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Research Paper:

- Mirza E, Oltulu R, Oltulu P, et al. Dry eye disease and ocular surface characteristics in patients with keratoconus. Saudi J Ophthalmol. 2022;36(1):117-21. doi: 10.4103/sjopt.sjopt_37_21.
- Vikse BE, Aasarød K, Bostad L, et al. Clinical prognostic factors in biopsy-proven benign nephrosclerosis. Nephrol Dial Transplant. 2003;18(3):517-23. doi: 10.1093/ndt/18.3.517.

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Single Author Books:
- Danovitch GM. Handbook of Kidney Transplantation. Boston: Little, Brown and Company (Inc.), 1996: 323-8.

Book Chapter:
- Soysal Z, Albek E, Eke M. Fetüs hakları. Soysal Z, Çakalır C, ed. Adli Tıp, Cilt III,İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi Yayınları, İstanbul, 1999:1635-50.
- Davison AM, Cameron JS, Grünfeld JP, et al. Oxford Textbook of Clinical Nephrology. In: Williams G, ed. Mesengiocapillary glomerulonephritis. New York: Oxford University Press, 1998: 591- 613.
- **Journal article published online ahead of print:**
- Doğan GM, Sığırcı A, Akyay A, et al. A Rare Malignancy in an Adolescent: Desmoplastic Small Round Cell Tumor. Turkiye Klinikleri J Case Rep. 10.5336/caserep.2020-77722. Published online: 31 December 2020.
- Cai L, Yeh BM, Westphalen AC, et al. Adult living donor liver imaging.DiagnIntervRadiol. 2016 Feb 24.doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Meeting Reports:
- Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report:
- Cusick M, Chew EY, Hoogwerf B, A et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis:
- Kaplan SI. Post-hospital home health care: elderly access and utilization (dissertation). St Louis (MO): Washington Univ; 1995.

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When sharing patient photos, ensure that the identity is not recognized one-to-one, and images sufficient to identify the disease should be shared. For sharing images that reveal the patient's identity, a consent form in which the patient authorizes the sharing of the image is necessary.

Table 1. Limitations according to article types

	limitation of article	abstract	references	Tables	Figures
Research Article	4000	300	50	6	6
Review	6000	300	85	6	10
Case Presentations	1500	200	15	3	5
Letters to the Editor	1000	(-)	8	(-)	(-)
Editorial	1000	(-)	20	3	3
Original Image Report	200	(-)	5	1	3

Article Types

Selcuk Medical Journal publishes the types of articles briefly described below:

Research Articles: This is the most important type of article that provides new results based on original research. The main text of original articles should be structured with the subheadings Introduction, Methods, Results, Discussion, Conclusion and References. Please refer to Table 1 for word count and specifications. Statistical analysis is often necessary to support leconclusions. Statistical analyses should be performed in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983:7;1489-93). Information on statistical analyses should be provided under a separate subheading in the Materials and Methods section and the statistical software used throughout the process should be indicated. Units should be prepared in accordance with the International System of Units (SI). Limitations, drawbacks and shortcomings of the article should be stated in the Discussion section before the conclusion paragraph.

Review Articles: Review articles should be articles that review a sufficient number of scientific articles, summarize the subject at the current level of knowledge and technology, evaluate and interpret the findings by comparing them. Techniques and applications in the latest scientific studies with all the developments in basic and applied sciences are evaluated. Reviews prepared by authors who have extensive knowledge of a particular field and have a scientific background with high citation potential will be accepted by our journal. Acceptance of manuscripts from these authors can also be by invitation. The main text should include Introduction, Clinical and Research Results and Conclusion. Please see Table 1 for word count and specifications.

Case Presentations: Educational case reports on rare cases or conditions that pose difficulties in diagnosis and treatment, offer new treatments or reveal information not included in the literature are accepted for publication in our journal. The case report should include the subheadings Introduction, Case Presentation and Discussion and Coclusion. Interesting and unusual pictures are an advantage in the evaluation process.

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If patient identity is disclosed in patient-identifying pictures, patient consent must be provided to share the picture. Please see Table 1 for word count and specifications.

Letter to the Editor: This type of article discusses important parts, overlooked aspects or missing parts of a previously published article. Articles on topics that may attract the attention of the journal, especially on topics that may attract the attention of readers, especially on educational topics, can be submitted in the form of Letters to the Editor. Readers can also submit their comments on published articles as a Letter to the Editor. Abstract, Keywords and Tables, Figures, Images and other media should not be included. The text should not include subheadings. Please see Table 1 for word count and specifications.

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Original Image Report: Interesting, descriptive or educational images (illustration or photography) from any field of medicine can be submitted for evaluation in this section, along with a few lines of explanatory text and references. Article length should not exceed 200 words. A summary, discussion, or conclusion is not required, but a brief title should be included. Please see Table 1 for word count and specifications.

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RESEARCH ARTICLE

Frequency of Congenital Malformations in The Fourth Level Neonatal Intensive Care Unit: 4 Year-Experience

Dördüncü Seviye Yenidoğan Yoğun Bakım Ünitesinde Doğumsal Malformasyonlarin Sıklığı: 4 Yıllık Deneyim

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ABSTRACT

Objective: Congenital malformations (CM) constitute one of the most important causes of neonatal and childhood deaths, chronic diseases and morbidity. This study aimed to identify CM, determine their frequency and investigate the factors that may be effective in etiology in patients treated in the Neonatal Intensive Care Unit(NICU) of Necmettin Erbakan University University Medicine Hospital.

Materials and Methods: The files of 4860 patients hospitalized in the NICU between October 1, 2017 and October 15, 2021 were retrospectively reviewed.

Results: A total of 4860 patients were investigated within the scope of the study, and CM were detected in 423 cases. When the distribution of malformations according to gestational age was examined, 55% of all malformations were seen in term babies. When the distribution according to maternal age was examined, it was seen that the majority were born to mothers under 35 years of age(80%). The frequency of CM was found to be 8.7%. When the distribution of malformations according to organ systems was examined, the most frequently affected system was the cardiovascular system(24.3%). This was followed by anomalies ofthe central nervous system(23.4%), genitourinary(18.2%), gastrointestinal(13.2%), head-neck-face(9.9%), respiratory(6.6%) and musculoskeletal(4.3%). The most common isolated anomaly was hydronephrosis(13.2%). The presence of genitourinary system malformations in babies of pregnant women who had urinary tract infections, the occurrence of cardiovascular and gastrointestinal anomalies in preterm babies, and the high mortality rate due to respiratory malformations were among the prominent findings of the study. Death occurred for various reasons during nıcu hospitalization in 13% of the cases. The most common anomalies among the babies who died were cardiovascular system anomalies(31%).

Conclusion: Determining the frequency of CM and determining the factors that may be effective in etiology in general and taking precautions accordingly will play an important role in both reducing morbidity and mortality and increasing the socioeconomic welfare of societies.

Keywords: Newborn, congenital malformation, frequency

ÖZET

Amaç: Konjenital malformasyonlar yenidoğan ve çocukluk çağı ölümlerinin, kronik hastalıkların ve morbiditenin en önemli nedenlerinden birini oluşturmaktadır. Bu çalışmada Necmettin Erbakan Üniversitesi Tıp Fakültesi Hastanesi Yenidoğan Yoğun Bakım Ünitesi'nde yatarak tedavi gören olgularda konjenital malformasyonların tanımlanması, sıklığının belirlenmesi ve etiyolojide etkili olabilecek faktörlerin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: 1 Ekim 2017 ile 15 Ekim 2021 tarihleri arasında yenidoğan yoğun bakım ünitesinde yatan 4860 hastanın dosyaları retrospektif olarak incelendi.

Bulgular: Çalışma kapsamında toplam 4860 hasta araştırıldı, 423 olguda konjenital malformasyon saptandı. Malformasyonların gebelik haftasına göre dağılımına bakıldığında, tüm malformasyonların % 55'i term bebeklerde görüldü. . Anne yaşına göre dağılımına bakıldığında büyük çoğunluğunun 35 yaş altı anneden doğduğu görülmektedir (% 80). Konjenital malformasyonların sıklığı % 8,7 olarak bulundu. Malformasyonların organ sistemlerine göre dağılımı incelendiğinde en sık etkilenen sistem kardiyovasküler sistemdi (%24,3). Bunu sırasıyla merkezi sinir sistemi (% 23,4), genitoüriner sistem (% 18,2), gastrointestinal sistem (% 13,2), baş-boyun-yüz (% 9,9), solunum (% 6,6) ve kas-iskelet sistemi (% 4,3) anomalileri izledi. En sık izole anomali hidronefroz (% 13,2) idi. İdrar yolu enfeksiyonu geçiren gebelerin bebeklerinde genitoüriner sistem malformasyonlarının varlığı, preterm bebeklerde kardiyovasküler ve gastrointestinal sistem anomalilerinin ortaya çıkması ve solunum sistemi malformasyonlarına bağlı yüksek mortalite oranı çalışmada öne çıkan bulgular arasındaydı. Olguların %13'ünde yenidoğan yoğun bakım yatışı esnasında çeşitli nedenlerle ölüm gerçekleşti. Ölen bebekler arasında en sık rastlanan anomaliler kardiyovasküler sistem anomalileriydi (%31).

Sonuç: Doğuştan malformasyonların sıklığının belirlenmesi ve genel olarak etyolojide etkili olabilecek faktörlerin belirlenerek buna göre önlemler alınması hem morbidite ve mortalitenin azaltılmasında hem de toplumların sosyoekonomik refahının artırılmasında önemli rol oynayacaktır.

Anahtar Kelimeler: Yenidoğan, konjenital malformasyon, sıklık

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INTRODUCTION

A congenital malformation (CM) or birth defect, is defined as any abnormality, either structural or functional, present at birth, which may have been inherited genetically, acquired during gestation, or inflicted with parturition (1). Congenital malformations constitute one of the most important causes of neonatal and childhood deaths, chronic diseases and morbidity (2). The incidence of congenital malformations varies between regions and countries depending on socio-economic status, nutritional habits, genetic and environmental factors (3). Congenital malformations pose a serious health problem in underdeveloped and developing countries and there isn't enough data regarding their etiology. Although it is known that some of them occur due to genetics, maternal diseases, exposure to teratogens and/or environmental reasons, the cause of approximately half of the cases is unknown (4).

Our study aims to determine the frequency of congenital malformations in Konya, a city with a large population density where our hospital is located. Additionally, it aims at determining the distribution of malformation cases according to the affected systems and the factors associated with these anomalies.

MATERIALS AND METHOD

Our study included cases with congenital malformations followed up in the Neonatal Intensive Care Unit of Necmettin Erbakan University Faculty of Medicine Hospital between October 1, 2017 and October 15, 2021. The files of each of the 4860 patients hospitalized in the neonatal intensive care unit between the specified dates were reviewed. Babies with clinical, genetic or radiological congenital malformations were selected. Stillbirth, medical termination, live birth cases that did not require intensive care, and malformation cases diagnosed after neonatal intensive care hospitalization were not included in the study. Isolated hydrocephalus cases without underlying central nervous system malformation were excluded from the study. Approval was obtained from the Necmettin Erbakan University Faculty of Medicine Clinical Research Ethics Committee for the study. All analyzes were performed in the SPSS 21.0 program. Arithmetic mean±standard deviation and median (min-max) values were used to summarize numerical data; frequency distributions (n) were used to summarize categorical data. The normal distribution of numerical data was tested using visual (Histogram) and analytical (Kolmogorov-Simirnov and Shapiro-Wilk tests) methods. In cases where the distribution was normal, the relationships between numerical data were evaluated using a single sample t test and an independent groups t test. In cases where the distribution was not normal, the Kruskal Wallis test was used in samples that were nonparametric equivalents of the same tests. The relationships between categorical data were investigated using the Chi-square test. Pearson correlation analysis was used to compare quantitative data with each other. The frequency of congenital anomalies, differences between genders, maternal infection and disease status, maternal age, gestational week and birth weight were calculated using the Chi-square and Fisher exact tests with a Type-1 error level of 0.05. Statistically, cases where p was less than 0.05 were considered significant.

RESULTS

Within the scope of the study, a total of 4860 patients receiving inpatient treatment in the neonatal intensive care unit of Necmettin Erbakan University Medical Faculty Hospital were studied, and a total of 423 cases with congenital anomalies were identified.

The incidence of malformations in patients treated in the neonatal intensive care unit was calculated as 8.7%. Looking at the distribution of malformations by organ systems, the most common anomalies were cardiovascular system anomalies (24.3%). The second most common were central nervous system anomalies (23.4%).These were followed by genitourinary, gastrointestinal, head-neck-facial, respiratory and musculoskeletal system anomalies, respectively (Table 1). The most common isolated anomaly in our study was hydronephrosis (13.2%). This was followed by meningomyelocele (11.8%) and cleft lip (7%), respectively.

Of the cases with congenital anomalies included in our study, 59% were of male and 41% were of female gender. The most common anomalies detected in total were cardiovascular system anomalies, while when evaluated according to gender, the most common malformations in males were genitourinary system anomalies and in females were central nervous system anomalies. Genitourinary and gastrointestinal system anomalies were 11% and 8% in females and 23% and 17% in males, respevtively, and the probability of genitourinary and gastrointestinal system anomalies was statistically significantly higher in males(p=0.001 and p=0.018).

In our study cohort, 84 mothers (19.8%) were found to have at least one maternal disease. The most common disease was gestational and/or pre-gestational diabetes, which was observed in 9.2% of all pregnant women and constituted 46.4% of all maternal diseases. Central nervous system (CNS) malformations were detected in 26% of children of diabetic mothers, while this rate was measured as 17% in children of non-diabetic mothers. This difference was statistically significant (p = 0.001).

A history of maternal infection was present in 8.5% of the cases included in our study. The majority of these infections (69.4%) were urinary tract infections. The most commonly

Table 1. Distribution of malformations by affected organ systems

Systems	n (%)
Cardiovascular system	103 (24.3)
Central nervous system	99 (23.4)
Genitourinary system	77 (18.2)
Gastrointestinal system	56 (13.2)
Head-neck -face	42 (9.9)
Respiratory system	28 (6.6)
Musculo-skeletal system	18 (4.3)
Total	423 (100)

Table 2. Distribution of cardiovascular anomalies in early and late preterm neonates

Malformations	Gestational week			p
	<34 weeks n (%)	34-36(6/7) weeks n (%)	Total n (%)	
Cardiovascular anomalies	27 (14)	24 (12)	51 (26)	
Other system anomalies	39 (21)	97 (53)	136 (74)	0.008
Total	66 (35)	121 (65)	187 (100)	

Table 3. Distribution of gastrointestinal anomalies in preterm and term neonates

Malformations	Gestational week			p
	<37 weeks n (%)	37≤ weeks n (%)	Total n (%)	
Gastrointestinal anomalies	34 (8)	22 (5)	56 (13) 0.025	
Other system anomalies	153 (36)	214 (51)		367 (87)
Total	187 (44)	236 (56) 423 (100)		

Table 4. Distribution of central nervous system anomalies in preterm and term neonates

Malformations	Gestational week			p
	<37 weeks n (%)	37≤ weeks n (%)	Total n (%)	
Central nervous system anomalies	29 (7)	70 (16)	99 (23)	0.004
Other system anomalies	158 (37)	166 (40)	324 (77)	
Total	187 (44)	236 (56)	423 (100)	

observed anomalies in the infants of mothers with urinary tract infections were genitourinary system malformations. Genitourinary malformations were present in 54% of infants born to mothers with urinary tract infections during pregnancy, compared to 18% in those without such infections. The incidence of genitourinary malformations was found to be significantly higher in the children of mothers who experienced urinary tract infections during pregnancy (p=0.007).

Among the malformed infants included in our study, 2.6% had mothers who did not receive folic acid supplementation during or prior to pregnancy. Neural tube defects were observed in 100% of infants whose mothers did not receive folic acid supplementation during pregnancy, compared to 16% of those whose mothers did. The occurrence of neural tube defects in infants born to mothers who did not receive folic acid supplementation during pregnancy was found to be statistically significant (p=0.001).

Upon evaluating the distribution of congenital malformations by gestational age, it was determined that 55.8% of all malformations occurred in term infants. Among neonates born before 34 weeks, 44% exhibited cardiovascular anomalies, whereas this figure was 20% among late preterm infants (between 34 and 36+6 weeks gestation). The increased frequency of cardiovascular system anomalies in infants born prior to 34 weeks, compared to those born in the late preterm period, was statistically significant. (p=0.008) (Table 2).

Gastrointestinal system anomalies were detected in 18% of the preterm infants included in our study, whereas this rate was 9% among term infants. The prevalence of gastrointestinal system anomalies was significantly higher in preterm infants compared to term infants. (p=0.025) (Table 3). A total of 70% of central nervous system anomalies were identified in term neonates, with this distribution showing statistical significance. (p=0.004) (Table 4).

A majority (62.9%) of the congenital anomalies in our study were identified in infants with a birth weight of 2500 grams or above. Seventy-six percent of central nervous system anomalies were observed in infants with a birth weight of 2500 grams or more. This proportion was also statistically significant. (p=0.012) (Table 5).

Table 5. Distribution of central nervous system anomalies according to birth weight

Malformations	Birth weight			p
	<2500 g n (%)	2500 g≤ n (%)	Total n (%)	
Central nervous system anomalies	23 (5)	76 (18)	99 (23)	0.012
Other system anomalies 1	34 (32)	190 (45)	324 (77)	
Total	157 (37)	266 (63)	423 (100)	

Table 6. Distribution of cardiovascular anomalies in very low and normal birth weight infants

Malformations	Birth weight			p
	<1500 g n (%)	2500 g≤ n (%)	Total n (%)	
Cardiovascular anomalies	21 (6)	41(13)	62 (19)	0.001
Other system anomalies	23 (8)	225 (73)	248 (81)	
Total	44 (14)	266 (86)	310 (100)	

In our study group, 41% of the infants diagnosed with cardiovascular anomalies had a birth weight of ≥2500 grams, 38% had a birth weight between 1500 and 2500 grams, and 21% had a birth weight below 1500 grams. Cardiovascular anomalies were found to be significantly more frequent in newborns with normal birth weight compared to those with very low birth weight. (p=0.001) (Table 6).

When the distribution of malformations according to maternal age was examined, the majority of cases (80%) were born to mothers under 35 years of age. Among cases with maternal age ≥35 years, the most common anomalies were cardiovascular system anomalies (36%). The rate of cardiovascular anomalies among infants born to mothers under 35 years of age was found to be 20%. The higher incidence of cardiovascular system anomalies in infants born to older mothers was also found to be statistically significant (p=0.001).

In our study group, 13% of the cases died during their admission to the neonatal intensive care unit for various reasons. Among the deceased infants, cardiovascular system anomalies were the most common anomalies observed (31%), whereas musculoskeletal system anomalies were the least common (4%). The most frequently detected isolated anomaly was congenital diaphragmatic hernia (22%). Among 28 cases with respiratory system malformations, 42% died during their stay in the neonatal intensive care unit. When compared to non-respiratory anomalies, the higher mortality rate in patients with respiratory system anomalies was found to be statistically significant (p=0.01).

DISCUSSION

The incidence of malformation in the cases treated in the neonatal intensive care unit, which we included in the study, was calculated as 8.7%.In studies conducted in different countries, the prevalence of congenital anomalies in live births varies between 2-3%; It was noted as 0.8% in England, 1.8% in Iran, 3.3% in Nigeria, 2% in Mexico, 3% in America, and 2% in Japan (5, 6, 7, 8, 9). In Turkiye, Tunçbilek et al. (10) reported the frequency of congenital anomalies as 3.7% in a comprehensive study that included data from 22 university hospitals. In our study, the frequency of congenital anomalies was generally found to be higher than other studies. The factors in obtaining this result include the fact that our study group consists of babies treated in the neonatal intensive care unit, cases with an antenatal diagnosis are referred to our hospital before or after birth because our hospital is the referral hospital in the region, the relatively lower tendency for pregnancy termination in antenatally diagnosed cases due to the socio-demographic characteristics of our region, and the relatively higher rate of consanguineous marriages in our region.

When factors influencing malformations in terms of gender were examined, it was observed that males had a higher incidence of malformations compared to female cases. Of the 423 malformation patients included in our study, 252 were male (59%) and 171 (41%) were female. This rate also coincides with the current study conducted by Özdil (13) in Turkiye with 12,053 cases. In our study, we detected genitourinary system and central nervous system anomalies as the most frequent anomalies in males and females, respectively. We identified genitourinary and gastrointestinal system malformations significantly higher in males compared to females (p=0.001 and p=0.018). In a study conducted in Europe by Garne et al. (14), renal anomalies were found to be higher in men. This result is compatible with our study. In two different studies, central nervous system anomalies were observed more frequently in the male gender (15, 16). Different information is given in the literature for digestive system anomalies; In a study conducted in Iran, gastrointestinal malformations were found to be higher in girls, while in America, the rates were found to be higher in boys (17, 18). Different results obtained from different studies may be due to the difference in the number of patients and other factors affecting malformations. Different results obtained from different studies may be due to the difference in the number of patients and other factors affecting malformations.

The most common maternal disease in our study was gestational and/or pregestational diabetes; Its frequency among all pregnant women was 9.2%, and its rate among mothers with maternal diseases was 46.4%. In a study conducted with a large patient population inTurkiye, the most common disease in mothers giving birth to babies with anomalies was reported as diabetes mellitus, which is also consistent with our study (15). In the study conducted by Akarsu et al. in the children of diabetic mothers (19), the most common anomalies were reported as cardiovascular anomalies. In another study as well, cardiovascular system anomalies were found to be the most frequent in infants of diabetic mothers, followed by gastrointestinal and genitourinary system anomalies in decreasing frequency (20). In our study, Genito-urinary system anomalies were the most common anomalies in the children of diabetic mothers; the central nervous system was in second place, and the cardiovascular system was in third place. The reason for this may be attributed to the difference in other environmental and genetic factors that may influence the formation of anomalies. Central nervous system malformations were found to be statistically significantly higher in children of

mothers with diabetes compared to those without (p=0.001). This result was also consistent with the literature (21, 22).

Infections during pregnancy are one of the causes of morbidity and mortality for both the mother and the fetus and may cause abortion, intrauterine death, congenital anomalies, and infection in the neonatal period (23, 24). Urinary tract infections are the most common health problem during pregnancy after anemia and are seen in approximately 17-20% of all pregnancies (25). In our study, 36 (8.5%) of 423 malformation cases had a history of maternal infection. Urinary tract infection accounted for 69.4% of pregnant women with maternal infections. There is no reported evidence in the literature suggesting that urinary tract infections during pregnancy directly result in congenital anomalies in the fetus (26, 27). In our study, however, we found a statistically significant higher incidence of genitourinary malformations in children of mothers who had urinary tract infections during pregnancy (p=0.007). Studies on this subject with larger patient groups may contribute to the literature.

It is known that folic acid replacement during pregnancy is effective in preventing the development of central nervous system anomalies, especially neural tube defects (28, 43). The mothers of 2.6% of the babies with malformations included in our study had not used folic acid during or before pregnancy Neural tube defect was present in all of these patients, and the occurrence of neural tube defects in the babies of mothers who had not taken folic acid replacement during pregnancy was found to be statistically significant (p = 0.001).

Approximately 12.5% of babies with congenital malformations are born prematurely (29, 30). Premature babies have a two-fold higher risk of having congenital anomalies compared to full-term babies (31). In our study, 44.2% of all malformations were found in premature babies. This result is consistent with the large patient-based study conducted by Özdil in 2012 (13). When organ systems are examined, the occurrence of cardiovascular system anomalies in premature cases was found to be statistically significant (p=0.008). Similarly, in a study conducted in the USA in 2007 and examining approximately 7000 cases, the probability of cardiovascular anomalies in premature babies was found to be high (42). Central nervous system anomalies were mostly seen in full-term babies. In an analysis of data from 13 states in the USA, cardiovascular and central nervous system anomalies were reported to be more common in full-term infants, while gastrointestinal system anomalies were more common in premature infants (31). Similarly, in our study, gastrointestinal anomalies were found to be significantly higher in preterm infants, and CNS anomalies were found to be significantly higher in term infants (p=0.025 and p=0.004).

Fetal growth is affected in most fetuses with congenital malformations (32, 44). It has been observed that the digestive system, genital organs and musculoskeletal system are particularly affected in malformed fetuses with intrauterine growth retardation (8). It has been reported that newborns with congenital heart disease (such as transposition of the great arteries, tetralogy of Fallot, hypoplastic left heart and coarctation of the aorta) show abnormal fetal development, especially in terms of weight (33, 45). When the malformation cases in our study were classified according to birth weight, 266 (62.9%) of the cases were 2500 grams and above, 113 (26.7%) were between 1500-2500 grams and 44 (10.4%) were below 1500 grams. These results are similar to a study conducted in a university hospital in Türkiye and examining 11,434 live births (13). In our study, central nervous system and cardiovascular anomalies were significantly more common in babies with a birth weight of 2500 grams and above (p=0.012 and p=0.001, respectively). In a study examining 329 cases with central nervous system anomalies in Turkey, the mean birth weight was reported as 3045 grams, which is consistent with our study (16). Similarly, in a retrospective study conducted in 2012 and evaluating congenital heart diseases, it was stated that congenital heart diseases were more common in babies with normal birth weight, which is consistent with our study (34).

Looking at the distribution of the cases included in our study by maternal age, it is notable that the majority of them were born to mothers under 35 years of age (80%). When the relationship between maternal age and congenital anomaly is examined in studies conducted in different regions in Turkey, it is seen that cases with anomaly are most frequently in the 21-30 age group (35, 36). The results of our study seem to be compatible with existing studies. Although advanced maternal age is one of the factors involved in the etiology of fetal anomalies, the fact that anomalies are seen more in babies of young mothers indicates the necessity of detailed prenatal diagnosis and follow-up for all patients. Advanced maternal age has also been found to be associated with congenital heart diseases (37, 46). In our study as well, cardiovascular system anomalies were found to be the most common anomaly in the babies of mothers aged 35 and over, and the presence of cardiovascular system anomalies in the babies of these mothers was found to be statistically significant (p = 0.001).

In the literature, it has been stated that central nervous system malformations are identified as the primary cause of stillbirths, and during the neonatal period, cardiovascular and pulmonary malformations are the most common causes of death (38). In Europe as well, the most common group of congenital anomalies leading to perinatal mortality has been reported to be congenital heart diseases and central nervous system malformations (39). Isolated congenital diaphragmatic hernias still have high mortality today (40). In a study conducted by Celayir and colleagues (41), the mortality rate in congenital diaphragmatic hernia was determined to be 73%. Death occurred in 54 cases (13%) for various reasons during neonatal intensive care unit admission within our study group. The most common anomalies found in the deceased infants were primarily cardiovascular system anomalies (31%), which is consistent with the literature. The most common isolated anomaly found in deceased infants was congenital diaphragmatic hernia (22%). Death occurred during neonatal intensive care admission in 12 of 28 cases with respiratory malformation (42%). All of these cases were as well cases of congenital diaphragmatic hernia. The high incidence of

mortality associated with respiratory system anomalies was found to be statistically significant (p = 0.01). When all this data was evaluated together, it was concluded that it was consistent with the literature.

CONCLUSION

Congenital malformations constitute one of the most important causes of neonatal and childhood deaths, chronic diseases and morbidity. Early and accurate diagnosis is important both for the medical termination decision and for treatment and prognosis in live-born cases, as well as for prenatal diagnosis and preventive medicine in subsequent pregnancies. As a result of this study, the rate of malformations in babies requiring neonatal intensive care was found to be 8.7%.The most frequently detected anomalies were cardiovascular system anomalies. The most frequently detected isolated anomaly was hydronephrosis. In our study, the presence of genitourinary system malformations in the children of pregnant women who had urinary tract infections was notable. In addition, the emergence of cardiovascular and gastrointestinal system anomalies in preterm babies and the high death rate from respiratory system malformations were among the other prominent findings. We expect our study to make a significant contribution to the literature by emphasizing that the incidence of congenital anomalies in live births may be directly affected by the high patient load of our quaternary center and the conservative socioeconomic profile of the region. In general, identifying the frequency of congenital malformations and determining the factors that may be effective in etiology and taking precautions accordingly will play an important role in reducing morbidity and mortality and increasing the socioeconomic welfare of societies.

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RESEARCH ARTICLE

The Management of Intussusception in Children: When to Observe, to Non-Surgically Reduce, and to Operate?

Çocuklarda İnvajinasyona Yaklaşım: Acil Ameliyat mı edilmeli? Redüksiyon mu Denenmeli? Takip mi Edilmeli?

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ABSTRACT

Objective: To evaluate demographic characteristics, treatment approaches, and outcomes of children diagnosed with intussusception via ultrasound (US) and develop an algorithm for managing these children.

Materials and Methods: Sixty-five patients diagnosed between 2020 and 2023 were evaluated. Length of invaginated segment, clinical findings, treatment approach, time from onset of symptom to admission, and results were examined.

Results: Median age was 34 months (range 2-156) (27 females, 38 males). Patients were grouped as follows: Group 1: Medical follow-up and treatment (n=24), median presentation time: 30.5 hours (8-48), median invaginated segment length: 32.5 mm (12-65). Group 2: Hydrostatic or contrast reduction under US/fluoroscopy (n=21), median presentation time: 24 hours (8-48), median invaginated segment length: 50 mm (20-120). Group 3: Emergency surgery (n=20), median presentation time: 36 hours (12-100), median invaginated segment length: 46 mm (20-100). Segment lengths of Group 1 and Groups 2 and 3 differed significantly (p=0.001, p=0.002). There was a significant difference in presentation time between Groups 2 and 3 (p=0.035), but not between Group 1 and the rest. Hydrostatic reduction failed in six patients in Group 2, requiring surgery. In Group 3, most patients undergoing surgery were reduced manually, but four required resection.

Conclusion: Intussusception can be transient in some cases. Intermittent US is an appropriate approach, especially for intussusceptions shorter than 32.5 mm. For longer segments, if the patient's general condition is good, hydrostatic reduction should be the preferred approach. However, in cases having serious clinical findings such as late presentation, palpation of abdominal masses, or presence of "currant jelly" stool, surgical intervention should be performed without delay.

Keywords: Children, hydrostatic reduction, intussusception, ultrasound

ÖZET

Amaç: Ultrasonografi ile invajinasyon tanısı konulan pediatrik hastaların demografik özelliklerini, tedavi yaklaşımlarını, sonuçlarını değerlendirmek ve çocuklarda invajinasyon yönetimi için bir algoritma oluşturulması hedeflenmiştir.

Gereç ve Yöntemler: Ocak 2020- Haziran 2023 tarihleri arasında kliniğimizde invajinasyon tanısı alan 65 olgu retrospektif olarak incelendi. Olguların yaş, cinsiyet, klinik bulguları, başvuru süresi, invajine segment uzunlukları, uygulanan tedavi yöntemleri ve sonuçları değerlendirildi.

Bulgular: Hastaların medyan yaşı 34 ay (2–156 ay), 27'si kız, 38'i erkektir. Olgular tedavi şekline göre üç gruba ayrılmıştır: Grup 1 (n=24): Medikal izlem. Medyan başvuru süresi 30,5 saat (8–48); invajine segment uzunluğu 32,5 mm (12–65). Grup 2 (n=21): Ultrason veya floroskopi eşliğinde hidrostatik/kontrast madde ile redüksiyon. Medyan başvuru süresi 24 saat (8–48); invajine segment uzunluğu 50 mm (20–120). Grup 3 (n=20): Acil cerrahi. Medyan başvuru süresi 36 saat (12–100); invajine segment uzunluğu 46 mm (20–100). Grup 1 ile Grup 2 ve 3 arasında segment uzunluğu açısından anlamlı fark bulunmuştur (p=0,001 ve p=0,002). Grup 2 ile 3 arasında başvuru süresi açısından da anlamlı fark mevcuttur (p=0,035). Grup 2'de 6 hastada redüksiyon başarısız olmuş ve cerrahi gerekmiştir. Grup 3'te cerrahi uygulanan olguların çoğu manuel olarak redükte edilmiş, ancak 4 olguda rezeksiyon yapılmıştır.

Sonuç: İnvajinasyon bazı durumlarda geçici olabilir. Özellikle 32,5 mm'den kısa segmentli invajinasyonlarda, aralıklı ultrasonografi ile takip uygun bir yaklaşımdır. Daha uzun segmentlerde, hastanın genel durumu iyi ise, cerrahi dışı güvenli bir yöntem olan hidrostatik redüksiyon tercih edilmelidir. Ancak geç başvuru, batında kitle palpasyonu veya kanlı dışkı varlığı gibi ciddi klinik bulguların eşlik ettiği olgularda, cerrahi müdahale geciktirilmeden yapılmalıdır.

Anahtar Kelimeler: Çocuk, hidrostatik redüksiyon, invajinasyon, ultrasonografi

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INTRODUCTION

The protrusion of the proximal intestine segment into the more distal intestinal section is known as intussusception. One of the most common causes of acute intestinal obstruction in toddlers and infants aged between four and 10 months is intussusception. The incidence of intussusception ranges from one to four in 2000 infants and children, and decreases beyond the age of two. The majority of studies describe a 2:1 or 3:2 ratio of males to girls with intussusception (1).

Typical symptoms include a sudden start of vomiting, intermittent abdominal pain, and "currant jelly" stool. The delays in therapy can result in a series of potentially fatal consequences, including tissue ischemia, necrosis, intestinal perforation, and vascular congestion and edema of the intussuscepted intestinal wall (2). Although ileo-colic intussusception is the most prevalent variety, ileo-ileal or colo-colic forms can also occur (3).

The requirement for surgery has been greatly decreased by fluoroscopy or ultrasound (US)-guided intussusception reduction in recent decades (4,5). US-guided hydrostatic reduction is more advantageous, even when the success rates of non-surgical interventions are comparable, since it is safe, easy to use, and radiation-free (6). The treatment modalities for intussusception may involve medical follow-ups or surgical interventions, including bowel resection. The treatment algorithm varies greatly depending on the condition of the patient. Therefore, the current study aimed to assess our intussusception experiences from January 2020 to June 2023, and based on our findings, we aimed to develop an algorithm for managing children with intussusception.

MATERIALS AND METHODS

The data obtained from the patients (38 males and 27 females) presenting to the pediatric emergency department of our hospital between January 2020 and June 2023 and diagnosed with intussusception were retrospectively analyzed. The patients diagnosed with intussusception were also divided into three groups based on the following criteria:

Group 1: Patients receiving medical follow-up and treatment consisted of those diagnosed with intussusception based on clinical history, physical examination findings, and abdominal US examination, and demonstrating spontaneous reduction. Close observation, including physical examinations every two hours and US at least once every six hours, is the recommended course of treatment for cases of intussusception not exhibiting clinical worsening, intestinal blockage, or acute abdominal findings.

Group 2: Patients treated with US or fluoroscopy guidance, hydrostatic water pressure, or radiopaque material. The main characteristic of this patient group was that they were treated with reduction methods other than surgical methods.

Group 3: Patients treated with surgical methods. Regardless of the cause, patients treated with surgical methods were included in this group.

In terms of the inclusion criteria, all patients under 16 years of age admitted to the pediatric emergency department of our hospital with complaints such as abdominal pain, vomiting, and restlessness, and diagnosed with intussusception after physical examination and further testing, were included in the study. However, as for the inclusion criteria, patients diagnosed with intussusception who refused surgical treatment were excluded from the study, and their treatment was continued at another center.

The data of all patients were obtained from the digital information system of the hospital and the files of patients. Age, gender, clinical findings, intussusception segment lengths measured by US, time from the onset of symptoms to presentation to our clinic, treatment methods and outcomes, and length of hospital stay were evaluated and recorded. Approval was obtained from the local ethics committee of the institution for the study (Registration number and date: 2024-4897, 05/04/2024).

The Statistical Package for Social Sciences, version 22.0 (SPSS, IBM Corp., Chicago, IL, USA) was used for statistical analyses. Visual histograms and probability charts were used to assess the suitability of the variables for normal distribution rates by using analytical techniques such as the Shapiro-Wilk and Kolmogorov-Smirnov tests. Frequency tables for ordinal variables and median and interquartile range (IQR) for deviant variables were utilized to display the descriptive analyses. The threshold for statistical significance was set at $p < 0.05$.

RESULTS

A total of 65 patients, 38 males and 27 females, were included, and the median age was 34 months (ranging from 2 to 156 months). When the patients were grouped based on age (younger than one year old, age between one and three years, age between three and six years, and older than six years), the number of patients in the groups included was 16, 20, 14, and 15, respectively (Table 1). US was used to diagnose all cases, except for one; in other words, this case was diagnosed with computerized tomography (CT). Based on US and CT findings, three types of intussusception were detected: Ileoileal or jejunojejunal, ileocolic, and colocolic in 42 patients. Of 42

Table 1. Types of intussusception according to age groups

Age (years)	Group 1 (n)	Group 2 (n)	Group 3 (n)	Total (n)
<1	4	5	7	16
1-3	6	8	6	20
3-6	7	4	3	14
>6	7	4	4	15
Total	24	21	20	65

Table 2. Demographics and characteristics of the patients

	Group 1	Group 2		Group 3	Total	p
		successed	failed			
Number of Patients (%)	24 (37)	15	6	20 (30.7)	65	
Gender M/F	12/12	8/7	3/3	15/5	38/27	
Median Age (months) (range)	48 (2-127)	33 (8-109)		26,5 (7-156)	34 (2-156)	> 0.05
Median Length of Involved Segment, (mm) (range)	32.5 (12-65)	50 (20-120)		46 (20-100)	40 (12-120)	<0.05*
Median Presentation Time (hours) (range)	30.5 (8-48)	24 (8-48)		36 (12-100)	33.8 (8-100)	<0.05**
Reccurence (%)	4 (16.6)	4 (19)		-	8 (12)	

Group 1. Transient intussusception
Group 2. Hydrostatic/ radiopaque material reduction
Group 3. Surgery
* Group 1 and 2
Group 1 and 3
** Group 2 and 3, F: Female, M: Male

patients, 11 were reported as ileoileal, 29 as ileocolic, and 2 as colocolic. The location of intussusception was not specified in the US investigations of the remaining 23 patients. While 24 of 65 patients (37%) were reduced spontaneously, 21 (32.3%) were reduced hydrostatically (n=16) or with radiopaque materials (n=5), and 20 underwent surgery (30.7%).

The patients were also grouped by the treatment modalities: Group 1: Medical follow-up and treatment (n=24), median presentation time: 30.5 hours (8–48), and median invaginated segment length: 32.5 mm (12–65). Group 2: Hydrostatic or radiopaque material reduction under US/ fluoroscopy (n=21), median presentation time: 24 hours (8–48), and median invaginated segment length: 50 mm (20–120). Group 3: Emergency surgery (n=20), median presentation time: 36 hours (12–100), and median invaginated segment length: 46 mm (20–100). There was a significant difference in segment length between Group 1 and Groups 2 and 3 (p=0.001 and p=0.002). No significant difference in presentation time was found between Group 1 and the other groups; however, the difference between Groups 2 and 3 was significant (p=0.035) (Table 2). Recurrence was observed in four cases in Group 1 and four cases in Group 2. Hydrostatic reduction failed in six patients in Group 2 (28.6%), requiring surgery (mean invaginated segment length 57.5 mm), with a reduction success of 71.4%, and of these six patients, one has Meckel's diverticula. In Group 3, while most patients undergoing surgery were reduced manually, four required resection; additionally, there were cases with a long admission time and poor clinical condition. "Currant jelly" stool was detected in four of those in Group 3, and a mass was palpated in two of them. Meckel's diverticula were detected in two of the Group 3 patients.

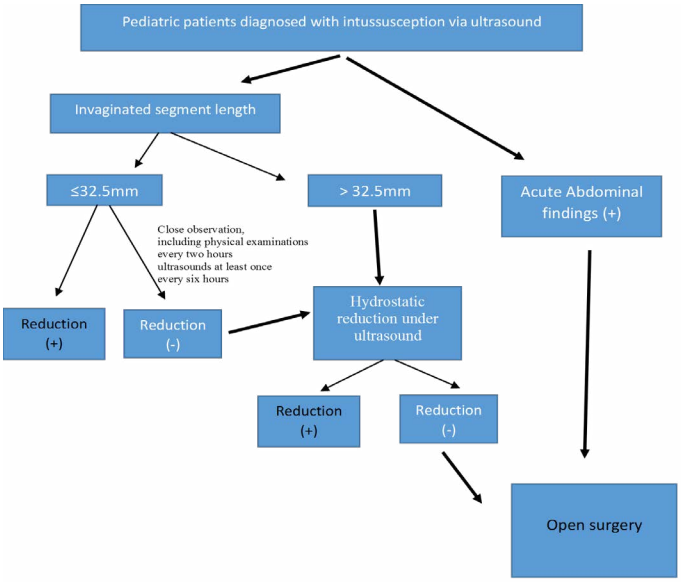

Figure 1. Intussusception management flow chart

DISCUSSION

Intussusception is one of the most common causes of intestinal obstruction in infants, and the majority of cases are identified earlier in recent decades as secondary due to the greater accessibility of US (7). Although intussusception is most commonly seen in infants aged between four and 10 months, the majority of cases occur before three years of age. In our case series, out of 65 patients, 36 (55.4%) were under the age of three. In most series, a higher incidence of intussusception has been reported in males, compared to females, typically with a male-to-female ratio of 2:1 or 3:2 (1). Consistent with the literature, our series also demonstrated a similar male-to-female ratio of 3:2.

Although the cause cannot be determined in most patients, the underlying leading point causing intussusception is detected in 2-50% of the cases, especially in older children (8). Mass lesions, including Meckel's diverticulum, lymphoma, intramural hematoma, or enlarged mesenteric lymph nodes, may be observed (9,10). Among the surgically treated cases, Meckel's diverticulum was identified in three patients in our series, suggesting that it was a potential leading point in these

cases.

In stable patients, intussusception can be treated with noninvasive methods without the need for surgical intervention. The first-line treatment is considered to be reducing the intussusception guided by fluoroscopy or US. This method is preferred when the condition of the patient is stable and there are no signs of complications, allowing for the treatment without resorting to surgery. This type of treatment is generally less invasive and offers a faster recovery time, compared to surgical interventions, which carry a higher risk of complications. However, if the intussusception becomes irreducible or if such complications as bowel perforation or ischemia occur, surgical intervention is necessary (11-14). For the majority of those with acute primary intussusception, nonoperative reduction should be tried. The reduction is carried out by rectal administration of air, liquid, or contrast material at controlled pressures (4,6,11,12).

US-guided hydrostatic reduction of intussusception seems to be a noninvasive therapeutic method because of its high success rates, ease of use, and no radiation exposure (6). Early presentation (<24 hours) and short intussusception segment (<3 cm) are favorably associated with successful outcomes (15). In our study, 21 patients with stable general conditions underwent hydrostatic or radiopaque material reduction under US or fluoroscopic guidance. Sixteen of these cases underwent US-guided hydrostatic reduction, while five were reduced using radiopaque material under fluoroscopic guidance. Six patients experienced recurrence and subsequently required open surgical intervention, with a success rate of 71.4%. Based on the literature, the reduction success was achieved at least at the rate of 80% and 95% (16). This relatively lower success rate may be attributed to the longer length of the intussuscepted segment, compared to other cases. US-guided hydrostatic reduction is considered a simple, highly successful, and radiation-free technique, particularly advantageous in the pediatric population.

When nonoperative approaches are unsuccessful, or if there is an intestinal perforation or indications of peritoneal irritation, surgery is recommended. If possible, manual reduction is the main goal during surgery. However, intussusception can result in problems such as intestinal necrosis, perforation, and sepsis, which call for more involved surgeries, like bowel resection. These situations are frequently linked to extended hospital stays and may potentially be fatal for patients whose diagnoses are delayed (17,18). Soleimanpour et al. found that younger children and those with bloody stools underwent open surgery more often (19). Twenty of our patients underwent open surgical intervention. The median age of these patients was 26.5 months, with a median invaginated bowel segment length of 46 mm. The median time from the onset of the symptom to hospital presentation was 36 hours. A statistically significant difference in segment length was observed between Groups 1 and 3, while a significant difference in presentation time was found between Groups 2 and 3. Three patients in Group 3 presented with characteristic "currant jelly" stools and underwent surgery due to the clinical signs of peritoneal irritation and the presence of a palpable abdominal mass.

Wang et al. defined transient intussusception as the spontaneous resolution of intussusception, usually without any intervention. In the same study, the researchers suggested that individuals with normal abdominal examination and radiograph results, no suspicion of a lead point, normal bowel circulation on US, and an intussusception segment of less than 3 cm were safe candidates for conservative follow-up (20,21). In our study, 24 of our patients were defined as transient intussusception (37%), and median presentation time and median invaginated segment length were 30.5 hours (8-48) and 32.5 mm, respectively (12-65).

The majority of authors believe that the judgment of attending surgeons, combining the clinical and radiological evidence with their own experience, is ultimately responsible for making the diagnosis, despite ongoing disagreements on the definition and clinical significance of transient intussusception (22,23). Based on previous reports, non-invasive techniques have a 10% risk of recurrence (24). Among our patients, recurrence was observed in four patients (16.6%) after transient intussusception.

A limitation of the present study was the retrospective nature of the data. Because just a small number of patients were involved and all procedures were carried out at a single institution, descriptive analyses rather than comparative ones were possible. Also, US investigations were not performed by a single radiologist.

CONCLUSION

Intussusception can be transient in some cases. Intermittent US is an appropriate approach, especially for intussusceptions shorter than 32.5 mm. For longer segments, if the general condition of the patient is good, it should first be monitored with intermittent US. If the invaginated segment does not reduce spontaneously, hydrostatic reduction should be the preferred approach. However, in cases accompanied by serious clinical findings such as late presentation, palpation of an abdominal mass, or the presence of "currant jelly" stool, surgical intervention should be performed without delay.

DECLARATIONS

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RESEARCH ARTICLE

Evaluation of Late-Term Effects of BNT162b2 mRNA COVID-19 Vaccine on Myocardial Perfusion by Myocardial Perfusion Scintigraphy

BNT162b2 mRNA COVID-19 Aşısının Miyokardiyal Perfüzyon Üzerindeki Geç Dönem Etkilerinin Miyokardiyal Perfüzyon Sintigrafisi ile Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to investigate the late-term effects of the BNT162b2 mRNA COVID-19 vaccine on myocardial perfusion using myocardial perfusion scintigraphy (MPS).

Materials and Methods: A retrospective analysis was conducted on 181 procedures involving pharmacological stress and rest single-photon emission computed tomography (SPECT) MPS performed between September 2020 and September 2023 in participants aged 18–70 years. Participants were divided into two groups: those who received the BNT162b2 mRNA vaccine (n=93) and those who did not (n=88). Individuals with prior cardiac surgery, severe valvular disease, atrial fibrillation, or other significant comorbidities affecting myocardial function were excluded. Demographic data, cardiovascular risk factors, and MPS parameters (end-diastolic volume [EDV], end-systolic volume [ESV], ejection fraction [EF], summed stress score [SSS]) were compared between groups.

Results: No significant intergroup differences were observed in age, sex, or cardiovascular risk factors ($p > 0.05$). The mean SSS was 2.54 ± 3.69 in vaccinated and 2.78 ± 4.15 in unvaccinated individuals ($p = 0.453$). Mean EF values between the vaccinated and unvaccinated groups were 64.27 ± 7.85% compared to 62.16 ± 9.79% ($p = 0.11$). No significant differences were observed in EDV (74.91 ± 18.63 ml vs. 77.18 ± 23.66 ml; $p = 0.48$) and ESV (27.58 ± 11.24 ml vs. 30.65 ± 15.69 ml; $p = 0.14$). No statistically significant difference was found in the frequency of ischemic MPS findings between the vaccinated and unvaccinated groups (34% vs. 35%; $p = 0.89$).

Conclusion: No adverse effects of the BNT162b2 mRNA vaccine on late-term myocardial perfusion or left ventricular function were detected.

Keywords: Myocardial Perfusion Scintigraphy, BNT162b2 mRNA Vaccine, Summed Stress Score, Cardiovascular Safety

ÖZET

Amaç: Bu çalışma, miyokard perfüzyon sintigrafisi (MPS) kullanarak BNT162b2 mRNA COVID-19 aşısının miyokard perfüzyonu üzerindeki geç dönem etkilerini araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Eylül 2020 ile Eylül 2023 tarihleri arasında 18-70 yaş arası katılımcılarda farmakolojik stres ve istirahat tek foton emisyon bilgisayarlı tomografi (SPECT) MPS içeren 181 hasta üzerinde retrospektif bir analiz gerçekleştirilmiştir. Katılımcılar iki gruba ayrılmıştır: BNT162b2 mRNA aşısı olanlar (n=93) ve olmayanlar (n=88). Önceden kalp cerrahisi geçirmiş, şiddetli kalp kapak hastalığı, atriyal fibrilasyon veya miyokardiyal fonksiyonu etkileyen diğer önemli komorbiditeleri olan bireyler çalışma dışı bırakıldı. Demografik veriler, kardiyovasküler risk faktörleri ve MPS parametreleri (diyastol sonu hacmi [EDV], sistol sonu hacmi [ESV], ejeksiyon fraksiyonu [EF], toplam stres skoru [SSS]) gruplar arasında karşılaştırıldı.

