one student was injured with a needle whose infectious disease status was unknown. All students who were injured were monitored for HIV, HBV and HCV, and no evidence of infection was detected in the first six months of serological blood test results (Table 3).

Table 3. Contaminated materials and 6th month control results (n=28).

Information		Data	Students' 6-month serological blood test results
Uncontaminated needles, n (%)	HIV, HBV, HCV	25 (89.3)	Negative
Contaminated needles, n (%)	HBV	2 (7.1)	Negative
Unknown source, n (%)		1 (3.6)	Negative

DISCUSSION AND CONCLUSION

SIIs pose the greatest threat to nursing students during clinical practice due to the risk of accidental exposure to body fluids and infected blood. In the current study, 13.7% of the students we followed for 14 weeks in two academic terms experienced a sharp object injury, 1% twice, and a total of 14.7% of the students experienced a sharp object injury. When the literature is examined, different results are observed worldwide, ranging from 14.1% to 64.5%.[13,15,23-26]

In a meta-analysis analyzing the prevalence of needlestick injuries in nursing students, articles between 2002 and 2021 were examined. The lowest overall prevalence was stated as 6%, and the highest as 51%. In addition, this study stated that it was 38% in Asian countries, 9% in the United States, and 30% in European countries.[27] When the results of this study are compared with the world literature, it is seen that it is at a very good level compared to other regions, except the United States. When current studies across Türkiye are examined, two studies stand out. In the first study, the SII rate of nursing students who practiced for four years was reported as 31%.[28] Another study conducted five years ago in the nursing department where this study was conducted reported the SII rate of nursing students as 27.8%.[22] Five years ago, this study found that students practiced at the patient's bedside across all grade levels due to the lack of a simulation laboratory. In this context, it is evaluated that the SII rates of students who practiced at the patient's bedside in the fourth grade decreased significantly after practicing in the simulation laboratory during the first, second and third grades.

Of the students who experienced a sharp object injury, 32.1% experienced injuries while performing a subcutaneous injection and 50% while recapping needles. When the literature is examined, "recapping the previously used syringes" is stated as the most common cause of SIIs.[22,23,26,28] The tiny and thin

needles used for subcutaneous injections make closure more difficult. A study on nurses showed that removing and/or replacing needle caps with bare hands was associated with a higher incidence of sharps injuries associated with insulin injection.[29] These findings highlight the need to avoid needle recapping strictly and to implement safer injection practices—particularly during subcutaneous procedures—to reduce sharp instrument injuries among nursing students effectively.

According to the study findings, nursing students experienced the most injuries in 39.3% of the internal medicine clinics, and 42.9% of them experienced injuries between the 21st and 40th days of their internship. In studies conducted in Türkiye, similar to the study, most injuries occurred in an internal medicine clinic.[15,28,30] The increase in the number of subcutaneous injections in treatment protocols at internal medicine clinics may explain this rise.

In the current study, injury rates were found to increase during the middle stages of clinical practice, coinciding with periods of greater procedural experience compared to the beginning of training. While the literature often attributes high rates of sharps injuries among nursing students to their inexperience,[12] our findings suggest that the accumulation of experience and the resulting self-confidence may paradoxically contribute to an increased risk of injury.

Specifically, 64.3% of students reported injuries due to carelessness and 17.9% due to rushing, supporting the notion that increased procedural workload and overconfidence may lead to lapses in attention and safety practices. Similarly, Palloş et al.[15] identified carelessness (51.1%) and rushing (27.7%) as the most common causes of injuries among nursing students. To mitigate injuries resulting from carelessness, it is essential to cultivate a strong culture of safety through continuous clinical mentoring, regular skill-based assessments, and reflective practices that encourage students to evaluate their actions and maintain focus during procedures critically.

Nevertheless, a notable proportion of students (32.1%) in our study reported that a lack of experience was also a contributing factor to their injuries. Consistently, previous research indicated that approximately 70% of students suffered needlestick injuries due to insufficient manual skills, attributable to limited experience.[12] Moreover, external factors such as a lack of supplies and unpredictable patient reactions were reported to have contributed to injury occurrence during clinical practice.

In addition to physical injuries, emotional reactions were frequently reported by students following sharp injuries. In our study, 64% of nursing students stated that they experienced anxiety, and 53.6% reported feelings of fear after injuries. This is consistent with previous findings, where anxiety and fear were reported by 43.4–55.3% of nursing students following needlestick injuries.[15,25] Similarly, studies conducted among nurses have shown that emotional changes following sharp injuries are common, with 58.6% of nurses reporting emotional distress.[29] Furthermore, fear of negative consequences may prevent students from reporting incidents, as indicated in previous studies.[23]

In conclusion, this study examines the incidence, underlying causes, and consequences of sharp instrument injuries among nursing students during their clinical placements. The results indicate that such injuries predominantly stem from inexperience, lapses in attention, and insufficient access to appropriate equipment. Furthermore, students frequently report experiencing emotional responses such as anxiety and fear following these incidents. The findings suggest that training conducted within simulation laboratories may contribute to a reduction in the occurrence of injuries. Nevertheless, as students gain confidence and clinical exposure, an associated risk of increased injury rates may emerge, possibly due to overconfidence or complacency. These outcomes underscore the urgent need to strengthen safe practice strategies within nursing education curricula. Moreover, ensuring robust supervision and implementing comprehensive support systems to address the emotional well-being of students are essential components in fostering both safety and resilience. By prioritizing injury prevention and promoting a culture of safety, nursing education programs can make a substantial contribution to the professional development of future nurses. This study was conducted at a single institution, which may limit the generalizability of the findings. Moreover, the low number of contaminated sharp object injury cases made it impractical to perform inferential statistical analyses such as chi-square or regression, as meaningful subgroup comparisons could not be achieved. Future research should involve multicenter studies with larger sample sizes to enhance generalizability and examine additional factors—such as institutional protocols, reporting practices, and coping strategies—that may influence the incidence and management of sharp instrument injuries among nursing students.

Ethics Committee Approval: For the implementation of the study, ethics committee approval was obtained from Duzce University Scientific Research and Publication Ethics Committee (Date: 20.10.2022, decision no: 22/417). Before starting data collection, institutional permissions and verbal and written consent were obtained from all student nurses participating in the study.

Conflict of Interest: No conflict of interest was dec-

lared by the authors.

Author Contributions: Concept – İK, EOB; Supervision – EOB, HA; Materials – İK; Data Collection and/or Processing – İK, EOB; Analysis and/or Interpretation – İK, EOB, HA; Writing – İK, EOB.

Peer-review: Externally peer-reviewed.

Acknowledgements: The authors thank all the nursing students who participated in the study.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):185-192 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):185-192*

Differences in Knee Morphology According to Age and Gender: An Evaluation Based on MRI

Yaş ve Cinsiyete Göre Diz Morfolojisindeki Farklılıklar: MRG Üzerinden Yapılan Bir Değerlendirme

[1]Bedrettin ÇİNPOLAT, [2]Meltem AÇAR GÜDEK, [3]Şirin ASLAN BARAN

[1]Departman of Dental Services, Vocational Higher School of Health Services, Tokat Gaziosmanpaşa University, Tokat, Türkiye
[2]Departman of Anatomy, Faculty of Medicine, Samsun University, Samsun, Türkiye
[3]Departman of Physical Therapy and Rehabilitation, Faculty o f Medicine, Tokat Gaziosmanpaşa University, Tokat, Türkiye

Bedrettin Çinpolat: https://orcid.org/0000 0002 3325 1522
Meltem Açar Güdek: https://orcid.org/0000 0002 4517 5889
Şirin Aslan Baran: https://orcid.org/0000 0003 0153 973X

ABSTRACT

Objective: The knee joint is an articulation exposed to excessive load during daily activities at all ages. There are ongoing discussions about the suitability of the currently used standard implants for this joint in terms of age and gender. In our study, we aimed to determine the possible morphometric differences of the bone structures involved in this joint according to age groups and gender.

Materials and Methods: The magnetic resonance (MR) images of the knee joints of 212 individuals (106 males, 106 females) aged between 18 and 69 years were retrospectively analyzed, and morphometric data were obtained from these images. Patients were separated according to age groups and gender, and the obtained data were analyzed.

Results: In the study, the measurement values related to the morphology of the femur, tibia, patella, and patellar ligament were generally higher in males than in females ($p<0.05$). When evaluated separately by sex, statistically significant differences were observed in certain morphometric parameters among the age groups ($p<0.05$).

Conclusions: Our study has shown that human knee anatomy varies significantly according to age and gender. These differences should be considered in the design of individualized and gender-specific knee joint prostheses.

Keywords: Gender, knee, knee joint, morphometry, MRI

ÖZ

Amaç: Diz eklemi günlük aktiviteler sırasında her yaşta aşırı yüke maruz kalan bir eklemdir. Günümüzde bu eklemeye uygulanan mevcut standart implantların yaşa ve cinsiyete uygunluğu ile ilgili tartışmalar devam etmektedir. Biz de çalışmamızda bu ekleme katılan kemik yapıların yaş gruplarına ve cinsiyete göre olası morfometrik farklılıklarının belirlenmesini amaçladık.

