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References should start on a separate page in the article file, not at the end of the article. Tables, table descriptions, images/figures and image/figure descriptions should also be added to the main article file on a separate page after the references. Table/Picture/figure descriptions should be immediately below the tables/ pictures/figures.

About article sections

1-Cover Page: The full title of the article in English and a short title containing no more than 50 characters, the full names and surnames of all authors, ORCID numbers, institutions, name of the corresponding author, work or mobile phone number, e-mail and correspondence address should be indicated. If the article has been previously presented as a paper, the place and date of the paper should be indicated. Information about the authors and their institutions should not be included in the main text (including the materials and methods section), tables, figures and video documents, except on the title page. Details of any grants or other sources of support and acknowledgments to individuals who contributed to the preparation of the manuscript but do not meet the criteria for authorship should also be included on the cover page.
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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.

Website and Social Media Channels: Author. Title. Website: URL. Date and year

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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

REVIEW

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RESEARCH ARTICLE

Retrospective Evaluation of Patients with Primary Immunodeficiency: Five Years of Experience

Primer İmmün Yetmezlik Tanısı ile Takip Edilen Hastaların Retrospektif Olarak Değerlendirilmesi: Beş Yıllık Deneyim

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ABSTRACT

Objective: This study aimed to gain a better understanding of the features of patients with primary immune deficiency diseases/inborn errors of immunity (PID/IEI) in our region.

Materials and Methods: In this study, the medical records of 1163 patients with IEI who had been followed up for 5 years were retrospectively reviewed.

Results: Of the patients, 714(61.3%) were boys and 449(38.6%) were girls. The mean age of diagnosis and diagnostic delay were found as 56.5 and 27.4 months, respectively. Immune deficiency linked to antibody deficiency comprised 90.2%(n= 1049)of all patients. The ratio and incidence of severe combined immunodeficiency(SCID) were 2.1% and approximately one in 10000 live-birth, respectively. The Complaints of respiratory tract infection and otitis media were significantly higher ($p<0.05$). The consanguinity percentage was 31.8%. First-degree cousin marriage was significantly higher in congenital defects of phagocyte, immune dysregulation, and combined immune deficiency than in other IEIs ($p<0.05$). The history of death of a previous sibling was 12.3%, IEI in the family was 10%, and growth and development retardation was 7.3% among our patients. While complete blood cell count(CBC) resulted in frequencies of anemia of 17.2%, neutropenia of 3.2%, lymphopenia of 5%, and thrombocytopenia of 1.9% in all patients, the lymphopenia ratio was 87% in those with SCID. Due to recurrent infections, 95.6% of patients were administered trimethoprim/sulfamethoxazole prophylaxis, and 5.8% received intravenous immunoglobulin replacement therapy. Forty-two percent of all patients were diagnosed with asthma during clinical follow-up, and chronic lung pathology was found in 7.8% of the patients.

Conclusion: This study reveals that primary immune deficiency frequency was found higher in Konya city than the stated prevalence in literature and consanguinity among parents may be a remarkable factor and the presence of lymphopenia may be a remarkable feature for SCID.

Keywords: Primary immunodeficiency, inborn errors of immunity, consanguinity, allergy, complication, childhood

ÖZET

Amaç: Bölgemizdeki Primer İmmün Yetmezlik / Doğuştan Bağışıklık Kusurları (PİY/ IEI) tanısıyla izlenen hastalarımızın özelliklerinin daha iyi anlaşılmasını sağlamaktır.

Gereç ve Yöntemler: Bu çalışmada beş yıllık bir sürede PİY tanısıyla takip edilen 1163 hastanın dosya kayıtları retrospektif olarak incelendi.

Bulgular: Hastalarımızın 714'ü (% 61,3) erkek ve 449'u (% 38,6) kızdı. Hastaların ortalama tanı yaşı 56,5 ay ve tanıda gecikme süresi ortalama 27,4 aydı. Hastalarımızın % 90,2'sini (n=1049) antikor eksikliğine bağlı immün yetmezlikler oluşturmaktaydı. Ağır kombine immün yetmezlik (AKİY) oranı %2,1 (n=23) ve görülme sıklığı yaklaşık olarak on bin canlı doğumda bir olarak tespit edildi. Hastaların başvuru yakınmaları arasında solunum yolu enfeksiyonları ve otitis media diğer başvuru yakınmalarına göre istatistiksel açıdan anlamlı olarak yüksekti ($p<0,05$). Hastalarımızın ebeveynleri arasında %31,8 oranında akraba evliliği yapıldığı saptandı. Birinci derece kuzen evliliklerinde fagositer sistem bozuklukları, immün sistemin regülasyon bozukluğuna bağlı hastalıklar ve kombine immün yetersizlikler diğer PİY'lere göre anlamlı olarak yüksek saptandı ($p <0,05$). Hastalarımızın % 12,3'ünde kardeş ölüm hikayesi, % 10'unun ailesinde ise PİY hikayesi ve % 7,3'ünde büyüme ve gelişme geriliği vardı. Tam kan sayımında anemi % 17,2, nötropeni % 3,2, lenfopeni % 5 ve trombositopeni % 1,9 oranında saptanırken AKİY tanılı hastalarımızda lenfopeni oranı % 87 idi. Tekrarlayan enfeksiyonlar nedeniyle %95,6 hastaya trimetoprim/sülfametoksazol profilaksisi ve % 5,8 oranında intravenöz immunglobulin destek tedavisi başlandı. Hastalarımızdan % 42'si klinik takibimizde astım tanısı aldı ve hastalarımızın % 7,8'inde ise kronik akciğer patolojilerinin varlığı saptandı.

Sonuç: Bu çalışma, Konya ve çevresinde PİY hastalıklarının literatürdeki sıklığından daha fazla görüldüğünü saptamış olup ebeveynler arası akraba evliliğinin önemli bir faktör oluduğunu ve lenfopeninin de AKİY hastalarında önemli bir özellik olabileceğini göstermiştir.

Anahtar Kelimeler: Primer immün yetmezlik, doğuştan bağışıklık kusurları, akraba evliliği, alerji, komplikasyon, çocukluk çağı

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INTRODUCTION

Inborn errors of immunity (IEI), formerly known as primary immunodeficiencies(PID), are a group of heterogeneous and hereditary disorders characterized by increased susceptibility to infections as a result of impairment in one or more of the immune system components, autoimmune diseases, and predisposition to the development of malignancy (1,2). When all innate immunity errors are considered, the incidence of these diseases is reported to be 1/2000–10,000 live births (1,3). Primary antibody deficiency is the most common type of IEI (4). The common clinical features of IEIs are the susceptibility to infections and the complaint of "having frequent infections." Classically, immunodeficiencies should be considered in children with a history of recurrent, severe infections that do not respond well to treatment or that result in complications (1-5). In this study, the clinical and laboratory characteristics of patients with inborn errors of immunity followed at our clinic were evaluated retrospectively to determine the regional features of patients with IEI by evaluating the clinical, laboratory, and sociodemographic variables.

MATERIALS AND METHODS

This study included 1163 patients with PID between 2006 and 2011. There were 5741 patients who were being followed up at the Department of Pediatric Allergy and Immunology during the same five year-period. This study was approved by our ethics committee (2012/32). PID diseases were classified according to the International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiencies(1). The International Union of Immunological Societies (IUIS) IEI Committee has divided PIDs into 10 classes according to their phenotypes, with the latest update(2).

The clinical, laboratory, radiological, and follow-up features of our patients with IEI were reviewed from the records of their Pediatric Immunology Cards and evaluated retrospectively. Consanguineous marriages were classified as those between first-degree (marriage between siblings' children), second-degree (marriage between siblings' grandchildren), and third-degree (more distant) relatives. If the height and weight measurements were below 2SD according to the normal values of Türkiye children, it was accepted as growth retardation. If absolute lymphocyte count (ALC) is less< 3000/mm^3 under one year of age and less than 1500/mm^3 over one year of age, lymphopenia was assessed, and if the absolute neutrophil count (ANC) was less than 1500/mm^3, it was assessed as neutropenia. Isohemagglutinin titers of less than 1/10 were significant.

Statistical evaluation of the data was performed using SPSS for Windows (version 20.0; SPSS Inc., U.S.A) software package. Fisher's chi-squared test and independent sample t-tests were used to compare the groups. Statistical significance was set at $P<0.05$.

RESULTS

Of the 5741 patients who visited the Department of Pediatric Allergy and Immunology during the five years between 2006 and 2011, 1163 were diagnosed with IEI. The annual number of patients who visited the outpatient clinics of the Department of Pediatrics was approximately 15.000 per year. According to this, approximately 1.5% of the patients who visited the outpatient clinics of the Department of Pediatrics and 20.2% of the follow-up patients at the Department of Pediatric Allergy and Immunology consisted of IEI cases.

Among 1163 patients with IEI, 714 (61.3%) were male and 449 (38.6%) were female, with a calculated male to female ratio of 1.59. The mean age at diagnosis of the patients was 56.5±58.3 months (1-996 months), the mean follow-up period was 12.1±15.3 months (0-117months) and the mean period of delay in diagnosis was 27.4 ±31 months (range, 1–438 months). Except for 9 cases, the rest of our patients were in the children's age group. The most commonly detected IEI in our patients was primary antibody deficiencies (PAD) (90.2%). This was followed by other non-well-defined immunodeficiency syndromes (4.9%), combined T and B-cell immunodeficiencies (2.5%), autoinflammatory diseases (1.02%), complement deficiencies (0.5%), phagocyte system disorders (0.25%), regulation disorders of the immune system (0.25%), and diseases characterized by a deficiency in the natural immune system (0.34%) (Table1). The rate of parental consanguinity was 31.8% (Table 2) in patients with IEI. The rate of consanguineous marriages was 74% in SCID, 66.7% in phagocytic system disorders, and 66.7% in diseases related to dysregulation of the immune system, 46.2% for common variable immune deficiencies, 43.3% for other well-defined immunodeficiencies, and 27% for antibody deficiencies. The rate of first-degree consanguineous marriage was found to be significantly higher in cases of phagocytic system disorder, diseases related to dysregulation disorders of the immune system, and combined immunodeficiencies than in other IEIs ($p<0.05$). Among these patients, 12.3% had a history of sibling death, 10% had a family history of IEI, and 7.3% had growth and developmental retardation.

The complaints of patients with IEI on admission were usually recurrent infections (Table 2). In patients with IEI, recurrent upper respiratory tract infections (URTI) were detected at a rate of 56.9%, asthma at a rate of 42%, recurrent lower respiratory tract infections (LRTI) at a rate of 17.2%, recurrent otitis media at a rate of 13.7%, sinusitis at a rate of 7.1%, gastroenteritis at a rate of 8.4%, oral moniliasis at a rate of 11.6%, urinary tract infection (UTI) at a rate of 3.4%, allergic skin findings at a rate of 3.2%, recurrent skin infections at a rate of 3.2%, recurrent lymphadenitis at a rate of 4.5%, sepsis at a rate of 1.9%, and meningitis at a rate of 0.2%. Upper and lower respiratory tract infections and otitis media were found at a significantly higher rate than other accompanying symptoms ($p<0.05$).

Anemia was detected in 200 patients (17.2%), neutropenia in 37 (3.2%), lymphopenia in 58 (5%), and thrombocytopenia in 22 (1.9%) with IEI. Neutropenia was detected in 66.7% of dysregulation disorders of the immune system, 33.3% in innate immune system defects, and 25% in combined immunodeficiencies and complement deficiencies

Table 1. The Classification Of Inborn Errors Of Immunity according to International Union of Immunological Societies (IUIS) 2019

	Female (N)	Male (N)	Total (N)	(IEI) %*(1163)
1. Combined T And B Cell Deficiencies	15	14	29	2.5
Severe Combined Immunodeficiency	10	13	23	2.1
Combined Immunodeficiency	1	-	1	0.08
CD3 Zeta Chain Deficiency	1	-	1	0.08
CD3 Gama Chain Deficiency	3	1	4	0.34
2. Antibody Deficiencies	388	661	1049	90.2
Transient Hypogammaglobulinemia Of Infancy	125	235	360	30.9
Unclassified Hypogammaglobulinemia	106	139	245	21
Physiological Hypogammaglobinemia	23	27	50	4.2
X-Linked Agammaglobulinemia	-	2	2	0.17
Autosomal Recessive Agammaglobulinemia	-	2	2	0.17
Common Variable Immunodeficiency	6	9	15	1.3
IgA Deficiency	76	99	175	15
Partially IgA Deficiency	65	78	143	12.2
Selective IgA Deficiency	11	21	32	2.72
IgM Deficiency	47	145	192	16.5
Partially IgM Deficiency	47	144	191	16.4
Selective IgM Deficiency	-	1	1	0.08
3.Other Well Defined Immunodeficiency Syndromes	31	28	59	4.9
Ataxia Telengiectasia	2	6	8	0.68
Nijmegan Breakage Syndrome	2	1	3	0.25
Bloom Syndrome	-	1	1	0.08
ICF Sendromu	-	1	1	0.08
Di George Syndrome	7	6	13	1.1
Hiper Ig E Syndrome	6	3	9	0.7
Down Syndrome	13	8	21	1.78
Kabuki Make-Up Syndrome	1	2	3	0.25
Cole Hughes Syndrome	-	1	1	0.08
4. Disease Of Immune Dysregulation	2	1	3	0.25
Chediak Higashi Syndrome	-	1	1	0.08
Griscelli Syndrome	2	-	2	0.17
5. Defects Of Phagocyte Number Or Function	1	2	3	0.25
Chronic Granulomatous Disease	1	2	3	0.25
6. Defects In Innate Immunity	4	-	4	0.34
IRAK4 Deficiency	1	-	1	0.08
Unknown Mutation	2	-	2	0.17
IL12R Deficiency	1	-	1	0.08
7. Autoinflammatory Disease	5	7	12	1.02
PFAPA Syndrome	4	7	11	0.94
8. Complement Deficiencies	3	3	6	0.5
9. Bone Marrow Failure	0	0	0	0
10. Phenocopies Of Inborn Errors Of Immunity	0	0	0	0

($p<0.05$). Lymphopenia was found in 75% of combined immunodeficiencies, 66.7% with innate immune system defects, 33.3% with dysregulation disorders of the immune system, and 26.7% with other well-defined immunodeficiencies ($p <0.05$). Anergy was detected in 86 (7.4%) patients who underwent tuberculin skin tests. According to the tuberculin skin test, isoniazid prophylaxis was initiated in 24 (2.1%) patients, and this condition was found at a significantly higher rate in phagocytic system disorders and complement system deficiencies ($p<0.05$). The isohemagglutinin titer was below 1/10 in 121 (10.4%) patients at admission. In the examination of peripheral blood lymphocyte subgroups, at least one subgroup was abnormal in 132 patients (36%). High specific IgE levels and/or positive skin prick test results were detected in 108 (9.3 %) patients.

The tonsils of 31 patients (2.7%) were found to be hypoplastic on physical examination. Hypoplastic tonsils were present in 51.9% of patients with combined immunodeficiency and in 50% of patients with innate immunity defects. Lymphoid tissue hypoplasia other than the tonsils was present in 50% of the patients with combined immunodeficiency and 33.3% of the patients with dysregulated diseases ($p<0.05$). Organomegaly was detected in all patients with immune dysregulation diseases, in 75% of the patients with phagocytic

Table 2. Demographic Data, Diagnostic Delay And Clinical Features Indifferent studies

	Number of IEI paients	M/F rate	Age of diagnosis (months)	Age of onset of symptoms (months)	Diagnostic delay (months)	Follow-up time	Consanguinity rate	Clinical features
Razael N et al.	930	1.7	24	-	31	-	68.5%	20% pneumonia 13% diarrhea 10% sinusitis 9% otitis media
Shabestari MS et al.	59	1.56	57	-	12	-	54%	67% pneumonia 29% diarrhea 28% sinusitis
Kılıç SS et al.	1435	1.56	4.71 (0-62)	2.47 (0-49)	26.9 (10-540)	-	14.3%	pneumonia sinusitis otitis media
Aldırmaz S et al.	168	1.76	52.8 (5-216)	-	-	-	16%	90.5% URTI 38.8% pneumonia 22.4% sinusitis
Kılıç M et al.	78	1.6	5.4 (0.4-19)	3 (0.1-180)	28.9 (0.2-108)	-	30.8%	65.4% pneumonia 55% URTI 16.7% diarrhea
Mohammadine jad P et al.	307	1.51	96 (1 month-56 years)	-	1.25 years (1week-28 years)	-	59%	36.5% pneumonia 21.8% diarrhea 15.6% sinusitis
Al-Tamemi S et al.	90	1.57	24 (1 week-16 years)	9 (1-144)	-	-	81%	42% pneumonia 27% abscess 12% BCGitis

system disorders, in 46.4% of the patients with combined immunodeficiency, and 33.3% of the patients of the patients with innate immunity defects ($p<0.05$).

We found that 95.6% of our patients were followed with antibiotic prophylaxis (trimethoprim/sulfamethoxazole: TMP-SMX), and 5.8% of the patients were treated with intravenous immunoglobulin (IVIG) replacement therapy. Radiological evaluation revealed chronic lung pathologies in 91 (7.8%) patients (16 patients with bronchiectasis, 1 patient with fibrotic changes, 2 patients with fungus, 1 patient with pleural thickening, 1 patient with bronchiolitis obliterans, and 1 patient with ground glass opacity and nodule), and asthma in 474 (42.1%) patients.

Between 2006 and 2011, there were an average of 35-38 thousand live births annually in Konya, and the population of Konya was approximately one million inhabitants. On average, about four to five patients are diagnosed with SCID annually among the patients who were admitted to our hospital from Konya. According to this, the SCID prevalence in our region can be estimated as approximately 1 out of 10.000 live births and the IEI prevalence as 1 in 1000 births. Consanguineous marriage was present in 17 (74%) of 23 patients diagnosed with SCID. Of these, 13 (52%) were first-degree relative. T-B-NK+ SCID was found in 13 patients, T-B+NK+ SCID in 2, T-B-NK- SCID in 2, and T-B+NK- SCID in six patients were classified according to peripheral blood lymphocyte subgroups. The ARTEMIS (n=2), ADA (n=2), JAK3 (n=2), RAG2 (n=1), and Gamma chain (X-linked SCID) (n=1) gene mutations were detected in 8 SCID patients whose mutation analysis could be studied, while one patient was also diagnosed with the Type III BLS (Bare Lymphocyte Syndrome) gene defect. According to the clinical findings detected in our SCID patients at the time of admission, LRTI were found at a rate of 69% (16), moniliasis at a rate of 73% (17), gastroenteritis at a rate of 56% (13), and sepsis at a rate of 39% (9). Nine (39%) patients had growth and developmental retardation and 20 (87%) patients had lymphopenia. Bacillus Calmette-Guérin (BCG) infection was observed at a rate of 13%, absence of thymus at a rate of 87% (20). All patients with SCID were treated with IVIG, TMP-SMX, and antifungal prophylaxis. The mean age at diagnosis of the 23 patients diagnosed with SCID (10F/13M) was 9.3±10.3 months (1-24 months), the mean age at the time of the study was 34±20.6 months (5-227 months), and the mean time of delay in diagnosis was 3.5±5.7 months (0-21 months). Twelve (52.1%) patients with SCID underwent hematopoietic stem cell transplantation (HSCT). Eight of these patients had T-B-SCID, four had T-B+SCID, and none of these patients were lost. The other 10 patients diagnosed with SCID died and one patient

Table 3. Distribution Of Inborn Errors Of Immunity In Different Studies

	1 Combined T and B cell deficiencies (%)	2 Antibody deficiencies (%)	3 Other well defined immunodeficiency syndromes (%)	4 Disease of immune dysregulation (%)	5 Defects of phagocyte number or function (%)	6 Defects in innate immunity (%)	7 Autoinflammatory disease (%)	8 Complement deficiencies (%)
Al-Tamemi S et al.	12	18	13	3	42	-	-	6
Carneiro-Sampaio M et al.	6.7	60.8	8.3	5.2	8.7	5.9	1.2	2.8
Mohammadinejad P et al.	11.7	38.4	16.9	3.6	14.7	1	11.4	2.3
Gathmann B et al.	7.78	55.2	15.6	3.74	8.4	0.78	1.95	4.6
Ödek Ç et al.	17.3	56.2	11.3	4.2	6.7	1	0.5	1.1
Aghamohammadi A et al.	22.3	32.3	17.2	2.6	17.4	1.6	5.2	1.4
Kilic SS et al.	2	73.9	5.5	0.7	3.5	1	13.3	0.4
Kılıç M et al.	7.7	71.8	10.3	-	1.3	-	-	5.1
DUR O et al.	12.4	81.4	2.2	0.5	1.5	0.25	0.5	1
ESID	7.6	56.14	15.16	3.7	8.6	0.97	1.94	4.1
Levia LE et al.	9.5	53.3	22.6	3.3	8.6	-	-	2.8
Razael N et al.	11	38.3	17.7	2.4	28.3	-	-	2.4
Sanal et al.	14	42	15	7	10	2	3	2
Yorulmaz A et al.	2.4	92.8	1.7	0.9	0.4	-	-	0.1
Our Study	2.5	90.2	4.9	0.25	0.25	0.34	1.02	0.5

with ADA deficiency was treated with ADA enzyme therapy.

DISCUSSION

The incidence of IEI in developed countries ranges from 1/10.000 to 1/100.000 (1). Although the exact incidence of IEI is not known in our country, where consanguineous marriages are common, it is expected that those with autosomal recessive inheritance are seen more commonly (3).

Mısırlıoğlu et al. reported that 2.1% of patients who visited their outpatient clinic had an IEI (4). In a previous study from our clinic, Yorulmaz et al. reported that about 25% of patients who applied to the outpatient clinic of Pediatric Allergy and Immunology and about 1% of patients who applied to the outpatient clinics of pediatrics had an IEI (3). In our study, approximately 1.5% of the patients visited the outpatient clinics of Pediatrics, and 20.2% of the patients followed the Department of Pediatric Allergy and Immunology consisted of IEI cases. The prevalence of IEI has been reported to be 3.72/100.000 in France (5), 4.4/100.000 in Oman (6), and 4.7/100.000 (7) in Qatar. The prevalence of IEI has been reported to be 30.5/100.000 in Türkiye (8). Although our study is not a prevalence study, Konya has a higher IEI and SCID prevalence than in the literature, and it supports the claim that IEI diseases are more common in our country.

PAD is the most common type of IEIs in children (8-15). This rate was reported as 18-61% in different countries and 56%-84.5% in Türkiye (6,8,12,16-22). The ratio of PAD (90.2%) in our study was higher than that reported in the literature and similar to the a previous study by Konya (3) (Table 3). This finding is because all types of IEIs are being followed at our department, which is the unique pediatric immunology center until 2011 in Konya, and our registry system is very good and sufficient to evaluate IEIs.

Previous studies have reported that IEI is more common in males. This finding depends on the M/F ratio of 1.5-1.7 in Iran (12,15,17), 0.56 in Brazil (21) and 0.58 in Germany (20). The M/F ratio has been reported as 1.36-3.2 in studies from Türkiye (4,3,8,19,22,23). Our study was also similar to these studies as having a male/female ratio of 1.59 and supports the claim that IEIs are seen at a higher rate among males.

The age of diagnosis and the diagnostic delay of IEI patients may vary in different studies as 1-8 years and 12-31 months (8,12,17,22), respectively. In the study by Yorulmaz et al., the age of diagnosis was 55.5 months and the delay in diagnosis was 24.3 months. In our study, the mean age at diagnosis was 56.5 months and and the delay in diagnosis was 27.4 months. Nine patients were adults. Because we are the only immunology center in the province where we are located, and because of our adult patients, our age at diagnosis and delay in diagnosis were found to be high compared to some studies (Table 2).

In our country, parental consanguinity varies according to region, but it has been reported to be approximately 32% (24). The parental consanguinity rates in patients with IEI have been reported as 14.3-68.5% in previous studies (3,4,6,20,21,25). In our study, parental consanguinity was found to be 31.8% among all IEI patients, and when compared with the study by Yorulmaz et al. (38%) in Konya between 2001 and 2006, the fall in the rate of parental consanguinity of IEI patients was remarkable. This finding suggests that the rate of parental consanguinity in our patients with IEI may change over time and has a downward trend due to migration to our region, but it is still high. Consanguineous marriage increases the risk of autosomal recessive diseases (3,10). In our study, only

one patient has X-linked inheritance, and consanguinity was found in 75% of patients with SCID. It is also important to identify genetic defects in patients with SCID because genetic counseling and prenatal diagnosis are required. Prenatal diagnosis can be made using amniocentesis and chorionic villus sampling for new pregnancies in cases with known genetic defects.

There could be a history of sibling death and a family history in patients with IEI. This prevalence was reported as 22-43.5% in Türkiye (3,16). In our study, 12.3% of the patients had a history of sibling death, and 10% had a family history of IEI. This low rate could be explained by the fact that the majority of our patients with IEI had PAD, which has a good survival rate with less severe disease without complications and death.

An increased incidence of infections in patients with IEI has been reported previously. In these studies, recurrent upper and lower respiratory tract infections, chronic diarrhea, and persistent oral candidiasis were common in patients with IEI (3,6,8,17,22,26). In our study, recurrent upper respiratory tract infections were found as the most common first admission complaint (56.9%), and asthma as the second most common (42%) and recurrent lower respiratory tract infections as the third most common (17.2%). These findings indicate that patients with IEI most commonly present with upper and lower respiratory tract infections and/or problems. Cytopenias are other warning signs of immunodeficiency for clinicians. The diagnosis of SCID is a pediatric emergency and early diagnosis is a life-saving approach. Although lymphopenia is present in almost all patients with SCID, it should be noted that these patients can have normal lymphocyte counts (3). Among our patients with SCID, 87% had lymphopenia and 13% had normal lymphocyte counts at admission. If the patient's medical history and physical examination are compatible with immunodeficiency, IEI should be considered, and advanced immunological evaluation should be performed even if the first-line immunological laboratory examinations are normal.

The incidence of SCID/CID in patients with IEI was reported as 2.5-22.5% in registry systems and literature (6,8,12-15,17-22). Yorulmaz et al. (3) reported that SCID was 2.4% among IEI patients between 2001 and 2006 in Konya (3) and we also found as 2.5% between 2006 and 2011 in the present study. The prevalence of SCID was estimated as approximately one in 10.000 live births in Konya and higher than one in 50-100 thousand in the literature (3). This was estimated to be the same as in the present study. This rate showed that SCID incidence was very high in Konya and did not change during a ten- year period. However, as there could be patients with SCID who applied to other health institutions without referring to our center and died before they could be diagnosed, we believe that the incidence of SCID in Konya is even higher than we estimated.

The most important problem with SCID is that early diagnosis is not possible because of a long delay in diagnosis. Al-Herz et al. reported a delay in the diagnosis of SCID of 7.5 months (27), and Reda et al. reported it as 6.6 months (28). In Europe, this is approximately 2.5-7 months (29). In Türkiye, the delay in the diagnosis of SCID is approximately 2–9 months (3, 16, 22, 30-34). (Table 2). In a previous study conducted between 2001 and 2006 at our center, Yorulmaz et al. reported that the mean delay in diagnosis was approximately 9 months (3). In our study, the delay in diagnosis was approximately 3.5 months between 2006 and 2011. It is noteworthy that the delay in diagnosis decreased from 9 to 3 months. This decrease is due to the training meetings held by our center to increase IEI awareness among physicians in Konya (34). This has also reduced the mortality rate after HSCT without organ complications, and was due to early diagnosis, resulting in a high survival rate in our patients.

In conclusion, patients with IEI are common because of the high rate of consanguineous marriages in our country. It is crucial to increase awareness of symptoms suggesting immunodeficiency among physicians who first evaluate these patients. In patients with recurrent and severe infections, it is essential to consider IEI diseases in the differential diagnosis and to prioritize immunologic evaluation so that these patients can be diagnosed at an early stage and treated early. As early diagnosis will save lives, the quality of life of patients and their families will increase, and it will be possible to provide genetic counseling or prenatal genetic diagnoses to families. For this purpose, it is important to establish awareness about warning symptoms for immunodeficient patients during medical education and training after graduation..

DECLARATIONS

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RESEARCH ARTICLE

Evaluation of Surgical Quality in Extremity Soft Tissue Sarcomas

Ekstremite Yumuşak Doku Sarkomlarında Cerrahi Kalitenin Değerlendirilmesi

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ABSTRACT

Objective: The exact treatment of extremity soft tissue sarcomas is extended surgical excision with this chemotherapy and/or radiotherapy. Despite surgical resection with a negative margin and adjuvant radiotherapy, extremity soft tissue sarcomas tend to local recurrence. This study assessed surgical quality by examining short- and long-term local recurrence ratios with the prognostic factors affecting local tumor control.

Materials and Methods: A retrospective examination was made of 130 patients treated for a diagnosis of soft tissue sarcoma localized in an extremity. The parameters affecting local recurrence were evaluated, such as the surgical margin, sarcoma size, depth, histotype, grade, the adjuvant/neoadjuvant treatment protocol, and unplanned surgery.

Results: The mean follow-up period of the patients was 44 months (range,20-70 months). Of the 118 patients who underwent extremity-sparing surgery, R0 resection was applied to 96, and R1 resection to 32. In the 20-month follow-up period, the local recurrence ratio was 19% in surgical border-negative patients and 28% in surgical border-positive patients. The local recurrence rates during the 3-year follow-up period were 24% in patients undergoing R0 surgical treatment only, 21% in those with R0 surgery+radiotherapy(RT), 34% following re-resection in those with R1, and 38% in those with R1 applied with RT only.

Conclusion: The local recurrence-free period is the most important marker of surgical margin quality. To provide optimal surgical quality, sarcoma cases should be discussed in multidisciplinary tumor panels and treatments must be personalized according to the clinical and demographic characteristics of the patient and the histopathological type of the sarcoma. The treatment of extremity soft tissue sarcomas must be performed by a specialized team with good knowledge of the physiopathology of sarcomas for optimal surgical margin and local control. Primary care physician training should be planned beyond direct patient referral to the sarcoma center for early diagnosis and treatment and to avoid unplanned surgery.

Keywords: Extremity soft tissue sarcoma, surgical margin, local recurrence-free interval

ÖZET

Amaç: Ekstremite yumuşak doku sarkomlarının esas tedavisi geniş cerrahi eksizyon ve buna kombine edilen radyoterapi ve/veya kemoterapidir. Ekstremite yumuşak doku sarkomları negatif sınırlı cerrahi rezeksiyon ve adjuvan radyoterapiye rağmen lokal tekrarlama eğilimindedir. Çalışmada cerrahi kalitesinin değerlendirilmesi amacıyla yakın ve uzak dönem lokal nüks oranları belirlendi. Bu çalışmanın amacı, tümörün lokal kontrolünde etkili olan prognostik faktörler dikkate alınarak cerrahi kalitenin değerlendirilmesidir.

Gereç ve Yöntemler: Ekstremite yerleşimli yumuşak doku sarkomu tanısıyla tedavi edilen 130 hasta retrospektif olarak incelendi. Lokal nükse etki eden cerahi sınır, sarkom boyutu, derinlik, histotip, grad ve adjuvan / neoadjuvan tedavi protokolü, plansız cerrahi gibi parametreler değerlendirilmeye alındı.

Bulgular: Hastaların ortalama takip süresi 44 ay(20-70) idi. Extremite koruyucu cerrahi uygulanan 118 hastanın 96'sına R0 rezeksiyon, 32' sine R1 rezeksiyon yapıldı. 20 aylık takiplerinde lokal nüks oranları; cerrahi sınır negatif olanlarda % 19, cerrahi sınır pozitif olanlarda ise % 28'dir. 3 yıllık takiplerimizdeki lokal nüks oranları; R0 sadece cerrahi tedavi uygulananlarda % 24, R0 olanlarda cerrahi+RT uygulananlarda % 21 iken, R1 olanlarda re-rezeksiyon sonrası % 34, R1 olup sadece RT uygulananlarda % 38 olarak bulundu.

Sonuç: Cerrahi sınır kalitesinin en önemli belirteci lokal rekürrenssiz süredir. Extremite yumuşak doku sarkomlarının tedavisi optimal cerrahi kaliteyi sağlayabilmek için sarkom vakaları multidisipliner tümör kurullarında tartışılmalı ve tedaviler hastanın klinik ve demografik özelliklerine ve sarkomun histopatolojik tipine göre bireyselleştirilmelidir. Yumuşak doku sarkomlarının cerrahi tedavisi fizyopatolojisine hakim özelleşmiş bir ekip tarafından yapılmalıdır. Erken tanı ve tedavinin sağlanabilmesi ve plansız cerrahinin önüne geçilmesi için birinci basamak hekimler ve hastalar için eğitimler planlanılmalı ve sarkom merkezine doğrudan sevk sağlanmalıdır.

Anahtar Kelimeler: Ekstremitelerin yumuşak doku sarkomu, cerrahi sınırlar, lokal rekürrensiz interval

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INTRODUCTION

Soft tissue sarcomas are a rarely seen type of cancer of mesenchymal origin, which constitute 1% of all malignant tumours seen in adults (1). They originate from many tissues and cells that form connective structures, such as muscles, blood vessels, nerves and fatty tissue. The incidence of soft tissue sarcoma is <5 cases per 100,000 adults (2). There are more than 70 histological subtypes and the soft tissue sarcomas seen most often in adults are undifferentiated high-grade pleomorphic sarcoma (malignant fibrous histiocytoma), liposarcoma, leiomyosarcoma, rhabdomyosarcoma, synovial sarcoma, and malignant perpheral nerve sheath tumour (3).

The basic treatment for extremity soft tissue sarcomas is wide surgical excision and the combination of surgery and radiotherapy and/or chemotheerapy (4). Optimal surgery should be performed by a specialised sarcoma team with good knowledge of the physiopathology of soft tissue sarcomas, and it should be aimed to obtain high tumour control and good functional results with minimal morbidity (5). High-grade soft tissue sarcomas require "wide" excision (>2cm) to minimise the development of local recurrence (6). However, this margin may not always be able to be achieved as tumours show variability in size, localisaton, and biological aggression, which may lead to an increase in amputative surgical procedures (7).