Bulgular: Yaş, cinsiyet veya kardiyovasküler risk faktörlerinde gruplar arasında anlamlı bir fark gözlenmedi ($p > 0,05$). Ortalama SSS, aşılananlarda 2,54 ± 3,69 ve aşılanmayanlarda 2,78 ± 4,15 idi ($p = 0,453$). Aşılanan ve aşılanmayan gruplar arasındaki ortalama EF değerleri sırasıyla %64,27 ± 7,85 ve %62,16 ± 9,79 idi ($p = 0,11$). EDV (74,91 ± 18,63 ml vs. 77,18 ± 23,66 ml; $p = 0,48$) ve ESV (27,58 ± 11,24 ml vs. 30,65 ± 15,69 ml; $p = 0,14$) arasında anlamlı bir fark gözlenmedi. Aşılanan ve aşılanmayan gruplar arasında iskemik MPS bulgularının sıklığı açısından istatistiksel olarak anlamlı bir fark bulunmamıştır (34% vs. 35%; $p = 0,89$).

Sonuç: BNT162b2 mRNA aşısının geç dönemde miyokardiyal perfüzyon veya sol ventrikül fonksiyonu üzerinde herhangi bir olumsuz etkisi tespit edilmemiştir.

Anahtar Kelimeler: Miyokard perfüzyon sintigrafisi, BNT162b2 mRNA Aşısı, Toplam Stres Skoru, Kardiyovasküler Güvenlik.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is one of the most highly transmissible infectious diseases worldwide, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus (1). During the early phase of the COVID-19 pandemic, preventive strategies were limited to the use of face masks, social distancing, and isolation of infected individuals. Subsequently, messenger RNA (mRNA)-based vaccines developed by Pfizer-BioNTech and Moderna were introduced and effectively employed to mitigate the global health crisis. These vaccines induce an immune response against SARS-CoV-2, either preventing infection or reducing disease severity. The rapid development and widespread administration of mRNA vaccines have played a crucial role in controlling the pandemic. However, as these vaccines were developed under emergency use authorization, ongoing concerns persist regarding their potential long-term cardiovascular effects (2–4). Reported cardiovascular adverse events following vaccination include myocarditis, pericarditis, arrhythmia, and thromboembolic complications, although the overall incidence of these conditions remains low (5–9). Myocardial perfusion scintigraphy (MPS) is an extensively used non-invasive functional imaging method for evaluating blood flow to the heart muscle. This technique is particularly effective in detecting myocardial ischemia, scarring, or other perfusion abnormalities (10).

In Türkiye, the BNT162b2 mRNA vaccine, developed by Pfizer-BioNTech, has been extensively administered. While the short-term cardiovascular effects of mRNA vaccines are relatively well known, their late-term effects on myocardial perfusion remain poorly understood. The aim of this study is to compare the late-term effects on myocardial perfusion between individuals who received the BNT162b2 mRNA vaccine and those who did not, using the MPS imaging method. The findings of this study may provide a better understanding of the late-term cardiovascular effects of the BNT162b2 mRNA vaccine.

MATERIALS AND METHODS

Research Methodology

This retrospective analysis encompassed patients aged from 18 to 70 years old who received MPS with pharmacologic stress and rest single-photon emission computed tomography (SPECT) from September 2020 to September 2023. The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Necmettin Erbakan University Ethics Committee (decision number: 2025/5625) on March 7, 2025.

The inclusion and exclusion criteria for participant selection in this study are outlined below.

Inclusion Criteria

• Referred for MPS due to clinical indications, including chest pain, dyspnea, or abnormal exercise stress test results suggestive of suspected coronary artery disease (CAD).

• Known vaccination status for the BNT162b2 mRNA vaccine (vaccinated or unvaccinated).

• Minimum interval of 6 months (180 days) between the last BNT162b2 vaccine dose and MPS for vaccinated patients.

Exclusion Criteria

• Confirmed atherosclerotic CAD (documented by angiography, coronary CT angiography, or history of myocardial infarction).

• History of heart failure, pulmonary thromboembolism, severe chronic obstructive pulmonary disease, malignancy, or renal failure.

• Prior cardiac surgery, severe valvular disease.

• Receipt of COVID-19 vaccines other than BNT162b2.

• Active or recent (<6 months) COVID-19 infection.

The medical history, clinical and demographic data, vaccination status, vaccine type, number of doses, and vaccination dates for all participants were collected and recorded from patient interviews and the electronic medical record system.

Patient Grouping

The patients were classified into two groups according to their receipt of the BNT162b2 mRNA vaccination aimed at the SARS-CoV-2 virus: one group received the vaccine, while the other group did not.

Acquisition and Analysis of SPECT Images

The patients were instructed to cease the use of calcium channel blockers, beta-blockers, nitrates, and caffeine-containing medications 24 to 48 h prior to the MPS imaging. The MPS investigation was conducted following the directives established by the European Society of Nuclear Medicine (11). A same-day protocol was employed for the stress-rest SPECT imaging. This approach involved an initial conducting of pharmacologic stress imaging, followed by rest imaging around 4 h later on the same day. Adenosine was supplied intravenously at a dosage of 140 µg/kg/min for a duration of 6 minutes during the pharmacologic stress test (11). Technetium-99m-methoxyisobutylisonitrile (Tc-99m MIBI) was administered as an intravenous bolus at the end of the 3rd min of adenosine infusion. Stress SPECT images were obtained 45 min post-injection of Tc-99m MIBI. During stress imaging, 8–12 mCi of Tc-99m MIBI was injected, whereas 24–36 mCi was provided during rest imaging approximately 4 h after the initial radiopharmaceutical injection (11).

The SPECT examination employed a dual-head camera (Siemens Medical Solutions, Forchheim, Germany) equipped with a low-energy high-resolution collimator. Eight-frame overlays were used, and a pulse length acceptability threshold of 20% was created. The data were recorded in a 64 × 64 matrix. Image interpretation was performed both visually and quantitatively using the Cedars-Sinai Quantitative Perfusion SPECT software. The left ventricular (LV) ejection fraction (EF) and wall motion were acquired from gated images around 4h after the initial radiopharmaceutical injection.

Stress and rest images were evaluated in a double-blind manner by two experienced nuclear medicine specialists using a 17-segment model of the left ventricle and a five-point scale (0 = normal perfusion, 1 = slightly reduced, 2 = moderately reduced, 3 = significantly reduced, 4 = perfusion defect) (12). Interobserver agreement was evaluated using Cohen's Kappa

coefficient, yielding a Kappa value of 0.85 (95% CI: 0.79–0.91), indicating excellent reproducibility. In instances of discord between the two specialists, further consultation was obtained from additional professionals within the department, and all discrepancies were solved through a consensus.

Perfusion scores were calculated to assess myocardial perfusion abnormalities and their severity. The summed stress score (SSS) represents the sum of all perfusion defects noted on the stress image, the summed rest score (SRS) indicates the sum of all defects detected on the rest image, and the summed difference score (SDS) is calculated from the difference among the stress and rest values (13). The QGS software autonomously calculated left ventricular functional parameters, encompassing left ventricular end-diastolic volume (EDV), left ventricular end-systolic volume (ESV), and EF. The patients were classified into two groups: those with an SSS of 0–3 and those with an SSS of 4 or higher. In this study, images having an SSS of 4 or higher were classified as abnormal.

Statistical Analyses

The sample size was calculated using G*Power 3.1 software, assuming a medium effect size (Cohen's d = 0.5), a significance level of 0.05, and a statistical power of 80%. Accordingly, a minimum of 64 participants per group was required. In the present study, a total of 93 participants were included in the vaccinated group and 88 individuals were in the unvaccinated group, both exceeding the minimum sample size needed to maintain adequate statistical power.

Statistical processing and analysis were performed using SPSS 25.0 software. To evaluate the normal distribution of numerical data, histogram plots, skewness, kurtosis, and the Kolmogorov-Smirnov test were employed. According to these analyses, age, ESV, EDV, and EF followed a normal distribution, while SSS did not. The Student's t-test was employed for regularly distributed variables, whereas the Mann-Whitney U test was used for non-normally distributed data. The chi-square test was used for categorical data. Descriptive statistics were provided as counts and percentages for qualitative data, and as means ± standard deviations or medians for quantitative data. For all studies, a p-value below 0.05 was assumed to indicate statistical significance.

RESULTS

The study involved a total of 181 individuals. The average age of the participants was 54.94 ± 10.03 years, with 53% identifying as female and 47% as male. All vaccinated subjects had received a minimum of two doses of the BNT162b2 mRNA vaccine. No significant differences were observed in age, gender, or cardiovascular risk factors (hypertension, diabetes, smoking, and family history) among the two groups (p> 0.05). Table 1 shows the clinical and demographic features of the patients. Table 2 presents a comparison of the quantitative data obtained from MPS and myocardial perfusion patterns

Table 1. Clinical and Demographic Characteristics of the Participants

General Characteristics		Vaccine + (n=93)	Vaccine – (n=88)	pValue
Age (Years)	Mean ± SD	53.96±9.36	55.97±10.73	0.185
Gender	Male/Female	43/50	42/46	0.841
Hypertension	Yes/No	46/47	49/39	0.402
Smoking	Yes/No	29/64	25/63	0.684
Diabetes mellitus	Yes/No	26/67	23/65	0.783
Hyperlipidemia	Yes/No	11/82	9/79	0.64
Family history of CAD	Yes/No	46/47	51/37	0.252
Chest pain	Yes/No	81/12	78/10	0.615
Dyspnea	Yes/No	21/72	17/71	0.566
Abnormal Stress ECG Test	Yes/No	49/44	46/42	0.837

SD: Standard Deviation; ECG: Electrocardiogram; n: sample size

Table 2. Comparison of MPS Data and Perfusion Patterns between Groups

MPS DATA		Vaccine + (n=93)	Vaccine – (n=88)	pValue
ESV (mL)	Mean ± SD	27.58 ±11.24	30.65± 15.69	0.14
EDV (mL)	Mean ± SD	74.91 ± 18.63	77.18 ± 23.66	0.48
EF (%)	Mean± SD	64.27 ± 7.85	62.16 ± 9.79	0.11
SSS	Mean± SD	2.54 ± 3.69	2.78 ± 4.15	
	Median (IQR 25-75)	0 (0-6)	0 (0-7)	0.45
SRS	Median (IQR 25-75)	0 (0-2)	0 (0-2)	0.79
MPS Result	Normal/Ischemia (%)	61/32 (66/34)	57/31 (65/35)	0.89

MPS: Myocardial Perfusion Scintigraphy; EDV: End-diastolic volume; ESV: End-systolic volume; SSS: Summed Stress Score; SRS: Summed Rest Score; SD: Standard Deviation, EF:Ejection Fraction; IQR: Inter Quartile Range; mL: milliliter; n: sample size

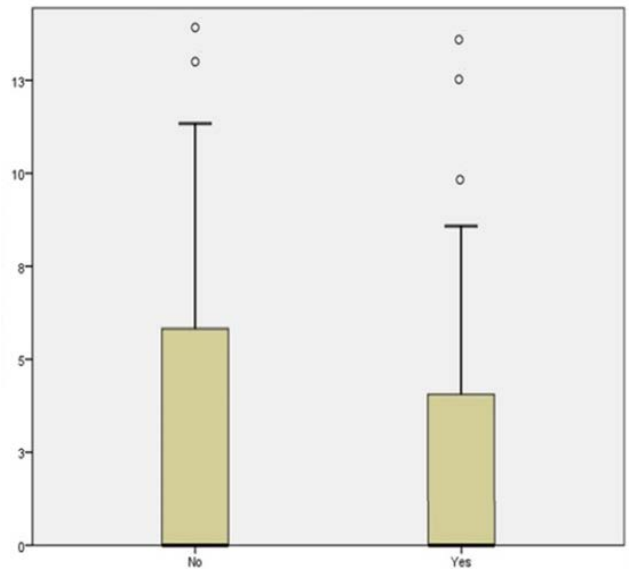

Figure 1. Distribution of Summed Stress Scores among vaccinated and unvaccinated participants.

Y-axis: Summed Stress Score (SSS) **X-axis:** Vaccination Status (vaccinated and unvaccinated)

between the two groups.

No substantial differences were detected between the two groups in any of the analyses ($p > 0.05$). Despite the vaccinated group exhibiting a lower SSS, no statistically significant difference between the two groups was observed ($p > 0.05$). The boxplot illustrating the distribution of SSS between vaccinated and unvaccinated participants is presented in Figure 1.

As can be seen in the figure, although the median SSS value was slightly lower in the vaccinated group compared with the unvaccinated group, this difference did not reach statistical significance ($p = 0.45$; Mann–Whitney U test).

DISCUSSION

The effectiveness of mRNA vaccines against COVID-19 infection in reducing disease severity and preventing hospitalizations was previously strongly demonstrated by randomized controlled trials and real-world data (14, 15). However, as with any medical intervention, concerns arose about potential side effects, particularly those affecting the cardiovascular system. While short-term adverse effects, such as myocarditis and pericarditis, were extensively documented in the literature (2-9), the long-term cardiovascular consequences of mRNA vaccines remain insufficiently explored. MPS is a recognized, harmless imaging modality used to evaluate myocardial blood flow. It excels in detecting myocardial ischemia, scarring, and other perfusion abnormalities (10). However, despite its widespread application, its use in evaluating the long-term effects of mRNA vaccines on myocardial perfusion remains limited. To bridge this gap in the literature, in the present study, we compared myocardial perfusion patterns between individuals vaccinated with BNT162b2 and those who were not. To the best of our knowledge, the present study is the first to assess the late-term effects of the BNT162b2 mRNA vaccine on myocardial perfusion using MPS.

We found no significant differences in myocardial perfusion parameters, including the SSS, between the vaccinated and unvaccinated groups. This suggests that BNT162b2 does not exert a detrimental effect on myocardial perfusion in the long term. This result is particularly reassuring in the context of concerns surrounding the long-term cardiovascular safety of mRNA vaccines. This evidence also aligns with extensive observational data, such as that from Barda et al. (16) who reported that serious cardiovascular events were rare in a nationwide study of BNT162b2 administration. mRNA vaccines such as BNT162b2 have been crucial in the pandemic response by generating a strong immune response against SARS-CoV-2, therefore avoiding or alleviating illness severity. However, cardiovascular adverse events reported in previous studies (5–9, 17) reinforced the ongoing debate on the long-term cardiovascular safety of mRNA vaccines. These observations fueled debates about the late-term cardiovascular safety of mRNA vaccines. The mechanisms underlying these adverse effects remain poorly understood. A prevailing hypothesis predicts that the SARS-CoV-2 spike protein, produced in response to mRNA vaccination, interacts with angiotensin-converting enzyme 2 (ACE2) receptors, which are abundantly expressed in cardiovascular tissues (18). This interaction may trigger T-cell activation, potentially leading to myocardial damage by targeting both the vaccine-induced spike protein and cardiac antigens (19, 20). Furthermore, another study suggested that myocarditis following BNT162b2 vaccination may be linked to an inflammatory process (21). However, whether these mechanisms translate into long-term perfusion abnormalities remains uncertain, warranting further research.

Previous studies provided positive insights into the safety profile of mRNA vaccines, helping to alleviate public concerns about their rapid development during the COVID-19 pandemic (14,15,17). Adverse effects observed in the myocardium, particularly in the early post-vaccination period, were frequently associated with inflammatory responses and endothelial dysfunction (23-27). For instance, in a prospective study, Yamaji (28) found that endothelial dysfunction in relatively healthy individuals following vaccination is transient, resolving within 6 months without affecting vascular smooth muscle function. In our study, the lack of significant perfusion differences between the two groups may be attributed to the resolution of endothelial dysfunction and the preservation of vascular smooth muscle function, as previously demonstrated, considering that the interval between vaccination and MPS was at least six months (28). In addition, a Nordic (29) cohort study demonstrated that the late-term cardiovascular effects of BNT162b2 are minimal. Since our study involved a minimum interval of six months between vaccination and MPS, these findings may account for the lack of perfusion differences

observed between the two groups. While our findings suggest that BNT162b2 does not adversely affect myocardial perfusion in the late-term, questions remain about its cardiovascular safety in higher-risk populations, such as those with pre-existing endothelial dysfunction or coronary artery disease. These groups may be more susceptible to vaccine-related cardiovascular effects due to the underlying vascular pathology. Future research would be needed to explore these populations using advanced imaging techniques to detect subclinical changes.

COVID-19 infection may cause myocardial damage through mechanisms such as cytokine-mediated inflammation or microvascular dysfunction, potentially impacting MPS findings. Although the present study excluded individuals with active or recent COVID-19 symptoms to minimize confounding, we cannot completely exclude the long-term myocardial effects of COVID-19 infection (13,18,30). Future research, including systematic documentation of COVID-19 history and serologic testing, would be needed to distinguish infection-related from vaccine-related cardiac effects. Furthermore, despite these data suggesting a positive assessment of BNT162b2's cardiovascular safety, the present study has several limitations. The one-center, retrospective study design and limited sample size (n = 181) may restrict generalizability of the findings. Furthermore, as a retrospective analysis, the present study is inherently limited in its ability to establish causal relationships and may be subject to selection bias, which should be considered when interpreting the results. Additionally, the study population consisted of individuals without previously known endothelial dysfunction, which may limit generalizability of the results to higher-risk populations. Although cardiovascular risk factors (e.g., high blood pressure, diabetes mellitus, dyslipidemia, cigarette smoking, age, gender, and family history) were similar between the vaccinated and unvaccinated groups, their potential impact on vaccine-related outcomes requires examination in larger cohorts.

Furthermore, due to the lack of documentation of booster doses in some patient records, we did not perform a comprehensive subgroup analysis based on the number of doses. Similarly, while the statistical methodology employed was sufficiently robust for primary comparisons, constraints inherent to the dataset and the moderate sample size limited the implementation of more sophisticated analytical techniques for subgroup evaluations. Consequently, a comprehensive investigation into potential heterogeneity and subtle patterns within these subgroups could not be conducted. Echocardiographic parameters were not systematically available due to the retrospective nature of the study; therefore, they were not included in the analysis to prevent selection bias. In addition, patients exhibiting ischemia identified using MPS were not routinely evaluated with coronary CT angiography or invasive coronary angiography due to the retrospective nature of the study. However, such complementary imaging could have provided valuable anatomical correlation. Future studies integrating MPS with coronary CT angiography or cardiac MRI are warranted to better delineate the etiology of perfusion abnormalities. Fronza et al. (31) demonstrated that cardiac MRI can assess subclinical effects in asymptomatic individuals post-mRNA vaccination. Finally, MPS's inability to directly evaluate microvascular function or subclinical inflammation suggests that subtle cardiovascular effects of the vaccine may have been overlooked. This suggests that complementary techniques, such as cardiac MRI, could prove valuable in future studies.

Despite the limitations outlined above, the present study makes a significant contribution to understanding BNT162b2's long-term cardiovascular safety and provides a reassuring perspective from a public health standpoint. The minimal impact of the vaccine on myocardial perfusion may support reliability of mRNA technology not only for combating COVID-19, but also for innovative applications such as cancer immunotherapy. This being said, in order to enhance the robustness of these findings, multicenter, prospective studies with extended follow-up periods would be necessary.

CONCLUSION

Unlike the short-term adverse effects of the BNT162b2 mRNA vaccine, in the present study, we focused on examining the long-term consequences on myocardial perfusion. No association was found between the BNT162b2 vaccine and increased myocardial ischemia. This result may help to alleviate concerns that the BNT162b2 mRNA vaccine could have a detrimental effect on myocardial perfusion in the long-term. It can be considered a reassuring finding, particularly in terms of public health. Further comprehensive and long-term studies would be needed to further strengthen the cardiovascular safety profile of mRNA vaccines.

DECLARATIONS

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RESEARCH ARTICLE

The Role of p40, p63, MAdL and TTF-1 in Differential Diagnosis of Primary Lung Adenocarcinoma, Squamous Cell Carcinoma and Metastatic Adenocarcinomas of The Lung

Primer Akciğer Adenokarsinomu ile Skuamöz Hücreli Karsinom Ayırımında ve Akciğerin Metastatik Adenokarsinomlarında p40, p63, MAdL ve TTF-1'in Rolü

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ABSTRACT

Objective: Lung cancer is the most common and fatal type of cancer in both women and men. Due to differences in treatment, it is important to accurately distinguish between lung cancer subtypes. Algorithms recommend using maximum of two markers (ie, a single adenocarcinoma marker and a single squamous marker) in each case to preserve tissue for molecular studies. This study aimed to determine the optimal combination of these markers.

Materials and Methods: This retrospective study included 62 cases diagnosed between 2010 and 2015, consisting of 29 primary lung adenocarcinoma (ADC), 19 squamous cell carcinoma (SCC), and 14 metastatic ADC to the lung. Immunohistochemical analyses for TTF-1, p40, p63, and MAdL were performed. Staining intensity and the percentage of positive tumor cells were recorded with sensitivity and specificity values also calculated.

Results: TTF-1 showed high intensity and positivity in 79.31% of primary lung ADCs, with a sensitivity of 96.55% and specificity of 100%. p40 showed high intensity staining in 84.21% of SCCs, with a sensitivity of 89.47% and specificity of 100%. p63 exhibited 100% sensitivity for SCC but low specificity (44.82%) due to focal positivity in ADCs. MAdL had 82.75% sensitivity and 100% specificity for ADC. No marker positively stained metastatic ADCs.

Conclusion: Of the tested markers, TTF-1 showed the highest diagnostic accuracy for ADC and p40 for SCC. MAdL could serve as a supportive marker in ADC. p63 should considered with caution due to its low specificity. Particularly in small biopsy samples, to preserve tissue for molecular studies, a limited panel combining p40 and TTF-1 immunohistochemical markers is recommended for routine diagnostic use.

Keywords: Lung cancer, p40, p63, MAdL, TTF-1

ÖZET

Amaç: Akciğer kanseri, hem kadınlarda hem de erkeklerde en sık görülen ve en ölümcül kanser türüdür. Tedavi farklılıkları nedeniyle, alt tipleri doğru bir şekilde ayırt etmek önemlidir. Algoritmalar, moleküler çalışmalar için dokuyu korumak amacıyla her vakada en fazla iki immunohistokimyasal belirteç (tek bir adenokarsinom belirteci ve tek bir skuamöz belirteç) kullanılmasını önermektedir. Bu çalışma, belirteçlerin optimal kombinasyonunu belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, 2010 ile 2015 yılları arasında tanı konulan 62 vaka, 29 primer akciğer adenokarsinomu (ADK), 19 skuamöz hücreli karsinom (SHK) ve 14 akciğere metastatik ADK dahil edilmiştir. İmmünohistokimyasal olarak TTF-1, p40, p63 ve MAdL uygulanmıştır. Boyama yoğunluğu ve pozitif tümör hücrelerinin yüzdesi kaydedilmiştir. Duyarlılık (sensitivite) ve özgüllük (spesifite) değerleri hesaplanmıştır.

Bulgular: TTF-1, primer akciğer ADK'larının %79,31'inde yüksek yoğunlukta pozitiflik gösterdi, duyarlılığı %96,55 ve özgüllüğü %100 idi. p40, SHK'ların %84,21'inde yüksek yoğunluklu boyanma gösterdi, duyarlılığı %89,47 ve özgüllüğü %100 idi. p63, SHK için %100 duyarlılık gösterdi, ancak ADK'larda fokal pozitiflik nedeniyle düşük özgüllük (44,82%) sergiledi. MAdL, ADK için %82,75 duyarlılık ve %100 özgüllük gösterdi. Hiçbir marker metastatik ADK'ları boyamadı.

Sonuç: ADK için TTF-1 ve SHK için p40 en yüksek tanısal doğruluğu gösterdi. MAdL, ADK'da destekleyici bir marker olarak kullanılabilir. p63, düşük özgüllüğü nedeniyle dikkatle yorumlanmalıdır. Özellikle küçük biyopsi örneklerinde, moleküler çalışmalar için dokuyu korumak amacıyla, rutin kullanım için p40 ve TTF-1 immünohistokimyasal marker kombinasyonundan oluşan sınırlı bir panel önerilir.

Anahtar Kelimeler: Akciğer kanseri, p40, p63, MAdL, TTF-1

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INTRODUCTION

Lung cancer (LC) ranks first in incidence and mortality among men and second among women. The incidence and mortality of LC in men is approximately twice as high as in women. Globally, LC accounts for 18.7% of all cancer related deaths, with 2.5 million new cases reported and 1.8 million deaths annually. In 2022, LC was the most frequently diagnosed malignancy, representing 12.4% of all cancers worldwide (1). Nearly 99% of lung tumors are carcinomas (2). Following a steady increase in recent years, lung adenocarcinoma (ADC) has now become the most common histological subtype, comprising more than 50% of all LCs (3). Clinically, primary LCs are classified into two major categories of importance: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). The lung is also among the most frequent metastatic sites, with 15-25% of metastatic tumors presenting in the pulmonary parenchyma. The most common primary origins of LCs include breast, colorectal, gastric, pancreatic, renal, malignant melanoma, prostate, thyroid, and gynecologic malignancies (4). Although SCLC is highly sensitive to chemotherapy and while surgical intervention provides no major prognostic benefit except for early stage disease, the mainstay of early-stage NSCLC treatment is surgery, complemented with oncologic therapies in advanced disease (5). Therefore, accurate pathological evaluation and classification are crucial in guiding treatment decisions. Since the implementation of the 2015 WHO Classification, immunohistochemistry (IHC) has become indispensable in the diagnostic work-up of lung carcinomas (6). In addition to distinguishing SCLC from NSCLC, IHC is also essential for the subclassification of NSCLC to lung ADC or squamous cell carcinoma (SCC) (7). To preserve tissue for molecular studies, current diagnostic algorithms recommend the use of no more than two IHC markers, typically one ADC marker and one squamous marker (8). In most tumors, accurate classification can be made with this limited panel.

Thyroid transcription factor-1 (TTF-1) is highly expressed in lung and thyroid carcinomas and is widely used in routine practice for diagnosing lung ADC (9-13). Currently, TTF-1 is the most commonly used marker to distinguish lung ADC from SCC and from metastatic ADCs to the lung (7,14). p63, first described in 1998, is a gene located on chromosome 3q27-29, consisting of 15 exons and encoding at least six protein isoforms (15). In humans, p63 is expressed in head and neck SCC, pulmonary SCC, esophageal SCC, urothelial carcinoma of the bladder, and gastric carcinoma (16-18). p40 is an isoform of p63, specifically the ΔNp63 isoform. Several studies have evaluated the role of p40 in differentiating pulmonary SCC from ADC, reporting superior p40 specificity for SCC compared with p63 (19). In studies conducted by Bishop et al. (20) and Nonaka et al. (21), p40 showed 100% sensitivity and specificity for the diagnosis of pulmonary SCC. Similarly, Tacha et al. reported 85% sensitivity and 98% specificity for p40 (22). MAdL is a recently introduced, highly specific marker for lung ADC, as described by Schultz et al. Cytoplasmic immunoreactivity for MAdL shows strong positive signals in type II alveolar epithelial cells and intraalveolar macrophages following standard staining protocol optimization (23).

Given the therapeutic implications of NSCLC subtyping, establishing a definitive differential diagnosis is essential. Nevertheless, diagnostic challenges can still arise, even when using conventional IHC markers. Therefore, there remains a need for novel IHC markers that can support the pathologist in refining differential diagnosis, highlighting the necessity for further research in this field. In this context, this study aimed to evaluate the diagnostic significance of p40, p63, MAdL, and TTF-1 expression in the differential diagnosis of lung ADC, SCC, and metastatic ADCs to the lung.

MATERIALS AND METHODS

Study Design and Case Selection

This retrospective study included 62 cases of lung ADC, SCC, and metastatic ADC to the lung. The cases were retrieved from the pathology archives of the Department of Medical Pathology, Faculty of Medicine, Necmettin Erbakan University, covering between March 2010 and May 2015. The sample set consisted of 29 cases of primary lung ADC, 19 cases of pulmonary SCC, and 14 cases of metastatic ADC diagnosed on transthoracic fine needle aspiration biopsies, bronchoscopy biopsies, or lobectomy specimens.

Ethics Approval

Ethical approval for the study was obtained from the Necmettin Erbakan University Meram Faculty of Medicine Drug and Non-Medical Device Research Ethics Committee (Approval No: 2013/543; Date: 06.12.2013).

Immunohistochemical Analysis

Formalin fixed, paraffin embedded tissue blocks that best represented the tumor and included adjacent nontumoral lung tissue were selected for IHC analysis. Sections of 4-5 µm thickness were cut and mounted on positively charged slides. Following deparaffinization, staining was performed with an automated IHC staining system (VENTANA BenchMark XT, Ventana Medical Systems, USA). The Ultraview Universal DAB Detection Kit (Cat. No: 760-500; Lot No: F00544) was used for secondary antibody detection.

The following primary antibodies were used:

- MAdL (1:100 dilution; Cat. No: MSK083-05, Zytomed, Germany)
- TTF-1 Ab-1 (1:50 dilution; Cat. No: MS-699-P0, P1; Thermo Scientific, USA)
- p63 Ab-1 (clone 4A4; 1:100 dilution; Cat. No: MS-1081-P0, P1; Thermo Scientific, USA)
- p40 (polyclonal; 1:100 dilution; Cat. No: PA5-28477; Thermo Scientific, USA)

Evaluation of Staining

Slides were stained with hematoxylin and eosin alongside IHC stained sections and were evaluated independently by two expert pathologists using a light microscope (Olympus BX51, Japan). For MAdL, cytoplasmic membranous staining was considered positive, while nuclear staining was accepted as positive for p40, p63, and TTF-1. Areas with the most abundant staining were selected, and 1000 tumor cells were counted at ×400 magnification to determine the percentage of positively

stained tumor cells.

The extent of staining for p40, p63, and TTF-1 was scored as:
(-) 0%
(+) 1-25%
(++) 26-50%
(+++) 51-75%
(++++): >75%
For MAdL, staining intensity was scored as:
(-) no staining
(+) weak
(++) moderate
(+++) strong

For statistical analyses, 0% was accepted as negative, (+) and (++) was low intensity staining, and (+++) or (++++) was high intensity staining. For MAdL, only (+++) was categorized as high intensity staining.

Statistical Analysis

All statistical analyses were performed with IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA). The sensitivity and specificity for each IHC marker was calculated as follows:
Sensitivity = True Positive / (True Positive + False Negative) × 100
Specificity = True Negative / (False Positive + True Negative) × 100

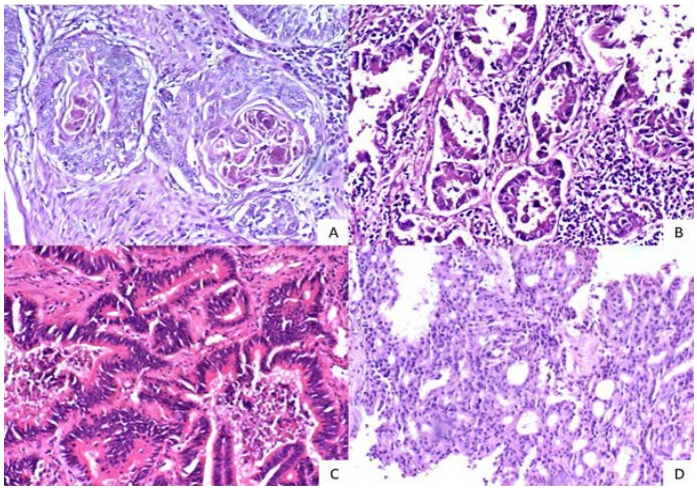

Figure 1. Hematoxylin and eosin stained slides of SCC, ADC, and metastatic ADC to lung

(A) SCC, hematoxylin and eosin, x100. (B) ADC, hematoxylin and eosin, x100. (C) Metastatic ADC (metastasis of colon ADC), hematoxylin and eosin, x100. (D) Metastatic ADC (metastasis of prostatic ADC), hematoxylin and eosin, x100.
ADC=adenocarcinoma. SCC=squamous cell carcinoma.

RESULTS

With the advent of molecular testing and targeted therapies in LC, the distinction between ADC and SCC and accurate histological subtyping have become increasingly crucial for delivering patient-specific treatments. ADC and SCC can be diagnosed based on morphology alone in 50-70% of cases; however, IHC is generally required for poorly differentiated tumors that lack a definitive morphology (8) (Figure 1). In this study, TTF-1 was accepted as the reference marker for primary lung ADC and p40 for SCC. The expression profiles of TTF-1, p63, p40, and MAdL were evaluated in primary lung ADC, pulmonary SCC, and metastatic ADC to the lung (Table 1). TTF-1 Expression: Among the 29 primary lung ADC cases, 16 had (++++) staining in the tumor area, seven showed (+++), one showed (++), and four showed (+), while one case was negative. Of the 28 positive cases, 23 displayed high intensity and five had low intensity staining (Figure 2). No staining was detected in SCC (n=19) or in metastatic ADC (n=14). TTF-1 positivity with high intensity was observed in 79.31% (23/29) of primary ADC cases, and low intensity staining was seen in 17.24% (5/29) of cases. The sensitivity and specificity of TTF-1 for primary ADC were 96.55% and 100%, respectively.

p63 Expression: All SCC cases stained positively for p63 (15 [++++] , two [+++], two [+], and none [++]), with 17 showing high intensity and two with low intensity staining. In primary lung ADC, 16 cases showed (+) and 13 were negative; all positive cells stained with low intensity (Figure 3). No staining was observed in metastatic ADC. Overall, p63 had 100% sensitivity for SCC, but specificity was 44.82% due to low intensity staining in 55.17% (16/29) of ADC cases. p40 Expression: In SCC, 13 cases showed (++++) staining, three (+++), and one (++), while two

Table 1. Evaluation of immunohistochemistry markers in all cases

Tumor type	**Squamous cell carcinoma (n=19)**				**Primary lung adenocarcinoma (n=29)**				**Metastatic adenocarcinoma to lung (n=14)**			
Staining Intensity	Negative	Positive (low)		Positive (high)		Negative	Positive (low)		Positive (high)		Negative	Positive (low)		Positive (high)	
	0	(+)	2 (+)	3 (+)	4 (+)	0	1 (+)	2 (+)	3 (+)	4 (+)	0	1 (+)	2 (+)	3 (+)	4 (+)
p63	0	2	0	2	15	13	16	0	0	0	14	0	0	0	0
p40	2	0	1	3	13	29	0	0	0	0	14	0	0	0	0
TTF-1	19	0	0	0	0	1	4	1	7	16	14	0	0	0	0
MAdL	19	0	0	0	*	5	8	5	11	*	14	0	0	0	*

*The intensity of staining for MAdL was scored at most as 3 (+), so no result value was written for these areas.

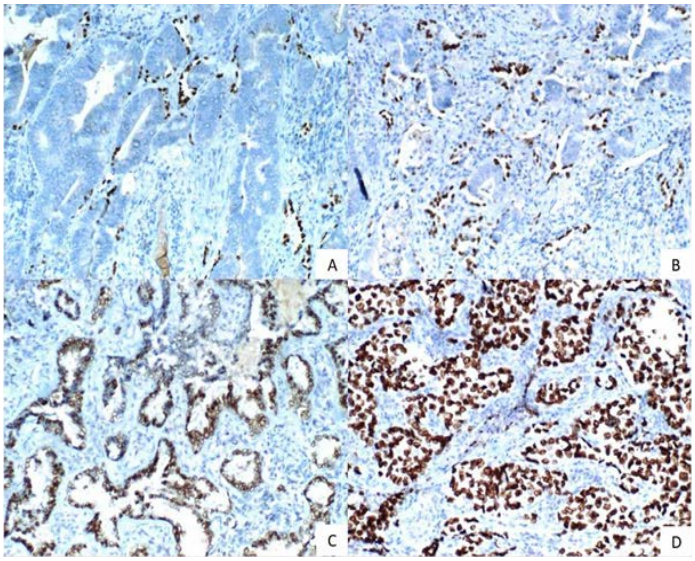

Figure 2. TTF-1 staining in primary lung ADC
(A) (+), x100. (B) (++), x100. (C) (+++), x100. (D) (++++), x100.
ADC=adenocarcinoma.

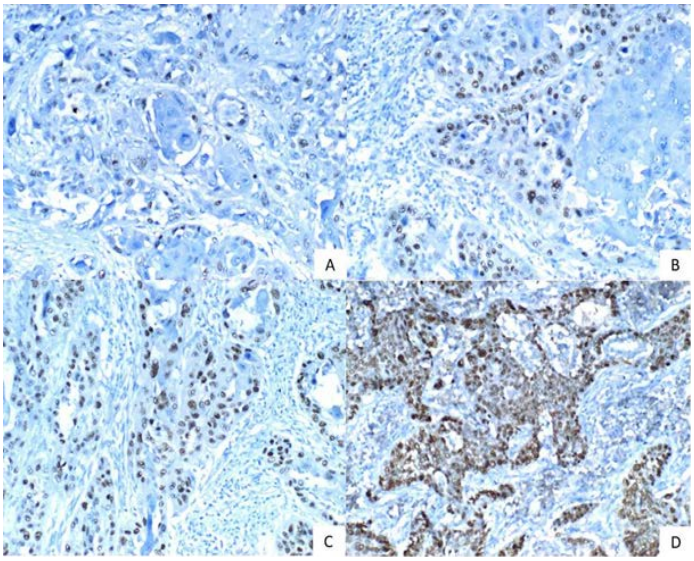

Figure 4. p40 staining in SCC
(A) (+), x100. (B) (++), x100. (C) (+++), x100. (D) (++++), x100.
SCC=squamous cell carcinoma.

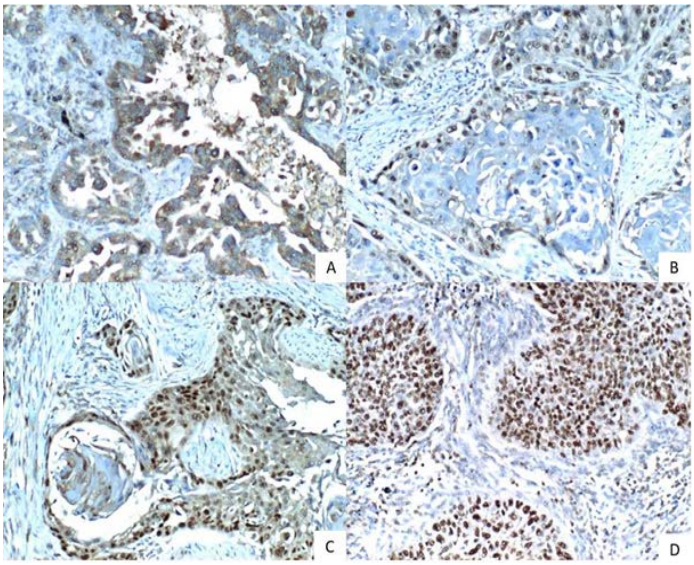

Figure 3. p63 staining in SCC and ADC
(A) p63 staining in ADC (+), x100. (B) p63 staining in SCC (+), x100. (C) p63 staining in SCC (+++), x100. (D) p63 staining in SCC (++++), x100.
ADC=adenocarcinoma. SCC=squamous cell carcinoma.

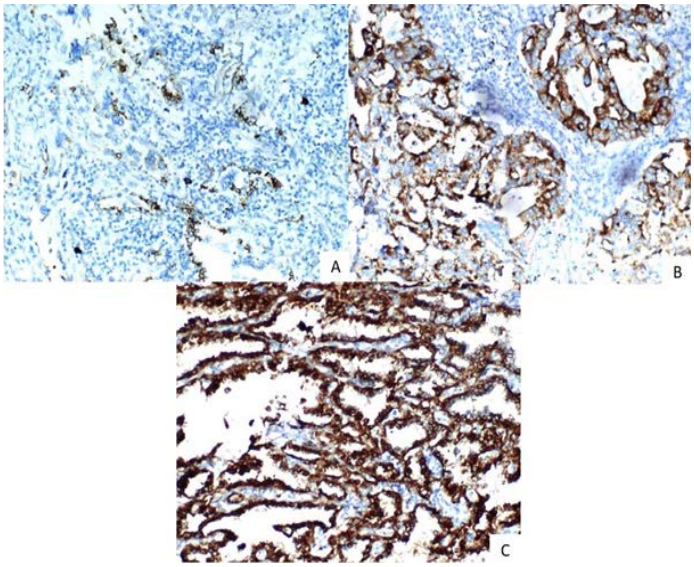

Figure 5. MAdL staining in primary lung ADC
(A) (+), x100. (B) (++), x100. (C) (+++), x100.
ADC=adenocarcinoma.

Table 2. Expression of p40 + p63 combined in cases of squamous cell carcinoma and primary lung adenocarcinoma

p40 + p63	Squamous cell carcinoma	Primary lung adenocarcinoma
Positive	19	16
Negative	0	13

Table 3. Expression of MAdL + TTF-1 combination in cases diagnosed with primary lung adenocarcinoma and squamous cell carcinoma

MAdL + TTF-1	Primary lung adenocarcinoma	Squamous cell carcinoma
Positive	28	0
Negative	1	19

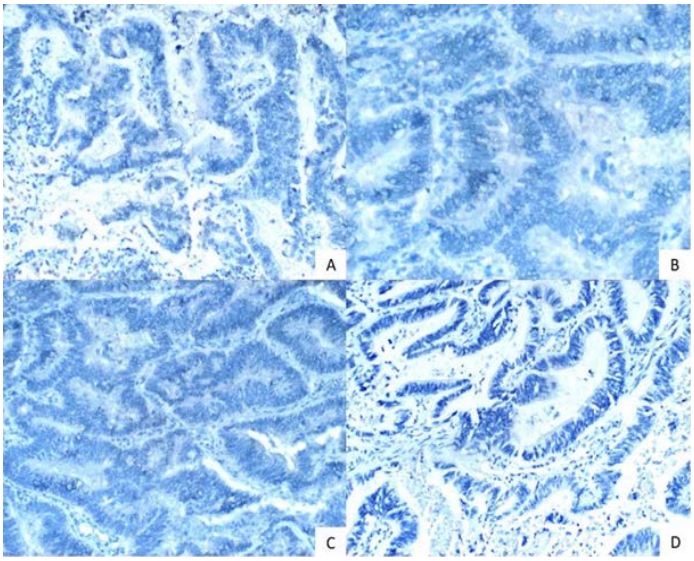

Figure 6. Metastatic ADC to lung (metastasis of colon ADC)
(A) TTF-1, x100. (B) p63, x100. (C) p40, x100. (D) MAdL, x100.
ADC=adenocarcinoma.

Table 4. Diagnostic values of p40, p63, MAdL, and TTF-1 in differential diagnosis

Marker	Tumor type	Sensitivity (%)	Specificity (%)
p40	Squamous cell carcinoma	89.47	100
p63	Squamous cell carcinoma	100	44.82
MAdL	Primary lung adenocarcinoma	82.75	100
TTF-1	Primary lung adenocarcinoma	96.55	100

were negative and none for (+). Of the 17 positive SCC cases, 16 showed high intensity and one had low intensity staining (Figure 4). No staining was observed in any primary lung ADC (n=29) or metastatic ADC (n=14). For SCC, p40 showed high intensity staining in 84.21% (16/19) and low intensity in 5.26% (1/19) of cases. The sensitivity and specificity of p40 for SCC were 89.47% and 100%, respectively.

MAdL Expression: In primary lung ADC, 11 cases showed (+++), five were (++), eight were (+), and five were negative. Among the 24 positive cases, 11 were high intensity and 13 were low intensity (Figure 5). No staining was detected in SCC (n=19) or metastatic ADC (n=14). For positive MAdL staining of ADC, 37.93% (11/29) showed was high intensity and 44.82% (13/29) showed low intensity. The sensitivity and specificity of MAdL for primary lung ADC were 82.75% and 100%, respectively. Combined p40 and p63: Cases were considered positive if either marker showed positive expression. All SCC cases were positive. In primary ADC, 16 cases were positive and 13 were negative, while all metastatic ADC cases were negative (Table 2). Combined sensitivity and specificity for SCC were 100% and 44.82%, respectively. Given the 100% specificity and 89.47% sensitivity, p40 alone was more meaningful for SCC diagnosis. Combined MAdL and TTF-1: Cases were considered positive if either marker showed positive expression. No SCC cases showed staining. In primary ADC, 28 were positive and one was negative; all metastatic ADCs were negative (Table 3). Combined sensitivity and specificity for ADC were 96.55% and 100%, identical to TTF-1 alone; thus, TTF-1 was more informative than MAdL for ADC diagnosis.

None of the four markers stained positively in metastatic ADCs (Figure 6). MAdL, athough 100% specific similar to TTF-1, had lower sensitivity and was insufficient alone. p63 showed excellent sensitivity but low specificity. The joint use of p40 for SCC and TTF-1 for ADC is recommended as the most reliable combination for differentiating between primary ADC and SCC in the lung (Table 4).

DISCUSSION

In our study and consistent with previous literature, TTF-1 and p40 were the most viable markers for distinguishing between primary ADC and SCC. Both of these markers are nuclear and prevent background staining caused by cytoplasmic antibodies (6). Moldvay et al. highlight the importance and reliability of TTF-1 for distinguishing between primary and metastatic lung ADCs, reporting TTF-1 expression as a reliable marker for identifying lung derived cancers. TTF-1 showed very high specificity (100%) and sensitivity (70%) in the differential diagnosis of ADCs originating in the lung and extrapulmonary metastatic ADCs (excluding thyroid tumors). Thus, TTF-1 is considered a very valuable marker that can be used routinely in IHC (14). In our study, TTF-1 had a sensitivity of 96.55% and a specificity of 100% for primary lung ADCs. No staining was detected in SCC or metastatic ADC. Thus, consistent with the literature, our study also highlights the diagnostic importance of TTF-1 in ADC. As a marker for SCC, p63 was more commonly used before the introduction of the p40 antibody. TTF-1 and p63 have been shown to be useful in distinguishing primary ADC from SCC. However, p40, a variant of p63, is reportedly more specific and sensitive for detecting a squamous histology (6). Uramoto et al. reported that p40 to be more specific than high molecular weight cytokeratin for identifying the SCC component (24). Bishop et al. showed that p40 and p63 have equal sensitivity (96%), but p40 provides higher specificity because it does not show false positives in ADCs (20). Butnor et al. reported that p40 and keratin 34βE12 as being more reliable than p63 for distinguishing SCLC from poorly differentiated NSCLC (25). Tatsumori et al. report p40 as the most sensitive marker for SCC (96.8%) and it also being useful for distinguishing between ADC, neuroendocrine carcinoma, and malignant mesothelioma (26). Furthermore,

Collins et al. report p40 being 89% sensitive and 100% specific for NSCLC (27).

In our study, p63 showed 89.47% sensitivity and 100% specificity in cases of SCC, demonstrating high intensity staining in 84.21% of these cases and low intensity staining in 5.26%. p63 showed 100% sensitivity, providing considerable benefit in diagnosis, but the 44.82% specificity caused some difficulties in differential diagnosis. p63 showed high intensity staining in 89.47% of SCC cases and low intensity staining in 10.52%. However, low intensity staining for p63 was also detected in 55.17% of ADC cases, and our statistical studies revealed that p63 had false positives for ADC. As supported by the literature, low intensity staining with p63 creates difficulties in differentiating SCCs from primary ADCs; therefore, p40 is evaluated as a more useful marker than p63 in the diagnosis and differential diagnosis of SCCs. There is currently only one published study related to MAdL, which included 362 cases of primary lung carcinoma and 111 cases of extrapulmonary carcinoma. 154 of the primary lung carcinomas were SCCs, 167 were ADCs, two were adenosquamous carcinomas, 19 were SCLCs, 17 were large cell carcinomas, and three were diagnosed as carcinoids. Of the extrapulmonary carcinomas, 28 were colon, 19 were breast, 11 were prostate, six were pancreatic, ten were gastric, 21 were renal, one was biliary tract, one was liver, three cases were endometrial, two cases urothelial, and eight cases were mesothelial in origin. Staining revealed positive expression of TTF-1 in 92.2% of ADCs and in 74.2% of cases when stained with MAdL. While TTF-1 expression was not observed in metastatic tumors originating from tissues other than the lung, MAdL positivity was detected in 4.7% (1/21) of cases with renal cell carcinoma metastasis (23). Due to the lack of sufficient studies on MAdL, our study is an important investigation into the feasibility of using MAdL alone or in combination with other IHC markers for the diagnosis and differential diagnosis of ADC.