Materyal ve Metot: 18-69 yaş aralığındaki 212 kişiye (106 erkek, 106 kadın) ait diz manyetik rezonans (MR) görüntüleri retrospektif olarak incelenerek bu görüntüler üzerinden morfometrik veriler elde edildi. Hastalar yaş gruplarına ve cinsiyete göre ayrılarak elde edilen veriler analiz edildi.

Bulgular: Çalışmada, femur, tibia, patella ve patellar ligamentin morfolojisi ile ilgili ölçüm değerleri genel olarak erkeklerde kadınlardan daha yüksek bulundu ($p<0,05$). Cinsiyetler ayrı olarak değerlendirildiğinde, yaş grupları arasında bazı morfometrik parametrelerde istatistiksel olarak anlamlı farklılıklar tespit edildi ($p<0,05$).

Sonuç: Çalışmamızda insan diz anatomisinin yaşa ve cinsiyete göre önemli farklılıklar içerdiği gösterilmiştir. Bu farklılıklar bireysel ve cinsiyete özgü diz eklemi protezi tasarımı çalışmalarında dikkate alınmalıdır.

Anahtar Kelimeler: Cinsiyet, diz, diz eklemi, morfometri, MRG

Sorumlu Yazar / Corresponding Author:
Bedrettin Çinpolat
Address: Departman of Dental Services, Vocational Higher School of Health Services, Tokat Gaziosmanpaşa University, Tokat, Türkiye.
Tel.: +90 554 466 66 88
E-mail: bedrettin.cinpolat@gop.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 12/04/2025
Kabul Tarihi/ Accepted: 15/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Çinpolat B and et al. Differences in Knee Morphology According to Age and Gender: An Evaluation Based on MRI. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):185-192. doi: 10.26453/otjhs.1674443

INTRODUCTION

The knee joint is a functional joint with a wide range of motion that supports body weight during various activities such as standing, walking, and running. Structurally, it consists of two joints: one between the tibia and femur within the synovial capsule and the other between the patella and the patellar surface of the femur. The joint between the femur and tibia supports body weight, while the joint between the patella and femur provides frictionless transfer of forces generated by the contraction of the quadriceps femoris muscle.[1]

During daily activities, the knee joint is exposed to excessive loads at all ages compared to other joints. In addition, sports activities that require running, jumping, balance, and physical contact make the joint more prone to injury. In addition to traumatic injuries, common problems of the knee joint include osteoarthritis, septic bursitis, tendonitis, and other conditions. Magnetic resonance imaging (MRI) is considered the most powerful radiological imaging technique for visualizing and diagnosing pathologies in the bones, ligaments, menisci, articular cartilage, tendons, synovium, and surrounding soft tissues of the knee joint.[1-4]

In our study, we aim to determine possible morphometric differences of the bone structures located in the knee joint according to age and gender, thus contributing to the increase of radiological knowledge about the region and providing insight to clinicians involved in regional rehabilitation.

MATERIALS AND METHODS

Ethical Approval: Our study was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (Date: 18.01.2024, decision no: 2024/01). The study was conducted following international declarations, guidelines, etc.

Patient Selection: The study included MRI records of 212 patients referred for knee imaging at Tokat Gaziosmanpaşa University Hospital between January 2017 and July 2024. Data were reviewed using Sectra Workstation IDS7 (v24.2.16.6066-2023) through the hospital's Picture Archiving and Communication System (PACS). The study included individuals aged 18–69 years with completed skeletal maturation and MRI scans of sufficient quality for radiological assessment. Exclusion criteria comprised congenital, traumatic, or inflammatory knee pathologies; fractures, dislocations, space-occupying lesions; radiological signs of osteoarthritis; prior knee surgeries; and artefacts or any factors that could impair measurement accuracy. Participants were stratified into three age groups: 18–34 years (Group 1), 35–49 years (Group 2), and 50–69 years (Group 3).[3] A total of 212 knees were evaluated, with an equal distribution of right and left knees (n=106 each) across both sexes. Demographic and imaging data (age, sex, laterality) were recorded using Microsoft Excel (Office 2013).

Measured Parameters: Information on the measured parameters of the femur, tibia, and patella is given below. Of these measured parameters, those expressing length were recorded in millimeters (mm), and those expressing angle were recorded in degrees (°).

The measured parameters of the femur bone are shown in Figure 1.

The measured parameters of the tibia bone are shown in Figure 2.

The measured parameters related to the patella and patellar ligament are shown in Figure 3.

MR Protocol: All images were obtained using a 1.5 Tesla MRI scanner (Signa EXCITE 14.0, GE Medical Systems, Waukesha, WI). Non-contrast sagittal, axial, and coronal MR images acquired in the extension position were evaluated in 212 patients. Measurements were performed on T1-weighted FSE sequences in the sagittal plane, PD-weighted FSE FS sequences in the axial plane, and PD-weighted FSE FS sequences in the coronal plane. The slice thickness was 4 mm for all images. All measurements were conducted by a single evaluator.

Statistical Analysis: Data analysis was performed using IBM SPSS Statistics version 22.0. Categorical variables were expressed as frequencies and percentages. The normality of continuous variables was assessed using visual methods and Kolmogorov-Smirnov/Shapiro-Wilk tests. For normally distributed variables, comparisons between independent groups were made using Student's t-test or One-Way ANOVA. Continuous variables were presented as mean ± standard deviation (SD). A p-value of <0.05 was considered statistically significant.

RESULTS

The 212 cases included in the study were evaluated in terms of gender, right and left knee separation, and age groups. Of the 212 cases, 106 (50%) were female and 106 (50%) were male. The age groups of the cases were divided into Group 1: 18-34 years, Group 2: 35-49 years, and Group 3: 50-69 years. The numbers of males and females and their distributions by age groups are presented in the tables (Tables 1 and 2).

Table 1 compares the measurement values of the anatomical structures related to the knee joint between males and females. In the male group, MCW, LCW, BW, MCH, LCH, ICW, ICD, TSD, TSW, MFW, LFW, TPW, IEW, MTPD, MTPL, LTPL, PL, PW, PTL values were found to be statistically significantly higher than in the female group

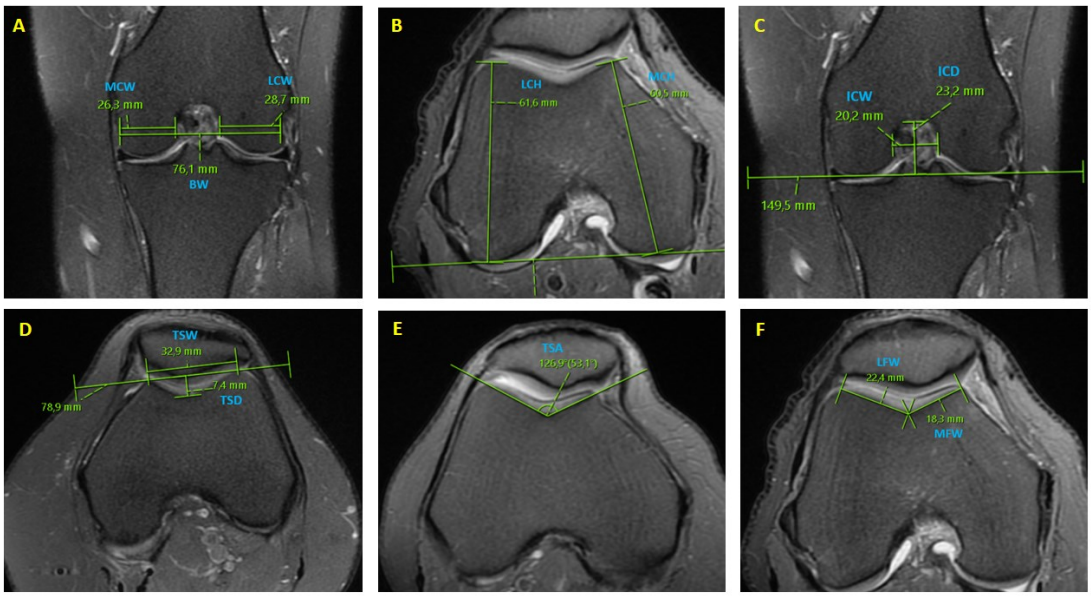

Figure 1. Parameters measured on the femur. A: In the coronal section of the left knee; The distance between the medial and lateral borders of the medial femoral condyle (MCW), and the distance between the medial and lateral borders of the lateral femoral condyle (LCW), and the distance between the medial border of the medial femoral condyle and the lateral border of the lateral femoral condyle (BW). B: In the axial section of the right knee; The greatest anteroposterior length of the lateral femoral condyle (LCH), and the greatest anteroposterior length of the medial femoral condyle (MCH). C: In the coronal section of the left knee; The distance between the medial border of the lateral femoral condyle and the lateral border of the medial femoral condyle (ICW), and the perpendicular distance from the apex of the intercondylar fossa to the line tangent to the lowest points of the femoral condyles (ICD). D: In the axial section of the left knee; the distance between the lateral and medial peaks of the patellar surface (TSW), and the length of the perpendicular dropped from the line passing through the lateral and medial summit points of the facies patellaris to the deepest point of the trochlear sulcus (TSD). E: In axial section of the right knee; The angle formed by the two lines connecting the deepest point of the trochlear sulcus to the highest points of the medial and lateral condyles (TSA). F: In the axial section of the right knee; Length of the lateral facet of the patellar surface of the femur (LFW), and Length of the medial facet of the patellar surface of the femur (MFW).