Local recurrence is the most important marker showing the quality of the surgery in soft tissue sarcomas. The surgical margin quality (negative vs. positive, R0 vs. R1) is more valuable than quantity (mm) in the prediction of outcomes (8). For the evaluation of surgical margins in this study, intraoperative photographs were taken of the tumoural mass, the excision region, and the surgical margins, the places most likely to be close to the margins were marked on the specimens, and the pathology data of the patients were used. The aim of the study was to evaluate the quality of the surgery taking into consideration the parameters of surgical margin, and tumour grade, type, localization, and histopathological type, which affect local control of the tumour.

MATERIALS AND METHODS

The study included evaluations of 130 patients with a diagnosis of soft tisssue sarcoma localised in an extremity who were treated in th Orthopaedics and Traumatology Clinic of Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital.

For the evaluation of surgical quality, short and long-term local recurrence rates were determined. Evaluations were made of the parameters affecting local recurrence, including surgical margins, sarcoma size, grade, and histopathological type, and adjuvant/neoadjuvant treatment protocols.

To be able to examine the effects on local recurrence in homogenous groups and to be able to make correct predictions of local recurrence in the long-term follow-up, primary cases and cases with sarcoma who presented with recurrence or residual mass after unplanned surgery in another centre, were evaluated separately.

After preoperative evaluation, the surgical technique performed on resectable masses was extremity-sparing wide resection, leaving a clean surgical margin of at least 1cm around the tumour, which would minimise functional losses. For a safe surgical margin, wide resection of the mass was performed with the fascia and bone cortex (in cases where necessary), which form major barriers. In primary cases, a neurovascular structure was accepted as high-risk margin, and vascular structures were dissected from the adventitia and nerves from the epineurium. Vascular allografting or autografting was performed in some patients. In primary cases that were not resectable, or cases presenting with recurrence or residual sarcoma, radical surgery was performed.

The R classification was used in the evaluation of surgical quality (Table 1) (9). The surgical margins were determined from the pathology data.

Patients with low-grade sarcoma were followed up every 3 months in the first year, every 6 months in the second year and then annually thereafter; high-risk patients with high-grade sarcoma who underwent unplanned surgery followed up with physical examination, regional ultrasonography (USG), chest radiography and tomography, bone scintigraphy, magnetic resonance imaging (MRI) and PET imaging when necessary, every 3 months for the first 2 years and every 6 months until the 5th year. The patients were followed up for mean 44 months (range, 20-70 months).

As the local recurrence-free period was evaluated as the most important indicator of surgical quality, the parameters of distant metastasis, complications, and mortality were included in the analyses.

Statistical Analysis

The study data were obtained from examination of the patient records, face-to-face and telephone interviews, and the data were then analyzed statistically using SPSS vn. 13.0 software. Some of the data were shown in tables as number and percentage and where appropriate as mean ± standard deviation (SD) values. The Chi-square significance test was used for statistical analysis.

RESULTS

Evaluations were made of 130 patients, comprising 68 males and 62 females with a mean age of 49.4 years (range, 6-82 years). Complaints on presentation were pain and swelling

Table 1. Classification of surgical margins according to American Joint Committee on Cancer (AJCC) Guideline

R Classification	Microscopic surgical margin	Macroscopic surgical margin	Surgical treatment
R0	-	-	Wide resection
R1	+	-	Marginal resection
R2	+	+	Intralesional resection

in 120 cases, and ulcerated bleeding mass in 10. Tumour size was determined to be 0-5cm in 18 patients, 5-10cm in 35, and >10cm in 77. Sarcoma localisation was observed to be in the thigh in 68 patients, in a lower extremity in 28, the cruris in 13, gluteal region in 11, foot and ankle in 6, and in the knee and popliteal region in 4 (Table 2).

The sarcomas had deep localisation in 114 cases, and were high grade in 106. Histopathologically, the most frequently seen sarcomas were malignant mesenchymal tumour in 67 cases, liposarcoma in 24, and undifferentiated high-grade pleomorphic sarcoma in 10. Of the patients included in the study, 103 were treated and followed up because of primary sarcoma, and 27 because of recurrence or residual mass. Of the cases presenting with recurrence or residual mass, re-resection was performed in 25 cases, of which 21 were also administered adjuvant radiotherapy (RT) and 4 were monitored only. Local recurrence was observed in 10 patients of the re-resection group.

Extremity-sparing surgery was performed on 116 patients, radical surgery on 12, and palliative RT was applied to 2. R0 resection was applied to 96 patients and R1 resection to 32. Of the 96 patients with R0 surgical margin, 45 underwent surgery only, and 51 were treated with surgery + RT. The mean follow-up period of the patients was 44 months (range, 20-70 months).

As adjuvant treatment, neoadjuvant RT was applied to 18 cases with large volume, and postoperative RT to 83 cases. Chemotherapy was applied neoadjuvant to 6 cases with metastasis and postoperatively to 24 cases according to the histopathological type.

During the 20-month follow-up period of 130 patients, the local recurrence rates were found to be 19% in cases with negative surgical margin, and 28% in those with positive surgical margin. At the end of a 3-year follow-up period, local recurrence rates were 24% in R0 cases applied with surgical treatment only, 21% in R0 cases applied with surgery+RT, 34% in R1 cases after re-resection, and 38% in R1 cases applied with RT only (Table 3).

DISCUSSION

The main treatment for soft tissue sarcoma with extremity localisation is preoperative planning and a sufficient width of surgical resection (10). In this retrospective study, which examined 130 patients with soft tissue sarcoma with extremity localisation, the surgical quality and factors affecting that were evaluated. The 75% R0 resection rate within the mean 44-month follow-up period of this study was consistent with

Table 2. Patient characteristics and tumour size, grade, and histopathology

Characteristic	Number	Percentage (%)
Age (mean 49.4 years)		
<60 years	112	86.1
>60 years	18	13.9
Gender		
Male	68	52.4
Female	62	47.6
Complaints on presentation		
Pain, swelling	120	92.4
Ulcerated bleeding mass	10	7.6
Localisation		
Upper extremity	28	21.5
Lower extremity	102	78.5
Tumour size		
0-5 cm	18	13.9
5-10 cm	35	26.9
≥10 cm	77	59.2
Depth		
Superficial	16	12.3
Deep	114	87.7
Histopathology		
Malignant mesenchymal tumour	67	51.5
Liposarcoma	24	18.4
Pleomorphic sarcoma	10	7.6
Synovial sarcoma	9	6.9
Other	20	15.6
Grade		
High grade	106	81.5
Low grade	24	18.5

Table 3. Presentation type, surgical method, surgical margin, adjuvant treatment, and local recurrence of the cases in the study.

	Number	Percentage (%)
Type of presentation		
Primary	103	79
Recurrence-residual	27	21
Surgical method		
Extremity-sparing	116	89
Amputation	12	9
Palliative RT	2	2
Surgical margin		
R0	96	75
R1	32	25
Radiotherapy		
Adjuvant	83	63.8
Neoadjuvant	18	13.8
Chemotherapy		
Adjuvant	24	18.4
Neoadjuvant	6	4.6
Unplanned surgery		
Re-resection+adjuvant RT	21	16.1
Re-resection	4	3
Palliative RT	2	1.5
Local recurrence (20-month follow-up period)		
R0 resection	19	19.7
R1 resection	9	28.1
Local recurrence (44-month follow-up period)		
R0 resection	23	23.9
R0 resection+RT	21	21.8
R1 (re-resection cases)+RT	7	33.3
R1 (Palliative RT)	2	100

Table 4. Previous studies related to the effects of surgical margins on local recurrence of soft tissue sarcomas

Reference	Localisation	No of patients	Mean follow-up period (months)	Surgical quality			
				Margin marker	Surgical margin (%)	Margin distribution	According to surgical margin
Harati et al.2017; Oncology	Extremity	643	64	Pathological margin, microscopic	R0 R1	-	32,9% 63,9%
Bilgeri A. et al. 2020[23]	Extremity/ trunk	305	60	Pathological margin, microscopic	R0 R1	-	17% 34%
Kainhofer V. et al.2016[22]	Extremity	265	-	Pathological margin, microscopic	R0 R1	-	16,5% 36,7%
Le Vay et al. 1994; PMH	Extremity/ trunk	321	80	No data	Wide: 1-4cm Doubtful: <1cm Positive 0mm	No data	7% 17%
Keus et al. 1994; NCL/ALH	Extremity	143	114	Pathological margin, 2cm/RT	Wide Close+RT Incom plete+RT	18% 45% 37%	19% 8% 16%
Trovik et al. 2000; SSG[28]	Extremity/ trunk	559	89	Pathological margin, Enneking	Sufficient Insufficient	75% 25%	15% 32%
Stefanovski et al. 2002; CRO[21]	Extremity/ trunk	395	35	Pathological margin, microscopic	Negative Positive	68% 32%	20% 35%
Stojadinovic et al. 2002; MSKCC[20]	Extremity	1156	50	Pathological margin, microscopic	Negative Positive	81% 19%	18% 35%
Koea et al. 2003; MSKCC	Extremity	911	35	Pathological margin, 1mm	Negative Positive	83% 17%	13% 22%
Eilber et al. 2003; UCLA	Extremity	607	88	Pathological margin, microscopic	Negative Positive	98% 2%	Not significant
Zagars et al. 2003; MDA[22]	Extremity/ trunk	1225	114	Pathological margin, microscopic	Negative Uncertain Positive	66% 19% 15%	12% 26% 38%
McKee et al. 2004; RPCI/SUNY[16]	Extremity/ trunk	111	80	Pathological margin, 1mm	>10mm 1-9mm 0mm	47% 41% 12%	16% 42% 42%
Gronchi et al. 2005;I INSCT[19]	Extremity	642	107	Pathological margin, 1mm	Negative Positive	87% 13%	12% 26%
Dickinson et al. 2006; WMC[17]	Not stated	324	32	Pathological margin, 1mm	>=1mm <1mm	67% 33%	2-fold risk 3-fold risk
Stoeckle et al. 2006;IB	Extremity/ Trunk	200	53	Surgery/ Pathological consensus UICC	R0 R1	74% 26%	7% 30%
C.Yıldız et al. 2003; GATA	Extremity	40	58	Pathological margin, 1mm	Negative Positive	85% 15%	0% 83.3%
CURRENT STUDY	Extremity	130	44	Surgery/ Pathological margin+RT	R0+RT R1	74% 26%	21% 34%

data in the literature of a range between 66% and 87.7%, and the local recurrence rate of 21% was at the upper limit of the literature data of 9-20% (11,12) (Table 4).

Most previous studies are in agreement on the point that the surgical margin is one of the strongest negative prognostic values for local control (13). Anatomic restrictions around the tumour make an actual wide resection impossible with a sufficiently safe margin without sacrificing critical anatomic

structures (eg., major nerves, blood vessels, bones and joints) (14). Azzarelli et al. demonstrated that it was almost impossible to obtain a 2 cm margin in all directions (15). McKee et al. reported that a surgical margin exceeding 1cm could only be obtained in 47% of patients (16), and Dickinson et al. were able to obtain a surgical margin >5mm in 54% of patients (17). In the current study, R0 resection was performed in 96 patients and R1 in 32, with 75% of the surgical margins reported to be negative and 25% positive. In contrast to the studies by Azzarelli (15), McKee (16), and Dickinson (17), which were based on the measured data of the surgical margin, the R classification was considered to be more effective and useful in the current study determination of surgical margin and evaluation of surgical quality rather than the evaluation of measurements. This was because there is no consensus on which tissues such as muscle tissue, fatty tissue, and neurovascular sheath and what width of excision of the sarcoma show that a safe surgical margin can be obtained (18).

The most important indicator of the quality of surgical treatment is local tumour control, which is determined primarily by the negativity of the surgical margin, tumour size, grade, localisation and histopathological type, adjuvant treatment combinations, and insufficient or unplanned surgery. In a study of 911 patients by Gronchi et al., local recurrence rates were reported to be 12% in the cases with negative surgical margin (87%) and 26% in cases with positive surgical margin (13%) (19). In another retrospective analysis of 2084 patients, Stojadinovic et al. determined recurrence rates in 15% of cases with negativity and 28% in those with positivity (20). In the current series of 130 patients, the local recurrence rates were determined to be 21% in R0 surgical resections and 34% in R1 resections. Although these rates were seen to be similar to those reported by Stefanovski (21), they were seen to be slightly higher in both R0 and R1 resections than the rates reported by Gronchi (19), Kainhofer (22), Bilgeri (23), and Stojadinovic (20). This was attributed to most of the current study patients having larger and higher grade sarcomas and that they presented late because of a low sociocultural level.

It has been reported that 70-80% of local recurrences occur within the first 3 years (24). To be able to make better comparisons between studies when reporting local results, the "local recurrence-free period" should be used. Short -term follow-up can overlook late recurrences associated with the tumour biology. Gronchi et al. found no difference between the local results of patients with positive and negative surgical margins in the short-term follow up, but a significant difference was determined at the end of the long-term follow-up period (19). As shown by Stojadinovic et al., while systemic risks are valuable in the early period, they become more important after local recurrence (20). The local recurrence rates in the current study were determined to be 19% in cases with negative surgical margin, and 28% in those with positive surgical margin in the 20-month follow-up period, and at the end of a 3-year follow-up period, 24% in R0 resections, 21% in those with R0 resection+RT, and 34% in R1 resections. The increase in local recurrence rates after 3 years compared to the short-term follow-up shows that long-term local recurrence results are more valuable, as stated by Gronchi (19) and Stojadinovic (20). In a study of 171 patients in the Royal Marsden Hospital (UK), Pitcher et al. explained local recurrence rates at the end of a 20-month follow-up period as 9% (15/171) isolated and 14% (24/171) immature (25). In the second reports, this rate was 20.6% (35/171) at the end of a 5.3-year follow-up period, and the actual local recurrence-free rate was stated to be 26% (37). As in those studies by Pitcher et al. (25, 26), a significant difference was determined in the long-term follow-up local rates in the current study between the cases with negative and positive surgical margins (R0 21%, R1 34%). This difference demonstrated that the system used is good in the determination of surgical quality

As size and grade together best define the biological aggression of soft tissue sarcomas, this is the most important prognostic factor for local control (4, 19, 27). In an analysis of 559 patients by the Scandinavian Sarcoma Group, a higher histological grade and surgical margin positivity were found to be independent risk factors for local recurrence (28). Localisation of the sarcoma has been found to contribute as much as size and grade to surgical success and therefore, local recurrence. The prognosis is always good in low-grade soft tissue sarcomas with superficial localisation (14). Rydholm and Rooser determined only 10% local recurrence in a minimum of 6 months of follow-up following wide resection in 48 patients with subcutaneous and intramuscular soft tissue sarcoma (29). As most of the cases in the current study had large sarcomas with deep localisation, local control was difficult. In a study by Simon and Enneking, the recurrence rates of soft tissue sarcoma after surgical resection were reported to be 38% in those with hip localisation, 48% in the thigh, and 58% in the foot and ankle (30). It is difficult to obtain surgical margin negativity in localisations such as the hand, foot and ankle, forearm, cruris, and popliteal region. Some of the current study cases with local recurrence despite extremity-sparing surgery + adjuvant RT were those with sarcoma localisation in the cruris, foot and ankle, forearm, and popliteal region. These results were consistent with the findings of the study by Simon and Enneking (30), stating that these localisations made R0 resection difficult, increased local recurrence and increased the need for amputation.

Another important factor affecting local tumour control is the histopathological type. Specific subtypes such as myxofibrosarcoma and undifferentiated pleomorphic sarcoma usually have an infiltrative growth pattern (31). The probability of local recurrence is high, independently of surgical margins (32). Therefore, evaluation specific for each histological subgroup is very important in surgical planning. In a homogenous myxofibrosarcoma series, Dadrass et al. reported that the local recurrence rates were higher in negative surgical margin resections than in other histological subtypes (33). A significant proportion of patients in the current series were found to have soft tissue sarcoma of a histological type with an infiltrative growth pattern, which could be one of the factors causing the higher rates of local recurrence in R0 and

R1 resections compared to the data in the literature.

Unplanned excision generally includes dissection along the tumour capsule and enucleation. Tumour tissue is left behind in 65% of these cases. Residual tumour is a risk factor for local recurrence and local recurrence can be seen in 75% of unplanned surgery cases (34). Of the 25 patients in the current study re-resection group, local recurrence was observed in 10. It has been previously reported that local recurrence is seen in 40% of patients in the re-resection group who present at the clinic following unplanned or insufficient surgery. In the MSKCC study by Lewis (35), the reason for a high rate of local recurrence was said to be that patients had undergone unplanned or insufficient surgery for a high grade soft tissue sarcoma with deep localisation and had been referred late to centres.

Radiotherapy combined with surgical treatment plays an important role in local tumour control of high-grade soft tissue sarcomas (36). In a series of 91 patients with high-grade soft tissue sarcomas, Yang et al. performed extremity-sparing surgery and adjuvant RT, and reported a decrease in local recurrence in the patients who had received RT (37). A retrospective study by De Laney et al. examined patients with gross and microscopic positive surgical margins who received RT for curative purposes, and concluded that if re-resection is possible without leaving a functional deficit, RT alone should not be selected (38). In the current study, the local recurrence rates at the end of a 3-year follow-up period were 24% in R0 cases receiving surgical treatment alone, 21% in R0 cases treated with surgery and RT, and 38% in R1 cases applied with RT only. Similar to the literature data of Yang (37) and De Laney (38), RT applied to cases in this series with R0 surgical margin reduced the rate of local recurrence, and there was observed to be an increase in local recurrence rates after the application of RT alone. In a retrospective study of 133 patientts, Khanfir et al. showed that when patients with a surgical margin <10mm received adjuvant RT, statistically significant local tumour control was achieved, and this was not obtained in patients with a surgical margin of ≥10mm (39). Similar results were reported by Baldini (40) and Sadoski (41). As stated in the studies by Khanfir (39) and Baldini (40), adjuvant RT in the current study was applied to high-risk nerve regions (neurovascular sheath) and to patients with a high probability of local recurrence, and there was observed to be a decrease in local recurrences (42).
This study had some limitations; first of all, besides being a retrospective study, the follow-up period is not very long. the number of patients is relatively small due to the low incidence of soft tissue sarcoma. in addition, the treatment of many sarcomas varies within itself and is not standardized. in addition, series that are completely homogeneous in terms of patient age, tumor types, sizes, grades and that include a large number of patients are only possible in multicenter studies. our study is a single center study.

In conclusion, for patients with soft tissue sarcoma with extremity localisation, the primary treatment option should be R0 resection protecting the extremity functions. The most valuable major indicator evaluating the quality of surgery of soft tissue sarcomas is the local recurrence-free interval. Therefore, importance must be given to the factors affecting local recurrence such as the surgical margin, size, grade, localisation and histopathological type of the tumour, and unplanned or insufficient surgery. In recent series the local recurrence-free rate varies between 9% and 20%. To be able to provide optimal surgical quality, sarcoma cases should be discussed in multidisciplinary tumour panels and treatments must be personalised according to the clinical and demographic characteristics of the patient and the histopathological type of the sarcoma. Training should be planned for primary care physicians and patients and patients should be referred directly to a sarcoma centre to enable early diagnosis and treatment and avoid unplanned surgery.

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OPEN

RESEARCH ARTICLE

A Single Centre Retrospective Analysis of Operated Intradural Spinal Tumor Cases

Opere İntradural Spinal Tümor Olguların Tek Merkezli Retrospektif Analiz Çalışması

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ABSTRACT

Objective: This study aimed to compare the outcomes of spinal intradural tumor patients treated surgically in our center with the results previously reported in the literature.

Materials and Methods: The study was approved by the ethics committee of Necmettin Erbakan University and conducted in accordance with the Declaration of Helsinki. Patient data used in the study were protected according to ethical rules and confidentiality principles. Parameters such as complaints at presentation, age, gender, neurological examination findings, tumor localization, extent of resection, histopathological diagnosis, Modified McCormick Scale (MMS), as well as operation method and complications, were evaluated. The extent of resection was analyzed in three groups as gross total resection (GTR), subtotal resection (STR) and biopsy (Bx).

Results: In the sample, 62.1% of the patients were female. The most common complaint was axial pain (41.3%). The most common neurological examination finding at the time of presentation across all patients was motor weakness (60.1%). Pathological examination of the tumors revealed meningiomas in 35 patients (42.6%), schwannomas in 17 patients (20.7%), and ependymomas in 9 patients (10.9%). Most of the identified meningiomas were localized in the thoracic region, while schwannomas were frequently localized in the lumbar region. The mean MMS was the highest (2.5) in patients with thoracally located masses. Partial or complete recovery was observed in 67% of the patients who underwent surgical treatment. The most common postoperative complication was neuropathic pain (10.9%).

Conclusion: Spinal tumor surgery is difficult and requires attention. Determining the specific tumor and its exact location is important for the reduction of mortality and morbidity in spinal tumors. Since excessive laminectomy during surgery may increase the risk of developing postoperative kyphosis, caution should be exercised. If more than two levels of laminectomy are required, stabilization may be needed to maintain sagittal balance. Early diagnosis and surgical treatment are important in patients with spinal intradural tumor.

Keywords: Spinal tumor, intradural tumor, spinal meningiomas, spinal schwannomas

ÖZET

Amaç: Bu çalışmanın amacı merkezimizde cerrahi olarak tedavi edilen spinal intradural tümör hastalarının literatür eşliğinde karşılaştırılmasıdır.

Gereç ve Yöntemler: Bu çalışma, Necmettin Erbakan Üniversitesi Etik Kurulu tarafından onaylandı ve Helsinki Bildirgesi'ne uygun olarak yürütüldü. Çalışmada kullanılan hasta verileri etik kurallara ve gizlilik ilkelerine göre korundu. Hastaların başvuru şikayetleri, yaşı, cinsiyeti, nörolojik muayene bulguları, tümör lokalizasyonu, rezeksiyon kapsamı, histopatolojik tanı, Modifiye McCormick Skalası (MMS), operasyon yöntemi ve komplikasyonu gibi parametrelerine bakıldı. Rezeksiyon kapsamı Gross total rezeksiyon (GTR), Subtotal rezeksiyon (STR) ve biyopsi (Bx) yapılan hastalar olmak üzere 3 grupta incelendi.

Bulgular: Bu çalışmada hastaların %62,1'i kadın idi. En sık görülen şikayet aksiyel ağrı (%41,3) idi. Tüm hastalar incelendiğinde başvuru anında en sık görülen nörolojik muayene bulgusu motor kuvvet kaybı idi (%60,1). Tümörlerin patolojik incelemeleri sonucunda 35 hastada (%42,6) menenjiom, 17 hastada (%20,7) schwannom, 9 hastada (%10,9) epandimom tespit edildi. Menenjiomların çoğu torakal bölgede yerleşmişken, schwannomların sıklıkla lomber bölgede yerleşim gösterdiği görüldü. Torakal yerleşimli kitlesi olan hastalarda MMS ortalaması en yüksek (2,5) olarak bulundu. Cerrahi tedavi uygulanan hastaların %67'sinde kısmen veya tam düzelme görüldü. En sık karşılaşılan postoperatif komplikasyon nöropatik ağrı (%10.9) oldu.

Sonuç: Spinal tümör cerrahisi zordur ve dikkat gerektirmektedir. Hangi tümöre ve hangi bölgeye nasıl yaklaşılacağının bilinmesi spinal tümörlerde mortalite ve morbiditenin azaltılmasında önemlidir. Cerrahideki zorluklara rağmen mikroşirürjikal tekniklerin gelişmesi, bipolar ve ultrasonik aspiratör kullanımının yaygınlaşması, peroperatif nöromonitör kullanımı ile komplikasyonsuz gross total rezeksiyon mümkündür. Cerrahi sırasında aşırı laminektomi, postoperatif kifoz gelişme riskini artırabilir; bu nedenle dikkat edilmelidir. İki seviyeden fazla laminektomi gerekiyor ise sagittal dengeyi korumak amaçlı stabilizasyon ihtiyacı doğabileceği akılda tutulmalıdır. Erken tanı ve cerrahi tedavi spinal intradural tümör hastalarında önemli yer tutmaktadır.

Anahtar Kelimeler: Spinal tümor, intradural tümor, spinal menengiom, spinal schwannom

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INTRODUCTION

Depending on their anatomical location, spinal tumors are broadly categorized into extradural (ED) (50%), intradural extramedullary (IDEM) (40%), and intradural intramedullary (IDIM) (4-10%). Spinal intradural tumors (SIDT) are rare and are mostly benign and primary tumors (1). In adults, primary spinal cord tumors are most commonly localized in IDEM (63-65%). IDEM tumors originate from meningoepithelial cells. Almost all IDEM tumors are of neuroepithelial origin (2). One of the rare causes of IDEM tumors is metastasis (3).

Although surgical resection is the mainstay of treatment for SIDTs, its indication remains debatable. The decision is usually based on neurologic findings. In this context, this study compares the presenting complaints, age, gender, neurological examination findings, tumor localization, extent of resection, histopathological diagnosis, Modified McCormick Scale (MMS), operative method, and complications of patients with SIDT treated surgically in our center.

MATERIALS AND METHODS

We retrospectively analyzed medical records of a total of 95 patients operated between 2012 and 2023 with the diagnosis of SIDT in our center. A total of 13 patients whose histopathological diagnosis could not be confirmed and whose examination and imaging records were not available were excluded from the sample. The following parameters were evaluated: complaints at presentation, age, gender, neurological examination findings, tumor localization, extent of resection, histopathological diagnosis, Modified McCormick Scale (MMS), operation method, and complications. According to the extent of resection, the following three groups were formed: (1) gross total resection (GTR); (2) subtotal resection (STR); and (3) biopsy (Bx). Gross total resection was defined as over 90% resection and below 10% residual tumor on postoperative control magnetic resonance imaging (MRI). Subtotal resection was considered as the extent of resection between GTR and Bx. Biopsy was defined as taking only a sufficiently small sample from the intradural tumor to make a diagnosis.

The results showed no difference between total and gross total resection in terms of recurrence.

Modified McCormick Scale was used to evaluate motor functions (see Table 1) (4). This scale is used to grade patients on a scale from 1 to 5 according to motor strength and sensory functions; with an increase of the deficit, the score increases.

RESULTS

Of the 82 patients with spinal tumors screened in our study, 51 were female and 31 were male. The mean age of the sample was 51.6 years in women and 56 years in men. Thoracic region was most commonly involved in women, while lumbar region was most commonly observed in men (see Table 2).

The most common presenting complaints were axial pain (41.3%), weakness (26.1%), numbness (25.6%), as well as urinary and faecal incontinence (6.7%). Depending on the level of tumor localization, patients were analyzed in the following: cervical, thoracic, thoracic 12- lumbar 1vertebral junction region, and lumbar region. According to this grouping, the most common complaints were axial pain in the cervical region, weakness in the legs in the thoracic region, pain and weakness in the legs in the T12-L1 junction region, and axial pain and pain in the legs in the lumbar region (see Table 3). The results of the analysis revealed that the most common neurological examination finding at presentation was motor weakness (60.1%), followed by sensory disturbances (58.5%) and the presence of pathological reflexes (50%). Motor impairment was observed in 80% of patients with thoracic involvement and thoraco-lumbar junction involvement. Sensory impairment was detected in all but one patient with cervical region involvement (see Table 4).

Table 1. Modified McCormick Scale

Grade	Explanation
I	Neurollogyically intact, ambulates normally, may have minimal dysesthesia
II	Mild motor or sensory deficit; patient maintains functional independence
III	Moderate deficit, limitation of function, independent with external aid
IV	Severe motor or sensory deficit, limit of function with a dependent patient
V	Paraplegic or quadriplegic, even if there is flickering movemenet

Table 2. Age and Gender Disribution By Level

		Cervical	Thoracic	T12-L1	Lumbar
Gender	Female (62,1%)	7	25	3	16
	Male (37,8%)	7	10	2	12
Age	0-18 (3,6%)	0	2	0	1
	19-35 (12,1%)	0	5	1	4
	36-50 (25,6%)	4	5	1	11
	51-65 (25,6%)	6	7	1	7
	65+ (32,9%)	4	16	2	5

Table 3. Complaints According to The Level of Tumor

		Cervical	Thoracic	T12-L1	Lumbar
Pain (41,3%)	Axial (43)	8	17	1	17
	Arm (1)	1	0	0	0
	Leg (33)	0	12	4	17
	Arm and Leg (2)	2	0	0	0
Numbness (25,6%)	Arm (4)	4	0	0	0
	Leg (40)	1	23	1	15
	Arm and Leg (5)	5	0	0	0
Urinary Incontinence (5,7%)		1	7	2	1
Faecal Incontinence (1%)		0	1	1	0
Weakness (26,1%)	Arm (6)	5	0	0	0
	Leg (38)	0	26	4	8
	Arm and Leg (6)	6	0	0	0

Table 4. Neurological Examination Findins According To Levels

		Cervical	Thoracic	T12-L1	Lumbar
Sensory Disturbances (58,5%)	Arm (5)	5	0	0	0
	Leg (36)	1	20	3	12
	Arm and Leg (7)	7	0	0	0
Numbness (25,6%)	Monoparesis (19)	7	7	1	4
	Paraparesis (25)	1	17	3	4
	Hemiparesisi (1)	0	1	0	0
	Quadriparesis (3)	2	1	0	0
	Pleji (2)	0	2	0	0
Bladder Sphincter Dysfunction (10,9%)		0	6	2	1
Anal Sphincter Dysfunction (2,4%)		0	1	1	0
Pathological Reflex (50%)	Babinski (34)	8	23	2	1
	Hoffman (7)	4	2	0	1
Deep Tendon Reflex (lower Limb)	Hyperactive (34)	9	24	0	0
	Hypoactive (19)	1	2	2	14
	Normoactive (6)	1	0	0	15
Deep Tendon Reflex (Upper Limb)	Hyperactive (5)	2	2	0	1
	Hypoactive (8)	4	1	1	2
	Normoactive (55)	2	27	4	22

Table 5. Histopathological Diagnoses and Tumor Localisation by Level

	Cervical	Thoracic	T12-L1	Lumbar
Menengioma (42,6)	11	24	0	0
Shwannoma (20,7%)	2	1	1	13
Ependymoma (10,9)	1	0	1	7
Metastatic tumors (3%)	0	2	0	1
Arachnoid Cyst (6,1%)	0	2	2	1
Meningothelial Hyperplasia (1,2%)	0	1	0	0
Cavernous Haemangioma (1,2%)	0	1	0	0
Plasmacytoma (1,2%)	0	1	0	0
B-cell NHL (1,2%)	0	1	0	0
Lipoma (1,2%)	0	1	0	0
Neurenteric Cyst (1,2%)	0	1	0	0
Mature Cystic Teratoma (1,2%)	0	0	0	1
Neurofibroma (1,2%)	0	0	0	1
Ependymal Cyst (1,2%)	0	0	0	1
Heamangioblastoma (1,2%)	0	0	0	1
Precursor B Cell Neoplasia (1,2%)	0	0	0	1
Low-Grade Glial Neoplasia (1,2%)	0	0	0	1
Atypical Lymphoid Infiltration (1,2%)	0	0	1	0
IDEM (75,6%)	12	29	4	17
IM (17%)	1	4	0	9
ID+ ED (7,3%)	1	2	0	2

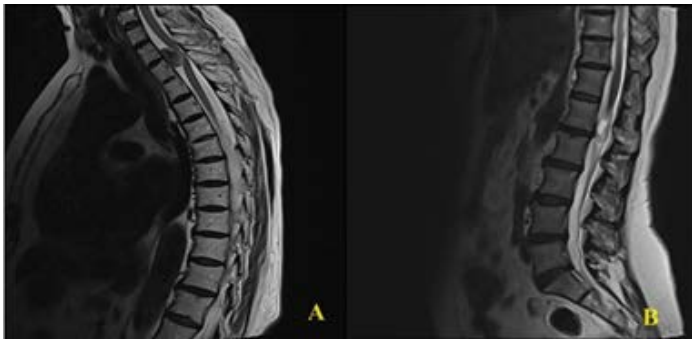

Figure 1. Histopathological Diagnoses and Tumor Localisation by Level
A. T2 sequence sagittal section magnetic resonance imaging (MRI) showing meningioma in the thoracic region
B. T2 sequence sagittal section MRI showing shwannoma in the lumbar region

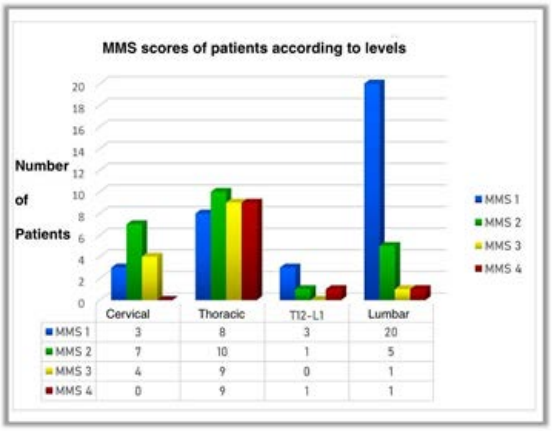

Figure 2. MMS Score of Patients According to Levels
MMS: Modified McCormick Scale

The results of our analysis of localization of the spinal tumors in the spinal canal showed that the tumor was located in IDEM in 62 patients (75.6%), IDIM in 14 patients (17%), and both intradural and extradural in 5 patients (7.3%). Pathological examination of the tumors revealed meningioma in 35 patients (42.6%), schwannoma in 17 patients (20.7%), ependymoma in 9 patients (10.9%), and arachnoid cyst in 5 patients (6.1%). Finally, metastatic tumors were detected in 3 patients (see Table 5). While most of the meningiomas were localized in the thoracic region, meningiomas were frequently found in the lumbar region (see Figure 1).

The analysis of the MMS scores of the patients at presentation according to the localization level of the tumor showed that the mean MMS score of the patients with thoracic mass (2.5) was higher than the others. In 74% of patients with lumbar masses, the mean MMS score was 1 (see Figure 2).

All patients included in the sample underwent surgical treatment. Regarding the extent of surgical resection, 62 patients underwent GTR, 18 patients underwent STR and 2 patients underwent Bx. Single level laminoplasty was performed in 13 patients, 2-level laminoplasty in 46 patients, 3-level laminoplasty in 7 patients, 4-level laminoplasty in 3 patients, single level laminectomy in 4 patients, 2-level laminectomy in 12 patients, and, finally, 3-level laminectomy in 1 patient (see Table 6).