In our study, which yielded results supporting the literature, MAdL showed 82.75% sensitivity and 100% specificity for ADC. Furthermore, the rate of ADC diagnosed cases showing positive expression with MAdL was 37.93% at high intensity and 44.82% at low intensity. TTF-1, on the other hand, showed rates of 79.31% for high intensity staining and 17.24% for low intensity staining. Since TTF-1 showed both 96.5% sensitivity and 100% specificity along with high intensity staining in 79.31% of ADC cases, it emerged as a more viable marker than MAdL for the diagnosis of ADC. When we evaluated the statistics regarding binary combinations, combined p40 and p63 staining evaluation revealed 100% sensitivity and 62.79% specificity for SCC cases. Since p40 alone showed 89% sensitivity and 100% specificity in the same cases, p40 was a more appropriate marker for SCC diagnosis. When MAdL and TTF-1 staining were evaluated together, they showed 96.55% sensitivity and 100% specificity for cases of ADC. These rates were the same when TTF-1 was used alone. Therefore, TTF-1 was more viable than MAdL for diagnosing lung ADC. For metastatic ADC, if thyroid cancers are suspected in the differential diagnosis or if there is a histopathological suspicion, the use of MAdL staining might be useful to exclude TTF-1 positive cases. The difficulties in diagnosis and differential diagnosis in LC necessitate the use of a panel of multiple IHC markers rather than focusing on a single marker. Therefore, similar studies exist that include specific markers for SCC and ADC, as in our study. Montezuna et al. used a panel consisting of four IHC markers—CK 7, CK 20, TTF-1, and p63—to distinguish primary and metastatic lung carcinomas in biopsies. TTF-1 is reportedly the best marker for ADC, while p40 (an isoform of p63), was found to be specific for SCC (28).

Pelosi et al. aimed to create a panel using the fewest markers to distinguish ADCs from SCCs, stating that a combination of TTF-1 and p40 IHC markers was the best approach for identifying ADCs and SCCs (29). Whithaus et al. used a panel containing Napsin A, CK 5/6, p63, and TTF-1 to distinguish ADCs from SCCs in their study, demonstrating that the Napsin A and p63 had 94% specificity and 96% sensitivity when distinguishing ADCs from SCCs (30).

Limitations

Since the subtypes included in the current lung classification exhibit morphologically distinct patterns (eg, lepidic and acinar), our study mainly included cases with a solid pattern that were difficult to distinguish between primary and metastatic LCs, and where additional tests were required for the differential diagnosis of primary ADC and SCC. The sample size was limited and based on data from a single center; therefore, the generalizability of the findings might be limited. Additionally, retrospective design could lead to missing data or recording errors. Another limitation was that power analysis was not performed at the beginning of the study due to the insufficient number of included metastatic ADC cases. However, the systematic investigation of the role of the combinations of markers used in the study for distinguishing ADC and SCC in the lung and the potential contribution of MAdL in thyroid derived tumors supports the consistency of the findings with the literature and the value of the study. Future multicenter, large sample, prospective studies could contribute to validating the findings by reducing the impact of these limitations.

CONCLUSION

The results of this study show that among the four evaluated IHC markers, TTF-1 and p40 were the most reliable and diagnostically valuable markers for distinguishing primary lung ADC and SCC. TTF-1 exhibited high sensitivity and specificity for primary lung ADC, whereas p40 showed excellent specificity and superior diagnostic performance for SCC compared with p63. Although MAdL showed high specificity for ADC, the lower sensitivity limits its use as a standalone marker; however, it could serve as a useful complementary marker in complex cases. Our findings suggest that TTF-1 could be useful for the differential diagnosis of metastatic ADCs other than thyroid carcinoma metastases, while MAdL might be useful in cases with a suspected diagnosis of thyroid carcinoma or a primary tumor of thyroid origin. The combined use of p40 and TTF-1 is recommended in an optimal limited

IHC panel for the differential diagnosis of NSCLC subtypes, particularly in small biopsy samples where tissue preservation is crucial for subsequent molecular testing.

DECLARATIONS

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OPEN

RESEARCH ARTICLE

Successfully Percutaneous Treatment with Ethyl Alcohol in Multiple Hepatic and Extrahepatic Hydatid Cysts; Long Term Outcomes

Çoklu Hepatik ve Ekstrahepatik Hidatik Kistlerde Etil Alkol ile Başarılı Perkütan Tedavi; Uzun Dönem Sonuçlar

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ABSTRACT

Objective: Hydatid cysts are primarily treated surgically, and surgical treatment is associated with high morbidity, mortality, and prolonged hospitalization. However, over the last two decades, minimally invasive percutaneous treatments that provide favorable outcomes with low morbidity and mortality have been developed. In this study, we aimed to demonstrate a percutaneous treatment for disseminated liver hydatid cysts (CE) and to evaluate the therapeutic success rates and the advantages of alcohol as a scolicidal and sclerosing agent.

Materials and Methods: We retrospectively investigated 132 percutaneously treated CEs in 23 patients who were admitted with disseminated hepatic and extrahepatic CE between September 2016 and December 2018, each of whom had fewer than three cysts. CE type 1 (Gharbi type 1) and CE type 3a (Gharbi type 2) hydatid cysts measuring <6 cm were treated with puncture, aspiration, injection, and reaspiration (PAIR), whereas those >6 cm were treated with catheterization (SPC). All CE cysts classified as types 2 and 3b (the latter corresponding to Gharbi type 3) were treated using the modified catheterization technique (MoCAT).

Results: All 132 lesions in 23 patients were successfully treated percutaneously. The following observations were recorded: pseudotumor appearance in 80 cysts (60.61%); more than 50% reduction in cystic volume in 33 cysts (25%); thickening of the cyst wall, irregular cyst contours, and membrane detachment (numbers were not reported); less than 50% reduction in cystic volume in 10 cysts (7.58%); and complete disappearance in 9 cysts (6.82%).

Conclusion: Percutaneous treatments are safe and effective for patients with disseminated hepatic and extrahepatic hydatid disease and should be considered first-line therapy because surgical interventions are associated with high morbidity. When appropriate safety limits and precautions are observed, alcohol appears to be a safe and effective treatment for disseminated disease, demonstrating both scolicidal and sclerosing properties.

Keywords: Disseminated hydatid cysts, ethyl alcohol injection, extrahepatic hydatid cysts, interventional radiology, percutaneous cyst treatment

ÖZET

Amaç: Kist hidatik, yüksek morbidite ve mortalite oranlarına sahip ve daha uzun hastanede kalış süreleri olan invaziv cerrahi yöntemlerle tedavi edilir. Ancak son yirmi yılda, düşük morbidite ve mortalite oranlarıyla mükemmel sonuçlar sağlayan minimal invaziv perkütan tedaviler geliştirilmiştir. Bu çalışmada, yaygın karaciğer hidatik kistlerinin (HK) perkütan tedavisini ve ayrıca skolisidal ve sklerozan bir ajan olarak alkolün terapötik başarı oranlarını, etkinliğini ve avantajlarını göstermeyi amaçladık.

Gereç ve Yöntemler: Eylül 2016 ile Aralık 2018 tarihleri arasında yaygın karaciğer ve karaciğer dışı HK nedeniyle başvuran, <3 kist içeren toplam 23 hastanın perkütan tedavi edilen 132 HK'sini retrospektif olarak inceledik. HK tip 1 (Gharbi tip 1) ve tip 3a (Gharbi tip 2) <6 cm hidatik kistleri ponksiyon, aspirasyon, enjeksiyon ve reaspirasyon (PAIR) yöntemi ile tedavi edilirken, >6 cm kistler kateterizasyon (SPC) yöntemi ile tedavi edildi. Tüm HK tip 2 ve tip 3b (Gharbi tip 3) kistleri modifiye kateterizasyon (MoCAT) tekniği ile tedavi edildi.

Bulgular: 23 hastadaki 132 lezyonun tamamı (%100) perkütan olarak başarıyla tedavi edildi. 80 kistte (%60,61) psödotümör görünümü, 33 kistte (%25) %50'den fazla hacim küçülmesi, kist duvarında kalınlaşma, kist konturlarında düzensizlik, membran dekolmanı ve 10 kistte (%7,58) kist hacminde %50'den az küçülme ve 9 kistte (%6,82) tamamen kaybolma tespit edildi.

Sonuç: Perkütan tedaviler, hepatik ve ekstrahepatik yaygın hidatik kistli hastalarda başarılı sonuçlar sağlayan güvenli ve etkili yöntemlerdir ve cerrahi tedavilerle yüksek morbidite oranları nedeniyle yaygın hastalık için ilk tedavi yöntemi olmalıdır. Güvenli sınırlar ve önlemler sağlandığı takdirde, skolisidal ve sklerozan bir ajan olarak alkol, yaygın hastalıkta güvenli ve etkili görünmektedir.

Anahtar Kelimeler: Dissemine hidatik kist, etil alkol enjeksiyonu, ekstrahepatik hidatik kistler, girişimsel radyoloji, perkütan kist tedavisi

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INTRODUCTION

Hydatid cyst (CE) is a parasitic zoonosis that is endemic to Turkey, the Mediterranean region, the Middle East, South America, Central Asia, Africa, New Zealand, and Australia. The larval form of Echinococcus granulosus causes CE (1). The liver is the primary site of CE, accounting for 50–70% of cases. Other organs, such as the lungs (5–30%), kidneys, spleen, muscles, brain, bones, peritoneum, heart, ovaries, adrenal glands, and thyroid gland, are also affected (2, 3).

In patients with hydatid cysts, invasive surgical methods are generally preferred despite their association with high morbidity, mortality, and prolonged hospital stays (4, 5). Over the last two decades, minimally invasive percutaneous treatments have yielded excellent outcomes, with low morbidity and mortality (6-13). In addition, medical treatment options for disseminated CE include albendazole (administered alone or in combination with praziquantel) or mebendazole (13-18). In this single-center study, we aimed to demonstrate percutaneous treatment of multiple hydatid cysts (CE) in the liver, spleen, lungs, and kidneys, and to assess the therapeutic success rates, the advantages of this approach, and the effectiveness of alcohol as a sclerosing and scolicidal agent.

MATERIALS and METHODS

Patients

Twenty-three patients (15 females and 8 males) admitted to the Interventional Radiology Unit between September 2016 and December 2018 for multiple hepatic and extrahepatic CEs (3–19 cysts) were retrospectively analyzed. The study was conducted in accordance with ethical principles and was approved by the Medical Faculty Local Ethics Committee (registration number 2020/2305). The benefits and complications of the procedure were explained to all patients, after which informed consent was obtained.

All CEs were primarily evaluated by ultrasonography (USG). Because of disseminated disease, CT scans of the chest and abdomen were obtained. No patients were diagnosed using serological tests. The definitive diagnosis of CE lesions was established by cytological examination of aspirates. Cysts were evaluated and classified according to the definitions of Gharbi et al. (19, 20) and the World Health Organization (WHO). The two classifications of hydatid cyst lesions are presented in Table 1.

Preliminary procedure evaluation

After obtaining informed consent, prophylactic oral albendazole (10 mg/kg/day) was administered starting 10 days before the procedure and continued for 3 months afterward to reduce the risk of secondary spread. Complete blood count, prothrombin time, partial thromboplastin time, international normalized ratio (INR), and platelet count were assessed before the procedures. Patients with INR <1.5 and platelet count >50.000 /µl were included in the procedure. Because of the risk of anaphylaxis, all patients were monitored post-procedure by the same anesthesiologist. Intravenous methylprednisolone (1 mg/kg) and diphenhydramine HCl (20 mg) were administered before the procedure to prevent allergic reactions and reduce the risk of anaphylaxis.

The Procedures

A single interventional radiologist with 15 years' experience performed the procedures under USG and fluoroscopic guidance. Under sterile conditions, local anesthesia with prilocaine hydrochloride was administered, and the targeted lesions were accessed under USG guidance. Hydatid cysts larger than 6 cm were treated with catheterization (SPC), whereas CE type 1 (Gharbi type 1) and CE type 3a (Gharbi type 2) cysts smaller than 6 cm were treated with puncture, aspiration, injection, and re-aspiration (PAIR). The modified catheterization (MoCAT) technique was applied to all CE types 2 and 3b (Gharbi type 3).

To access the CE lesions during the PAIR procedure, approximately 50% of the cyst sac fluid volume (calculated from USG measurements) was aspirated with an 18-G needle. Under USG guidance, a contrast agent (sodium amidotrizoate, Urografin, Bayer) was injected either until a volume corresponding to 10–20% of the cyst volume (calculated from USG measurements) was reached or until the cyst contour was clearly delineated, to evaluate cyst integrity and relationships with adjacent structures. After the cyst was re-aspirated, the cavity was filled with contrast medium (approximately 10–20% of the aspirated volume) and absolute alcohol (98%,

Table 1. Classifications of hydatid cyst lesions.

WHO-IWGE	Gharbi	Ultrasonographic features	Status
CL	-	Unilocular cyst, no cyst wall, echo-free, non-pathognomonic findings	Active
CE1	Type I	Smooth, echo-free content single-cell simple cyst, wall, mobile internal echogenicity (snowflake mark)	Active
CE2	Type III	Multivesicular, multi-stage cyst, daughter cysts, wheel-like / rosette-like / honeycomb pattern	Active
CE3A	Type II	Membrane cyst (water lily sign)	Transient
CE3B	Type III	Cyst with solid matrix	Transient
CE4	Type IV	Heterogeneous hypoechoic or hyperechoic cyst. No daughter cyst	Passive
CE5	Type V	Thick, calcified walled solid cyst	Passive

WHO-IWGE: The World Health Organization Informal Working Group on Echinococcosis, CL: cystic lesion, CE: cystic echinococcosis

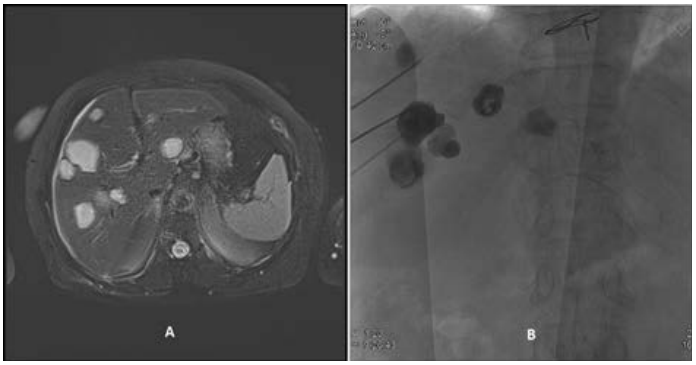


Figure 1. Section A represents disseminated hydatid cysts with diameters less than 6 cm are observed in the right and left lobes of the liver on T2-weighted MR sections in the axial plan. Section B represents fluoroscopic images of disseminated hydatid cysts treated percutaneously with PAIR technique.

approximately 30–50% of the aspirated volume). Before re-aspirating the injected alcohol-opaque mixture, an interval of 7–10 minutes was allowed to observe the separation of the endocyst from the pericyst (Figure 1).

Using the SPC method, an 8-Fr catheter (Bioteq, Taipei, Taiwan) was inserted into the cyst via the trocar technique under USG guidance. After the cyst contents were aspirated, it (the cyst) was refilled with 20–30% of the aspirated volume, and the integrity of the cyst and its relationships with surrounding structures were assessed under fluoroscopic guidance. After re-aspiration, the cavity was filled with absolute alcohol (98% ethanol; approximately 30–50% of the aspirated volume) and a contrast medium (10% of the cystic volume). The cyst cavity was re-aspirated after 20 minutes. To avoid ethanol intoxication resulting from large cyst diameters, numerous cysts, or insufficient emptying of ethanol during drainage, each cavity was irrigated with 500 mL of saline (0.9% NaCl) and then allowed to drain (Figure 2).

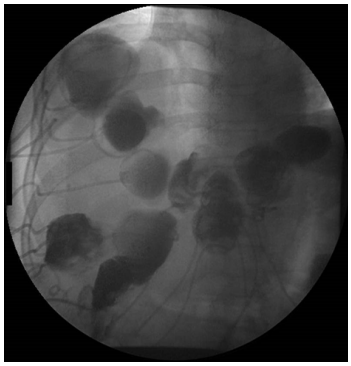


Figure 2. Fluoroscopic images of hepatic and left renal localized disseminated hydatid cysts treated percutaneously.

Operators accessed the cysts under USG guidance using the MoCAT technique with a 14-Fr catheter. The cyst contents were evacuated as completely as possible; the cavity was then irrigated with saline and aspirated. Daughter vesicles were fragmented by negative pressure and aspirated through the catheter. After complete aspiration of the daughter cysts, cystography was performed to confirm the absence of communication between the cyst and the bile ducts, and the cyst was subsequently reaspirated. Absolute ethanol (approximately 30–50% of the aspirated volume) and a contrast medium (approximately 10% of the cystic volume) were then injected into the cavity. After a 20-minute wait, the cyst was re-aspirated. After the catheter was secured to the skin, the cysts were drained into collection bags.

During the procedure, the total volume of absolute alcohol administered to any patient did not exceed 500 mL. All patients were monitored at the Interventional Radiology Unit after the procedures for early complications, including ethanol intoxication. Patients treated percutaneously were hospitalized for one day after the procedure and underwent USG evaluation the following day. Catheters were removed when drainage from the cavity was less than 10 mL/day.

Follow-up

Sonography was used for patient follow-up at 1, 4, 7, 10, and 13 months after the initial procedure and annually thereafter. In follow-up evaluations of treated hydatid cysts, changes in size, volume, contents, and wall properties were examined. Increased cystic wall thickness and echogenicity; decreased cyst size and volume; complete separation of the endocyst from the pericyst; decreased acid content; and resolution of the pseudotumor appearance were considered positive indicators of recovery. Hydatid cyst recurrence was defined as an insufficient reduction in the size of treated CE lesions and the emergence of new daughter cysts (7-11).

Statistical Analysis

Data obtained in this study were analyzed using the Statistical Analysis System (SAS University Edition), version 9.4. Categorical variables were expressed as counts and percentages. Mixed-effects models were used to compare the numerical variables. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The mean age of the 23 patients (8 males and 15 females) was 46.78 ± 20.05 years (range 18–83 years). Cysts were classified as follows: 115 (87.12%) CE type 1 (Gharbi type 1), 12 (9.09%) CE type 3a (Gharbi type 2), and 5 (3.79%) CE type 2 (Gharbi type 3). The mean cyst diameter was 52.7 ± 26.1 mm. Among all cysts, 87 (67.42%) were located in the right hepatic lobe and 40 (30.30%) in the left hepatic lobe. Additionally, two cysts (1.52%) were located extrahepatically in the left kidney, and one cyst (0.75%) was located in the rectus muscle. Five patients had pulmonary hydatid cysts.

All 132 lesions in 23 patients were successfully treated percutaneously. The mean number of treated cysts per patient was 5.74 (range, 3–19). PAIR, SPC, and MoCAT were used to treat

Table 2. Demographics and characteristics of the patients

Method	Frequency	Percent	Cumulative Frequency	Cumulative Percent
PAIR	81	61,36	81	61,36
SPC	46	34,85	127	96,21
MoCAT	5	3,79	132	100

PAIR: Puncture of cyst, Aspiration of cyst contents, Injection to sterilize the cyst, and Re-aspiration, SPC: Single Puncture Catheterization, MoCAT: Modified Catheterization Technique

Table 3. Follow-up results of percutaneous treatments.

Final image	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Disappeared	33	25	33	25
Pseudotumor	80	60,61	113	85,81
<50%	9	6,82	122	92,42
>50%	10	7,58	132	100

Table 4. Results of treatment with percutaneous methods.

Treatment method	Final image				
Frequency	Disappeared	Pseudotumor	<50%	>50%	Total
PAIR	32	47	1	1	81
	39,51	58,02	1,23	1,23	
SPC	1	28	8	9	46
	2,17	60,87	17,39	19,57	
MoCAT	0	5	0	0	5
	0	100	0	0	132
Total	33	80	9	10	

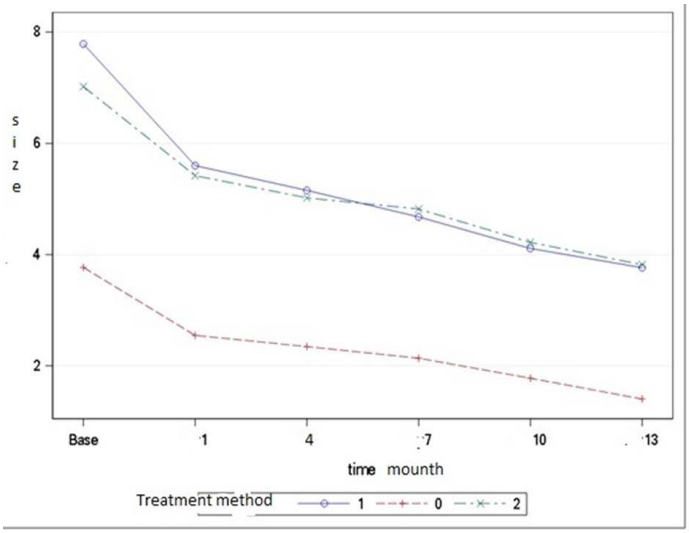
PAIR: Puncture of cyst, Aspiration of cyst contents, Injection to sterilize the cyst, and Re-aspiration, SPC: Single Puncture Catheterization, MoCAT: Modified Catheterization Technique

81 (61.36%), 46 (34.85%), and 5 (3.79%) of the CEs, respectively (Table 2). In addition to the hepatic cysts, two renal CEs and one CE in the rectus muscle were treated percutaneously. Following surgical treatment of lung-localized CEs, disseminated hepatic CEs were treated percutaneously.

The mean follow-up period was 19 months, with a range of 13–45 months. By the 13th month of follow-up, the mean diameter of effectively treated CEs was 23.3 ± 17.6 mm. At the 13-month follow-up, features of the cysts treated with different percutaneous methods are summarized in Tables 3–5. Despite a statistically significant reduction in lesion size was detected with all three percutaneous treatment methods (Student's t-test, $p < 0.001$), pseudotumor formation remained the most common outcome. The following findings were observed: pseudotumor-like appearance in 80 cysts (60.61%); more than 50% volume reduction in 33 cysts (25%); irregular cyst contours; cyst wall thickening; less than 50% volume reduction with membrane detachment in 10 cysts (7.58%); and complete disappearance in 9 cysts (6.82%). A local recurrence was observed in a degenerated hydatid cyst during the patient's second year, and the cyst was retreated using the PAIR method. Most patients who underwent catheterization were hospitalized for 1–2 days, whereas those treated with the PAIR method were discharged on the same day following 5–6 hours of observation. The mean duration of hospitalization was 1.52 ± 2.5 days (range: 0–35 days).

None of our patients experienced major complications, such as anaphylaxis, rupture, or intra-abdominal dissemination, and no deaths occurred. Only six patients experienced minor complications. Complications are listed in Table 6. Despite prophylaxis, minor allergic reactions (urticaria) and bile fistulae were detected in two patients each (8.7%). Fistula flow rates were measured in patients with biliary fistulas. Two patients with high-flow fistulae (>300 mL/day) whose fistula flows had not decreased for more than one week underwent endoscopic treatment. After an endoscopic intervention, a patient with a high-flow bile fistula developed an abscess containing two cysts and was recatheterized with larger-caliber catheters and treated with daily irrigation and appropriate medications (Figure 3). In one patient who presented with cholestasis, the germinative membranes of the cyst extended into both the intrahepatic and extrahepatic biliary tracts. In this patient, the cyst was punctured and a catheter was placed. Intracavitary germinative membranes were aspirated, and the bile ducts were accessed via the fistula. After the balloon dilatation of the sphincter of Oddi, the germinative membranes were displaced from the bile ducts into the duodenal lumen.

Table 5. Follow-up sizes of hydatid cysts treated with percutaneous methods.



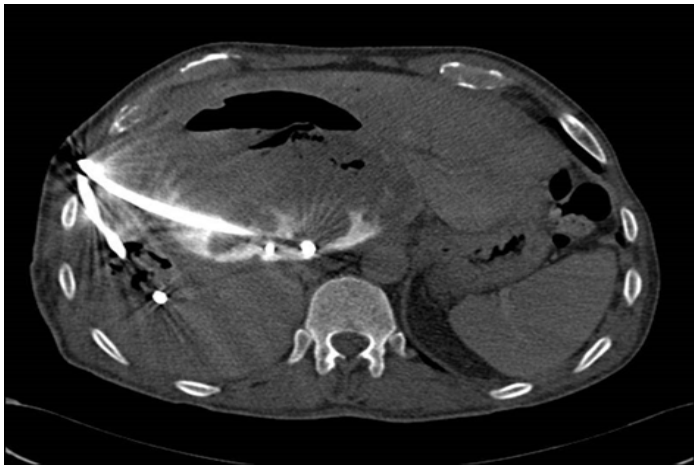


Figure 3. Images of percutaneous treatment of a patient who had high-flow bile fistula and developed abscess in the hydatid cysts cavities after the endoscopic intervention. CT axial plane images show the infected hydatid cyst cavities with wide-diameter drainage catheters.

Table 6. Minor complications of percutaneous treatments.

Complications	Frequency	Percent	Cumulative frequency	Cumulative percent
None	17	73,91	17	73,91
Urticaria	2	8,7	19	82,61
Abscess	2	8,7	21	91,3
Fistula	2	8,7	23	100

DISCUSSION

The results of this study indicate that percutaneous treatment should be the initial procedure for hepatic and extrahepatic CEs and that the application of absolute alcohol as a sclerosing and scolicidal agent is safe and effective. Ultrasonography is a widely used imaging modality for the screening and diagnosis of CE lesions (3, 21). Conversely, USG is used during treatment and follow-up (3). Cyst types are defined by USG findings according to the Gharbi and WHO classifications (19, 20). Computed tomography (CT) images of the CE are not pathognomonic and may be mistaken for benign lesions (e.g., congenital cysts, pseudocysts, and hematomas) or malignant lesions (e.g., solitary or multiple metastases) (22, 23). However, CT is superior to magnetic resonance imaging (MRI) in detecting lesional and wall calcifications. MRI, an effective imaging modality for detecting soft-tissue hydatid cysts, clearly demonstrates the separation between the pericyst and the endocyst. The cystic wall demonstrates low signal intensity on both T1- and T2-weighted images (24). In this study, USG was used for the primary diagnosis and follow-up of CE lesions. However, CT or MRI scans were performed to exclude extrahepatic disease in patients with disseminated hepatic disease. In addition to hepatic CEs, hydatid cysts were identified in the kidneys of two patients and the lungs of five patients.

Albendazole and mebendazole (benzimidazoles) are used in the medical treatment of CE lesions. It has been reported in the past few years that the combination of praziquantel and albendazole has yielded better results (14-18) However, the use of these agents alone in medical treatment may be insufficient, particularly for large-diameter hydatid cysts. These agents are administered before and after percutaneous treatment to prevent abdominal dissemination and recurrence (7, 11). In this study, oral albendazole was administered to all patients for 10 days before and 3 months after the procedure. Although surgical treatments are associated with high morbidity and mortality rates, poor cost-effectiveness, and other disadvantages, such as invasiveness, they remain the standard treatment for hydatid cysts. Surgical procedures are associated with an even higher risk of morbidity and mortality in the presence of disseminated disease (4, 5, 25-27). We believe that medical treatment and percutaneous interventions should be

preferred in cases of disseminated disease.

Percutaneous treatments are less invasive and reliable alternatives to surgery. These modalities should be preferred for treating hepatic and extrahepatic CE lesions because they are associated with lower rates of complications and recurrence, and shorter hospital stays (6-13). Percutaneous treatment of hepatic CEs can be performed using PAIR, SPC, or MoCAT. In the method described by Akhan et al (8), cysts greater than 6 cm are treated by catheterization. Alcohol, used as a sclerosing agent, was usually injected the day after the procedure. Nayman et al. (11]) reported a therapeutic success rate of 97.7% and minor and major complication rates of 11.7% and 0.55%, respectively, in patients treated solely with the modified PAIR technique. In the present study, we employed different percutaneous treatment modalities, selected according to the location, size, and type of each lesion, to maximize therapeutic success and minimize complications and recurrences. Hydatid cysts larger than 6 cm were treated with catheterization (SPC), whereas CE type 1 (Gharbi type 1) and CE type 3a (Gharbi type 2) hydatid cysts smaller than 6 cm were treated with puncture, aspiration, injection, and re-aspiration (PAIR). A modified catheterization technique (MoCAT) was performed in all cases of CE types 2 and 3b (Gharbi type 3).

The success of percutaneous treatments may vary depending on lesion type and size. Kabaalioğlu et al. (13) reported an 80% success rate among 77 hydatid cyst lesions treated with the PAIR method. In that study, success rates were higher for CE type 1 (Gharbi type 1) and CE type 3a (Gharbi type 2) lesions than for CE type 2 and CE type 3b (Gharbi type 3) lesions. Our success rate was 99.25%. All three percutaneous treatment methods produced a statistically significant decrease in lesion size. In patients treated with the PAIR method, the complete disappearance rate was 6.82%, higher than those for the other two techniques. This result confirms that the rate of complete disappearance increases as cystic volume decreases. Consistent with the literature, pseudotumor formation was the most common finding across all three methods used in our study. In a study by Yağcı G et al (27), the reported recurrence rates were 16.2%, 3.3%, and 3.5% for laparotomic surgery, laparoscopic surgery, and PAIR, respectively. In the present study, only one CE lesion (0.75%) recurred and was successfully treated with an additional percutaneous intervention. None of the patients required surgical intervention.

Percutaneous treatments can also be performed using various agents. The most commonly used endocavitary scolicidal agent is hypertonic saline (8, 28). However, ethanol is used for its sclerosing effect in larger catheterized lesions. Alcohol has well-known scolicidal and sclerosing effects that are greater than those of 20% hypertonic saline (29). Since alcohol injection provides both scolicidal and sclerosing effects during a single session, the procedure is completed with a single agent (30). In large-volume cysts, the germinative membrane prevents drainage of residual alcohol, which we believe increases the risk of intoxication. In a study by See Young Jang et al. (31), up to 500 mL of alcohol was instilled in a single session to achieve effective ablation of hepatic cysts. Danny Cheng et al (32) recommend limiting the volume of ethanol to 100 mL in adults undergoing treatment for simple hepatic cysts to prevent systemic alcohol intoxication and monitoring patients for signs of alcohol intoxication. In the present study, we injected up to 500 mL of absolute alcohol into the cyst cavities of patients with large-volume, disseminated hydatid cysts and maintained exposure for 20 minutes while patients were repositioned into different orientations. Each cavity was subsequently irrigated with 500 mL of saline and left to drain freely. At follow-up, we observed that irrigation with saline did not reduce the sclerosing effect and that the cysts' response to percutaneous treatment was consistent with the literature. We propose that saline irrigation removes residual alcohol from the cystic cavity, thereby reducing the risk of alcohol intoxication in patients with large-diameter or multiple cysts.

Another reason alcohol is not preferred as a primary therapeutic agent is the risk of sclerosing cholangitis secondary to bile leakage. In patients with cysts that communicate with the bile ducts, the use of 20% hypertonic saline solution is recommended because of the risk of sclerosing cholangitis (8). In our study, two patients developed biliary fistulas after percutaneous treatments. Despite intracavitary injection of alcohol, used as a scolicidal agent, none of the patients developed symptoms consistent with sclerosing cholangitis. A bile fistula becomes noticeable after the first puncture, when the cyst contents are aspirated and the pressure is lowered (33). Therefore, we believe that in patients with no bile leak detected on the initial cystogram, alcohol, when injected at volumes not exceeding 30% of the cyst volume, neither enters the biliary tract nor causes sclerosing cholangitis. Allergic reactions — even anaphylactic reactions, which are typically characterized by urticaria, mucosal erythema, and swelling — are adverse events that may result from cyst rupture, leakage, and spillage (1, 34). In the literature, various methods to mitigate leakage risk have been described. Kabaalioğlu et al. (13) minimized the risk of leakage from all right-lobe cysts by employing an intercostal approach through the liver parenchyma. Corona et al. (35) used a coaxial system, consisting of a 20-cm-long needle enclosed within a 10-Fr outer sheath, to reduce the risk of leakage. In the present study, some patients did not develop anaphylaxis despite undergoing 18–19 punctures for disseminated disease. In our opinion, rapid reduction of intracystic pressure in large-diameter cysts by single-stage trocar catheterization without dilatation decreases the risk of leakage of fluid into adjacent tissues or the peritoneal cavity. In this study, only two patients developed minor allergic reactions consistent with urticaria; both responded to treatment with antihistamines and steroids.

Although the patient cohort was smaller than planned, the available sample size still allowed us to generate meaningful findings that enhance therapeutic approaches and prognostic assessments for patients with hydatid disease. In conclusion, percutaneous treatments are safe and effective, providing successful outcomes for patients with disseminated hepatic and extrahepatic hydatid cysts. They should be initial treatments for disseminated disease, because surgical treatment is associated

with high morbidity. If appropriate limits and precautions are observed, alcohol appears to be a safe and effective scolicidal and sclerosing agent in disseminated disease.

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RESEARCH ARTICLE

Elevated Baseline Systemic Inflammation Indices Predict Poor Response and Higher Relapse Risk in Chronic Spontaneous Urticaria Patients on Omalizumab

Omalizumab Kullanan Kronik Spontan Ürtiker Hastalarında Yüksek Bazal Sistemik İnflamasyon İndeksleri Zayıf Yanıtı ve Yüksek Nüks Riskini Öngörmektedir

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ABSTRACT

Objective: This study aims to assess how baseline Systemic Immune-Inflammation Index (SIRI) and Aggregate Index of Systemic Inflammation (AISI) values relate to six-month clinical outcomes of Omalizumab treatment in patients with chronic spontaneous urticaria (CSU). Additionally, whether these systemic inflammatory markers could serve as predictors for relapse risk following discontinuation of therapy has been evaluated.

Materials and Methods: In this single-center study, a total of 312 CSU patients who were on Omalizumab treatment have been retrospectively analyzed. The overall response to the therapy is evaluated at the end of a 6-month follow-up period, while 217 patients who gave up Omalizumab treatment after the successful control period have also been evaluated afterwards for any relapse situations over a 12-month period. A favorable response is detected as achieving a Urticaria Control Test (UCT) score ≥12. The predictive accuracy of inflammatory indices and potential relapse-related variables have also been examined in the study.

Result: It is seen that the baseline SIRI (Median 1.47 vs. 1.06; p<0.001) and AISI (Median 452.98 vs. 306.06; p<0.001) values of the non-responder group (n=38) are statistically significantly higher than those of the responder group (n=274). Both AISI (AUC=0.744) and SIRI (AUC=0.727) have demonstrated a strong performance in predicting non-response. In the relapse analysis subgroup (n=217), patients who relapsed (n=122) have had significantly higher baseline SIRI (p=0.012) and AISI (p=0.024) values compared to those who remained in remission (n=95).

Conclusion: It is concluded that baseline SIRI and AISI values are valuable, practical, and cost-effective biomarkers for predicting an inadequate response to Omalizumab treatment and the risk of post-treatment relapse in patients with CSU. They have the potential to serve as helpful tools for clinicians to guide the treatment decisions and optimize the management of patients.

Keywords: Biomarkers, Omalizumab, Recurrence, Treatment Outcome, Urticaria

ÖZET

Amaç: Kronik Spontan Ürtiker (KSÜ) hastalarında Omalizumab'a altı aylık klinik yanıtı ve tedavi kesimi sonrası uzun vadeli nüks riskini öngörmede bazal Sistemik İmmün-İnflamasyon İndeksi (SIRI) ve Agregat Sistemik İnflamasyon İndeksi'nin (AISI) prediktif performansını değerlendirmektir.

Gereç ve Yöntemler: Bu tek merkezli, retrospektif çalışmaya 312 KSÜ hastası dahil edildi; tedavisi kesilen 217 hasta nüks açısından takip edildi. Birincil sonlanım 6. ayda iyi tedavi yanıtı (Ürtiker Kontrol Testi [ÜKT] skoru ≥12), ikincil sonlanım tedavi kesimi sonrası nüks olarak tanımlandı. Performans ROC analizi ve lojistik regresyon ile değerlendirildi.

Bulgular: Yanıt vermeyen grubun (n=38) bazal SIRI (Medyan 1.47 vs. 1.06; p<0.001) ve AISI (Medyan 452.98 vs. 306.06; p<0.001) değerleri, yanıt veren gruba (n=274) göre anlamlı olarak daha yüksekti. Yanıt vermemeyi öngörmede hem AISI (AUC=0.744) hem de SIRI (AUC=0.727) güçlü performans gösterdi. Nüks alt grubunda (n=217), nüks gelişenlerin (n=122) bazal SIRI (p=0.012) ve AISI (p=0.024) değerleri remisyonda kalanlara (n=95) göre anlamlı düzeyde yüksekti.

Sonuç: Bazal SIRI ve AISI değerleri, KSÜ hastalarında Omalizumab'a yetersiz yanıtı ve nüks riskini öngörmede değerli, pratik ve uygun maliyetli biyobelirteçlerdir. Bu indeksler, tedavi kararlarına rehberlik etmede ve hasta yönetimini optimize etmede klinisyenlere yardımcı olabilir.

Anahtar Kelimeler: Ürtiker, Omalizumab, Biyobelirteçler, Tedavi Sonucu, Nüks

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INTRODUCTION

Chronic spontaneous urticaria (CSU) is a long-lasting inflammatory skin disorder driven by immune dysregulation. It affects nearly 1% of people worldwide, visibly diminishing the quality of life and imposing a notable financial strain on healthcare systems (1). Although the anti-IgE monoclonal antibody Omalizumab has introduced a major therapeutic advancement for individuals unresponsive to conventional therapy, its effectiveness is not absolute. From 30% to 40% of the patients demonstrate only partial benefit, and have relapse rates between 33% and 67%. Moreover, these patients are reported as following discontinuation of the treatment (2, 3). These observations highlight that CSU continues to pose substantial difficulties in everyday clinical practice.

The pathophysiology of CSU is largely mediated through IgE-dependent mast-cell activation, which serves as the central pathway targeted by Omalizumab (4). Numerous biomarker such as C-reactive protein (CRP), total IgE, and eosinophil counts have been evaluated as potential indicators of therapeutic outcomes; nonetheless, none have shown a stable predictive value for a routine use (3). Over recent years, systemic inflammation indices based on complete blood count parameters, including the neutrophil-to-lymphocyte ratio, have been reported to correlate with disease activity and therapeutic response across multiple chronic inflammatory conditions, such as rheumatologic disorders and malignancies (5, 6).

Despite these observations, at CSU, novel composite indices readily derivable from basic laboratory data have not been sufficiently explored. To the best of our knowledge, Systemic Immune-Inflammation Index (SIRI) and Aggregate Index of Systemic Inflammation (AISI) have not been systematically evaluated yet among CSU patients regarding both treatment response and the risk of relapse concurrently. Among these, SIRI and the AISI provide an integrated reflection of systemic inflammatory status. It is seen that there is a considerable gap in literature regarding baseline markers that reliably predict long-term remission or relapse risks after the discontinuation of Omalizumab (7-10).

Accordingly, this study primarily aims to assess the predictive value of baseline SIRI and AISI levels for six-month treatment response to Omalizumab in CSU patients. The secondary objective is to explore whether these baseline inflammatory indices can estimate the likelihood of relapse following the end of therapy. It is assumed that higher baseline SIRI and AISI values are linked to suboptimal treatment outcomes and a greater relapse probability.

MATERIAL AND METHOD

Study Design

It is a retrospective and single-center study based on observational analysis. Data collection and evaluation period was from January 2021 to August 2025.

Ethical Approval

Ethical clearance for this research was granted by the Institutional Research Ethics Committee (Decision No: 2025/5983). Considering the retrospective character of the study and the use of anonymized records, the requirement for individual informed consent was waived by the committee. All study procedures adhered to the ethical standards outlined in the Declaration of Helsinki.

Study Population and Sample

• ***Participants:*** The study consists of patients aged 18 years and older who were initiated on Omalizumab therapy for a diagnosis of CSU. These patients attended the Allergy and Immunology outpatient clinic of a tertiary hospital between January 2021 and August 2025. A total of 474 patient records have been reviewed for the study.

• ***Inclusion Criteria:***

1. Age:18 and ≥ 18 years.
2. A confirmed diagnosis of CSU, by a specialist physician.
3. The initiation of Omalizumab treatment with at least a six-month follow-up period.

• ***Exclusion Criteria:***

1. The use of systemic corticosteroids within the four weeks prior to laboratory data collection (to exclude the potential confounding effect of steroids on neutrophil and lymphocyte counts).
2. The presence of an active infection or a known history of malignancy.
3. A concomitant systemic inflammatory or autoimmune disease (e.g., Lupus, Rheumatoid Arthritis).
4. Missing baseline complete blood count or 6-month Urticaria Control Test (UCT) data required for analysis.
5. The loss to follow-up.

• ***Sample Size:*** Following an initial screening of 474 patient records, 162 patients were excluded from the study regarding the exclusion criteria. The reasons for exclusion included concomitant autoimmune disease (n=32), a history of malignancy (n=3), missing data required for analysis (n=66), systemic steroid use within the preceding four weeks (n=29), and loss to follow-up (n=32). Consequently, a total of 312 patients who met all inclusion criteria have been included in the primary analysis for treatment response. A secondary analysis for relapse has been conducted on a subgroup of these patients whose Omalizumab therapy was successfully discontinued. For the relapse analysis, non-responders (n=38) and responders who were lost to follow-up or continued treatment without cessation (n=57) were excluded to isolate a cohort suitable for observing drug-free remission failures. As a result, a final cohort of 217 patients for the long-term relapse analysis have been determined. The two-stage patient selection process is shown in Figure 1.

The Procedure and Data Collection

As it is an observational study, no interventional procedures have been applied to the participants. The demographic, clinical, and laboratory variables have been retrospectively retrieved from the hospital's information system (HIS) and electronic medical records. The degree of the control of the disease is determined through the UCT, a valid and widely used assessment tool. All laboratory analyses have been performed in the central hospital laboratory by following standard

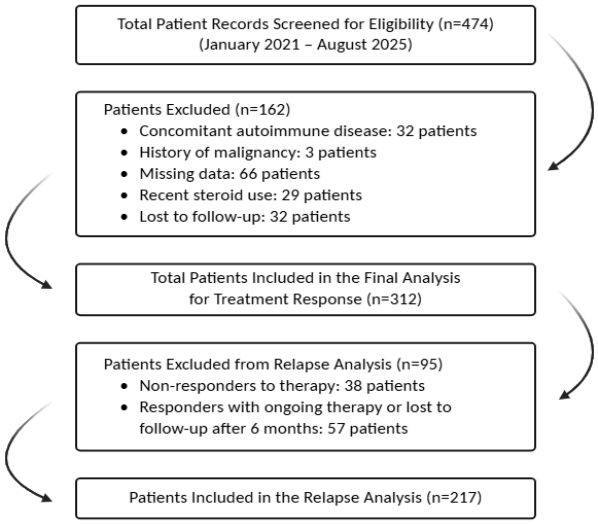

Figure 1. The flowchart of patient selection for primary and secondary analyses

procedures as a part of the routine clinical practice. All patients received subcutaneous Omalizumab at a standard dose of 300 mg every 4 weeks.

Variables and Outcomes

The basic demographic data (age and gender), the clinical characteristics (the duration of symptoms, the presence of angioedema and the initial UCT score), and laboratory parameters (complete blood count, CRP, ESR, IgE, TSH, anti-TPO, AST, ALT, Creatinine) have been collected as independent variables. SIRI is calculated by using the formula [(Neutrophil × Monocyte) / Lymphocyte], and AISI is calculated by using the formula [(Neutrophil × Monocyte × Platelet) / Lymphocyte].

• ***Primary Outcome:*** The primary outcome of the study can be stated as a good response to Omalizumab therapy at the 6-month follow-up period. A good response is defined as a UCT score ≥12. (11)

• ***Secondary Outcome:*** The secondary outcome of the study can be stated as the development of relapse in patients whose treatment was successfully discontinued. Relapses are defined as the recurrence of symptoms requiring renewed medical treatment in patients who were followed for at least one year after the end of Omalizumab therapy.

Statistical Analysis

All statistical analyses have been conducted by using SPSS Statistics software, version 25.0 (IBM Corp., Armonk, NY, USA). The statistical significance is defined as a two-tailed p value of less than 0.05. The distribution normality of continuous variables is examined by means of the Kolmogorov-Smirnov test. Variables following a normal distribution are summarized as mean ± standard deviation (SD), whereas those not normally distributed are presented as median values with interquartile ranges (25th–75th percentile). Categorical variables are shown as absolute numbers (n) and corresponding percentages (%).

The comparisons between the "responder" group and the "non-responder" group as well as the "relapser" subgroup and the "non-relapser" the subgroup are also performed. For non-normally distributed continuous data, the Mann–Whitney U test is applied. Categorical comparisons are analyzed by using either the Chi-square test or Fisher's Exact test. A complete case analysis method is adopted for the study.

The diagnostic capacity of baseline biomarkers that showed statistical significance in univariate analyses for predicting treatment response and relapse is assessed through Receiver Operating Characteristic (ROC) curve analysis. The area under the curve (AUC), its 95% confidence interval (CI), and the p value are determined for each biomarker. The optimal cutoff

Table 1. The demographic and baseline clinical characteristics of the study population (n=312)

Clinical Characteristics	Value	Laboratory Parameters	Value
Age (years)	41.0 (30.25 – 50.00)	Neutrophil (x10^3/μL)	4.60 (3.72 – 5.78)
Gender, n (%)		Lymphocyte (x10^3/μL)	2.43 (1.97 – 2.80)
Female	200 (64.1)	Monocyte (x10^3/μL)	0.56 (0.46 – 0.69)
Male	112 (35.9)	Platelet (x10^3/μL)†	295.38 ± 63.35
Symptom Duration (months)	24.0 (10.00 – 60.00)	ESR (mm/hour)	8.0 (5.00 – 11.00)
Presence of Angioedema, n (%)		CRP (mg/L)	3.0 (1.49 – 5.00)
Yes	116 (37.2)	Total IgE (IU/mL)	107.5 (30.00 – 214.00)
No 196 (62.8)		Creatinine (mg/dL)	0.76 (0.66 – 0.91)
Baseline UCT Score	4.0 (2.00 – 5.00)	AST (U/L)	15.5 (11.83 – 18.50)
6-Month UCT Score	15.0 (13.00 – 16.00)	ALT (U/L)	15.25 (11.25 – 20.35)
		TSH (μIU/mL)	1.81 (1.20 – 2.50)
		Anti-TPO (IU/mL)	11.15 (9.00 – 17.80)
		SIRI	1.10 (0.82 – 1.49)
		AISI	327.43 (221.16 – 447.90)

Numerical values are presented as Median (25th–75th percentile). Data marked with † are presented as Mean ± Standard Deviation. Categorical variables are presented as number (n) and percentage (%).

Abbreviations: UCT, Urticaria Control Test; ESR: Erythrocyte sedimentation rate CRP, C-reactive protein; IgE, Immunoglobulin E; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TSH, Thyroid-stimulating hormone; Anti-TPO, Anti-thyroid peroxidase antibody; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation.

threshold is obtained by using Youden's Index (J = sensitivity + specificity – 1).

Finally, a multivariable binary logistic regression model is constructed in order to determine the independent predictors associated with treatment response and relapse. Variables identified as significant in univariate analyses are included in the model. The outcomes are reported as odds ratios (ORs) together with their 95% confidence intervals (CIs). SIRI and AISI are included in separate multivariable logistic regression models to avoid multicollinearity, given their mathematical derivation from shared blood parameters.

RESULT

Baseline Characteristics of the Groups

The basic demographic and clinical characteristics of the study population are summarized and shown in Table 1. The median age of the 312 included patients is 41.0 (30.25–50.00) years, and 64.1% (n=200) are female. The median duration of symptoms before Omalizumab treatment is 24.0 (10.00–60.00) months, and 37.2% of the patients (n=116) have had a history of angioedema.

Primary Outcome: Response to Omalizumab Therapy

For the study, the baseline characteristics of patients who responded (responders, n=274) and did not respond (non-responders, n=38) to Omalizumab therapy have been compared. It is seen that the median baseline SIRI value of the non-responder group is statistically significantly higher than that of the responder group (1.47 vs. 1.06; p<0.001). Similarly, AISI is also found to be significantly higher in the non-responder group (452.98 vs. 306.06; p<0.001). A detailed comparison of the groups is presented in Table 2.