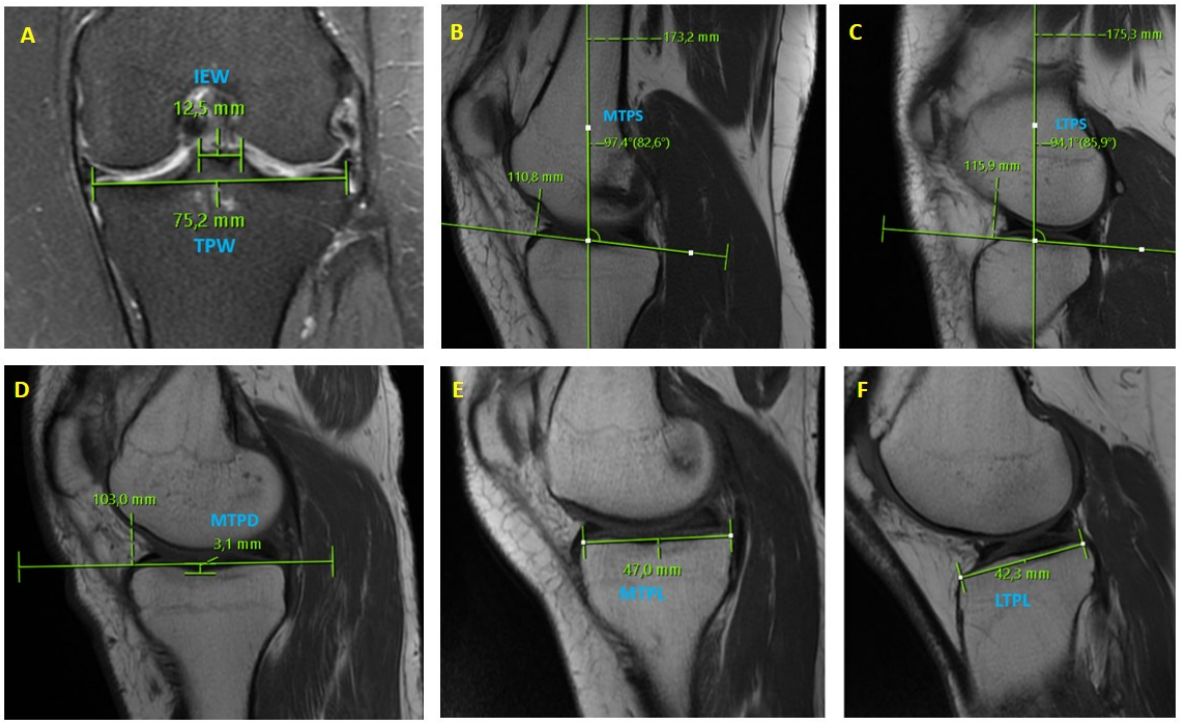

Figure 2. Measured parameters of the tibia. A: In the coronal section of the left knee; The length of the line drawn between the lateral and medial borders of the tibia, parallel to the superior surface of the tibial plateau (TPW), and the length between the highest points of the lateral intercondylar tubercle and the medial intercondylar tubercle (IEW). B: In the sagittal section of the left knee; The angle between the longitudinal line drawn equidistant from both cortices at the midline of the tibial shaft and the line connecting the anterior and posterior summit points of the medial tibial plateau (MTPS). C: In the sagittal section of the left knee; The angle between the longitudinal line drawn equidistant from both cortices at the midline of the tibial shaft and the line connecting the anterior and posterior points of the lateral tibial plateau (LTPS). D: In the sagittal section of the left knee; The length of the perpendicular dropped from the line connecting the anterior and posterior summit points of the medial tibial condyle to the deepest point of the medial condyle (MTPD). E: In the sagittal section of the right knee; The length of the line connecting the anterior and posterior summit points of the medial tibial condyle (MTPL). F: In the sagittal section of the right knee; The length of the line connecting the anterior and posterior summit points of the lateral tibial condyle (LTPL).

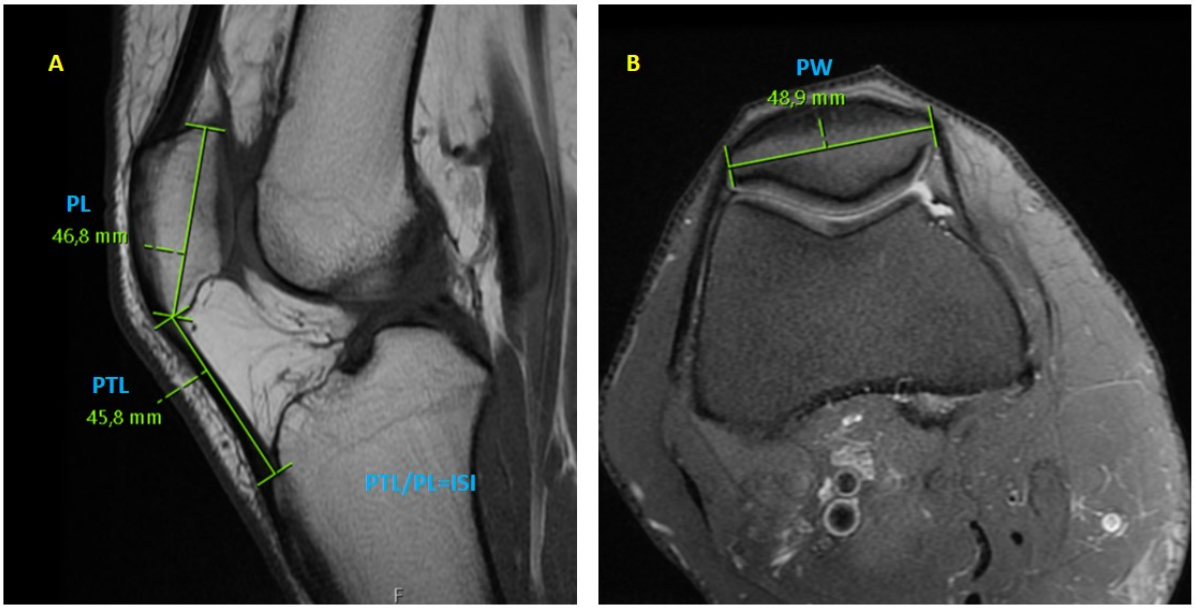

Figure 3. Measured parameters of the patella. A: In the sagittal section of the right knee; The maximum longitudinal length of the patella (PL), and the length of the patellar ligament (PTL), and the patellar ligament to patellar length ratio (ISI). B: In the axial section of the right knee; The maximum transverse width of the patella (PW).

Table 1 Comparison of morphological measurements between genders.

Parameters	Male (n=106) (Mean ± SD)	Female (n=106) (Mean ± SD)	p-value
MCW	26.61 ± 1.98	23.17 ± 1.82	**0.000**
LCW	28.92 ± 2.25	25.01 ± 2.17	**0.000**
BW	76.45 ± 4.02	66.56 ± 3.71	**0.000**
MCH	61.00 ± 4.27	54.25 ± 3.26	**0.000**
LCH	61.66 ± 4.14	55.14 ± 3.45	**0.000**
ICW	20.72 ± 2.14	18.16 ± 2.47	**0.000**
ICD	24.58 ± 2.60	21.85 ± 2.09	**0.000**
TSD	7.79 ± 1.31	6.81 ± 1.19	**0.000**
TSW	37.97 ± 2.70	33.57 ± 2.40	**0.000**
TSA(°)	128.28 ± 5.84	129.54 ± 7.02	0.155
LFW	23.33 ± 2.07	20.43 ± 1.80	**0.000**
MFW	17.07 ± 2.18	14.56 ± 1.57	**0.000**
TPW	77.51 ± 4.27	68.19 ± 3.40	**0.000**
IEW	13.11 ± 1.80	12.10 ± 1.74	**0.000**
MTPS (°)	4.82 ± 1.68	5.71 ± 2.17	**0.001**
LTPS (°)	3.60 ± 1.97	3.79 ± 2.26	0.510
MTPD	3.11 ± 0.81	2.56 ± 0.62	**0.000**
MTPL	48.80 ± 3.65	42.47 ± 2.72	**0.000**
LTPL	39.22 ± 3.84	34.21 ± 3.01	**0.000**
PL	44.02 ± 3.17	38.11 ± 2.69	**0.000**
PW	45.64 ± 3.59	39.21 ± 2.64	**0.000**
PTL	46.36 ± 5.42	42.96 ± 4.74	**0.000**
ISI	1.05 ± 0.14	1.13 ± 0.14	**0.000**

n: sample size; SD: Standard deviation; P-values ($p<0.05$) are highlighted in bold; MCW: Medial condylar width; LCW: Lateral condylar width; BW: Bicondylar width; MCH: Medial condyle height; LCH: Lateral condyle height; ICW: Intercondylar width; ICD: Intercondylar depth; TSD: Trochlear sulcus depth; TSW: Trochlear sulcus width; TSA: Trochlear sulcus angle; LFW: Lateral facet width; MFW: Medial facet width; TPW: Tibial plateau width; IEW: Intercondylar eminence width; MTPS: Medial tibial plateau slope; LTPS: Lateral tibial plateau slope; MTPD: Medial tibial plateau depth; MTPL: Medial tibial plateau length; LTPL: Lateral tibial plateau length; PL: Patellar length; PW: Patellar width; PTL: Patellar tendon length; ISI: Install Salvati Indeks.