The results of the evaluation of postoperative clinical results revealed that, according to the extent of resection, 67% of all patients showed partial/complete postoperative

Table 6. MMS Score of Patients According to Level

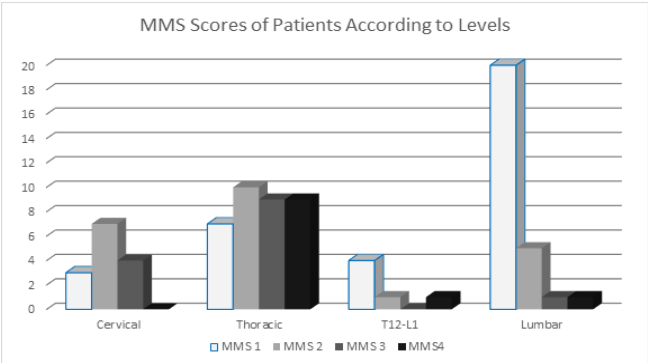

Table 8. Clinical Results According to The Extent of Resection

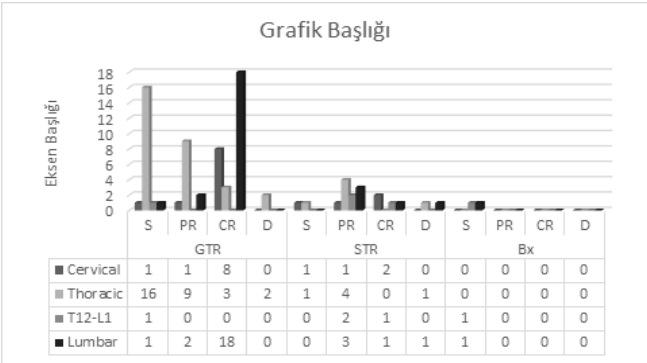

Table 7. Surgical Treatment

	Single level laminoplasty	2 level laminoplasty	3 level laminoplasty	4 level laminoplasty	Single level laminectomy	2 Level laminectomy	3 level laminectomy
Cervical	1	9	1	0	2	1	0
Thoracic	6	20	2	0	1	10	1
T12- L1	0	2	2	1	0	0	0
Lumbar	6	15	2	2	1	1	0

Table 9. Postoperative Complication

Postoperative Complication	Cervical	Thoracic	T12-L1	Lumbar
Neuropathic Pain	3	1	1	4
Wound Site Infection	0	0	0	1
Bos Fistula	0	0	0	1
Faecal-Urinary Incontinence	1	0	1	0
Pneumonia	0	1	0	0

improvement. Complete recovery (CR) was observed in 29 (46.7%) and partial recovery (PR) in 11 (17.7%) of 62 patients who underwent GTR. Of the 18 patients who underwent STR, 10 (55%) had PR and 4 (22.2%) had CR. The clinic was the same (S) in both patients who underwent biopsy. The neurological examination showed that the condition of the 2 patients who underwent GTR and 1 patient who underwent STR was deteriorated (D) in the postoperative period (see Figure 3).

Neuropathic pain developed in 9 patients (10.9%) as postoperative complication. Rarely, wound site infection was observed in 1 patient, Cerebrospinal fluid (CSF) fistula in 1 patient, faecal-urinary incontinence in 2 patients, and pneumonia in 1 patient (Table 9). Recurrence was observed in 1 (2.8%) patient with meningioma, 1 (5.9%) patient with schwannoma, and 1 (25%) patient with arachnoid cyst in the 5th postoperative year; 1 (33%) patient with metastasis in the 3rd month; 2 patients with haemangioblastoma and non-Hodgkin's lymphoma in the 1st year.

DISCUSSION

Intradural spinal tumors constitute 4% of all spinal tumors and 90% of them are extramedullary. For most part, intradural spinal tumors are benign tumors presenting clinically with mass effect rather than tissue invasion. In previous studies, the segmental distribution of spinal tumors was found to vary in different case series. In the series of Baykaner et al. (5), 56% thoracic, 24% lumbar, and 20% cervical localizations were reported. Furthermore, as reported by Temiz et al. (6), the most common localizations were thoracic and lumbar regions and both regions were found to be equal (29.78%). Total resection was achieved with microsurgery in the treatment of spinal tumors (7).

Meningiomas originate from arachnoid villi, dural fibroblasts and pia mater where the nerve root sheath meets the dura. Together, they constitute 25% of all intradural tumors. Meningiomas are more common in women than in men and are typically observed in patients aged between 40 and 50 years old. Spinal involvement is more common in children. Thoracic, cervical and lumbar regions are most commonly involved (8). The most common presenting complaint is loss of strength (92.5%), followed by sensory disturbance (60.9%), pain (53%_, and sphincter disturbance (50%). (9). Furthermore, previous neurological examination findings in spinal meningioma patients revealed that motor disorder findings were 99%, sensory disorder findings were 97% and sphincter disorder findings were 51% in Solero's meningioma series (9). Surgical treatment was applied in the treatment of cases like other spinal tumor treatments. Differently, bipolar coagulation of the dura from which the meningioma originates is recommended in the surgical treatment of meningioma because it causes less recurrence (8).

Schwannomas are benign tumors originating from the sensory branches of the cranial or spinal nerves, mostly with IDEM involvement. Unlike intracranial schwannomas, spinal schwannomas are more common in males than in females. (male/female ration = 3:1). Schwannomas are most commonly found in the thoracic region, followed by the caudal region. Schwannomas cause complaints such as radicular pain (80%) or loss of motor power and sphincter problems (10%). Since only one nerve root is frequently affected, segmental pain also occurs (10). there is evidence to suggest that the most common examination findings in patients with spinal schwannomas concerned the loss of strength (20%) and sensory deficit (16.7%) (11). Previous studies reported that ependymomas are most commonly located in the lumbar region (57%) and secondly in the cervical region (12). In children, these tumor are more commonly located in the conus (7). In Cooper's study (12), the complaints of patients with ependymoma were reported as pain, sensory disturbance, loss of strength and sphincter disturbance in order of frequency. Ependymoma is frequently centrally located. Epandimomas cause paresis in the late period. Accordingly, in patients with epandimoma, the whole spinal axis should be scanned (13).

In the present study, gender distribution of all spinal tumor patients was 3/2 (male/female) and the mean age was 53.8 years, which is consistent with the literature. Most of the identified cases were benign tumors. With regard to anatomical localization, extramedullary localization was the most common (75.6%). Both intradural and extradural localization were found in 7.3% and intramedullary localization in 17%. The most common site was thoracic region (42.6%), while the second most common site was lumbar region (34.1%). In our series, patients presented with pain (41.3%), loss of strength (26.1%), sensory disturbance (25.6%), and sphincter disturbance (6.7%), respectively. In the initial neurological examination, 60.1% of the patients reported having motor impairment, 58.5% had sensory impairment, and 13.3% had sphincter impairment. An evaluation of the MMS scores at the time of presentation showed that in the patients with thoracic mass with 2.5 points had the highest score.

In our study, meningioma was found to be the most common intradural tumor, with incidence rates exceeding those previously reported in the literature (42.6%). These cases involved thoracic and then cervical regions, respectively,

in accordance with the literature. The second most common tumor (20.7%) in our series was schwannoma. Contrary to several previous reports, schwannomas in our results were most commonly seen in the lumbar region (76.4%) and less frequently in the thoracic region (5.8%). Ependymomas involved the lumbar region were the most frequent (77.7%) in our series, which is fully aligned with the literature. Spinal tumor surgery is difficult and requires attention. Determining the specific tumor and its exact location is important to reduce mortality and morbidity in spinal tumors. Despite the difficulties in surgery, gross total resection without complications is possible with the development of microsurgical techniques, the widespread use of bipolar and ultrasonic aspirators, and the use of peroperative neuromonitoring.

However, considering the risk of postoperative kyphosis development from excessive laminectomy, surgery requires extra care. If over two levels of laminectomy are required, it stabilization may be needed to maintain sagittal balance. Lateral masses in the cervical region should be exposed and protected. In our case series, all patients underwent surgical treatment with posterior intervention (laminectomy, laminotomy, laminoplasty). Laminoplasty was performed in 78.5% of patients with cervical IDD masses, 70% of patients with thoracic IDD masses, all patients with T12-L1 localized IDD masses, and 92.6% of patients with lumbar IDD masses.
Postoperative partial or complete recovery was observed in 67% of all patients.

CONCLUSION

Spinal tumors are an important disease group in neurosurgical practice. Imaging and clinical findings should be carefully evaluated in patients to be operated for spinal tumor. Relevant surgical method(s) should be determined by considering all possible postoperative outcomes. The present study has several limitations. First, considering the retrospective nature of the present research, a bias may during data collection and analysis cannot be completely ruled out. Second, our sample consisted of 82 patients. By performing multi-center meta-analysis studies, the results of this and similar studies can be generalized to larger populations. In this study, recurrence and complications were evaluated in the 5-year postoperative follow-up of the patients. Meta-analysis studies involving more patients with longer follow-up periods in patients operated for spinal intradural tumors may reveal the complication and recurrence rates more clearly. Conducting prospective studies with larger cohorts in the future would provide a more comprehensive understanding of the outcomes of spinal tumor surgery.

DECLARATIONS

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

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OPEN

RESEARCH ARTICLE

Exploring the Link Between Serum Magnesium Levels and Acne Vulgaris Severity

Serum Magnezyum Seviyeleri ve Akne Vulgaris Şiddeti Arasındaki İlişkinin İncelenmesi

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ABSTRACT

Objective: Acne vulgaris is a prevalent long-term inflammatory skin disorder that notably impacts the quality of life, especially in teenagers and young adults. Although the pathogenesis of acne is influenced by multiple factors, the contribution of micronutrients like magnesium is not yet fully elucidated. This study sought to explore the relationship between serum magnesium concentrations and the severity of acne as assessed by the Global Acne Grading System (GAGS).

Materials and Methods: A case-control study with a prospective design was carried out at a single center between March and August 2023, including 60 individuals diagnosed with acne vulgaris and 60 healthy controls matched by age and sex, all between 18 and 30 years old. The severity of acne was evaluated using the GAGS and classified as mild, moderate, or severe. Serum magnesium levels were determined through the Xylidyl Blue colorimetric assay. Data were analyzed using SPSS version 29. For continuous variables not normally distributed, the Kruskal–Wallis H test was employed, with statistical significance defined as $p < 0.05$.

Results: The study included 34 female and 26 male acne patients and 31 female and 29 male healthy controls. No statistically significant differences were observed in serum magnesium levels among acne severity groups or between patients and controls ($p > 0.05$). Although the moderate acne group had slightly higher mean magnesium levels compared to mild and severe groups, the differences were not statistically significant. Magnesium concentrations remained within normal limits across all groups.

Conclusion: Our results indicate that there is no significant association between serum magnesium levels and the severity of acne. While systemic magnesium seems to have a limited role in the pathogenesis of acne, topical magnesium preparations might provide therapeutic advantages due to their anti-inflammatory and antimicrobial properties. Further studies are necessary to better understand its efficacy.

Keywords: Acne vulgaris, acne severity, global acne grading system, magnesium

ÖZET

Amaç: Akne vulgaris, özellikle ergenler ve genç yetişkinlerde yaşam kalitesini önemli ölçüde etkileyen yaygın, uzun süreli bir inflamatuvar cilt hastalığıdır. Aknenin patogenezi çok sayıda faktörden etkilenmekle birlikte, magnezyum gibi mikrobesinlerin katkısı henüz tam olarak aydınlatılamamıştır. Bu çalışma, serum magnezyum konsantrasyonları ile Global Akne Derecelendirme Sistemi (GAGS) ile değerlendirilen akne şiddeti arasındaki ilişkiyi araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Mart ve Ağustos 2023 tarihleri arasında tek bir merkezde prospektif tasarımlı bir vaka-kontrol çalışması yürütülmüştür. Çalışmaya, yaş ve cinsiyet açısından eşleştirilmiş, 18-30 yaş aralığında 60 akne vulgaris tanısı almış birey ve 60 sağlıklı kontrol dahil edilmiştir. Akne şiddeti, GAGS kullanılarak değerlendirilmiş ve hafif, orta veya şiddetli olarak sınıflandırılmıştır. Serum magnezyum seviyeleri, Xylidyl Blue kolorimetrik yöntemiyle belirlenmiştir. Veriler SPSS sürüm 29 kullanılarak analiz edilmiştir. Normal dağılım göstermeyen sürekli değişkenler için Kruskal-Wallis H testi kullanılmış ve istatistiksel anlamlılık $p <0.05$ olarak kabul edilmiştir.

Bulgular: Çalışmaya 34 kadın ve 26 erkek akne hastası ile 31 kadın ve 29 erkek sağlıklı kontrol dahil edilmiştir. Akne şiddet grupları arasında veya hasta ve kontroller arasında serum magnezyum seviyelerinde istatistiksel olarak anlamlı bir farklılık gözlemlenmemiştir ($p> 0.05$). Orta akne grubunda hafif ve şiddetli gruplara kıyasla ortalama magnezyum seviyeleri biraz daha yüksek olmasına rağmen, bu farklılıklar istatistiksel olarak anlamlı değildi. Tüm gruplarda magnezyum konsantrasyonları normal sınırlar içinde kalmıştır.

Sonuç: Sonuçlarımız, serum magnezyum seviyeleri ile akne şiddeti arasında anlamlı bir ilişki olmadığını göstermektedir. Sistemik magnezyumun akne patogenezinde sınırlı bir rolü var gibi görünse de topikal magnezyum preparatları anti-enflamatuar ve antimikrobiyal özellikleri nedeniyle terapötik avantajlar sağlayabilir. İleri çalışmalar, bu potansiyel tedavi yönteminin etkinliğini ve mekanizmasını daha iyi anlamak için gereklidir.

Anahtar Kelimeler: Akne vulgaris, akne şiddeti, global akne derecelendirme sistemi, magnezyum

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INTRODUCTION

Acne is a common skin condition that affects 9% of the world's population (1,2). Although more frequently observed in females, acne affects around 85% of adolescents during their lifetime and can persist into adulthood (3,4). Acne lesions are broadly divided into two categories: non-inflammatory types, such as open and closed comedones, and inflammatory types (5). These lesions mostly happen in areas with many sebaceous glands, like the face and chest (6). While the diagnosis of acne is typically straightforward, the polymorphic nature and distribution of lesions can complicate the assessment of disease severity. In most cases, laboratory investigations are not required. However, if there is a suspicion of underlying systemic or secondary causes, further evaluation may be warranted (7). Although the number and types of acne lesions may vary significantly among individuals, assessing clinical severity requires both a thorough physical examination and, ideally, photographic documentation of the lesions (8). Two primary parameters are considered in acne grading: the type of lesions and the extent of the affected skin surface area. The Global Acne Grading System (GAGS) is a widely used, standardized tool that evaluates acne severity based on lesion type and anatomical distribution, aided by textual descriptions and/or photographs (9). GAGS is favored in clinical practice due to its simplicity, reproducibility, and ability to account for lesion size, type, and degree of inflammation. It also enables clinicians to monitor disease progression by focusing on dominant lesion types. Based on this system, acne severity is categorized as mild, moderate, severe, or very severe (9,10).

Recent studies have investigated diet and micronutrients' impact on skin conditions (11–13). In the course of research, it has been demonstrated that the levels of zinc are lower in individuals with acne than in healthy controls. Furthermore, both oral and topical zinc formulations have been shown to be efficacious in the treatment of acne (14,15). Magnesium is an indispensable intracellular cation that fulfils a pivotal role in a multitude of biological processes, encompassing energy metabolism, oxidative phosphorylation, glycolysis, and macromolecule synthesis. Given its physiological importance, magnesium may have a potential role in acne pathogenesis. However, current literature examining the relationship between magnesium and acne remains scarce and inconclusive (16–22). The objective of the present study is to examine the relationship between serum magnesium levels and the severity of acne vulgaris.

MATERIALS AND METHODS

Patients and data collection

This prospective, single-center case-control study was carried out between March 1 and August 1, 2023. Participants were between 18 and 30 years of age and included patients with varying severities of acne vulgaris, as well as age- and sex-matched healthy controls who attended our dermatology outpatient clinic during the study period. All individuals provided written informed consent prior to participation. Inclusion criteria were as follows: patients aged 18–30 years with a clinical diagnosis of acne vulgaris and healthy controls with no history of acne or other chronic skin conditions. Exclusion criteria included: individuals younger than 18 or older than 30 years; those with other dermatologic disorders (e.g., rosacea, seborrheic dermatitis); systemic diseases such as diabetes or renal/liver failure; pregnant or breastfeeding women; and individuals who had recently used systemic/topical retinoids, corticosteroids, antibiotics, dietary supplements, or hormonal therapy. Patients with known metabolic or endocrine disorders were also excluded.

The severity of acne was evaluated using the Global Acne Grading System (GAGS). GAGS allocate a specific weighting factor to each anatomical site, taking into account surface area, lesion distribution, and the density of pilosebaceous units. The severity of lesions (comedones, papules, pustules, and nodules) is graded numerically and subsequently multiplied by a regional factor to derive a local score. The total GAGS score is obtained by summing these local scores. Based on their total scores, patients were classified into three categories: mild, moderate, and severe acne, with the 'severe' and 'very severe' groups merged for the purpose of analysis." Acne severity was assessed by a single dermatologist blinded to the magnesium levels.

For biochemical analysis, a 5 mL peripheral venous blood sample was obtained from each participant. These samples were allowed to clot at room temperature for a one-hour duration, subsequent to which they underwent centrifugation at 2500 revolutions per minute (rpm) for 10 minutes. The resulting serum was then aliquoted and stored at –20°C until further analysis. Serum magnesium levels were measured using the Xylidyl Blue colorimetric method on an Olympus AU2700 autoanalyzer, in accordance with the manufacturer's protocol.The study followed the 1964 Helsinki Declaration and its later amendments. Ethics committee approval was obtained (Decision No: 2022-16/139).

Statistical analysis

Statistical analyses were conducted utilizing IBM SPSS Statistics, version 29. Continuous variables are presented using the mean ± standard deviation and median [range], while categorical variables are reported as frequencies and percentages. For continuous variables exhibiting non-normal distributions across independent groups, comparisons were performed using the Kruskal–Wallis H test. The Shapiro–Wilk test was employed to assess the normality of continuous variables. Associations between categorical variables were evaluated using the Pearson's chi-squared test. Statistical significance was defined as a p-value of less than 0.05 ($p<0.05$). A post hoc power analysis was conducted using G*Power software (version 3.1). Based on an assumed medium effect size ($f = 0.30$), a significance level (α) of 0.05, and a desired power ($1-\beta$) of 0.80, the achieved sample size of 120 participants was determined to be adequate for detecting medium to large effect size differences.

RESULTS

One hundred twenty individuals, including 60 patients

with acne vulgaris (34 females, 26 males) and 60 age- and gender-matched healthy controls (31 females, 29 males), were enrolled in the study. Participants were aged 18 to 30, with an average age of 22.83 ± 3.08 years. The average age of the acne group was 21.55 ± 2.47 years, while that of the control group was 24.12 ± 3.11 years. The distribution of participants by gender is given in Table 1. No statistically significant association was observed between gender and the acne-control groups (p>0.05). Furthermore, both the acne and control groups exhibited a homogeneous distribution with respect to gender. Analysis of the data revealed that within the male sample, eight individuals presented with mild acne (30.8%), twelve with moderate acne (46.2%), and six with severe acne (23.1%). In the female sample, 12 individuals (35.3%) had mild acne, eight individuals (23.5%) had moderate acne, and 14 individuals (41.2%) had severe acne (Table 2). No statistically significant association was observed between gender and GAGS grades (p>0.05). Furthermore, GAGS grades demonstrated homogeneity across genders. A statistical analysis was performed to ascertain potential differences in magnesium levels between the case and control groups. The normality of the data distribution was assessed using the Shapiro-Wilk test. The results of this assessment indicated that the magnesium values within the control and mild acne groups did not conform to a normal distribution (p<0.05). The Kruskal-Wallis H test was employed for comparisons between independent groups with non-normally distributed data. The magnesium values ranged from 1.6 to 3.1; the results are provided in Table 3. Average magnesium levels vary among acne groups, with the moderate acne group (2.0650 ± 0.2412) having higher levels than the mild acne group (2.0100 ± 0.1334) and the severe acne group (1.9850 ± 0.2207). Magnesium levels were normal across all samples from the acne groups. Moreover, statistical analysis revealed no significant difference in magnesium values between individuals in the acne vulgaris and control groups (p>0.05) (Figure 1).

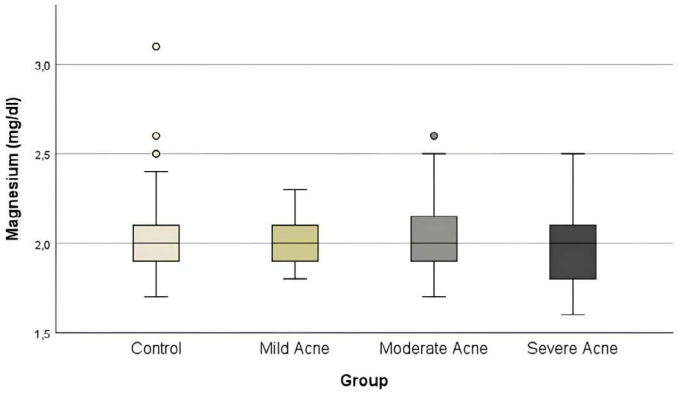

Figure 1. Box plot of serum concentration of Magnesium (mg/dl) in Healthy Control, Mild, Moderate and Severe acne patient groups.

Table 1. Gender of persons, Distribution of Findings, and Relationship with Status (Case-Control)

Gender	Status		Total n (%)	Chi-square Test
	Acne	Control		
Male	26 (47.3)	29 (52.7)	55 (45.8)	χ2=0.302 p=0.583
Female	34 (52.3)	31 (47.7)	65 (54.2)	

Table 2. Gender of persons, Distribution of Findings, and Relationship with GAGS

Gender	GAGS			Total n (%)	Chi-square Test
	Mild Acne	Moderate Acne	Severe Acne		
Male	8 (30.8)	12 (46.2)	6 (23.1)	26 (43.3)	χ2=3.801 p=0.150
Female	12 (35.3)	8 (23.5)	14 (41.2)	34 (56.7)	

GAGS: Global Acne Grading System

Table 3. Relationship between persons' magnesium levels and Status (Case-Control)

Magnesium Levels	GAGS	Mean±SD	Median [Min-Max]	Kruskal-Wallis H
	Control	2.0283±0.2478	2 [1.6-3.1]	χ2=0.926 p=0.819
	Mild Acne	2.0100± 0.1334	2 [1.8-2.3]	
	Moderate Acne	2.0650±0.2412	2 [1.7-2.6]	
	Severe Acne	1.9850±0.2207	2 [1.6-2.5]	

GAGS: Global Acne Grading System

DISCUSSION

Acne is a prevalent and intricate dermatological condition that impacts individuals across the globe. It has various causes and involves diverse factors contributing to its development. The pathological process in acne formation occurs due to some events related to the pilosebaceous unit following and affecting each other. This process involves excessive keratin production, increased sebum production, colonization by anaerobic bacteria, and an inflammatory response (23). Beyond these, emerging findings suggest that changes within the acne lesion are evident. The immune system plays a significant role, stimulated by factors such as Cutibacterium acnes phylotypes, antimicrobial peptides, sebaceous glands, matrix metalloproteinases, and other immune pathways (24). Contemporary investigations into acne pathogenesis underscore the crucial equilibrium among C. acnes phylotype members and the cutaneous microbiota. Emerging evidence posits that the proliferation of C. acnes is not the primary etiological factor in acne development. Rather, acne formation is attributed to a reduction in microbial diversity on the skin and the subsequent activation of innate immunity, culminating in a sustained inflammatory condition (25).

Trace elements, macro minerals, and vitamins are fundamental components playing vital roles in our body's biochemical processes and the immune system. Alterations in their normal homeostasis can harm various biological processes and lead to undesired complications (26,27). Macro minerals, particularly zinc, have been used since ancient times for their therapeutic effects on the skin (28). Zinc is vital for skin health, controlling inflammation, and renewing skin cells (29). Several studies have looked into the impact of zinc levels on acne vulgaris (15-30). Liu et al. found that applying zinc alone or with antibiotics like erythromycin and clindamycin positively affects acne (31).

Magnesium is essential for energy production, muscle contraction, maintaining heart rhythm, nerve transmission, and immune system function. It contributes to glutathione synthesis, DNA/RNA production, and bone development (32). Magnesium is thought to affect sebocytes and the inflammation process in acne pathogenesis. It enhances skin moisture and permeability, promotes skin cell growth for barrier repair, and decreases inflammation and epidermal differentiation. It is hypothesized that hypomagnesemia may elevate inflammatory markers and influence androgen hormones, particularly testosterone, through the stimulation of the hypothalamic-pituitary-gonadal (HPG) axis, consequently leading to increased testosterone secretion. Elevated testosterone levels can increase the activity of sebaceous glands, leading to higher sebum production and exacerbating acne formation (19).

We analyzed magnesium levels in patients with acne vulgaris compared to a healthy control group. The findings revealed no statistically significant difference in magnesium levels between the two groups across the various GAGS grades (p=0.819). Our study's findings are consistent with two previous studies (Saleh et al. and Salma et al., which also found no statistically significant difference in magnesium levels between different severities of acne vulgaris (p>0.05) (21,22). In contrast to the present investigation, Saleh et al. reported reduced magnesium levels in the severe acne group relative to the mild acne group. Tamara et al. found a direct link between acne severity and magnesium levels, but their cross-sectional design and observational nature raise concerns about the evidence (19). Chandrasekaran et al. discovered a distinct inflammatory reaction in the skin of people with magnesium deficiency (33).

Welch et al. investigated the antibacterial efficacy of topical mesoporous magnesium carbonate (MMC), employing Staphylococcus epidermidis as the model organism. This bacterium is frequently found in acne vulgaris lesions because it is common in human skin and develops antibiotic resistance. MMC has a potent antibacterial effect on bacteria, mainly attributed to the environmental change in alkalinity (34). Across two clinical investigations, Fabbrocini et al. administered liposomal magnesium in conjunction with folic acid and topical antibiotics, and a reduction in acne lesions was noted (35). Koshel and Chebotarev divided 252 patients with connective tissue dysplasia and acne into two groups in a separate study. They added magnesium-containing drugs to the regimen of the second group (126 individuals) and observed an improvement in acne severity (36). While magnesium has been shown to reduce acne in these studies, combining treatments in both studies limits their findings. It is challenging to attribute the healing of acne lesions solely to magnesium.

Muyan Li et al.'s investigation of 1137 women revealed significantly elevated copper concentrations (P<0.001) and reduced serum calcium levels (P<0.001) in individuals with polycystic ovary syndrome (PCOS) compared to controls. No significant differences were detected in serum zinc, magnesium, or iron levels between the groups. Within the PCOS cohort, higher magnesium levels were associated with the presence of acne (P=0.020), while lower magnesium levels correlated with hirsutism (P=0.037). This suggests a correlation between magnesium concentrations and acne and hirsutism in PCOS patients (37). Jaripur et al., in their study on 64 PCOS patients, divided them into two groups, one of which received daily oral magnesium oxide supplementation of 250 mg (for ten weeks). They reported no significant effect of this supplementation on acne severity (20).

Study limitations

Limitations of the present study include the relatively small sample size restricted to individuals aged 18–30 years, which may limit the generalizability of the findings. Furthermore, as this was a single-center study, the results may not fully represent populations with diverse geographic and sociodemographic characteristics. Finally, only serum magnesium levels were evaluated, whereas cellular or tissue magnesium measurements could provide a more comprehensive understanding of its role in acne pathogenesis.

CONCLUSIONS

In conclusion, our findings do not support a significant role for serum magnesium levels in acne severity. While oral magnesium shows limited benefit, topical magnesium formulations may have potential due to their anti-inflammatory and antibacterial effects. Further research is warranted to clarify these observations.

DECLARATIONS

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OPEN RESEARCH ARTICLE

Evaluation of Hematologic Inflammatory Markers in Missed Abortus: A Retrospective Case-Control Study

Missed Abortus Olgularında Hematolojik İnflamatuvar Belirteçlerin Değerlendirilmesi: Retrospektif Bir Vaka Kontrol Çalışması

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ABSTRACT

Objective: This study aims to evaluate the relationship between hematological inflammatory markers neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) and missed abortion, as well as to investigate their potential predictive roles.

Materials and Methods: In this retrospective cross-sectional study, the missed group included 150 pregnant women diagnosed with missed abortion between the ages of 18 and 40. This group was compared to a control group of 150 pregnant women with healthy singleton pregnancies, matched according to gestational week. Demographic data and laboratory results for all cases were collected retrospectively from the hospital automation system. Exclusion criteria included multiple pregnancy, recurrent pregnancy loss, chronic illness, history of malignancy, smoking or alcohol use, hereditary thrombophilia, and a history of anhydramnios.

Results: The demographic characteristics of the groups were similar (p>0.05). Mean lymphocyte levels were higher in the missed abortion group compared to the control group (p=0.037). The median NLR value was 2.88 (2.26–3.66) in the control group and 2.62 (1.81–3.44) in the missed abortion group, showing a significant difference (p=0.018). No significant differences were observed between the groups in other hematological parameters (WBC, neutrophil count, RBC, platelet count, HCT, MCV, MPV, PDW, RDW, INR, and hemoglobin) or in inflammatory indices such as PLR (p=0.057) and SII (p=0.073). In the subgroup analysis of pregnancies under 12 weeks, WBC and lymphocyte levels were higher in the missed abortion group, whereas PLR was higher in the control group (p<0.05).

Conclusion: The etiology of missed abortion remains unexplained in most cases. This study suggests that NLR and lymphocyte levels may have predictive value in the diagnosis of missed abortion. Particularly in early pregnancy, careful evaluation of these parameters may contribute to the identification of high-risk cases.

Keywords: Missed abortion, inflammatory markers, NLR, PLR, SII

ÖZET

Amaç: Bu çalışmanın amacı, hematolojik inflamatuar belirteçler olan Nötrofil/Lenfosit Oranı (NLR), Trombosit/Lenfosit Oranı (PLR) ve Sistemik İmmün-İnflamatuar İndeks (SII) ile missed abortus arasındaki ilişkiyi değerlendirmek ve bu belirteçlerin öngörüdeki potansiyel rollerini araştırmaktır.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışmada, 18–40 yaş aralığında missed abortus tanısı alan 150 gebeden oluşan missed grubu ile gebelik haftasına göre eşleştirilmiş, sağlıklı tekil gebelikleri bulunan 150 gebeden oluşan kontrol grubu karşılaştırılmıştır. Çalışmaya dahil edilen tüm olguların demografik verileri ve laboratuvar sonuçları, hastane otomasyon sisteminden retrospektif olarak elde edilmiştir. Çoğul gebelik, tekrarlayan gebelik kaybı, kronik hastalık, kanser öyküsü, sigara/alkol kullanımı, kalıtsal trombofili ve anhidroamniyoz öyküsü olanlar çalışma dışı bırakılmıştır.

Bulgular: Grupların demografik özellikleri benzerdi (p>0,05). Missed abortus grubunda ortalama lenfosit düzeyleri kontrol grubuna göre daha yüksekti (p=0,037). NLR medyan değeri de kontrol grubunda 2,88 (2,26–3,66) iken, missed grubunda 2,62 (1,81–3,44) olarak saptandı ve bu fark anlamlıydı (p=0,018). Diğer hematolojik parametreler (WBC, nötrofil sayısı, RBC, trombosit sayısı, HCT, MCV, MPV, PDW, RDW, INR ve hemoglobin) ile inflamatuvar belirteçlerden PLR (p=0,057) ve SII (p=0,073) açısından gruplar arasında belirgin fark izlenmedi. Alt grup analizinde (gebelik <12 hafta), missed abortus grubunda WBC ve lenfosit düzeyleri daha yüksek, PLR ise kontrol grubunda daha yüksek bulundu (p<0,05).

Sonuç: Missed abortus etiyolojisi çoğu vakada açıklanamamaktadır. Bu çalışma, NLR ve lenfosit düzeylerinin missed abortus tanısında prediktif değer taşıyabileceğini göstermektedir. Özellikle gebeliğin erken döneminde bu parametrelerin dikkatle değerlendirilmesi, riskli olguların belirlenmesine katkı sağlayabilir.

Anahtar Kelimeler: Missed abortus, inflamatuar belirteçler, NLR, PLR, SII

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INTRODUCTION

Missed abortion is defined as the intrauterine retention of a nonviable fetus before the 20th week of gestation (1). Miscarriage occurs in nearly 15% of clinically identified pregnancies (2). Loss of pregnancy without medical intervention is frequently observed and represents a significant health issue among women of reproductive age, with about 25% of women experiencing at least one miscarriage during their lifetime (3). Abortions are categorized as threatened, inevitable, complete, incomplete, septic, missed, or anembryonic types. In missed abortion cases, the precise moment of fetal demise is generally unknown (4). It is one of the most frequent complications in early pregnancy (5). The etiopathogenesis of missed abortion includes several factors such as chromosomal anomalies, advanced maternal age, previous pregnancy losses, endocrine disorders, obesity, diabetes, thyroid disorders, inherited thrombophilia, drug and substance use, infections, cervical insufficiency, and uterine structural abnormalities (e.g., fibroids, polyps, septum, or intrauterine adhesions (2,6). However, in nearly 50% of cases, no underlying cause can be identified.

Although inflammation is recognized as a normal physiological process during early pregnancy, pathological examinations of curettage specimens often show inflammation as the most common histopathological finding (7,8). The exact timing and mechanism by which inflammation leads to miscarriage remain unclear (9). Inflammatory markers, such as the values of PLR and NLR, are obtained through complete blood counts that include lymphocyte, neutrophil, and platelet counts. These markers are commonly used to evaluate systemic immune response and infection. Recently, these ratios have been linked to chronic inflammatory diseases, cardiovascular conditions, and malignancies (10–12). In this context, the Systemic Immune-Inflammation Index (SII), calculated as (neutrophil count × platelet count) divided by lymphocyte count, is seen as a more comprehensive parameter that indicates both systemic inflammation and immune response.