The performance of baseline SIRI and AISI values in predicting non-response to therapy is evaluated with ROC curve analysis. The performance of AISI (AUC=0.744; 95% CI: 0.665–0.824; p<0.001) is slightly superior to that of SIRI (AUC=0.727; 95% CI: 0.648–0.806; p<0.001) in predicting non-response. The optimal cutoff values and diagnostic performance metrics for these biomarkers are summarized in

Table 2. The comparison of basic demographic, clinical, and laboratory characteristics of the patients according to the treatment response status

Clinical / Laboratory Characteristic	Non-responder Group (n=38)	Responder Group (n=274)	p-value
Age (years)	40.0 (28.75 – 51.00)	42.0 (30.75 – 50.00)	0.427
Gender, female, n (%)	26 (68.4)	174 (63.5)	0.554
Symptom duration (months)	17.0 (8.00 – 51.00)	24.0 (10.00 – 60.00)	0.896
Presence of angioedema, n (%)	18 (47.4)	100 (36.5)	0.195
Baseline UCT Score	4.0 (1.75 – 4.00)	4.0 (2.00 – 5.00)	0.083
Neutrophil ($x10^9$/L)	6.00 (4.79 – 6.87)	4.42 (3.66 – 5.58)	<0.001
Lymphocyte ($x10^9$/L)	2.25 (1.80 – 2.87)	2.44 (2.00 – 2.80)	0.377
Monocyte ($x10^9$/L)	0.60 (0.47 – 0.77)	0.56 (0.46 – 0.68)	0.260
Platelet ($x10^9$/L)	303.0 (277.5 – 328.0)	288.5 (250.0 – 335.0)	0.071
ESR (mm/hour)	8.0 (5.0 – 12.75)	8.0 (5.0 – 11.0)	0.258
CRP (mg/L)	4.05 (2.74 – 6.00)	3.00 (1.36 – 5.00)	0.309
Total IgE (IU/mL)	61.5 (18.75 – 169.75)	109.0 (45.0 – 214.0)	0.096
Creatinine (mg/dL)	0.80 (0.66 – 0.87)	0.76 (0.66 – 0.91)	0.980
AST (U/L)	15.15 (12.0 – 17.60)	15.50 (11.80 – 18.63)	0.332
ALT (U/L)	15.10 (10.30 – 19.40)	15.30 (11.50 – 20.50)	0.504
TSH (μIU/mL)	1.84 (1.20 – 2.59)	1.76 (1.20 – 2.49)	0.849
Anti-TPO (IU/mL)	13.0 (9.0 – 36.0)	12.1 (9.0 – 18.8)	0.076
SIRI	1.47 (1.22 – 2.07)	1.06 (0.81 – 1.44)	<0.001
AISI	452.98 (388.57 – 646.50)	306.06 (213.68 – 427.74)	<0.001

Data are presented as Median (25th–75th percentile) for continuous variables and as number (n) and percentage (%) for categorical variables. P-values are calculated by using the Mann-Whitney U test for continuous variables and the Chi-Square test for categorical variables. Statistically significant p-values (p < 0.05) are highlighted in bold.

Abbreviations: UCT, Urticaria Control Test; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; IgE, Immunoglobulin E; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TSH, Thyroid-stimulating hormone; Anti-TPO, Anti-thyroid peroxidase antibody; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation.

Table 3. The performance of baseline SIRI and AISI in predicting non-response to omalizumab therapy

Biomarker	AUC (Area Under the Curve)	95% Confidence Interval	p-value	Optimal Cutoff Value	Sensitivity (%)	Specificity (%)
SIRI	0.727	0.648 – 0.806	<0.001	>1.285	65.8	68.2
AISI	0.744	0.665 – 0.824	<0.001	>349.87	68.4	60.9

Abbreviations: SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation; AUC, Area Under the Curve; CI, Confidence Interval. Optimal cutoff values were determined using Youden's Index.

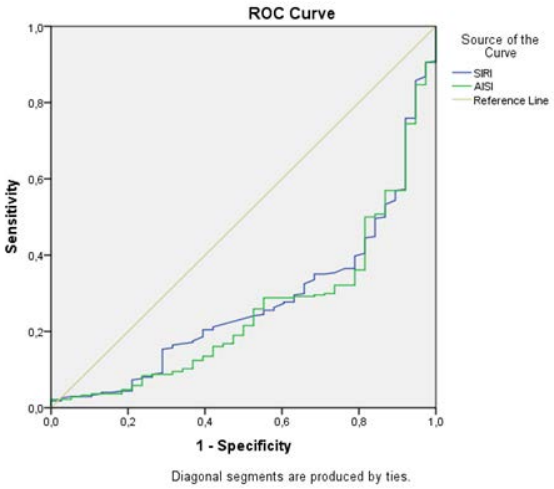

Figure 2. The receiver operating characteristic (ROC) curve for predicting non-response to omalizumab therapy
The ROC curve illustrates the diagnostic performance of the baseline Systemic Immune-Inflammation Index (SIRI) and the Aggregate Index of Systemic Inflammation (AISI) in distinguishing between patients who responded and those who did not respond to Omalizumab treatment.

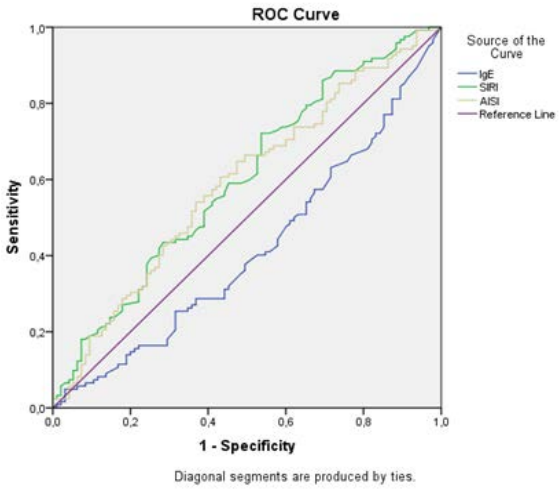

Figure 3. The receiver operating characteristic (ROC) curve for predicting relapse after treatment discontinuation
The ROC curve illustrates the diagnostic performance of baseline Total Immunoglobulin E (IgE), the Systemic Immune-Inflammation Index (SIRI), and the Aggregate Index of Systemic Inflammation (AISI) in predicting disease relapses after Omalizumab cessation.

Table 4. The binary logistic regression analysis of independent factors predicting response to omalizumab therapy

Model	Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Model 1	SIRI	0.466	0.305 – 0.713	<0.001
	Age	1.008	0.982 – 1.036	0.542
	Baseline UCT	1.143	0.975 – 1.338	0.099
Model 2	AISI	0.997	0.996 – 0.999	<0.001
	Age	1.009	0.982 – 1.037	0.520
	Baseline UCT	1.147	0.978 – 1.345	0.091

The analysis identifies independent predictors for a good response to Omalizumab therapy, defined as a 6-month Urticaria Control Test (UCT) score ≥ 12. Two separate multivariable models are constructed to avoid multicollinearity between SIRI and AISI. Statistically significant p-values ($p < 0.05$) are highlighted in bold.
Abbreviations: SIRI, Systemic Immune-Inflammation Index; UCT, Urticaria Control Test; AISI, Aggregate Index of Systemic Inflammation; OR, Odds Ratio; CI, Confidence Interval.

Table 3, and the corresponding ROC curves are shown in Figure 2.

In the multivariable binary logistic regression analysis performed to identify independent risk factors for non-response, an increased SIRI value is found to be an independent factor that reduced the likelihood of a good treatment response (Odds Ratio [OR]: 0.466; 95% CI: 0.305–0.713; p<0.001). AISI, which has been examined in a separate model, is similarly identified as an independent risk factor (OR: 0.997; 95% CI: 0.996–0.999; p<0.001). The results of the analysis are presented in Table 4.

Secondary Outcome: Relapse after Treatment Discontinuation

During the long-term follow-up of 217 patients whose Omalizumab therapy was successfully discontinued, relapse is observed in 56.2% of the patients (n=122), while 43.8% (n=95) remained in remission. When the baseline characteristics of the relapsing and non-relapsing groups are compared, it is determined that the baseline SIRI (Median 1.29 vs. 1.17; p=0.012) and AISI (Median 357.38 vs. 302.65; p=0.024) values are significantly higher in the group that relapsed. Conversely, the median baseline Total IgE is significantly lower in the relapsing group compared to the non-relapsing group (Median 94.05 vs. 119.0; p=0.026). The comparison results are presented in Table 5.

The performance of these three biomarkers in predicting relapses has been evaluated with ROC curve analysis. SIRI

Table 5. The comparison of baseline demographic and clinical characteristics of patients according to relapse status

Variable	Non-relapser Group (n=95)	Relapser Group (n=122)	p-value
Age (years)	42.0 (31.0 – 49.0)	42.0 (33.0 – 52.0)	0.477
Gender, female, n (%)	54 (56.8)	79 (64.8)	0.086
Symptom Duration (months)	15.0 (8.00 – 48.00)	24.0 (12.00 – 60.00)	0.080
Presence of Angioedema, n (%)	28 (29.5)	50 (41.0)	0.080
Baseline UCT Score	4.0 (3.00 – 4.00)	4.0 (3.00 – 5.00)	0.340
Neutrophil ($x10^9$/L)	4.25 (3.60 – 5.00)	4.64 (4.00 – 5.70)	0.446
Lymphocyte ($x10^9$/L)	2.43 (2.00 – 2.82)	2.43 (1.97 – 2.80)	0.137
Monocyte ($x10^9$/L)	0.56 (0.48 – 0.68)	0.56 (0.46 – 0.68)	0.080
Platelet ($x10^9$/L)	288.5 (250.0 – 331.0)	293.0 (253.0 – 334.5)	0.854
ESR (mm/hour)	8.0 (5.00 – 12.00)	9.0 (5.00 – 15.00)	0.657
CRP (mg/L)	3.00 (1.26 – 4.26)	3.07 (1.80 – 5.00)	0.390
Total IgE (IU/mL)	119.0 (56.00 – 241.50)	94.05 (41.98 – 192.00)	0.026
Creatinine (mg/dL)	0.78 (0.70 – 0.91)	0.77 (0.65 – 0.89)	0.240
AST (U/L)	14.90 (12.25 – 18.10)	15.50 (13.18 – 18.43)	0.120
ALT (U/L)	14.80 (11.45 – 19.85)	15.75 (11.98 – 20.43)	0.477
TSH (µIU/mL)	1.55 (1.02 – 2.50)	1.88 (1.21 – 2.59)	0.125
Anti-TPO (IU/mL)	13.00 (9.00 – 22.72)	11.00 (9.00 – 18.76)	0.569
SIRI	1.17 (0.87 – 1.47)	1.29 (1.02 – 1.66)	0.012
AISI	302.65 (220.19 – 405.05)	357.38 (264.12 – 451.33)	0.024

Numerical values are presented as Median (25th–75th percentile), while categorical variables are presented as n (%). P-values were calculated using the Mann-Whitney U test for continuous variables and the Chi-Square test for categorical variables. Statistically significant p-values ($p < 0.05$) are highlighted in bold.
Abbreviations: UCT, Urticaria Control Test; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; IgE, Immunoglobulin E; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TSH, Thyroid-stimulating hormone; Anti-TPO, Anti-thyroid peroxidase antibody; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation.

Table 6. The univariate and multivariate analyses of baseline biomarkers for predicting relapse after treatment discontinuation

Variable	Univariate ROC Analysis		Multivariate Logistic Regression Analysis	
	AUC (95% CI)	p-value	Odds Ratio (OR) (95% CI)	p-value
Total IgE	0.587 (0.511 – 0.663)	0.029	0.999 (0.998 – 1.000)	0.056
SIRI	0.599 (0.523 – 0.675)	0.012	1.863 (0.860 – 4.034)	0.115
AISI	0.589 (0.513 – 0.665)	0.024	1.001 (0.999 – 1.003)	0.434

The multivariable logistic regression analysis identifies independent predictors for relapse after Omalizumab discontinuation; this model included all three variables (Total IgE, SIRI, and AISI) together. Optimal cutoff values from the univariate ROC analysis are: Total IgE ≤ 94.05 (Sensitivity 50.0%, Specificity 62.1%); SIRI > 1.165 (Sensitivity 59.8%, Specificity 50.5%); and AISI > 357.38 (Sensitivity 50.0%, Specificity 64.2%).
Abbreviations: IgE, Immunoglobulin E; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation; OR, Odds Ratio; CI, Confidence Interval; AUC, Area Under the Curve.

(AUC=0.599; p=0.012), AISI (AUC=0.589; p=0.024), and Total IgE (AUC=0.587; p=0.029) all demonstrated a statistically significant but weak performance in predicting relapses. These results are summarized in Table 6, and the corresponding ROC curves are shown in Figure 3.

In the multivariable logistic regression model, which included these three factors, has found to be significant in the univariate analysis and none of the variables are identified as statistically significant, independent predictors of relapse (p>0.05 for all). The results are presented in Table 6.

DISCUSSION

The primary finding of this study is that baseline systemic inflammation indices, specifically SIRI and the AISI, are found to be valuable biomarkers in patients with CSU. These indices, derived from the complete blood count, can predict both the initial response to Omalizumab therapy and the long-term risk of relapse after treatment discontinuation. Our study confirmed the hypothesis that higher baseline systemic inflammatory activity is associated with both a poorer initial response to Omalizumab and a higher risk of post-treatment relapse.

In this study, patients exhibiting an inadequate clinical response to Omalizumab have demonstrated significantly elevated baseline SIRI and AISI levels. This reinforces the notion that CSU represents not only a localized cutaneous condition but also encompasses a systemic inflammatory component. This aligns with previous investigations reporting increased systemic inflammatory mediators, including C-reactive protein and interleukin-6, among individuals with CSU (12-14). To date, the neutrophil-to-lymphocyte ratio (NLR) has been the most extensively studied neutrophil-derived index linked to CSU activity (15-17). The present study contributes to the existing literature by emphasizing that broader and composite

indices such as SIRI and AISI, which incorporate monocyte and platelet parameters, are also relevant in CSU. Indeed, these results are in parallel with findings from rheumatologic and oncologic research, where elevated SIRI and AISI values have been associated with unfavorable prognosis and diminished therapeutic responsiveness (18). Our findings are partly consistent with large-scale real-world studies. For instance, Marzano et al. identified high baseline UAS7 and IgE levels as predictors of relapse, whereas this study highlights the role of systemic inflammation indices (10). Similarly, Kucharczyk et al. emphasized the complexity of predicting relapse, which supports our finding that traditional markers alone might be insufficient without composite indices like SIRI (7).

Notably, more conventional inflammation markers such as CRP and eosinophil count are not found to be as significant predictors of Omalizumab response in this study. This is consistent with the conflicting results in the literature; while some studies report a weak association with these markers, many, like ours, have not detected a significant relationship (19). A possible reason for this discrepancy might be that composite indices like SIRI and AISI better reflect the complex interaction and balance between different arms of the immune system, such as innate and adaptive immunity, than a single biomarker does. The logistic regression analysis, which demonstrated SIRI and AISI as independent predictors, statistically substantiates the importance of this immune balance concept. Although the Odds Ratio for AISI is found to be 0.997, suggesting a minimal effect per unit, it can be interpreted in the context of the index's wide numerical range (often 0–1000+). Therefore, larger fluctuations in AISI values are required to reflect clinically significant changes in inflammatory status.

The analysis of relapses after treatment discontinuation provided some of the most novel insights of the study. The association between high baseline SIRI and AISI and an increased risk of relapse suggests that persistent subclinical systemic inflammation might be a factor that prevents sustained remission even after treatment is stopped. It is conceptually consistent with the reports from other autoimmune diseases, such as rheumatoid arthritis, where the risk of relapse after discontinuing biological therapy is associated with high baseline inflammatory activity. For instance, in patients with inflammatory bowel disease (IBD), the risk of relapsing after stopping biological therapy increases significantly with clinical indicators of active inflammation, such as steroid dependency or perianal disease (20). Similarly, in patients with autoimmune hepatitis, high levels of active CD4□T-peripheral helper cells, CD8□T cells, and BAFF levels before treatment cessation have been identified as strong biomarkers for relapse (21). These data reveal that in various autoimmune diseases, the risk of relapsing after discontinuing biological therapy is closely related to the levels of inflammatory activity before or during the treatment.

A particularly noteworthy finding from the data is that lower baseline Total IgE levels have predicted an increased risk of relapse. Although this might seem contradictory to the pathophysiology of CSU at first glance, it is consistent with current literature suggesting the disease's heterogeneous nature and its different immunological subtypes. It is reported that CSU comprises at least two distinct endotypes, type I (IgE-mediated autoallergic) and type IIb (IgG-mediated autoimmune), and that these subtypes exhibit significant differences in disease severity, treatment response, and biomarker levels (22, 23). It is suggested that patients with low IgE levels might belong to the type IIb autoimmune CSU subtype, which is characterized by mast cell activation primarily driven by functional IgG autoantibodies (24). In this patient group, the therapeutic effect of Omalizumab is thought to occur through non-IgE-mediated mechanisms, such as down-regulating the expression of high-affinity IgE receptors (FcεRI) on mast cells and basophils, rather than by neutralizing free IgE (25). Therefore, these underlying autoimmune processes might make disease recurrence more likely upon treatment cessation. Clinically, this suggests that while low Total IgE alone is a risk factor, its evaluation in conjunction with elevated SIRI/AISI could better identify patients with 'autoimmune-enriched' endotypes who are prone to rapid relapse. In such cases, the decision to discontinue treatment should be taken into consideration with a greater caution. These findings contribute to the identification of biomarkers that can predict relapses after Omalizumab and highlight the importance of a personalized approach in CSU treatment.

The findings of this study are believed to hold important practical implications for the clinical management of CSU patients. SIRI and AISI values, which can be easily calculated from a routine complete blood count before treatment, can offer clinicians the opportunity to identify patients with a potentially lower response to Omalizumab at an early stage. This 'at-risk' patient group might be a candidate for closer monitoring or for alternative treatment combinations that can be developed in the future. Similarly, the presence of high SIRI/AISI or very low Total IgE values in a patient for whom treatment discontinuation is planned can be considered as a warning sign of a high relapse risk. This might warrant a reconsideration of the decision to discontinue therapy.

This study has several strengths that contribute significantly to literature. Firstly, the large sample size of over 300 patients and the ability to analyze long-term relapse data in a subgroup of this population (n=217) have increased the statistical potency of the study. The most important methodological strength can be considered as the control for the known effects of systemic corticosteroids on neutrophil-based markers. It is achieved by using the recent use of steroids as an exclusion criterion. This approach has strengthened the likelihood that our findings are directly related to the disease's underlying inflammatory activity.

On the other hand, the present study also has certain limitations. The primary limitation stems from its retrospective design, which might have introduced information bias due to non-standardized documentation in patient records. This also restricts the ability to establish a clear causal relationship for the observed associations. Additionally, as the study is carried out at a single center, the external validity and generalizability

of the findings to broader populations might be constrained.

Consequently, the inability to demonstrate statistically independent effects for individual markers in the multivariable relapse analysis warrants careful interpretation. This outcome might be primarily attributed to the multicollinearity between SIRI and AISI, as they are mathematically derived from shared hematological parameters. Furthermore, the multifactorial nature of relapse mechanisms suggests that other unmeasured variables are likely to influence the remission durability. Finally, the relatively limited sample size of the relapse subgroup might have restricted the statistical strength of the study that is necessary to isolate these independent associations.

CONCLUSION

In brief, the findings of this study indicate that baseline SIRI and AISI levels represent a practical, reliable, and cost-efficient biomarkers to estimate both inadequate therapeutic response to Omalizumab and the likelihood of relapses after treatment withdrawal in patients with CSU. These might serve as valuable adjunctive tools to assist clinicians in guiding treatment strategies and improving overall patient management. Future prospective, multicenter studies with larger cohorts are required to validate these cut-off values and confirm the clinical utility of these biomarkers in routine practice.

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RESEARCH ARTICLE

Association Between Sleep Problems and Quality of Life in Idiopathic Parkinson's Disease: Findings from Multiple Centers in Türkiye

İdiyopatik Parkinson Hastalığında Uyku Sorunları ve Yaşam Kalitesi Arasındaki İlişki: Türkiye'deki Çeşitli Merkezlerden Elde Edilen Bulgular

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ABSTRACT

Objective: This study investigated the prevalence of sleep disturbances and their association with sleep quality and overall well-being in Turkish patients diagnosed with idiopathic Parkinson's disease.

Materials and Methods: This collaborative cross-sectional study included a total of 451 patients with idiopathic Parkinson's disease across Türkiye. Demographic characteristics and relevant clinical information were systematically recorded. Sleep quality, health-related quality of life, and depressive symptoms were assessed using the Parkinson's Disease Sleep Scale, Parkinson's Disease Questionnaire 39, and Beck Depression Inventory, respectively.

Results: The mean age of the participants was 69.13 ± 11.27 years. According to the modified Hoehn and Yahr staging, most patients were categorized as stage 1 (24.8%), while very few had stage 5 disease (1.3%). Depressive symptoms were moderate in 30.6%, minimal in 29.9%, mild in 24.6%, and severe in 14.9% of the participants. Older age was associated with a significant decline in both sleep onset and sleep benefit scores. Longer disease duration and higher disease stage were associated with decreases in all domains of sleep quality. Depression scores were directly correlated with quality-of-life scores ($p<0.001$), indicating a strong association between increased depressive symptoms and poorer quality of life in all domains.

Conclusion: Sleep disturbances are prevalent in individuals with Parkinson's disease and have a marked adverse impact on their emotional state and daily functioning. Addressing these sleep problems may contribute to better emotional well-being and enhanced quality of life in this population.

Keywords: Parkinson's disease; sleep-wake cycle disorders; quality of life

ÖZET

Amaç: Bu çalışmada, Türkiye'de İdiyopatik Parkinson Hastalığı (İPH) olan hastalarda uyku bozukluklarının yaygınlığının araştırılması ve bu bozuklukların hastaların uyku ve yaşam kalitesini nasıl etkilediğinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Türkiye'de yürütülen bu çok merkezli çalışmada, 451 IPH hastası değerlendirildi. Hastaların demografik ve klinik verileri kaydedildi. Değerlendirmeler Parkinson Hastalığı Uyku Ölçeği, Parkinson Hastalığı Anketi ve Beck Depresyon Envanteri kullanılarak yapıldı.

Bulgular: IPH tanısı olan 451 hastanın ortalama yaşı 69,13±11,27 yıldı. Modifiye Hoehn Yahr Ölçeği'ne göre en sık görülen hastalık evresi %24,8 ile evre 1 iken, en az görülen evre ise %1,3 ile evre 5 idi. Hastaların %30,6'sında orta şiddette depresyon, %29,9'unda minimal depresyon, %24,6'sında hafif depresyon, %14,9'unda ise ağır depresyon saptandı. Hasta yaşı arttıkça uyku başlangıcı ve uyku faydası puanları anlamlı derecede azaldı. Hastalık süresi ve evresi arttıkça uyku kalitesinin tüm alt parametrelerinde azalma görüldü. Yaşam kalitesi alt parametreleri ve toplam puanları arttıkça depresyon puanı da artmaktaydı. Yaşam kalitesi alt parametrelerinin tümü ile depresyon arasında güçlü pozitif korelasyon vardı ($p<0,001$).

Sonuç: Uyku bozuklukları IPH hastalarında yaygındır ve depresyon ve yaşam kalitesini büyük ölçüde olumsuz etkiler. Parkinson hastalarında uyku bozukluklarının kontrol altına alınmasıyla yaşam kalitesi artırılabilir.

Anahtar Kelimeler: Parkinson hastalığı; uyku-uyanıklık bozuklukları; yaşam kalitesi

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INTRODUCTION

Idiopathic Parkinson's disease (IPD) presents with the cardinal motor findings of rigidity, bradykinesia, involuntary shaking at rest (resting tremor), and impaired balance (postural instability). It ranks as the second most common neurodegenerative condition globally, after Alzheimer's disease. Pathologically, the disorder is marked by the gradual degeneration of dopaminergic neurons in the nigrostriatal pathway and the intracellular accumulation of abnormally folded protein aggregates known as Lewy bodies. Disease progression causes gradual deterioration of motor function (1). The relationship between Parkinson's disease and sleep disorders is strong and closely linked to the natural course of the disease. Aside from the hallmark motor symptoms of Parkinson's disease, early neurodegeneration affecting the brainstem, hypothalamus, and networks regulating circadian rhythm leads to sleep–wake cycle disruption. Conditions such as insomnia, rapid eye movement (REM) sleep behavior disorder, excessive daytime sleepiness, restless legs syndrome, and circadian rhythm disturbances are significantly more prevalent in this population compared to the general population. In particular, REM sleep behavior disorder (RBD) reflects early brainstem involvement of α-synuclein pathology and is therefore considered a prodromal marker of Parkinson's disease. Sleep disorders are associated with greater motor symptom severity, cognitive impairment, autonomic dysfunction, and depression, exerting an independent negative impact on patient quality of life (2).

Impaired circadian rhythm and decreased REM transition time are expected outcomes in Parkinson's disease. The decline in sleep efficiency and total sleep duration is related to an increase in respiratory and motor events. In Parkinson's disease, dystonic movements of the limbs tend to occur more frequently during nighttime sleep. Due to bradykinesia, these individuals have a limited ability to alter their sleeping posture, resulting in greater discomfort and involuntary dystonic activity that may exacerbate motor symptoms (3,4). Sleep patterns are further disturbed by alterations in dopaminergic, serotonergic, and noradrenergic transmission. It is believed that this condition may lead to an increase in cataplexy-like attacks due to heightened daytime sleepiness, potentially exacerbated by high doses of non-ergot dopamine agonists, although evidence remains insufficient. The use of dopamine agonists such as L-Dopa/carbidopa may cause the sudden onset of sleep during the day (4). Given the chronic and progressive course of Parkinson's disease, which often extends beyond 15 years, sustaining an optimal quality of life in affected individuals is essential (5). This requires effective management of motor symptoms as well as non-motor symptoms such as sleep disturbances, autonomic dysfunction, anxiety, depression, and fatigue (6).

Although there are no definitive data concerning the prevalence of IPD in Türkiye, the global prevalence is reported to be approximately 14.2/100,000 individuals. In addition, IPD is more common in men and its incidence increases with age (7). Given its prevalence in the general population, recognizing the characteristic symptoms and defining disease-related parameters are essential for guiding appropriate treatment and rehabilitation strategies. In this cross-sectional multicenter analysis conducted in Türkiye, we examined the prevalence of sleep disturbances among individuals diagnosed with idiopathic Parkinson's disease and explored their influence on both sleep quality and overall well-being.

MATERIALS AND METHODS

Participants

Recruitment and setting

This multicenter study included 451 individuals diagnosed with IPD who were under follow-up either in tertiary-level neurology outpatient clinics or in the movement disorder units of education and research hospitals across Türkiye. All participants enrolled voluntarily and provided informed consent. Demographic and clinical data, including sex, age, disease duration, Hoehn and Yahr (H&Y) stage, current medications, and relevant personal and family medical history were documented using a structured data form. Clinical outcomes were assessed using the Parkinson's Disease Sleep Scale to evaluate nocturnal sleep disturbances, the Parkinson's Disease Questionnaire (PDQ-39) to measure health-related quality of life, and the Beck Depression Inventory (BDI) to assess the severity of depressive symptoms.

Inclusion criteria

1. Age ≥ 18 years
2. Currently under follow-up for IPD at one of the participating centers
3. Provision of voluntary informed consent

Exclusion criteria

1. Diagnosis of atypical parkinsonism (Parkinson-plus syndromes) or secondary parkinsonism
2. Known diagnosis of sleep disorder
3. Engaged in shift work
4. Current use of pharmacological agents known to affect sleep regulation (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors)
5. Moderate or severe dementia according to the Clincial Dementia Rating Scale
6. Adjustments to antiparkinsonian therapy (medication or dosage) within the month preceding enrollment

Study Design

This multicenter, cross-sectional study was conducted through the collaboration of Turkish Neurological Society (TNS) Movement Disorders Working Group members employed in participating centers, under the leadership of the Turkish Neurological Society Quality of Life Working Group. Ethical approval for the study was granted by the Institutional Review Board of Kütahya University of Health Sciences (2021-04/05).

Outcome Measures

Descriptive Data Form: A structured data form was developed by the research team to document each participant's age, sex, disease duration, H&Y stage, current treatment regimen, and relevant personal or family medical history. Modified Hoehn and Yahr Scale: The H&Y scale is widely

employed to evaluate symptom severity and monitor disease progression in IPD (8). The stages are defined as follows:

- ***Stage 1:*** Cardinal symptoms (tremor, rigidity, or bradykinesia) present unilaterally
- ***Stage 1.5:*** Unilateral symptoms and axial involvement
- ***Stage 2:*** Bilateral symptoms with preserved balance; possible speech abnormalities, impaired posture, and gait abnormality
- ***Stage 2.5:*** Mild bilateral involvement with a normal pull test response
- ***Stage 3:*** More severe bilateral symptoms with impaired balance; independent in physical functioning
- ***Stage 4:*** Advanced disease; able to stand but requires assistance to function
- ***Stage 5:*** Confined to a wheelchair or bedridden

Parkinson's Disease Sleep Scale: The scale comprises 15 items designed to evaluate various aspects of sleep: overall quality of nocturnal sleep (item 1), difficulty initiating and maintaining sleep (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychotic symptoms (items 6 and 7), frequency of nocturnal urination (items 8 and 9), nocturnal motor problems (items 10–13), perceived benefit from sleep and morning well-being (item 14), and daytime sleepiness (item 15). Each item is scored on a scale from 0 (very severe complaints) to 10 (no complaints), yielding a maximum total score of 150. A higher score reflects a lower frequency of sleep-related complaints and better sleep quality (9).

Parkinson's Disease Questionnaire 39: The PDQ-39 questionnaire, originally developed by Peto and colleagues in 1995, has been validated for use in Turkish populations, with its reliability well established in earlier studies (10). It is regarded as the primary instrument for measuring health-related quality of life among individuals with Parkinson's disease.

Beck Depression Inventory: The Turkish adaptation of the BDI was validated and shown to be reliable by Hisli and colleagues (11). The inventory comprises 21 multiple-choice items designed to assess the intensity of depressive symptoms. Total scores range from 0 to 63, with higher values indicating greater symptom severity.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed through visual inspection and statistical tests. Continuous variables were expressed as mean

Table 1. Demographic and clinical data of the participants

		Mean ± SD	Median (range)
	Age (years)	69.13 ± 11.27	71 (22-93)
	Height (cm)	167.28 ± 8.68	168 (140-190)
	Weight (kg)	75.78 ± 11.58	75 (50-130)
	Disease duration (years)	5.60 ± 4.69	5 (1-35)
		n	**%**
Gender	Female	202	44.8
	Male	249	55.2
Marital status	Married	377	83.6
	Single	74	16.4
Educational level	Illiterate	40	8.9
	Literate	37	8.2
	Primary school	179	39.7
	Middle school	73	16.2
	High school	85	18.8
	University and above	37	8.2
Family history of PD	Present	451	100
	Absent	361	80
Disease stage (according to the Modified Hoehn and Yahr Scale)	Stage 1	112	24.8
	Stage 1.5	89	19.7
	Stage 2	101	22.4
	Stage 2.5	61	13.5
	Stage 3	49	10.9
	Stage 4	33	7.3
	Stage 5	6	1.3
Medication/Treatment	Apomorphine pump	1	0.2
	Deep brain stimulation	1	0.2
	Dopamine agonist	83	18
	Levodopa	393	87
	MAO-B inhibitor	23	5.1

n: number of participants, SD: standard deviation

± standard deviation or as median values with corresponding ranges. Categorical variables were presented as frequencies and percentages. Correlation analyses employed Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation for non-normally distributed data. Statistical significance was defined as $p < 0.05$.

RESULTS

The study included 451 IPD patients with a mean age of 69.13 ± 11.27 years and mean disease duration of 5.60 ± 4.69 years. Only 20% of the participants reported a family history of Parkinson's disease. Based on the H&Y, the most common stage was stage 1 (24.8%), while the least common was stage 5 (1.3%). Most of the patients were primary school graduates. Pharmacological management included levodopa in 87% of patients and dopamine agonists in 18% (Table 1).

The participants' mean total sleep score was 87.22 ± 36.30, and their mean total health-related quality of life score was 16.78 ± 11.61. Depressive symptoms were classified as moderate in 30.6%, minimal in 29.9%, mild in 24.6%, and severe in 14.9% of the patients (Table 2). Older age was correlated with a decline in sleep onset and sleep benefit scores. Longer disease duration was associated with reductions in all sleep domain scores, indicating a decline in sleep quality. Higher disease stage according to the H&Y scale was also correlated with lower scores for all sleep domains (Table 3).

Patient age demonstrated a significant positive correlation with mobility, activities of daily living, and cognitive function scores ($p < 0.001$). As expected, longer disease duration and higher H&Y stage were associated with a decline in all domains of health-related quality of life ($p < 0.001$). In addition, both disease duration and H&Y disease stage were positively associated with the severity of depressive symptoms ($p < 0.001$) (Table 4). Negative correlations were observed between sleep and depression scores ($p < 0.001$), indicating that depressive symptoms tended to increase in association with reduced sleep quality (Table 5). Similarly, depression score was directly correlated with health-related quality-of-life scores (p

Table 2. Mean sleep and quality-of-life scores and classification of depressive symptom severity

		Mean ± SD	Median (range)
Sleep	Overall quality of nighttime sleep	5.91±2.71	6 (0-10)
	Onset of asleep	11.32±5.76	12 (0-20)
	Nocturnal restlessness	11.30±6.66	12 (0-20)
	Nocturnal psychosis	12.67±6.93	15 (0-20)
	Nocturia	11.98±5.73	13 (0-20)
	Motor symptoms at night	22.94±11.99	24 (0-40)
	Benefitting from sleep	5.16±3.17	5 (0-10)
	Daytime sleepiness	5.75±2.92	6 (0-10)
	Total score	87.22±36.30	89 (9-149)
Quality of life	Mobility	18.51±11.54	18 (0-40)
	Activities of daily living	10.31±6.92	11 (0-24)
	Emotional well-being	10.17±6.21	10 (0-24)
	Stigma	4.40±4.24	4 (0-16)
	Social support	2.68±2.86	2 (0-11)
	Cognition	6.21±3.61	6 (0-15)
	Communication	2.88±2.69	2 (0-11)
	Bodily discomfort	4.90±3.07	5 (0-12)
	Total score	16.78±11.61	15 (0-60)
Depression		**n**	**%**
	Minimal	135	29.9
	Mild	111	24.6
	Moderate	138	30.6
	Severe	67	14.9

n: number of participants, SD: standard deviation

Table 3. Correlation of sleep-related variables with age and clinical characteristics

		Overall quality of nocturnal sleep	Sleep onset	Nocturnal restlessness	Nocturnal psychosis	Nocturia	Motor symptoms at night	Sleep benefit	Daytime sleepiness	Total score
Age	r	-0.142**	-0.149**	-0.109*	-0.064	-0.026	-0.087	-0.147**	-0.094*	-0.107*
	p	0.002	0.002	0.021	0.174	0.586	0.064	0.002	0.046	0.023
Disease duration	r	-0.205**	-0.154**	-0.124**	-0.102*	-0.128**	-0.097*	-0.113*	-0.165**	-0.151**
	p	<0.001	0.001	0.008	0.03	0.006	0.039	0.017	<0.001	0.001
Disease stage†	r	-0.283**	-0.223**	-0.182**	-0.137**	-0.174**	-0.186**	-0.157**	-0.174**	-0.222**
	p	<0.001	<0.001	<0.001	0.004	<0.001	<0.001	0.001	<0.001	<0.001

†According to the modified Hoehn and Yahr Scale; r: correlation coefficient; *p < 0.05, **p < 0.01

Table 4. Correlation of quality-of-life variables and depression with age and clinical characteristics

		Mobility	ADL	Emotional well-being	Stigma	Social support	Cognition	Communication	Bodily discomfort	Depression
Age	r	0.245**	0.165**	0.095*	-0.038	0.017	0.198**	0.053	0.089	0.110*
	p	<0.001	<0.001	0.043	0.424	0.712	<0.001	0.263	0.059	0.019
Disease duration	r	0.355**	0.395**	0.318**	0.303**	0.185**	0.337**	0.359**	0.330**	0.328**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Disease stage*	r	0.660**	0.586**	0.403**	0.335**	0.149**	0.421**	0.444**	0.405**	0.459**
	p	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001

ADL: activities of daily living, r: correlation coefficient; *p < 0.05, **p < 0.01

Table 5. Correlation between sleep-related variables and depression

		Sleep onset	Nocturnal restlessness	Nocturnal psychosis	Nocturia	Motor symptoms at night	Sleep benefit	Daytime sleepiness	Total sleep score	Depression
Overall sleep quality	r	0.618**	0.474**	0.406**	0.340**	0.493**	0.473**	0.353**	0.614**	-0.490**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Sleep onset	r	-	0.629**	0.542**	0.504**	0.616**	0.624**	0.447**	0.782**	-0.370**
	p	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Nocturnal restlessness	r	0.629**	-	0.575**	0.536**	0.758**	0.561**	0.488**	0.845**	-0.230**
	p	<0.001	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Nocturnal psychosis	r	0.542**	0.575**	-	0.606**	0.682**	0.452**	0.425**	0.794**	-0.235**
	p	<0.001	<0.001	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Nocturia	r	0.504**	0.536**	0.606**	-	0.606**	0.407**	0.392**	0.736**	-0.206**
	p	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001	<0.001	<0.001
Motor symptoms at night	r	0.616**	0.758**	0.682**	0.606**	-	0.597**	0.512**	0.917**	-0.225**
	p	<0.001	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001	<0.001
Sleep benefit	r	0.624**	0.561**	0.452**	0.407**	0.597**	-	0.489**	0.698**	-0.282**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001
Daytime sleepiness	r	0.447**	0.488**	0.425**	0.392**	0.512**	0.489**	-	0.608**	-0.319**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-	<0.001	<0.001
Total sleep score	r	0.782**	0.845**	0.794**	0.736**	0.917**	0.698**	0.608**	-	-0.326**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-	<0.001
Depression	r	-0.370**	-0.230**	-0.235**	-0.206**	-0.225**	-0.282**	-0.319**	-0.326**	-
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-

r: correlation coefficient, p < 0.05

Table 6. Correlation between quality-of-life variables and depression

		Mobility	ADL	Emotional well-being	Stigma	Social support	Cognition	Communication discomfort	Bodily
Depression	r	0.667**	0.659**	0.787**	0.598**	0.391**	0.694**	0.675**	0.556**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mobility	r	-	0.794**	0.618**	0.428**	0.254**	0.522**	0.591**	0.526**
	p	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ADL	r	0.794**	-	0.604**	0.491**	0.253**	0.531**	0.596**	0.449**
	p	<0.001	-	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Emotional well-beingr		0.618**	0.604**	-	0.606**	0.453**	0.606**	0.572**	0.538**
	p	<0.001	<0.001	-	<0.001	<0.001	<0.001	<0.001	<0.001
Stigma	r	0.428**	0.491**	0 .606**	-	0.380**	0.492**	0.593**	0.409**
	p	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001	<0.001
Social support	r	0.254**	0.253**	0.453**	0.380**	-	0.417**	0.351**	0.305**
	p	<0.001	<0.001	<0.001	<0.001	-	<0.001	<0.001	<0.001
Cognition	r	0.522**	0.531**	0.606**	0.492**	0.417**	-	0.619**	0.565**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	-	<0.001	<0.001
Communication	r	0.591**	0.596**	0.572**	0.593**	0.351**	0.619**	-	0.446**
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-	<0.001
Bodily discomfort	r	0.526**	0.449**	0.538**	0.409**	0.305**	0.565**	0.446**	-
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-

ADL: activities of daily living, r: correlation coefficient, p < 0.05

< 0.001), indicating that increased depressive symptoms were associated with poorer quality of life in all domains (Table 6).

DISCUSSION

This cross-sectional research evaluated sleep quality and depressive symptoms in 451 individuals with IPD from multiple clinics in Türkiye. The findings demonstrated a significant relationship between sleep-related disturbances, depressive symptoms, and health-related quality of life. We observed that most of the patients were prone to depression. Higher disease stage and longer disease duration were also associated with an increase in sleep disturbances. Additionally, the education level was generally low in our sample. Menza et al. categorized sleep disorders in Parkinson's disease under the following

headings: Insomnia, RBD, sleep apnea, vivid dreaming, excessive daytime sleepiness, and sleep attacks (12). RBD is a parasomnia common in Parkinson's disease and characterized by loss of muscle atonia during REM sleep. Multicenter studies have shown that RBD is a prodromal marker that can precede the development of overt motor symptoms in Parkinson's disease. Clinical data indicate that individuals with RBD exhibit non-motor symptoms similar to those in Parkinson's disease, leading to a lower quality of life and accelerated cognitive decline (2).

The management of sleep disorders in patients with Parkinson's disease is individualized according to symptomatology and generally requires a combination of non-pharmacological interventions and targeted pharmacotherapy. These non-pharmacological approaches include sleep hygiene training, regular exercise, scheduling of activity and light exposure, and cognitive behavioral therapy, particularly for insomnia (2). Continuous positive airway pressure is recommended for patients with sleep apnea. Regarding pharmacotherapy, melatonin or clonazepam have been suggested to reduce the risk of injury in RBD. In patients with excessive daytime sleepiness, initial management involves addressing the sedative burden and any comorbid conditions disrupting nighttime sleep (e.g., sleep apnea, restless legs syndrome, nocturnal akinesia), and wakefulness-promoting agents may be used in refractory cases. For insomnia, sedatives/hypnotics should be used cautiously and as briefly as possible due to the risk of confusion and falls in IPD (13). Periodic limb movements during sleep or restless legs syndrome associated with motor involvement of the disease cause awakenings and impair the quality of sleep (14). Evidence from the present study demonstrates strong correlations among various sleep-related parameters, as well as correlation between these parameters and external factors. A decreased ability to fall asleep increases daytime sleepiness, and increased motor symptoms at night trigger nocturnal psychosis. In addition to multidisciplinary treatment, sleep disorders should be considered a separate pathology, and disease-related effects on sleep subparameters should also be mitigated. Improving sleep patterns can lead to more restorative rest, thereby enhancing overall quality of life for these patients.

Quality of life is a subjective yet crucial construct that serves to evaluate therapeutic interventions and reflect an individual's psychological, physical, and social functioning. In a multifaceted disorder such as Parkinson's disease, which is characterized by progressive disability, the continuous evaluation of quality of life becomes indispensable (15). In the present study, depressive symptoms were associated with reduced mobility, lower emotional well-being, and diminished cognitive and communicative performance. Increased physical strain and limitations in activities of daily living were also related to poorer overall quality of life. In a study including 158 patients with Parkinson's disease, Karlsen et al. (16) reported that despite receiving the most modern care available, there was still a decline in quality of life. Social isolation and emotional reactivity exacerbated stress and anxiety in patients with advanced disease stage according to the H&Y scale. Based on these findings, the authors concluded that decreased quality of life might increase the public health burden (16). Considering the long life expectancy of individuals diagnosed with Parkinson's disease, maintaining their well-being is essential. A key result emerging from the current study is that with longer disease duration and higher disease stage, patients exhibited deterioration in both emotional well-being and cognitive function. Parkinson's disease is primarily managed pharmacologically. Levodopa is effective in alleviating the cardinal motor symptoms of the disease. Medication use is important for controlling motor fluctuations. The disease is typically managed by adjusting the dose of levodopa or adding MAO-B inhibitors or dopamine agonists to the treatment regimen. The use of dopaminergic drugs, especially dopamine agonists, is often reduced to manage emergent impulse control disorders. Although Parkinson's disease is incurable, pharmacological and non-pharmacological treatments are utilized for the purpose of enhancing patient quality of life (17). The present analysis revealed that pharmacotherapy in this cohort was largely based on levodopa and dopamine agonists. This is an indication that evidence-based pharmacological guidelines are generally adopted in the management of IPD. Deep brain stimulation was utilized less frequently as a treatment option in this Turkish cohort.

Sleep problems, disease-related decline in quality of life, and pharmacological burden collectively contribute to the development of psychopathological clinical conditions in patients with IPD over time. Depression and anxiety have emerged as the most prevalent psychiatric comorbidities reported in this population (18,19). Approximately one-third of patients with IPD exhibit depressive symptoms which may persist at mild levels and progressively worsen to moderate or severe intensity over time (20). Therefore, recognition and optimal treatment of depression are essential. The pathophysiological basis of depression linked to IPD has yet to be fully elucidated, although it may precede motor symptoms. The disease presents with structural alterations and reductions in dopamine, serotonin, and norepinephrine levels, which contribute to the depressive phenotype. Several studies have proposed that deep brain stimulation may be considered as a potential treatment for depression. Evidence suggests that subthalamic nucleus stimulation may provoke suicidal behavior in some cases, in contrast to pallidal stimulation, which has been associated with improvements in mood and depressive symptoms (20). Consistent with this, our findings revealed a positive correlation between depression and the progression and duration of IPD.

Study Limitations

A primary limitation of this research was the lack of objective measures to confirm sleep disturbances. Additionally, the majority of participants were in the early to moderate stages of Parkinson's disease, which may influence the generalizability of the findings. Furthermore, the participants had a wide age range. In future studies, the confounding effects of age-related factors can be mitigated with age-stratified analyses. Lastly, the

considerable variance in disease duration among participants can be considered another limitation.

CONCLUSION

The present analysis underscores the interrelation between sleep disturbances, depressive symptoms, and health-related quality of life in individuals with IPD, a common neurodegenerative disorder. This multicenter study contributes valuable clinical insights to the literature by comprehensively evaluating these multifaceted parameters within a large Turkish cohort.

DECLARATIONS

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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RESEARCH ARTICLE

Effect of Radioactive Iodine Ablation Therapy on Ovarian Reserve in Patients with Differentiated Thyroid Cancer

Diferansiye Tiroid Kanserli Hastalarda Radioaktif İyot Ablasyon Tedavisinin Ovaryan Rezerve Etkisi

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ABSTRACT

Objective: Radioactive iodine (RAI) ablation therapy is widely used in the management of differentiated thyroid cancer (DTC). However, its potential adverse effects on ovarian reserve in premenopausal women remain an important clinical concern. This study aimed to investigate the association between RAI ablation therapy and ovarian reserve in premenopausal patients with differentiated thyroid cancer.

Materials and Methods: This study included 66 premenopausal women aged 18–45 years with DTC. Among these patients, 46 received RAI therapy and 20 did not. Serum anti-Müllerian hormone (AMH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and thyroid-stimulating hormone (TSH) levels were measured. To evaluate in-dependent association between RAI therapy and ovarian reserve, a multivariable linear regres-sion analysis was performed with AMH as the dependent variable.

Results: AMH levels were significantly lower in patients who received RAI therapy compa-red with those who did not (1.34 ± 0.37 ng/mL vs 1.79 ± 0.25 ng/mL, p = 0.001). No signifi-cant differences were observed between the groups in serum FSH, LH, or E2 levels. AMH levels did not differ significantly according to RAI dose categories of 75, 100, and 150 mCi (p = 0.073). In the multivariable linear regression analysis, RAI therapy remained indepen-dently associated with lower AMH levels (β = −0.41, p = 0.003). Age was also independently associated with AMH levels (β = −0.36, p = 0.010).

Conclusion: RAI therapy was associated with lower AMH levels in premenopausal women with DTC, suggesting a potential adverse effect on ovarian reserve. Larger prospective studies are needed to confirm these findings.

Keywords: Differentiated thyroid cancer, radioactive iodine, ovarian reserve, anti-Müllerian hormone.

ÖZET

Amaç: Radyoaktif iyot (RAI) ablasyon tedavisi, diferansiye tiroid kanseri (DTK) yönetimin-de yaygın olarak kullanılmaktadır. Bununla birlikte, premonopoz kadınlarda over rezervi üze-rindeki olumsuz etkileri klinik endişe oluşturmaktadır. Bu çalışmada, RAI ablasyon tedavisinin premenopozal DTK hastalarında over rezervi ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışmaya, 18–45 yaş aralığında 66 premenopozal DTK hastası dahil edildi. Hastaların 46'sı RAI tedavisi almış, 20'si ise almamıştı. Serum anti-Müllerian hormon (AMH), folikül stimülan hormon (FSH), luteinizan hormon (LH), östradiol (E2) ve tiroid sti-mülan hormon (TSH) düzeyleri ölçüldü. RAI tedavisi ile over rezervi arasındaki bağımsız iliş-kiyi değerlendirmek amacıyla, bağımlı değişken olarak AMH düzeyinin alındığı çok değişkenli doğrusal regresyon analizi yapıldı.

Bulgular: AMH düzeyi, RAI tedavisi alan hastalarda almayanlara göre anlamlı derecede daha düşüktü (1.34 ± 0.37 ng/mL'ye karşı 1.79 ± 0.25 ng/mL, p = 0.001). Gruplar arasında serum FSH, LH ve E2 düzeyleri açısından anlamlı fark saptanmadı. AMH düzeyleri, 75, 100 ve 150 mCi RAI doz gruplarına göre anlamlı farklılık göstermedi (p = 0.073). Çok değişkenli doğrusal regresyon analizinde, RAI tedavisi daha düşük AMH düzeyleri ile bağımsız olarak ilişkili bu-lundu (β = −0.41, p = 0.003). Yaş da AMH düzeyi ile bağımsız olarak ilişkiliydi (β = −0.36, p = 0.010).

Sonuç: Premenopozal DTK hastalarında RAI tedavisi, daha düşük AMH düzeyleri ile ilişkili bulundu ve bu durum over rezervi üzerinde olası olumsuz bir etkiye işaret etmektedir. Bu bul-guların doğrulanması için daha geniş prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Diferansiye tiroid kanseri, radyoaktif iyot, over rezervi, anti-Müllerian hormon.