($p < 0.05$). MTPS and ISI values were found to be statistically significantly lower in males than in females ($p < 0.05$).

Table 2 compares the measurement values of anatomical structures related to the knee joint in males and females of different age groups. The ICD value in Group 1 was significantly higher than in the other two groups. In males, the MFW value was found to be significantly lower in Group 1 compared to the other groups. TPW value was significantly higher in Group 3 than in Groups 1 and 2. In addition, the PTL and ISI values in Group 1 were found to be significantly higher than the other two groups ($p<0.05$). In females, the ICD value, PTL value and ISI value in Group 3 were found to be significantly lower than the other two groups, while the TPW value was found to be significantly higher than Groups 1 and 2 ($p <0.05$) (Table 2).

Table 2. Comparison of morphological measurements of male and female ındividuals according to age groups.

Parameters	Male (Mean ± SD)				Female (Mean ± SD)			
	Group 1 (Age: 18-34) (n=35)	Group 2 (Age: 35-49) (n=39)	Group 3 (Age: 50-69) (n=32)	p-value	Group 1 (Age: 18-34) (n=16)	Group 2 (Age: 35-49) (n=35)	Group 3 (Age: 50-69) (n=55)	p-value
MCW	26.5 ± 2.18	26.43 ± 2.02	27.11 ± 1.65	0.225	22.86 ± 1.45	22.76 ± 1.69	23.52 ± 1.94	0.115
LCW	28.52 ± 2.67	29.01 ± 2.02	29.26 ± 2.01	0.394	24.66 ± 1.99	25.21 ± 2.61	24.98 ± 1.93	0.703
BW	75.97 ± 4.17	76.14 ± 4.20	77.35 ± 3.57	0.316	66.59 ± 3.09	66.04 ± 3.49	66.88 ± 4.02	0.583
MCH	60.72 ± 4.69	60.40 ± 4.26	62.04 ± 3.73	0.249	54.75 ± 2.93	54.15 ± 3.31	54.18 ± 3.37	0.810
LCH	61.50 ± 4.99	61.36 ± 3.78	62.22 ± 3.59	0.663	55.28 ± 3.45	55.20 ± 3.21	55.05 ± 3.65	0.963
ICW	20.86 ± 1.85	20.61 ± 2.44	20.69 ± 2.09	0.874	18.87± 2.51	17.84 ± 2.42	18.15 ± 2.49	0.392
ICD	25.58 ± 2.72	24.21 ± 2.46	23.94 ± 2.38	**0.018**	22.95 ± 2.25	22.03 ± 2.10	21.42 ± 1.94	**0.029**
TSD	7.50 ± 1.14	7.92 ± 1.43	7.95 ± 1.30	0.273	7.01 ± 1.41	6.55 ± 1.31	6.93 ± 1.03	0.275
TSW	37.18 ± 2.51	38.06 ± 2.93	38.73 ± 2.44	0.061	32.02 ± 1.90	33.61 ± 1.71	33.99 ± 2.73	**0.014**
TSA (°)	129.2 ± 5.17	127.5 ± 6.42	128.0 ± 8.81	0.441	126.6 ± 6.69	131.3 ± 7.60	129.2 ± 6.50	0.075
LFW	23.06 ± 2.02	23.31 ± 2.24	23.65 ± 1.94	0.520	20.21 ± 1.76	20.21 ± 1.60	20.64 ± 1.94	0.487
MFW	16.20 ± 2.25	17.37 ± 1.87	17.65 ± 2.23	**0.012**	13.99 ± 1.37	14.36 ± 1.52	14.86 ± 1.61	0.099
TPW	76.56 ± 3.84	76.96 ± 4.38	79.23 ± 4.19	**0.021**	66.77 ± 2.48	67.70 ± 3.14	68.91 ± 3.65	**0.049**
IEW	12.98 ± 1.87	13.18 ± 1.91	13.16 ± 1.63	0.876	11.93 ± 1.67	12.16 ± 1.63	12.11 ± 1.86	0.907
MTPS (°)	5.09 ± 1.65	4.57 ± 1.74	4.84 ± 1.66	0.432	5.14 ± 2.04	5.73 ± 2.58	5.88 ± 1.92	0.493
LTPS (°)	4.17 ± 1.84	3.41 ± 2.05	3.21 ± 1.90	0.101	3.60 ± 1.69	4.26 ± 2.93	3.55 ± 1.88	0.331
MTPD	3.02 ± 0.67	3.22 ± 0.95	3.09 ± 0.78	0.571	2.71 ± 0.74	2.64 ± 0.59	2.46 ± 0.59	0.248
MTPL	48.32 ± 3.62	48.51 ± 4.01	49.70 ± 3.16	0.250	41.96 ± 3.39	42.29 ± 2.41	42.73 ± 2.71	0.548
LTPL	39.16 ± 3.90	38.39 ± 3.49	40.30 ± 4.03	0.113	34.18 ± 2.70	34.32 ± 2.55	34.14 ± 3.37	0.961
PL	43.53 ± 3.34	44.05 ± 2.77	44.53 ± 3.45	0.442	37.87 ± 2.58	37.97 ± 1.99	38.27 ± 3.10	0.813
PW	45.61 ± 3.29	45.37 ± 4.29	45.99 ± 2.99	0.774	38.88 ± 2.07	39.27 ± 2.32	39.26 ± 2.99	0.866
PTL	48.11 ± 3.93	45.30 ± 5.87	45.73 ± 5.91	**0.040**	45.12 ± 5.70	43.76 ± 3.95	41.83 ± 4.66	**0.023**
ISI	1.11 ± 0.12	1.03 ± 0.13	1.03 ± 0.17	**0.030**	1.19 ± 0.19	1.15 ± 0.12	1.09 ± 0.13	**0.029**

n: sample size; SD: Standard deviation; P-values ($p<0.05$) are highlighted in bold; MCW: Medial condylar width; LCW: Lateral condylar width; BW: Bicondylar width; MCH: Medial condyle height; LCH: Lateral condyle height; ICW: Intercondylar width; ICD: Intercondylar depth; TSD: Trochlear sulcus depth; TSW: Trochlear sulcus width; TSA: Trochlear sulcus angle; LFW: Lateral facet width; MFW: Medial facet width; TPW: Tibial plateau width; IEW: Intercondylar eminence width; MTPS: Medial tibial plateau slope; LTPS: Lateral tibial plateau slope; MTPD: Medial tibial plateau depth; MTPL: Medial tibial plateau length; LTPL: Lateral tibial plateau length; PL: Patellar length; PW: Patellar width; PTL: Patellar tendon length; ISI: Install Salvati Indeks.

DISCUSSION AND CONCLUSION

Numerous studies have investigated the complex morphology of the knee joint using various imaging modalities.[4-6] However, due to the clinical importance of this region, the continuous evolution of surgical techniques, and ongoing debates regarding the appropriateness of standard implants across different age and gender groups, this study aimed to examine knee joint morphology in relation to age and gender.

This study is notable for its sample size and methodological comprehensiveness. A total of 212 cases (106 males, 106 females) aged between 18 and 69 years were divided into three age groups, and 23 morphometric parameters of the distal femur, proximal tibia, and patella were assessed.

Regarding distal femur morphology, values such as MCW, LCW, BW, MCH, and LCH were significantly greater in males ($p<0.05$), consistent with findings by Sharma et al.,[4] who also reported larger femoral condyles in males based on MRI data. Similar outcomes were reported in studies using CT, X-ray, and dry bone analysis, highlighting consistent sex-based anatomical differences.[5,6]

Measurement techniques and reference points vary across morphometric studies, which are often based on dry bones, radiographs, CT, MRI, cadaveric studies, or 3D modelling.[7] Ethnic variation is also a prominent factor. For instance, Prithishkumar et al.[8] found that knee dimensions differ significantly across ethnic groups, and Kwak et al.[9] reported larger measurements in Western populations compared to Asians. These findings support the notion that ethnic differences influence knee anatomy, which should be considered in prosthesis design.

The intercondylar fossa, a region closely associated with anterior cruciate ligament injuries, was evaluated in our study via ICW and ICD measurements. Both values were significantly higher in males ($p<0.05$), corroborating findings from similar studies.[6,10]

The trochlear sulcus plays a key role in patellofemoral stability. In our study, TSD, TSW, LFW, and MFW were significantly higher in males, whereas TSA showed no significant gender difference despite being higher in females. These findings are consistent with those of Günaydın and Duran,[11] Hsu et al.,[12] and Hasler et al.,[13] who also reported sex-based differences in trochlear morphology.