These parameters may help clarify inflammatory processes involved in diseases with unknown causes. Since the cause remains unclear in nearly half of missed abortion cases, this study aimed to assess the relationship between hematological inflammatory markers and missed abortion and to explore their potential as predictive indicators.

MATERIALS AND METHODS

The study was conducted at the Obstetrics and Gynecology Clinic of a tertiary hospital from January to June 2023. It used a retrospective case-control design. The case group included 150 pregnant women aged 18-40 who met the inclusion criteria and were diagnosed with missed abortion before 20 weeks. The control group consisted of 150 pregnant women with healthy singleton pregnancies, matched for gestational age at the time of diagnosis in the missed abortion group. All control group participants had routine outpatient follow-up records confirming uncomplicated pregnancies that extended beyond the 20th week of gestation. Inclusion criteria included being between 18 and 40 years old, having a singleton pregnancy of less than 20 weeks, newly diagnosed pregnant women in whom the fetal heartbeat has been detected as absent in the case group, and healthy pregnant women at the same gestational weeks in the control group. Exclusion criteria included multiple pregnancies, a history of recurrent miscarriage, chronic illnesses (such as hypertension, diabetes mellitus, thyroid, and rheumatologic diseases), history of malignancy, alcohol consumption, smoking, hereditary thrombophilia, and anhydramnios.

Demographic data and laboratory results were retrospectively collected from the hospital's electronic database. For the missed abortion group, laboratory values were recorded at the time of diagnosis and hospital admission. For the control group, laboratory data were obtained from the same gestational week as their matched cases, specifically from routine outpatient visits during scheduled antenatal check-ups. This method ensured that both groups were compared using laboratory values taken during the same gestational period and under standardized clinical conditions.

This retrospective case-control study was approved by the local Ethics Committee with an assigned approval number (22.09.2023/ 17/15)

Statistical Analysis

The sample size was calculated using G*Power software. Assuming a moderate effect size (0.5), $\alpha = 0.05$, and a power of 95%, the minimum required sample size was determined to be 210 participants, with at least 105 in each group. Data analysis was performed using IBM SPSS Statistics version 27. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequency and percentage. For comparisons of categorical variables, Pearson's Chi-square test was used when expected frequencies were sufficient; otherwise, Fisher–Freeman–Halton test was applied. For continuous variables, independent t-test was used for normally distributed data and Mann–Whitney U test for non-normally distributed data. Receiver Operating Characteristic (ROC) curve analysis was performed to assess the discriminatory power of markers.A p-value <0.05 was considered statistically significant.

RESULTS

The study comprised a total of 300 participants — 150 with missed abortion and 150 healthy controls. The groups were found to be demographically similar, with no statistically significant differences ($p>0.05$). Table 1 shows the demographic characteristics. Except for lymphocyte count, there were no significant differences between the control and missed abortion groups across routine hematologic indices. The lymphocyte count was higher in the missed abortion group (2.18 ± 0.70 vs. 2.02 ± 0.61 $\times 10^3/\mu L$), and this difference was statistically significant ($p=0.037$; mean difference −0.158, 95% CI −0.306 to −0.010; effect size −0.242). Table 2 presents a comparison of laboratory parameters between the groups.

When comparing inflammatory markers, the control group showed a higher median NLR than the missed group (2.88 [2.26–3.66] vs. 2.62 [1.81–3.44]); this difference was statistically

Table 1. Descriptive Characteristics of Pregnant Women

Variable	Control Group (N=150)	Missed Group (N=150)	t/χ^2	p
Age (years)	26.80 ± 5.36	26.66 ± 5.75	0.218	0.827
Height (cm)	160.82 ± 5.26	161.73 ± 4.00	-1.679	0.094
Weight (kg)	63.50 ± 10.79	64.40 ± 8.41	-0.806	0.421
BMI (kg/m^2)	24.56 ± 4.09	24.55 ± 3.04	0.034	0.973
Gravida	2.15 ± 1.10	2.33 ± 1.33	-1.321	0.187
Parity	1.15 ± 1.10	1.31 ± 1.33	-1.137	0.257
Living Children	1.15 ± 1.10	1.30 ± 1.32	-1.090	0.277
Nationality (Turkish/Syrian)	135 (90.0%) / 15 (10.0%)	126 (84.0%) / 24 (16.0%)	2.387	0.169
Education Level	Various	Various	0.877	0.825
Employment (Yes/No)	76 (50.7%) / 74 (49.3%)	72 (48.0%) / 78 (52.0%)	0.213	0.729
Gestational Age (<12 / ≥12 weeks)	100 / 50	101 / 49	0.015	1.000

Table 2. Comparison of Laboratory Parameters Between Groups (N=300)

Laboratory Parameter	Control Group	Missed Abortion Group	95% confidence intervals (95% CI)	Effect Size	p-value (t/U)
Hemoglobin (g/dL)	12.50 ± 1.03	12.44 ± 1.30	0.053 (−0.214 to 0.319)	0.045	0.698
Platelet (10^3/μL)	258.67 ± 58.28	260.92 ± 66.80	−2.255 (−16.499 to 11.989)	−0.036	0.756
Lymphocyte (10^3/μL)	2.02 ± 0.61	2.18 ± 0.70	−0.158 (−0.306 to −0.010)	−0.242	0.037
Hematocrit (%)	37.35 ± 2.70	37.68 ± 3.49	−0.332 (−1.040 to 0.376)	−0.107	0.357
MCV (fL)	84.05 ± 5.22	83.94 ± 5.41	0.114 (−1.094 to 1.322)	0.022	0.853
INR	1.07 ± 0.08	1.07 ± 0.08	0.003 (−0.014 to 0.021)	0.046	0.694
WBC (10^3/μL)	8.59 (7.24–9.82)	8.55 (7.08–10.3)	−0.130 (−0.650 to 0.390)	0.030	0.650
Neutrophil (10^3/μL)	5.71 (4.60–6.97)	5.58 (4.39–6.84)	0.100 (−0.340 to 0.520)	−0.031	0.644
RBC (×10^6/μL)	4.44 (4.19–4.73)	4.51 (4.23–4.73)	−0.060 (−0.160 to 0.030)	0.092	0.167
MPV (fL)	10.4 (9.9–11.1)	10.4 (9.8–11.1)	≈0.000 (−0.200 to 0.200)	0.005	0.944
PDW (fL)	11.80 (10.6–13.3)	11.90 (10.5–13.3)	≈0.000 (−0.500 to 0.400)	≈ 0.000	0.998
RDW (%)	13.4 (12.6–14.4)	13.1 (12.6–14.6)	0.100 (−0.200 to 0.300)	−0.035	0.603

MPV: mean platelet volume; PDW: platelet distribution width; RDW-SD: red blood cell distribution width; WBC: white blood cell, RBC:red blood count

significant (p=0.018; mean/median difference=0.320, 95% CI 0.063–0.564) with a small effect size (−0.158). PLR was numerically higher in controls (130 [109–163] vs. 120 [94.7–151]); however, the difference did not reach statistical significance (difference=9.295, 95% CI −0.233–18.973; p=0.057; effect size=−0.127). SII showed a similar, non-significant trend favoring controls (733 [562–972] vs. 649 [452–913]; difference=69.112, 95% CI −5.745–146.063; p=0.073; effect size=−0.120). Overall, only NLR differed significantly between groups, and the effect sizes across markers were consistently small. Table 3 presents the distribution of NLR, PLR, and SII values across different groups.

ROC analyses for NLR, PLR, and SII were conducted to assess their ability to predict missed abortion. All parameters had AUC values below 0.5, indicating limited discriminative power. For transparency, ROC curves and AUCs with 95% confidence intervals are shown in Table 4 and Figure 1. Due to the non-significant AUC results, these findings lack clinical predictive value. In the subgroup analysis for pregnancies less than 12 weeks, the missed group exhibited a higher median WBC count compared to controls (8.54 [7.27–10.4] vs. 7.93 [6.71–9.30] ×10^3/μL), with statistical significance (p=0.020; effect size=0.16). The mean lymphocyte count was also higher in the missed group (2.29±0.73 vs. 1.99±0.58 ×10^3/μL), indicating a strong difference (p=0.001; effect size=0.46). Conversely, the median PLR was higher in the control group (132 [111–167] vs. 119 [92.9–148]), and this difference was statistically

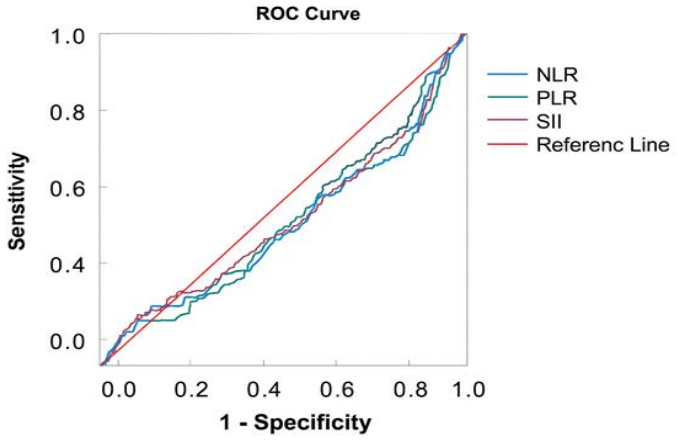

Figure 1. ROC Curve of NLR, PLR, and SII for Predicting Missed Abortion.

Table 3. Distribution of NLR, PLR, and SII Values by Group

Inflammatory Marker	Control Group (N=150)	Missed Group (N=150)	95% confidence intervals (95% CI)	Effect Size	P value
NLR	2.88 (2.26–3.66)	2.62 (1.81–3.44)	0.320 (0.063 to 0.564)	−0.158	0.018
PLR	130 (109–163)	120 (94.7–151)	9.295 (−0.233 to 18.973)	−0.127	0.057
SII	733 (562–972)	649 (452–913)	69.112 (−5.745 to 146.063)	−0.120	0.073

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio; SII: Systemic Immune-Inflammation Index
The Mann-Whitney U test was used. Values are given as median (25th–75th percentile). Differences are presented as Missed – Control with 95% confidence intervals. Effect sizes are given rank biserial correlation (r) for Mann–Whitney U. p-values indicate statistical significance ($p < 0.05$).

Table 4. ROC Analysis Results for Determining the Predictive Value of NLR, PLR, and SII in Pregnant Women According to Group

Laboratory Parameters	Area Under the Curve(AUC)	Standard Error	p	95% Confidence Interval	
				Lower	Upper
NLR	0.421	0.033	0.018	0.355	0.486
PLR	0.436	0.033	0.057	0.371	0.501
SII	0.440	0.033	0.073	0.375	0.506

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio; SII: Systemic Immune-Inflammation Index

Table 5. Laboratory Parameters and Inflammatory Markers in Pregnancies Under 12 Weeks Weeks by Group (N=20)

Parameter		Control Group (N=100)	Missed Group (N=101)	95% confidence intervals CI	Effect Size	p-value (t/U)
WBC (10^3/μL)	Med. (25-75th)	7.93 (6.71–9.30)	8.54 (7.27–10.4)	0.017–0.024	0.16	0.020
Hemoglobin(g/dL)	$\bar{x}$±SS	12.64 ± 1.06	12.46 ± 1.26	-0.15–0.50	0.15	0.278
Neutrophil (10^3/μL)	Med. (25-75th)	5.22 (4.33–6.23)	5.58 (4.47–7.04)	0.178–0.198	0.09	0.188
Platelet(10^3/μL).	$\bar{x}$±SS	259.33 ± 52.50	265.16 ± 70.73	-23.15–11.49	0.09	0.507
Lymphocyte(10^3/μL).	$\bar{x}$±SS	1.99 ± 0.58	2.29 ± 0.73	-0.49–-0.12	0.46	0.001
RBC (×10^6/μL)	Med. (25-75th)	4.50 (4.30–4.74)	4.55 (4.32–4.74)	0.404–0.429	0.06	0.414
Hematocrit(%)	$\bar{x}$±SS	37.79 ± 2.51	38.02 ± 3.25	-1.03–0.58	0.08	0.582
MCV(fL)	$\bar{x}$±SS	83.86 ± 4.75	83.79 ± 5.45	-1.35–1.50	0.02	0.916
MPV (fL)	Med. (25-75th)	10.40 (9.90–11.0)	10.50 (9.90–11.2)	0.624–0.649	0.03	0.632
PDW (fL)	Med. (25-75th)	11.80 (10.6–13.3)	11.90 (10.6–13.7)	0.692–0.715	0.03	0.702
RDW(%)	Med. (25-75th)	13.5 (12.6–14.4)	13.1 (12.7–14.4)	0.595–0.620	0.04	0.600
INR	$\bar{x}$±SS	1.07 ± 0.08	1.07 ± 0.08	-0.02–0.02	0.02	0.895
NLR	Med. (25-75th)	2.68 (2.22–3.50)	2.52 (1.84–3.23)	0.081–0.095	0.12	0.089
PLR	Med. (25-75th)	132 (111–167)	119 (92.9–148)	0.005–0.010	0.18	0.009
SII	Med. (25-75th)	683 (534–890)	649 (485–893)	0.307–0.331	0.07	0.317

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio; SII: Systemic Immune-Inflammation Index, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio; SII: Systemic Immune-Inflammation Index
Notes: Normally distributed variables were analyzed with independent samples t-test (reported as mean ± SD); non-normally distributed variables were analyzed with Mann–Whitney U (reported as median [25th–75th percentile]). Differences are presented as Missed – Control with 95% confidence intervals. Effect sizes are given as Cohen's d for t-tests and rank biserial correlation (r) for Mann–Whitney U. Bold p-values indicate statistical significance ($p < 0.05$).

Table 6. ROC Analysis of NLR, PLR, SII and Lymphocyte for Group-wise Prediction in Pregnancies <12 Weeks' Gestation

Laboratory Parameter	Area Under the Curve (AUC)	Standard Error	p	95% Confidence Interval		Cut-off	Sensitivity	Specificity
				Lower	Upper			
NLR	0.430	0.041	0.089	0.351	0.510	-	-	-
PLR	0.394	0.040	0.009	0.316	0.472	131.69	%40	%50
SII	0.459	0.041	0.317	0.379	0.539	-	-	-
Lymphocyte	0.607	0.040	0.009	0.529	0.685	2.09	%51	%58

NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio; SII: Systemic Immune-Inflammation Index

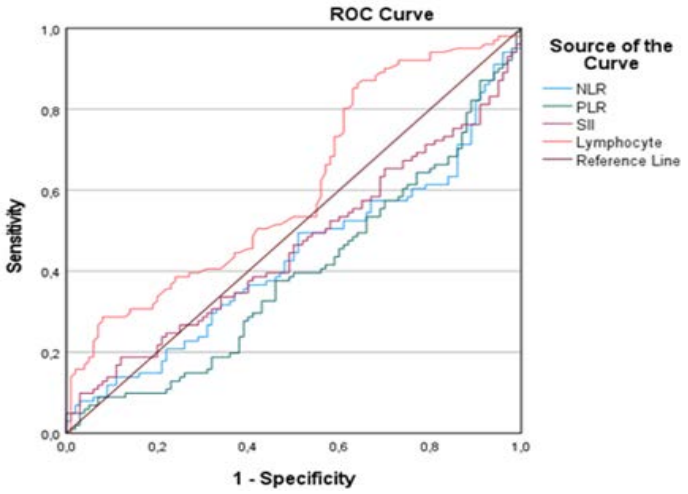

Figure 2. ROC Curve of NLR, PLR, and SII for Predicting Missed Abortion.

significant (p=0.009; effect size=0.18). Other hematologic indices did not differ significantly between groups; NLR showed a nonsignificant increasing trend in controls, and SII remained similar. Table 5 shows the laboratory parameters and inflammatory markers in pregnancies under 12 weeks, categorized by group.

In the study, the predictive capability of NLR, PLR, SII, and lymphocyte levels in different groups during pregnancies of less than 12 weeks was evaluated using ROC curves. The AUC for lymphocytes was 0.607 (SE=0.040; p=0.009; 95% CI: 0.529–0.685), indicating limited discriminative ability; at a cutoff of 2.09, sensitivity was 51%, and specificity was 58%. For PLR, the AUC was 0.394 (SE=0.040; p=0.009; 95% CI: 0.316–0.472), which is below 0.5 and statistically significant; this suggests weak discrimination and an opposite trend (higher PLR may be associated with the control group). At a cutoff of 131.69, sensitivity was 40%, and specificity was 50%. NLR (AUC 0.430; SE=0.041; p=0.089; 95% CI: 0.351–0.510) and SII (AUC 0.459; SE=0.041; p=0.317; 95% CI: 0.379–0.539) did not show significant discriminative ability; cutoff values were not reported for either marker. Table 6 and Figure 2 show the ROC analysis results evaluating the predictive value of NLR, PLR, SII, and lymphocyte levels for pregnancies under 12 weeks of gestation.

DISCUSSION

In this study missed ve control group comparisons showed a significantly higher lymphocyte count in the missed abortion group and lower NLR values. These findings imply a possible change in the immune response linked to early pregnancy loss. Increased lymphocyte levels may indicate a shift from innate immunity, which is neutrophil-driven, to adaptive immune responses fueled by lymphocytes, possibly reflecting an immune regulation imbalance. Prior research also supports this link, suggesting that altered lymphocyte-mediated immunity and maternal-fetal tolerance could be involved in missed abortions (13). Although PLR and SII values did not achieve statistical significance in the overall population, their borderline p-values (p=0.057 and p=0.073, respectively) suggest possible biological relevance. SII, which combines neutrophils, lymphocytes, and platelets, is considered a comprehensive inflammatory marker (14). While our results did not show significant differences, the slight downward trends in PLR and SII in the missed abortion group are notable.

Previous studies, reported higher SII levels in cases of threatened or missed abortion (15-16), which may reflect temporal or population differ. Th1/Th2 balance is directly related to lymphocytes because this balance is one of the main mechanisms that determines how the immune system works during pregnancy. A Th2-dominant immune response is essential for successful pregnancy maintenance, while a shift toward Th1-type cytokine profile has been associated with pregnancy loss. Alterations in circulating lymphocyte populations may reflect this imbalance (17). In the subgroup analysis of pregnancies <12 weeks (n=201), WBC and lymphocyte levels were significantly higher in the missed abortion group (p=0.020 and p=0.001, respectively), while PLR was significantly lower (p=0.009). This suggests that immune dysregulation may be more prominent in very early gestational losses. The elevated lymphocyte levels may reflect a Th1-skewed immune response, associated with cytotoxic T-cell activation and fetal rejection mechanisms (18). In contrast, the decrease in PLR might indicate impaired platelet-mediated immune signaling, which may impact placental development.

Interestingly, in the <12-week subgroup, the ROC analysis demonstrated that lymphocyte count had a modest predictive value (AUC = 0.607; p=0.009), while PLR also showed fair discriminative ability (AUC = 0.394; p=0.009). These results support the hypothesis that inflammatory markers, especially lymphocyte-driven indices, may provide valuable insights into early pregnancy failure. A lower PLR may reflect diminished platelet-mediated immune and paracrine signaling at the maternal–fetal interface (e.g., reduced P-selectin/CD40L interactions and growth-factor release), processes that support trophoblast invasion and spiral-artery remodeling. Consistent with this mechanism, human studies have reported lower mean platelet volume (a surrogate of platelet activation) in miscarriage cohorts, aligning with the notion of blunted platelet activity (19--21). Taken together, a decrease in PLR could plausibly contribute to impaired placental development through attenuated platelet–trophoblast and platelet–immune cross-talk (22-23). Previous studies show mixed results: Liu et al. reported no significant differences in NLR or PLR values between groups, while another study found elevated SII in missed abortion (14,24). These inconsistencies may stem from sample size, gestational age differences, or inclusion/exclusion criteria, using a self-controlled design, found no difference in SII between pregnancy and abortion periods, further emphasizing individual variability (25). The gestational age-specific nature of immune modulation is essential. Our study found that immune marker patterns differ between early (<12

weeks) and later gestation (≥12 weeks), showing a dynamic shift in maternal immune tolerance as pregnancy advances. This aligns with longitudinal studies demonstrating that NLR increases with gestational age, while PLR may decrease (18).

In our study, the missed abortion group showed a lower NLR and higher lymphocyte count compared to healthy controls. Although elevated NLR has been widely associated with adverse pregnancy outcomes, our findings may reflect early gestational immune modulation or a compensatory Th2-shift following fetal demise. Similar immunological alterations have been suggested in rheumatic pregnancies and early pregnancy complications, where altered NLR and lymphocyte activity indicate systemic immune imbalance (26).

Study Limitaitons

The study was conducted at a single tertiary center, which might limit how well the findings apply to different populations or healthcare settings. The research focused on basic hematologic indices (e.g., NLR, PLR, SII) and did not include cytokine levels, T-cell subsets, or hormonal measurements, which could provide more detailed insights into the immune mechanisms. Although laboratory data for the missed abortion group were collected at the time of hospital admission and gestational age matching was used, a limitation remains because the exact timing of fetal demise could not be determined. This uncertainty may have caused slight physiological variations in inflammatory markers between the groups.

CONCLUSION

This study found higher lymphocyte counts and lower NLR in missed abortion cases, especially before 12 weeks of gestation, indicating a Th1-dominant immune response and reduced maternal-fetal tolerance. Although PLR and SII did not significantly differ overall, their patterns in early pregnancy suggest they could serve as early biomarkers. Further multicenter studies with matched gestational ages are necessary to confirm these findings and determine whether such hematological changes cause or result from early pregnancy loss.

DECLARATIONS

Conflict of Interest: *The authors declare that there is no conflict of interest.*

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RESEARCH ARTICLE

Systemic Inflammatory Response Index (SIRI) in Hypersensitivity Pneumonitis: Association with Clinical Course and Mortality

Hipersensitivite Pnömonisinde Sistemik İnflamatuar Yanıt İndeksi (SIRI): Klinik Seyir ve Mortalite ile İlişkisi

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ABSTRACT

Objective: Hypersensitivity pneumonitis (HP) is an interstitial lung disease that can range in its course from reversible inflammation to progressive fibrosis. Identifying reliable biomarkers to predict disease phenotype and prognosis remains a major clinical challenge. This study aimed to evaluate the prognostic significance of the Systemic Inflammatory Response Index (SIRI) in patients with HP and to investigate its association with clinical parameters, pulmonary function, and mortality.

Materials and Methods: A retrospective analysis was conducted on 73 patients diagnosed with HP between 2014 and 2022. Patients were classified into fibrotic and non-fibrotic groups based on clinical, radiological, and histopathological criteria. Hematological indices including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR) and SIRI were calculated. Kaplan–Meier and Cox regression analyses assessed survival outcomes and independent predictors of mortality.

Results: SIRI levels were significantly higher in patients with fibrotic HP and those who died during follow-up. SIRI correlated positively with inflammatory markers, and negatively with pulmonary function (Forced Vital Capacity), carbon monoxide diffusion capacity (DLCO%)) and 6-minute walk distance. ROC analysis demonstrated high diagnostic accuracy for SIRI in differentiating fibrotic HP (AUC = 0.858) and predicting mortality (AUC = 0.932), with an optimal mortality cut-off of 1.92. Kaplan–Meier survival curves illustrated significantly shorter survival in patients with SIRI >1.92 compared to those with SIRI ≤1.92, with a Log-Rank test confirming this difference (mean survival time 74.6 ± 3.2 months vs. 127.7 ± 2.9 months; $p < 0.001$). In multivariable Cox analysis, fibrotic phenotype, reduced DLCO%, and SIRI >1.92 were independent predictors of mortality.

Conclusion: SIRI, as a quantitative indicator of systemic inflammation, may be regarded as a meaningful biomarker for predicting disease severity and mortality risk in patients with hypersensitivity pneumonitis. While more evidence is needed before integration into routine clinical use, it holds potential as a supportive tool for risk stratification, early detection of fibrotic progression, and long-term management strategy planning.

Keywords: Fibrosis, Hypersensitivity pneumonitis, Neutrophil-to-lymphocyte ratio, Systemic Inflammatory response index, Interstitial lung disease

ÖZET

Amaç: Hipersensitivite pnömonisi (HP), reversibl inflamasyondan ilerleyici fibrozise kadar değişen bir seyir gösterebilen intersitisyel akciğer hastalığıdır. Hastalık fenotipinin ve prognozunun öngörülmesine yönelik güvenilir biyobelirteçlerin tanımlanması günümüzde önemli bir klinik gereksinimdir. Bu çalışmada, Sistemik İnflamatuar Yanıt İndeksi'nin (SIRI) HP'deki prognostik değerinin değerlendirilmesi ve klinik parametreler, solunum fonksiyonları ile mortalite arasındaki ilişkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: 2014–2022 yılları arasında HP tanısı alan 73 hastanın retrospektif verileri analiz edilmiştir. Hastalar, klinik, radyolojik ve histopatolojik bulgulara göre fibrotik ve non-fibrotik olarak sınıflandırılmıştır. Hematolojik inflamatuar parametreler (Nötrofil/lenfosit oranı (NLR), monosit/lenfosit oranı (MLR) ve SIRI hesaplanmıştır. Kaplan–Meier ve Cox regresyon analizleri ile sağkalım ve mortaliteye etki eden bağımsız değişkenler değerlendirilmiştir.

Bulgular: SIRI düzeyleri, fibrotik HP fenotipinde hastalarında ve takip sürecinde hayatını kaybedenlerde anlamlı şekilde daha yüksekti. SIRI, inflamatuar belirteçler ile pozitif, pulmoner fonksiyon parametreleri (Zorunlu Vital Kapasite), Karbonmonoksit Difüzyon Kapasitesi (DLCO%)) ve 6 dakikalık yürüme mesafesi ile negatif korelasyon gösterdi. ROC analizi ile SIRI'nin fibrotik HP'yi ayırt etmede (AUC = 0,858) ve mortaliteyi öngörmede (AUC = 0,932) yüksek tanısal doğruluğa sahip olduğu gösterildi; mortalite için optimal kesme değeri ise 1,92 olarak belirlendi. Kaplan–Meier sağkalım eğrileri, SIRI >1,92 olan hastalarda sağkalımın anlamlı şekilde daha kısa olduğunu gösterirken, Log-Rank testi bu farkı doğruladı (ortalama sağkalım süresi 74,6 ± 3,2 ay vs. 127,7 ± 2,9 ay; $p < 0,001$). Çok değişkenli Cox regresyon analizinde ise fibrotik fenotip, azalmış DLCO% ve SIRI >1,92 mortalitenin bağımsız belirleyicileri olarak bulundu.

Sonuç: SIRI, sistemik inflamasyonun kantitatif bir göstergesi olup, HP hastalarında hastalık şiddeti ve mortalite riskinin öngörülmesinde anlamlı bir biyobelirteç olarak değerlendirilebilir. Rutin klinik kullanıma entegrasyonu için daha fazla kanıta ihtiyaç duyulmakla birlikte, risk sınıflaması, fibrotik progresyonun erken saptanması ve uzun dönem yönetim stratejilerinin belirlenmesinde destekleyici bir araç olarak potansiyel taşıyabilir.

Anahtar Kelimeler: Fibrozis, Hipersensitivite pnömonisi, Nötrofil/lenfosit oranı, Sistemik inflamasyon yanıt indeksi, İnterstisyel akciğer hastalığı

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INTRODUCTION

Hypersensitivity pneumonitis (HP) is an immune-mediated interstitial lung disease that develops in susceptible individuals following inhalation of various environmental or occupational antigens (1). The disease triggers intense inflammation in the small airways and lung parenchyma and may progress to pulmonary fibrosis in some patients. Both cellular and humoral immune mechanisms contribute to HP pathogenesis, with T lymphocytes, macrophages, and cytokines playing central roles. This immune response can lead to persistent inflammation and fibrosis in certain individuals. However, predicting which patients will develop fibrotic disease or experience poor clinical outcomes remains challenging (1). Clinically, HP is classified into fibrotic and non-fibrotic phenotypes, with the presence of fibrosis being the most important prognostic factor influencing disease progression and mortality (2). Biomarkers are essential tools for early diagnosis, prognosis, and treatment monitoring. An ideal biomarker should be non-invasive, easily accessible, reliable, and cost-effective. Currently, no specific laboratory test exists for diagnosing HP, assessing disease activity, or predicting progression.

Recently, hematologic inflammatory markers derived from neutrophil, monocyte, and lymphocyte counts such as the systemic inflammatory response index (SIRI) have gained attention for their prognostic value in various diseases (3,4). Investigating the diagnostic and prognostic utility of SIRI in HP could provide valuable insights to improve patient management and outcomes. Recently, novel biomarkers combining various white blood cell types have been introduced. Hematological inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and SIRI have been linked to the prognosis of several chronic diseases. These markers, derived from neutrophil, monocyte, and lymphocyte counts, have demonstrated significant prognostic value across multiple malignancies (5,6). Furthermore, SIRI has shown predictive utility in cardiovascular diseases, stroke, breast cancer, and nasopharyngeal carcinoma (7,8,9). For instance, a retrospective study involving 2.802 patients with acute ischemic stroke identified a SIRI cutoff value of ≥2.74 as an independent predictor of increased risk for stroke-associated pneumonia (10).

Despite these promising findings, no specific biomarker currently exists for the diagnosis or monitoring of hypersensitivity pneumonitis. Therefore, the aim of this study was to evaluate the prognostic value of the SIRI in patients with hypersensitivity pneumonitis and to investigate its association with clinical parameters, pulmonary function, and survival outcomes.

MATERIALS AND METHODS

Patients and Study Design

This retrospective, single-center study was conducted with the approval of the Clinical Research Ethics Committee of Gazi University (decision number 986, dated November 6, 2024). The study included 73 patients who were diagnosed with and treated for HP between February 2014 and December 2022. The data analyzed included clinical findings, imaging results, and histopathological diagnoses (when available). Patients followed at our hospital for HP were categorized into fibrotic or non-fibrotic HP groups based on symptom duration, imaging findings, bronchoalveolar lavage (BAL) results, and histological data, in accordance with the 2020 American Thoracic Society (ATS) / Japanese Respiratory Society (JRS) / Latin American Thoracic Association (ALAT) Clinical Practice Guideline for the Diagnosis of Hypersensitivity Pneumonitis in Adults (2).

Demographic data (age, sex, region of residence, occupation, etc.), tobacco use, comorbidities, current and prior treatments, history of environmental or occupational exposure, HP phenotypes, pulmonary function test results (Forced Vital Capacity (FVC ml, FVC %), Forced Expiratory Volume in 1 Second (FEV1 ml, FEV1 %), FEV1/FVC), carbon monoxide diffusion capacity (DLCO, DLCO/VA), six-minute walk test (6MWT) performance, and neutrophil, platelet, and monocyte counts were recorded on standardized patient follow-up forms. Reported symptoms included dyspnea, cough, chest pain, sputum production, and fatigue.

Bronchoscopic Evaluation and Diagnostic Sample Collection

Patients were evaluated for suspected interstitial lung disease (ILD) based on medical history, clinical presentation, and radiological findings. In cases where differential diagnosis could not be established, tissue sampling was performed using bronchoscopic or surgical methods. Bronchoscopic procedures were conducted in the hospital's pulmonology unit using a 2.8 mm fiberoptic flexible bronchoscope (Olympus). Bronchoalveolar lavage (BAL) was performed by instilling 100–150 mL of sterile saline into the most affected segment as identified on high-resolution computed tomography (HRCT). Microscopic cell counts in BAL fluid were analyzed by the pathology department. A lymphocyte count greater than 20% in BAL was considered supportive for the diagnosis of HP. Although not routinely recommended, a decreased CD4/CD8 ratio was also considered helpful in differential diagnosis.

In selected cases, transbronchial biopsy was performed via fiberoptic bronchoscopy targeting regions identified on HRCT. For patients requiring surgical sampling, video-assisted thoracoscopic surgery (VATS) was performed by the thoracic surgery team to obtain lung tissue for histopathological analysis.

Analysis of Hematologic Parameters and Inflammatory Indices

Complete blood count analyses were performed in our hospital laboratory using the spectrophotometric/impedance method (Beckman Coulter LH 780 Analyzer; Beckman Coulter, Inc., CA, USA). Erythrocyte sedimentation rate (ESR) was measured using a spectrophotometric method and C-reactive protein (CRP) levels were determined by a turbidimetric assay from peripheral blood samples collected at the time of diagnosis. Importantly, all blood samples were obtained prior to the initiation of any pharmacological treatment, including corticosteroids and immunosuppressive agents, to avoid potential confounding effects of treatment on hematologic and inflammatory parameters. Additionally, patients with

active infections, malignancies, or active rheumatologic diseases were carefully excluded based on clinical evaluation, laboratory tests, and medical history to minimize potential confounding factors affecting CRP and other inflammatory markers. NLR, MLR, and SIRI values were calculated based on neutrophil, monocyte, and lymphocyte counts at diagnosis using the following formulas:

NLR (Neutrophil-to-Lymphocyte Ratio) = Neutrophil count / Lymphocyte count

MLR (Monocyte-to-Lymphocyte Ratio) = Monocyte count / Lymphocyte count

SIRI (Systemic Inflammatory Response Index) = (Neutrophil count × Monocyte count) / Lymphocyte count

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as means (± standard deviation) for normally distributed continuous variables, and medians (minimum-maximum) for non-normally distributed continuous variables. Categorical variables are presented as counts and percentages (%). The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test, and parametric tests were applied for normally distributed data.

The Pearson's χ^2 (chi-square) test was used to analyze categorical variables. The Student's t-test was used for comparisons of normally distributed continuous variables between two groups. The relationships between variables were evaluated using Pearson's correlation coefficient.

Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off values of the markers for differentiating between fibrotic and nonfibrotic HP and predicting mortality. The area under the curve (AUC), sensitivity, and specificity were calculated for each biomarker. Univariable and multivariable Cox proportional hazards regression analyses were performed to identify factors associated with mortality and determine independent predictors. A two-tailed p-value < 0.05 was considered statistically significant throughout the analyses.