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INTRODUCTION

Although thyroid cancers constitute less than 2% of all cancers worldwide, they represent the most common endocrine malignancy. According to a study conducted by the Turkish Public Health Institute Cancer Department in 2020, thyroid cancer was the second most common cancer among women and the ninth most common among men. Differentiated thyroid carcinomas (DTC) account for 92.2% of all thyroid cancers (papillary carcinoma 82.2%, follicular carcinoma 6.1% and Hürthle cell carcinoma 3.9%) (1,2). Radioactive iodine (RAI) ablation therapy is widely used in patients diagnosed with differentiated thyroid cancer to reduce the risk of recurrence by ablating residual thyroid tissue after surgery. In addition, RAI is used to treat unknown or suspected metastatic diseases. RAI ablation therapy has been associated with a statistically significant increase in secondary malignancies. In particular, when the total RAI dose exceeds 500–600 mCi, the risk of leukemia and solid organ tumors increases significantly. In addition to the risk of malignancy, RAI ablation therapy may cause sialadenitis, dry mouth, dental caries, and nasolacrimal duct stenosis. Moreover, RAI ablation therapy may adversely affect the male and female gonads (3).

Anti-Müllerian hormone is secreted by granulosa cells of primary and preantral ovarian follicles and is considered one of the most reliable biomarkers of ovarian reserve. In addition, follicle-stimulating hormone, luteinizing hormone, and estradiol are key reproductive hormones regulated by the hypothalamic–pituitary–gonadal axis and are frequently used to evaluate ovarian function (4). In this study, we aimed to investigate the effects of radioactive iodine ablation therapy on the ovarian reserve in patients with differentiated thyroid cancer.

MATERIALS AND METHODS

This case–control analytical study evaluated the effect of RAI ablation therapy on the ovarian reserve in patients with well-differentiated thyroid cancer. The study included 46 patients aged 18–45 years who received RAI treatment and 20 patients who did not receive RAI treatment, all of whom had been diagnosed with differentiated thyroid cancer and presented to the Endocrine Diseases Outpatient Clinic of Yüzüncü Yıl University between February 1, 2019, and June 30, 2019. The exclusion criteria were as follows: refusal to participate in the study, age <18 or >45 years, use of oral contraceptive drugs, diagnosis of polycystic ovary syndrome, diagnosis of diabetes mellitus, history of oophorectomy, infertility, and presence of an active malignancy. Ethical approval for the study was obtained from the Yüzüncü Yıl University Non-Drug and Non-Medical Device Research Ethics Committee before the initiation of the study (date: November 13, 2018, decision number: 3). During the implementation phase, patients were informed about the purpose of the study and written and verbal informed consent was obtained from those who agreed to participate.

This study was financially supported by the Scientific Research Projects Coordination Unit of Yüzüncü Yıl University (Project No: TTU-2019-8096). Patients who agreed to participate were asked about their age, height, weight, age at menarche, number of children prior to RAI therapy (if applicable), menstrual status after RAI therapy, and number of children after RAI therapy. In addition, patients' medical records were retrospectively reviewed to obtain tumor size, administered RAI dose, and date of RAI ablation therapy. Anthropometric measurements were obtained by measuring the height and body weight. The body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). BMI was classified as underweight (<18.50 kg/m^2), normal weight (18.50–24.99 kg/m^2), overweight (25.0–29.99 kg/m^2), or obese (≥30.0 kg/m^2).

At the time of routine outpatient blood sampling, a single 3-mL blood sample was additionally obtained from each patient and placed into dry biochemistry tubes without an anticoagulant. Samples were centrifuged at 3500 rpm for 10 minutes, and the serum was aliquoted into 1-mL Eppendorf tubes and stored at −80°C until analysis. The reference ranges used were as follows: TSH 0.57–4.2 µIU/mL, FSH 0–12.4 mIU/mL, LH 0–8.6 mIU/mL, estradiol (E2) 21–251 pg/mL, and AMH 0.08–20 ng/mL. Serum FSH and E2 levels were measured using the chemiluminescent microparticle immunoassay (CMIA) method on an Abbott Architect ci16200 autoanalyzer in the hospital's biochemistry laboratory. The serum FSH levels were expressed in mIU/mL, while the serum E2 levels were expressed in pg/mL. Serum LH levels were measured using CMIA on an Abbott Architect i2000 autoanalyzer and expressed in mIU/mL. Serum AMH levels were measured using the enzyme-linked immunosorbent assay (ELISA) method on a Biotek Instruments ELx800 reader. AMH concentrations were expressed in ng/mL (Table 1). For the AMH assay, 50 µL of standard was added to nine wells starting from the second column, followed by 50 µL of streptavidin-Horseradish Peroxidase (HRP). For sample wells, 40 µL of sample, 10 µL of AMH antibody 1, and 50 µL of streptavidin-HRP were added (Figure 1). The plate was gently shaken, covered, and incubated at 37°C for 60 minutes. After incubation, the wells were washed five times with washing solution prepared by diluting the wash buffer 30-fold with distilled water (250 mL). After washing, 50 µL of Chromogen Reagent A and 50 µL of Chromogen Reagent B were added to each well and incubated at 37°C for 10 minutes. The reaction was stopped by adding 50 µL of stop solution to each well (Figure 2). Absorbance was measured at 450 nm. A standard curve was generated using CurveExpert 1.4 software based on standard concentrations and optical densities, and sample concentrations were calculated accordingly.

To account for potential confounding factors affecting ovarian reserve, a multivariable linear regression analysis was performed with AMH as the dependent variable. Independent variables included age, body mass index (BMI), TSH level, tumor diameter, and time elapsed since RAI therapy. Variables that were clinically relevant or showed potential association in univariate analyses were included in the model. All data were entered into the Statistical Package for the Social Sciences (SPSS) version 22.0 software. Descriptive statistics were expressed as frequencies, percentages, means, standard deviations, and minimum and maximum values. Normality of

Table 1. Standard solutions for AMH were prepared

Standard no	Concentration	Process
Standard no:5	12 ng/ml	120 µl original standart + 120 µl standart dilution
Standard no:4	6 ng/ml	120 µl standart no: 5 + 120 µl standart dilution
Standard no:3	3 ng/ml	120 µl standart no: 4 + 120 µl standart dilution
Standard no:2	1.5 ng/ml	120 µl standart no: 3 + 120 µl standart dilution
Standard no:1	0.75 ng/ml	120 µl standart no: 2 + 120 µl standart dilution

Figure 1. Appearance of the plate after adding the sample, antibody and Streptavidin HRP

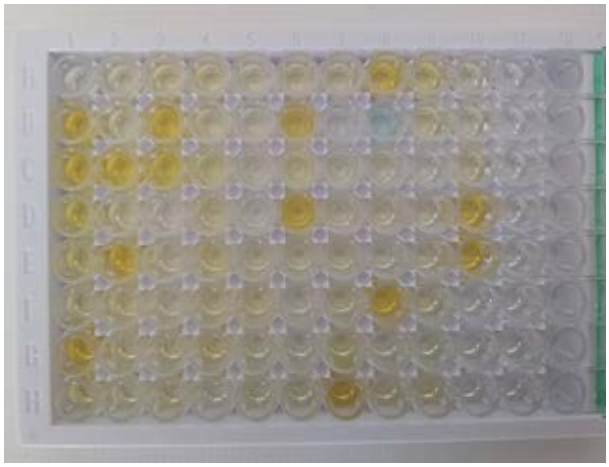

Figure 2. Appearance of the plate after adding the stop solution

continuous variables was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Variables that were not normally distributed were analyzed using non-parametric tests. For quantitative variables, an independent t-test was used for normally distributed data, while Mann–Whitney U and Kruskal–Wallis tests were used for non-normally distributed data. Statistical significance was defined as $p<0.05$. The correlations between parameters were evaluated using Spearman's rank correlation analysis ($r\square$) because some variables did not follow a normal distribution. The strength of correlation coefficients was interpreted as weak (0.000–0.249), moderate (0.250–0.499), strong (0.500–0.749), and very strong (0.750–1.000).

RESULTS

Baseline demographic and clinical characteristics of the study population are presented in Table 2. The RAI-treated and RAI-untreated groups were comparable in terms of age and BMI, and no statistically significant differences were observed between the groups for these variables. The mean age of the RAI-treated group was 36.65 ± 6.68 years, whereas the mean age of the RAI-untreated group was 35.10 ± 7.96 years ($p = 0.557$). Similarly, BMI values were comparable between the two groups (28.2 ± 5.48 vs 26.7 ± 3.58 kg/m^2, $p = 0.339$). However, tumor diameter was significantly larger in the RAI-treated group compared with the RAI-untreated group (24.76 ± 13.8 mm vs 6.46 ± 3.59 mm, $p = 0.001$). In addition, TSH levels were significantly lower in the RAI-treated group (0.46 ± 0.43 µIU/mL vs 1.22 ± 0.91 µIU/mL, $p = 0.011$).

Biochemical parameters of the study groups are summarized in Table 3. AMH levels were significantly lower

Table 2. Demographic Characteristics

	RAI-treated Mean ± SD	RAI-untreated Mean ± SD	p
Age	36,65±6,68	35,10±7,96	0,557
BMI	28,2±5,48	26,7±3,58	0,339
Number of children		3,30±2,25	0,972
Age at RAI	33,5±6,59	-	-
RAI dose	109,24±22,58	-	-
Tumor diameter	24,76±13,8	6,46±3,59	0,001
TSH	0,46±0,43	1,22±0,91	0,011

Table 3. Biochemical parameters in the RAI-treated and RAI-Untreated groups

	RAI-treated Mean ± SD	RAI-untreated Mean ± SD	p
AMH	1,34±0,37	1,79±0,25	0,001
FSH	6,65±3,94	4,75±2,22	0,077
LH	4,95±3,51	4,48±2,68	0,603
E2	71,9±59,6	62,8±58,2	0,587

Table 4. Comparison of AMH levels according to RAI dose

	75 mci (n=3)	100 mci (n=33)	150 mci (n=10)	p
AMH	1,32±0,42	1,29±0,31	1,67±0,55	0,073

Table 5. Correlation between AMH and biochemical and demographic parameters

	RAI -treated (n=46)		RAI-untreatred (n=20)	
	rS	p	rS	p
Age	-0,181	0,265	0,081	0,764
Time since treatment	0,00	1,00	0,00	1,00
BMİ	-0,191	0,238	0,559	0,025
RAİ dose	0,116	0,475	-	-
TSH	-0,115	0,498	0,293	0,290
FSH	0,147	0,399	-0,543	0,045
LH	0,051	0,767	-0,345	0,208
E2	0,068	0,681	-0,233	0,422

in the RAI-treated group compared with the RAI-untreated group (1.34 ± 0.37 ng/mL vs 1.79 ± 0.25 ng/mL, p = 0.001). No statistically significant differences were observed between the two groups with respect to serum FSH, LH, or estradiol levels. When AMH levels were grouped according to RAI doses of 75, 100, and 150 mCi, no statistically significant differences was observed between RAI dose and AMH levels (p = 0.073) (Table 4). Spearman correlation analysis was performed to evaluate relationships between AMH levels and clinical parameters. In the RAI-untreated group, a strong negative correlation was observed between FSH and AMH levels (r□ = –0.543, p = 0.045) (Figure 3). In contrast, no significant correlations were detected between AMH levels and age, BMI, TSH, or RAI dose in the RAI-treated group (r□ = 0.559, p = 0.025) (Table 5).

To further evaluate the independent association between RAI therapy and AMH levels, a mul-tivariable linear regression analysis was performed, adjusting for potential confounders inclu-ding age, BMI, TSH level, tumor diameter, and time since treatment. As shown in Table 6, RAI therapy remained independently associated with lower AMH levels (β = –0.41, p = 0.003). Age was also significantly associated with AMH levels (β = –0.36, p = 0.010). In contrast, BMI, TSH level, tumor diameter, and time since treatment were not significant pre-dictors of AMH levels in the adjusted model. Menstrual irregularities were more frequently reported in the RAI-treated group. Among the 46 patients undergoing RAI therapy, only 8 (17.9%) reported a regular menstrual cycle, whereas 9 (45%) in the RAI-untreated group reported regular menstruation.

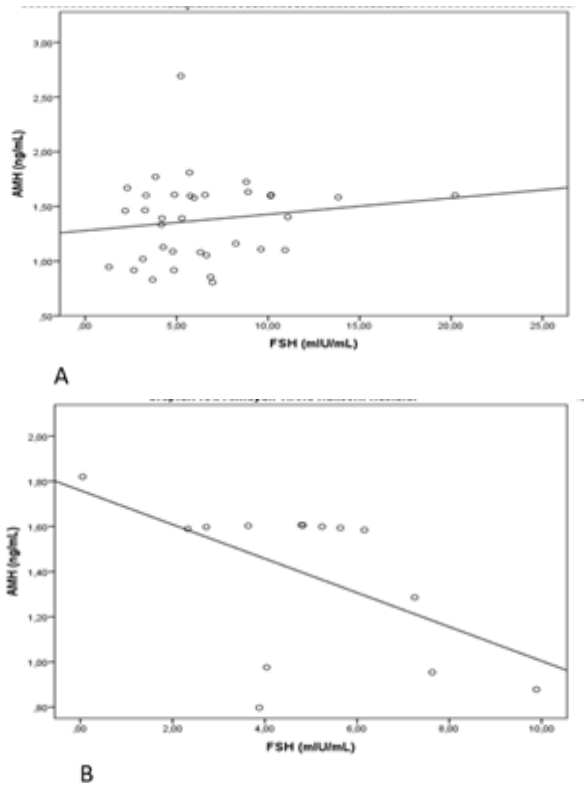

Figure 3. Correlation between AMH and FSH. A. RAI-treated (n=46, rs 0.147, p=0.238) and B. RAI-untreated (n=20, rs-0.543, p=0.045)

Table 6. Adjusted Multivariable Linear Regression Analysis for Factors Associated with AMH Levels

Variable	β (Standar-dized)	B (Unstandar-dized)	Standard Error	95% CI	p
RAI therapy (yes vs no)	−0.41	−0.45	0.14	−0.73 – −0.17	0.003
Age (years)	−0.36	−0.04	0.02	−0.07 – −0.01	0.010
BMI (kg/m^2)	−0.12	−0.02	0.02	−0.05 – 0.01	0.220
TSH (μIU/mL)	−0.08	−0.03	0.03	−0.08 – 0.02	0.310
Tumor diameter (mm)	−0.05	−0.01	0.01	−0.03 – 0.01	0.420
Time since treatment (months)	0.03	0.01	0.01	−0.01 – 0.03	0.560

DISCUSSION

The present study investigated the association between radioactive iodine (RAI) ablation therapy and ovarian reserve in premenopausal women with differentiated thyroid cancer. Our findings demonstrated that AMH levels were significantly lower in patients who received RAI therapy compared with those who did not receive RAI treatment. Since AMH is considered one of the most reliable biomarkers of ovarian reserve, these findings suggest that RAI therapy might be associated with reduced ovarian reserve in this patient population. According to the most recent American Thyroid Association (ATA) guidelines published in 2025, RAI therapy remains an important therapeutic option for selected patients with differentiated thyroid cancer, particularly in those with intermediate- and high-risk disease. However, the potential adverse effects of RAI therapy on reproductive function and gonadal tissues remain an important clinical concern, especially in young women of reproductive age (5).

Ovarian reserve represents the quantity and quality of the remaining follicular pool in the ovaries. Several serum markers have been used to evaluate reproductive status and ovarian reserve. Ovarian aging has been studied using AMH, FSH, LH, and estradiol levels. AMH is mainly secreted from primary and preantral follicles, and its levels are independent of those of gonadotropins. Low AMH levels are associated with natural ovarian aging and infertility (6). In addition, fluctuations in AMH levels during the menstrual cycle suggest that AMH plays a role in folliculogenesis (7). Since 1949, studies have reported the occurrence of early menopause following high-dose RAI therapy (8). Ceccarelli et al. reported an earlier age at menopause in women treated for thyroid cancer with RAI therapy and levothyroxine suppressive therapy compared with women treated with levothyroxine for goiter (9). In another study conducted in France in 1989, temporary amenorrhea lasting up to 12 months was documented in 27% of premenopausal women with thyroid cancer following RAI therapy (10). Women who developed temporary amenorrhea were older (38.9 ± 7.1 vs. 32.2 ± 6.1 years; p <0.001) and showed increased FSH levels. However, unlike in men and consistent with the authors' own observations, this effect was not related to the administered dose. These findings are consistent with the results of our study. In a study by Sawka et al., temporary amenorrhea observed in women receiving RAI ablation therapy after thyroid cancer was considered an acute effect of RAI treatment. The rate of temporary amenorrhea was reported to range between 12% and 30% among women who previously had regular menstrual cycles. The damage caused by RAI ablation therapy may contribute to the expected decline in ovarian function and may accelerate follicular atresia in premenopausal women by reducing the viable follicle pool. It has been estimated that ovarian damage after RAI therapy may cause menopause to occur approximately one year earlier than in the general population (11). However, based on analyses of retrospective studies conducted between 1960 and 2002 (12-15), it has been suggested that temporary menstrual irregularities are probably insignificant, as there is no clear evidence of reduced fertility in these women.

In our study, AMH levels were 1.34 ± 0.37 ng/mL in the group of patients with differentiated thyroid cancer who received RAI ablation therapy, while it was significantly higher in the control group at 1.79 ± 0.25 ng/mL (p = 0.001). Similarly, in a study conducted by Acıbucu et al. in 2016, AMH, FSH, LH, E2, TSH, and creatinine levels were compared between 45 premenopausal women with differentiated thyroid cancer treated with RAI and 40 healthy women; AMH levels were found to be lower in the RAI-treated group (16). In contrast to the healthy women included in the control group of the study by Acıbucu et al., the control group in our study consisted of women diagnosed with differentiated thyroid cancer.

Yaish et al., included 30 women with differentiated thyroid cancer who received RAI therapy. Baseline AMH measurements were obtained at 3, 6, 9, and 12 months according to RAI dose. None of the patients had previously received RAI or been exposed to radiation. The participants were aged 20-45 years. A significant decline in AMH levels were observed at all time points. Specifically, three months after RAI, AMH levels were 49% lower than baseline (1.9 ± 0.38 vs. 3.250 ± 0.56 ng/mL; p = 0.001). Partial recovery was subsequently observed, and AMH levels plateaued at nine months; however, concentrations at one year remained 32% below baseline (p = 0.016). AMH levels at 6, 9, and 12 months after treatment were 2.23 ± 0.43, 2.47 ± 0.47, and 2.36 ± 0.47 ng/mL, respectively. In 82% of the participants, final AMH levels remained below baseline values, indicating that serum AMH levels were still 32% lower one year after treatment (2.36 ± 1.88 ng/mL; p<0.005). The only continuous variables associated with AMH decline at three months were age (r = 0.51; p = 0.02) and age at menarche (r = 0.48; p = 0.03). Notably, RAI dose was not associated with AMH decline. None of the patients smoked or used oral contraceptives. Older patients (≥35 years) were significantly more likely to experience a marked decrease in AMH at three months compared with younger patients (63.7% ± 18.5 vs

33.1% ± 29.2; p = 0.01) (17). Consistent with our study, ovarian reserve was adversely affected in women with differentiated thyroid cancer receiving RAI ablation therapy, and RAI dose did not have a significant effect on AMH levels (p = 0.073).

Supporting our findings, Evranos et al. conducted a study in Turkey in 2018 that included 33 premenopausal women with differentiated thyroid cancer who received RAI ablation therapy. AMH, FSH, LH, and E2 levels were measured during the follicular phase at 3, 6, and 12 months after RAI therapy. The mean AMH level prior to RAI ablation therapy was 3.25 (0.32–17.42) ng/mL, while AMH levels at 3, 6, and 12 months after treatment were 1.00 (0.01–3.93), 1.13 (0.08–6.12), and 1.37 (0.09–6.1) ng/mL, respectively. The authors observed a significant decrease in AMH levels following RAI ablation therapy (p = 0.001) (18). In our study, consistent with the findings of Evranos et al., no significant differences were observed in FSH, LH, and E2 levels after RAI therapy (p > 0.05). FSH levels fluctuate during the menstrual cycle; therefore, repeated measurements are required. AMH levels, however, are more stable. FSH, E2, and inhibin B indirectly reflect ovarian reserve, but cyclic variation complicates their correlation with ovarian reserve. As observed in our study and previous studies, while variability was noted in FSH and E2 levels when assessing ovarian reserve, AMH levels were relatively more stable. Measurement of AMH levels is recommended for evaluating age-related gonadal reserve in premenopausal women with thyroid cancer (19).

In our study of premenopausal women with a history of differentiated thyroid cancer, AMH levels were significantly lower (1.34 ± 0.37 ng/mL; p = 0.001) in the group receiving ablative RAI therapy following thyroidectomy. In contrast, Giusti et al. reported no significant differences in AMH levels between 34 women treated with RAI and 23 women who did not receive RAI among 57 patients with differentiated thyroid cancer (20). In the study by Giusti et al., the mean age was 40.7 ± 6.7 years in the RAI-treated group and 41.6 ± 7.4 years in the control group, whereas in our study, the mean age was 36.65 ± 6.68 years in the RAI-treated group and 35.10 ± 7.96 years in the control group. This difference in age distribution may account for the discrepancies between the findings. Indeed, in a study conducted by Lee et al. in healthy women, the mean AMH level was 2.3 ng/mL in women aged 38–40 years and 1.4 ng/mL in women aged 40–43 years (21). In addition, AMH shows small inter and intra-cycle variability and gradually declines with age, and AMH levels become undetectable after menopause (22,23).

More recent studies have also evaluated ovarian reserve and reproductive outcomes in women undergoing RAI therapy. Kim et al. reported that radioactive iodine therapy may be associated with a measurable decline in ovarian reserve markers, particularly AMH levels, in women with differentiated thyroid cancer (24). Similarly, Anderson et al. emphasized that cancer therapies involving ionizing radiation may adversely affect ovarian reserve and reproductive function in young female patients (25). In addition to hormonal markers, recent studies have also investigated long-term reproductive outcomes in thyroid cancer survivors. Lamartina et al. reported that although ovarian reserve markers may decline following treatment, many thyroid cancer survivors maintain the ability to conceive and achieve successful pregnancies (26). Likewise, Rizzo et al. demonstrated that fertility and pregnancy outcomes after RAI therapy are generally reassuring, although careful reproductive counseling may be warranted for women of reproductive age undergoing treatment (27). Unfortunately, long-term fertility outcomes, such as pregnancy rates, or live birth rates were not systematically recorded in our cohort. Future studies assessing reproductive outcomes after RAI therapy would provide more clinically meaningful insights.

Study Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings and introduce potential selection bias. Second, baseline pre-treatment AMH levels were not available, which precluded an intra-individual longitudinal assessment of ovarian function before and after radioactive iodine therapy. Third, the relatively small sample size, particularly in the RAI-untreated control group, may reduce the statistical power to detect subtle associations, including dose–response relationships. In addition, other important determinants of ovarian reserve such as smoking status, detailed reproductive history, and long-term fertility outcomes were not systematically captured. Another important limitation is the relatively small sample size and single-center design of the study. These factors may limit the generalizability of the findings and reduce statistical power. Therefore, multicenter studies with larger patient populations are required to validate these observations. Finally, hormonal measurements were obtained at a single time point, and dynamic changes over time could not be evaluated in this study. Therefore, larger prospective studies with longitudinal hormonal and reproductive outcome assessments are required to confirm and extend our findings.

CONCLUSION

In conclusion, our findings demonstrate an association between RAI therapy and lower AMH levels in premenopausal women with differentiated thyroid cancer. These findings suggest that RAI therapy may be associated with reduced ovarian reserve. However, due to the cross-sectional design and the absence of baseline AMH measurements, causal inference cannot be established. Larger prospective studies are needed to further clarify this relationship.

DECLARATIONS

Conflict of Interest: *The authors declare no conflicts of interest related to this study.*

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RESEARCH ARTICLE

Diagnostic Value of Preoperative Imaging Modalities and Their Association with Clinical Parameters in Lesion Localization in Primary Hyperparathyroidism

Primer Hiperparatiroidizmde Preoperatif Görüntüleme Yöntemlerinin Tanısal Değeri ve Klinik Parametrelerle İlişkisi

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ABSTRACT

Objective: The aim of the study was to assess the diagnostic value of preoperative imaging modalities for identifying primary hyperparathyroidism (PHPT) and to examine the clinical and biochemical characteristics associated with successful lesion localization.

Materials and Methods: Data from 216 patients who underwent parathyroidectomy for PHPT and had successful preoperative localization from neck ultrasonography (USG) and Tc-99m sestamibi scintigraphy were analyzed retrospectively. Cases that were not initially localized by imaging were evaluated based on 4D-CT or 18F-fluorocholine PET/CT reports. The associations between accurate localization with imaging modalities and the clinical and biochemical characteristics were investigated.

Results: The combined use of neck USG and Tc-99m sestamibi scintigraphy had a sensitivity of 55.1% and a positive predictive value of 96.3% for detecting hyperfunctional lesions. Multivariable analysis revealed that a parathyroid gland size greater than 1 cm (odds ratio [OR]=2.521, p=0.002), serum intact parathyroid hormone (iPTH) concentration greater than 134 ng/L (OR=2.270, p=0.007), and the presence of normocalcemic PHPT (OR=2.546, p=0.023) were independently associated with successful localization when using USG and sestamibi scintigraphy together.

Conclusions: Combined neck USG and Tc-99m sestamibi scintigraphy are particularly effective for localizing of PHPT in patients with larger glands, higher iPTH levels, and normocalcemic PHPT, potentially obviating the need for advanced imaging in selected cases.

Keywords: Primary hyperparathyroidism, neck ultrasonography, Tc-99m sestamibi scintigraphy, 4D-CT, 18F-fluorocholine PET/CT

ÖZET

Amaç: Primer hiperparatiroidizmde preoperatif görüntüleme yöntemlerinin tanısal değerini değerlendirmek ve lokalizasyon başarısı ile klinik ve biyokimyasal özellikler arasındaki ilişkiyi incelemek.

Gereç ve Yöntemler: Primer hiperparatiroidizm nedeniyle paratiroidektomiye giden ve preoperatif dönemde başlangıçta lokalizasyon amaçlı boyun ultrasonografisi ve Tc-99m sestamibi sintigrafisi yapılmış 216 hastanın verileri retrospektif olarak analiz edildi. Başlangıç görüntüleme yöntemleriyle lokalize edilemeyen olgular, 4-boyutlu BT ve/veya 18F-kolin PET-BT raporları temel alınarak değerlendirildi. Görüntüleme yöntemlerinin doğru lokalizasyon sonuçları ile klinik ve biyokimyasal özellikler arasındaki ilişkiler analiz edildi.

Bulgular: Boyun ultrasonografisi ve Tc-99m sestamibi sintigrafisinin kombine kullanımı, hiperfonksiyonel lezyonların saptanmasında %55,1 duyarlılık ve %96,3 pozitif prediktif değer göstermiştir. Çok değişkenli analizde ise, paratiroid bez boyutunun >1 cm olması (OR=2,521, p=0,002), serum iPTH düzeyinin >134 ng/L olması (OR=2,270, p=0,007) ve normokalsemik primer hiperparatiroidizm varlığı (OR=2,546, p=0,023), kombine USG ve sestamibi sintigrafisi ile başarılı lokalizasyonun bağımsız belirleyicileri olarak saptanmıştır.

Sonuç: Kombine boyun ultrasonografisi ve Tc-99m sestamibi sintigrafisi, özellikle daha büyük bez boyutu, yüksek iPTH düzeyleri ve normokalsemik primer hiperparatiroidizm varlığında etkili olup, seçilmiş hastalarda ileri görüntüleme yöntemlerine olan gereksinimi ortadan kaldırabilir.

Anahtar Kelimeler: Primer hiperparatiroidizm, boyun ultrasonografisi, Tc-99m sestamibi sintigrafisi, 4-boyutlu BT, 18F-kolin PET/BT

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INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by autonomous overproduction of parathyroid hormone (PTH), leading to disturbances in calcium–phosphate homeostasis (1). The clinical presentation of PHPT ranges from an asymptomatic state to severe disease involving multiple organ systems (2). PHPT can result in nephrolithiasis, impaired renal function, osteoporosis or fragility fractures, neurocognitive or gastrointestinal dysfunction, and increased cardiovascular morbidity (3,4). In clinical practice, approximately 80% of patients with PHPT are asymptomatic, with diagnosis often incidental during routine measurements of serum calcium and PTH levels (2). The most common cause of PHPT is a solitary adenoma (75–85%), followed by multiglandular hyperplasia (10%), double adenomas (4%), and, rarely, parathyroid carcinoma (1%) (5).

Treatment decisions for PHPT are based on the presence of symptoms and evidence of skeletal demineralization or renal involvement. Surgical removal of the hyperfunctioning gland is considered the definitive treatment for PHPT, whereas monitoring and follow-up are recommended for asymptomatic patients who do not meet the surgical criteria (5). Preoperative localization of the responsible parathyroid tissue is crucial for treatment planning. In recent years, the standard surgical approach has advanced from bilateral neck exploration, in which all four glands are examined, to minimally invasive parathyroidectomy (MIP), which involves targeted removal of the affected gland following unilateral exploration (6).

Currently, neck ultrasonography (USG) and technetium-99m sestamibi scintigraphy are the standard first-line imaging modalities for preoperative lesion localization in PHPT (1). The reported sensitivity of USG for lesion localization ranges 29–73%, while Tc-99m sestamibi scintigraphy has a sensitivity of 50–70% and a specificity of 77–87%. Several studies have shown that combining sestamibi scintigraphy with single-photon emission CT (SPECT) improves sensitivity (3). However, each imaging modality has inherent strengths and limitations, and diagnostic performance can vary depending on patient-related and gland-related factors (1,5).

In cases where USG and sestamibi scintigraphy yield negative or discordant results, 4D-CT has been shown to be an effective alternative for preoperative localization (7). By providing detailed anatomical information on the size and location of abnormally positioned parathyroid glands, 4D-CT has emerged as potentially more sensitive and accurate, with reported sensitivities ranging 70–92% (3). Fine-needle aspiration biopsy (FNAB) with PTH washout is also increasingly used in clinical practice to differentiate parathyroid lesions from other suspicious lesions detected on imaging and to aid with localization; however, there is no current consensus regarding the optimal cutoff value for PTH washout in parathyroid tissue (8). Another imaging modality used in cases of uncertain localization is 18F-fluorocholine PET/CT, which has shown higher sensitivity than USG and scintigraphy. Nevertheless, due to limited availability and high cost, 18F-fluorocholine PET/CT has yet to be adopted for routine use (1).

In this study, we aimed to evaluate the diagnostic value of imaging modalities for localizing parathyroids in PHPT preoperatively and to investigate the relationship between localization success in patients requiring advanced imaging after failed initial localization studies and clinical and biochemical characteristics.

MATERIALS AND METHODS

Patients

This retrospective cohort study included patients aged 18 years and older diagnosed with PHPT at the Endocrinology Clinic of Ankara Training and Research Hospital between January 2020 and June 2025. These patients met the surgical criteria according to the report of the 5th International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, and subsequently underwent parathyroidectomy (9). In our center, the diagnosis of PHPT was established by the presence of hypercalcemia on at least two separate occasions in conjunction with inappropriately elevated serum intact PTH (iPTH) levels (reference ranges: serum calcium 8.5–10.5 mg/dL and PTH 15–65 ng/L).

The exclusion criteria were the presence of secondary or tertiary hyperparathyroidism, absence of at least two preoperative imaging studies, detection of malignancy on postoperative histopathological examination, a history of previous central neck surgery, persistent or recurrent PHPT, hereditary or lithium-associated hyperparathyroidism, and incomplete medical records.

Preoperative Imaging Studies

All patients underwent neck USG and Tc-99m sestamibi scintigraphy to localize the pathological parathyroid gland. Tc-99m sestamibi scintigraphy was performed using a dual-phase protocol with early and delayed imaging, and SPECT/CT was used when considered necessary by the nuclear medicine physician. Images were interpreted by nuclear medicine physicians. Neck USG was performed by an endocrinologist with at least 5 years of experience in parathyroid USG using a high-resolution linear transducer (7–12 MHz). In patients where imaging failed to localize the lesion, further evaluation was conducted with 4D-CT and 18F-fluorocholine PET/CT. Data for USG, Tc-99m sestamibi scintigraphy, and 4D-CT were obtained from the hospital imaging database, while 18F-fluorocholine PET/CT reports were retrieved from patient medical records. 18F-fluorocholine PET/CT findings were evaluated based on the reports of experienced nuclear medicine specialists. The accuracy of radiological localization was assessed in comparison with intraoperative surgical findings. Lesions that were suspicious for adenoma or hyperplasia on initial neck USG but not visualized on Tc-99m sestamibi scintigraphy or lesions detected on repeat USG guided by findings from advanced imaging modalities, underwent ultrasound-guided FNAB. PTH washout analysis was performed on the aspirated material, and a washout PTH level higher than the corresponding serum iPTH level was considered a positive result.

In our clinical practice, the two primary imaging modalities requested for lesion localization in patients with PHPT and

to indicate surgery are neck USG and Tc-99m sestamibi scintigraphy. The addition of low-resolution SPECT is decided by the nuclear medicine department. If the lesion could not be detected by either imaging methods or the PTH washout result of a suspicious ultrasonographic lesion was negative, 4D-CT was requested provided that there were no contraindications. Patients in whom lesion localization was unsuccessful despite the use of these imaging modalities were referred to external centers for 18F-fluorocholine PET/CT, and evaluation was based on radiology reports. Regardless of whether patients presented with previous USG reports, all were re-evaluated with neck USG at our clinic for their parathyroid gland. Patients with localized hyperfunctioning parathyroid lesions were referred for MIP whereas those without successful localization underwent surgical neck exploration.

During data collection, the localization of the hyperfunctioning parathyroid lesion (ie, right superior, right inferior, left superior, left inferior, or ectopic) and the presence of concomitant thyroid nodules were recorded. For each imaging modality, sensitivity and positive predictive value (PPV) were calculated.

Assessment Parameters

Normocalcemic PHPT (NPHPT) was defined as persistently normal albumin-corrected serum calcium levels in the presence of elevated PTH concentrations, after exclusion of secondary causes of hyperparathyroidism (10). Patients' demographic characteristics and clinical status were recorded. The presence of symptoms was defined as the occurrence of at least one complaint related to hyperparathyroidism, including fatigue, constipation, weakness, muscle or bone pain, and depressive symptoms. Bone mineral densitometry results were evaluated as normal bone density, osteopenia, or osteoporosis in individuals aged 50 years and older, and as bone mass lower than expected for age or normal bone mass for age in individuals older than 50 years. Each condition constituting an indication for surgery was assigned 1 point, and the total score (range: 0–5 points) was calculated accordingly. Preoperative laboratory parameters, including serum iPTH, albumin-corrected calcium, phosphorus, 25-hydroxyvitamin D [25(OH)D], glomerular filtration rate (GFR), thyroid-stimulating hormone (TSH), free thyroxine (FT4), anti-thyroid peroxidase antibody (anti-TPO), and 24-hour urinary calcium excretion were evaluated by reviewing electronic medical records. When available, tissue PTH washout values and pathology report data were also recorded. Anti-TPO positivity was defined as the presence of autoimmune thyroid disease. The maximum diameter of the excised parathyroid lesion was recorded from the surgical specimen. Based on histopathological examination, lesions were classified as either adenoma, hyperplasia, atypical adenoma, or carcinoma. A successful surgical outcome was defined as the normalization of serum iPTH and calcium levels within the first 24 hours postoperatively, along with histopathological confirmation that the excised tissue was consistent with parathyroid tissue.

Ethical Approval

The study was approved by the local ethics committee (January 14, 2026/687) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using SPSS v.20 software. The normality of distribution was tested using the Kolmogorov–Smirnov test. Data showing a normal distribution are presented as mean ± standard deviation (SD), while data not showing a normal distribution are presented as median (min–max). Categorical variables are expressed as n (%). The Mann–Whitney U test was used for comparisons between continuous variables that did not show a normal distribution. Comparisons between categorical variables were made using the Chi-squared ($\chi 2$) or Fisher's exact tests. The localization rates (sensitivity) and PPVs of imaging methods for parathyroid lesions were calculated. Additionally, the evaluation of independent variables affecting the localization of imaging methods was performed using logistic regression analysis. Sensitivity was defined as the proportion of hyperfunctioning glands correctly localized by imaging. The specificity represented the proportion of non-localized cases correctly identified as negative within the parathyroid gland localization framework. The PPV indicated the probability that a lesion identified by imaging corresponded to the surgically confirmed pathological gland, whereas negative predictive value (NPV) reflected the probability that a non-localizing result truly corresponded to the failure to localize the lesion. Additionally, independent predictors of localization success were evaluated using multivariable logistic regression analysis. Variables with $p<0.20$ in univariate analysis were considered for inclusion in the multivariable model. The Enter method was used for multivariable logistic regression analysis. Since all included patients had surgically confirmed PHPT, specificity and NPV could not be calculated within the classical disease-present or disease-absent framework. Therefore, additional receiver operating characteristic analyses were performed by defining imaging outcome as localized versus non-localized lesions. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 216 patients who underwent parathyroidectomy for PHPT and had preoperative lesion localization with neck USG and Tc-99m sestamibi scintigraphy were included in the study. Of the patients, 86.1% were female and 75.9% were asymptomatic. The demographic and laboratory characteristics of the patients are presented in Table 1. The median albumin-corrected serum calcium level was 11.1 mg/dL (range: 9.3–14), and the median iPTH level was 125.5 ng/L (range: 25–531). According to preoperative imaging results, the most common lesion localizations responsible for PHPT were the right superior (43.1%) and right inferior (28.2%) glands. In seven patients, preoperative localization findings were not concordant with intraoperative surgical findings. Postoperative histopathological examination revealed adenoma as the cause of PHPT in 90.3% of cases. The localization performance of initial conventional preoperative imaging modalities is shown in Table 2. The combined use of neck USG and sestamibi

Table 1. Demographic and clinical characteristics of patients with PHPT

Variables		Patients with PHPT (n=216)
Age (years)		55 (23–81)
Sex (n, %)		
	Female	186 (86.1%)
	Male	30 (13.9%)
PHPT according to serum calcium levels (n, %)		
	Hypercalcemic	38 (17.6%)
	Normocalcemic	178 (82.4%)
Symptoms (n, %)		
	Absent	164 (75.9%)
	Present	52 (24.1%)
Nephrolithiasis (n, %)		
	Absent	158 (73.1%)
	Present	58 (26.9%)
Bone mineral density (n, %)		
	≥50 years	164 (75.9%)
	Normal	28 (17.1%)
	Osteopenia	51 (31.1%)
	Osteoporosis	85 (51.8%)
	<50 years	52 (24.1%)
	Low bone mass for age	35 (67.3%)
	Normal bone mass for age	17 (32.7%)
Indications for surgery		
	Symptomatic (n, %)	52 (24.1%)
	Asymptomatic (n, %)	164 (75.9%)
	<50 years	36 (21.9%)
	Serum Ca ≥mg/dl above the limit of normal	30 (1.8%)
	Skeletal involvement	77 (46.9%)
	Renal involvement	177 (81.9%)
Number of surgical indications (n)		2 (0–5)
Autoimmune thyroid disease (n, %)		
	Absent	86 (39.8%)
	Present	130 (60.2%)
Thyroid nodule (n, %)		
	Absent	74 (34.3%)
	Present	142 (65.7%)
eGFR (ml/min/1.73m^2)		94 (46–126%)
TSH (mIU/L)		1.69 (0.2–8)
Alb-sCa (mg/dl)		11.1 (9.3–14)
P (mg/dl)		2.7 (1–4.4)
CaxP (mg^2/dl^2)		29.75 (12.8–46.33)
iPTH (ng/L)		125.5 (25–531)
24-hour urinary calcium (mg/day)		359 (28.2–1254)
25 (OH) vitamin D (µ/L)		19.65 (3–52)
Parathyroid gland localization (n, %)		
	Right superior	93 (43.1%)
	Right inferior	61 (28.2%)
	Left supeior	18 (8.3%)
	Left inferior	39 (18.1%)
	Ectopic (mediastinal)	5 (2.3%)
Parathyroid gland size (cm)		1 (0.4–5)
Histopathology (n, %)		
	Adenoma	195 (90.3%)
	Hyperplasia	16 (7.4%)
	Atypical adenoma	5 (2.3%)
	Carcinoma	0 (0%)

eGFR=estimated glomerular filtration rate. Alb-sCa=albumin-corrected serum calcium. Ca=calcium. P=phosphorus. CaxP=calcium–phosphorus product. iPTH=intact parathyroid hormone. PHPT=primary hyperparathyroidism. TSH=thyroid-stimulating hormone. Symptomatic status was defined as the presence of at least one hyperparathyroidism-related complaint (eg, fatigue, constipation, weakness, musculoskeletal pain, or depressive symptoms). Renal involvement was defined as the presence of nephrolithiasis or nephrocalcinosis.
Skeletal involvement was defined as a history of fragility fracture or osteoporosis on bone mineral density assessment (DXA T-score ≤−2.5). Data are presented as median (min–max) for non-normally distributed variables and as n (%) for categorical variables.

Table 2. Localization rates of parathyroid lesions using preoperative imaging modalities in patients with PHPT

Imaging modality	Number of examinations (n)	Localization rate (n, %)	PPV (n, %)
USG	216	171/216 (79.2%)	164/171 (95.9%)
Sestamibi	216	131/216 (60.6%)	127/131 (96.9%)
USG and sestamibi	216	119/216 (55.1%)	115/119 (96.63%)
4D-CT	104	69/104 (66.3%)	63/69 (91.3%)
18F-fluorocholine PET/CT	16	11/16 (68.7%)	11/11 (100%)
USG/sestamibi	216	183/216 (84.7%)	176/183 (96.2%)
USG/sestamibi/4D-CT	104	88/104 (84.6%)	82/88 (93.2%)
USG/sestamibi/18F-fluorocholine PET/CT	16	12/16 (75%)	12/12 (100%)
Triple-modality imaging	104	88/104 (84.6%)	82/88 (93.2%)
Quadruple-modality imaging	16	12/16 (75%)	12/12 (100%)

USG=ultrasonography. 4D-CT=4-dimensional computed tomography. ^{18}F-fluorocholine PET/CT=fluorine-18 fluorocholine positron emission tomography/computed tomography. PPV=positive predictive value. Triple-modality imaging=USG/sestamibi/4D-CT. Quadruple-modality imaging=USg/sestamibi/4D-CT/^{18}F-fluorocholine PET/CT. Categorical variables are presented as n (%).

Table 3. Localization rates and positive predictive values of imaging modalities according to quartiles of preoperative serum calcium and parathyroid hormone levels

Alb-sCa vs iPTH	USG (n=216)		Sestamibi (n=216)		USG with sestamibi (n=216)		4D-CT (n=104)		^{18}F-fluorocholine PET/CT (n=16)	
	Localizasion (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)	Localization (n, %)	PPV (n, %)
Alb-sCa (mg/dl)										
<10.7	44/50 (88%)	43/44 (97.7%)	36/50 (72%)	35/36 (97.2%)	33/50 (66%)	32/33 (96.9%)	18/23 (78.3%%)	17/18 (94.4%)	1/1 (100%)	1/1 (100%)
10.7–11	42/57 (73.7%)	40/42 (95.2%)	32/57 (56.1%)	31/32 (96.9%)	29/57 (50.9%)	28/29 (96.5%)	17/26 (65.4%)	15/17 (88.2%)	2/5 (40%)	2/2 (100%)
11.1–11.4	45/54 (83.3%)	41/45 (91.1%)	32/54 (59.3%)	30/32 (93.7%)	29/54 (53.7%)	27/29 (93.1%)	20/28 (71.4%)	17/20 (85%)	2/2 (100%)	2/2 (100%)
>11.4	40/55 (72.7%)	40/40 (100%)	31/55 (56.4%)	31/31 (100%)	28/55 (50.9%)	28/28 (100%)	14/27 (51.9%)	14/14 (100%)	6/8 (75%)	6/6 (100%)
iPTH (ng/L)										
<96	38/54 (70.4%)	35/38 (92.1%)	29/54 (53.7%)	27/29 (93.1%)	26/54 (48.1%)	24/26 (92.3%)	13/27 (48.1%)	9/13 (69.2%)	6/9 (66.7%)	6/6 (100%)
96–125	41/54 (75.9%)	40/41 (97.6%)	29/54 (53.7%)	28/29 (96.5%)	26/54 (48.1%)	25/26 (96.1%)	21/28 (75%)	21/21 (100%)	2/2 (100%)	2/2 (100%)
126–172	44/54 (81.5%)	42/44 (95.4%)	36/54 (66.7%)	35/36 (97.2%)	33/54 (61.1%)	32/33 (96.9%)	20/27 (74.1%)	18/20 (90%)	0/1 (0%)	N/A
>172	48/54 (79.2%)	47/48 (97.9%)	37/54 (68.5%)	37/37 (100%)	34/54 (63%)	34/34 (100%)	15/22 (68.2%)	15/15 (100%)	3/4 (75%)	3/3 (100%)

Alb-sCa=albumin-corrected serum calcium. iPTH=intact parathyroid hormone. USG=ultrasonography. 4D-CT=4-dimensional computed tomography. PPV=positive predictive value. NA=not applicable.

scintigraphy yielded a sensitivity of 55.1% and a PPV of 96.3% for detecting hyperfunctioning parathyroid lesions. In patients with unsuccessful localization with initial imaging and who subsequently underwent advanced imaging, the sensitivity of localization was 66.3% for 4D-CT and 68.7% for 18F-fluorocholine PET/CT, with PPVs of 91.3% and 100%, respectively. Figure 1 illustrates the localization outcomes of lesions that could not be identified by either neck USG or sestamibi scintigraphy during the initial preoperative evaluation in patients with PHPT following additional imaging modalities.

The localization rates and PPVs of imaging modalities according to quartiles of preoperative serum calcium and iPTH levels are presented in Table 3. When serum calcium levels exceeded 11.4 mg/dL, the PPV of all four imaging modalities was 100%. Similarly, when iPTH levels were greater than 172 ng/L, the PPV reached 100% in patients whose lesions were localized by both neck USG and sestamibi scintigraphy. Comparisons of demographic and clinical characteristics according to localization status of preoperative imaging modalities are summarized in Table 4. Patients whose lesions were localized by either neck USG or sestamibi scintigraphy had significantly higher median iPTH levels compared with those without successful localization (p=0.024 and p=0.049, respectively). A comparison of demographic and clinical characteristics between patients whose parathyroid lesions were localized by USG and sestamibi scintigraphy combined versus those who were not is presented in Table 5. Significant

Table 4. Comparison of demographic and clinical characteristics of patients according to localization status of preoperative imaging modalities in PHPT

Variables	USG (n=216)			Sestamibi (n=216)			4D-CT (n=104)			18F-fluorocholine PET/CT (n=16)		
	(+) (n=171)	(-) (n=45)	p value	(+) (n=131)	(-) (n=85)	p value	(+) (n=69)	(-) (n=35)	p value	(+) (n=11)	(-) (n=5	p value
Age (years	55 (25–81)	57 (23–79)	0.168	55 (25–77)	57 (23–81)	0.205	59 (25–79)	54 (23–77)	0.018*	49 (23–58)	54 (40–59)	0.364
Sex (n, %)			0.183			0.746			0.825			1.000
Female	150 (87.7%)	36 (80%)		112 (85.5%)	74 (87.1%)		58 (84.1%)	30 (85.7%)		7 (63.6%)	4 (80%)	
Male	21 (12.3%)	9 (20%)		19 (14.5%)	11 (12.9%)		11 (15.9%)	5 (14.3%)		4 (36.4%)	1 (20%)	
PHPT according to serum calcium levels (n, %)			0.085			0.070			0.686			1.000
Hypercalcemic	137 (80.1%)	41 (91.1%)		103 (78.6%)	75 (88.2%)		57 (82.6%)	30 (85.7%)		10 (90.9%)	5 (100%)	
Normocalcemic	34 (19.9%)	4 (8.9%)		28 (21.4%)	10 (11.8%)		12 (17.4%)	5 (14.3%)		1 (9.1%)	0 (0%)	
Symptoms (n, %)			0.133			0.075			0.259			0.509
Absent	126 (73.7%)	38 (84.4%)		94 (71.8%)	70 (82.4%)		56 (81.2%)	25 (71.4%)		5 (72.7%)	8 (100%)	
Present	45 (26.3%)	7 (15.6%)		37 (28.2%)	15 (17.6%)		13 (18.8%)	10 (28.6%)		3 (27.3%)	0 (0%)	
Number of surgical indications	2 (0–5)	2 (0–5)	0.577	2 (0–5)	2 (0–5)	0.579	2 (0–4)	2 (0–5)	0.328	2 (0–5)	2 (1–2)	0.137
Target organ involvement												
Skeletal involvement	83 (48.5%)	25 (55.6%)	0.402	64 (48.9%)	44 (51.8%)	0.676	39 (56.5%)	20 (57.1%)	0.952	6 (54.5%)	2 (40%)	1.000
Renal involvement	139 (81.3%)	38 (84.4%)	0.624	108 (82.4%)	69 (81.2%)	0.813	60 (87%)	29 (82.9%)	0.574	9 (81.8%)	4 (80%)	1.000
Autoimmune thyroid disease (n, %)			0.512			0.168			0.845			1.000
Absent	70 (40.9%)	16 (35.6%)		57 (43.5%)	29 (34.1%)		25 (36.2%)	12 (34.3%)		6 (54.5%)	2 (40%)	
Present	101 (59.1%)	29 (64.4%)		74 (56.5%)	56 (65.9%)		44 (63.8%)	23 (65.7%)		5 (45.5%)	3 (60%)	
Thyroid nodule (n, %)			0.883			0.084			0.288			0.299
Absent	59 (34.5%)	15 (33.3%)		39 (29.8%)	35 (41.2%)		27 (39.1%)	10 (28.6%)		3 (27.3%)	3 (60%)	
Present	112 (65.5%)	30 (66.7%)		92 (70.2%)	50 (58.8%)		42 (60.9%)	25 (71.4%)		8 (72.7%)	2 (40%)	
eGFR (ml/min/1.73m^2)	95 (46–126)	89 (51–124)	0.080	96 (48–124)	90 (46–126)	0.071	89 (51–126)	94 (46–124)	0.609	95 (77–124)	100 (95–118)	0.173
TSH (mIU/L)	1.78 (0.2–8)	1.6 (0.42–5.4)	0.490	1.69 (0.4–5.6)	1.74 (0.2–8)	0.968	1.85 (0.2–8)	1.6 (0.51–5.4)	0.698	1.52 (0.66–4.08)	2.98 (1.5–5.4)	0.089
Alb-sCa (mg/dl)	11 (9.3–14)	11.1 (9.6–13.8)	0.258	11 (9.3–14)	11.1 (9.5–13.8)	0.180	11 (9.6–13.4)	11.2 (9.5–13.8	0.077	11.5 (9.6–13.8)	10.9 (10.9–12.2)	0.278
P (mg/dl)	2.7 (1–4.34)	2.57 (1.2–4.4)	0.268	2.65 (1–4.4)	2.77 (1.47–4.34)	0.612	2.77 (1.2–4.4)	2.53 (1.47–3.4)	0.104	2.53 (1.6–4.4)	2.8 (2.56–3.21)	0.193
CaxP (mg^2/dl^2)	29.76 (12.8–46.33)	29.44 (14.04–42.24)	0.443	29.37 (12.8–45.36)	30.24 (17.05–46.33)	0.397	30.24 (14.04–46.33)	29.44 (17.05–39.98)	0.139	29.85 (19.6–42.2)	33.02 (28–34.99)	0.282
iPTH (ng/L)	133 (25–531)	108 (70.2–431)	0.024*	135 (25–531)	117 (59.9–431)	0.049*	126 (59.9–453)	108 (70.2–331)	0.154	94 (73–331)	80 (70.2–385)	0.865

eGFR=estimated glomerular filtration rate. Alb-sCa=albumin-corrected serum calcium. P=phosphorus. Ca×P=calcium–phosphorus product. iPTH=intact parathyroid hormone. PHPT=primary hyperparathyroidism. TSH=thyroid-stimulating hormone. USG=ultrasonography. 4D-CT=4-dimensional computed tomography. ^{18}F-fluorocholine PET/CT=fluorine-18 fluorocholine positron emission tomography/computed tomography. A p value <0.05 was considered statistically significant and is indicated by an asterisk (*).