Morphometric parameters of the proximal tibia, such as TPW, IEW, MTPD, MTPL, and LTPL, were significantly greater in males ($p<0.05$), while MTPS was higher in females. These findings align with studies by Sharma et al.,[4] Yue et al.,[6] and Yanagisawa et al.,[14] all of whom observed larger tibial measurements in males. Research also links increased tibial slope with ACL injuries. Kodama et al.[15] demonstrated that higher MTPS values correlate with increased rates of ACL degeneration and medial meniscus root tears. Weinberg et al.[16] found that MTPS exceeds LTPS, and both values are generally greater in females, which was partially supported by our findings.

Patellar and patellar ligament morphometry (PL, PW, PTL, and ISI) revealed that PL, PW, and PTL were significantly greater in males, while ISI was higher in females ($p<0.05$). These results are supported by multiple studies, including those by Nguyen et al.,[17] Meier et al.,[18] Le Hoang et al.,[19] and Hong et al.,[20] which showed similar gender-based patterns in patellar measurements and ISI values.

Our study is limited by its focus on a single ethnic group (Turkish individuals), which may restrict generalizability. Ethnic differences in patellar dimensions have been demonstrated by Pontoh et al.[21] and Jain et al.,[22] who reported smaller patellae in Asian populations compared to Western populations.

In terms of age, ICD, ISI, and PTL values were significantly higher in younger adults in both sexes, while TPW was significantly greater in older adults ($p<0.05$). Other parameters showed no significant age-related variation. While previous studies have explored these measurements by gender and ethnicity, age-related differences remain less frequently addressed, making this aspect of our study a noteworthy contribution.

In conclusion, along with those of comparable studies, indicate that knee joint anatomy varies significantly with ethnicity, age, and gender. Understanding the morphometric characteristics of knee bone structures is crucial for prosthesis design, especially given that total knee arthroplasty is performed across all age groups for various indications. It has been reported that most commercially available prostheses are based on Western anatomical data and may not be suitable for many Asian populations. In the current era of personalized arthroplasty, the appropriateness of standard implant designs in relation to age and gender remains a subject of ongoing debate. In this context, we believe that knee prosthesis design should take into account gender, age, and ethnic anatomical differences. This study has certain limitations. First, the data were derived solely from individuals of Turkish ethnicity, limiting generalizability. Second, all measurements were based on MRI, as CT images were not available for most patients. While MRI offers high-resolution soft tissue imaging, CT is generally preferred for detailed bone structure evaluation. A comparative analysis using both modalities on the same joints would provide more comprehensive insights. Lastly, due to the retrospective nature of the study, patient-specific data such as dominant side, height, and weight could not be collected. The potential influence of these variables, particularly the height and weight of the morp-

hometric parameters, should be explored in future research.

Ethics Committee Approval: Our study was approved by Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (Date: 18.01.2024, decision no: 2024/01). The study was conducted following international declarations, guidelines, etc.
Conflict of Interest: No conflict of interest was declared by the authors.
Author Contributions: Concept – BÇ, MAG; Supervision – BÇ, MAG, ŞAB; Materials – MAG, ŞAB; Data Collection and/or Processing – BÇ; Analysis and/or Interpretation – BÇ, MAG, ŞAB; Writing – BÇ, MAG.
Peer-review: Externally peer-reviewed.
Other Information: PhD Thesis production

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):193-199 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):193-199*

Apoptotic and Antiproliferative Effects of *Ajuga reptans* L. Ethanol Extract via Inhibition of NF-κB and eNOS Activity in HCT116 Colon Cancer Cells

Ajuga reptans L. Etanol Özütünün HCT116 Kolon Kanseri Hücrelerinde NF-κB ve eNOS Aktivitesinin Inhibisyonu Yoluyla Apoptotik ve Antiproliferatif Etkileri

[1]Ilker KILICCIOGLU, [1]Gorkem DULGER, [2]Basaran DULGER

[1]Department of Medical Biology, Faculty of Medicine, Duzce University, 81620, Konuralp/Duzce, Türkiye
[2]Department of Biology, Faculty of Science and Arts, Duzce University, 81620, Konuralp/Duzce, Türkiye

Ilker Kiliccioglu: https://orcid.org/0000-0003-3367-9665
Gorkem Dulger: https://orcid.org/0000-0002-1506-1549
Basaran Dulger: https://orcid.org/0000-0002-3184-2652

ABSTRACT

Objective: This study aimed to investigate the ethanol extract of *Ajuga reptans* L. (Lamiaceae) on cell proliferation, apoptotic response, expression levels of Caspase-3, NF-κB and eNOS proteins on HCT116 human colorectal carcinoma cells.

Materials and Methods: *A. reptans* was extracted using a Soxhlet apparatus with ethanol, and the obtained extract was applied to HCT116 and HUVEC cells (as healthy controls) in increasing concentrations (0–800 µg/mL). Cell viability was analysed by the WST-1 assay at 24 h and 48 h. Morphological changes were observed via inverted microscopy. ELISA was performed to quantify Caspase-3, NF-κB, and eNOS protein levels.

Results: *A. reptans* ethanol extract showed concentration and duration-dependent cytotoxic effects on HCT116 cells, with IC_{50} values of 206.9 µg/mL (24 h) and 147.5 µg/mL (48 h). Minimal cytotoxicity was observed in HUVEC cells. Microscopy confirmed morphological signs of apoptosis in HCT116 cells. ELISA results demonstrated increased Caspase-3 and decreased NF-κB and eNOS levels, indicating induction of apoptosis and suppression of pro-survival pathways.

Conclusions: The ethanol extract of *Ajuga reptans* selectively inhibited the proliferation of colorectal cancer cells by apoptotic induction and modulation of NF-κB and eNOS signaling, suggesting its potential as a plant-based adjunctive agent in colorectal cancer therapy.

Keywords: *Ajuga reptans*, caspase-3, colon cancer, eNOS, NF-κB

ÖZ

Amaç: Bu çalışmanın amacı, *Ajuga reptans* L. (Lamiaceae) etanol ekstraktının, HCT116 insan kolorektal karsinom hücrelerinde hücre proliferasyonu, apoptotik yanıt, Kaspaz-3, NF-κB ve eNOS proteinlerinin ifade düzeyleri üzerine etkilerini araştırmaktır.

Materyal ve Metot: *A. reptans* bitkisi Soxhlet cihazı kullanılarak etanol ile ekstrakte edilmiştir. Elde edilen ekstrakt, HCT116 ve HUVEC (sağlıklı kontrol) hücrelerine artan konsantrasyonlarda (0–800 µg/mL) uygulanmıştır. Hücre canlılığı, WST-1 testi ile 24 ve 48 saatlik sürelerde değerlendirilmiştir. Morfolojik değişiklikler inverted mikroskopi ile incelenmiştir. Kaspaz-3, NF-κB ve eNOS protein düzeylerinin kantifikasyonu için ELISA analizi uygulanmıştır.

Bulgular: *A. reptans* ekstraktı, HCT116 hücrelerinde konsantrasyona ve süreye bağımlı sitotoksik etki göstermiştir; IC_{50} değerleri sırasıyla 24 saatte 206.9 µg/mL, 48 saatte 147.5 µg/mL olarak hesaplanmıştır. HUVEC hücrelerinde minimum düzeyde sitotoksisite gözlenmiştir. Mikroskobik incelemeler, HCT116 hücrelerinde apoptozu düşündüren morfolojik değişiklikleri doğrulamıştır. ELISA analizleri, Caspase-3 düzeylerinde artış ve NF-κB ile eNOS düzeylerinde azalma göstermiştir.

Sonuç: *Ajuga reptans*'ın etanolik ekstraktı, kolorektal kanser hücrelerinde seçici proliferasyon baskılanması, apoptoz indüksiyonu ve NF-κB ile eNOS sinyallerinin modülasyonu yoluyla antikanser etki göstermiştir. Bu bulgular, ekstraktın kolorektal kanser tedavisinde bitki kaynaklı tamamlayıcı bir ajan olarak potansiyelini ortaya koymaktadır.

Anahtar Kelimeler: Ajuga reptans, eNOS, kaspaz-3, kolon kanseri, NF-κB

Sorumlu Yazar / Corresponding Author:
Ilker Kiliccioglu
Department of Medical Biology, Faculty of Medicine, Duzce University, Konuralp Campus, 81620 Duzce - Türkiye
Tel.: 05376518429
E-mail: ilkerkiliccioglu@duzce.edu.tr

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 28/04/2025
Kabul Tarihi/ Accepted: 16/06/2025
Online Yayın Tarihi/ Published: 30/06/2025

Atıf / Cited: Kiliccioglu İ and et al. Apoptotic and Antiproliferative Effects of Ajuga reptans L. Ethanol Extract via Inhibition of NF-κB and eNOS Activity in HCT116 Colon Cancer Cells. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2):193-199. doi: 10.26453/otjhs.1685503

INTRODUCTION

Phytochemicals have been shown to exhibit anticancer effects by modulating molecular pathways involved in cell cycle modulation, apoptosis, inflammation, and angiogenesis.[1,2] *Ajuga reptans* L. is a perennial plant belonging to the Lamiaceae family, and is broadly spread across Europe and Asia. Traditionally used for its anti-inflammatory, antioxidant, hepatoprotective, and wound-healing properties, recent studies have begun to explore its potential anticancer activities.[3,4]

Phytochemical analyses have identified several secondary metabolites in *A. reptans*, including important phenolic compounds, which are known for their biological activities.[5,6] These constituents are hypothesized to regulate various cellular targets and pathways associated with cancer development and progression.