RESULTS

A total of 73 patients diagnosed with hypersensitivity pneumonitis were included in this study. The mean age was 63 ± 12.7 years, with females comprising 65.8% of the study population (Table-1). The most frequently reported symptoms were dyspnea (82.2%) and cough (79.4%) (Table-1). A majority of patients (84.9%) had a history of exposure to one or more predefined environmental factors. Bird breeding was the most prevalent exposure, reported in 58.9% of patients, followed by farming (27.4%), poultry handling (16.4%), and agricultural or livestock activities (13.7%). Notably, one patient (1.36%) was a trombone player. Pharmacological treatment was administered to 63 patients, including corticosteroids in 62, azathioprine in 18, mycophenolate mofetil in 9, and nintedanib in 4 patients. Pulmonary function assessment revealed significantly greater impairment in patients with fibrotic HP (n = 42) compared to those with nonfibrotic HP (n = 31). Likewise, the 6MWT distance was significantly reduced in patients with fibrotic HP (238.5 ± 140.3 meters) compared to those with nonfibrotic HP (342.7 ± 132.8 meters; p = 0.015), indicating a substantial decline in functional exercise capacity in the presence of fibrotic involvement.

In the overall cohort, the mean values of MLR, NLR, and SIRI were 0.30 ± 0.13, 3.27 ± 2.44, and 2.27 ± 2.18, respectively. Stratification by radiological phenotype revealed significantly higher levels of all three inflammatory indices in the fibrotic HP group (NLR: 4.69 ± 3.02; MLR: 0.38 ± 0.18; SIRI: 3.50 ± 2.79)

Table 1. Patients' Demographic, Clinical, and Hematologic Characteristics

Variables	n (%) / Mean ± SD/ Med(Min-Max) n=73
Demographic Data	
Mean age (years)	63 ± 12.7
Gender, n (%)	
Female	48(65.8%)
Male	25(34.2%)
BMI	26.7±6.8
Smoking history (pack-years)	12.1±17.4
Symptoms	
Dyspnea	60(82.2%)
Cough	58(79.4%)
Chest pain	51(71.8%)
Fatigue	39(54.9%)
Sputum	23(32.4%)
Comorbid Conditions, n (%)	
Hypertension	21(28.8%)
Coronary Artery Disease	12(16.4%)
Diabetes Mellitus	9(12.3%)
Hyperlipidemia	7(9.6%)
Hypothyroidism	6(8.2%)
Pulmonary Function Test Parameters	
FVC, ml	1931.6±1103.7
FVC, %	70.8±24.1
FEV1, mL	2113.6±1223.6
FEV1, %	71.6±31.1
DLCO, %	35.1(20.6-90.3)
DLCO/VA	50.3(40.2-117.4)
6MWT, m	291.4±138.6
Laboratory Findings	
Hemoglobin (g/dL)	14.1±1.5
Hematocrit (%)	41.5±4.5
WBC (109 /L)	11.9±3.7
Neutrophils (109 /L)	7.3±4.1
Platelets (109 /L)	286.4±95.8
Lymphocytes (109 /L)	2.1±0.9
Monocytes (109 /L)	0.6±0.35
NLR	3.27 ± 2.44
MLR	0.30 ± 0.13
SIRI	2.27 ± 2.18
CRP (mg/L)	8.55(1.61-70.4)
ESR (mm/h)	16.9 ±9.7

SD: Standard deviation;BMI: Body Mass Index; FVC: Forced vital capacity;FEV1:Forced Expiratory Volume in 1 Second; DLCO: Diffusing capacity of the lung for carbon monoxide; DLCO/VA: DLCO adjusted for alveolar volume;6MWT: 6-minute walk test;WBC: White blood cell count; MLR: Monocyte-to- Lymphocyte Ratio; NLR: Neutrophil-to-Lymphocyte Ratio; SIRI: Systemic Inflammation Response Index; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate

Table 2. Comparison of Clinical and Laboratory Parameters Between Deceased and Surviving Patients Diagnosed with Hypersensitivity Pneumonitis

Parameter	Deceased (n = 22) Mean ± SD Med (Min-Max)	Survived (n = 51) Mean±SD Med (Min-Max)	P-value
Mean age (years)	65 ± 14.2	60.4 ± 11.3	0.161
BMI	24.3±7.7	27.3±6.8	0.647
Smoking history (pack-years)	12.7 ± 17.9	11.8 ± 16.9	0.780
FVC, %	56.77±14.43	69.48±19.7	0.004
DLCO, %	24.3 (20.6- 76.1)	39.5 (32.6-90.3)	0.038
6MWT, m	224.2±141.5	353.7±138.8	0.002
Hemoglobin (g/dL)	14.7±1.9	13.6±1.6	0.677
Neutrophils (109 /L)	9.1±4.7	5.7±2.2	0.001
Lymphocytes (109 /L)	2.1±0.7	2.6±0.8	0.077
Monocytes (109 /L)	0.97±0.3	0.59±0.2	0.003
CRP (mg/L)	16.7 (2.4-70.4)	7.3 (1.6-41.2)	0.034
NLR	4.53±2.33	2.48±0.91	0.001
MLR	0.38±0.18	0.22±0.04	0.001
SIRI	3.63±2.94	1.40±0.62	0.001

BMI: Body Mass Index ,FVC: Forced Vital Capacity,DLCO: Diffusing Capacity of the Lung for Carbon Monoxide, 6MWT: 6-Minute Walk Test, CRP: C-Reactive Protein, NLR: Neutrophil to Lymphocyte Ratio,MLR: Monocyte to Lymphocyte Ratio, SIRI: Systemic Inflammation Response Index

compared to the nonfibrotic group (NLR: 2.15 ± 0.89; MLR: 0.23 ± 0.08; SIRI: 1.30 ± 0.63), with all comparisons achieving statistical significance ($p < 0.001$). In the comparison between deceased and surviving patients, all three inflammatory markers NLR, MLR, and SIRI were significantly elevated in the deceased group. The mean NLR was 4.53 ± 2.33 in deceased patients compared to 2.48 ± 0.91 in survivors ($p = 0.001$). The mean MLR and SIRI values were both significantly higher in deceased patients compared to survivors ($p = 0.001$ for both) (Table-2).

Correlation analysis was performed to evaluate the relationships between SIRI and various clinical and laboratory parameters. Significant positive correlations were observed between SIRI and CRP ($r = 0.122$, $p=0.031$), ESR ($r = 0.298$, $p=0.012$), NLR ($r = 0.789$, $p < 0.001$), MLR ($r =0.642$, $p < 0.001$), and neutrophil count ($r = 0.455$, $p < 0.001$). Conversely, SIRI showed significant negative correlations with FVC% ($r = 0.266$, $p= 0.034$), DLCO% ($r =0.166$, $p < 0.05$), and 6MWT ($r = 0.114$, $p= 0.046$). These findings suggest that elevated SIRI levels are not only indicative of systemic inflammation but are also associated with diminished pulmonary function in patients with hypersensitivity pneumonitis. The overall median survival time in the study population was 99 (6-130) months, with 22 of 73 patients (30.1%) dying during the follow-up period. To evaluate the prognostic utility of SIRI, ROC analysis was conducted. The AUC was 0.858 (95% CI: 0.771–0.945, $p < 0.001$), indicating good discriminatory ability. Using a cut-off value of 1.86, SIRI demonstrated a sensitivity of 90.5% and a specificity of 76.9% for distinguishing fibrotic from non-fibrotic hypersensitivity pneumonitis patients (Figure 1).

Furthermore, the optimal cut-off value for mortality discrimination was identified as 1.92, with an AUC of 0.932 (95% CI: 0.878–0.987, $p < 0.001$), yielding a sensitivity of 90.9% and specificity of 80.4% (Figure 2).

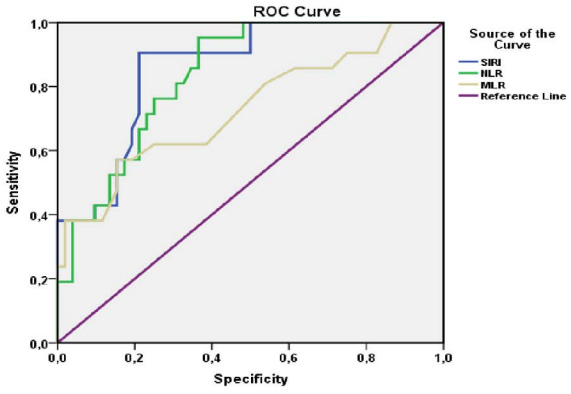

Figure 1. ROC curve for SIRI distinguishing fibrotic and non-fibrotic hypersensitivity pneumonitis.

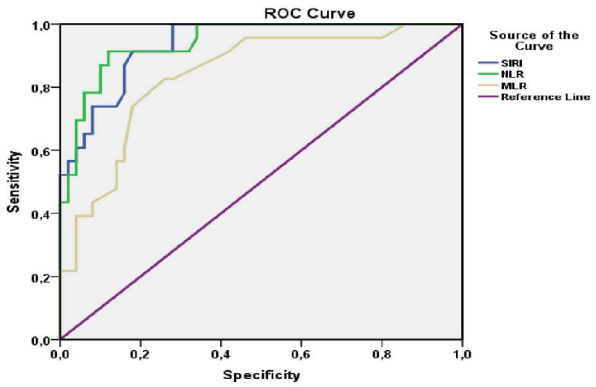

Figure 2. ROC curve of SIRI for mortality discrimination in hypersensitivity pneumonitis patients

Table 3. Univariable and Multivariable Cox Proportional Hazards Regression Analyses for All-Cause Mortality

Variable	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Age (per year)	1.04 (1.01 – 1.08)	0.015	1.03 (1.00 – 1.07)	0.061
Gender (Female)	1.21 (0.58 – 2.53)	0.610	1.05 (0.67 – 1.87)	0.722
Fibrotic HP	2.65 (1.32 – 5.31)	0.006	2.21 (1.08 – 4.52)	0.030
DLCO (%)	0.96 (0.93 – 0.99)	0.012	0.97 (0.94 – 0.99)	0.021
FVC (%)	0.92 (0.94 – 0.98)	0.010	0.98 (0.95 – 1.00)	0.067
6MWT	0.998 (0.994 – 1.002)	0.210	0.996 (0.993 – 0.999)	0.112
SIRI > 1.92	4.78 (2.01 – 11.36)	0.001	3.89 (1.57 – 9.63)	0.003
NLR	1.38 (1.12 – 1.69)	0.002	1.12 (0.91 – 1.38)	0.280
MLR	1.22 (0.97 – 1.52)	0.085	1.11 (0.89 – 1.39)	0.350

FVC: Forced Vital Capacity, DLCO: Diffusing Capacity of the Lung for Carbon Monoxide, 6MWT: 6-Minute Walk Test, CRP: C-Reactive Protein, NLR: Neutrophil to Lymphocyte Ratio,MLR: Monocyte to Lymphocyte Ratio, SIRI: Systemic Inflammation Response Index

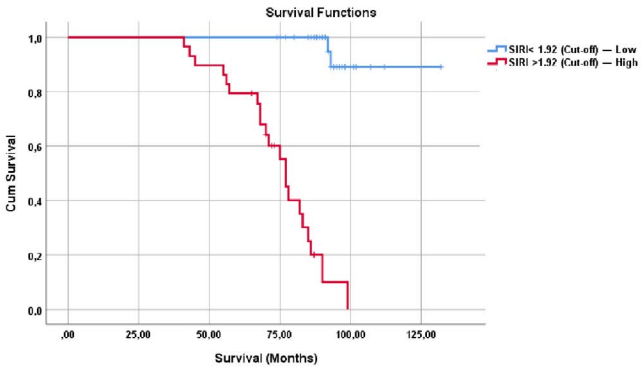

Figure 3. Kaplan–Meier survival curves based on SIRI cut-off value (1.92) in hypersensitivity pneumonitis patients.

Kaplan–Meier survival curves were plotted to illustrate the difference in survival between patients with SIRI >1.92 and those with SIRI ≤1.92. The mean survival time in the high SIRI group was 74.6 ± 3.2 months, with a median survival of 77.0 months (95% CI: 73.0–81.0). In contrast, patients in the low SIRI group had a significantly longer mean survival time of 127.7 ± 2.9 months, and the median survival was not reached due to low mortality. The Log-Rank test revealed a statistically significant difference between the groups ($\chi^2 = 50.98$, $p < 0.001$), confirming that elevated SIRI levels were strongly associated with increased mortality risk in patients with hypersensitivity pneumonitis (Figure-3).

In order to further investigate predictors of mortality, Cox proportional hazards regression analysis was performed. In the univariable analysis, older age, fibrotic HP pattern, reduced DLCO%, reduced FVC%, elevated NLR, and SIRI >1.92 were significantly associated with an increased risk of death (Table-3). However, in the multivariable Cox model, only fibrotic HP (HR: 2.21; 95% CI: 1.08–4.52; p = 0.030), lower DLCO% (HR: 0.97; 95% CI: 0.94–0.99; p = 0.021), and SIRI >1.92 (HR: 3.89; 95% CI: 1.57–9.63; p = 0.003) remained independently associated with mortality (Table-3).

DISCUSSION

HP is a complex inflammatory and/or fibrotic lung disease affecting the parenchyma and small airways. Identification of novel prognostic biomarkers in HP is critical to improving patient management by facilitating more precise disease phenotyping, risk stratification, evaluation of disease severity, monitoring of treatment response, and prediction of progression to fibrosis. While inflammatory markers such as NLR, MLR and SIRI have been investigated in various pulmonary diseases, their prognostic utility in HP remains inadequately studied. Our findings suggest that these markers, particularly SIRI, hold promise as reliable prognostic indicators in HP, effectively differentiating fibrotic from non-fibrotic disease and predicting patient mortality. NLR, MLR, and SIRI can be easily calculated from complete blood counts and serve as indicators of systemic inflammation. These markers have been extensively studied in a variety of diseases, including cardiovascular, rheumatologic, infectious conditions, and malignancies, for their predictive value regarding morbidity and mortality (11-14). Notably, elevated NLR and platelet-to-lymphocyte ratio (PLR) values have been associated with decreased survival in both small-cell and non-small cell lung cancers, as well as increased mortality in pulmonary thromboembolism (15,16). Consistent with our findings, Yao et al. (17). reported significantly higher NLR values in nonsurvivors compared to survivors, and found a positive correlation between NLR and CRP levels.

In a large cross-sectional study involving 7,153 patients with type 2 diabetes mellitus (T2DM), the mean NLR, MLR, and SIRI values were reported as 2.19 ± 1.34, 0.27 ± 0.12, and 1.24 ± 0.98, respectively, and were found to be associated with diabetic kidney disease (18). In comparison, our study population exhibited higher mean values for these inflammatory markers (NLR: 3.27 ± 2.44, MLR: 0.30 ± 0.13, and SIRI: 2.27 ± 2.18), which may reflect the distinct inflammatory burden in hypersensitivity pneumonitis patients. Systemic inflammation plays a key role in the pathogenesis and progression of ILD, including pulmonary fibrosis (19). In a study on idiopathic pulmonary fibrosis (IPF), the mean NLR was reported as 2.5 (range 1.8–3.3), and elevated NLR levels were significantly associated with worse clinical outcomes, including increased mortality, higher hospitalization rates, greater pulmonary function

decline, impaired 6MWT performance, and reduced quality of life (20). These findings are consistent with our results, which showed that increased NLR levels were significantly associated with the fibrotic phenotype of hypersensitivity pneumonitis, lower DLCO and 6MWT values, and higher mortality. Recent evidence has emphasized the prognostic relevance of SIRI in various chronic inflammatory conditions. Elevated SIRI has been independently associated with increased cardiovascular and all-cause mortality in chronic kidney disease (21), as well as higher mortality risk in asthma patients (22), underscoring its utility as a systemic inflammatory biomarker. In line with these data, our study is the first, to our knowledge, to investigate the prognostic significance of SIRI in patients with hypersensitivity pneumonitis. We found that elevated SIRI levels were significantly associated with fibrotic disease phenotype, impaired pulmonary function (DLCO%, FVC%, 6MWT), and most importantly, independently predicted mortality. Taken together, these results suggest that SIRI may serve as a simple and effective biomarker to aid in the risk stratification and prognostic assessment of patients with HP.

Furthermore, complementary studies have expanded the understanding of SIRI's role in respiratory and systemic inflammatory diseases. A cross-sectional study utilizing NHANES data demonstrated that SIRI is an independent risk factor for chronic obstructive pulmonary disease (COPD), showing stronger predictive value than other inflammatory markers, particularly among current smokers (23). Similarly, in patients with rheumatoid arthritis (RA), elevated SIRI levels were associated with increased all-cause and cardiovascular mortality, with the association being more pronounced in females and individuals with higher BMI (24). These findings reinforce the broad clinical relevance of SIRI as a marker of systemic inflammation and prognosis across diverse chronic diseases, supporting its potential utility in managing patients with hypersensitivity pneumonitis. In the study of Biyik et al. involving 332 patients with pancreatitis, SIRI demonstrated a significant predictive value for both severe acute pancreatitis and acute kidney injury (AUC = 0.782; 95% CI = 0.699–0.865, and AUC = 0.776; 95% CI = 0.715–0.837, respectively) (25). Similarly, a 2022 study reported that SIRI served as an independent predictor of poor functional outcomes in ischemic stroke patients, with a moderate discriminative performance (AUC = 0.714; 95% CI: 0.658–0.765) (26). These findings reinforce the utility of SIRI as a systemic inflammatory biomarker across a wide range of acute and chronic conditions.

In light of these previous reports, our study adds to the growing body of evidence by demonstrating that SIRI not only distinguishes between fibrotic and non-fibrotic hypersensitivity pneumonitis with high accuracy (AUC = 0.858), but also independently predicts mortality (AUC = 0.932), which, to our knowledge, has not been previously described in the context of HP. These results underscore the potential clinical utility of SIRI in the risk stratification and prognostic evaluation of HP patients and support its integration into routine clinical assessment. Immunopathological studies have demonstrated that neutrophils and monocytes/macrophages are the primary cells involved in the early inflammatory response in HP. For instance, in experimental HP models, IL-17A production predominantly originates from neutrophils and monocytes/macrophages, and neutrophil depletion has been reported to significantly reduce the development of fibrosis (27). In this context, elevated neutrophil and monocyte counts may trigger the pro-fibrotic transformation of inflammation processes characterized by alveolar tissue damage and increased cytokine release, which subsequently leads to remodeling. Conversely, a decreased lymphocyte ratio may indicate mechanisms such as impaired regulatory T cell function, inadequate regulation of adaptive immune responses, or lymphocyte exhaustion. These cellular dynamics biologically underpin the strong association observed between the SIRI calculated as (neutrophils × monocytes) / lymphocytes and clinical outcomes including fibrotic phenotype, poor pulmonary function, and mortality.

This study has several limitations. First, its retrospective and single-center design may introduce selection and information bias, and limits the generalizability of the findings to broader populations. Second, the relatively small sample size reduces statistical power, particularly for subgroup and multivariable analyses, and increases the risk of type II errors. Third, although inflammatory markers were measured prior to treatment initiation, only baseline values were analyzed; dynamic changes over time were not assessed. Additionally, the lack of an external validation cohort limits the ability to generalize the proposed SIRI cut-off values. Finally, despite efforts to account for comorbidities, unmeasured confounders such as subclinical infections or other inflammatory conditions may have influenced the biomarker levels. Therefore, prospective, multicenter studies with larger patient cohorts are needed to validate these results.

CONCLUSION

This study demonstrates that the SIRI, a simple, accessible, and cost-effective biomarker derived from routine blood parameters, is significantly associated with disease severity, fibrotic phenotype, impaired pulmonary function, and mortality in patients with hypersensitivity pneumonitis. Notably, SIRI showed strong discriminatory power in differentiating fibrotic from non-fibrotic HP and served as an independent predictor of mortality, outperforming other commonly used inflammatory indices such as NLR and MLR. These findings suggest that SIRI may have potential as a valuable tool for risk stratification and prognostic evaluation in clinical practice.

DECLARATIONS

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RESEARCH ARTICLE

Association of Aldosterone Excess with Hematological Parameters and Inflammatory Indices in Hypertensive Patients

Hipertansif Hastalarda Aldosteron Fazlalığının Hematolojik Parametreler ve İnflamatuvar İndekslerle İlişkisi

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ABSTRACT

Objective: Despite being one of the most common causes of secondary hypertension, primary aldosteronism (PA) is frequently underdiagnosed. This study aimed to evaluate the associations between biochemical markers used in PA screening (plasma aldosterone concentration [PAC], plasma renin activity [PRA], and aldosterone-to-renin ratio) and routinely measured hematological parameters (leukocyte, neutrophil, lymphocyte, and platelet counts), as well as inflammatory indices derived from these parameters (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], and the Systemic Immune-Inflammation Index [SII]).

Materials and Methods: This retrospective study analyzed data from 169 hypertensive patients who underwent PA screening between January 2021 and December 2023. Patients were grouped according to PAC cut-off values of ≥15 ng/dL and ≥30 ng/dL. Associations between PAC, PRA, and hematological parameters were assessed using correlation, multivariable linear regression, and receiver operating characteristic (ROC) curve analyses.

Results: Platelet count was significantly higher in patients with PAC ≥15 ng/dL and PAC ≥30 ng/dL ($p = 0.041$ and $p < 0.001$, respectively). In multivariable regression analyses, platelet count ($p = 0.001$), PLR ($p = 0.012$), and SII ($p = 0.044$) remained independently associated with PAC. In ROC analysis, platelet count demonstrated statistically significant discriminative performance for PAC ≥30 ng/dL (AUC = 0.727, $p = 0.001$).

Conclusion: Leukocyte-based hematological parameters and inflammatory indices were not significantly associated with PA screening markers. However, the modest association between platelet count and PAC suggests a potential link with aldosterone activity. Further studies are needed to clarify the clinical relevance of this finding.

Keywords: Hypertension, Neutrophil-to-Lymphocyte Ratio, Systemic Immune-Inflammation Index, Platelet, Platelet-to-Lymphocyte Ratio

ÖZET

Amaç: Primer aldosteronizm (PA), sekonder hipertansiyonun en yaygın nedenlerinden biri olmasına rağmen sıklıkla tanı konulamamaktadır. Bu çalışmada, PA taramasında kullanılan biyokimyasal belirteçler olan plazma aldosteron konsantrasyonu (PAC), plazma renin aktivitesi (PRA) ve aldosteron-renin oranı (ARR) ile hemogram analizinden elde edilen lökosit, nötrofil, lenfosit ve trombosit (PLT) sayıları ve bu parametrelerden türetilen nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) ve Sistemik İmmün-İnflamasyon İndeksi (SII) gibi göstergeler arasındaki ilişkilerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Ocak 2021–Aralık 2023 tarihleri arasında PA taraması yapılan 169 hipertansif hastanın verileri analiz edildi. Hastalar PAC eşik değerlerine göre ≥15 ng/dL ve ≥30 ng/dL olmak üzere iki gruba ayrıldı. PAC, PRA ve hematolojik parametreler arasındaki ilişkiler korelasyon analizi, çok değişkenli lineer regresyon ve ROC eğrisi analizi kullanılarak değerlendirildi.

Bulgular: Trombosit sayısı, hem PAC ≥15 ng/dL hem de PAC ≥30 ng/dL gruplarında anlamlı olarak daha yüksek bulundu (sırasıyla $p = 0.041$ ve $p < 0.001$). Çok değişkenli regresyon analizinde PLT ($p = 0.001$), PLR ($p = 0.012$) ve SII ($p = 0.044$) PAC ile bağımsız olarak ilişkili kaldı. ROC analizinde trombosit sayısının PAC ≥30 ng/dL için istatistiksel olarak anlamlı bir ROC paterni gösterdiği saptandı (AUC = 0.727; $p = 0.001$).

Sonuç: Lökosit temelli hematolojik parametreler ve inflamatuvar indeksler PA tarama belirteçleri ile anlamlı ilişki göstermemiştir. Bununla birlikte, trombosit sayısı ile PAC arasındaki mütevazı ilişki, trombosit sayısının aldosteron aktivitesi ile ilişkili olabileceğini düşündürmektedir. Bu bulgunun klinik öneminin netleşmesi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Hipertansiyon, nötrofil/lenfosit oranı, sistemik immün-inflamasyon indeksi, trombosit, trombosit/lenfosit oranı

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INTRODUCTION

Primary aldosteronism (PA) is the most common cause of secondary hypertension (1). The prevalence of PA in the general hypertensive population is approximately 5.9%, but it may reach up to 20% among patients with resistant hypertension (2). Despite being associated with an increased risk of cardiovascular events and target organ damage, PA often remains an underrecognized cause of hypertension (1,3). Although effective targeted treatment options are available, the complexity of the diagnostic process and the limited applicability of screening algorithms in routine clinical practice result in a high rate of underdiagnosis (4,5). This situation highlights the need for practical, low-cost, and accessible biomarkers that can support early diagnosis and risk stratification in PA.

In recent years, basic cellular parameters obtained from hemogram analysis (leukocyte, neutrophil, lymphocyte, and platelet counts) and indices derived from these parameters (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], and Systemic Immune-Inflammation Index [SII]) have been extensively studied in the diagnostic and prognostic assessment of many systemic diseases, particularly cardiovascular conditions (6,7). Various studies have demonstrated that aldosterone exerts significant effects not only on sodium retention and blood pressure regulation but also on vascular inflammation, endothelial dysfunction, and hemostatic balance (8). These pathophysiological effects may be indirectly reflected in circulating blood elements and inflammatory markers. Considering the impact of glucocorticoids on leukocyte distribution and platelet functions, it can be suggested that aldosterone, another adrenal-derived steroid hormone, may similarly affect the hematological system (9).

In this context, examining the association between hyperaldosteronism due to PA and hematological parameters may help identify complementary biomarkers for screening and risk stratification. However, direct human data regarding the effects of aldosterone on the hematological system remain limited, and current knowledge is largely based on indirect observations and experimental studies (10,11).

In this study, we aimed to evaluate the associations between biochemical markers used in PA screening (plasma aldosterone concentration [PAC], plasma renin activity [PRA], and aldosterone-to-renin ratio [ARR]) and hematological parameters (leukocyte, neutrophil, lymphocyte, and platelet counts), as well as inflammatory indices derived from these parameters (NLR, PLR, and SII) in hypertensive individuals. We also sought to explore their potential value as non-invasive and easily accessible screening tools that may assist in risk stratification for PA, particularly in individuals with elevated PAC levels.

MATERIALS AND METHODS

Study Design and Population

This retrospective study included 169 patients who were referred to the endocrinology outpatient clinic for evaluation of secondary hypertension and underwent screening tests for PA between January 2021 and December 2023. Demographic, clinical, and laboratory data were retrospectively obtained from the electronic health record system of the hospital.

Patient Selection

The inclusion criteria were established indications for PA screening, including resistant hypertension, hypertension accompanied by hypokalemia (even when induced by diuretic use), adrenal incidentaloma, early-onset hypertension, obstructive sleep apnea, and a family history of PA. The exclusion criteria were age under 18, pregnancy, chronic kidney disease, renovascular disease, pheochromocytoma, and other causes of secondary hypertension; conditions that could potentially affect hematological parameters (diabetes mellitus, malignancy, autoimmune or autoinflammatory diseases, hematologic disorders, chronic liver disease, and active/chronic infections); and routine use of drugs known to influence hematological parameters, including acetylsalicylic acid, steroidal and non-steroidal anti-inflammatory agents, or comparable medications.

PA screening was conducted only in patients for whom testing protocols were consistent with current guidelines (12,13). Accordingly, essential criteria for inclusion involved the discontinuation of medications affecting the renin-aldosterone axis (diuretics, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists) at least two to four weeks before testing in patients on antihypertensive therapy. If necessary, alpha blockers and/or non-dihydropyridine calcium channel blockers, which are known to have minimal effects on ARR, were used. In hypokalemic cases, serum potassium levels were normalized prior to testing. All biochemical measurements were performed in the morning, after at least two hours in the upright position, and under standard laboratory conditions. Patients who did not comply with pre-test preparation or laboratory standards were excluded from the study.

Laboratory Parameters and Subgroup Analysis

In this study, leukocyte, neutrophil, lymphocyte, and platelet counts derived from hemogram analysis were evaluated as basic hematological parameters. The inflammatory markers derived from these values, namely NLR, PLR, and SII, were also analyzed.

NLR, PLR, and SII values were calculated using the following formulas:

- NLR = neutrophil count / lymphocyte count
- PLR = platelet count / lymphocyte count
- SII = (platelet count × neutrophil count) / lymphocyte count (14)

PA screening was conducted in accordance with widely accepted screening principles based on renin suppression and aldosterone elevation. Accordingly, the cut-off values were ≥15 ng/dL for PAC, <1 ng/mL/h for PRA, and >30 for ARR (9,11). In addition, an alternative threshold of PAC ≥30 ng/dL was analyzed to allow for the comparison of individuals with more pronounced aldosterone excess (12,13). Since the primary aim of the study was to evaluate the biological relationships

between screening markers and hematological parameters in hypertensive individuals undergoing PA screening, second-step confirmatory suppression tests recommended in the presence of strong clinical and laboratory suspicion (e.g., the saline infusion test or the captopril challenge test) were beyond the scope of this study and were not evaluated.

Laboratory Analysis

All biochemical analyses were performed in the central laboratory of our hospital. For hemogram analysis, venous blood samples were collected into ethylenediaminetetraacetic acid-containing tubes (Vacutainer, Becton, Dickinson and Company, USA) and analyzed within two hours. Hematological parameters were assessed using a Sysmex XN-10 automated hematology analyzer (Sysmex Inc., Kobe, Japan). All internal and external quality control results remained within acceptable limits throughout the analysis.

PAC was measured using the chemiluminescent immunoassay method with the Diasorin Liaison XL system (DiaSorin®, Italy). PRA was analyzed using the radioimmunoassay method with a gamma counter. For both PAC and PRA measurements, intra- and inter-assay coefficient of variation values were determined to be less than 5%. ARR was calculated by dividing PAC by PRA.

Ethical Approval

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and ethical approval was obtained from the Ethics Committee for Non-Drug and Non-Medical Device Research of a local tertiary care training and research hospital, with the decision dated May 9, 2024, and numbered 2024/012.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics (v. 27.0). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Variables exhibiting a normal distribution were presented as mean ± standard deviation, whereas non-normally distributed data were reported as median (25th–75th percentile). For comparisons between groups, the independent-samples t-test was used for normally distributed variables, while the Mann-Whitney U test was applied for those not normally distributed.

Associations between PAC, PRA, ARR, and hematological/inflammatory parameters were evaluated using Spearman correlation analysis. To identify variables independently associated with PAC levels, univariable and multivariable linear regression analyses were performed. Additionally, the performance of platelet count, PLR, and SII across PAC categories (≥15 ng/dL and ≥30 ng/dL) was evaluated using Receiver Operating Characteristic (ROC) curve analysis, and the area under the curve, optimal cut-off, sensitivity, and specificity values were calculated. A p-value of <0.05 was considered the threshold for statistical significance in all analyses.

RESULTS

The study included 169 patients, with a mean age of 43.60 ± 12.75 years (range, 19–66 years). Of the patients, 114 (67.5%) were women and 55 (32.5%) were men. Table 1 summarizes descriptive statistics regarding demographic characteristics, variables associated with hyperaldosteronism, and hematological and inflammatory parameters. To evaluate associations between PAC levels and hematological and inflammatory parameters, the patients were first grouped based on a PAC cut-off of 15 ng/dL and then analyzed using a 30 ng/dL cut-off.

In the analysis based on the 15 ng/dL cut-off value, platelet count was found to be significantly higher in the group with PAC levels ≥15 ng/dL (p = 0.041). In contrast, no statistically significant differences were observed in leukocyte, neutrophil, and lymphocyte counts or in the remaining hematological and

Table 1. Baseline Demographic Characteristics and Laboratory Parameters of the Sample

Variable	n = 169[1]
Age (years)	43.60 ± 12.75
Sex, n (%)	
Female	114 (67.5%)
Male	55 (32.5%)
PAC (ng/dL)	11.8 (8.215–19.700)
PRA (ng/mL/hour)	2.41 (0.90–5.53)
ARR (ng/dL per ng/mL/h)	5.67 (2.56–12.07)
Glucose (mg/dL)	96.92 ± 11.57
Creatinine (mg/dL)	0.778 ± 0.168
Leukocyte count ($\times 10^3/\mu L$)	7.75 ± 1.79
Neutrophil count ($\times 10^3/\mu L$)	4.29 (3.63–5.52)
Lymphocyte count ($\times 10^3/\mu L$)	2.22 (1.90–2.71)
Platelet count ($\times 10^9/L$)	272 (224.5–320.5)
SII	496.60 (399.50–707.75)
NLR	1.86 (1.53–2.53)
PLR	114.72 (92.27–152.73)

[1]n (%), mean ± standard deviation, median (25th–75th percentile)
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone-to-renin ratio; SII, Systemic Immune-Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

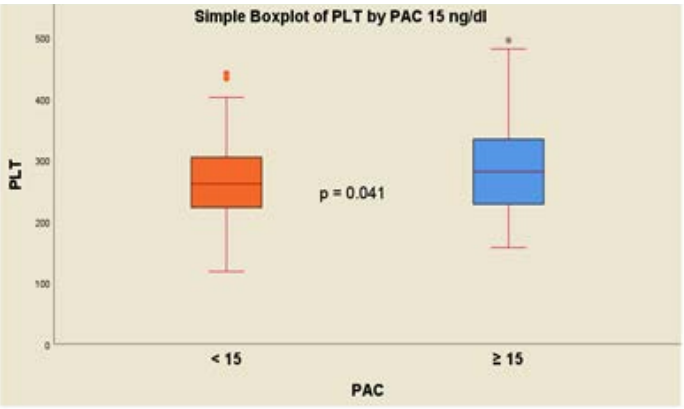

Figure 1. Boxplot graph showing the distribution of platelet count (PLT) in the group with plasma aldosterone concentration (PAC) ≥15 ng/dL

Table 2. Hematological and Inflammatory Parameters by PAC (<15 vs. ≥15 ng/dL)

Variable	PAC <15 ng/dL (n = 108[1])	PAC ≥15 ng/dL (n = 61[1])	p[2]
LEU (×10³/μL)	7.72 ± 1.88	7.78 ± 1.64	0.837
NEU (×10³/μL)	4.16 (3.47–5.00)	4.75 (3.80–5.62)	0.370
LYM (×10³/μL)	2.24 (1.89–3.07)	2.19 (1.72–2.98)	0.935
PLT (×10³/μL)	261 (221–305)	281 (215–323)	0.041
NLR	1.82 (1.39–2.37)	2.04 (1.51–2.71)	0.436
PLR	110.5 (92.3–144.5)	118.7 (97.5–160.0)	0.138
SII	479.9 (366.8–608.2)	538.8 (405.5–710.4)	0.094

[1]Presented as n (%), mean ± standard deviation, or median (25th–75th percentile), [2]Mann-Whitney U test or independent-samples t-test
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; SD, standard deviation; LEU, leukocyte count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; SII, Systemic Immune-Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 3. Hematological and Inflammatory Parameters by PAC (<30 vs. ≥30 ng/dL)

Variable	PAC <30 ng/dL (n = 147[1])	PAC ≥30 ng/dL (n = 22[1])	p[2]
LEU (×10³/μL)	7.71 ± 1.78	8.00 ± 1.91	0.474
NEU (×10³/μL)	4.26 (3.61–5.55)	4.72 (3.66–5.47)	0.573
LYM (×10³/μL)	2.21 (1.87–2.70)	2.24 (1.99–2.81)	0.489
PLT(×10³/μL)	263.00 (223.00–302.50)	335.00 (270.25–393.00)	<0.001
NLR	1.85 (1.53–2.48)	2.05 (1.35–2.63)	0.870
PLR	112.27 (92.00–146.91)	147.73 (93.12–205.14)	0.114
SII	488.23 (380.42–643.85)	595.51 (415.28–951.64)	0.086

[1]Presented as n (%), mean ± standard deviation, or median (25th–75th percentile), [2]Mann–Whitney U test or independent-samples t-test
Abbreviations: PAC, plasma aldosterone concentration; PRA, plasma renin activity; LEU, leukocyte count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; SII, Systemic Immune-Inflammation Index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

inflammatory parameters (NLR, PLR, and SII) (Table 2). In the comparison based on the 30 ng/dL cut-off, platelet count was statistically significantly elevated in patients with PAC levels ≥30 ng/dL ($p < 0.001$). Although NLR, PLR, and SII showed a trend toward higher values in the elevated PAC group, the differences did not reach statistical significance (Table 3). Boxplot graphs illustrating the distribution of platelet count in groups with PAC levels ≥15 ng/dL and ≥30 ng/dL are presented in Figures 1 and 2, respectively.