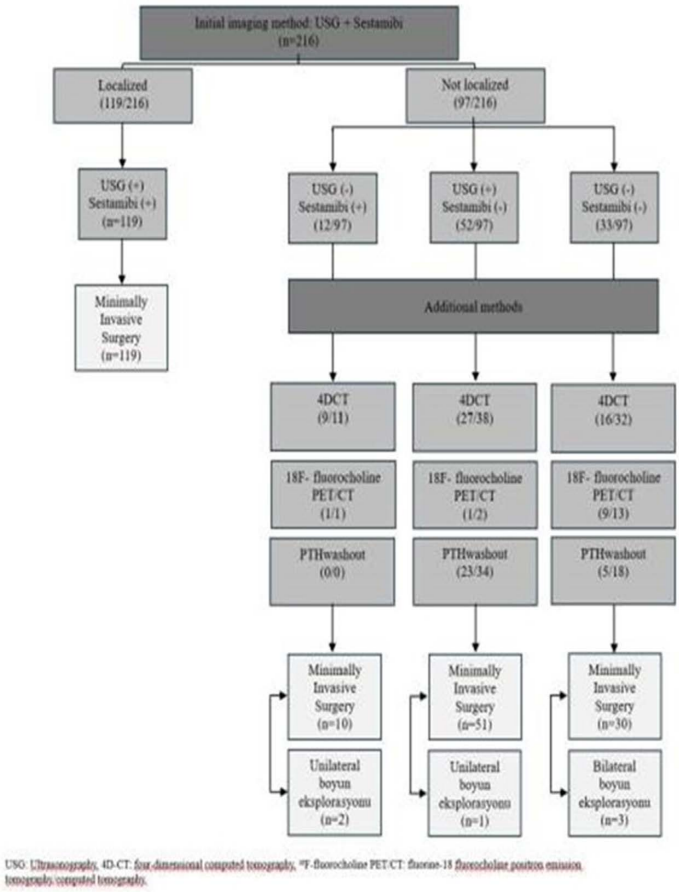

Figure 1. Localization of lesions not identified by initial preoperative imaging with neck ultrasonography and Tc-99m sestamibi scintigraphy in patients with primary hyperparathyroidism using additional imaging modalities

differences were observed between the two groups in terms of symptom presence (p=0.042), GFR (p=0.032), iPTH levels (p=0.049), and parathyroid gland size (p<0.001). Patients in whom parathyroid adenomas were successfully localized using combined USG and sestamibi scintigraphy were more likely to be symptomatic, had higher iPTH levels, and had larger gland sizes.

Univariate and Multivariate Analyses

For combined USG and sestamibi imaging , univariate analyses were initially performed to identify independent variables significantly associated with successful lesion localization. Variables not directly associated with localization were subsequently excluded, and multivariable logistic regression analyses were conducted to establish independent predictors of successful lesion localization (Table 5). For univariate logistic regression analysis, age (p=0.142), hypercalcemic PHPT or NPHPT status (p=0.072), autoimmune thyroid disease (p=0.065), parathyroid gland size (p=0.001), and iPTH level (p=0.005) met the predefined p<0.20 threshold and were therefore considered for inclusion in the multivariable model. Although symptom presence and estimated GFR also met the p<0.20 criterion in univariate analysis, these variables were not included in the multivariable model due to the lack of clinically meaningful association with parathyroid gland localization success.

For multivariable logistic regression analysis, parathyroid gland size (>1 cm), iPTH level (>134 ng/L), and NPHPT were identified as independent predictors of successful lesion localization with the combined use of USG and sestamibi. Among these, parathyroid gland size emerged as the strongest predictor; a gland diameter greater than 1 cm increased the likelihood of successful localization approximately 2.5-fold (odds ratio [OR]=2.521, p=0.002). Similarly, an iPTH level greater than 134 ng/L was independently associated with higher localization success (OR=2.270, p=0.007). NPHPT was borderline significant in univariate analysis (p=0.072) but became an independent predictor in the multivariable model (OR=2.546, p=0.023), suggesting that when evaluated alongside other covariates, the presence of normocalcemia could additionally contribute to localization success.

DISCUSSION

Accurate localization of the pathological parathyroid lesion is essential for the surgical management of PHPT (1). Neck USG and Tc-99m sestamibi scintigraphy are the commonest first-line localization modalities for PHPT (5). When USG and sestamibi imaging are concordant, the success rate of MIP increases significantly (3). Although some studies suggest that performing both imaging modalities can be unnecessary and not cost-effective when sestamibi and USG localize the lesion to the same region, lesion localization with at least two imaging modalities remains important for MIP (6). To date, there is no clear consensus regarding the optimal imaging modality for parathyroid adenoma localization (3). Localization of a parathyroid lesion by a single imaging modality or discordant localization findings between two imaging studies can create diagnostic and surgical challenges (2). Comparing the relative effectiveness of different imaging modalities is difficult, and no single technique or imaging algorithm has been definitively proven to be superior for parathyroid lesion localization (4). In a study evaluating preoperative imaging results in 220 patients with PHPT who underwent parathyroidectomy, USG identified hormonally active lesions in approximately 75% of patients and with an accuracy of 82% (5). Nasiri et al., in their study of 80 patients with PHPT, detected enlarged parathyroid glands in 76.3% of cases and reported sensitivity and PPV values of 83.5% for USG. In the same study, sestamibi scintigraphy localized adenomas in 78.8% of patients, with sensitivity at 85% and PPV value at 91.3% (11). In our study, lesion localization was achieved by USG in 79.2% of patients with a PPV of 95.9%, while sestamibi scintigraphy achieved localization in 60.9% of patients with a PPV of 96.9%. Although older reports in the literature suggest that combining USG and sestamibi imaging

could achieve localization sensitivities exceeding 90%, subsequent studies have shown substantially lower sensitivity rates ranging 33–92% (6). In our cohort, combined localization with both USG and sestamibi scintigraphy was observed in 55.1% of patients, with a PPV of 96.3%. Although the sensitivity of the combined approach was moderate (55.1%), the high PPV (96.3%) indicates strong reliability when localization is positive. For the surgical management of PHPT, high PPV is clinically valuable because positive localization supports MIP, whereas negative or non-localizing results do not exclude disease, rather, they indicate the need for additional imaging or bilateral exploration. When initial localization methods, such as USG and sestamibi scintigraphy, fail to provide definitive results, 4D-CT can be used as a complementary imaging modality for parathyroid gland localization (8). Day et al. reported a sensitivity of 89% and a PPV of 74% for 4D-CT in 872 patients with PHPT who had unsuccessful lesion localization using USG and sestamibi scintigraphy, and they suggested that 4D-CT could be considered a first-line imaging modality (12). In our study, 4D-CT successfully localized parathyroid lesions in 16 of 33 patients who could not be localized by USG and sestamibi scintigraphy. In patients with PHPT, 18F-fluorocholine PET/CT is recommended as a highly sensitive imaging modality when localization cannot be achieved using conventional methods; however, limitations related to accessibility and cost restrict its widespread use in clinical practice (13). In our study, only 16 of 97 patients whose lesions could not be localized by neck USG and sestamibi scintigraphy underwent 18F-fluorocholine PET/CT. Hyperfunctioning lesions were successfully identified in 68.7% of this subgroup of patients, with a PPV of 100%. Another approach contributing to preoperative localization was PTH washout from suspicious lesions. PTH washout was performed in 18 lesions that were not detected by initial imaging modalities but were considered suspicious based on advanced imaging, leading to successful identification of a hyperfunctioning gland in five patients.

Several studies in the literature have evaluated potential clinical, biochemical, and lesion-related factors that could influence the accuracy of preoperative lesion localization in PHPT. Previous studies have shown that larger parathyroid glands are more readily detected by USG. It has been suggested that an increased number of mitochondria in larger glands leads to higher metabolic activity, thereby facilitating improved visualization on sestamibi scintigraphy. In a study of 100 patients with PHPT, adenoma size was the only significant determinant of accurate localization using USG and sestamibi scintigraphy, whereas age, sex, lesion location (right vs left or superior vs inferior), serum calcium concentration, iPTH level, and urinary calcium excretion were not associated with imaging success (14). Similarly, in a large study by Berber et al. involving 1845 patients with PHPT, gland size was an independent predictor of accurate lesion localization with both USG and sestamibi scintigraphy (15). Consistent with these findings, our study showed that a parathyroid gland size greater than 1 cm significantly increased the likelihood of successful localization using both USG and sestamibi scintigraphy. Small parathyroid adenomas or hyperplasia can yield false-negative results on conventional preoperative imaging. Importantly, discordant or negative imaging findings do not necessarily indicate multiglandular disease; it has been suggested that approximately 70% of such patients can still have single-gland disease amenable to minimally invasive surgery. 4D-CT could be a valuable preoperative imaging modality, particularly in cases with small adenomas or mild hypercalcemia (16). In general, higher serum calcium and iPTH levels are associated with larger parathyroid adenomas, which are more easily localized using USG and sestamibi scintigraphy. This relationship could explain the observed linear correlation between increasing serum calcium and iPTH levels and improved localization sensitivity and PPV when USG and sestamibi scintigraphy are used in combination. Previous studies have also shown that preoperative serum calcium and iPTH levels, which correlate with disease severity, are associated with localization sensitivity on USG and sestamibi scintigraphy (17). Although higher serum calcium and iPTH levels are generally associated with larger adenomas and improved localization sensitivity, our finding that lesion localization success with combined USG and sestamibi was higher in NPHPT than in hypercalcemic PHPT appears, at first glance, to diverge from the existing literature. This unexpected observation could be explained by referral patterns inherent to tertiary referral centers. A substantial proportion of patients with hypercalcemic PHPT referred to our institution represent selected, complex cases, including those with prior unsuccessful localization attempts, ectopic gland locations, or multiglandular disease. Notably, all ectopic cases in our cohort were included in the non-localized lesion group, and these were more frequently observed among patients who were hypercalcemic. This finding suggests that referral bias might have enriched the hypercalcemic subgroup with technically challenging cases, thereby reducing overall localization success in the group. In contrast, patients with NPHPT were more often evaluated at our center as first-line cases without prior failed localization attempts. Therefore, our findings should not be interpreted to be indicating intrinsically easier localization in NPHPT, rather, as reflecting the case-mix and referral patterns characteristic of a tertiary care center.

In our study, when serum calcium levels exceeded 11.4 mg/dL, the PPV reached 100% across all four imaging modalities. Additionally, an iPTH level greater than 134 ng/L was identified as a predictive factor for increased lesion localization success using USG and/or sestamibi scintigraphy. Low serum 25-hydroxyvitamin D (25OHD) levels are commonly observed in PHPT and have been associated with a more severe biochemical phenotype, including higher iPTH levels and larger adenoma size (18). However, in our study, serum 25OHD levels were not significantly associated with preoperative lesion localization success. This finding is consistent with previous reports, including the study by Tassone et al., which showed that vitamin D deficiency did not influence the likelihood of positive imaging localization in patients with PHPT (19). Taken together, these data suggest that although vitamin D status can reflect disease severity, it does not appear to independently

affect the performance of preoperative imaging modalities.

The diagnostic performance of USG is highly dependent on the operator's experience. Detection of small adenomas, retropharyngeal or retroesophageal glands, and ectopic mediastinal parathyroid glands can be particularly challenging with USG (20). In a study by Balci et al., the sensitivity of USG for detecting a single adenoma was 89.7%, whereas the PPV for right and left lateralization and quadrant localization was 83.6% and 80.9%, respectively (13). Compared with USG, scintigraphy is less operator-dependent and is more useful for lateralization than for precise quadrant localization (20). For the localization of hyperfunctioning parathyroid glands, 4D-CT has shown higher sensitivity, specificity, and accuracy for lateralization compared with quadrant localization (12). In a study of 44 patients with PHPT evaluating the role of 4D-CT in lesion localization, sensitivity was as 93%, and 4D-CT was particularly useful in detecting ectopic lesions. In that study, 52.1% of parathyroid lesions were located on the left, 35.4% on the right, and 12.5% were bilateral, while 76% were inferiorly located and 24% superiorly located (8). In our cohort, lesion location influenced imaging success only for USG, whereas no such association was observed for scintigraphy, 4D-CT, or PET/CT. This finding might reflect the intrinsic characteristics of USG, which is highly dependent on anatomical accessibility, cervical compartment depth, and operator expertise. Glands located in deeper or anatomically complex regions could therefore be more challenging to detect with USG. In contrast, functional and cross-sectional imaging modalities provide broader anatomical coverage and are less constrained by superficial anatomical windows, potentially reducing the effects of precise gland location on localization performance.

The coexistence of PHPT and thyroid disease has been reported in 17–84% of cases (21–26). Ryan et al. identified multinodular goiter in 50% and Hashimoto's thyroiditis in 17% of patients with PHPT (23). Thyroid nodules and lymph nodes can mimic parathyroid adenomas and reduce the sensitivity of imaging studies (4). In addition, the presence of autoimmune thyroid disease can influence scintigraphy imaging results (27). In our study, the autoimmune thyroid disease and the thyroid nodules were not associated with an increased likelihood of parathyroid lesion localization by imaging modalities. This finding might indicate that, in our cohort, coexisting thyroid disease did not substantially impair imaging performance.

Study Limitations

Our study has several limitations. First, its retrospective design might have introduced selection bias. Second, the study was conducted in a single tertiary referral center, which could limit the generalizability of the findings. Third, not all patients underwent the same advanced imaging modalities and the number of patients evaluated with 18F-fluorocholine PET/CT was relatively small. Lastly, imaging results were based on clinical reports rather than centralized image re-evaluation. Despite these limitations, the relatively large patient cohort and comprehensive evaluation of multiple imaging modalities represent strengths of our study.

CONCLUSION

Our study showed that the combined use of neck USG and Tc-99m sestamibi scintigraphy was associated with a higher likelihood of successful lesion localization in patients with hyperfunctioning parathyroid glands larger than 1 cm, serum iPTH levels exceeding 134 ng/dL, and NPHPT. In these patient subgroups, adequate lesion localization with initial imaging modalities could reduce the need for advanced imaging techniques.

DECLARATIONS

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RESEARCH ARTICLE

The Impact of Ferritin Levels on Outcomes of Allogeneic Hematopoietic Stem Cell Transplantation: Real-Life Data

Ferritin Düzeylerinin Allojeneik Hematopoietik Kök Hücre Nakli Sonuçları Üzerine Etkisi: Gerçek Yaşam Verileri

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ABSTRACT

Objective: This retrospective study aimed to evaluate the effects of ferritin level on outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) including the neutrophil/platelet engraftment, febrile neutropenia, transplant related mortality (TRM), graft versus host disease (GvHD), sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) and overall survival (OS).

Materials and Methods: Sixty-nine patients with ferritin values measured at the beginning of allo-HSCT between 2018 - 2021 were enrolled in this study. The ferritin cut-off value was determined as 1000ng/mL and the patients were divided into 2 groups (<1000 ng/mL vs ≥1000 ng/mL).

Results: The median age was 32 years (23-49) and 38 (55.1%) of them female in all cohorts. Most of them (47.8%) were diagnosed with acute myeloid leukemia, followed by aplastic anemia (18.8%) and acute lymphoblastic leukemia (17.4%), respectively. The median ferritin level was 1080 ng/mL (505-1650) in all cohorts. Ferritin levels had no statistically significant effect on the engraftment, the febrile neutropenia, TRM and SOS/VOD (p>.05). The median OS in patients with ferritin level ≥1000 ng/mL and ferritin level <1000 ng/mL 4 months (95% CI: 1.4-6.6) and 8 months (95% CI: 0-24.2), respectively. There was no statistically significant correlation between ferritin value and OS (p=0.206). There was no statistically significant difference between the ferritin groups on both acute and chronic GvHD (p=0.713 and p=0.999, respectively).

Conclusion: Our study did not demonstrate any negative effects of serum ferritin levels on allo-HSCT outcomes; however, large-scale prospective studies are needed to clarify the effect of iron overload on the outcomes of allo-HSCT.

Keywords: Ferritin, hematopoietic stem cell transplantation, prognostic factors

ÖZET

Amaç: Bu retrospektif çalışma ferritin düzeyinin; nötrofil/trombosit engraftmanı, febril nötropeni, transplantasyonla ilişkili mortalite (TRM), greft-versus host hastalığı (GvHH), sinüzoidal obstrüksiyon sendromu (SOS)/venöz oklüzyon hastalığı (VOH) ve genel sağkalım (OS) gibi allojeneik hematopoietik kök hücre transplantasyon (allo-HKHT) sonuçları üzerindeki etkilerini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: 2018-2021 yılları arasında allo-HSCT başlangıcında ferritin değerleri ölçülen 69 hasta bu çalışmaya dâhil edilmiştir. Ferritin eşik değeri 1000 ng/mL olarak belirlenmiş ve hastalar 2 gruba ayrılmıştır (<1000 ng/mL ve ≥1000 ng/mL).

Bulgular: Çalışmada ortanca yaş 32 (23-49) yıl olup, bunların 38'i (%55,1) kadındı. Çoğu (%47,8) akut miyeloid lösemi tanılı olup, bunu sırasıyla aplastik anemi (%18,8) ve akut lenfoblastik lösemi (%17,4) izledi. Tüm kohortta ortanca ferritin düzeyi 1080 ng/mL (505-1650) olup ferritin düzeyinin engraftman, febril nötropeni, TRM ve SOS/VOH üzerinde istatistiksel olarak anlamlı bir etkisi yoktu (p>.05). Ferritin düzeyi ≥1000 ng/mL ve ferritin düzeyi <1000 ng/mL olan hastalarda ortanca OS sırasıyla 4 ay (%95 CI: 1,4-6,6) ve 8 ay (%95 CI: 0-24,2) olarak bulunmuştur. Ferritin değeri ile OS arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır (p=0,206). Akut ve kronik GvHH açısından ferritin grupları arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (sırasıyla p=0,713 ve p=0,999).

Sonuç: Çalışmamız, serum ferritin düzeylerinin allo-HKHT sonuçları üzerinde herhangi bir olumsuz etkisini göstermemiştir; ancak, demir yükünün allo-HKHT sonuçları üzerindeki etkisini açıklığa kavuşturmak için büyük ölçekli prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Ferritin, hematopoietik kök hücre nakli, prognostik faktörler

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is still only curative treatment methods for many benign and malign hematological diseases which increased in recent years with the increase in donor options and regulation of conditioning regimens (1-3). However, transplant related mortality (TRM) including infections, graft versus host disease (GvHD), and therapy-related toxicity are still major complications for allo-HCT (4,5). Iron overload is an adverse prognostic factor for patients undergoing allo-HCT which is related to increased poor outcomes, including high infection rates, high TRM, and lower survival. Additionally iron overload was associated with an important risk factor for hepatic sinusoidal obstruction syndrome as well as for both acute GvHD and chronic GvHD in allo-HCT (6-8). Serum ferritin, magnetic resonance imaging (MRI) of liver (T2 or R2 MRI), superconducting susceptometry (SQUID) and liver biopsy were some methods of evaluating iron overload (5, 9, 10).

Ferritin is an iron storage protein and measurement in the plasma which is commonly used in clinical practice to assess iron overload due to its inexpensive, noninvasive method and easy accessibility (11, 12). In the literature, a serum ferritin level exceeding 1000 µg/L (or >1000 ng/mL) is commonly used as the threshold for detecting iron overload, which correlates with a higher likelihood of complications. Elevated pre-transplant ferritin levels have been reported to increase the risk of non-relapse mortality following HCT and adversely impacts on overall survival and increases the GVHD after allogeneic HCT in the literature (13-15). We aimed to evaluate the effects of ferritin level on outcomes including the neutrophil/platelet engraftment status, febrile neutropenia rate, TRM, GvHD, sinusoidal obstruction syndrome (SOS)/veno-occlusive disease (VOD) and overall survival (OS) of allo-HCT in this study.

MATERIALS AND METHODS

Sixty-nine patients with ferritin values measured at the beginning of transplantation who underwent allo-HCT between January 2018-June 2021 were included in this study. The clinical and laboratory parameters were collected from the hospital registry system. This study was formally approved by Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (permission date: 29.06.2021, approval number: 2021/2250). It was performed following the ethical principles set forth in the Declaration of Helsinki.

Study design

Laboratory parameters were including alanine aminotransferase (ALT), creatinine, ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were evaluated. Using a ferritin cutoff of 1000 ng/mL, patients were divided into 2 groups: ferritin levels <1000 ng/mL vs. ≥ 1000 ng/mL. The outcomes, including the neutrophil/platelet engraftment status, febrile neutropenia rate, TRM in the first 30 days, and OS were evaluated according to the ferritin level. The following provides the definitions of the outcomes analyzed in this study. Neutrophil engraftment; the first of three consecutive days with an absolute neutrophil count ≥ 0.5×10^9/L after stem cell infusion. Platelet engraftment; the first of three consecutive days with a platelet count ≥ 20×10^9/L in the absence of transfusion. Febrile neutropenia; the occurrence of a body temperature ≥ 38 °C in the setting of a neutrophil count < 0.5×10^9/L. Transplant related mortality; the first 30 days after allo-HSCT without any evidence of disease relapses or progression after stem cell infusion. Overall survival; the time interval from the date of the first day of allo-HCT to death from any cause or last follow-up.

The Glucksberg scale was used in the assessment of acute GvHD (16). Similarly, the National Institutes of Health (NIH) Consensus Criteria were used in the assessment of chronic GvHD (17). Baltimore criterion was used for diagnosis of SOS/VOD (18).

Statistical analyses

The analysis of all data was performed with the SPSS 22.0 program. Categorical variables were summarized using frequencies (n) and percentages (%), while continuous variables were presented as medians and quartiles (quartile 1 [Q1], quartile 3 [Q3]), values. The Mann–Whitney U test was applied to compare non-normally distributed continuous variables, and categorical variables were assessed using either Pearson's chi-square test or Fisher's exact test, depending on the data. Univariate survival outcomes were analyzed using Kaplan–Meier methods with weighted Log-rank tests. The possible significant parameters with p≤0.20 in univariate tests were included in the multivariate analysis. Multivariable analysis was performed using Cox's proportional hazard model. A p<0.05 was regarded as statistically significant for all analyses.

RESULTS

The study population had a median age of 32 years (23-49) and 38 (55.1%) of them female. The most common diagnosis was acute myeloid leukemia (AML) (47.8%), followed by aplastic anemia (AA) (18.8%) and acute lymphoblastic leukemia (ALL) (17.4%), respectively. In addition to these diseases, 3 (4.3%) patients were diagnosed with myelodysplastic syndrome (MDS), 3 (4.3%) patients with chronic myeloid leukemia (CML), 3 (4.3%) patients with primary myelofibrosis (MF), 1 (1.4%) patient with post-essential thrombocythemia MF and 1 (1.4%) patient with paroxysmal nocturnal hemoglobinuria. The median ferritin level was 1080 ng/mL (505-1650) in all groups. The patients' demographic and clinical characteristics at the time of transplantation were summarized in Table 1 after stratification according to ferritin levels. Comparative analysis between the groups showed no significant differences with respect to demographic characteristics (age and sex) or biochemical parameters, including CRP, ALT, LDH, and creatinine (p > 0.05). AML diagnosis was higher in the group with ferritin ≥1000 ng/mL (61.5%) than in the group with ferritin <1000 ng/mL (30%). Again, patients with non-AML, ALL and AA diagnoses were more in the group with ferritin <1000 ng/mL (26.7%) than in the group with ≥1000 ng/mL (7.7%). A statistically significant difference in diagnostic status was found between the ferritin groups (p = 0.043).

Table 1. The demographic and clinical characteristics of the patients at the time of transplantation according to the ferritin level

	Ferritin <1000 ng/mL n:30 (%)	Ferritin ≥1000 ng/mL n:39 (%)	p value
Median age (Q1-Q3)	34 (23-48)	32 (23-49)	0.856
Sex			
Male	15 (50)	16 (41)	0.618
Female	15 (50)	23 (59)	
Diagnosis			
AML	9 (30)	24 (61.5)	0.043*
ALL	6 (20)	6 (15.4)	
AA	7 (23.3)	6 (15.4)	
Others	8 (26.7)	3 (7.7)	
The median time to allo-HSCT from diagnosis, months (Q1-Q3)	4 (2-7)	5 (3-10)	0.279
LDH level			
Normal	14 (46.7)	27 (69.2)	0.084
High	16 (53.3)	12 (30.8)	
CRP level			
Normal	9 (30)	11 (28.2)	0.999
High	21 (70)	28 (71.8)	
ALT level			
Normal	23 (76.7)	26 (66.7)	0.429
High	7 (23.3)	13 (33.3)	
Creatinine level			
Normal	29 (97.1)	38 (97.4)	0.999
High	1 (2.6)	1 (2.9)	
Median ferritin, ng/mL (Q1-Q3)	382.2 (255.1-606.1)	1650.0 (1247.3-1975.7)	NA

Allo-HSCT; allogeneic hematopoietic stem cell transplantation, AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, AA; aplastic anemia, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, CRP; C-reactive protein.NA; not-applicable
* Pearson's chi-squared test, p<0.05

The median interval from diagnosis to allo-HSCT was 4 months (1-158 months). Peripheral blood served as the only stem cell source in all groups. The median counts of infused stem cells were 7.20x106/kg (6.10-8.13x106/kg) in all cohorts. The HLA-full-matched related donor was used most frequently as the donor type, which was used in 52 (75.4%) patients. A reduced conditioning regimen was used most frequently as the conditioning regimen, which was used in 40 (58%) patients. Fludarabine plus cyclophosphamide plus anti-thymocyte globulin (ATG) regimen was primarily used as a reduced-intensity regimen, which was used in 15 (37.5%) patients. Treosulfan plus fludarabine plus ATG and fludarabine plus amsacrine plus cytarabine (FLAMSA) therapy were the other most used RIC regimens which were used in 9 (22.5%) and 9 (22.5%) patients, respectively. Busulfan plus cyclophosphamide was used as the MAC regimen, which was used in 26 (89.7%) patients. Cyclosporine A plus methotrexate combination was used in all patients due to GvHD prophylaxis. The transplantation characteristics and outcomes were shown according to the ferritin levels in Table 2. Comparison of the ferritin levels revealed no significant differences in $CD34^+$ stem cell dose, donor type, or conditioning regimen ($p > 0.05$). Ferritin levels had no statistically significant effect on the transplant outcomes, including engraftment status/times, the febrile neutropenia rates, hospitalization times, the rates TRM and SOS/VOD ($p>0.05$).

Response assessment could be performed in 47 (68.1%) patients at 3 months after transplantation. Twenty-two (31.9%) patients died before response assessment could be performed. Complete response was detected in 38 (80,9%) patients in all cohorts. There was no statistically significant effect of ferritin

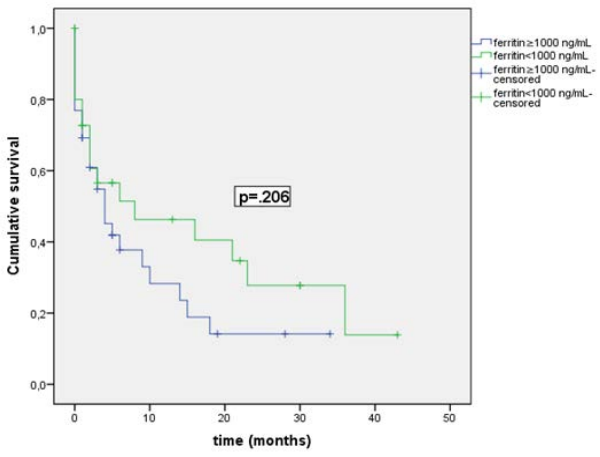

Figure 1. Kaplan–Meier curves for overall survival according to the ferritin level

Table 2. The transplantation characteristics and outcomes according to the ferritin levels

	Ferritin <1000 ng/mL n: 30 (%)	Ferritin ≥1000 ng/mL n: 39 (%)	p value
Median infused CD34+ count (Q1-Q3), x106/kg	7.45 (7.00-8.80)	6.95 (5.90-7.90)	0.166
Donor type			
Matched sibling	25 (83.3)	27 (69.2)	
Matched unrelated	3 (10)	6 (15.4)	0.380
Haploidentical	2 (6.7)	6 (15.4)	
Conditioning regimen			
Myeloablative	12 (40)	17 (43.6)	0.957
Reduced intensity conditioning	18 (60)	22 (56.4)	
Neutrophil engraftment status			
Yes	23 (76.7)	30 (76.9)	0.999
No	7 (23.3)	9 (23.1)	
Median time of neutrophil engraftment (Q1-Q3), day	15 (13-20)	16 (13-20)	0.766
Platelet engraftment status			
Yes	23 (76.7)	30 (76.9)	0.999
No	7 (23.3)	9 (23.1)	
Median time of platelet engraftment (Q1-Q3), day	15 (14-20)	16 (14-22)	0.678
Febrile neutropenia rate			
Yes	20 (66.7)	31 (79.5)	0.355
No	10 (33.3)	8 (20.5)	
Median hospitalization time (Q1-Q3), day	18 (16-23)	20 (16-25)	0.456
Transplant related mortality rates, (%)	8 (26.6)	9 (23)	0.783
Response at 3 months	n:21	n:26	
CR	19 (90.5)	19 (73.1)	
PR	0	1 (3.8)	0.287
Refractory	2 (9.5)	6 (23.1)	
Acute GvHD status			
Yes	4 (13.3)	3 (7.7)	0.713
No	26 (86.7)	36 (92.3)	
Chronic GvHD status			
Yes	6 (20)	8 (20.5)	0.999
No	24 (80)	31 (79.5)	
SOS/VOD			
Yes	4 (13.3)	4 (10.3)	0.987
No	26 (86.7)	35 (89.7)	

CR: complete response, GvHD: graft versus host disease, PR: partial response, SOS/VOD: Sinusoidal obstruction syndrome/veno-occlusive disease

value on response status (p=0.287) (Table 2)

The median OS was 4 months (95% CI: 1.4–6.6) in patients with ferritin levels ≥1000 ng/mL and 8 months (95% CI: 0–24.2) in those with ferritin levels <1000 ng/mL. No statistically significant association was observed between ferritin levels and OS (p = 0.206) (Figure 1). At the time of the last follow-up, 24 patients (34.7%) were alive. Acute GvHD occurred in 7 (10.1%) patients as only liver acute GvHD in 3 (4.3%) patients, only skin acute GvHD in 1 (1.4%) patient, only gastrointestinal acute GvHD in 1 patient (1.4%), and both gastrointestinal and liver acute GvHD in 2 (2.9%) patients. Grades III/IV acute GvHD occurred in 4 (5.8%) patients. Chronic GvHD occurred in 14 (20.2%) patients (9 limited and 5 extended. Comparison between the ferritin groups showed no statistically significant variation in the rates of acute or chronic GvHD (p=0.713 and p=0.999, respectively) (Table 2). In the univariate analysis, factors significantly associated with overall survival (OS) included the time from diagnosis to allo-HSCT, alanine aminotransferase (ALT) levels, creatinine levels, ferritin levels, the presence of febrile neutropenia, and infused $CD34^+$ cell counts (Table 3). In the multivariable Cox regression analysis, the time from diagnosis to allo-HSCT, creatinine levels, febrile neutropenia, and infused $CD34^+$ cell counts remained independent predictors of OS (Table 3).

DISCUSSION

In this study, the effect of ferritin levels on allo-HCT outcomes was evaluated. The ferritin levels had no effect on the early outcomes including the engraftment status, engraftment times, the febrile neutropenia rates, hospitalization times, and 1-month TRM rates (p>0.05). Gu et al. reported that no significant relationship was observed between iron levels (serum ferritin <1000 ng/mL vs. ≥1000 ng/mL) and both myeloid and platelet reconstitution (p = 0.441 and p = 0.579,

Table 3. Univariate and multivariate analysis of overall survival

Parameters for OS	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	p	Hazard ratio	95% confidence interval	p
Age (years)	1.006	0.987-1.025	0.529			
Gender (female)	1.448	0.798-2.628	0.224			
The median time to allo-HSCT from diagnosis months	1.010	1.001-1.019	0.037	1.033	1.008-1.059	0.009
ALT level	1.006	0.999-1.013	0.119	-	-	-
Creatinine level	3.184	0.796-12.741	0.102	5.110	1.043-25.034	0.044
CRP level	0.970	0.879-1.071	0.546			
Ferritin level	1.001	0.988-0.0002	0.172	-	-	-
LDH level	0.9908	0.997-1.005	0.372			
Febrile neutropenia	2.844	1.264-6.398	0.0115	3.846	1.496-9.886	0.005
CD34+ cell counts in the transplant	1.102	0.965-1.258	0.154	1.228	1.056-1.428	0.007
Acute GvHD	0.972	0.384-2.481	0.953			
Chronic GvHD	0.631	0.308-1.290	0.207			

ALT; alanine aminotransferase, CRP; C-reactive protein, GvHD: Graft-versus-host disease, LDH; lactate dehydrogenase, OS: overall survival.

respectively) and the median serum ferritin levels before transplantation was 561 (223-846) µg/L in this study (19). In similar, another study reported that both neutrophil and platelet engraftment day were not affected by iron overload (p=0.710 and p=0.190, respectively). In the same study, iron overload had no poor effect on 3-months and 1-year TRM rates (iron overload group; 8.3% and 17.5%, non-iron overload group; 4.5% and 26.5%, respectively, p=0.940) (20). Our results on the effects of iron overload on engraftment and TRM are in line with the existing literature. However, Pullarkat et al. found that the high ferritin (≥1000 ng/mL) had increased day 100 mortality (median pre-transplant serum ferritin 952 ng/ml, range from 10 to 10 000 ng/ml, ferritin ≥1000 ng/mL; 20%, ferritin <1000 ng/mL; 9%, p=0.038) (6).

In a retrospective study, the patients with MDS who underwent allo-HSCT divided into two groups: the effective treatment group (ferritin <1000 µg/L) and iron overload group (ferritin ≥1000 µg/L). The effective treatment group demonstrated a significantly lower incidence of infections than the iron overload group (36.8% vs. 82.4%, p = 0.002) (19). Sivgin et al. analyzed the effects of pre-transplant serum ferritin levels (ferritin level ≥1000ng/mL or <1000 ng/mL) in patients who had undergone allo-HSCT. It was reported that patients who developed infectious complications exhibited significantly higher pre-transplant serum ferritin levels (p < 0.05) (21). Contrary to the literature, iron overload was not adversely affected on febrile neutropenia in our study.

In a prospective study, 45 patients with acute leukemia and myelodysplastic syndrome who underwent allo-HCT were evaluated. They found that pre-HCT iron overload (median ferritin 1432 ng/ml (20–6989) was not associated with increased mortality and relapse (22). In a meta-analysis including four studies, 276 patients who underwent allo-HCT was analyzed. This meta-analysis reported that serum ferritin >1000 ng/mL had significant effect on OS but not ferritin >2500 ng/mL (15). However, ferritin levels (<1000 ng/mL vs ≥1000 ng/mL) had no effect on overall survival in our study (p=0.206). There are different studies in the literature reporting the relationship between iron load and GvHD. Pullarkat et al. reported that ferritin levels >1000 ng/mL was associated with common acute GvHD (6). A separate retrospective analysis reported an association between pre-transplant ferritin concentrations >400 µg/L and a decreased incidence of chronic GvHD following allo-HCT (23). In contrast, Penack et al. found no significant relationship between serum ferritin levels and the occurrence of either acute or chronic GvHD (24). In our study, no statistically significant relationship was detected between ferritin levels and either acute or chronic GvHD (p = 0.713 and p = 0.999, respectively).

İron overload is known important risk factor for SOS/VOD in patients who underwent allo-HSCT. Several trials have reported a significant association between iron overload and SOS/VOD. In one study, elevated ferritin levels exceeding 1000 ng/mL were linked to an increased risk of SOS, with an odds ratio of 2.49 (95% CI, 1.54–4.02) (25). A retrospective study in pediatric patients identified elevated pre-transplant serum ferritin as a major risk factor for SOS/VOD. Ferritin levels >2400 ng/mL were associated with a significantly increased incidence of SOS/VOD compared with levels ≤2400 ng/mL (29.7% vs. 7.4%, p = 0.005) (26). In contrast, there was not significantly association between the serum ferritin levels and SOS/VOD in our study (p=0.987).

Study Limitations

This study has certain limitations. First, its retrospective design and the relatively small, heterogeneous cohort for allo-HCT. Second, ferritin is a positive acute-phase markers and it may not always show iron overload. However, we prefer ferritin firstly to show the iron overload because it is easily accessible and non-invasive method. For a more transparent interpretation of survival data, our cohort was not a heterogeneous group.

CONCLUSION

In conclusion, our study did not show the poor effects of the serum ferritin levels on the transplantation outcomes, but large prospective studies are needed to clarify the impact of iron overload on outcomes of allo-HCT.

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RESEARCH ARTICLE

BK Virus Detection by Real-Time Polymerase Chain Reaction in Sjögren's Syndrome, Rheumatoid Arthritis, and Behçet's Disease

Sjögren Sendromu, Romatoid Artrit ve Behçet Hastalığında Gerçek Zamanlı Polimeraz Zincir Reaksiyonu ile BK Virüsü Tespiti

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ABSTRACT

Objective: Autoimmune diseases are chronic conditions with largely unclear etiology, affecting patients' quality of life and increasing healthcare costs. This study aimed to investigate the relationship between Rheumatoid arthritis, Sjögren's syndrome, Behçet's disease, and BK virus.

Materials and Methods: This study was conducted between August 2017 and August 2018 in the Central Laboratory of the Department of Medical Microbiology. A total of 120 adults were enrolled, including patients diagnosed with Rheumatoid arthritis, Sjögren's syndrome, Behçet's disease (n=30 each) attending the Rheumatology outpatient clinic, and healthy controls from the General Internal Medicine outpatient clinic (n=30). BK virus was detected in urine and serum samples using Real-Time PCR. Multivariate logistic regression analysis was performed to identify independent factors associated with urinary BK virus positivity, including age and disease groups.

Results: The mean ages were 43.03±19.43 years in controls, 54.33±12.03 in Rheumatoid arthritis, 50.76±10.29 in Sjögren's syndrome, and 42.63±10.88 in Behçet's disease groups. Urinary BK virus positivity was detected in 1/30 (3.3%) controls, 7/30 (23.3%) Rheumatoid arthritis patients, 7/30 (23.3%) Sjögren's syndrome patients, and 4/30 (13.3%) Behçet's disease patients. BK virus positivity was significantly higher in the Sjögren's syndrome (p=0.016) and Rheumatoid arthritis groups (p=0.049) compared with controls. In multivariate logistic regression analysis, both Rheumatoid arthritis and Sjögren's syndrome were identified as independent predictors of BK virus positivity (OR=8.83; 95% CI: 1.01–76.96; p=0.049). Although positivity was higher in Behçet's disease patients, the difference was not statistically significant.

Conclusion: Urinary BK virus positivity was significantly more frequent in patients with Rheumatoid arthritis and Sjögren's syndrome than in healthy controls. These findings suggest a potential association between BK virus and certain autoimmune diseases. Larger, well-designed prospective studies are warranted to clarify the role of BK virus in autoimmune disease pathogenesis.

Keywords: BK virus, Rheumatoid arthritis, Sjogren's syndrome, Behcet's Disease, Real-Time PCR

ÖZET

Amaç: Otoimmün hastalıklar, etiyolojisi büyük ölçüde belirsiz olan kronik hastalıklardır ve hastaların yaşam kalitesini olumsuz etkilemekte, sağlık hizmeti maliyetlerini artırmaktadır. Bu çalışmada, Romatoid artrit, Sjögren sendromu ve Behçet hastalığı ile BK virüsü arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışma, Ağustos 2017–Ağustos 2018 tarihleri arasında Tıbbi Mikrobiyoloji Anabilim Dalı Merkez Laboratuvarında gerçekleştirilmiştir. Çalışmaya romatoloji polikliniğinde Romatoid artrit, Sjögren sendromu ve Behçet hastalığı tanısı almış hastalar (her grupta n=30) ile genel dahiliye polikliniğinden sağlıklı kontroller (n=30) olmak üzere toplam 120 erişkin birey dâhil edilmiştir. BK virüsü, idrar ve serum örneklerinde Real-Time PCR yöntemi ile araştırılmıştır. İdrarda BK virüsü pozitifliği ile ilişkili bağımsız faktörleri belirlemek amacıyla yaş ve hastalık gruplarını içeren çok değişkenli lojistik regresyon analizi yapılmıştır.

Bulgular: Kontrol, Romatoid artrit, Sjögren sendromu ve Behçet hastalığı gruplarının yaş ortalamaları sırasıyla 43,03±19,43, 54,33±12,03, 50,76±10,29 ve 42,63±10,88 yıl olarak bulundu. İdrarda BK virüsü pozitifliği kontrol grubunda 1/30 (%3,3), Romatoid artrit grubunda 7/30 (%23,3), Sjögren sendromu grubunda 7/30 (%23,3) ve Behçet hastalığı grubunda 4/30 (%13,3) olarak saptandı. BK virüsü pozitifliği, Sjögren sendromu (p=0,016) ve Romatoid artrit (p=0,049) gruplarında kontrol grubuna göre anlamlı derecede daha yüksek bulundu. Çok değişkenli lojistik regresyon analizinde, Romatoid artrit ve Sjögren sendromunun BK virüsü pozitifliği için bağımsız belirleyiciler olduğu saptandı (OR=8,83; %95 GA: 1,01–76,96; p=0,049). Behçet hastalığı grubunda pozitiflik daha yüksek olmakla birlikte, bu fark istatistiksel olarak anlamlı bulunmadı.

Sonuç: İdrarda BK virüsü pozitifliği, Romatoid artrit ve Sjögren sendromu hastalarında sağlıklı kontrollere göre anlamlı derecede daha yüksek bulunmuştur. Bu bulgular, BK virüsü ile bazı otoimmün hastalıklar arasında olası bir ilişki olduğunu düşündürmektedir. BK virüsünün otoimmün hastalıkların patogenezindeki rolünü netleştirmek için daha geniş ve iyi tasarlanmış prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: BK virüs, Romatoid artrit, Sjögren sendromu, Behçet Hastalığı, Real-Time PCR

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INTRODUCTION

BK polyomavirus has an icosahedral structure and consists of a circular, double-stranded DNA genome. It belongs to the Betapolyomavirus genus within the Polyomaviridae family. The virus lacks an envelope and contains a small icosahedral capsid, approximately 40–44 nm in diameter, formed by the structural proteins VP1, VP2, and VP3. Among these, VP1 is responsible for binding to host cell receptors, thereby enabling the virus to enter its target cells (1). Although the impact of BK virus in kidney and hematopoietic stem cell transplant recipients has been well established, its effects on other organ systems remain incompletely understood (2). Rheumatoid arthritis (RA) is a systemic autoimmune disorder marked by persistent inflammation and symmetrical involvement of the synovial joints (3). It causes progressive erosive inflammation that, if not effectively managed, may lead to joint destruction, deformities, functional disability, and can even be life-threatening despite current treatment options. The etiology of RA has not yet been fully clarified (4,5). Sjögren's syndrome (SS) is a long-standing systemic autoimmune disorder with an unclear etiology, distinguished by the infiltration of lymphocytes into exocrine glands (6). Behçet's disease (BD), initially identified in 1937 by Turkish dermatologist Prof. Dr. Hulusi Behçet, is clinically characterized by a triad of symptoms: oral ulcers, genital ulcers, and hypopyon uveitis (7).

A possible association between BK virus (BKV) and systemic lupus erythematosus, one of the major rheumatological diseases, was proposed by Gupta et al. in a study published in 2017 (8). In light of these findings, the present study aimed to investigate whether a similar relationship exists between RA, SS, and BD and BKV, and, if so, to determine the prevalence of BKV activity in these conditions. In this study, the presence of BKV was investigated in urine and serum samples from 120 individuals (control, RA, SS, and BD groups) using Real-Time PCR (RT-PCR).

MATERIALS AND METHODS

Study Design and Participants: This study was designed as a cross-sectional observational study conducted between August 2017 and August 2018. This study was conducted in the Central Laboratory of the Department of Medical Microbiology, Faculty of Medicine, between August 2017 and August 2018. Blood and urine samples were collected, with informed consent, from adult patients diagnosed with RA, SS, and BD who presented to the Rheumatology outpatient clinic. Control group samples were obtained from adult patients attending the General Internal Medicine outpatient clinic. A total of 240 samples (120 blood and 120 urine) from 120 individuals were examined for BKV. Sample Collection and PCR Analysis: BKV nucleic acids were detected using the RT-PCR method. Blood samples collected in CBC tubes were centrifuged at 4000 rpm for 6 minutes to separate serum. Serum and urine samples were then transferred into sterile, screw-capped Eppendorf tubes using sterile pipette tips, labeled, and stored in a −20°C deep freezer until analysis.

Ethical Approval: Ethics committee approval was obtained from the local ethics committee (Decision No: 15/22, Date: 16.11.2017).

Statistical Analysis: Statistical analyses were performed using SPSS version 20.0 (IBM Corp. USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as counts and percentages. Comparisons between groups were conducted using the chi-square test or Fisher's exact test for categorical variables, as appropriate. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) was performed, followed by post hoc comparisons using Tukey's test. The sample size was based on the available number of eligible patients during the study period. Post-hoc power analysis based on the observed effect size (OR = 8.826, α=0.05) indicated that the achieved power was >80%, suggesting that the sample size was sufficient to detect the observed associations.

To identify factors associated with BK virus urine RT-PCR positivity, multivariable logistic regression analysis was performed. BK virus positivity was defined as the dependent variable, while age and disease groups (Rheumatoid arthritis, Sjögren syndrome, and Behçet's disease; reference group: controls) were included as independent variables. All variables were entered into the model simultaneously using the Enter (forced entry) method. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Model fit and explanatory power were assessed using Cox & Snell R^2 and Nagelkerke R^2. A p-value of 0.05 was considered statistically significant.