Among the key molecular players implicated in colon cancer pathogenesis are nuclear factor kappa B (NF-κB) and endothelial nitric oxide synthase (eNOS). NF-κB is an important transcription factor that modulates proteins involved in inflammatory and apoptotic pathways. Its abnormal activation has been commonly detected in colon cancer and is associated with chemoresistance and poor prognosis.[7] Similarly, eNOS, which catalyzes the production of nitric oxide (NO), plays a dual role in cancer, but its overexpression has been linked to enhanced tumor angiogenesis and metastatic potential in colorectal tumors.[8]

In this study, we aimed to observe the anticancer potential of ethanol extract of *A. reptans* on HCT116 human colorectal carcinoma cells. Specifically, we assessed its effects on cell proliferation, apoptotic response, and modulation of NF-κB and eNOS expression levels. To our knowledge, this is the first study to systematically investigate the cellular processes underlying the effects of *A. reptans* on colon cancer cells, highlighting its potential as a novel phytotherapeutic agent.

MATERIALS AND METHODS

Ethics Committee Approval: This study was conducted using commercial cell culture. Approval from an ethics committee is not necessary.

Ethanol Extraction of Ajuga reptans: The aerial parts of the plant were collected in April 2024 from the campus area of Duzce University, Türkiye (Voucher number: GD 06-04-24; 40º54'25"N, 31º11'5"E) alt. 248 m). For the extraction procedure, 20 g of the powdered plant material was macerated in 200 mL of ethanol (Merck) in a Soxhlet extractor (Termal Lab, Istanbul, Türkiye) for 12 h. After the extracts were passed through Whatman filter No. 1, the ethanol was removed with a rotary evaporator at 55°C. The dried extracts obtained were dissolved in dimethyl sulfoxide to a final concentration of 100 mg/mL.

Cell Culture: HCT116 colon cancer cells and HUVEC (human umbilical vein endothelial cells) were used in this study. HCT116 is a human colorectal carcinoma cell line derived from the colon tissue of a male patient. These cells exhibit microsatellite instability and carry a mutant KRAS allele while retaining the wild-type p53 gene. HCT116 cells are adherent and grow as an epithelial monolayer with relatively high proliferation rates. Due to their sensitivity to various chemotherapeutic agents, HCT116 cells serve as an important model for evaluating cytotoxicity, apoptosis, cell cycle, and signaling pathways in colorectal cancer studies. Cells were cultured in RPMI-1640 and DMEM mediums (Capricorn Scientific, Germany) supplemented with heat inactivated 10% fetal bovine serum, 200 mM L-glutamine, 100 U/mL penicillin, and 100 mg/mL streptomycin (Capricorn Scientific, Germany) in a humidified incubator (Nuve, Ankara, Türkiye) at 37ºC with 5% CO_2.

Cell Viability Assay: The effect of *A. reptans* ethanol extract on cell viability was analyzed using the WST-1 cell proliferation assay kit (Abcam, Cambridge, UK) according to the manufacturer's instructions. HCT116 and HUVEC cells were seeded in 96-well plates at a density of 5×10^3 cells per well and incubated for 24 h to allow cell attachment. Cells were then treated with various concentrations of the extract (0, 100, 200, 400, 600, and 800 µg/mL) for 24 and 48 h. After treatment, 10 µL WST-1 reagent was added to each well and incubated for 2 hours. Absorbance was measured at 450 nm using a microplate reader (Allsheng Instruments, Hangzhou, China). Each experiment was performed in three independent replicates.

Morphological Evaluation: To evaluate morphological changes, both HCT116 and HUVEC cells were seeded in 6-well plates at 3×10^5 cells/well and treated with the ethanol extract at 100, 200 and 400 µg/mL concentrations. After 24 h of treatment, morphological alterations were visualised with an inverted microscope (Euromex, Arnhem, Netherlands) equipped with a CMEX-5 Pro camera at 20x magnification (Olympus CKX53).

Protein Isolation and ELISA Assay: Following treatment with the extract, total protein was isolated from HCT116 cells using RIPA lysis buffer (A.B.T, Ankara, Türkiye). Protein concentrations were quantified using the bicinchoninic acid (BCA) assay (ABP Biosciences, USA). The expression levels of Caspase-3, eNOS and NF-κB were measured using human-specific ELISA kits (BT LAB, Shanghai, China and ELK Biotechnology CO., Ltd, Denver,

USA), following the manufacturers' protocols. Optical densities were read at 450 nm on an ELISA reader (Allsheng Instruments, Hangzhou, China). Each experiment was performed in three independent replicates.

***Statistical Analysis**:* GraphPad Prism 9.0 was used to perform the statistical analysis. Statistical significance was determined using one-way ANOVA and two-way ANOVA, followed by Dunnett's post-hoc test. A significance level of $p<0.05$ was accepted as significant.

RESULTS

Figure 1A shows that the ethanol extract of *A. reptans* exhibited a dose-dependent antiproliferative effect with an IC_{50} value of 206.9 µg/mL for 24 h. Cell proliferation decreased significantly as the concentration of the extract increased, indicating strong cytotoxic activity in the applied dose range. The IC_{50} value was 147.5 µg/mL for 48 h (Figure 1B). This result indicated that the anticancer activity of the extract increased with the incubation time.

As shown in Figure 2, *A. reptans* ethanol extract significantly reduced cell viability in a dose and time -dependent profile. Cell proliferation decreased by up to 22% for increasing concentrations at 24 h. This antiproliferative effect was more pronounced at 48 h. Above 200 µg/mL, the proliferation inhibition of HCT116 cells exceeded 50%. These data highlighted that the inhibitory effect of *A. reptans* on the proliferation of HCT116 colon cancer cells was concentration and exposure time-dependent.

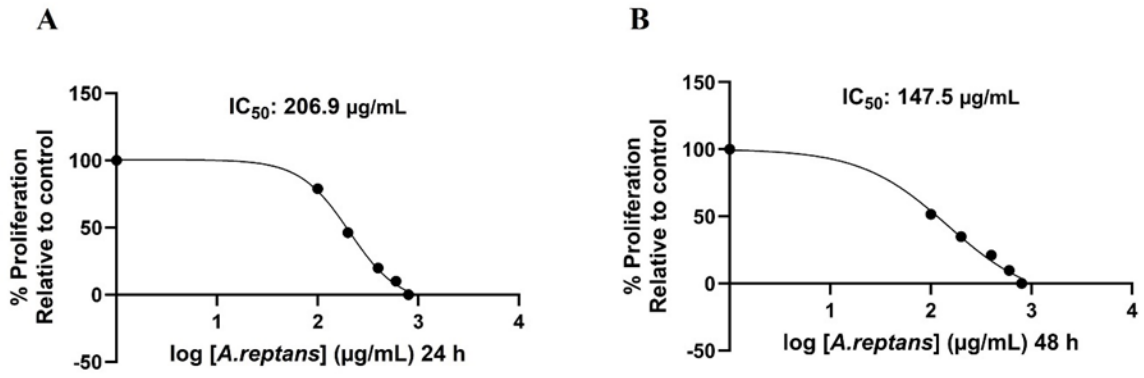

Figure 1. Antiproliferative effect curves of *A. reptans* ethanol extract on HCT116 colon cancer cells. A: Antiproliferative effect for 24 h; B: Antiproliferative effect for 48 h.

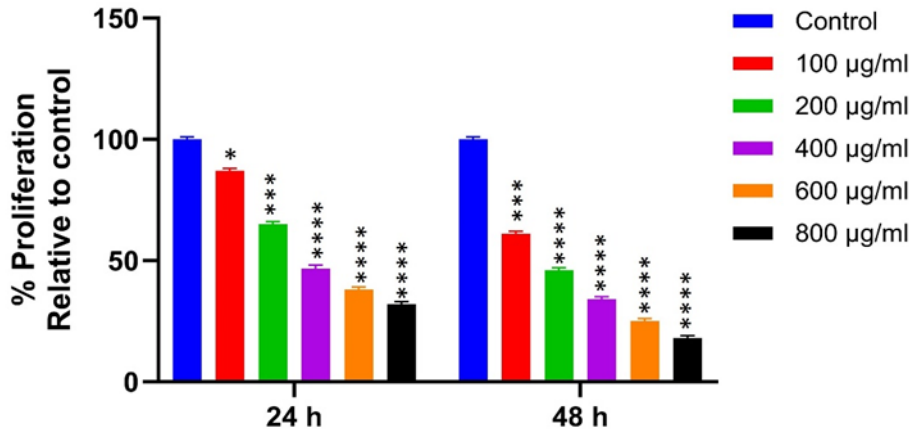

Figure 2. The antiproliferative effect of *A. reptans* ethanol extract on HCT116 colon cancer cells for 24 h and 48 h. *: $p<0.05$; ***: $p<0.001$; ****: $p<0.0001$.

To evaluate the selectivity of the extract towards cancer cells, concentrations were applied to HUVEC cells. As shown in Figure 3, *A. reptans* showed relatively low cytotoxicity in HUVEC cells. Only slight decreases in proliferation were observed at higher concentrations (600 and 800 µg/mL) at 48 h. These results indicate that the toxicity of *A. reptans* extract towards healthy cells is quite low.