In the analysis stratified by PRA levels, no statistically significant differences were observed in hematological and inflammatory parameters between the <1 ng/mL/h (n = 46) and ≥1 ng/mL/h (n = 123) groups ($p > 0.05$). Similarly, there were no statistically significant differences in these parameters between patients with ARR <30 (n = 149) and those with ARR ≥30 (n = 20) ($p > 0.05$). When comparing the subgroup of patients meeting both criteria (PRA <1 ng/mL/h and PAC ≥15 ng/dL) (n = 15) with those not meeting these criteria (n = 154), there were no statistically significant differences in any of the evaluated parameters ($p > 0.05$). The median NLR value was found to be higher in patients with PAC ≥15 ng/dL [2.22 (1.81–2.96)], with this difference approaching statistical significance ($p = 0.080$).

Hematological and inflammatory parameters were also compared using the Mann-Whitney U test between the high-risk patient group meeting all biochemical criteria suggestive of PA (PAC ≥15 ng/dL, PRA <1 ng/mL/h, and ARR >30; n = 9) and those not meeting these criteria (n = 160). No statistically significant differences were observed for leukocyte count ($p = 0.721$), neutrophil count ($p = 0.944$), lymphocyte count ($p = 0.209$), platelet count ($p = 0.641$), NLR ($p = 0.307$), PLR ($p = 0.193$), or SII ($p = 0.462$).

Associations between screening markers and hematological and inflammatory parameters were assessed using Spearman correlation analysis (n = 169). A weak but statistically significant positive correlation was observed between PAC and platelet count (rho = 0.176; $p = 0.022$) (Figure 3). However, there were no statistically significant correlations between PAC and the

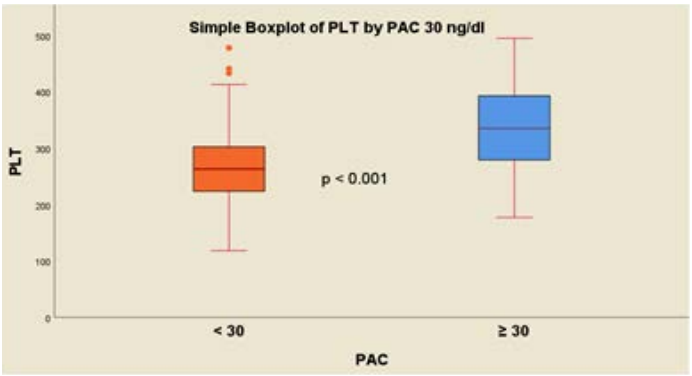

Figure 2. Boxplot graph showing the distribution of platelet count (PLT) in the group with plasma aldosterone concentration (PAC) ≥30 ng/dL

Table 4. Univariable Linear Regression Analyses of Variables Associated with Plasma Aldosterone Concentration

	Unstandardized Coefficients		Standardized Coefficients	95% CI		
Variable	**B**	**Std. Error**	**β**	**Lower Bound**	**Upper Bound**	**p**
Age (years)	-0.185	0.100	-0.143	-0.382	0.011	0.064
Sex (Female)	4.040	2.709	0.115	-1.309	9.389	0.138
Glucose (mg/dL)	-0.034	0.111	-0.024	-0.254	0.185	0.758
Creatinine (mg/dL)	-3.260	7.641	-0.033	-18.346	11.827	0.670
LEU (10^3/μL)	0.175	0.716	0.019	-1.237	1.588	0.807
NEU (10^3/μL)	0.419	0.917	0.035	-1.392	2.230	0.648
LYM (10^3/μL)	-0.340	1.783	-0.015	-3.861	3.181	0.849
PLT (10^3/μL)	0.068	0.018	0.286	0.033	0.102	<0.001
PLR	0.082	0.027	0.229	0.029	0.136	0.003
NLR	0.491	1.483	0.026	-2.437	3.419	0.741
SII	0.009	0.004	0.165	0.001	0.017	0.032

Abbreviations:
PAC, plasma aldosterone concentration; LEU, leukocyte count; NEU, neutrophil count; LYM, lymphocyte count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index; CI, confidence interval; B, unstandardized coefficient; β (beta), standardized coefficient.

remaining parameters and indices (p > 0.05). In addition, PRA and ARR had no statistically significant correlations with any of the evaluated variables (p > 0.05). Univariable linear regression analyses were conducted to assess the associations between PAC levels and clinical, biochemical, and hematological parameters (n = 169). These analyses revealed that platelet count, PLR, and SII were positively associated with PAC (p < 0.05), with the strongest association observed for platelet count. The results of all univariable regression analyses are summarized in Table 4.

To determine factors independently associated with PAC levels, three separate multivariable linear regression models were constructed (Table 5). Since platelet count is a component of PLR and SII, these indices were analyzed in separate models to avoid multicollinearity and clarify their individual associations. All models included age, sex, glucose, and creatinine as covariates. In Model 1, neutrophil, lymphocyte, and platelet counts were added to the covariates, and only platelet count was found to be a statistically significant predictor of PAC levels (B = 0.068, p = 0.001). In Model 2, PLR was included instead of the individual hematological components and was also significantly associated with PAC levels (B = 0.071, p = 0.012); however, this model demonstrated a lower explanatory power than Model 1 (R^2 = 0.084, p = 0.028). In Model 3, SII and age emerged as statistically significant predictors (B = 0.008, p = 0.044 and B = -0.217, p = 0.045, respectively), although this model had the lowest explanatory power among the three.

ROC analyses were performed to evaluate how platelet count, PLR, and SII performed across different PAC categories (≥15 ng/dL and ≥30 ng/dL), and the area under the curve, optimal cut-off, sensitivity, and specificity values were calculated for each parameter. The corresponding results are presented in Table 6 and Figure 4.

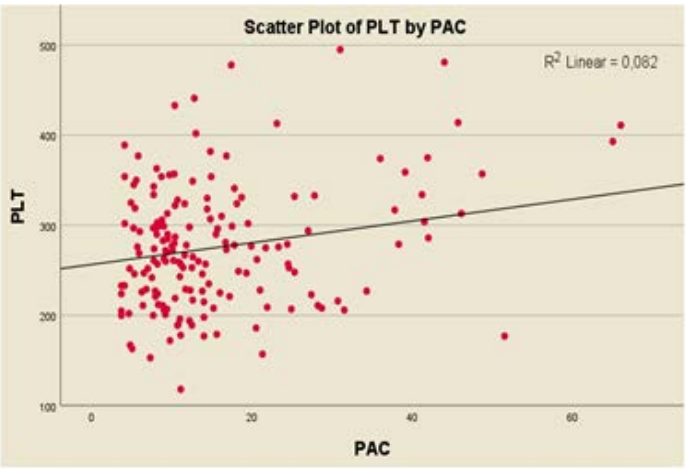

Figure 3. Scatter plot graph showing the association between plasma aldosterone concentration (PAC) and platelet count (PLT)

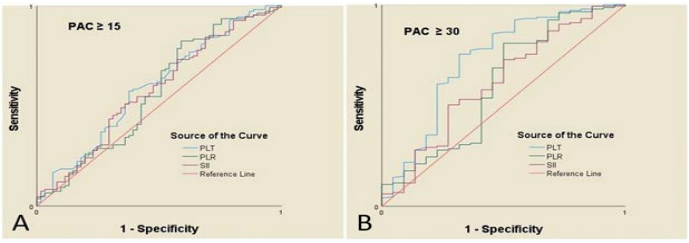

Figure 4. Receiver operating characteristic (ROC) curves of platelet count (PLT), platelet-to-lymphocyte ratio (PLR), and Systemic Immune-Inflammation Index (SII), demonstrating their statistical performance across plasma aldosterone concentration (PAC) categories:
A) PAC ≥15 ng/dL,
B) PAC ≥30 ng/dL.

Table 5. Comparison of multivariable linear regression models assessing factors associated with plasma aldosterone concentration

Model	Independent Predictor(s) and p-values	Model	
		R^2	p
Model 1 (PLT)*	Platelet count (p = 0.001)	0.115	0.006
Model 2 (PLR)*	PLR (p = 0.012)	0.084	0.028
Model 3 (SII)*	SII (p = 0.044), Age (p = 0.045)	0.068	0.044

*Note:
Model 1 includes age, sex, glucose, creatinine, neutrophil count, lymphocyte count, and platelet count.
Model 2 includes: age, sex, glucose, creatinine, neutrophil count, and PLR.
Model 3 includes: age, sex, glucose, creatinine, and SII.
Abbreviations: PLR, platelet-to-lymphocyte ratio; SII, Systemic Immune-Inflammation Index

Table 6. ROC analysis of PLT, PLR, and SII for PAC thresholds ≥15 and ≥30 ng/dL

Variable	PAC (ng/dL)	AUC	p	95% CI	Optimal Cut-off	Sensitivity (%)	Specificity (%)
PLT	≥15	0.595	0.041	0.504–0.686	273.000	62.3	57.4
	≥30	0.727	0.001	0.595–0.858	304.000	68.2	75.5
PLR	≥15	0.569	0.138	0.474–0.664	151.630	41.0	82.4
	≥30	0.605	0.114	0.460–0.749	154.320	50.0	81.0
SII	≥15	0.578	0.094	0.486–0.669	602.970	42.6	73.1
	≥30	0.614	0.086	0.479–0.748	488.900	72.7	50.3

Abbreviations: PAC, plasma aldosterone concentration; PLT: platelet count; PLR: platelet-to-lymphocyte ratio; SII: Systemic Immune-Inflammation Index; AUC: area under the curve; CI: confidence interval.

DISCUSSION

This study evaluated the associations between PA screening markers, hematological parameters, and inflammatory indices in 169 hypertensive individuals. The potential contribution of these parameters to the screening process was also assessed. A particularly strong and consistent positive correlation was observed between platelet count and PAC. Subgroup analyses using PAC cut-offs of ≥15 ng/dL and ≥30 ng/dL revealed a statistically significant increase in platelet count with higher PAC levels. Univariable regression analyses indicated positive associations of PAC with platelet count, PLR, and SII. In multivariable models, platelet count remained the strongest independent marker, while PLR and SII retained weaker but significant associations. In contrast, no significant differences were observed between PAC and other hematological parameters. Furthermore, none of the hematological parameters or inflammatory indices had significant correlations with PRA or ARR. In ROC analysis, the discriminative performance of platelet count, PLR, and SII for PAC ≥15 ng/dL was low but showed improvement at PAC ≥30 ng/dL.

Overall, hemogram-derived inflammatory indices showed no significant association with aldosterone excess, except for a modest correlation with platelet count. The absence of significant associations between PAC and leukocyte, neutrophil, and lymphocyte counts or NLR suggests that these markers offer limited value in reflecting biological variability in aldosterone levels. The weak associations observed for PLR and SII appear to stem from the contribution of platelet count in the calculation of these indices. Moreover, the lack of significant associations between PRA and hematological parameters or inflammatory indices indicates that these indices also provide limited information regarding renin suppression. The low sensitivity and specificity of platelet count in the PAC ≥15 ng/dL category suggest that its contribution at this level is limited. In contrast, the improved discriminative performance of platelet count at PAC ≥30 ng/dL suggests that this parameter may provide supportive information in identifying individuals with more pronounced aldosterone elevation when planning PA screening. Although this finding does not indicate diagnostic utility, it suggests a modest association and underscores the need for further research to identify hypertensive patients who may have underlying hyperaldosteronism.

Current guidelines recommend ARR as the first-line screening test in high-risk patients in the presence of suppressed renin and elevated aldosterone levels. However, PA frequently remains undiagnosed in clinical practice due to suboptimal guideline implementation, variability in ARR cut-off values, and challenges in test standardization. Furthermore, PAC levels can be influenced by various external factors, such as medications, posture, and sodium intake, further reducing the diagnostic reliability of the test (12,13). Given these limitations, there has been growing research interest in complementary biomarkers that may allow PA to be identified more easily and reliably. Accordingly, various inflammatory markers such as high-sensitivity C-reactive protein, serum amyloid A, homocysteine, plasminogen activator inhibitor-1, and malondialdehyde have been investigated. Hemogram-derived inflammatory indices have also been explored as potential tools to differentiate hyperaldosteronism from other forms of hypertension (10). However, none of these parameters have yet been validated for routine clinical use.

The established association between hematological parameters and cardiovascular disease supports their

consideration as potential biomarkers in PA, a condition in which similar pathophysiological mechanisms are implicated. One such marker, NLR, reflects systemic inflammation and is one of the most commonly associated inflammatory indices in cardiovascular diseases. Large-scale studies in recent years have shown that NLR is an independent prognostic marker in predicting both all-cause and cardiovascular mortality (15). Nevertheless, data regarding the relationship between NLR and PA remain limited, and findings in the literature are largely heterogeneous. Some studies have reported lymphopenia and increased NLR in patients with PA, suggesting that this increase may be associated with major cardiovascular events and may serve as an independent risk marker for long-term prognosis (16,17). In contrast, in our study, lymphocyte count, neutrophil count, and NLR were not significantly associated with PAC or PRA. This finding is consistent with a multicenter study by Libianto et al., in which NLR levels did not significantly differ between patients with PA and hypertensive controls (10).

SII and PLR are derived inflammatory indices derived from blood cell counts: SII incorporates neutrophils, platelets, and lymphocytes, whereas PLR uses only platelets and lymphocytes. There is strong evidence in the literature linking high SII levels with mortality and disease severity (18–20). While PLR is also recognized as an inflammation marker (21), evidence for its relationship with PA remains limited. In our study, despite increased PAC levels, SII and PLR exhibited only a limited and statistically non-significant upward trend, and correlation analyses failed to demonstrate significant associations between these indices and PAC. However, in multivariable regression analyses, both PLR and SII were significantly associated with PAC. To isolate the individual effect of each index and avoid model multicollinearity, we analyzed platelet count, PLR, and SII in separate multivariable models. The decreasing statistical strength from platelet count to PLR and SII suggests that the associations observed for these indices may primarily reflect the influence of platelet count within their calculations. Supporting this, no similar pattern was observed for NLR, which does not include platelets in its composition. This indicates that the associations detected for PLR and SII may reflect platelet-dependent contributions rather than independent marker characteristics and that the specificity of these indices may therefore be limited. Considering this potential contribution, the association between platelet count and PAC was evaluated separately in our study, and a modest but statistically significant result was obtained.

Aldosterone affects more than vascular dysfunction and inflammation. It may also promote thrombosis through alterations in coagulation, impaired fibrinolysis, and endothelial dysfunction (22). These prothrombotic effects are associated with increased oxidative stress, production of reactive oxygen species, and reduced bioavailability of nitric oxide (23). Experimental animal models and in vitro studies have shown that aldosterone can affect platelet function and increase platelet accumulation in regions prone to endothelial injury (24-26). Moreover, chronic hyperaldosteronism has been reported to facilitate platelet aggregation and increase thrombotic susceptibility by disrupting the nitric oxide/cyclic guanosine monophosphate signaling pathway (27). The presence of mineralocorticoid receptors on platelet membranes further supports the possibility that aldosterone may exert direct effects on these cells (28). Evidence for the direct effects of aldosterone on platelets in human studies is limited. Existing knowledge consists primarily of indirect findings, such as changes in platelet function observed after treatment with renin-angiotensin-aldosterone system inhibitors (29,30).

The limited sensitivity and specificity of the PAC ≥15 ng/dL cut-off used in PA screening indicate that platelet count alone is not sufficient for diagnostic identification of aldosterone excess, although it may still reflect associated biological changes. Nevertheless, it is notable that the increase in platelet count becomes more apparent when PAC levels rise substantially. Particularly, the elevated platelet count observed at PAC ≥30 ng/dL may provide an indirect indication of hematological changes accompanying aldosterone excess. In current guidelines, PAC ≥30 ng/dL is considered a strong criterion for suspicion of PA when accompanied by appropriate clinical and laboratory findings, and it may even support surgical decision-making without adrenal venous sampling in some younger patients (13). The finding in this study that platelet count > 304,000/mm^3 had 68.2% sensitivity and 75.5% specificity in individuals exceeding PAC ≥30 ng/dL suggests that this parameter may provide modest complementary support in screening at higher PAC levels. Further research is needed to clarify the clinical relevance of this observation.

Due to the study methodology, the associations between first-stage PA screening criteria and hematological parameters were evaluated. Since confirmatory suppression tests were not performed, a definitive PA diagnosis could not be established, and comparisons between PA and essential hypertension were therefore not possible. Nonetheless, a small subgroup within our data who met first-stage criteria and could be considered at high risk for PA was examined separately. However, no statistically significant difference was detected in platelet count in this subgroup. A limited number of studies in the literature similarly report that platelet levels do not differ significantly between patients with PA and those with essential hypertension (10,31). The absence of an observed association between platelet count and PRA or ARR in our study is also consistent with these findings. At the same time, subgroup analyses showed that platelet count tended to increase with higher PAC levels, and this association remained independent in multivariable models, suggesting that although platelet count lacks diagnostic utility, it may still provide limited but clinically relevant supplementary information regarding biological variability in aldosterone levels.

According to current hypertension guidelines, mineralocorticoid receptor antagonists are recommended as the first-line treatment in patients with PA who are not suitable candidates for surgery. Despite this, platelet count is not yet considered in the selection of antihypertensive agents or in decisions regarding the initiation of antiplatelet therapy (32,33).

Medications acting on the renin-angiotensin-aldosterone system, especially angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists, not only suppress aldosterone secretion but also have regulatory effects on platelet function (29,30,34). These pharmacological observations support a possible pathophysiological link between aldosterone and platelet levels. In our study, the parallel trend between platelet count and changes in PAC levels provides an additional finding consistent with this possible link; however, it does not allow for any diagnostic or prognostic interpretation. Therefore, there is a need for larger studies including functional platelet parameters and long-term outcome data to determine the clinical relevance of platelets.

Study limitations

One major strength of this study is the simultaneous evaluation of both basic biochemical tests (PAC, PRA, and ARR) and various hematological parameters in a screening population composed of hypertensive individuals undergoing PA screening. However, the study also has several limitations. Specifically, it has a single-center, retrospective design, which may lead to selection bias and limits causal inference. In addition, second-stage confirmatory tests (e.g., the saline suppression test and the captopril challenge test) were not performed; therefore, patients with PA subtypes confirmed through adrenal venous sampling could not be included. Thus, it was not possible to evaluate potentially more pronounced differences in hematological parameters among patients with true PA. The lack of a significant difference in platelet count in the subgroup with simultaneous renin suppression and aldosterone elevation can be attributed to the limited sample size, preventing definitive conclusions.

As another limitation, the cut-off value determined for platelet count (304,000/mm^3) falls within the normal reference range, which necessitates cautious interpretation of this finding in a clinical context. Moreover, as the study evaluated associations only, the results cannot be interpreted as indicating causality. The low R^2 values in regression models indicate that most of the variation in PAC remains unexplained and that the effects of unmeasured confounders (particularly body mass index and smoking) may be substantial. Failure to control for these variables is another factor limiting the generalizability of the results. Lastly, as the study did not allow subgroup analyses based on hypertension stages or complications, a more detailed assessment of the relationship between hematological markers and disease severity could not be undertaken.

CONCLUSION

In this study, with the exception of platelet count, which had a modest association with aldosterone levels, none of the remaining hematological parameters or inflammatory indices derived from these parameters had significant associations with biochemical tests used in PA screening. The association between platelet count and PAC was consistently observed across multiple analytical approaches and was more pronounced in subgroups with markedly elevated PAC levels. Although these findings do not support platelet count as a diagnostic marker for PA, they suggest that it may provide modest supplementary information on hematological changes accompanying aldosterone excess. Larger, prospective studies including patients with confirmed PA are needed to clarify the clinical validity and potential applications of this observation.

DECLARATIONS

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RESEARCH ARTICLE

Preoperative Predictors of Coexistent Papillary Thyroid Carcinoma in Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

Papiller Benzeri Nükleer Özellikler Gösteren Noninvaziv Foliküler Tiroid Neoplazilerinde Eşlik Eden Papiller Tiroid Karsinomu için Preoperatif Öngördürücü Faktörler

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ABSTRACT

Objective: To evaluate the clinical, ultrasonographic, and cytological characteristics of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and to identify preoperative factors associated with coexistent papillary thyroid carcinoma (PTC).

Materials and Methods: This retrospective study included a total of 115 patients histopathologically diagnosed with NIFTP after thyroidectomy. Demographic, ultrasonographic, cytological, and pathological data were analyzed. Nodules were classified according to the European Thyroid Imaging and Reporting Data System (EU-TIRADS) and the Bethesda cytology categories. The patients were divided into two groups: "NIFTP without coexistent PTC" and "NIFTP with coexistent PTC". Comparative and logistic regression analyses were performed to identify predictors of concomitant PTC.

Results: The mean age was 46.78±13.98 years, and 74.8% were female. The mean size of NIFTP nodules was 23.15±16.70 mm. According to the EU-TIRADS classification, 44.3% of nodules were category 3, 14.8% category 4, and 37.4% category 5. Cytology results were most frequently Bethesda I (27.0%), II (32.2%), and III (24.3%). Coexistent PTC was identified in 33 patients (28.7%). In the results of univariate analysis, smaller nodule size (OR 0.956, 95% CI 0.924-0.990, p = 0.010) was significantly associated with coexistent PTC, while EU-TIRADS category 5 (OR 2.288, 95% CI 1.002-5.228, p = 0.050) showed borderline significance. In multivariate analysis, only smaller nodule size remained an independent predictor (OR 0.951, 95% CI 0.909-0.995, p = 0.030).

Conclusion: Smaller nodule size was found to independently predict coexistent PTC in NIFTP, whereas suspicious sonographic features such as solid composition, presence of a halo, or high EU-TIRADS scores were not independent predictors. Careful evaluation of smaller nodules may improve preoperative risk stratification and guide surgical decision-making.

Keywords: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), papillary thyroid carcinoma (PTC), thyroid nodule, nodule size, predictive factors

ÖZET

Amaç: Papiller benzeri nükleer özellikler gösteren noninvaziv foliküler tiroid neoplazisi (NIFTP) olgularının klinik, ultrasonografik ve sitolojik özelliklerini değerlendirmek ve papiller tiroid karsinomunun (PTK) eşlik etmesi ile ilişkili preoperatif faktörleri belirlemek.

Gereç ve Yöntemler: Bu retrospektif çalışmaya tiroidektomi sonrası histopatolojik olarak NIFTP tanısı konulan 115 hasta dâhil edildi. Demografik, ultrasonografik, sitolojik ve patolojik veriler analiz edildi. Nodüller, Avrupa Tiroid Görüntüleme Raporlama ve Veri Sistemi (EU-TIRADS) ve Bethesda sitoloji sınıflamasına göre değerlendirildi. Hastalar "PTK eşlik eden NIFTP" ve "PTK eşlik etmeyen NIFTP" olarak iki gruba ayrıldı. Eşzamanlı PTK'yi öngördüren faktörleri belirlemek için karşılaştırmalı ve lojistik regresyon analizleri yapıldı.

Bulgular: Hastaların ortalama yaşı 46.78±13.98 yıl olup %74.8'i kadındı. NIFTP nodüllerinin ortalama boyutu 23.15±16.70 mm idi. EU-TIRADS sınıflamasına göre nodüllerin %44.3'ü kategori 3, %14.8'i kategori 4 ve %37.4'ü kategori 5 olarak değerlendirildi. Sitoloji sonuçları en sık Bethesda I (%27.0), II (%32.2) ve III (%24.3) olarak raporlandı. Otuz üç hastada (%28,7) eşzamanlı PTK saptandı. Tek değişkenli analizde küçük nodül boyutu (OR 0.956, %95 GA 0.924–0.990, p=0.010) eşlik eden PTK ile anlamlı şekilde ilişkili bulunurken, EU-TIRADS kategori 5 (OR 2.288, 95% GA 1.002-5.228, p=0.050) sınırda anlamlılık gösterdi. Çok değişkenli analizde ise yalnızca küçük nodül boyutu bağımsız bir öngördürücü olarak kaldı (OR 0.951, 95% GA 0.909-0.995, p=0.030).

Sonuç: NIFTP olgularında, daha küçük nodül boyutu eşlik eden PTK'nin bağımsız bir öngördürücüsü olarak saptanırken; solid kompozisyon, halo varlığı veya yüksek EU-TIRADS skorları gibi şüpheli sonografik özellikler ise bağımsız öngördürücüler olarak bulunmadı. Küçük nodüllerin dikkatli değerlendirilmesi, preoperatif risk sınıflandırmasının geliştirilmesine ve cerrahi karar sürecinin yönlendirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Papiller benzeri nükleer özellikler gösteren noninvaziv foliküler tiroid neoplazisi (NIFTP), papiller tiroid karsinomu (PTK), tiroid nodülü, nodül boyutu, öngördürücü faktörler

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INTRODUCTION

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), recognized in 2016 as a reclassified form of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), represents a distinct diagnostic category within thyroid pathology (1). The 2016 reclassification was prompted by evidence that these tumors exhibit a remarkably indolent course, with an exceedingly rare likelihood of recurrence or metastasis, thereby differentiating them from classical papillary thyroid carcinoma (PTC) (1, 2).

The recognition of NIFTP as a separate entity has considerably affected diagnostic terminology, operative strategies, and clinical follow-up practices. Considering that these lesions lack invasive features and high-risk molecular alterations (e.g., BRAF V600E mutation), they are now regarded as borderline neoplasms—biologically indolent, yet not entirely within the spectrum of benign thyroid disease (1, 3, 4). Therefore, precise recognition of NIFTP is crucial to avoid unnecessary aggressive treatment and to mitigate the emotional and clinical burden that often accompanies a "cancer" diagnosis (1, 5).

Despite these advances, distinguishing NIFTP from other follicular-patterned thyroid neoplasms before surgery remains challenging. Cytological evaluation through fine-needle aspiration biopsy (FNAB) frequently results in indeterminate classifications (Bethesda III or IV), primarily because of overlapping features with follicular adenoma and encapsulated PTC (6, 7). Similarly, since NIFTP nodules rarely display microcalcifications, irregular margins, or other high-risk echogenic features characteristic of malignant disease, sonographic assessment typically yields indeterminate impressions (8, 9).

Although NIFTP generally follows an indolent clinical course, several reports documented its coexistence with PTC, either within the same lobe or contralaterally, in roughly 15–46% of patients (10 - 13). Although the clinical relevance of this coexistence is not yet fully understood, it may influence surgical decision-making, particularly the choice between lobectomy and total thyroidectomy, as well as long-term follow-up protocols (14). Therefore, a comprehensive understanding of the clinical, cytological, and imaging determinants of concomitant PTC is critical to refine management strategies and to avoid unwarranted therapeutic procedures.

To clarify these issues, the present study aimed to evaluate the clinical, ultrasonographic, and cytological profiles of patients with NIFTP and to determine factors associated with the coexistence of PTC. We also investigated whether specific preoperative ultrasonographic parameters, including nodule size, composition, echogenicity, margin regularity, shape, calcification pattern, presence of a halo, and European Thyroid Imaging and Reporting Data System (EU-TIRADS) score, could serve as predictors of coexisting PTC. By elucidating these associations, this study aims to refine preoperative risk stratification and facilitate more individualized surgical decision making when NIFTP is considered in the differential diagnosis.

MATERIALS AND METHODS

Study Design and Population

This retrospective observational study included patients who underwent thyroidectomy at a tertiary referral center between January 2019 and April 2025. Among all patients who had thyroidectomy during this period, those diagnosed histopathologically with NIFTP were identified and included in the sample.

Patients with incomplete ultrasonographic, cytological, or histopathological data were excluded. Ultimately, a total of 115 patients with confirmed NIFTP were enrolled in the analysis.

Data Collection

Clinical, radiological, cytological, and histopathological data collected from institutional electronic medical records were retrospectively reviewed. Demographic variables such as age and sex, and ultrasonographic features including nodule size (maximum diameter in millimeters), composition (solid, mixed cystic, spongiform, or completely cystic), echogenicity (hypoechoic, isoechoic, or hyperechoic), margin regularity, shape (taller-than-wide or wider-than-tall), calcification pattern (microcalcification, macrocalcification, or peripheral), presence of a halo, and EU-TIRADS category were recorded.

The results of FNAB, categorized according to the Bethesda System, the type of surgery performed (total thyroidectomy or hemithyroidectomy), histopathological findings such as NIFTP focality (unifocal or multifocal), coexistence of PTC (in the same or contralateral lobe), and follow-up data including recurrence status were also collected.

The patients were divided into two groups according to the presence of coexistent PTC: those with NIFTP without coexistent PTC (Group 1) and those with NIFTP and coexistent PTC (Group 2). Comparisons among these groups were performed in terms of demographic, ultrasonographic, and cytological characteristics.

Ultrasonographic Evaluation

All thyroid ultrasonography examinations were performed using high-resolution ultrasound devices by an experienced endocrinologist. Each nodule's ultrasonographic features were recorded according to the EU-TIRADS criteria. When multiple nodules were present, the index nodule was defined as the one corresponding to the histopathological NIFTP lesion.

FNAB

FNAB was performed under ultrasound guidance with a 25-gauge needle. Cytological findings were categorized using the Bethesda system (I–VI). For the patients with multiple nodules, the FNAB result corresponding to the nodule that was later identified as NIFTP on pathology was used for the subsequent analysis.

Histopathological Evaluation

All surgical specimens were reviewed by experienced pathologists. NIFTP diagnosis was made based on the diagnostic framework outlined by the World Health Organization (WHO) (15) and the Endocrine Pathology Society (16). These criteria require that the lesion is encapsulated or clearly demarcated from the surrounding thyroid parenchyma, exhibits a predominantly follicular growth pattern, and

displays the characteristic nuclear features of PTC. In addition, the absence of capsular or vascular invasion, tumor necrosis, or increased mitotic activity is mandatory for the diagnosis.

All cases showing invasive features or true papillary structures were excluded. The presence, location, and histological subtype of any coexisting PTC were also recorded.

Follow-Up

Postoperative follow-up information was collected from patient charts in the outpatient setting. The patients were followed at regular intervals with clinical examination, thyroid function tests, and neck ultrasonography. Recurrence was defined as the reappearance of disease confirmed by imaging or histology during follow-up.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk tests. The data following a normal distribution were summarized as mean ± standard deviation, whereas non-normally distributed data were presented as median with interquartile range (Q1–Q3). Categorical variables were described using frequencies and percentages. Between-group comparisons were performed using the independent-samples t-test or Mann–Whitney U test for continuous variables, and the chi-square or Fisher's exact test for categorical variables, as appropriate. Multivariate logistic regression analysis was conducted to identify independent predictors of coexistent PTC. EU-TIRADS 5 was included in the model as a composite variable representing high-risk ultrasonographic features (i.e., microcalcification, taller-than-wide shape, irregular margins, and hypoechogenicity). These component variables were not entered individually to prevent multicollinearity.

The results were presented as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). Statistical significance was defined as a p-value below 0.05.

Ethical Considerations

Necmettin Erbakan University (NEU) Medical School Ethics Committee approved the study (Approval No: 2025/2077) on October 24, 2025. The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived.

RESULTS

This study included a total of 115 individuals diagnosed with NIFTP. The participants had a mean age of 46.78 ± 13.98 years, and females accounted for 74.8% of the sample. Total thyroidectomy was performed in 76.5% of patients, and hemithyroidectomy in 23.5%. Most NIFTPs were unifocal (94.8%), with 5.2% being multifocal. The median follow-up period amounted to 51 months (interquartile range, 38-64 months). Only one case (0.9%) experienced recurrence during follow-up, which had initially presented as isolated NIFTP (Table 1).

The mean nodule size was 23.15 ± 16.70 mm. Most nodules exhibited a solid composition (66.1%), followed by a mixed cystic pattern (30.4%). Isoechoic echogenicity was slightly more common (47.8%) than hypoechoic appearance (41.7%). Irregular margins were observed in 21.7% of nodules, while a taller-than-wide shape was noted in 19.1%. Microcalcifications were present in 18.3%, macrocalcifications in 25.2%, and a peripheral halo was observed in 26.1% of nodules. According to the EU-TIRADS classification, 44.3% of nodules were category 3, 14.8% category 4, and 37.4% category 5 (see Table 1).