RESULTS

The demographic data of the study groups showed that the mean age was 43.03 ± 19.43 years in the control group, 54.33 ± 12.03 years in the RA group, 50.76 ± 10.29 years in the SS group, and 42.63 ± 10.88 years in the BD group. A significant difference in mean age was detected overall between groups (p=0.003), with post-hoc analysis showing higher mean age in the RA group compared with the control and BD groups. However, no significant differences were observed between the BD and SS groups in comparison to the control group (p = 1.000). Within the study population, the control group consisted of 13 males and 17 females; the RA group comprised 10 males and 20 females; the SS group included 1 male and 29 females; and the BD group was composed of 12 males and 18 females. A statistically significant difference in gender distribution was observed between the SS group and the other groups (p=0.003). A statistically significant difference was observed between the groups in terms of organ involvement due to rheumatological disease (p = 0.001).

During sample collection, participants were asked whether they had received quinolone-derived antibiotics within the past two weeks, as quinolones have been reported to be effective against BKV (9). Evaluation of the groups regarding recent quinolone use revealed no statistically significant differences (p= 0.131). The demographic data are presented in Table 1.

Table 1. Demographic and clinical characteristics of the study groups

Variable	Control group (n=30) (Group1)	Rheumatoid Arthritis (n=30) (Group2)	Sjogren Syndrome (n=30) (Group3)	Behcet's Disease (n=30) (Group4)
Age (years)	43.03±19.43	54.33±12.03	50.76±10.29	42.63±10.88
Gender (M/F)	13/17 (%43/%56)	10/20 (%33/%66)	1/29 (%3/%96)	12/18 (%40/%60)
Disease duration (Years)	0.0±0.0	8.23±4.76 (2-19)	7.1±6.05 (1-30)	10.30±8.56 (2-30)
Due to disease (Yes/No)	0/30 (%0/%100)	3/27 (%10/%90)	10/20 (%33/%66)	17/13 (%66/%33)
Quinolone use (Yes/No)	0/30 (%0/%100)	1/29 (%3/%96)	2/28 (%6/%93)	2/28 (%6/%93)

Table 2. Inferential statistical analysis of demographic and clinical variables

Variable	Statistical test	Statistic value	p-value	Effect size
Age	One-way ANOVA (post hoc Tukey)	F(3.116)=3.16	0.003	G1–G2: d = 0.70 (moderate–large) G2–G4: d = 1.02 (large)
Gender	Chi-square / Fisher's exact test	χ^2 = 14.28	0.003	Cramér's V = 0.345 (moderate)
Disease duration	One-way ANOVA	F(3,116)=2.24	0.412	—
Due to disease	Chi-square / Fisher's exact test	χ^2 = 30.76	0.001	Cramér's V = 0.506 (moderate–large)
Quinolone use	Chi-square / Fisher's exact test	χ^2 = 2.29	0.131	—

Table 3. Distribution of urine and plasma BKV PCR positivity among disease groups

Variable	Control group (n=30) (Group1)	Rheumatoid Arthritis (n=30) (Group2)	Sjogren Syndrome (n=30) (Group3)	Behcet's Disease (n=30) (Group4)	Statistic	p	Effect size
Urine BKV PCR (–/+) Significant difference between Group 1 and Group 3 (p = 0.016).	1/29	7/23	7/23	4/26	χ^2 = 6.38	0.016	Cramér's V = 0.23 (small-moderate)
Plasma BKV PCR (–/+) No statistically significant difference between the groups.	0/30	0/30	0/30	0/30	χ^2 = 1.017	1.000	—

In the control group, 1 of 30 urine samples tested positive for BKV by RT-PCR. Among the 30 patients diagnosed with RA, BKV positivity was detected in 7 urine samples. Of these RA patients, 3 who were receiving biological therapies tested positive, while 4 who were not receiving biological therapies were also positive. Comparison of the total RA group with the control group using the chi-square test revealed a statistically significant difference (p = 0.049). However, no significant difference in BKV positivity was observed between RA patients using biological drugs and those not using them (p= 0.409). These results indicate that biological therapy does not appear to affect urinary BKV positivity in patients with RA (Table 2-3).

Table 4. Multivariate logistic regression analysis of factors affecting BK virus urine RT-PCR positivity.

VARIABLE	B	S.E.	p	OR	95% CI (OR)	
					Lower	Upper
Age	0.022	0.026	0.406	1.022	0.971	1.076
Rheumatoid Arthritis	2.178	1.105	0.049	8.826	1.012	76.960
Sjogren Syndrome	2.178	1.105	0.049	8.826	1.012	76.960
Behcet's Disease	1.495	1.150	0.194	4.462	0.468	42.514
Constant	-0.470	1.512	0.756	0.625	-	-
Cox & Snell R Square=0.292; Nagelkerke R Square=0.501						

Abbreviations: B, regression coefficient; S.E., standard error; OR, odds ratio; CI, confidence interval; reverse transcription polymerase chain reaction; BK virus, BK polyomavirus. Control group was used as the reference category. Cox & Snell R^2 and Nagelkerke R^2 values indicate the explanatory power of the logistic regression model.

BKV positivity was detected in 7 of 30 patients with Sjögren's syndrome by urine RT-PCR. Chi-square analysis demonstrated a statistically significant difference between the control group and patients with Sjögren's syndrome (p = 0.016). In patients with Behçet's disease, BKV positivity was detected in 4 of 30 urine samples. Comparison between the control group and BD patients showed no statistically significant difference (p = 1.000).

Multivariable analysis of factors associated with BK virus positivity

To identify independent factors associated with urine BKV RT-PCR positivity and to control for potential confounding variables, a multivariable logistic regression analysis was performed. Age and disease groups (RA, SS, and BD) were included in the model, with the control group serving as the reference category. The results of the logistic regression analysis are presented in Table 4. The multivariable model demonstrated moderate to good explanatory power, with a Cox & Snell R^2 value of 0.292 and a Nagelkerke R^2 value of 0.501, indicating that approximately 50% of the variance in BK virus urine RT-PCR positivity was explained by the model.

Age was not independently associated with BKV positivity (OR = 1.022; 95% CI: 0.971–1.076; p = 0.406). In contrast, both RA and SS were found to be significant independent predictors of urine BKV RT-PCR positivity. Patients with Rheumatoid arthritis had an approximately 8.8-fold increased odds of BKV positivity compared with the control group (OR = 8.826; 95% CI: 1.012–76.960; p = 0.049). Similarly, patients with SS exhibited a comparable increase in risk (OR = 8.826; 95% CI: 1.012–76.960; p = 0.049). Although patients with BD showed a higher odds of BKV positivity compared with controls, this association did not reach statistical significance (OR = 4.462; 95% CI: 0.468–42.514; p = 0.194).

DISCUSSION

Polyomaviruses, including BK virus, are non-enveloped DNA viruses with an icosahedral capsid (10). Studies have reported BKV seropositivity in approximately 80% of adults (11). In a study conducted in our country, the seroprevalence of BKV was found to be 10.2% among kidney transplant patients (12). BKV is transmitted through close contact, respiratory routes, oral exposure, and perinatally. Most individuals are exposed to BKV during childhood, which is believed to account for the high seropositivity observed in adults (13). Following primary infection, which may be asymptomatic or symptomatic, BKV remains latent in the kidneys and B lymphocytes. BKV-associated diseases typically arise in immunocompromised individuals, such as those with AIDS, leukemia, or organ transplant recipients (14). When an organ transplant is performed from a BKV-seropositive donor to a BKV-seronegative recipient, severe complications may occur in the recipient (15). BKV can be detected in urine, stool, blood, and cerebrospinal fluid, with urine samples recommended for screening due to the higher viral load compared to plasma (16).

BK virus is an agent that has been rarely investigated outside of its known associations with urogenital and meningeal manifestations. This study was conducted to investigate the possible association between BKV and RA, SS, and BD. Virus isolation and serological identification are not commonly employed for the diagnosis of BK virus. Nucleic acid amplification methods, particularly PCR, are widely used due to their high specificity (17). Accordingly, this study utilized RT-PCR for the detection of BKV. In a study by Gupta et al. conducted between 2014 and 2016, urine and blood samples were collected from 32 pediatric patients with SLE (26 girls, 6 boys; aged 4–18 years) at 3–6 and 9–12 months and analyzed using RT-PCR. Only 13 of the 32 patients completed the full 12-month follow-up. BKV was detected in 9 of 97 urine samples and 10 of 96 blood samples. BK viruria was observed in 28% (9/32) of patients, while BK viremia was observed in 22% (7/32). Both viremia and viruria were detected in 4 patients; only viruria in 3 patients; and only viremia in 5 patients. Microscopic hematuria was noted in only 1 patient. No false-positive results due to drugs or laboratory factors triggering BKV reactivation were reported (8).

In a case reported by Melis et al. in 2018, a 60-year-old female patient with SLE, who had been receiving azathioprine and medrol for 2 years since the age of 40, was admitted with complaints of lower extremity weakness and personality changes. Brain MRI revealed hyperintensities in the frontal and parietal lobes. Brain biopsy demonstrated demyelination along with histiocytic and atypical cells, and hematoxylin and eosint staining was performed. PCR analysis of the left frontal

biopsy confirmed BKV positivity, establishing a viral etiology for the patient's symptoms. Consequently, palliative treatment was administered (18). Jung Li et al. investigated BKV infection in patients with SLE and found that viral loads were higher in those who had undergone kidney transplantation compared to patients without transplants. They attributed this difference to the effects of immunosuppressive therapy. Furthermore, they suggested that BKV positivity in non-transplant patients might result from compromised immune function in these individuals (19).

In a 2015 case report by Whittemore et al. a 55-year-old male patient with RA presented with increased serum creatinine and dyspnea. The patient had a history of SS, chronic kidney disease, and hypertension, and had been receiving mycophenolate mofetil and tacrolimus for 6 years. Despite normal ultrasound findings and the absence of hematuria or proteinuria in the urine, the patient's renal function continued to deteriorate. Initially treated with meropenem, the patient's renal condition worsened despite treatment, leading to a suspicion of drug toxicity, prompting discontinuation of the medications. However, renal function continued to decline, and a kidney biopsy was performed. Microscopic examination revealed BKV-associated cellular changes. Subsequently, BKV PCR testing of serum and urine confirmed the presence of the virus. The patient was treated with intravenous immunoglobulin, quinolone, and leflunomide, which resulted in a full recovery (20). In a 2014 study, Calderon et al. investigated BKV in the salivary glands of two HIV-positive patients and one kidney transplant recipient. BKV DNA was isolated from the throat washings of both HIV-positive and HIV-negative patients. The study found that the replicative rate of BKV in the salivary glands was faster than in the kidneys, suggesting that BKV may exhibit tropism for the salivary glands. The authors hypothesized that mouth ulcers observed in HIV-positive patients could be attributed to BKV infection and emphasized the need for a larger study to further explore this potential association (21).

Wunderink et al. conducted a retrospective study between 2003 and 2013 to examine the relationship between HLA positivity and BK viremia in 407 liver donor-recipient pairs. BK viremia developed in 111 patients within one year post-transplant. Among the HLA alleles, recipient HLA-C7 and HLA-DR12 were associated with a higher risk of viremia, whereas HLA-A30, B13, B51, C15, and DR13 were linked to a lower risk. In particular, HLA-B51 was significantly correlated with a decreased risk of viremia. Multivariate analysis indicated that HLA-B51 positivity, observed in 36 recipients (9%), was associated with an approximately fivefold reduction in the risk of viremia (22). In a 2015 case report by Taşkapan et al, a 52-year-old female patient, who had received a renal transplant 3 months prior, presented to the neurology clinic with complaints of an inability to stand and walk. The patient had been started on mycophenolate mofetil, tacrolimus, and methylprednisolone, and was diagnosed with acute motor-axonal polyneuropathy based on clinical examinations. Due to the potential risk of new neurotoxicity, plasma exchange was performed for 10 days, and oral tacrolimus was switched to rapamycin. Despite these interventions, the patient's symptoms worsened, and BKV was detected in the patient's serum by PCR. Further examinations revealed no other abnormalities. The patient's condition improved, and she began walking 15 days after initiating treatment with intravenous immunoglobulin (IVIG) and quinolone (23).

In our study, we analyzed blood and urine samples from patients with RA, SS, BD, and a control group. No significant differences were observed between groups regarding the use of quinolone in the last two weeks. BKV was not detected in any of the serum samples by RT-PCR. However, urine RT-PCR revealed BK viruria in 1 out of 30 patients (3.33%) in the control group, 7 out of 30 patients (23.33%) in the RA group, 7 out of 30 patients (23.33%) in the SS group, and 4 out of 30 patients (13.33%) in the BD group. Chi-square analysis showed a significant difference between the RA and SS groups versus the control group, whereas no significant difference was found between the BD group and the control group. To further evaluate independent factors associated with BK viruria, a multivariate logistic regression analysis was performed. In this model, age was not found to be a significant predictor of urinary BKV RT-PCR positivity. However, both RA and SS were identified as independent risk factors for BK viruria. Patients in the RA group had an approximately 8.8-fold increased odds of BKV positivity compared to the control group (OR=8.83, 95% CI: 1.01–76.96, p=0.049). Similarly, SS was also associated with a significantly increased risk of BK viruria with the same magnitude of effect (OR=8.83, 95% CI: 1.01–76.96, p=0.049). Although the BD group demonstrated a higher odds ratio compared to controls, this association did not reach statistical significance. The model showed a moderate-to-good explanatory power, with a Cox & Snell R^2 of 0.292 and a Nagelkerke R^2 of 0.501.

These findings may suggest a possible association between BK viruria and RA or SS that appears to be independent of age; however, due to the cross-sectional design of the study, causal relationships cannot be established. Comparisons with population-based seroepidemiological data were limited. Differences in methodologies and patient populations across studies limited direct comparisons with the existing literature. We believe that large-scale, multi-faceted comparative studies are necessary to better understand the pathogenesis of BKV in patients with RA and SS, both of which showed statistically significant associations with the virus in our study.

Study Limitations

Several limitations of this study should be acknowledged. Another limitation of this study is the relatively small sample size in each disease group. Although statistically significant associations were observed for Rheumatoid arthritis and Sjögren's syndrome, the limited number of participants may reduce the generalizability of the findings. Due to the well-known epidemiological characteristics of Sjögren's syndrome, there was a marked female predominance in this group. This imbalance may have limited the statistical power to fully assess the independent effect of sex in multivariable analyses. Therefore, findings related to gender should be interpreted with caution.

CONCLUSION

The present study demonstrates a higher frequency of BK viruria in patients with RA and SS compared to healthy controls, while no significant association was observed in patients with BD. The absence of BK viremia and the lack of an association with age suggest that BKV reactivation in these patient groups may be localized and related to disease-specific immune dysregulation rather than demographic factors. Although the clinical significance of asymptomatic BK viruria remains to be fully elucidated, these findings contribute to the existing literature by highlighting a potential relationship between BKV and selected autoimmune rheumatic diseases.

DECLARATIONS

Conflict of Interest: *The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.*

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RESEARCH ARTICLE

Development and Initial Validation of the Clinical Patient Behavior Scale: A Multidimensional Assessment Approach

Klinik Hasta Davranışı Ölçeğinin Geliştirilmesi ve İlk Doğrulama Çalışması: Çok Boyutlu Bir Değerlendirme Yaklaşımı

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ABSTRACT

Objective: Patient behavior in clinical settings plays a critical role in shaping care processes, communication quality, and treatment outcomes. While existing research has largely focused on adherence and patient satisfaction, there remains a lack of comprehensive instruments that capture the multidimensional nature of patient behavior within clinical interactions. This study aimed to develop and initially validate the Clinical Patient Behavior Scale (CPBS), a multidimensional instrument designed to assess patient behaviors in clinical settings based on healthcare professionals' evaluations.

Materials and Methods: This methodological study was conducted with 300 nurses working in a university hospital. An initial item pool of 30 items was generated through a comprehensive literature review and expert evaluation. Content validity was established using expert ratings. Construct validity was assessed using Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA). Internal consistency reliability was evaluated using Cronbach's alpha coefficients.

Results: The CPBS demonstrated excellent sampling adequacy (KMO = 0.939) and a significant Bartlett's test of sphericity ($p < 0.001$). EFA revealed a five-factor structure explaining 73.37 % of the total variance. CFA indicated excellent model fit (CFI = 0.992, TLI = 0.991, RMSEA = 0.016). All factor loadings were statistically significant. The overall internal consistency of the 30-item scale was high (Cronbach's alpha = 0.92).

Conclusion: The CPBS provides initial evidence of a theoretically grounded and psychometrically robust instrument for assessing patient behavior as a multidimensional construct in clinical settings. The findings represent initial validation evidence, and further studies are recommended to examine cross-cultural validity, temporal stability, and external validity across diverse healthcare contexts of BK virus in autoimmune disease pathogenesis.

Keywords: Patient behavior, scale development, validity, reliability, psychometrics, clinical assessment

ÖZET

Amaç: Klinik ortamlardaki hasta davranışı, bakım süreçlerini, iletişim kalitesini ve tedavi sonuçlarını şekillendirmede kritik bir rol oynar. Mevcut araştırmalar büyük ölçüde uyum ve hasta memnuniyetine odaklanırken, klinik etkileşimler içindeki hasta davranışının çok boyutlu doğasını yakalayan kapsamlı araçların eksikliği devam etmektedir. Bu çalışma, sağlık profesyonellerinin değerlendirmelerine dayanarak klinik ortamlardaki hasta davranışlarını değerlendirmek üzere tasarlanmış çok boyutlu bir araç olan Klinik Hasta Davranışı Ölçeği'ni (CPBS) geliştirmeyi ve ilk olarak doğrulamayı amaçlamıştır.

Gereç ve Yöntemler: Bu metodolojik çalışma, bir üniversite hastanesinde çalışan 300 hemşire ile gerçekleştirilmiştir. Kapsamlı bir literatür taraması ve uzman değerlendirmesi yoluyla 30 maddeden oluşan bir ilk madde havuzu oluşturulmuştur. İçerik geçerliliği, uzman değerlendirmeleri kullanılarak belirlenmiştir. Yapı geçerliliği, Keşifsel Faktör Analizi (EFA) ve Doğrulayıcı Faktör Analizi (CFA) kullanılarak değerlendirilmiştir. İç tutarlılık güvenilirliği, Cronbach alfa katsayıları kullanılarak değerlendirilmiştir.

Bulgular: CPBS, mükemmel örneklem yeterliliği (KMO = 0,939) ve anlamlı bir Bartlett küresellik testi ($p < 0,001$) göstermiştir. Açıklayıcı faktör analizi (EFA), toplam varyansın %73,37'sini açıklayan beş faktörlü bir yapı ortaya koymuştur. Doğrulayıcı faktör analizi (CFA), mükemmel model uyumu göstermiştir (CFI = 0,992, TLI = 0,991, RMSEA = 0,016). Tüm faktör yükleri istatistiksel olarak anlamlıdır. 30 maddelik ölçeğin genel iç tutarlılığı yüksektir (Cronbach alfa = 0,92).

Sonuç: CPBS, klinik ortamlarda hasta davranışını çok boyutlu bir yapı olarak değerlendirmek için teorik olarak temellendirilmiş ve psikometrik olarak sağlam bir araç için ilk kanıtları sunmaktadır. Bulgular, ilk doğrulama kanıtlarını temsil etmektedir ve çeşitli sağlık hizmeti bağlamlarında kültürlerarası geçerlilik, zamansal istikrar ve dış geçerliliğin incelenmesi için daha fazla çalışma önerilmektedir.

Anahtar Kelimeler: Hasta davranışı, ölçek geliştirme, geçerlilik, güvenilirlik, psikometri, klinik değerlendirme

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INTRODUCTION

Patient behavior in clinical settings plays a significant role in shaping the quality and effectiveness of nursing care. Healthcare delivery is inherently relational, and nurse–patient interactions constitute one of the most continuous and intensive forms of professional contact within clinical environments. The quality of these interactions influences communication, adherence to treatment, patient safety, and overall care outcomes (1,2). While extensive research has examined nurses' competencies, communication skills, and professional performance, comparatively limited attention has been directed toward systematically assessing patient behaviors that directly affect nursing care processes.

Patient behaviors in clinical settings encompass a broad spectrum, ranging from cooperative engagement and respectful communication to non-adherence, resistance to care, verbal aggression, and disruptive conduct. Positive patient engagement has been associated with improved adherence and better health outcomes (3). Conversely, challenging patient behaviors may interfere with nursing interventions, disrupt workflow, increase emotional labor, and contribute to occupational stress (4,5). Nurses are particularly vulnerable to such behaviors due to their sustained bedside presence and responsibility for direct care (6).

Existing literature has primarily focused on related but narrower constructs, such as patient satisfaction (7), treatment adherence (8), patient engagement (3), and workplace violence against healthcare staff (5). However, these constructs do not comprehensively capture the range of patient behaviors encountered in everyday nursing practice. Instruments assessing workplace violence typically emphasize severe aggression, whereas satisfaction scales reflect patients' perceptions of care rather than observable behaviors affecting care delivery. Consequently, there remains a lack of a structured and validated tool specifically designed to assess patient behaviors within the context of nursing care.

From an organizational perspective, exposure to challenging patient behaviors has been linked to burnout, emotional exhaustion, and reduced job satisfaction among nurses (9,10). The Job Demands–Resources model suggests that persistent interpersonal stressors may deplete professional resources and negatively influence well-being and performance (10). Systematic assessment of patient behaviors may therefore contribute not only to improving care quality but also to enhancing work environment management and nurse well-being.

In light of this gap, there is a need for a valid and reliable instrument to systematically assess patient behaviors encountered in nursing care. To our knowledge, no existing instrument comprehensively captures patient behavior as a multidimensional construct within clinical interactions. Accordingly, this study aimed to develop and initially validate a measurement tool to assess patient behaviors in clinical settings as evaluated by nurses. Rather than focusing solely on treatment adherence, the scale conceptualizes patient behavior as a multidimensional construct that includes cooperation, communication patterns, behavioral compliance, and respect for professional boundaries within the nurse–patient interaction. This study was conducted to develop a valid and reliable measurement tool to assess patient behaviors in clinical settings as evaluated by nurses.

MATERIALS AND METHODS

Study Design

The study was designed as a methodological study.

Setting and Time

The study was conducted in Necmettin Erbakan University Hospital in 2026.

Population and Sample

In methodological studies, it is recommended that the sample size should be 5–10 times the number of items in the scale (11–14). In this study, based on the relevant literature, it was aimed to reach a sample of 300 participants. A total of 308 nurses agreed to participate in the study. After data screening, 300 questionnaires with complete responses were included in the final analysis, corresponding to a response rate of 97.4%. Since the draft scale consisted of 30 items, the sample size met the recommended criterion of at least 10 participants per item.

Data Collection Tools

The "Personal Information Form" and the "Draft Clinical Patient Behavior Scale" were used as data collection tools in the study.

Personal Information Form:

It includes 6 items regarding the personal and professional characteristics of the participants, which are thought to be related to the research variables.

Draft Clinical Patient Behavior Scale (CPBS):

The draft scale, created as a result of a comprehensive literature review, consists of 30 items written in the present tense and is structured as a 5-point Likert type (1: Strongly Disagree, 2: Disagree, 3: Neutral, 4: Agree, 5: Strongly Agree). The draft scale was theoretically structured to represent five domains: Compliance with Treatment and Care Instructions (CTCI), Cooperation and Professional Respect (CPR), Communication and Demand Balance (CDB), Compliance with Behavioral and Service Rules (CBSR), and Professional Boundaries and Authority Awareness (PBAA). Items 16, 17, 18, 20, 21, 22, 23, 24, 26, 27, 28, 29, and 30
are reverse scored (Figure 1).

Data Collection

Data were collected face-to-face using a cross-sectional design in 2026.

Data Analysis

For statistical analysis, descriptive data analysis, Cronbach's alpha reliability analysis, exploratory factor analysis (EFA), and confirmatory factor analysis (CFA) were applied. Statistical analysis findings were obtained using R software (R Core Team, 2023). Data were collected once from the sample group, and no test–retest analysis was performed due to the cross-sectional design of the study.

Ethical Considerations

Approval was obtained from the ethics committee of

Clinical Patient Behavior Scale (CPBS)

Respondent: Healthcare professionals (nurses)
Response type: 5-point Likert scale
1 = Strongly disagree
2 = Disagree
3 = Undecided
4 = Agree
5 = Strongly agree

Items
1. The patient complies with mobilization instructions promptly and appropriately.
2. The patient cooperates with the nurse during the care process.
3. The patient uses respectful language in communication with the nurse.
4. The patient fully complies with postoperative care instructions.
5. The patient adapts to the care process without needing reminders.
6. The patient acts in accordance with the nurse's directions.
7. The patient acts in accordance with medication and pain management instructions.
8. The patient expresses their needs in an appropriate time and manner.
9. The patient avoids behaviors that may disrupt the care process.
10. The patient respects the nurse's professional decisions.
11. The patient follows the given care instructions correctly and regularly.
12. The patient communicates their requests taking care priorities into account.
13. The patient behaves in accordance with ward rules.
14. The patient exhibits an attitude that accepts the nurse's role in the care process.
15. The patient distinguishes between urgent and routine requests and communicates them.
16. The patient avoids following the given instructions. (Reverse)
17. The patient makes requests to the nurse that are outside the scope of care. (Reverse)
18. The patient uses bossy or condescending language in communication. (Reverse)
19. The patient exhibits similar attitudes towards the doctor and nurse.
20. The patient is more demanding in communication with the nurse compared to the doctor. (Reverse)
21. The patient interferes with the treatment plan. (Reverse)
22. The patient adopts a hotel/accommodation approach without considering ward rules and the hospital environment. (Reverse)
23. The patient requests to smoke despite ward rules. (Reverse)
24. The patient makes requests regarding alcohol consumption in the hospital environment. (Reverse)
25. The patient accepts the professional role and responsibility boundaries of the nurse.
26. The patient expresses problems related to the hospital system by holding the nurse respon-sible. (Reverse)
27. The patient uses the amount of payment made as justification for requesting privileges. (Reverse)
28. The patient exhibits a persistent attitude regarding issues outside the nurse's authority. (Reverse)
29. The patient requests personal contact information from the nurse. (Reverse)
30. The patient makes individual requests that are outside the scope of care. (Reverse)

Sub-Dimensional Structure

Sub-dimension	Number of items	Item No.
Complience to Treatment/Care Instructions	8	1,4,6,7,11,16*,21*
Cooperation and Professional Respect	6	3,8,10,14,19,20*
Communication and Demand Balance	6	5,9,12,15,18*,22*
Compliance with Code of Conduct and Service	4	13,17*,23*,24*
Professional Boundaries and Authority Awareness	6	25,26*,27*,28*,29*,30*
Total	30	

Reversed items: 16,17,18,20,21,22,23,24,26,27,28,29,30
Scoring
- Minimum score: 30
- Maximum score: 150
- Reversed items are reverse coded: 1 ↔ 5, 2 ↔ 4, 3 = 3

Figure 1. Clinical Patient Behavior Scale (CPBS)

a Necmettin Erbakan University (decision number 2026-1393) to conduct the study. During the implementation of the questionnaire, written and verbal informed consent was obtained from the participants, and data were collected from those who agreed to participate.

Limitations of the Study

Since the study is a scale development study conducted in Turkish society, it needs to be tested in different professional groups and cultures before being used.

RESULTS

Participant Characteristics

Of the total 300 nurses participating in the study, 83% (n:166) were female and 17% (n:34) were male, with a mean age of 30.52 (SD=5.43). Of the participants, 89% had a bachelor's degree and 11% had a postgraduate degree; 68% worked in surgical units and 32% in internal medicine units. Additionally, when participants' experience was examined, it was determined that they had been working as nurses for an average of 8.52 (SD=5.37) years and had been working in the same hospital for an average of 7.10 (SD=4.58) years.

Descriptive Statistics and Item Analyses of the Scale

When the lowest and highest scores obtained from the scale items, as well as the mean scores and standard deviations of the items, were examined across the entire dataset, it was observed that the scores ranged between 1 and 5. The highest mean score in the scale was 4.00 (SD=0.84) for the item "The patient complies with mobilization instructions in a timely and appropriate manner," while the lowest mean score was 2.52 (SD=1.3) for the item "The patient makes requests from the nurse outside the scope of care."

For the reliability analysis of the scale, when the item-total score correlations of all items were examined, it was found that the item-total correlation values ranged between 0.59 and 0.89 and were statistically significant ($p<0.001$). In addition, the Cronbach's alpha value of the scale was determined to be 0.92,

Table 1. Results of Exploratory Factor Analysis of the Draft Clinical Patient Behavior Scale (CPBS) (N:300)

Item No	Compliance to Treatment/Care Instructions	Cooperation and Professional Respect	Communication and Demand Balance	Compliance with Code of Conduct and Service	Professional Boundaries and Authority Awareness
N1	0.729				
N2	0.774				
N4	0.769				
N6	0.706				
N7	0.702				
N11	0.692				
N16	0.692				
N21	0.694				
N3		0.749			
N8		0.611			
N10		0.687			
N14		0.696			
N19		0.692			
N20		0.691			
N5			0.624		
N9			0.645		
N12			0.555		
N15			0.707		
N18			0.617		
N22			0.667		
N13				0.632	
N17				0.621	
N23				0.708	
N24				0.718	
N25					0.675
N26					0.721
N27					0.703
N28					0.698
N29					0.745
N30					0.744
Reported Variance Ratio	16.400	15.230	12.000	13.840	15.900

KMO = 0.939 X2(476) = 8360.480; Bartlett Sphericity Test (p) < 0.001

Total Explained Variance Ratio = 73.37

Table 2. Draft Clinical Patient Behavior Scale (CPBS) Adherence Indices

Chi-square	df	GFI	AGFI	CFI	TLI	NNFI	RMSEA
449.281	421	0.960	0.955	0.992	0.991	0.991	0.016

df: Degrees of freedom, GFI: Goodness of Fit Index, AGFI: Adjusted Goodness of Fit Index, CFI: Comparative Fit Index, TLI: Unscaled Fit Index, NNFI: Unscaled Fit Index, RMSEA: Root Mean Squared Error of Estimation

Table 3. Confirmatory Factor Load Statistics for the Draft Clinical Patient Behavior Scale (CPBS).

Sub-dimension/Item No	B	SH	z	Std (B)	p
Treatment and Care					
Compliance to Treatment/Care Instructions					
N1	1			0.562	<0.001
N2	0.954	0.069	13.919	0.492	<0.001
N4	0.936	0.069	13.735	0.501	<0.001
N6	0.715	0.037	19.531	0.617	<0.001
N7	0.766	0.038	20.069	0.659	<0.001
N11	1.180	0.079	15.048	0.596	<0.001
N16	0.930	0.043	21.737	0.775	<0.001
N21	0.911	0.041	20.708	0.610	<0.001
Cooperation and Professional Respect					
N3	0.848	0.040	20.940	0.700	<0.001
N8	0.812	0.044	16.242	0.602	<0.001
N10	0.825	0.043	20.708	0.654	<0.001
N14	0.749	0.036	20.405	0.714	<0.001
N19	0.876	0.044	19.636	0.608	<0.001
N20	0.998	0.088	15.736	0.608	<0.001
Communication and Demand Balance					
N5	0.828	0.040	18.550	0.632	<0.001
N9	1.183	0.079	15.048	0.594	<0.001
N12	1.202	0.080	14.906	0.620	<0.001
N15	1.002	0.071	13.002	0.518	<0.001
N18	0.930	0.043	21.737	0.775	<0.001
N22	0.715	0.037	19.531	0.617	<0.001
Behavioral and Service Compliance with Rules					
N13	1.496	0.093	16.138	0.713	<0.001
N17	0.947	0.069	13.735	0.503	<0.001
N23	1.285	0.083	15.4550	0.660	<0.001
N24	0.964	0.069	13.921	0.492	<0.001
Professional Boundaries and Authority Awareness					
N25	0.836	0.040	20.867	0.720	<0.001
N26	0.890	0.042	21.332	0.725	<0.001
N27	1411	0.091	15.495	0.624	<0.001
N28	1.409	0.091	15.545	0.623	<0.001
N29	0.886	0.043	20.704	0.694	<0.001
N30	0.556	0.034	16.439	0.470	<0.001

Table 4. Reliability Analysis Results

Scale and Sub-Dimensions	Cronbach's Alpha Values
Compliance to Treatment/Care Instructions	0.85
Cooperation and Professional Respect	0.83
Communication and Demand Balance	0.88
Compliance with Code of Conduct and Service	0.80
Professional Boundaries and Authority Awareness	0.88
Total	0.92

Table 5. Distribution of Draft Clinical Patient Behavior Scale (CPBS) Scores (N:300)

Item No	Average	SS	Med	Min-Max
N1 (The patient follows mobilization instructions in a timely and appropriate manner.)	4.00	0.84	4.00	1-5
N2 (The patient works collaboratively with the nurse throughout the patient care process.)	3.80	0.92	4.00	1-5
N3 (The patient uses respectful language in their communication with the nurse.)	2.97	1.05	3.00	1-5
N4 (The patient fully complies with postoperative care instructions (corset, dressing, drain, hygiene, etc.).)	3.81	0.81	4.00	1-5
N5 (The patient adapts to the care process without needing reminders.)	3.64	0.90	4.00	1-5
N6 (The patient complies with the nurse's instructions during patient care procedures.)	2.65	1.16	3.00	1-5
N7 (The patient follows the medication and pain management instructions.)	3.20	1.02	3.00	1-5
N8 (The patient expresses their needs in an appropriate time and manner.)	2.65	1.16	3.00	1-5
N9 (Avoids behaviors that could disrupt the patient care process.)	3.48	0.86	4.00	1-5
N10 (The patient respects the nurse's professional decisions.)	2.60	1.12	3.00	1-5
N11 (The patient follows the given care instructions correctly and regularly.)	3.48	0.86	4.00	1-5
N12 (The patient communicates their requests, taking care priorities into account.)	2.54	1.10	2.00	1-5
N13 (The patient behaves in accordance with the service rules.)	3.55	0.89	4.00	1-5
N14 (The patient demonstrates an attitude that acknowledges the nurse's role and authority in the care process.)	2.90	1.16	3.00	1-5
N15 (The patient reports their urgent and routine requests, distinguishing between them.)	2.88	1.11	3.00	1-5
N16 (The patient avoids following the given instructions. (Reverse item))	3.48	0.86	4.00	1-5
N17 (The patient makes requests to the nurse that are outside the scope of care. (Reverse item)	2.52	1.30	2.00	1-5
N18 (Uses authoritarian or condescending language in patient communication. (Reverse item))	3.20	1.02	3.00	1-5
N19 (The patient displays similar attitudes towards the doctor and nurse.)	3.73	0.84	4.00	1-5
N20 (Patients are more demanding in their communication with nurses than with doctors. (Reverse item))	3.09	1.10	3.00	1-5
N21 (The patient exhibits behavior that interferes with the treatment plan. (Reverse item))	3.07	1.10	3.00	1-5
N22 (The patient adopts a hotel/accommodation approach without considering service rules and the hospital environment. (Reverse item))	3.47	0.94	4.00	1-5
N23 (The patient insists on smoking despite the service rules. (Reverse item))	3.56	0.82	4.00	1-5
N24 (The patient makes requests regarding alcohol consumption in the hospital setting. (Reverse item))	3.77	0.92	4.00	1-5
N25 (The patient accepts the nurse's professional role and the limits of her responsibilities.	3.13	1.07	3.00	1-5
N26 (The patient expresses their concerns about the hospital system, holding the nurse responsible. (Reverse item))	2.93	1.18	3.00	1-5
N27 (The patient uses the amount of payment made as justification for claiming preferential treatment. (Reverse item))	3.43	1.02	4.00	1-5
N28 (The patient is persistent in matters outside the nurse's area of authority. (Reverse item))	2.87	1.11	3.00	1-5
N29 (The patient requests personal contact information from the nurse. (Reverse item))	2.65	1.16	3.00	1-5
N30 (The patient makes individual requests that fall outside the scope of care. (Reverse item)	2.93	1.18	3.00	1-5
Total Score	95.98	31.58	101	30-150

and no item was found that would significantly increase the alpha coefficient.

Psychometric Evaluation of the Clinical Patient Behavior Scale

Content and Language Validity:

For the content and language validity of the 30-item draft scale, expert opinions from 9 specialists were obtained using the Davis technique. Experts were asked to evaluate language validity as "Not appropriate (1), Slightly appropriate (2), Appropriate (3), Very appropriate (4)" and content validity as "Not appropriate (1), Appropriate (2)." Based on the evaluations and suggestions from the experts, 4 items were removed from the draft scale and 4 new items were added by the researchers, resulting in a final draft scale of 30 items. As a result of the evaluation of expert opinions, the Content Validity Index (CVI) values of the 30 items ranged between 0.80 and 1.00. Since there were no items with a CVI value below 0.80, the scale took its final form with 30 items.

Construct Validity

Exploratory Factor Analysis (EFA):

The EFA results are presented in Table 1. To determine the factor structure of the scale, EFA was conducted using Principal Components Analysis and Varimax rotation techniques. Before performing EFA, the Kaiser-Meyer-Olkin (KMO) test was conducted to assess the suitability of the sample size for factor analysis, and the KMO value was found to be 0.939. In addition, when the results of Bartlett's test of sphericity were evaluated, the chi-square value was found to be significant ($\chi^2(476)=8360.480$, $p<0.01$) (Table 1).

After confirming the suitability of the data for factor analysis, EFA was performed using the Principal Components Analysis method to examine the factor structure of the scale. Varimax rotation was applied, and the results indicated a five-factor structure (Table 1).

It was determined that the factor loadings of the items ranged between 0.624 and 0.774. Based on the content of the items under each factor, the first factor (n=8) was named "Complience to Treatment/Care Instructions"; the second factor (n=6) "Cooperation and Professional Respect"; the third factor (n=6) "Communication and Demand Balance"; the fourth factor (n=4) "Compliance with Code of Conduct and Service"; and the fifth factor (n=6) "Professional Boundaries and Authority Awareness." The explained variance ratios were 16.40% for the first factor, 15.23% for the second factor, 12% for the third factor, 13.84% for the fourth factor, and 15.90% for the fifth factor, with a total explained variance of 73.37% (Table 1).

Confirmatory Factor Analysis (CFA):

For construct validity, CFA was conducted using the Diagonally Weighted Least Squares (DWLS) estimation method. Table 2 presents the fit indices of the CFA results for the developed Clinical Patient Behavior Scale, including Chi-square, GFI, AGFI, CFI, TLI, IFI, and RMSEA values. The CFA loading statistics of the scale are presented in Table 3.

Reliability Analysis:

Cronbach's alpha coefficient was examined as an indicator of internal consistency, and the total scale Cronbach's alpha value was found to be 0.92. For the subdimensions, Cronbach's alpha values were determined as 0.85 for Complience to Treatment/Care Instructions, 0.83 for Cooperation and Professional Respect, 0.88 for Communication and Demand Balance, 0.80 for Compliance with Code of Conduct and Service, and 0.88 for Professional Boundaries and Authority Awareness (Table 4).

In addition, Composite Reliability (CR) and Average Variance Extracted (AVE) values were calculated to provide further evidence of reliability and convergent validity. CR values ≥0.70 and AVE values ≥0.50 were considered acceptable indicators of adequate reliability and construct validity.

Item Analyses:

The analysis results of participants' responses to the scale items are presented in Table 5.

The three items with the highest mean scores were respectively: "The patient complies with mobilization instructions in a timely and appropriate manner" (m1=4.00), "The patient fully complies with postoperative care instructions (corset, dressing, drain, hygiene, etc.)" (m4=3.81), and "The patient cooperates with the nurse during the care process" (m2=3.80).

The three items with the lowest mean scores were respectively: "The patient makes requests from the nurse outside the scope of care" (m17=2.52), "The patient communicates requests by considering care priorities" (m12=2.54), and "The patient expresses needs at an appropriate time and manner" (m8=2.65) (Table 5).

DISCUSSION

Conceptual Foundation of Patient Compliance in Nursing

Patient compliance with nursing instructions is grounded in the broader theoretical framework of treatment adherence. The World Health Organization defines adherence as the extent to which a person's behavior corresponds with agreed recommendations from a healthcare provider (1). Contemporary models conceptualize adherence as a multidimensional and dynamic process including initiation, implementation, and persistence (2). Variability in adherence behaviors across clinical populations further demonstrates that compliance is not a fixed trait but context-sensitive (3).

Improving adherence requires multifaceted strategies rather than single-component interventions (4). Communication quality has consistently been identified as a central determinant of adherence outcomes (5). Evidence from nursing communication research also indicates that effective interaction enhances patient understanding and cooperation (6). The multidimensional structure identified in the present study reflects these theoretical foundations.

The Nurse–Patient Relationship as a Determinant of Compliance

The findings reinforce the role of relational care in shaping compliance behaviors. Patients report that empathy, clarity, and active listening influence their willingness to follow care instructions (7). The nurse–patient relationship has been described as a dynamic and therapeutic interaction that affects

engagement and well-being (8).

Perceived caring behaviors are associated with improved cooperation and satisfaction (9), and relational dimensions in nursing have long been emphasized in the literature (10). Conversely, negative experiences within care environments may undermine compliance. The concept of "othering" represents a relational barrier that can weaken trust (11). Patients may also experience suffering caused by care practices, which negatively impacts engagement (12).

Professional identity and clarity of the nursing role influence communication style and care consistency (13). Patient-centred care frameworks further emphasize shared decision-making and partnership as core elements in improving adherence-related outcomes (14). These perspectives align with the relational dimensions identified in the developed scale.

Psychometric Strength and Methodological Rigor

The scale development process adhered to established psychometric principles. Theoretical grounding and systematic item development were ensured in accordance with recommended scale construction procedures (15). Best practices for scale validation emphasize comprehensive content validation and construct testing (16).

Content validity procedures were conducted using the Content Validity Index framework (17). Construct validity analyses were performed in line with structural equation modeling guidelines (18) and multivariate data analysis standards (19). Reliability interpretations were based on classical psychometric criteria (20) and contemporary health measurement recommendations (21). The overall research design was structured according to established clinical research methodology (22).

Clinical Implications

The results indicate that patient compliance with nursing instructions should be conceptualized as a relational and system-level phenomenon rather than solely an individual patient behavior.

Strengthening communication competencies among nurses may enhance adherence outcomes (5,6). Structured communication training, reflective practice modules, and patient-centred care integration into nursing curricula may improve instructional effectiveness (14).

Healthcare institutions should also recognize the influence of professional identity and supportive work environments on care delivery (13). Preventing negative relational experiences, including marginalization or relational distancing (11,12), may foster trust and cooperation.

The developed scale offers a structured tool for evaluating compliance within nursing contexts. It may be used to assess communication-based interventions, quality improvement initiatives, and patient-centred care programs. Routine compliance assessment may contribute to improved treatment effectiveness and overall care quality (1).

Theoretical Implications

This study contributes to the theoretical understanding of compliance by positioning it within the relational domain of nursing practice. While adherence has traditionally been conceptualized as an individual behavioral construct (1,3), contemporary models highlight its interactive and process-oriented nature (2).

The findings suggest that compliance emerges from the interplay between communication quality, professional identity, and care environment dynamics. By operationalizing compliance within a structured nursing-specific framework, the study expands adherence theory into the context of nursing instruction and relational care.

The scale provides an empirical foundation for future theoretical refinement, including exploration of mediating variables such as trust, perceived caring, and professional role clarity.

Study Limitations

Several limitations should be acknowledged. First, both EFA and CFA were conducted on the same sample, which may limit the generalizability of the factor structure and increase the risk of overfitting. Future studies should validate the model using independent and larger samples.

Second, the data were based solely on nurse-reported evaluations, which may introduce subjective bias and common method variance. Incorporating patient-reported outcomes and observational data would strengthen the robustness of the findings.

Third, the study was conducted in a single institution, limiting external validity. Replication across different healthcare settings and cultural contexts is recommended.

Fourth, test–retest reliability was not assessed, preventing evaluation of temporal stability. Future longitudinal studies are needed to address this limitation.

Finally, some items may reflect context-specific behaviors influenced by institutional norms and cultural expectations, which should be considered in cross-cultural applications of the scale (16,21).

The findings suggest that patient behavior in clinical settings cannot be reduced to a single dimension such as adherence. Instead, it reflects a complex interactional process shaped by communication patterns, role expectations, and contextual factors within the healthcare environment. This multidimensional perspective distinguishes the CPBS from traditional adherence-focused instruments and supports its relevance for nursing practice.

Unlike traditional adherence-focused frameworks, the present study conceptualizes patient behavior as a broader multidimensional construct that extends beyond compliance to include communication patterns, relational dynamics, and professional boundary awareness.

Although Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA) were conducted on the same dataset, this approach is considered acceptable in preliminary scale development studies. However, it may increase the risk of model overfitting. Therefore, the findings should be interpreted as initial evidence of construct validity, and future studies are strongly recommended to replicate the factor structure using independent samples.

Exploratory Factor Analysis was conducted using Principal

Components Analysis (PCA) with Varimax rotation to identify the underlying structure. Although PCA is primarily a data reduction technique, it has been widely used in early-stage scale development studies. Future research may benefit from using common factor methods such as Principal Axis Factoring to further validate the latent structure.

In addition to internal consistency, construct validity was supported by strong factor loadings and excellent model fit indices. However, convergent and discriminant validity should be further examined in future studies using external constructs. The inclusion of related measures such as patient adherence, communication quality, or patient engagement scales would strengthen the nomological validity of the instrument.

CONCLUSION

The CPBS provides a theoretically grounded and psychometrically supported tool for assessing patient behaviors in nursing contexts. The results should be considered as initial validation evidence. Further research is needed to establish cross-cultural validity, temporal stability, and predictive utility of the scale in diverse clinical settings.

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REVIEW

Medial and Lateral Meniscus Bucket Handle Tears: A Comprehensive Review

Medial ve Lateral Menisküs Kova Sapı Yırtıkları: Kapsamlı Bir Derleme

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ABSTRACT
Bucket-handle tears represent a distinct and clinically significant subgroup of meniscal injuries characterized by displacement of a longitudinally torn meniscal fragment into the intercondylar notch. These lesions commonly produce mechanical symptoms, including knee locking, restricted range of motion (ROM), and acute functional impairment, often necessitating prompt surgical intervention. Although medial bucket-handle tears are encountered more frequently, lateral bucket-handle tears pose unique diagnostic and therapeutic challenges because of their stronger association with acute trauma and anterior cruciate ligament injuries. Accurate diagnosis relies heavily on magnetic resonance imaging (MRI), where classic findings such as the double posterior cruciate ligament sign, absent bow-tie sign, and fragment-in-notch sign facilitate detection. Current treatment strategies emphasize meniscal preservation through repair rather than meniscectomy, given the critical role of the meniscus in load transmission, joint stability, and long-term cartilage preservation. Surgical decision-making should consider tear chronicity, reducibility, tissue quality, vascular zone involvement, and concomitant procedures such as anterior cruciate ligament reconstruction. Differences between medial and lateral bucket-handle tears influence repair techniques, healing potential, and postoperative rehabilitation protocols. This comprehensive review summarizes the current evidence regarding the epidemiology, pathomechanics, clinical presentation, imaging characteristics, treatment strategies, and outcomes of medial and lateral bucket-handle meniscal tears. By emphasizing the anatomical and biomechanical distinctions between these entities, this review aims to provide a practical framework for optimized diagnosis, individualized treatment planning, and improved clinical outcomes in patients with bucket-handle meniscal injuries.

Keywords: Bucket handle tear, meniscus, medial meniscus, lateral meniscus, meniscal repair, knee arthroscopy

ÖZET
Kova sapı menisküs yırtıkları, longitudinal menisküs yırtığının bir parçasının interkondiler çentiğe yer değiştirmesi ile karakterize, klinik açıdan önemli bir menisküs yaralanması alt grubunu oluşturur. Bu lezyonlar sıklıkla diz kilitlenmesi, hareket kısıtlılığı ve akut fonksiyon kaybı ile seyreder ve çoğu zaman cerrahi müdahale gerektirir. Medial kova sapı yırtıkları daha sık görülmekle birlikte, lateral kova sapı yırtıkları genellikle akut travma ve ön çapraz bağ yaralanmaları ile daha yakın ilişkilidir ve tanı ile tedavi açısından özgün zorluklar barındırır. Tanıda manyetik rezonans görüntüleme (MRG) temel rol oynamakta olup, double posterior cruciate ligament bulgusu, bow-tie kaybı ve interkondiler çentikte fragman bulgusu gibi klasik işaretler yol göstericidir. Tedavi yaklaşımında güncel eğilim, menisküsün biyomekanik ve kondral koruyucu rolü nedeniyle menisektomi yerine menisküs onarımını ön plana çıkarmaktadır. Cerrahi karar sürecinde yırtığın süresi, redükte edilebilirliği, doku kalitesi, vasküler zon yerleşimi ve eşlik eden cerrahiler dikkate alınmalıdır. Medial ve lateral kova sapı yırtıkları arasındaki anatomik ve biyomekanik farklar, cerrahi teknik seçimi, iyileşme potansiyeli ve rehabilitasyon protokollerini doğrudan etkilemektedir. Bu derleme, medial ve lateral menisküs kova sapı yırtıklarının epidemiyolojisi, patomekaniği, klinik bulguları, görüntüleme özellikleri, tedavi stratejileri ve prognozunu güncel literatür ışığında bütüncül olarak değerlendirmeyi amaçlamaktadır.