Microscopic examination revealed distinct morphological changes in HCT116 cells after treatment with 100, 200, and 400 µg/mL of *A. reptans* ethanol extract for 24 h (Figure 4). Treated cancer cells appeared shrunken with condensed cytoplasm and membrane blebbing, which are hallmarks of apoptotic cell death. In contrast, HUVEC cells largely retained their normal spindle-like morphology, and minimal morphological changes were observed even at higher extract concentrations, further supporting selective toxicity against cancer cells.

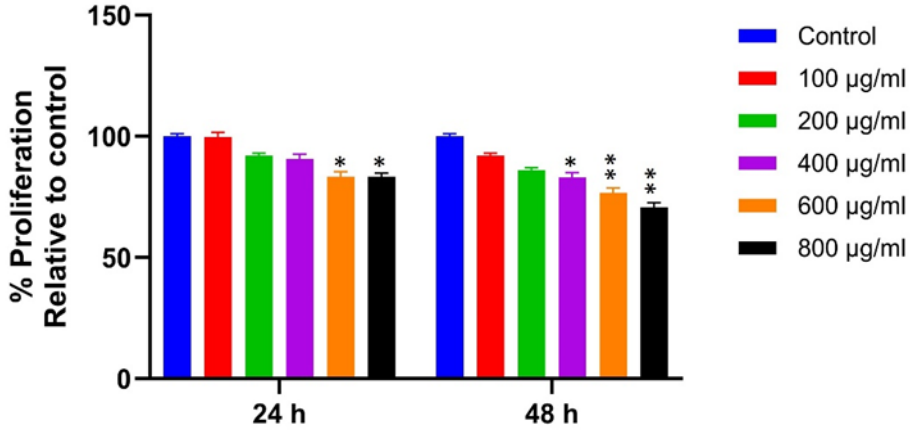

Figure 3. The minimal cytotoxicity level of *A. reptans* ethanol extract on HUVEC cells. *: p<0.05; **: p<0.01.

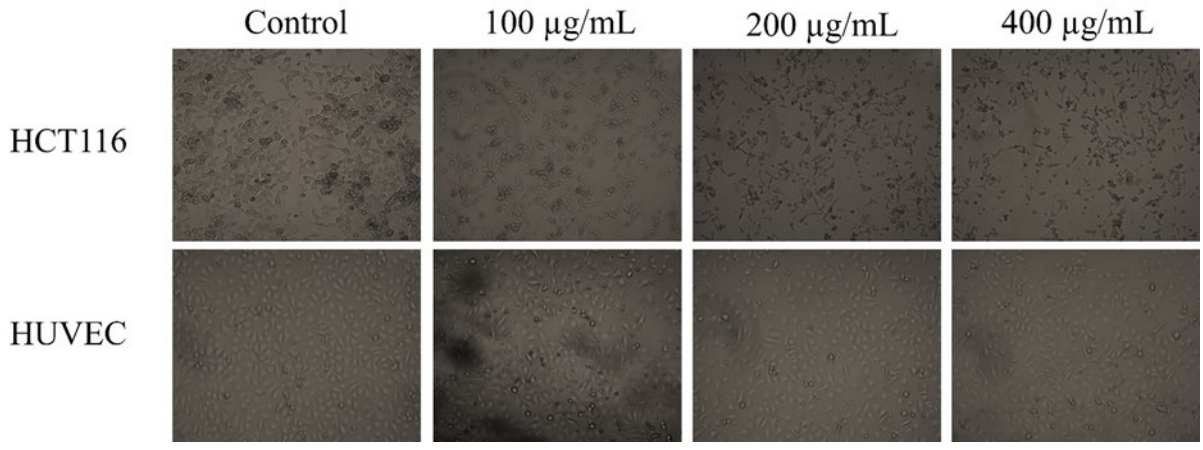

Figure 4. Inverted microscope examination of morphological changes in HCT116 and HUVEC cells upon *A. reptans* treatment.

A. reptans ethanol extract significantly increased the expression of Caspase-3 at 200 and 400 µg/mL, indicating induction of apoptosis. In addition, NF-κB and eNOS levels were significantly down-regulated compared to control ($p < 0.01$ to $p < 0.001$), indicating inhibition of pro-survival and inflammatory pathways (Figure 5). These results suggest that A. reptans induces apoptosis in colorectal cancer cells via caspase activation and regulation of NF-κB and eNOS signaling.

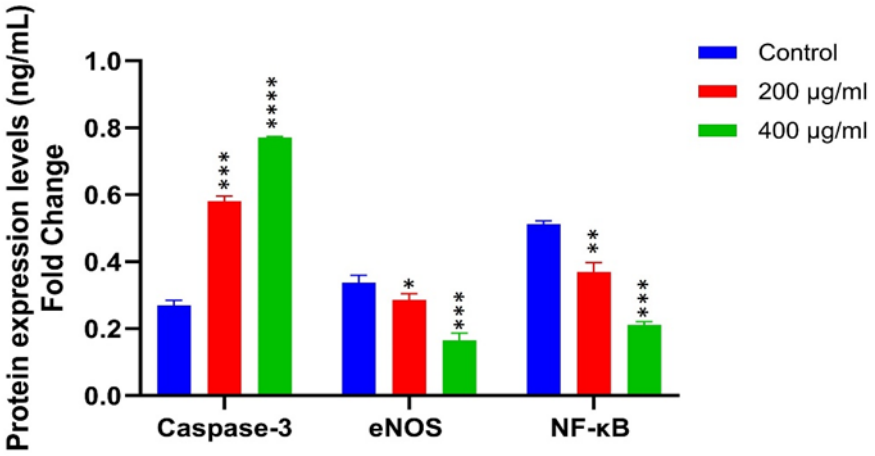

Figure 5. Effect of *A. reptans* ethanol extract on the expression levels of Caspase-3, eNOS and NF-κB proteins in HCT116 colon cancer cells. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; ****: $p<0.0001$.

DISCUSSION AND CONCLUSION

The present study provides novel insights into the anticancer potential of *Ajuga reptans* ethanol extract on HCT116 human colorectal carcinoma cells, highlighting its selective cytotoxicity, time and dose-dependent antiproliferative activity, and its ability to regulate apoptotic and inflammatory pathways. These findings provide important evidence to support the therapeutic potential of plant-derived compounds in the treatment of colorectal cancer.[9,10]

Our dose-response analyses revealed that *A. reptans* extract significantly inhibited the proliferation of HCT116 cells, with an IC_{50} value of 206.9 µg/mL at 24 h, which decreased to 147.5 µg/mL at 48 h. The reduction in IC_{50} over time reflects an enhanced cytotoxic efficacy with prolonged exposure. These results are in agreement with previous studies reporting the cytotoxic potential of *A. reptans* and other *Ajuga* species on various cancer cell lines. *A. reptans* extracts showed cytotoxic effects on prostate cancer cell lines by inhibiting cell proliferation and inducing apoptosis at concentrations of 300 µM and 500 µM, respectively. Similarly, methanolic and water extracts of *A. orientalis* showed moderate cytotoxic activity against various cancer cell lines. These findings suggest a broad-spectrum anticancer potential in the *Ajuga* genus.[11]

Importantly, when tested on HUVEC cells, *A. reptans* ethanol extract showed minimal cytotoxicity, even at higher concentrations (600–800 µg/mL). This selectivity toward cancer cells while sparing normal cells is crucial for the development of safer chemotherapeutic agents. Morphological analysis under inverted microscopy further supported the cytotoxic findings. These observations support that *A. reptans* induces cell death via apoptotic mechanisms rather than necrosis, minimizing the inflammatory response.

Caspase-3 is a key executioner protease in the apoptotic cascade, responsible for cleavage of structural and regulatory cellular proteins.[12] Its activation is widely regarded as a hallmark of apoptosis, and its induction by *A. reptans* suggests that the extract facilitates intrinsic apoptotic signaling. In addition, NF-κB levels were significantly reduced following extract treatment. NF-κB is a transcription factor that regulates genes involved in cell survival, proliferation, and inflammation. Its constitutive activation has been linked to tumorigenesis, metastasis, and chemoresistance in colorectal cancer.[13] Inhibiting NF-κB can sensitize cancer cells to apoptosis and disrupt their proliferative advantage.[14] Therefore, the downregulation of NF-κB by *A. reptans* may partly explain the enhanced apoptosis and reduced proliferation observed.

Similarly, the downregulation of endothelial nitric oxide synthase (eNOS) further supports the anti-tumor effects of the extract. eNOS can support tu-

mor growth by promoting angiogenesis and tumor blood supply under pathological conditions.[15] Reduced eNOS expression may contribute to an anti-angiogenic effect, thereby limiting tumor progression. These results suggest that *A. reptans* interferes not only with tumor cell survival and proliferation but also with their microenvironmental support systems.

Phytochemical constituents potentially responsible for these effects include phytoecdysteroids, iridoid glycosides, flavonoids, and diterpenes, all of which have been reported in the *Ajuga* genus.[6,16] For instance, 20-hydroxyecdysone, a major ecdysteroid in *A. reptans*, has been shown to modulate signaling pathways associated with apoptosis and inflammation.[17-19] However, future studies involving chromatographic isolation and compound-specific testing are necessary to identify and characterize the bioactive principles responsible for the observed effects.