Based on FNAB results, the distribution across Bethesda categories was determined as follows: Bethesda I (27.0%), Bethesda II (32.2%), Bethesda III (24.3%), Bethesda IV (1.7%), and Bethesda V (8.7%); no cases were reported as Bethesda VI. Coexistent PTC was identified in 33 of 115 patients (28.7%). Specifically, PTC was located on the same side as the NIFTP lesion in 11 patients (9.6%) and on the contralateral side in 22 patients (19.1%). Detailed clinical, ultrasonographic, and cytological characteristics are summarized in Table 1.

Furthermore, the sample was divided into two groups: Group 1 (NIFTP only, n = 82) and Group 2 (NIFTP with concomitant PTC, n = 33). In the comparison between Group 1 and Group 2, the mean nodule size was significantly larger in Group 1 than in Group 2 (28.35 ± 16.40 mm vs. 19.60 ± 13.50 mm, p = 0.008). The presence of microcalcifications was higher in cases with concomitant PTC (30.3% vs. 13.4%), although this difference did not reach statistical significance (p = 0.064). The frequency of EU-TIRADS 5 was significantly higher in cases with concomitant PTC (51.5% vs. 31.7%, p = 0.047). No statistically significant intergroup differences were observed in terms of irregular margins, taller-than-wide shape, hypoechogenicity, or the presence of a halo (p = 0.871, 0.095, 0.254, and 0.175, respectively). FNAB cytology distributions did not differ significantly between groups (p = 0.755) (see Table 2).

In the univariate analysis, smaller nodule size (OR: 0.956, 95% CI: 0.924-0.990, p = 0.010) was significantly associated with coexistent PTC, whereas EU-TIRADS category 5 was only marginally associated (OR: 2.288, 95% CI: 1.002-5.228, p = 0.050). The results of the multivariate analysis revealed that the nodule size remained the only independent predictor of coexistent PTC (OR: 0.951, 95% CI: 0.909-0.995, p = 0.030), while EU-TIRADS category 5 was not significantly associated with coexistent PTC (p = 0.697) (see Table 3).

DISCUSSION

In a sample of 115 patients diagnosed with NIFTP, we characterized ultrasonographic, cytological, and histopathological features to explore potential predictors of coexisting PTC. The results of our analysis revealed that smaller nodule size independently predicted the presence of concomitant PTC, whereas higher EU-TIRADS categories were more common in such cases, but lost significance in multivariate modeling. Consistent with previous reports, most patients were middle-aged women, and NIFTP exhibited an indolent course, with only a single recurrence observed over prolonged follow-up.

The mean age (~47 years) and female predominance (≈75%) in our sample aligned with previous studies reporting

Table 1. Clinical, ultrasonographic, and cytological characteristics of patients with non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Variables	n=115
Age (years)	46.78±13.98
Gender	
Female, n (%)	86 (74.8)
Male, n (%)	29 (25.2)
Ultrasonographic features	
Nodule Size (mm)	23.15±16.70
Composition	
Solid, n (%)	76 (66.1)
Mixed cystic, n (%)	35 (30.4)
Spongiform, n (%)	2 (1.7)
Completely cystic, n (%)	2 (1.7)
Echogenicity	
Hypoechoic, n (%)	48 (41.7)
Isoechoic, n (%)	55 (47.8)
Hyperechoic, n (%)	12 (10.4)
Margins	
Irregular, n (%)	25 (21.7)
Regular, n (%)	90 (78.3)
Shape	
width < height, n (%)	22 (19.1)
width > height, n (%)	93 (80.9)
Echogenic foci	
Microcalcifications, n (%)	21 (18.3)
Macrocalcifications, n (%)	29 (25.2)
Peripheral calcifications, n (%)	0 (0.0)
None or comet-tail, n (%)	65 (56.5)
Halo	
Yes	30 (26.1)
No	85 (73.9)
EU-TIRADS	
2 (Benign)	4 (3.5)
3 (Low-risk)	51 (44.3)
4 (Intermediate-risk)	17 (14.8)
5 (High-risk)	43 (37.4)
Cytological results of FNAB	
No FNAB	7 (6.1)
Bethesda 1 (Non-diagnostic)	31 (27.0)
Bethesda 2 (Benign)	37 (32.2)
Bethesda 3 (AUS)	28 (24.3)
Bethesda 4 (Follicular neoplasm)	2 (1.7)
Bethesda 5 (Suspicious for malignancy)	10 (8.7)
Bethesda 6 (Malignant)	0 (0.0)
Type of surgery	
Total thyroidectomy	88 (76.5)
Hemithyroidectomy	27 (23.5)
Number of NIFTP foci	
Unifocal	109 (94.8)
Multifocal	6 (5.2)
Follow-up period, months	51.00 (38.00-64.00)
Recurrence	
Yes	1 (0.9)
No	114 (99.1)
Accompanied by PTC	
No	82 (71.3)
On the same side	11 (9.6)
On the opposite side	22 (19.1)

Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.
Abbreviations: EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNAB, Fine-needle aspiration biopsy; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma;

Table 2. Comparison of preoperative ultrasonographic and cytological characteristics among patients with NIFTP alone and those with concomitant PTC

	Group 1 n=82	Group 2 n=33	p value
Age (years)	47.68±14.29	44.54±13.10	0.278
Sex			
Male, n (%)	19 (23.2)	10 (30.3)	0.576
Female, n (%)	63 (76.8)	23 (69.7)	
Ultrasonographic features			
Nodule size (mm)	28.35±16.40	19.60±13.50	0.008*
Solid	51 (62.2)	25 (75.8)	0.241
Hypoechoic	31 (37.8)	17 (51.5)	0.254
Irregular margins	17 (20.7)	8 (24.2)	0.871
width < height	12 (14.6)	10 (30.3)	0.095
Microcalcifications	11 (13.4)	10 (30.3)	0.064
Halo presence	18 (22.0)	12 (36.4)	0.175
EU-TIRADS category 5	26 (31.7)	17 (51.5)	0.047*
Cytological results			
No FNAB	4 (4.9)	3 (9.1)	0.755
Bethesda 1	25 (30.5)	6 (18.2)	
Bethesda 2	26 (31.7)	11 (33.3)	
Bethesda 3	19 (23.2)	9 (27.3)	
Bethesda 4	1 (1.2)	1 (3.0)	
Bethesda 5	7 (8.5)	3 (9.1)	
Bethesda 6	0 (0.0)	0 (0.0)	

Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables and frequency (percentage) for categorical variables.
Group 1: NIFTP only
Group 2: NIFTP with concomitant PTC
Abbreviations: EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNAB, Fine-needle aspiration biopsy; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma
*Statistically significant, p<0.05

Table 3. Univariate and multivariate logistic regression analyses of factors associated with the coexistence of PTC in patients with NIFTP.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	1.442 (0.585-3.554)	0.427	0.978 (0.947-1.010)	0.172
Sex, male	0.984 (0.955-1.013)	0.276	1.677 (0.616-4.565)	0.312
Nodule size	0.956 (0.924-0.990)	0.010*	0.951 (0.909-0.995)	0.030*
Solid	1.900 (0.763-4.732)	0.168	0.711 (0.225-2.247)	0.561
Halo presence	2.032 (0.842-4.904)	0.115	2.276 (0.881-5.886)	0.090
EU-TIRADS category 5	2.288 (1.002-5.228)	0.050	1.217 (0.453-3.272)	0.697

Abbreviations: CI, confidence interval; EU-TIRADS, European Thyroid Imaging Reporting and Data System; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; OR, odds ratio; PTC, papillary thyroid carcinoma.
*Statistically significant, p<0.05

that NIFTP occurs most frequently in middle-aged women (17, 18). NIFTP is currently regarded as a follicular-derived thyroid neoplasm with indolent biological behavior, reclassified from the noninvasive EFVPTC following recognition of its excellent prognosis and absence of invasive potential (1, 11, 19).

In our sample, most nodules exhibited a solid composition and were predominantly isoechoic (47.8%) or hypoechoic (41.7%). Microcalcifications were relatively infrequent, observed in approximately 18% of cases. These ultrasonographic characteristics are broadly consistent with previous reports, which described NIFTP as typically presenting with regular margins, an oval or round shape, and a lack of overtly malignant features (20 - 22). Previous studies reported that microcalcifications are relatively uncommon in NIFTP as compared to classical PTC (23, 24). Similarly, Yang and Fried observed that NIFTP lesions frequently resemble minimally invasive encapsulated tumors, appearing as well-circumscribed nodules with smooth margins and either isoechoic or mildly hypoechoic echogenicity-features that contrast with the more suspicious ultrasound patterns of infiltrative PTC (20).

In the present study, 37.4% of NIFTP nodules were classified as EU-TIRADS 5, a proportion higher than those reported in

most previous series. By contrast, the distribution of EU-TIRADS 3 (44.3%) and EU-TIRADS 4 (14.8%) categories in the sample was largely comparable to prior studies, where most NIFTPs were assigned to low-to-intermediate EU-TIRADS risk levels. The relatively greater proportion of EU-TIRADS 5 nodules observed in our series may reflect overlapping ultrasonographic features between NIFTP and classical PTC rather than methodological or selection-related factors. Overall, these findings support previous evidence that NIFTP predominantly presents with low-to-intermediate risk sonographic patterns, although a subset may display higher EU-TIRADS scores despite their indolent histopathologic nature (23, 25, 26).

Cytologically, the sample demonstrated a predominance of Bethesda I and II categories, accompanied by a notably high proportion of Bethesda III cases. The latter finding is well aligned with previous studies showing that NIFTP is frequently associated with indeterminate cytology, most often within the Bethesda III category (7). Considering that cytology alone cannot reliably distinguish NIFTP from benign follicular lesions, definitive diagnosis depends on comprehensive histopathologic assessment (1 - 3, 6). In their systematic review and meta-analysis, Bongiovanni et al. reported that cytological diagnoses associated with NIFTP span a wide spectrum, from non-diagnostic to malignant, with most cases falling into indeterminate categories. The authors further emphasized that additional cytological and/or molecular features need to be identified to enable more accurate presurgical recognition of NIFTP (7). While the proportion of indeterminate (Bethesda III) cases in our cohort was comparable to that reported by Bongiovanni et al., we observed a relatively higher frequency of non-diagnostic (Bethesda I) and benign (Bethesda II) cytology results. This difference may reflect variations in cytologic interpretation, sample adequacy, or institutional practices, as well as subtle nuclear features that make NIFTP challenging to identify on cytology alone.

The coexistence of NIFTP with other thyroid tumors is well documented in the literature, with reported rates ranging from 14.7% to 46.3% (10, 12, 13, 19, 27). In the largest retrospective series available to date, Vignali et al. analyzed a total of 451 NIFTP cases and found that 43.7% were associated with concomitant thyroid lesions, either benign or malignant, most commonly PTC. The authors also reported that NIFTPs coexisting with malignant tumors were significantly smaller ($p < 0.001$) (11). Similarly, Seo et al. reported that 26.7% of NIFTPs coexisted with other malignant thyroid tumors, including conventional, infiltrative, and follicular variants of PTC. Importantly, the coexistence was more frequent among subcentimeter NIFTPs (43.0%) as compared to those ≥1.0 cm (17.8%), suggesting a potential association between smaller tumor size and multifocality (10). In line with earlier reports, our results demonstrated a coexistence rate of 28.7%, with smaller nodule size identified as an independent predictor of concurrent PTC. This observation may indicate that smaller NIFTPs are more likely to arise in a multifocal thyroid environment or that, due to biological or sampling factors, their reduced size increases the likelihood of detecting coexistent microcarcinomas. Consistently with this observation, our study demonstrated that smaller nodules had higher odds of harboring concurrent PTC. similarly, previous studies proposed that small PTC foci can be more easily missed during preoperative assessment and that multifocal micro-PTCs may preferentially occur alongside otherwise benign-appearing nodules, although direct comparative evidence remains limited (28, 29).

In our analysis, higher EU-TIRADS scores were more frequent among the cases with coexistent PTC; however, after adjustment for nodule size, this feature lost independent significance after, possibly reflecting collinearity and indicating that nodule size is the dominant predictive factor. Our findings highlight the importance of detailed ultrasonographic evaluation, particularly in smaller nodules diagnosed as NIFTP candidates, to screen for possible coexistent malignancy. Since NIFTP itself carries an extremely favorable prognosis and very low recurrence, the detection of synchronous PTC is clinically meaningful and may influence the extent of surgery and postoperative surveillance. While conservative management (lobectomy) is frequently preferred when imaging and cytology suggest low-risk features, surgeons and clinicians must remain cautious of potential occult PTC in the contralateral lobe, especially in populations where multifocal microscopic disease is more common.

Limitations

This study has several limitations. It is retrospective in design, which introduces inherent biases. Furthermore, interobserver variability in ultrasonographic interpretations and cytopathologic classification cannot be fully excluded. In addition, the subgroup of patients with coexisting PTC was relatively small, which may limit power in the multivariate model. Finally, our findings are based on a single-center cohort; external validation in multi-center or prospective settings would strengthen generalizability.

CONCLUSION

In summary, among patients with NIFTP, smaller nodule size emerged as an independent predictor of coexisting PTC. However, suspicious ultrasound features such as solid composition, presence of a halo, and higher EU-TIRADS scores were not independently predictive in multivariate modeling. These findings suggest that closer attention to smaller thyroid nodules and careful imaging reassessment may be warranted when NIFTP is considered in the differential diagnosis or when planning surgery for indeterminate or low-risk follicular-patterned lesions. Further validation of these predictors through well-designed, multicenter prospective studies is warranted to enhance preoperative risk assessment and to optimize clinical decision making.

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RESEARCH ARTICLE

Evaluation of The Ocular Surface with and Without Preservatives in the Treatment of Patients Undergoing Cataract Surgery

Katarakt Ameliyatı Yapılan Hastaların Tedavisinde Prezervanlı ve Prezervansız İlaç Kullanımı İle Oküler Yüzeyin Değerlendirilmesi

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ABSTRACT
Objective: The present study aims to evaluate the effect of medical treatment, with and without preservatives, on the ocular surface in patients without dry eye who underwent phacoemulsification surgery.
Materials and Methods: The study comprised a total of 70 patients. Following the operation, the patient was administered moxifloxacin 8x1 for a period of one week, followed by a course of steroid treatment spanning four weeks. The initial dosage of the steroids was 8x1, which was then reduced by two drops on a weekly basis. The patients were divided into two groups according to steroid use. Dexasine SE (Group 1, preservative-free) was prescribed to 35 patients, while Dexasine (Group 2, with preservatives) was prescribed to 35 patients. Schirmer's test and the evaluation of corneal and conjunctival staining were conducted before the operation, and then at one week, one month, and three months post-surgery.
Results: The mean age of the study participants was 72.03 years (±6.29) in Group 1 and 71.43 years (±5.12) in Group 2, with no statistically significant difference between the two groups (p=0.66). A comparison between Groups 1 and 2 revealed a significant discrepancy in Schirmer I, Break Up Time scores, and corneal conjunctival staining at the conclusion of the initial week and initial month. However, no substantial difference was observed at the three-month mark.
Conclusion: In patients without dry eyes, dry eye tests may deteriorate on the ocular surface for up to the first 3 months preservatives contained in the drops used before and after surgery. Therefore, the use of medication without the concomitant use of a preservative should be the preferred option.

Keywords: Schirmer I test, BUT, corneal conjunctival staining, cataract, phacoemulsification

ÖZET
Amaç: Bu çalışma kuru göz hastalığı bulunmayan ve fakoemülsifikasyon cerrahisi geçirmiş bireylerde, prezervan içeren ve prezervan içermeyen topikal tedavilerin postoperatif dönemde oküler yüzey sağlığı üzerine etkilerini değerlendirmek amacıyla yapılmıştır.
Gereç ve Yöntemler: Çalışma toplam 70 hastayı kapsamaktadır. Ameliyattan sonra, hastalara bir hafta boyunca 8x1 moksifloksasin uygulandı, ardından dört hafta süren bir steroid tedavisi uygulandı. Steroidlerin başlangıç dozu 8x1 idi ve daha sonra haftalık olarak 2 damla azaltıldı. Hastalar steroid kullanımına göre iki gruba ayrıldı. 35 hastaya Dexasine SE (Grup 1, Prezervansız), 35 hastaya ise Dexasine (Grup 2, Prezervanlı) reçete edildi. Schirmer testi ile kornea ve konjonktiva boyanmasının değerlendirmesi ameliyattan önce, ameliyattan bir hafta, bir ay ve üç ay sonra yapıldı.
Bulgular: Çalışmaya katılan hastaların ortalama yaşı Grup 1'de 72,03 ± 6,29 yıl, Grup 2'de ise 71,43 ± 5,12 yıl olarak hesaplandı; iki grup arasında yaş açısından istatistiksel olarak anlamlı bir fark bulunmadı (p = 0,66). Grup 1 ve Grup 2 karşılaştırıldığında, postoperatif 1. hafta ve 1. ayda Schirmer I testi sonuçları, gözyaşı kırılma zamanı skorları ile kornea ve konjonktiva boyanma düzeyleri arasında her iki grupta da istatistiksel olarak anlamlı fark saptandı (p<0,05). Ancak 3. ay değerlendirmelerinde bu parametreler açısından gruplar arasında anlamlı bir fark izlenmedi (p>0,05).
Sonuç: Kuru gözü olmayan hastalarda, fakoemülsifikasyon ameliyatı öncesinde ve sonrasında kullanılan damlaların içerdiği prezervanlara bağlı olarak ilk 3 aya kadar oküler yüzeyde kuru göz testlerinde bozulma olabilmektedir. Bu nedenle prezervansiz ilaç kullanımı tercih edilmelidir.

Anahtar Kelimeler: Schirmer I testi, BUT, kornea konjonktiva boyanması, katarakt, fakoemülsifikasyon

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INTRODUCTION

Cataract surgery is among the most prevalent surgical procedures in current clinical practice, playing a pivotal role in enhancing patients' visual acuity. Postoperative complications may be observed in patients following ocular surgery despite the success of the intervention. A range of alterations to the ocular surface may be identified during this period. Contemporary advances in techniques and minimally invasive approaches in anterior segment surgery have been developed to mitigate ocular surface damage during surgery. This paper is intended to provide a comprehensive overview of the subject. Nevertheless, despite these advances, ocular surface problems, especially dry eye, are prevalent after cataract and refractive surgery. Moreover, patients suffering from dry eye syndrome often experience an exacerbation of symptoms in the postoperative period. Postoperative complaints frequently include symptoms such as stinging and burning, even though the surgical procedure itself was uneventful (1). It is therefore important to review the risk factors, determine the mechanisms that trigger dry eye, and choose appropriate treatments to reduce postoperative complaints and obtain a healthy ocular surface.

The increase in dry eye symptoms after anterior segment surgeries, such as cataract surgery, is associated with the effects of the drugs used, independent of the surgery itself. The use of topical medications in the postoperative treatment process may exacerbate dry eye symptoms by having various effects on the tear film (2). Postoperative use of topical drops is a component of the healing process, and drops are commonly used for approximately one month. The drops used contain preservative active ingredients, highlighting the potential impact of preservatives on the ocular surface. Specifically, the use of topical medications containing preservatives has been associated with toxic effects that may adversely affect the ocular surface. Prolonged use of these medications can lead to alterations in the ocular surface as well as symptoms such as tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, and corneal surface disruption (3,4).

Benzalkonium chloride (BAC), a widely used preservative in ophthalmic formulations, is a quaternary ammonium compound known to exert various toxic effects on the ocular surface with prolonged use. Numerous studies have demonstrated that BAC contributes to corneal epithelial damage, goblet cell loss, and tear film instability (3-5). Additionally, it has been suggested that BAC triggers several cellular mechanisms, including oxidative stress, the release of pro-inflammatory cytokines, and apoptosis, ultimately leading to ocular surface inflammation and epithelial injury. These pathological processes compromise tear film stability, intensify conjunctival inflammation, and may induce degenerative changes in both corneal and conjunctival tissues over time (6-9).

The objective of this study is to compare the effects of preservative-containing and preservative-free ophthalmic medications on the ocular surface following cataract surgery. To achieve this aim, the study will assess their impact on tear film stability, conjunctival inflammation, corneal epithelial integrity, and overall ocular surface health. The findings are expected to inform strategies for optimizing ocular surface management in the postoperative period.

MATERIAL AND METHODS

This prospective study was conducted in a tertiary care ophthalmology center between January 2024 and July 2024. The study was approved by the independent ethics committee of our hospital, and all the patients signed the informed consent form (Decision No: 2024/11/67).

Patient Selection and Grouping

The patients included in the study were selected to ensure a homogeneous distribution in terms of age, gender, and oculomotor health. The operated eye was randomized between the two groups, and the patients were divided into two main groups according to the steroid treatment used:

Group 1: 35 patients treated with dexamethasone sodium phosphate (Dexasine SE®, preservative-free formulation, Abdi İbrahim Ilac, Türkiye).

Group 2: 35 patients treated with dexamethasone sodium phosphate (Dexasine®, preservative-containing formulation, Abdi İbrahim Ilac, Türkiye)

Surgery Protocol

The surgical procedure was conducted using the standard phacoemulsification (Phaco) technique. Preoperatively, the patients received 0.1% diclofenac sodium eye drops, administered as one drop three times daily starting one day before surgery. The operations were performed under local anesthesia. Following topical anesthetic application, the ocular surface was disinfected with 5% povidone-iodine solution. The mean duration of the surgery was approximately 15 minutes.

Postoperative Treatment Protocol

In the postoperative period, the following treatment protocols were routinely applied to the patients. First, the patients received moxifloxacin 0.5% (eight times daily) for one week as an antibiotic treatment. Steroid treatment was initiated with dexamethasone sodium phosphate (Dexasine or Dexasine SE) eight times a day for the first week and continued for a total of 4 weeks, with a gradual reduction of two drops every week.

Ocular Surface Assessments

A primary objective of this study was to investigate changes in the ocular surface throughout the postoperative treatment period. To this end, ocular surface parameters were assessed preoperatively and at the end of the first week, first month, and third month following surgery. The evaluations were conducted using the following clinical parameters:

1. Schirmer I Test (Sch.I): This test, which evaluates tear production, was performed in each patient at three different times before and after surgery. A Sch.I test value of ≤10 mm was considered to indicate the presence of dry eye disease (10).

2. Break Up Time (BUT) Score: This test, performed to determine tear film stability, measures the time the tear film

remains intact. A BUT of ≤10 seconds was considered indicative of tear film instability (11).

3. Corneal and Conjunctival Staining (CCS): CCS involves the staining of the cornea and conjunctiva with fluorescein dye to assess epithelial damage on the ocular surface. The extent of damage was determined by analyzing the images obtained after staining. CCS was graded using the Oxford grading scheme, with a score of 0 considered normal (12).

Statistical Analysis

The data from this study were analyzed using SPSS (Statistical Package for the Social Sciences, version 22.0; IBM Corp., Armonk, NY, USA) software. Continuous variables were reported as mean ± standard deviation (SD). Categorical variables were analyzed using either the Chi-square test or Fisher's Exact Test, as appropriate. Changes over time were assessed using a repeated measures analysis of variance (ANOVA) for normally distributed data to assess changes related to the three study periods before and after surgery (postoperative one week, one month, and three months). We considered a p-value of less than 0.05 to be statistically significant.

RESULTS

The mean age of the study participants was 72.03±6.29 years in Group 1 and 71.43±5.12 years in Group 2, and there was no statistically significant difference between the two groups (p=0.66). Similarly, there was no significant difference in the duration of surgery between Group 1 (7.28±1.19 minutes) and Group 2 (7.24±1.30 minutes) (p=0.87). In Group 1, the Sch.I and BUT values showed a significant decrease at the end of the first week (p<0.05). However, these parameters began to improve by the end of the fourth week and approached preoperative levels by the third month (p=0.59, p=0.08) (Table 1). In Group 2, significant changes in the Sch.I and BUT values were observed at both the first week and first month (p<0.05). Nevertheless, by the third month, these parameters had returned to preoperative values (p>0.05). Specifically, the BUT value had completely normalized by the third month with no statistically significant difference from baseline (p=1.0) (Table 2).

Comparative analysis demonstrated significant differences between Groups 1 and 2 across time points in both Sch.I test values and BUT (p<0.01). In Group 1, both the Sch.I test values and the BUT showed a more pronounced decrease in the early period, followed by partial recovery during follow-up; in contrast, Group 2 maintained higher Sch.I and BUT values at all the time points, demonstrating a significant advantage over Group 1 in terms of tear secretion and tear film stability (p<0.01) (Figures 1 and 2).

Table 1. Changes in Ocular Surface Parameters Over Time in Group 1 and Group 2

Group	Timepoint	Schirmer I (mm)	p (Sch.I)	BUT (s)	p (BUT) Conjunctival Staining	Corneal	p (CCS)
Group 1	Preoperative	16.2 ± 3.3	–	14.4 ± 1.7	–	0.00	–
	1 Week	13.6 ± 3.1	<0.001	13.0 ± 2.0	<0.001	0.08	0.83
	1 Month	15.2 ± 3.0	<0.001	14.0 ± 1.7	<0.001	0.02	0.32
	3 Months	16.0 ± 2.9	0.59	14.4 ± 1.5	0.08	0.00	1.0
Group 2	Preoperative	17.9 ± 3.6	–	14.4 ± 0.3	–	0.00	–
	1 Week	14.9 ± 3.4	<0.001	12.7 ± 0.3	<0.001	0.37	0.03
	1 Month	16.7 ± 3.2	<0.001	13.8 ± 0.3	0.04	0.28	0.006
	3 Months	17.4 ± 3.2	0.12	14.6 ± 0.3	1.0	0.02	0.32

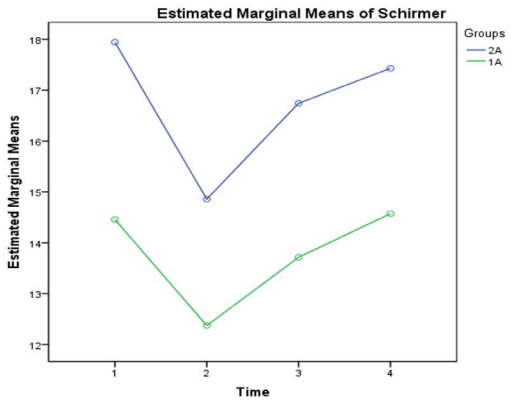

Figure 1. Changes in Schirmer I Test Values Over Time in Group 1 and Group 2

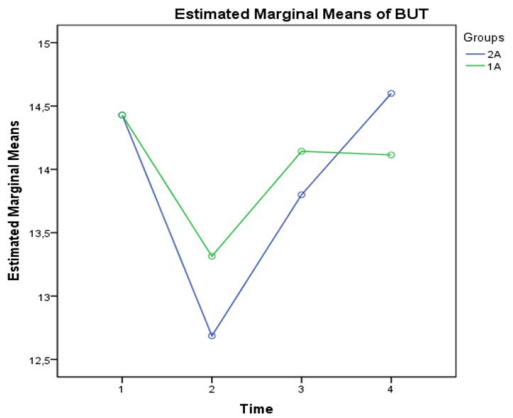

Figure 2. Changes in Tear Film Break-Up Time (BUT) Over Time in Group 1 and Group 2

DISCUSSION

The present study demonstrated that the use of eye drops containing protective agents after cataract surgery can significantly influence ocular surface health in patients without pre-existing dry eye syndrome. The findings indicate that the surgical process impacts tear film stability and the ocular surface not only through mechanical interventions but also via the pharmacological agents administered. A marked deterioration in tear film stability was observed, particularly during the first postoperative month, and this effect was noted to persist up to the third month. These results highlight the clinical relevance of using preservative-free eye drops to promote and maintain ocular surface integrity in the postoperative period. In the present study, particular emphasis was placed on the impact of detergent-type preservatives, such as BAC, on the ocular surface. BAC has been shown to disrupt the lipid layer of the tear film, leading to tear film instability, goblet cell loss, and conjunctival squamous metaplasia (13,14). These findings provide strong evidence in favor of using preservative-free eye drops to maintain optimal ocular surface health. This conclusion is further supported by similar studies in the existing literature, which have reported that both clinical and laboratory outcomes are more favorable with preservative-free formulations, particularly in patients diagnosed with dry eye disease (15,16).

In another study, the patients in the preservative-free group demonstrated superior outcomes in ocular surface tests and impression cytology findings among individuals with dry eye disease (17). Furthermore, other studies in the literature, such as that by Akçay et al., emphasize that dry eye symptoms may worsen following surgery, highlighting the importance of addressing this issue in patient counseling and postoperative treatment planning (18). These observations underscore the need for caution regarding the prolonged and intensive use of preservatives in ophthalmic treatments. The findings of our study suggest that the tear film instability and ocular surface alterations observed after cataract surgery are attributable not only to the surgical procedure itself but also to the pharmacological components of the medications administered postoperatively. Current guidelines recommend the preferential use of preservative-free ophthalmic formulations after cataract surgery, particularly in patients at risk of dry eye disease or ocular surface dysfunction. However, in daily clinical practice, preservative-containing eye drops are still commonly prescribed due to factors such as cost, availability, and established prescribing habits. Our findings indicate that postoperative tear film instability and ocular surface alterations are influenced not only by surgical trauma but also by the pharmacological properties of postoperative medications, thereby supporting a more selective and risk-based use of preservative-free treatments.

Study Limitations

This study has several limitations. First, the relatively small sample size may limit the generalizability of the findings. Future research involving larger patient cohorts is needed to validate and strengthen these results. Second, the study did not include a detailed comparison of different preservative types, which could have helped to further elucidate the specific effects of various postoperative eye drops. Lastly, the follow-up period was relatively short; longer-term studies may provide a more comprehensive understanding of ocular surface recovery and the sustained impact of postoperative treatments.

CONCLUSION

In conclusion, preservative-containing eye drops used during the postoperative period may transiently disrupt tear film stability and exert adverse effects on ocular surface health. These effects are most prominent during the first postoperative month but generally tend to resolve and return to baseline by the third month. A preference for preservative-free eye drops may represent an important strategy for preserving ocular surface health following surgery. Moreover, in clinical practice, patients should be informed about the potential adverse effects of preservative-containing agents, and the ocular surface should be carefully monitored for signs of dry eye. Future large-scale, long-term studies are warranted to further elucidate these findings and to support the development of evidence-based postoperative management protocols.

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RESEARCH ARTICLE

Comprehensive Histochemical Evaluation of Age-Related Intervertebral Disc Degeneration

İntervertebral Diskte Yaşlanmaya Bağlı Dejeneratif Değişikliklerin Ayrıntılı Histokimyasal Analizi

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ABSTRACT

Objective: The intervertebral disc (IVD) is a fibrocartilaginous structure that plays a critical role in transmitting spinal loads and maintaining mobility. Age-related degeneration of the IVD leads to the disruption of structural integrity, reduction in mechanical function, and the development of clinical symptoms such as back and neck pain. During the degenerative process, matrix composition, cellular organization, and mechanical resilience are significantly affected. The aim of this study was to investigate the histological and histochemical changes occurring in IVDs across different age groups using various staining techniques and to evaluate their relationship with the degeneration process.

Materials and Methods: This study included 30 patients aged between 40 and 70 years who underwent surgical procedures for disc herniation during which IVD specimens were obtained. Patients were divided into four age groups: Age40s (40–49 years, n=9), Age50s (50–59 years, n=7), Age60s (60–69 years, n=8), and Age70s (70–79 years, n=6). Surgical specimens were fixed in 10% formalin, processed routinely, and embedded in paraffin. Sections of 5 µm in thickness were cut from the paraffin blocks and stained with hematoxylin and eosin, toluidine blue, Masson's trichrome, Congo red, and the Armed Forces Institute of Pathology method. Histological changes were examined under a light microscope and semi-quantitatively scored.

Results: With advancing age, IVD tissues exhibited a marked decrease in proteoglycan content, an increase in collagen fiber density, accumulation of lipofuscin granules, and the presence of amyloid deposits. In the older age groups, the matrix was observed to become denser and more fibrotic, and to show disruption of the lamellar organization.

Conclusion: Histochemical staining techniques are effective in the detailed identification of cellular and extracellular matrix changes occurring during IVD aging and degeneration. These methods contribute to the characterization of age-related structural alterations and provide valuable information for comparative histopathological assessments of the degenerative process.

Keywords: Aging, degenerative disc disease, histochemistry, intervertebral disc

ÖZET

Amaç: Omurlar arası disk (intervertebral disk, IVD), omurga yüklerinin iletilmesi ve hareket kabiliyetinin sağlanmasında kritik rol oynayan fibro-kıkırdak yapıda bir oluşumdur. Yaşlanmaya bağlı olarak gelişen IVD dejenerasyonu, yapısal bütünlüğün bozulmasına, mekanik fonksiyonların azalmasına ve klinik olarak bel ve boyun ağrısı gibi semptomlara yol açmaktadır. Dejeneratif süreçte matriks kompozisyonu, hücresel organizasyon ve mekanik dayanıklılık belirgin şekilde etkilenmektedir. Bu çalışmanın amacı, farklı yaş gruplarında IVD'de meydana gelen histolojik ve histokimyasal değişiklikleri çeşitli boyama teknikleri ile ayrıntılı olarak ortaya koymak ve bu değişikliklerin dejenerasyon süreciyle ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışmaya, 40–70 yaş aralığında olup disk herniasyonu tanısıyla cerrahi müdahale sırasında IVD materyali elde edilen toplam 30 hasta dahil edilmiştir. Hastalar, yaş aralıklarına göre dört gruba ayrılmıştır: 40–49 yaş aralığını kapsayan Yaş40 grubu (n=9), 50–59 yaş aralığını kapsayan Yaş50 grubu (n=7), 60–69 yaş aralığını kapsayan Yaş60 grubu (n=8) ve 70–79 yaş aralığını kapsayan Yaş70 grubu (n=6). Elde edilen cerrahi materyaller %10'luk formalin ile fikse edilmiş, rutin takip işlemlerinden geçirilerek parafine gömülmüştür. Parafin bloklardan 5 µm kalınlığında kesitler alınmış ve Hematoksilen–Eozin (H&E), Toluidin Mavisi, Masson Trikrom, Kongo Kırmızısı ve Armed Forces Institute of Pathology (AFIP) yöntemleri ile boyanmıştır. Histolojik değişiklikler ışık mikroskobu altında değerlendirilmiş ve yarı kantitatif yöntemle skorlanmıştır.