Anahtar Kelimeler: Kova sapı yırtığı, menisküs, medial menisküs, lateral menisküs, menisküs onarımı, diz artroskopisi

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INTRODUCTION

The menisci are essential fibrocartilaginous structures that play a critical role in knee joint biomechanics by contributing to load transmission, shock absorption, joint stability, lubrication, and proprioception (1–3). Disruption of meniscal integrity alters tibiofemoral contact mechanics and has been consistently associated with accelerated cartilage degeneration and the development of early osteoarthritis (4,5). Bucket-handle tears constitute a clinically important subgroup of meniscal injuries. They are defined as displaced longitudinal tears in which a central fragment of the meniscus is displaced into the intercondylar notch, often resulting in mechanical knee locking and limitation of extension (6,7). Bucket-handle tears account for approximately 10–26% of meniscal injuries and frequently require surgical treatment because of persistent mechanical symptoms (8).

Medial bucket handle tears are more commonly encountered, largely attributed to the lower mobility and stronger capsular attachments of the medial meniscus (9). In contrast, lateral bucket handle tears are more frequently associated with acute traumatic events and concomitant anterior cruciate ligament (ACL) injuries, and may present with subtler clinical findings (10,11). Despite sharing a similar morphological pattern, medial and lateral bucket handle tears differ substantially in terms of injury mechanism, reducibility, tissue quality, vascular supply, and healing potential (12). Historically, bucket handle tears were predominantly treated with partial or subtotal meniscectomy to rapidly alleviate mechanical symptoms. However, long-term follow-up studies have demonstrated that meniscectomy significantly increases joint contact pressures and is associated with a higher risk of radiographic and symptomatic osteoarthritis (4,13). These findings have contributed to a paradigm shift favoring meniscal preservation, with repair now favored whenever technically and biologically feasible. Advances in arthroscopic techniques, repair devices, and biological augmentation have expanded the indications for meniscal repair, even in complex and displaced tear patterns such as bucket handle lesions (14,15). Nevertheless, successful repair remains technically demanding and is influenced by several factors, including tear chronicity, tissue quality, vascular zone involvement, and the presence of concomitant procedures such as ACL reconstruction (16,17).

Timely and accurate preoperative diagnosis is essential to optimize surgical outcomes. Magnetic resonance imaging (MRI) remains the gold standard for detecting bucket handle tears, with classic signs such as the double posterior cruciate ligament sign, absent bow-tie sign, and fragment-in-notch sign commonly described (18,19). However, diagnostic pitfalls persist, particularly in lateral bucket handle tears and in cases with associated ligamentous injuries, potentially leading to delayed treatment and reduced reparability (20). Despite their clinical importance, the literature on bucket handle meniscal tears remains fragmented, with many studies focusing on isolated aspects such as imaging features or surgical techniques. Comprehensive reviews that integrate diagnostic strategies, treatment decision-making, and prognostic factors-while explicitly addressing differences between medial and lateral bucket handle tears-are limited. Therefore, an updated and holistic synthesis of current evidence is warranted. The purpose of this review is to provide a comprehensive evaluation of medial and lateral meniscus bucket handle tears, focusing on epidemiology, pathomechanics, clinical presentation, imaging characteristics, treatment strategies, and outcomes. Emphasis is placed on anatomical and biomechanical distinctions between medial and lateral lesions to support individualized clinical decision-making and improve patient outcomes.

Definition and Classification

A bucket handle meniscal tear is classically defined as a displaced longitudinal tear in which a central fragment of the meniscus is detached and displaced toward the intercondylar notch while remaining attached at its anterior and posterior horns (21,22). This displacement produces the characteristic "handle-like" configuration, from which the injury derives its name, and frequently results in mechanical knee symptoms such as locking, catching, or loss of full extension. Bucket handle tears differ fundamentally from simple longitudinal meniscal tears due to their unstable and displaced nature. While nondisplaced longitudinal tears may remain asymptomatic or minimally symptomatic, bucket handle tears typically cause acute functional impairment and often require urgent surgical intervention (23). The displaced fragment may intermittently reduce or remain permanently incarcerated within the intercondylar notch, influencing both clinical presentation and reparability. From an anatomical perspective, bucket handle tears most commonly involve the medial meniscus, particularly the posterior horn and midbody regions (11). This predominance is attributed to the relative immobility of the medial meniscus, its firm capsular attachments, and its role as a secondary stabilizer in the anterior cruciate ligament–deficient knee (24). In contrast, lateral bucket handle tears occur less frequently but are strongly associated with acute rotational trauma and concomitant ACL injuries, often presenting in younger and more athletic populations (25).

Several classification approaches have been proposed to better characterize bucket handle tears and guide treatment decisions. One commonly used method categorizes tears based on reducibility into reducible and irreducible bucket handle tears. Reducible tears can be anatomically repositioned during arthroscopy, whereas irreducible tears are often associated with chronicity, deformation of the fragment, synovial scarring, or poor tissue quality, limiting repair options (26). Another clinically relevant classification considers tear chronicity, typically divided into acute and chronic lesions. Acute bucket handle tears, usually defined as those treated within six weeks of injury, demonstrate higher rates of successful reduction and healing following repair. Chronic tears, by contrast, are more likely to exhibit plastic deformation, fraying, and compromised vascularity, reducing the likelihood of successful meniscal preservation (27). Bucket handle tears may also be classified according to vascular zone involvement, including red–red, red–white, and white–white zones. Tears involving the peripheral vascularized zones show superior

healing potential and are more amenable to repair, whereas centrally located tears carry a higher risk of repair failure (28). This classification remains particularly important when selecting repair techniques and counseling patients regarding prognosis.

Finally, bucket handle tears should be distinguished from other displaced meniscal lesions, such as flap tears, parrot-beak tears, and meniscal root tears, which differ in biomechanical consequences and treatment strategies (29). Accurate classification of bucket handle tears is therefore essential for appropriate surgical planning, prognostic assessment, and comparison of outcomes across studies.

EPIDEMIOLOGY AND MECHANISM OF INJURY

Bucket handle tears account for approximately 10–26% of all meniscal tears and represent one of the most common causes of a mechanically locked knee (30). They predominantly affect young and middle-aged adults, with a higher incidence reported in males, likely reflecting greater exposure to high-demand occupational and sporting activities (31). Athletic populations, particularly those involved in pivoting sports such as soccer, basketball, and skiing, demonstrate an increased risk of bucket handle meniscal injuries (32). From an epidemiological standpoint, the medial meniscus is involved in the majority of bucket handle tears, with reported medial-to-lateral ratios ranging from 2:1 to 4:1 (11). This disparity is attributed to fundamental anatomical and biomechanical differences between the medial and lateral menisci. The medial meniscus is more firmly attached to the joint capsule and medial collateral ligament, resulting in reduced mobility and increased susceptibility to shear forces during rotational loading (33). Lateral bucket handle tears, although less frequent, exhibit a distinct epidemiological profile. They are more commonly observed in younger patients and are strongly associated with acute traumatic events, particularly in the setting of anterior cruciate ligament (ACL) rupture (34,35). Several studies have demonstrated that lateral bucket handle tears are disproportionately represented in acute ACL-injured knees, suggesting a shared injury mechanism involving high-energy rotational forces and anterior tibial translation (36).

The mechanism of injury in bucket handle tears typically involves a combination of axial loading, knee flexion, and rotational stress. In medial bucket handle tears, injury often occurs during a twisting movement on a flexed knee with the foot planted, producing excessive posterior horn loading and longitudinal fiber disruption (37). In contrast, lateral bucket handle tears are more frequently associated with acute pivot-shift–type mechanisms, where rapid internal rotation of the femur on a relatively fixed tibia leads to sudden meniscal displacement (37). Chronicity also plays a key role in the epidemiological characterization of bucket handle tears. Medial bucket handle tears are more likely to become chronic due to intermittent reduction of the displaced fragment and delayed presentation, particularly in patients without dramatic acute trauma (27,38). Conversely, lateral bucket handle tears often present acutely with pronounced mechanical symptoms, prompting earlier diagnosis and intervention (25). The relationship between bucket handle tears and ACL injury is of particular clinical importance. The medial meniscus functions as a secondary stabilizer in ACL-deficient knees, and repetitive instability episodes increase the risk of medial bucket handle tearing over time (24). Conversely, lateral meniscal bucket handle tears are frequently sustained at the time of initial ACL rupture, reflecting acute overload rather than chronic degeneration (39).

Understanding the epidemiological patterns and injury mechanisms of medial and lateral bucket handle tears is essential for accurate diagnosis, anticipation of associated injuries, and formulation of appropriate treatment strategies. These distinctions have direct implications for surgical timing, repair feasibility, and long-term prognosis.

CLINICAL PRESENTATION AND PHYSICAL EXAMINATION

Bucket handle meniscal tears typically present with acute mechanical symptoms driven by displacement of the torn fragment into the intercondylar notch. The hallmark clinical feature is a mechanically locked knee, most commonly manifesting as an extension block with inability to fully extend the knee (7). Patients frequently describe a sudden painful episode during twisting or pivoting, followed by catching, locking, or a sensation that "something is stuck inside the knee" (40). Pain is often localized to the involved compartment and may be accompanied by joint line tenderness. However, pain intensity can be variable and may be less prominent than the mechanical limitation, particularly when the displaced fragment remains incarcerated and the knee rests in a flexed position (41). Effusion is common, especially in acute traumatic tears, and when concomitant ligamentous injuries are present (34,35). In ACL-injured knees, symptoms related to instability may coexist or dominate the presentation, potentially obscuring the diagnosis of a bucket handle tear (25,36). Several features may help differentiate medial from lateral bucket handle tears clinically. Medial bucket handle tears more often occur in the setting of chronic or recurrent instability episodes (e.g., ACL deficiency) and may present after a period of intermittent symptoms before frank locking develops (24). Lateral bucket handle tears are more frequently associated with acute pivot-shift–type trauma and may present abruptly with prominent locking, particularly in young athletic patients with acute ACL rupture (39). Nevertheless, clinical overlap is substantial, and definitive compartmental differentiation based on symptoms alone is unreliable.

Physical examination begins with assessment of ROM, where a true mechanical block-most commonly preventing terminal extension-should raise suspicion for a displaced meniscal fragment (7). Joint line tenderness remains a widely used sign but has only moderate diagnostic accuracy when used in isolation (42). Traditional provocative tests such as the McMurray test may reproduce pain or a palpable click; however, reported sensitivity varies widely and performance is examiner-dependent (43). The Thessaly test was initially described as highly accurate, yet subsequent studies and meta-analyses have demonstrated more modest diagnostic performance and limited utility as a standalone test, particularly in acute settings

with pain and guarding (44). Therefore, while a combination of history and examination findings can raise suspicion, imaging-most commonly MRI-remains critical for confirmation and surgical planning. Importantly, clinicians should distinguish a true locked knee from "pseudo-locking," which may occur due to pain, effusion, or muscle spasm without a mechanical obstruction. Pseudo-locking is more typical of acute synovitis, loose bodies, or severe effusion and may improve with analgesia and aspiration, whereas mechanical locking due to a bucket handle tear typically persists until reduction or surgical treatment (45). In cases of suspected locked knee, early orthopedic evaluation is recommended because prolonged displacement may reduce reparability by promoting fragment deformation and synovial scarring (26,27).

Overall, clinical presentation and examination provide essential early recognition cues for bucket handle meniscal tears, but diagnostic certainty generally requires MRI. Recognizing patterns of mechanical locking and considering associated injuries-particularly ACL ruptur-are key to timely management and optimal outcomes.

Imaging Evaluation

Magnetic resonance imaging (MRI) is the imaging modality of choice for the evaluation of suspected bucket handle meniscal tears, owing to its high soft-tissue contrast resolution and ability to visualize meniscal morphology, displacement, and associated intra-articular pathology (8,18). Accurate preoperative identification of a bucket handle tear is critical, as delayed diagnosis may result in chronic displacement, reduced reparability, and inferior clinical outcomes (26,27). Several classic MRI signs have been described to facilitate the diagnosis of bucket handle tears. The double posterior cruciate ligament (PCL) sign is one of the most well-known findings, occurring when a displaced meniscal fragment lies parallel and anterior to the intact PCL, mimicking a second ligamentous structure (Figure-1) (8,18). This sign is highly specific but relatively insensitive, as it is primarily observed in displaced medial meniscus tears and requires sufficient fragment size and orientation to be visualized (46). Another commonly reported finding is the absent bow-tie sign, which refers to the loss of the normal meniscal body appearance on consecutive sagittal images (19). In a normal knee, the meniscal body is visualized on at least two adjacent sagittal slices; absence of this configuration suggests meniscal displacement. Although sensitive, this sign is not specific to bucket handle tears and may be observed in other complex or macerated meniscal injuries (18,47).

Additional supportive signs include the fragment-in-notch sign, characterized by visualization of the displaced meniscal fragment within the intercondylar notch on coronal or axial images, and the anterior flipped meniscus sign, in which the fragment is displaced anteriorly toward the anterior horn (Figure-2)(18,19). Evaluation in multiple imaging planes is essential, as reliance on a single sign or plane increases the risk of misdiagnosis. MRI diagnosis of lateral bucket handle tears presents unique challenges. The greater mobility of the lateral meniscus, combined with its anatomical relationship to the popliteus tendon and hiatus, may allow partial reduction of the fragment during imaging, leading to false-negative findings (20). Moreover, lateral bucket handle tears are frequently associated with acute ACL rupture, hemarthrosis, and synovial reaction, which may obscure meniscal morphology and complicate interpretation (34,36). False-negative MRI examinations have been reported in up to 15–30% of bucket handle tears, particularly in the lateral compartment and in the acute post-injury setting (22,48). Conversely, false-positive interpretations may occur when normal variants, postoperative changes, or meniscofemoral ligaments are mistaken for displaced meniscal fragments (49). Therefore,

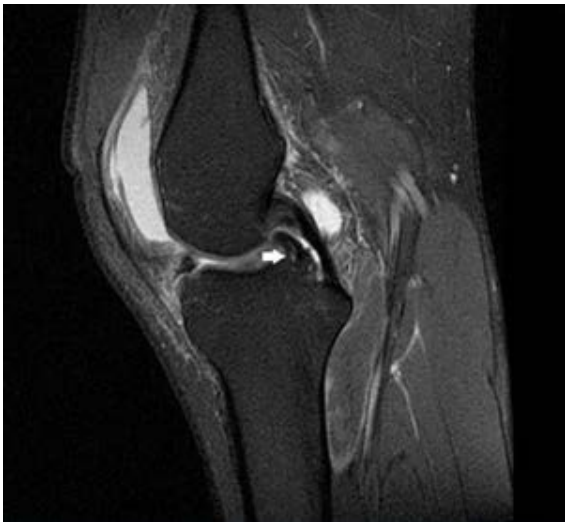

Figure 1. Double posterior cruciate ligament (Double PCL) sign on MRI

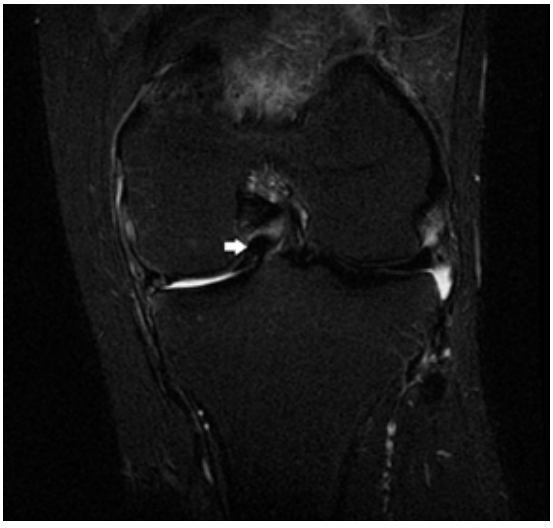

Figure 2. Coronal magnetic resonance imaging demonstrating a displaced medial meniscal fragment within the intercondylar notch.

MRI findings must always be interpreted in conjunction with clinical presentation and physical examination.

Advanced imaging techniques, including three-dimensional MRI sequences and higher-field-strength scanners, have demonstrated improved visualization of meniscal anatomy; however, their routine clinical superiority over standard protocols remains under investigation (50). Recently, artificial intelligence–assisted MRI interpretation has shown promise in meniscal tear detection, but its specific role in identifying displaced bucket handle tears has yet to be fully validated (51). In summary, MRI plays a pivotal role in the diagnosis and preoperative assessment of bucket handle meniscal tears. Familiarity with classic imaging signs, awareness of diagnostic pitfalls-particularly in lateral tears-and correlation with clinical findings are essential to optimize diagnostic accuracy and guide timely surgical management.

TREATMENT STRATEGIES

The primary goals in the treatment of bucket handle meniscal tears are relief of mechanical symptoms, restoration of meniscal anatomy, and preservation of long-term knee joint function. Because displaced bucket handle tears frequently result in a locked knee, surgical intervention is generally indicated, particularly in the presence of persistent mechanical block, pain, or functional limitation (7,26).

Indications for Surgery

Nonoperative management has a very limited role in bucket handle tears due to the unstable and displaced nature of the lesion. Conservative treatment may be considered only in rare cases where spontaneous reduction occurs, symptoms resolve completely, and imaging confirms a stable meniscal configuration (38). In most patients, however, delayed treatment increases the risk of chronic displacement, fragment deformation, and reduced reparability (26,27). Urgent arthroscopic intervention is recommended in cases of true mechanical locking to prevent irreversible meniscal damage and secondary chondral injury (7,13).

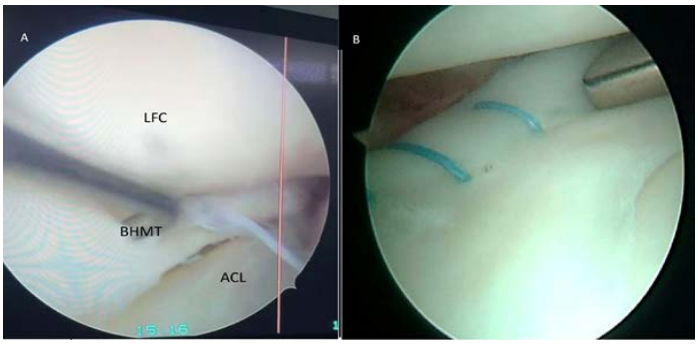

Figure 3. A. Lateral bucket handle meniscal tear arthroscopic image B. Arthroscopic image after meniscus repair (LFC : Lateral femoral condyl, ACL : Anterior cruciate ligament, BHMT : Bucket handle meniscal tear)

Meniscal Repair versus Meniscectomy

Current treatment paradigms strongly favor meniscal preservation whenever feasible. Numerous biomechanical and clinical studies have demonstrated that meniscectomy-particularly subtotal or total resection-leads to increased tibiofemoral contact pressures and a significantly higher risk of early osteoarthritis (4,13,52). Consequently, meniscal repair is preferred, especially in young and active patients.

Meniscal repair is generally indicated when the tear is:

- Reducible
- Located in the vascularized red–red or red–white zone
- Associated with good tissue quality
- Addressed in an acute or subacute setting (16,28)

Partial meniscectomy may be necessary in irreducible tears, severely degenerated tissue, chronic plastic deformation, or when stable fixation cannot be achieved despite adequate reduction (13,53).

Repair Techniques

Several arthroscopic repair techniques are available for bucket handle tears, including inside-out, outside-in, and all-inside methods (Figure-3). The inside-out technique remains the gold standard for many surgeons due to its strong fixation and versatility, particularly for large displaced fragments (14,15). All-inside devices offer reduced operative time and lower neurovascular risk, though concerns regarding implant-related complications and cost persist (54). Hybrid techniques combining inside-out sutures with all-inside devices are frequently employed to optimize fixation along the entire tear length (55).

Medial versus Lateral Considerations

Medial bucket handle tears are often more challenging to reduce due to chronicity and tissue stiffness, particularly in ACL-deficient knees (24). However, when successfully repaired-especially in conjunction with ACL reconstruction-healing rates are favorable (17,25). Lateral bucket handle tears, although less common, tend to be more acute and exhibit superior healing potential due to better vascularity and meniscal mobility (25,34). Repair success rates for lateral tears are generally higher, particularly when performed at the time of acute ACL reconstruction (25,39).

Role of Concomitant ACL Reconstruction

Concomitant ACL reconstruction has been shown to significantly enhance meniscal healing by improving joint stability and increasing intra-articular bleeding, which may promote biological repair (16,17). Therefore, combined procedures are often recommended when bucket handle tears coexist with ACL rupture. Overall, treatment strategies for bucket handle meniscal tears should be individualized, taking into account tear characteristics, patient factors, chronicity, and associated injuries, with a strong emphasis on meniscal preservation.

POSTOPERATIVE REHABILITATION

Postoperative rehabilitation after bucket handle meniscal repair aims to protect the repair construct, facilitate biological healing, restore range of motion (ROM), and enable safe return to function while minimizing the risk of re-tear. Rehabilitation

protocols vary widely in the literature, reflecting differences in tear patterns, repair techniques, concomitant procedures, and surgeon preference (56,57). Nevertheless, most contemporary approaches balance early controlled motion with protection from excessive shear and compressive loads across the repair site.

Weight-Bearing

Weight-bearing recommendations typically depend on tear location, fixation stability, and whether concomitant anterior cruciate ligament (ACL) reconstruction is performed. For isolated bucket handle repairs, many protocols advocate protected or partial weight-bearing for the first 2–4 weeks, progressing to full weight-bearing as tolerated by 4–6 weeks, often with the knee in a brace locked in extension during ambulation in the early phase (58,59). The rationale is to reduce posterior horn shear forces and limit deep flexion loading that may jeopardize suture integrity.

Range of Motion

Early controlled ROM is generally encouraged to reduce stiffness and prevent arthrofibrosis, particularly after locked-knee presentations. However, excessive flexion may increase meniscal extrusion and posterior horn stress. Consequently, many protocols limit flexion to 0–90° during the first 4–6 weeks, followed by gradual progression toward full flexion (60). Extension is commonly allowed early, as terminal extension typically imposes less shear stress on the meniscal repair compared with deep flexion positions.

Bracing

A hinged knee brace is frequently used in the early postoperative period, especially for displaced bucket handle repairs, to control ROM and maintain extension during ambulation. Bracing may be used for 4–6 weeks depending on stability, patient compliance, and associated procedures (15,58).

Strengthening and Functional Training

Quadriceps activation is initiated early using isometric exercises and closed-chain activities within protected ROM. Strengthening typically progresses from isometrics and straight-leg raises to closed-chain strengthening (e.g. mini-squats within limited flexion) and proprioceptive training after the early healing phase (57,61). High-load open-chain hamstring exercises and deep squatting are generally avoided early due to increased posterior horn strain.

Return to Sport

Return-to-sport decisions should be individualized, incorporating clinical examination, functional testing, and the presence of concomitant ACL reconstruction. For isolated meniscal repairs, running is often permitted around 10–12 weeks, while pivoting sports may be delayed until 4–6 months, depending on healing and neuromuscular recovery (62). When combined with ACL reconstruction, rehabilitation is primarily guided by ACL timelines, and return to pivoting sports is often delayed to 6–9 months or longer, based on strength symmetry and functional readiness (63).

Medial versus Lateral Considerations

Although evidence is limited, some clinicians advocate slightly more cautious progression for medial bucket handle repairs, particularly when chronicity or posterior horn involvement is prominent, due to potentially higher shear forces during daily activities (17). Lateral repairs, often performed in the acute setting with better tissue quality, may tolerate earlier progression, but robust comparative evidence remains insufficient. Therefore, rehabilitation should be tailored primarily to tear characteristics, fixation security, and associated injuries rather than laterality alone.

In summary, postoperative rehabilitation after bucket handle meniscal repair should follow a structured, criterion-based approach that emphasizes early controlled motion, protected loading, progressive strengthening, and individualized return-to-sport criteria. Close coordination between surgeon, physiotherapist, and patient is crucial to optimize healing and functional outcomes.

OUTCOMES AND PROGNOSIS

Clinical outcomes after bucket handle meniscal tears depend primarily on whether the meniscus is preserved, the biological environment of healing, and the presence of concomitant injuries-most notably anterior cruciate ligament (ACL) rupture. Across multiple cohorts, meniscal repair has consistently been associated with superior long-term joint preservation compared with meniscectomy, albeit with a higher short-term risk of reoperation due to re-tear or incomplete healing (13,23).

Repair Success and Failure Rates

Reported healing and success rates after arthroscopic repair of bucket handle tears vary due to heterogeneous definitions of "healing," differences in tear chronicity, repair techniques, and follow-up duration. In general, contemporary studies report clinical success rates commonly in the 70–90% range, particularly in acute, reducible tears with good tissue quality and peripheral vascular zone involvement (64). Failures most frequently occur within the first 1–2 years and are driven by recurrent displacement, suture failure, inadequate biological healing, or unrecognized instability (16,56).

Impact of Concomitant ACL Reconstruction

Concomitant ACL reconstruction is among the most influential prognostic factors. Combined procedures have been associated with higher healing rates and lower failure risk compared with isolated meniscal repair, likely due to restoration of stability and increased intra-articular bleeding that may enhance healing biology (17). Conversely, uncorrected ACL deficiency increases repetitive shear forces on the meniscus, which may predispose to repair failure, particularly for medial posterior horn lesions (25,27).

Medial versus Lateral Bucket Handle Tears

Although bucket handle tears share a common displaced longitudinal morphology, outcomes may differ by laterality. Lateral bucket handle tears are often repaired in the acute setting and may demonstrate favorable healing potential due to better mobility and vascular characteristics of the lateral meniscus, with several series reporting comparatively higher success rates (25,54). Medial bucket handle tears, particularly when chronic or occurring in ACL-deficient knees, may be more

difficult to reduce and may exhibit lower tissue compliance, potentially increasing the risk of incomplete healing or subsequent re-tear if stability is not addressed (24,27). Nonetheless, when medial tears are repaired promptly and/or combined with ACL reconstruction, clinical outcomes are generally good and joint-preserving compared with resection (17,27).

Meniscectomy and Osteoarthritis Risk

While partial meniscectomy reliably alleviates mechanical symptoms, substantial evidence links meniscal tissue loss to increased contact stresses and accelerated osteoarthritic change. This is especially relevant in bucket handle tears, where the temptation to resect a displaced fragment must be balanced against long-term cartilage preservation (5,13,52). Consequently, modern consensus emphasizes "save the meniscus" whenever feasible, particularly in young active patients (23,53).

Prognostic Factors

Key predictors of favorable outcome after bucket handle repair include: acute treatment, reducible tears, peripheral vascular zone involvement, good tissue quality, stable fixation, and correction of concomitant instability (e.g., ACL reconstruction) (6,16,27). Negative prognostic factors include chronicity with fragment deformation, poor meniscal tissue quality, central avascular location, high-grade chondral lesions, and persistent instability (27,30,52). In summary, outcomes after bucket handle meniscal tears are optimized when meniscal preservation is achieved under stable biomechanical conditions and within a biologically favorable window. Appreciating differences between medial and lateral lesions and addressing associated ACL pathology are central to improving healing rates and long-term joint health.

CONCLUSION

Bucket handle tears of the meniscus represent a distinct and clinically important subset of meniscal injuries due to their displaced morphology, propensity to cause mechanical knee locking, and frequent need for surgical intervention. Although medial bucket handle tears are encountered more commonly, lateral bucket handle tears pose unique diagnostic and therapeutic challenges, particularly because of their strong association with acute trauma and anterior cruciate ligament (ACL) rupture. Accurate and timely diagnosis is critical. Magnetic resonance imaging remains the cornerstone of preoperative evaluation, yet clinicians must be aware of its limitations-especially in lateral tears and acute injury settings-to avoid false-negative interpretations. Correlation of imaging findings with a characteristic clinical presentation of true mechanical locking is essential to guide early and appropriate management. Contemporary treatment strategies emphasize meniscal preservation whenever feasible. Arthroscopic repair of bucket handle tears has demonstrated favorable clinical outcomes and superior long-term joint preservation compared with meniscectomy, despite a higher short-term risk of reoperation. Factors such as tear chronicity, reducibility, tissue quality, vascular zone involvement, and correction of concomitant instability-most notably through ACL reconstruction-play decisive roles in determining healing and prognosis.

Medial and lateral bucket handle tears should not be regarded as a single entity. Differences in meniscal mobility, vascularity, injury mechanism, and association with ligamentous pathology influence reducibility, repair strategy, rehabilitation, and ultimate outcomes. Appreciating these distinctions allows for more individualized surgical decision-making and optimized patient counseling. Postoperative rehabilitation is a critical component of successful treatment and should follow a structured, criterion-based approach that balances protection of the repair with early controlled motion and progressive functional restoration. Failure patterns and complications are most often related to inadequate stabilization, poor biological healing environments, or unaddressed knee instability. In conclusion, optimal management of bucket handle meniscal tears requires an integrated understanding of anatomy, biomechanics, imaging, and surgical principles. A tailored approach that prioritizes meniscal preservation, addresses associated injuries, and accounts for medial–lateral differences is essential to improve healing rates, preserve joint health, and achieve durable long-term outcomes.

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CASE REPORT

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Invasive Squamous Cell Carcinoma Arising in Long-Standing Chromoblastomycosis Requiring Limb Amputation: A Case Report

Uzun Süreli Kromoblastomikoz Zemininde Gelişen İnvaziv Skuamöz Hücreli Karsinom: Olgu Sunumu

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ABSTRACT
Chromoblastomycosis is a chronic granulomatous infection of the skin and subcutaneous tissue caused by melanized fungi introduced through traumatic implantation. Although typically indolent, long-standing lesions may undergo malignant transformation into squamous cell carcinoma (SCC). We report a 77-year-old man with a 10-year history of a verrucous lesion on the right foot, which progressively enlarged and evolved into a non-healing ulcer. Histopathological examination revealed a well-differentiated invasive SCC infiltrating the reticular dermis, associated with dense fibrosis, chronic granulomatous inflammation, and numerous muriform bodies consistent with chromoblastomycosis. Due to extensive tissue destruction and functional impairment, lower limb amputation was performed. This case highlights the carcinogenic potential of chronic inflammatory dermatoses and underscores the critical role of histopathological evaluation and long-term surveillance in persistent chromoblastomycosis.

Keywords: Chromoblastomycosis, squamous cell carcinoma, chronic inflammation, malignant transformation.

ÖZET
Kromoblastomikoz, travmatik inokülasyon yoluyla deriye giren melanin içeren mantarların neden olduğu, deri ve subkutan dokunun kronik granülomatöz bir enfeksiyonudur. Genellikle yavaş seyirli olmakla birlikte, uzun süreli lezyonlar skuamöz hücreli karsinom (SCC) gelişimine dönüşebilir. Bu yazıda, sağ ayakta kronik verrüköz lezyonu bulunan ve zamanla iyileşmeyen ülser haline ilerleyen 77 yaşında bir erkek hasta sunulmaktadır. Histopatolojik incelemede, retiküler dermisi infiltre eden iyi diferansiye invaziv SCC; buna eşlik eden yoğun fibrozis, kronik granülomatöz inflamasyon ve kromoblastomikoz ile uyumlu çok sayıda muriform cisim saptanmıştır. Geniş doku destrüksiyonu ve fonksiyon kaybı nedeniyle alt ekstremite amputasyonu uygulanmıştır. Bu olgu, kronik inflamatuvar dermatozların karsinojenik potansiyelini vurgulamakta ve persistan kromoblastomikoz olgularında dikkatli histopatolojik değerlendirme ile uzun dönem izlem gerekliliğine dikkat çekmektedir.

Anahtar Kelimeler: Kromoblastomikoz, skuamöz hücreli karsinom, kronik inflamasyon, malign dönüşüm.

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INTRODUCTION

Chromoblastomycosis (CBM) is a chronic granulomatous infection of the skin and subcutaneous tissue caused by melanized fungi of the order Chaetothyriales, primarily Fonsecaea and Cladophialophora species (1,3). Infection occurs through traumatic inoculation of fungal elements and predominantly affects rural populations in tropical and subtropical regions (1–3). Clinically, CBM typically begins as papules or plaques that gradually progress into verrucous, hyperkeratotic, cauliflower-like lesions, which may persist for decades (2,3). Histopathologically, the disease is characterized by the presence of muriform (sclerotic) bodies within a granulomatous inflammatory background (1,3).

Chronic lesions frequently exhibit fibrosis and pseudoepitheliomatous hyperplasia, which may mimic squamous cell carcinoma (SCC) (3). Although uncommon, malignant transformation into SCC has been consistently reported in long-standing, untreated cases (4,5). Herein, we report a case of invasive SCC arising in chronic chromoblastomycosis requiring limb amputation.

CASE

A 77-year-old man presented with a 10-year history of a verrucous lesion on the right foot, with progressive enlargement and eventual evolution into a chronic, non-healing ulcer. The patient reported irregular use of oral antifungal therapy (itraconazole) over several years, without sustained clinical response. Given the progressive growth and ulceration, malignant transformation was suspected, and the patient underwent lower limb amputation. Gross examination revealed an extensive verrucous and ulcerated lesion involving the skin and underlying soft tissues (Fig. 1).

Figure 1. Gross specimen of a transtibial (below-knee) amputation showing an ulcerated and verrucous cutaneous lesion involving the foot in a background of long-standing chromoblastomycosis.

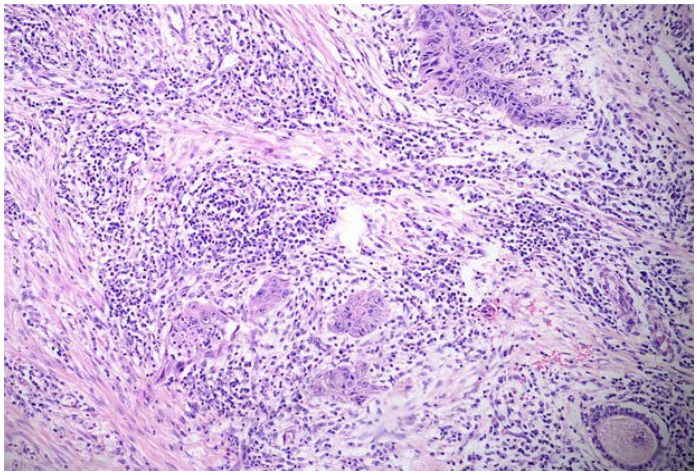

Figure 2. H&E, X20; Area of the neoplasm characterized by irregular squamous nests infiltrating the deep dermis with an associated inflammatory response.

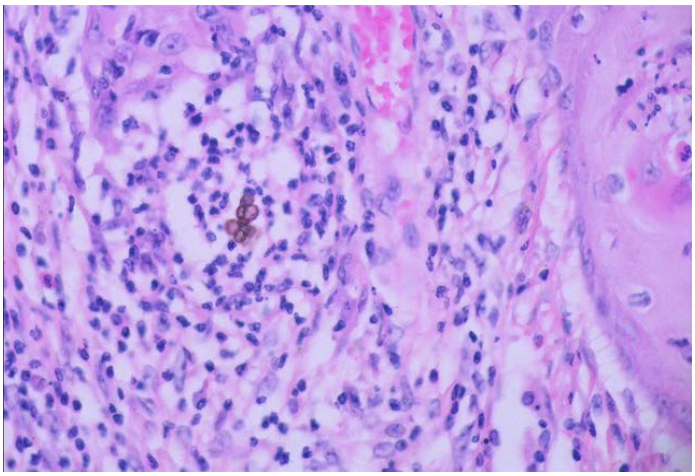

Figure 3. H&E, X40; Dermal granulomatous inflammation containing characteristic pigmented muriform (sclerotic) bodies, consistent with chromoblastomycosis.

Microscopic examination showed a well-differentiated invasive squamous cell carcinoma composed of irregular nests and cords infiltrating the reticular dermis to a depth of 4 mm, with prominent keratin pearl formation (Fig. 2). No angiolymphatic or perineural invasion was identified. The adjacent epidermis exhibited pseudoepitheliomatous hyperplasia. The dermis showed marked fibrosis, chronic granulomatous inflammation, and neutrophilic aggregates. Numerous pigmented muriform (sclerotic) bodies were identified within the inflammatory foci, confirming chromoblastomycosis (Fig. 3). Given the characteristic pigmentation of these fungal elements on hematoxylin–eosin staining, additional histochemical stains

were not required. Surgical margins, including skin, soft tissue, and bone, were free of carcinoma. After two years of follow-up, the patient remains disease-free. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

DISCUSSION

Malignant transformation of chromoblastomycosis into squamous cell carcinoma, although uncommon, is well documented, particularly in long-standing lesions. In a Brazilian series of seven cases, all patients developed SCC after more than 10 years of disease duration, frequently requiring amputation due to extensive local invasion (4). Similarly, individual reports have described malignant transformation in chronic, often inadequately treated infections, highlighting the role of persistent inflammation and suboptimal treatment (6). Chronic inflammation and sustained epithelial regeneration are key drivers of inflammation-associated carcinogenesis. In chromoblastomycosis, persistent infection creates a microenvironment characterized by fibrosis, immune dysregulation, and continuous epithelial proliferation, promoting genomic instability and ultimately facilitating malignant transformation (4).

Histopathological examination remains the cornerstone for distinguishing pseudoepitheliomatous hyperplasia from true invasive carcinoma. This reactive epithelial proliferation may closely resemble well-differentiated SCC, particularly in superficial or limited biopsy specimens, making the identification of dermal granulomatous inflammation and muriform bodies essential to avoid misdiagnosis (3). In contrast, true SCC is defined by destructive stromal invasion, cytologic atypia, and keratin pearl formation, as observed in the present case.

Clinically, features such as rapid growth, ulceration, or lack of response to therapy should raise suspicion for malignant transformation (4). The present case is consistent with prior reports and further supports the role of chronic inflammation, fibrosis, and sustained epithelial regeneration in carcinogenesis associated with chromoblastomycosis. Management remains challenging due to fibrosis and chronic tissue damage resulting from long-standing infection. In advanced cases, radical surgical interventions, including amputation, may be required (4,5). Early recognition and close surveillance of chronic chromoblastomycosis lesions are essential to prevent delayed diagnosis of malignant transformation.

DECLARATIONS

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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Author Contributions: *Concept: G.R, Design: J.V, Data Collection or Processing: P.C, Analysis or Interpretation: L.B, Literature Search: J.V, Writing: G.R.*

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CASE REPORT

Delayed Distal LAD Perforation After Elective PCI: Successful Treatment with Coil Embolization

Elektif PCI Sonrası Gecikmiş Distal LAD Perforasyonu: Koil Embolizasyonu ile Başarılı Tedavi

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ABSTRACT
Although uncommon, coronary artery perforation (CAP) during percutaneous coronary intervention (PCI) can lead to serious, potentially fatal outcomes.The risk of CAP is notably higher during complex coronary interventions, particularly in cases involving chronic total occlusions (CTO) and heavily calcified lesions. Early recognition and prompt management of life-threatening consequences such as cardiac tamponade are critical for improving patient outcomes and reducing mortality. Management strategies vary depending on the severity and location of the perforation and may include prolonged balloon inflation, the implantation of covered stents, pericardiocentesis, or coil embolization for distal vessel perforations. In this report, we present a case of distal left anterior descending artery (LAD) perforation leading to cardiac tamponade, successfully managed with emergency pericardiocentesis and coil embolization.

Keywords: Coronary artery perforation, coil embolization, cardiac tamponade, pericardiocentesis, autotransfusion

ÖZET
Nadir görülse de, perkütan koroner girişim (PKG) sırasında koroner arter perforasyonu (KAP) ciddi ve potansiyel olarak ölümcül sonuçlara yol açabilir. KAP riski, özellikle kronik total oklüzyonlar (KTO) ve ağır kalsifiye lezyonlar içeren karmaşık koroner girişimler sırasında belirgin şekilde daha yüksektir. Kardiyak tamponad gibi yaşamı tehdit eden sonuçların erken teşhisi ve hızlı tedavisi, hasta sonuçlarını iyileştirmek ve mortaliteyi azaltmak için kritik öneme sahiptir. Tedavi stratejileri, perforasyonun şiddetine ve yerine bağlı olarak değişir ve uzun süreli balon şişirme, greft stent implantasyonu, perikardiyosentez veya distal damar perforasyonları için koil embolizasyonu içerebilir. Bu raporda, kardiyak tamponada yol açan distal sol ön inen arter (LAD) perforasyonu olgusunun acil perikardiyosentez ve koil embolizasyonu ile başarılı tedavisini sunduk.

Anahtar Kelimeler: Koroner arter perforasyonu, koil embolizasyonu, kardiyak tamponad, perikardiyosentez, ototransfüzyon

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INTRODUCTION

Coronary artery perforation (CAP) is an infrequent yet potentially fatal complication of percutaneous transluminal coronary angioplasty, with reported incidence rates ranging from 0.1% to 0.7% (1). The choice of management varies according to factors such as the perforation's anatomical site, its severity, and the resulting hemodynamic impact (2). While graft stent implantation is generally preferred for large vessel perforations, coil embolization and similar techniques are typically employed for perforations involving small-caliber distal branches or collateral vessels.

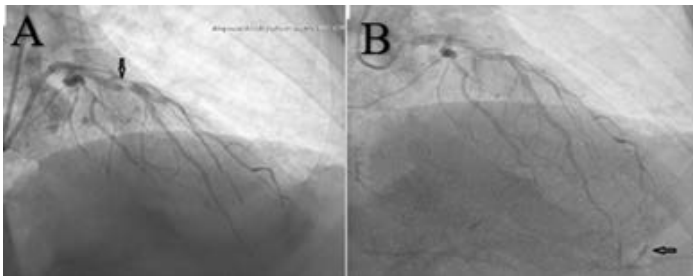

Figure 1A. Pre-procedural coronary angiography showing a significant stenotic lesion (~80%) in the mid-segment of the left anterior descending (LAD) artery near the origin of the second diagonal branch.

Figure 1B. Post-procedural coronary angiography demonstrating contrast extravasation (faint contrast clouding) in the distal LAD, consistent with vessel perforation.

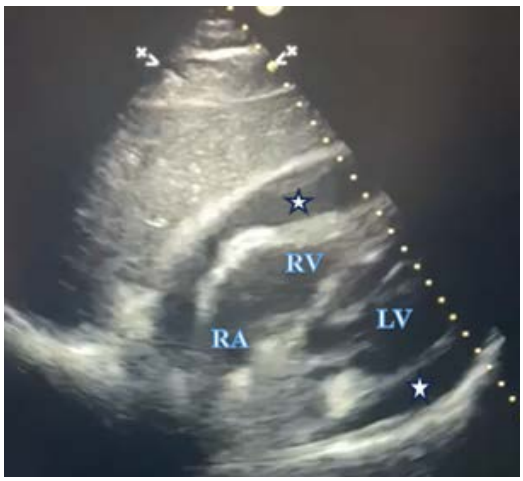

Figure 2. Subcostal transthoracic echocardiographic image showing a large pericardial effusion (*) surrounding the heart, causing compression of the right atrium, consistent with cardiac tamponade. (RA: Right atrium RV: Left ventricle LV: Left ventricle)

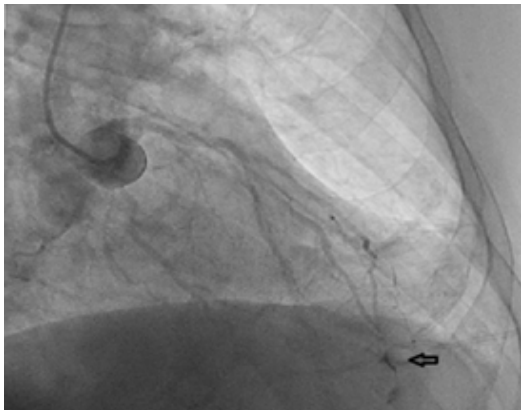

Figure 3. Two 2 mm * 6 cm concerto helix ev 3 coils were placed in the distal LAD.

In this case report, we discuss the management and clinical course of a patient who developed a distal left anterior descending artery (LAD) perforation following percutaneous coronary intervention, successfully treated with coil embolization.

CASE REPORT

A 56-year-old male patient with a history of hypertension and obesity presented to our clinic with unstable angina. Coronary angiography revealed chronic total occlusion (CTO) of the right coronary artery (RCA) and a significant stenosis (~80%) in the mid-segment of the LAD near the origin of the second diagonal branch (Figure 1A). It was decided to perform staged revascularization, prioritizing the LAD lesion first, with elective intervention planned for the RCA CTO at a later date. The LAD was cannulated using a 7F 3.5 Extra Backup (EBU) guiding catheter. A 0.014-inch floppy guidewire was successfully advanced through the lesions in both the LAD and the diagonal branch. A provisional stenting strategy was planned. A 3.0 × 18 mm drug-eluting stent (DES) was implanted into the LAD, followed by post-dilatation with a 3.0 × 15 mm non-compliant (NC) balloon at high pressure. Post-procedural angiography demonstrated preserved flow in the diagonal branch with satisfactory stent expansion and no residual stenosis.

However, during follow-up after the procedure, the patient developed dyspnea and hypotension. Bedside transthoracic echocardiography revealed a massive pericardial effusion consistent with cardiac tamponade (Figure 2). Emergency pericardiocentesis was performed, and 500 mL of pericardial fluid was reinfused via a femoral venous catheter (autotransfusion). Suspecting coronary perforation, the patient was immediately taken back to the catheterization laboratory. Control angiography revealed contrast extravasation from a small distal branch of the LAD (Figure 1B). A microcatheter was advanced to the perforation site, and two 2 mm × 6 cm Concerto Helix EV3 coils were successfully deployed through the microcatheter into the distal LAD (Figure 3). Subsequent

control angiography confirmed cessation of extravasation. The patient's hemodynamic stability was restored, and his subsequent clinical course was uneventful.

DISCUSSION

Coronary artery perforation, while rare, remains a critical complication of PCI with the potential for severe clinical consequences. With the increasing prevalence of interventions for complex lesions, there has been a partial rise in the incidence of perforations. This complication can lead to serious clinical consequences such as cardiac tamponade, hemodynamic deterioration, and elevated in-hospital mortality rates (3). Nevertheless, early recognition and timely intervention are crucial in reducing the risk of adverse outcomes. Coronary artery perforations are generally categorized according to their anatomical location into major vessel, distal vessel, and septal-epicardial collateral perforations. Among these, distal perforations—particularly those linked to the use of polymer-coated guidewires—are frequently attributed to distal wire migration. It has been reported that approximately 90% of coronary perforations caused by guidewires are associated with polymer-coated wires (4). Although floppy guidewires are generally considered safer than stiff guidewires frequently used in CTO procedures, distal wire migration and perforation can still occur, especially in tortuous or angulated vessels. This case underlines the importance of not only the guidewire's stiffness, but also its tip shape, flexibility, and maneuverability in preventing distal perforations. Coronary artery perforations are assessed according to their severity using the Ellis classification. Ellis Type 3 perforation represents the most severe form, characterized by a tear in the vessel wall >1 mm in size and significant contrast leakage into the pericardial cavity, often resulting in cardiac tamponade, which requires immediate intervention. Following pericardiocentesis, autotransfusion is effective in reducing the need for blood transfusion, while facilitating hemodynamic stabilization and preventing adverse outcomes until further interventional treatment can be performed.

Graft stent implantation is the primary therapeutic approach for major vessel perforations. However, for smaller distal vessel perforations, embolization techniques using various embolic materials are commonly employed. In procedures involving microcatheter-guided embolization, various materials such as autologous thrombus, subcutaneous fat or autologous skin, microcoils, gelatin sponge, and polyvinyl alcohol particles have been successfully utilized (5). Since 2017, the umbrella technique has been introduced, wherein a part of the angioplasty balloon is inflated to create an umbrella-like structure at the distal perforation site, blocking blood flow. This structure is then pushed distally with an uninflated balloon, and the balloon and guidewire are retracted to leave the umbrella in place at the perforation site (6). Although the umbrella technique allows for rapid deployment in distal vessel perforations, it requires careful consideration due to potential risks such as distal embolization.

In addition, based on personal experience, the use of balloon fragments, cut tips of guidewires, or absorbable suture materials as embolic agents has also been reported in the literature (7-9). In cases of small vessel perforations, these treatment approaches can play a vital role in preventing fatal outcomes. In the management of guidewire-induced coronary artery perforations, intracoronary thrombin injection via a microcatheter is another alternative treatment option. In this technique, thrombin is directly applied to the perforation site to achieve rapid hemostasis (10).

This case demonstrates that coil embolization is an effective and safe treatment option for distal coronary artery perforation. Early diagnosis and appropriate intervention in these rare yet life-threatening complications of percutaneous coronary interventions significantly reduce mortality and morbidity.

CONCLUSION

In this case, the successful management of tamponade following distal LAD perforation through coil embolization and pericardiocentesis demonstrates that such complications can be effectively treated. This case highlights the important role of coil embolization in the management of distal coronary artery perforations and underscores the critical importance of experience and preparedness in dealing with complications that may arise during percutaneous coronary interventions.

DECLARATIONS

Conflict of Interest: *The authors declare that they have no conflict of interest.*

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