In conclusion, these findings suggest that *A. reptans* ethanol extract exerts its anticancer effects through a multi-faceted mechanism involving the induction of apoptosis, suppression of inflammatory signaling, and selective cytotoxicity. Our results showed that this plant has significant potential as a complement to conventional treatments. Further studies, including in vivo validation, pharmacokinetic profiling, and target identification, are warranted to advance *A. reptans* as a candidate for colorectal cancer therapy.

Ethics Committee Approval: This study was conducted using commercial cell culture. Approval from an ethics committee is not necessary.

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

Author Contributions: Concept – IK, GD; Supervision – BD; Materials – IK, GD; Data Collection and/or Processing – BD; Analysis and/or Interpretation – IK; Writing –IK, GD.

Peer-review: Externally peer-reviewed.

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OTJHS
Online Turkish Journal of Health Sciences

e-ISSN: 2459-1467

OTSBD
Online Türk Sağlık Bilimleri Dergisi

Online Turkish Journal of Health Sciences 2025;10(2):200-202 *Online Türk Sağlık Bilimleri Dergisi 2025;10(2):200-202*

Letter to Editor for The Diagnostic Value of Neutrophil/Lymphocyte Ratio in Distinguishing Peripheral and Central Vertigo in Patients with Dizziness

Editöre Mektup: Baş Dönmesi Olan Hastalarda Periferik ve Santral Vertigonun Ayırt Edilmesinde Nötrofil/Lenfosit Oranının Tanısal Değeri

[1]Nedim UZUN

[1]Department of Emergency Medicine, Gaziosmanpaşa Education and Research Hospital, Istanbul, Türkiye

Nedim Uzun: https://orcid.org/0000-0001-9593-5869

ABSTRACT
The study titled "Diagnostic Value of Neutrophil/Lymphocyte Ratio in Distinguishing Peripheral and Central Vertigo in Patients with Dizziness" explores the utility of the neutrophil-to-lymphocyte ratio (NLR) as a diagnostic marker for differentiating central and peripheral vertigo. Findings reveal that NLR is significantly higher in central vertigo cases (median: 3.99 vs. 2.32; p<0.001), with a proposed cut-off value of 3.25. The retrospective study, involving 260 patients, highlights NLR's potential as a cost-effective, rapid diagnostic tool in emergency settings. However, its retrospective design and the need for validation across diverse populations suggest the necessity for further prospective research to confirm diagnostic accuracy and explore underlying mechanisms.
Keywords: Emergency department, differential diagnosis, dizziness, neutrophil/lymphocyte ratio, vertigo

ÖZ
"Baş Dönmesi Olan Hastalarda Periferik ve Santral Vertigonun Ayırt Edilmesinde Nötrofil/Lenfosit Oranının Tanı Değeri" başlıklı çalışma, nötrofil-lenfosit oranının (NLR) santral ve periferik vertigoyu ayırt etmede tanısal bir belirteç olarak kullanılabilirliğini araştırıyor. Bulgular, santral vertigo vakalarında NLR'nin anlamlı derecede daha yüksek olduğunu (medyan: 3,99 vs. 2,32; p<0,001) ve 3,25'lik bir eşik değer önerildiğini gösteriyor. Retrospektif bir çalışma olan bu araştırma, 260 hastayı kapsıyor ve NLR'nin acil durumlarda hızlı, ucuz bir tanı aracı olarak potansiyelini vurguluyor. Ancak, retrospektif tasarımı ve farklı popülasyonlarda doğrulanma ihtiyacı, tanısal doğruluğun teyit edilmesi ve altta yatan mekanizmaların araştırılması için ileri prospektif çalışmaların gerekliliğine işaret ediyor.
Anahtar Kelimeler: Acil servis, ayırıcı tanı, baş dönmesi, nötrofil/lenfosit oranı, vertigo

Sorumlu Yazar / Corresponding Author:
Nedim Uzun
Department of Emergency Medicine, Gaziosmanpaşa Education and Research Hospital, Istanbul, Türkiye
Tel.: +90 505 632 22 97
E-mail: nedimuzun@gmail.com

Yayın Bilgisi / Article Info:
Gönderi Tarihi/ Received: 12/03/2025
Kabul Tarihi/ Accepted: 21/04/2025
Online Yayın Tarihi/ Published: 30/12/2025

Atıf/ Cited: Onur B and et al. The Inflammatory Response in Geriatric Patients. *Online Türk Sağlık Bilimleri Dergisi* 2025;10(2).200-202. doi: 10.26453/otjhs.1656078

Dear Editor,

I read with great pleasure the article titled "Diagnostic Value of Neutrophil/Lymphocyte Ratio in Distinguishing Peripheral and Central Vertigo in Patients with Dizziness" published in your journal, Online Turkish Journal of Health Sciences.[1] I am writing to share my thoughts on this article. The study stands out as an important investigation into the diagnostic value of the neutrophil/lymphocyte ratio (NLR) in differentiating peripheral and central vertigo in patients presenting to the emergency department with dizziness symptoms. The methodology, findings, and conclusions of the study provide valuable insights into the use of NLR in clinical practice.

Strengths of the Study: The article makes a significant contribution to clinical practice by demonstrating that NLR can be used to differentiate between central and peripheral vertigo in patients presenting to the emergency department with dizziness. NLR, being an easily obtainable and low-cost parameter, can be a useful tool in settings requiring rapid decision-making, such as the emergency department. Retrospective Design and Large Sample Size: The study features a retrospective design encompassing 260 patients. This large sample size enhances the statistical power of the findings and supports the generalizability of the results. Additionally, the comparison of demographic characteristics such as age, gender, and comorbidities between central and peripheral vertigo groups demonstrates the comprehensive nature of the analysis.[1] Diagnostic Value of NLR: The study reveals that NLR is significantly higher in patients with central vertigo. This finding suggests that NLR can be used in the diagnosis of central vertigo and may support the need for neuro-

logical imaging in these patients. This could provide a significant advantage in the rapid diagnosis and treatment processes in emergency departments.[3]

The literature on the role of inflammatory markers such as NLR in clinical diagnosis and prognosis has accumulated significantly in recent years. In this context, there are studies examining the diagnostic and prognostic value of inflammatory indices in various clinical scenarios, including vertigo, testicular torsion, acute aortic dissection, incarcerated hernia, acute cholecystitis, and multiple sclerosis. Ethics committee approval is not required for a letter to the editor.

NLR in Differentiating Vertigo

In a study by Sertbaş et al., NLR was found to be significantly higher in patients with central vertigo (median: 3.99 vs. 2.32; $p<0.001$).[1] This finding supports the use of NLR as a rapid and low-cost diagnostic tool in the emergency department. Similarly, NLR has been shown to have acceptable diagnostic power (AUC: 0.75) in differentiating testicular torsion from epididymo-orchitis, while newer indices such as the pan-immune inflammation value (PIV) have demonstrated superior performance (AUC: 0.81).[4] Duyan et al. highlighted that NLR, PLR, and SII independently predict in-hospital mortality in Stanford Type B acute aortic dissection (BAAD) (OR: 9.16-8.57).[5] These results reflect the critical role of inflammation in vascular pathologies. In incarcerated inguinal hernias, NLR, SII, and PIV have been shown to have acceptable diagnostic power (AUC: 0.738-0.765) in predicting strangulation.[6] These findings underscore the importance of inflammatory markers in the early detection of conditions requiring surgical urgency in the emergency department. In the detection of multiple sclerosis (MS) relapses, NLR, RLR, and SII have demonstrated excellent diagnostic performance (AUC: 0.81-0.87).[7] This is a significant finding highlighting the association between peripheral inflammation and central nervous system involvement. In differentiating complicated appendicitis, NLR, SIRI, and PIV have shown acceptable diagnostic value (AUC: 0.735-0.783), while the HALP score has limited diagnostic value (AUC: 0.64).[8] This reflects the potential of indices derived from routine blood parameters in surgical decision-making processes.

Areas for Improvement

Retrospective Design: The retrospective nature of the study increases the likelihood of some data being missing or inaccurately recorded. Future prospective studies could more precisely evaluate the diagnostic value of NLR.[9]

Definitive Threshold for NLR: While the NLR threshold of 3.25 determined in the study is useful for differentiating central and peripheral vertigo, this value needs to be validated in different populations and clinical settings. Additionally, the potential influence of other inflammatory conditions on NLR should be considered.[10]

In conclusion, this study makes a significant contribution by demonstrating that NLR can be used to differentiate between central and peripheral vertigo in patients presenting to the emergency department with dizziness. The use of easily obtainable parameters like NLR in settings requiring rapid decision-making, such as the emergency department, can expedite diagnostic processes and improve patient management. However, the retrospective nature of the study and the need to validate the definitive NLR threshold open an important area for future research.

Sincerely.

Ethics Committee Approval: Ethics committee approval is not required.

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

Author Contributions: Concept – NU; Supervision – NU; Materials – NU; Data Collection and/or Processing – NU; Analysis and/or Interpretation – NU; Writing – NU

Peer-review: Editorial review

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