Bulgular: Yaş ilerledikçe IVD dokusunda proteoglikan içeriğinde belirgin azalma, kollajen lif yoğunluğunda artış, lipofuksin granüllerinin birikimi ve amiloid depozitlerinin oluşumu gözlenmiştir. İleri yaş gruplarında matriks yapısının yoğunlaştığı, fibrotik karakterin belirginleştiği ve lameller organizasyonun düzenliliğini kaybettiği saptanmıştır.

Sonuç: Histokimyasal boyama teknikleri, IVD yaşlanması ve dejenerasyonu sürecinde meydana gelen hücresel ve ekstrasellüler matriks değişikliklerinin ayrıntılı olarak belirlenmesinde etkili yöntemlerdir. Bu yöntemler, yaşa bağlı yapısal değişikliklerin karakterizasyonuna katkı sağlamakta ve dejeneratif sürecin histopatolojik değerlendirilmesinde karşılaştırmalı çalışmalar için değerli bir temel oluşturmaktadır.

Anahtar Kelimeler: Yaşlanma, dejeneratif disk hastalığı, histokimya, omurlar arası disk

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INTRODUCTION

The intervertebral disc (IVD) is a fibrocartilaginous structure that transmits and distributes spinal loads between the vertebral bodies while also allowing mobility (1). It is structurally organized with a centrally situated nucleus pulposus (NP), characterized by high water content and abundant proteoglycans, encased by the annulus fibrosus (AF), which comprises concentrically layered lamellae enriched with collagen. Thin cartilaginous endplates (CEPs) located on the superior and inferior surfaces of the disc regulate the nutrition and metabolic exchange of the IVD (2). The outer annulus comprises highly organized collagen lamellae, where type I collagen fibers are aligned in parallel with longitudinal fibroblasts (3, 4). The inner annulus, in contrast, has a more cartilage-like structure, containing chondrocyte-like cells and higher levels of type II collagen and proteoglycans (5). The centrally located NP consists of a highly hydrated, gelatinous matrix rich in proteoglycans, mainly synthesized by large notochordal cells. Together, the AF, NP, and CEPs constitute the essential components of the functional spinal motion segment, enabling the IVD to provide shock absorption during load bearing and resist tensile and torsional forces (6).

Age-related degenerative joint disorders are among the most common chronic conditions, exerting a profound impact on public health and generating substantial social and economic challenges (7). In the elderly, IVD degeneration and osteoarthritis are the primary causes of persistent joint-related pain and functional impairment (8). Impaired mobility, in turn, is widely recognized as a strong predictor of functional decline, loss of autonomy, and mortality in later life (9). Accordingly, safeguarding joint integrity, and particularly that of IVDs, plays a pivotal role in sustaining mobility with advancing age. IVDs tend to manifest age-related degenerative changes earlier than many other connective tissues (10). As the NP ages, its proteoglycan content and hydration progressively diminish, resulting in a gradual shift toward a more fibrotic composition. These alterations promote the development of fissures, reduce NP volume and intradiscal pressure, and ultimately lead to a measurable loss of disc height. Over time, oxidative modification of matrix proteins produces further structural changes, transforming the translucent and gelatinous NP into a yellow, fibrotic tissue. This transition is compounded by the accumulation of lipofuscin, a brown "aging pigment" formed through the slow peroxidation of lipids (11).

Amyloidosis is a systemic disorder characterized by the extracellular deposition of misfolded protein aggregates in various tissues and organs. Depending on the site of deposition, these amyloid accumulations can disrupt normal function through mechanical compression or by triggering degenerative changes (12). IVDs are frequently reported as sites of localized articular amyloid deposition and, in some cases, as a location affected by systemic forms. While the mechanisms underlying this phenomenon are not fully understood, it has been suggested that intrinsic properties of the IVD extracellular matrix may favor amyloid aggregation. Small, localized deposits are not uncommon within IVDs and have been documented in both pathological and age-related contexts (13).

The present study aimed to investigate the histological alterations occurring in disc cells throughout the processes of IVD aging and degeneration, and to characterize these changes with the application of various histochemical staining techniques. Specifically, assessments were performed to evaluate cell type, cellular density, proliferative activity, accumulation of lipofuscin granules as an indicator of cellular senescence, and deposition of amyloid plaques.

MATERIALS AND METHODS

Patient Selection and Sample Collection

This study included 30 patients aged 40–70 years who underwent surgical removal of IVD material due to disc herniation in the Department of Neurosurgery of Medova Hospital. Written informed consent was provided by all participants. Residual disc material obtained during surgery was used for the study. To ensure the consistency and relevance of the findings, samples from young adult patients under 40 years of age were excluded. Therefore, analyses were conducted on samples from patients aged 40 and above, representing sufficiently aged discs. This approach allowed for the assessment of histological changes associated with both age-related degeneration and reduced physical activity, providing a clearer understanding of pathological features in a more representative patient population. Ethical approval for the study was granted by the Non-Drug and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University on June 13, 2025 (Approval No: 2025/5818).

Inclusion criteria were as follows:

- Radiological confirmation of disc herniation by MRI or CT
- Availability of surgically obtained disc material
- Complete recording of the patient's clinical and demographic data (age, sex, symptom duration, level of herniation, etc.)

Exclusion criteria were as follows:

- Presence of pathologies other than disc herniation, such as infection, tumor, or trauma
- Insufficient or damaged tissue material

Clinical data of the patients were obtained from hospital records and surgical notes.

Patients were divided into four age groups for analysis: Age40s (40–49 years, n=9), Age50s (50–59 years, n=7), Age60s (60–69 years, n=8), and Age70s (70–79 years, n=6).

Histological Analyses

IVD tissues were fixed in 10% neutral buffered formalin. Following fixation, samples were dehydrated through a graded ethanol series (70%, 80%, 90%, 96%, and absolute alcohol; 1 h each). Dehydrated specimens were cleared in xylene and subsequently infiltrated with molten paraffin in a laboratory oven for 4–5 h. Tissues were then embedded in paraffin to obtain paraffin blocks. Serial sections of 5 µm in thickness were cut using a rotary microtome. For deparaffinization, the sections were immersed in xylene (3 × 20 min) and rehydrated through descending grades of ethanol (100%, 90%, 80%, 70%,

and 50%). The slides were then stained with hematoxylin and eosin (H&E), toluidine blue, Masson's trichrome, Congo red, and the Armed Forces Institute of Pathology (AFIP) lipofuscin staining method. After staining, sections were mounted with Entellan® mounting medium. All stained sections were examined using a Zeiss Primo Star light microscope, and digital images were captured and analyzed with the Zeiss AxioCam ERc 5s imaging system. Histological alterations in the IVD tissues were evaluated for each age group according to predefined criteria (Table 1) (14). Scoring was performed independently by two blinded observers.

Hematoxylin–Eosin Staining

H&E staining was employed to score and evaluate the proliferation of hypertrophic chondrocytes, as well as granular alterations characterized by eosinophilic granular material within the fibrocartilaginous matrix, under light microscopy (15).

Masson's Trichrome Staining

Masson's trichrome staining (BesLab, Lot: 072022.036) was performed to demonstrate vascularization and the structural organization of collagen fibrils within the IVD tissue (16).

AFIP Method for Lipofuscin

Deparaffinized sections were passed through distilled water and stained with Kinyoun carbol fuchsin (J-608-1) for 30 min, then rinsed with tap water. Sections were dipped in acid alcohol (J-608-3) until pale pink, rinsed under tap water for 5 min, and washed with distilled water. Counterstaining was performed with picric acid (J-608-2) until sections appeared yellow. Sections were then dehydrated in 95% and absolute alcohol, cleared with xylene, and cover-slipped with Entellan®. On each slide, lipofuscin granules were observed as red-orange structures in yellow-stained areas and were scored accordingly (17,18).

Congo Red Staining

Congo red staining was used to detect amyloid protein in IVD tissue (19). Deparaffinized sections were stained according to the instructions for the Pato Lab Congo Red Staining Kit (PLKit10-150).

Toluidine Blue Staining

A stock solution was formulated by dissolving 0.1 g of toluidine blue powder (Sigma-Aldrich, T3260) in 100 mL of distilled water, which was subsequently diluted at a ratio of 1:2.

Table 1. Comparative scoring of age-related morphological alterations in intervertebral discs by different histological stains

	Score	Scoring criteria	
		Hematoxylin and Eosin (H&E)	
Hypertrophic chondrocyte proliferation	0	No hypertrophic chondrocytes	Fig.1-b
	1	Few hypertrophic chondrocytes (minimal foci, not diffuse)	
	2	Moderate hypertrophic chondrocytes (several foci of clustering)	
Eosinophilic granular structure	0	No eosinophilic granular structures	Fig.1-c
	1	Few eosinophilic granular structures (isolated foci)	
	2	Prominent eosinophilic granular structures (diffuse or multiple dense foci)	
		Masson's Trichrome (MT)	
Vascularization	0	No vascularization	Fig.2-b
	1	Mild vascularization	
	2	Marked vascularization	
Structure of collagen fibrils	0	Collagen fibrils well-organized, no structural disruption	Fig.2-c
	1	Mild irregularity (partial misalignment or waviness in some fibrils)	
	2	Marked irregularity (diffuse misalignment, fragmentation, or dense fibrotic areas)	
		Armed Forces Institute of Pathology Staining Protocol (AFIP)	
Presence of lipofuscin granules	0	No lipofuscin granules	Fig.3-b
	1	Few lipofuscin granules (isolated or small foci)	
	2	Marked lipofuscin granules (diffuse or multiple dense foci)	
		Congo Red (CR)	
Amyloid deposits	0	No amyloid deposits	Fig.4-b
	1	Mild amyloid deposits (few or isolated foci)	
	2	Marked amyloid deposits (diffuse or multiple dense foci)	
		Toluidine Blue (TB)	
Intense metachromatic staining	0	No or minimal metachromatic staining	Fig.5-b
	1	Mild metachromatic staining (few small areas)	
	2	Intense and widespread metachromatic staining (large, prominent areas)	

Sections were stained with this solution for 40 s. Toluidine blue interacts with acidic mucopolysaccharides (e.g., chondroitin sulfate, keratan sulfate), producing metachromasia. The stain was used to visualize cartilage-like structures, proteoglycan content, and mucopolysaccharides (14).

Statistical Analysis

All data were expressed as mean ± standard deviation. The normality of the data distribution was assessed using the Shapiro–Wilk normality test. Statistical comparisons among groups were performed using one-way ANOVA, followed by the Tukey post hoc test. Values of $p < 0.05$ were considered statistically significant. Statistical analyses were performed using GraphPad Prism 5.0 Demo and Microsoft Office 365 software.

RESULTS

Hematoxylin and Eosin Staining Findings

Examination of H&E-stained sections from all age groups revealed that those obtained from the Age40s group exhibited a more organized lamellar structure, with uniformly shaped chondrocytes and fewer eosinophilic regions. With advancing age, disruptions in lamellar organization and the development of fissures were observed, along with more prominent chondrocyte clusters and an increase in eosinophilic regions. Based on these changes, hypertrophic chondrocyte proliferation scores were significantly higher in the Age60s and Age70s groups compared to the Age40s group, whereas eosinophilic granular structure scores were significantly higher in the Age60s group compared to the Age40s group (Figure 1).

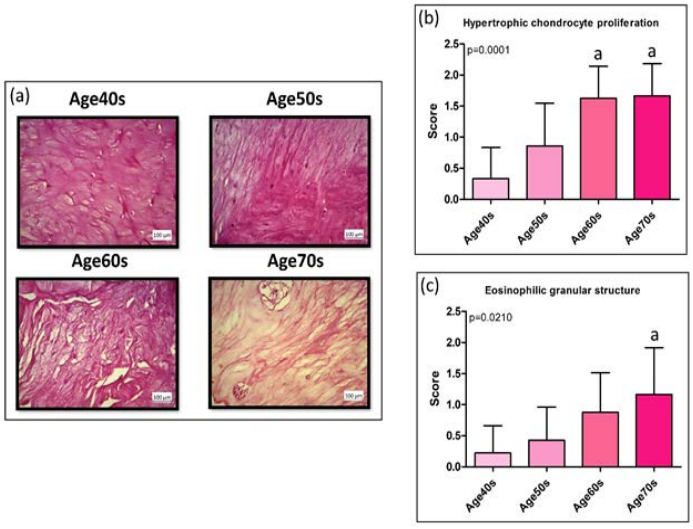

Figure 1. (a) Histological images of intervertebral disc tissue stained with hematoxylin and eosin, (b) histological scoring of hypertrophic chondrocyte proliferation, (c) histological scoring of eosinophilic granular structures. The letter "a" indicates a statistically significant difference ($p < 0.05$) compared to the Age40s group.

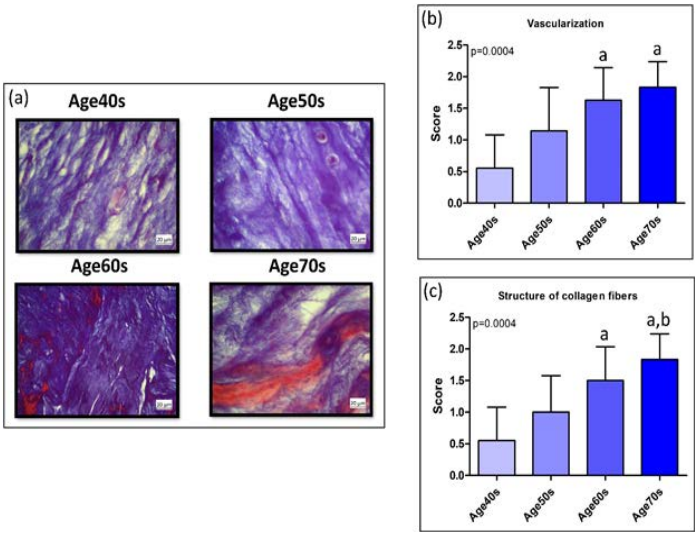

Figure 2. (a) Histological images of intervertebral disc tissue stained with Masson's trichrome, (b) histological scoring of vascularization, (c) histological scoring of collagen fibril structure. The letters "a" and "b" indicate statistically significant differences ($p < 0.05$) compared to the Age40s and Age50s groups, respectively.

Masson's Trichrome Staining Findings

Examination of Masson's trichrome-stained sections from each age group revealed that the blue tone indicating collagen was lighter in sections from the Age40s group compared to the other groups. In particular, the Age60s and Age70s groups showed a darker blue tone, reflecting higher collagen contents. This finding suggests an age-related increase in fibrosis. Statistical evaluation of the scoring based on collagen staining intensity demonstrated a significant increase in vascularization in the Age60s and Age70s groups compared to the Age40s group. Moreover, structural alterations in collagen fibers were more pronounced in the Age60s and Age70s groups than in the Age40s group. The score indicating collagen fiber alterations in the Age70s group was also statistically significantly different from that of the Age50s group (Figure 2).

AFIP Method for Lipofuscin Findings

Examination of IVD tissue samples stained with the AFIP method to detect the presence of lipofuscin granules showed red-orange lipofuscin granules within yellow-stained background structures. The presence of these granules was decreased in the Age40s and Age50s groups compared to the Age60s and Age70s groups. Based on the scoring data, a significant difference existed between the Age70s and Age40s groups (Figure 3).

Congo Red Staining Findings

In cases of Congo red-positive staining, amyloid plaques in the disc tissue appeared red. Examination of stained preparations from all age groups revealed very faint coloration

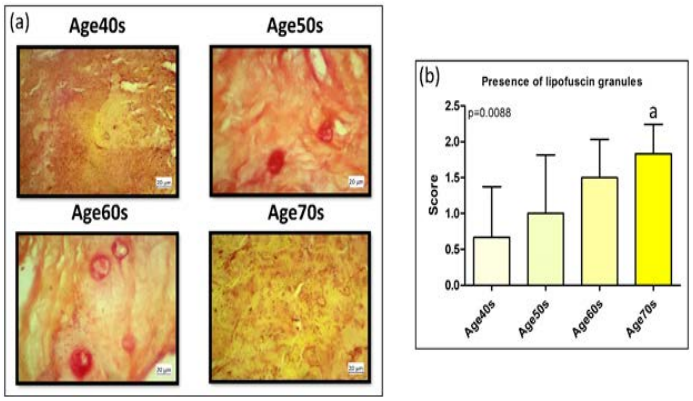

Figure 3. (a) Histological images of intervertebral disc tissue stained using the AFIP method, (b) histological scoring of the presence of lipofuscin granules. The letter "a" indicates a statistically significant difference ($p < 0.05$) compared to the Age40s group.

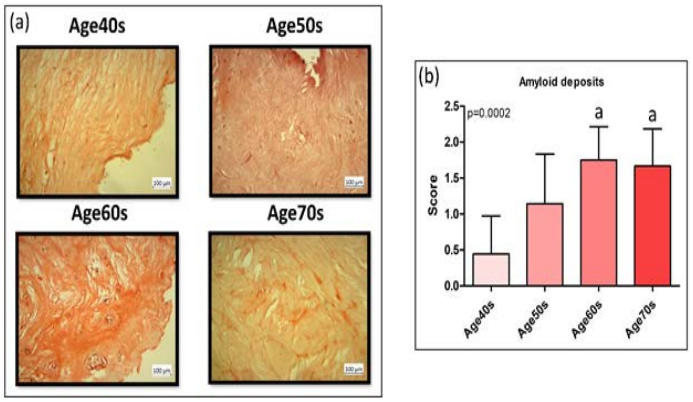

Figure 4. (a) Histological images of intervertebral disc tissue stained with Congo red, (b) histological scoring of amyloid deposits. The letter "a" indicates a statistically significant difference ($p < 0.05$) compared to the Age40s group.

with minimal red areas in the Age40s group, indicating little to no amyloid deposition. In contrast, in the older groups, and particularly in the Age60s and Age70s groups, more distinct red-orange areas were observed, consistent with Congo red-positive regions suggestive of amyloid accumulation. Statistical analysis identified a significant difference between the Age60s and Age70s groups compared to the Age40s group (Figure 4).

Toluidine Blue Staining Findings

Because toluidine blue is a metachromatic dye, it clearly reveals age-related changes in proteoglycan content and matrix structure in IVDs. Examination of the sections showed that the Age40s and Age50s groups exhibited relatively more intense metachromatic (blue-purple) staining due to their higher proteoglycan content. In contrast, the Age60s and Age70s groups had reduced metachromasia and lighter staining. Statistical analysis of the staining intensity scores indicated significant differences between the Age60s and Age70s groups compared to the Age40s group (Figure 5).

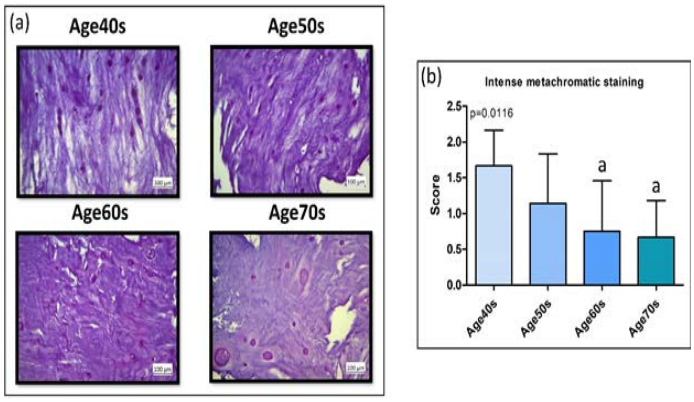

Figure 5. (a) Histological images of intervertebral disc tissue stained with toluidine blue, (b) histological scoring of intense metachromatic staining. The letter "a" indicates a statistically significant difference ($p < 0.05$) compared to the Age40s group.

DISCUSSION

The histopathological examination of IVD tissues continues to serve as a fundamental reference method in the evaluation of degenerative processes. However, more detailed characterization and interpretation of IVD pathologies could contribute to a better understanding of the mechanisms underlying the clinical complications of current treatments. Moreover, reaching a consensus on the simultaneous changes occurring in realms such as cellular function, matrix composition, and biomechanical behavior would allow histological findings to be interpreted more comprehensively from both mechanistic and clinical perspectives. In this context, the structural changes that occur in IVDs throughout life ultimately lead to tissue degeneration and the need for medical intervention. Although the patients included in this study were within different age ranges, they had all been diagnosed with disc herniation as a result of degenerative changes observed in their disc structures.

Numerous studies have reported a marked increase in the proliferative activity of chondrocytic cells during disc aging and degeneration. Miyamoto et al. (20) documented heterogeneous levels of cartilage tissue proliferation in cervical discs collected from murine models simulating cervical spondylosis. Similarly, Johnson et al. (21) observed that in degenerative human discs, proliferative activity was predominantly concentrated in regions containing dense cell clusters. Consistent with these findings, Zhao et al. (22) demonstrated that chondrocytic cells in herniated human cervical discs, which stained positively

for proliferating cell nuclear antigen, were typically localized in clusters adjacent to tissue fissures. Furthermore, both the number and size of these clusters near cracks and fissures were shown to increase with age in human lumbar discs. Collectively, these observations suggest that enhanced proliferation of chondrocytic cells constitutes a common histological marker of disc degeneration and may serve as a morphological indicator of disease progression. The findings of our H&E-stained sections were consistent with previously reported observations regarding chondrocytic cell proliferation.

The eosinophilic granular staining observed in our study is consistent with lipofuscin accumulation, which is described in the literature as one of the histological markers of disc aging and degeneration. Lipofuscin is an age-related pigment that accumulates in lysosomes as a byproduct of cellular metabolism. Saluja et al. (23) and Gower and Pedrini (24) reported that lipofuscin granules are frequently observed in both the AF and NP, particularly in advanced degenerative discs. Veroutis et al. (25) developed the GL13 staining method, which confirmed the association of lipofuscin accumulation with senescence in human disc tissues and demonstrated a significant increase in pigment-positive cells in herniated discs. These findings suggest that the eosinophilic granular staining observed in our study is not merely a morphological alteration but also an indicator of the biological process of cellular senescence, associated with aging and degeneration in disc cells.

Advanced degenerative changes have been particularly associated with alterations in collagen type and organization. Meisel et al. (26) demonstrated that degenerative discs exhibit increased type I collagen accumulation, a reduction in fibril diameter, and the formation of a denser, more fibrotic matrix. Additionally, age-related collagen deterioration is known to be linked not only to mechanical stress but also to molecular-level post-translational modifications. Gruber et al. (27) noted that age-related IVD changes, including the compaction and structural irregularity of collagen fibrils, are closely associated with cellular senescence, oxidative stress, and the accumulation of advanced glycation end products. Consistent with these findings, the present study demonstrated increased collagen fiber deposition in aged discs, as confirmed by Masson's trichrome staining. These alterations reflect the pronounced fibrotic remodeling that typifies advanced disc aging.

Although there is consensus in the literature that blood vessels are limited to the outer AF in normal adult IVDs, there is still debate as to whether vascular ingrowth occurs into the inner portions of the discs during degeneration. Corroborating this hypothesis, Freemont et al. (28) and Johnson et al. (29) identified vascularized areas within IVDs at sites where the lamellar organization of the AF was compromised. Consistent with our observations, multiple studies have documented the occurrence of vascular penetration into the inner annular layers in discs exhibiting advanced age-related or degenerative changes (30, 31). Stefanakis et al. (32) proposed that annular fissures or tears arising during disc degeneration promote vascular ingrowth, primarily as a consequence of localized proteoglycan depletion.

Lipofuscin accumulation in IVD degeneration is considered an important histological indicator of cellular senescence and oxidative stress in the tissue. Urban and Roberts (33) attributed lipofuscin accumulation in these tissues to the avascular nature of the IVD, resulting in a lack of nutrients and growth factors. On the other hand, Dimozi et al. (34) proposed that the intense stress to which IVD cells are exposed may trigger premature senescence. Zhao et al. (35) further demonstrated that excessive mechanical forces on IVD cells, particularly tensile forces applied to the AF, can suppress autophagy and induce premature aging in vitro in AF cells of the IVD. In line with these studies, we also found increased lipofuscin granules in the IVDs of elderly individuals using the AFIP method.

Amyloid deposits within or around joints have been reported in patients with severe arthropathy associated with systemic amyloidosis. Electron microscopy studies have revealed the accumulation of fibrils with ultrastructural features characteristic of amyloid in intervertebral discs. Consistent with this, Wullbrand et al. (36) demonstrated that amyloid deposition in IVDs, including both surgically removed tissues and autopsy samples, increases with age. Similarly, Madhani et al. (37) reported that individuals undergoing decompression surgery for cervical or lumbar spinal stenosis who had amyloid deposits in the ligamentum flavum and disc tissue were significantly older than those without such deposits. Consistent with these findings, our study also demonstrated a greater presence of amyloid deposits in IVDs from elderly individuals stained with Congo red.

One of the most prominent biochemical changes observed in the degenerative process is the reduction in proteoglycan content. Proteoglycans, the main components of the IVD extracellular matrix, maintain disc hydration and matrix organization. In particular, aggrecan, the most abundant proteoglycan in the IVD, decreases during degeneration, negatively affecting the mechanical strength and functional integrity of the tissue. Urban and Roberts (33) noted that the loss of proteoglycans reduces the osmotic pressure and water retention capacity of the NP. Antoniou et al. (38) demonstrated that aggrecan synthesis decreases and proteoglycans undergo degradation with age. Similarly, Boos et al. (39) histologically confirmed that proteoglycan content is significantly reduced in older age groups, contributing to the loss of disc elasticity. In line with these findings, our study demonstrated weaker metachromatic staining in toluidine blue-stained sections of the older groups due to decreased proteoglycan content.

Study Limitations

Due to the retrospective design of this study, the effects of additional factors that may influence IVD degeneration, such as diabetes mellitus, obesity, smoking, mechanical stress, scoliosis, postural abnormalities, and chronic inflammatory processes, could not be fully controlled. Although individuals under 40 years of age were excluded in order to reduce age-related variability, the influence of potential confounding factors could not be entirely eliminated. Such limitations should be taken into account while interpreting our findings.

CONCLUSION

Comparisons of staining methods have the potential to facilitate the selection of appropriate techniques for the histological evaluation of degenerative changes in human IVDs. The findings of this study offer guidance in efforts to achieve a more detailed characterization of structural alterations in different regions of the IVD and contribute to improving comparability across different studies.

DECLARATIONS

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OPEN REVIEW

From Microscope to Machine: A practical Guide to PD-L1 Testing in NSCLC

Mikroskoptan Yapay Zekâya: Küçük Hücreli Dışı Akciğer Kanserinde PD-L1 Testine Pratik Yaklaşım

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ABSTRACT

Objective: PD-L1 immunohistochemistry (IHC) is an essential predictive biomarker test guiding immune checkpoint inhibitor (ICI) treatment in individuals with non-small cell lung cancer (NSCLC). However, variability in antibody clones, scoring systems (Tumor Proportion Score (TPS), Combined Positive Score (CPS), Immune Cell scoring (IC)), and pre- analytical/analytical conditions complicates interpretation and reproducibility—especially in small biopsies and cytological specimens in NSCLC. To review current practices, challenges, and advances in PD-L1 testing in NSCLC, with emphasis on tumor heterogeneity, cytological limitations, and the evolving role of artificial intelligence (AI)-based digital pathology tools. We also aimed to explore how multimodal approaches, including radiomics, may complement tissue-based assessment and improve patient selection for ICI therapy.

Materials and Methods: A comprehensive literature review was performed, focusing on studies evaluating PD-L1 expression in NSCLC using validated clones (22C3, 28-8, SP263, SP142), cytology– histology concordance, pre-analytical factors, and AI-based PD-L1 scoring platforms. The search covered publications from January 2020 to June 2025. Data were synthesized thematically, addressing technical variables, interpretive variability, and emerging digital solutions.

Results: PD-L1 expression in NSCLC is affected by spatial heterogeneity and technical variables, leading to diagnostic inconsistency. Cytological specimens pose unique challenges due to limited architecture and fixation artifacts. Inter-observer variability is highest in the 1– 49% TPS range. AI-assisted algorithms and digital platforms have demonstrated improved reproducibility (κ up to 0.74), accuracy (up to 95%), and potential correlation with clinical outcomes. Commercial AI platforms, such as Lunit SCOPE PD-L1 and HALO Lung PD-L1 AI, achieved up to 92% accuracy and reduced borderline misclassification rates by 18–30%. Radiomics using PET-based imaging—incorporating SUVmax, metabolic tumor volume, and heterogeneity indices—shows promise as a non-invasive adjunct, particularly when tissue sampling is limited.

Conclusions: Reliable PD-L1 testing requires clone-specific validation, adherence to standardized protocols, and awareness of sample limitations. Integration of AI-based digital pathology and radiomics can enhance diagnostic precision, particularly in ambiguous or limited samples.

Keywords: PD-L1, heterogeneity, artificial intelligence (AI), digital cytopathology pathology, multimodal approach.

ÖZET

Amaç: PD-L1 immünohistokimyası (IHC), küçük hücreli dışı akciğer kanseri (KHDAK) olan bireylerde immün kontrol noktası inhibitörü (ICI) tedavisini yönlendiren temel bir prediktif biyobelirteç testidir. Ancak antikor klonlarındaki, derecelendirme sistemlerindeki (Tümör Oranı Skoru (TPS), Kombine Pozitif Skor (CPS), İmmün Hücre skoru (IC)) ve pre-analitik/analitik koşullardaki değişkenlik, özellikle KHDAK'ta küçük biyopsiler ve sitolojik örneklerde yorumlamayı ve tekrarlanabilirliği zorlaştırmaktadır. Bu derlemede, tümör heterojenliği, sitolojik kısıtlılıklar ve yapay zekâ (AI) tabanlı dijital patoloji araçlarının gelişen rolü vurgulanarak, KHDAK'ta PD-L1 testindeki güncel uygulamaları, zorlukları ve gelişmeleri gözden geçirmek amaçlanmıştır. Ayrıca radyomiklerin de dahil olduğu multimodal yaklaşımların doku temelli değerlendirmeyi nasıl tamamlayabileceğini ve ICI tedavisi için hasta seçiminde iyileşme sağlayıp sağlayamayacağını incelemeyi hedefledik.

Gereç ve Yöntemler: Ocak 2020 ile Haziran 2025 arasında yayımlanmış çalışmalar taranarak, KHDAK'ta PD-L1 ekspresyonunu doğrulanmış klonlar (22C3, 28-8, SP263, SP142), sitoloji–histoloji uyumu, pre-analitik faktörler ve AI tabanlı PD-L1 skorlama platformları ile değerlendiren çalışmalar üzerine kapsamlı bir literatür taraması yapıldı. Veriler, teknik değişkenlikleri, yorumlayıcı farklılıkları ve ortaya çıkan dijital çözümleri ele alan tematik bir sentez ile analiz edildi.

Bulgular: KHDAK'ta PD-L1 ekspresyonu, mekânsal heterojenite ve teknik değişkenliklerden etkilenmekte olup tanısal tutarsızlığa yol açmaktadır. Sitolojik örnekler, sınırlı mimari yapı ve fiksasyon artefaktları nedeniyle benzersiz zorluklar oluşturur. Gözlemciler arası değişkenlik, özellikle %1–49 TPS aralığında en yüksektir. AI destekli algoritmalar ve dijital platformlar, iyileştirilmiş tekrarlanabilirlik (κ 0.74'e kadar), doğruluk (%95'e kadar) ve klinik sonuçlarla olası korelasyon göstermiştir. Lunit SCOPE PD-L1 ve HALO Lung PD-L1 AI gibi ticari AI platformları, %92'ye varan doğruluk oranı elde etmiş ve sınırda sonuçlardaki yanlış sınıflandırma oranlarını %18–30 azaltmıştır. PET tabanlı görüntüleme kullanan radyomikler—SUVmax, metabolik tümör hacmi ve heterojenlik indekslerini içeren—özellikle doku örneklemesinin sınırlı olduğu durumlarda invaziv olmayan bir tamamlayıcı yöntem olarak umut vadetmektedir.

Sonuç: Güvenilir PD-L1 testi, klonlara özgü validasyon, standart protokollere uyum ve örnek sınırlılıklarının farkında olunmasını gerektirir. AI tabanlı dijital patoloji ve radyomiklerin entegrasyonu, özellikle belirsiz veya sınırlı örneklerde tanısal doğruluğu artırabilir.

Anahtar Kelimeler: PD-L1, heterojenite, yapay zekâ (AI), dijital sitopatoloji, multimodal yaklaşım.

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INTRODUCTION

Programmed Death-Ligand 1 (PD-L1) is a transmembrane protein that plays a key role in suppressing immune activity and preserving immune tolerance. In healthy physiological states, it is essential for preventing excessive immune reactions and regulating autoimmune responses. However, in malignancies such as NSCLC, tumor cells exploit this mechanism by overexpressing PD-L1 to evade immune surveillance. By binding to the PD-1 receptor on T cells, PD-L1 suppresses T-cell activation, effectively weakening the immune response (1,2). This interaction leads to the suppression of T cell proliferation, a decrease in cytokine production, and the induction of apoptosis in T cells. In tumors with a high neoantigen burden, such as NSCLC, the immune system is often primed to mount strong cytotoxic responses (3). However, due to immune checkpoint hijacking, this increased antigenicity frequently fails to translate into effective tumor clearance. In the tumor microenvironment, pro-inflammatory cytokines such as interferon-gamma (IFN-γ) further stimulate PD-L1 expression on tumor cells, enhancing adaptive immune resistance. In addition to cytokine signaling, oncogenic pathways such as PI3K/AKT and JAK/STAT have also been implicated in the upregulation of PD-L1, contributing to immune escape mechanisms (4).

The advent of ICIs has markedly shifted the treatment landscape across stages of NSCLC. Agents targeting the PD-1/PD-L1 axis—such as nivolumab and pembrolizumab—have reactivated suppressed T cells and improved clinical outcomes in selected patient populations. In early-stage NSCLC, neoadjuvant immunotherapy has raised pathological complete response (pCR) rates from as low as 2.2% to approximately 24% (5,6). In locally advanced cases, ICIs have increased overall survival from 33% to around 42%, while in metastatic disease, median overall survival has nearly doubled from 14 to 26 months. Despite these advances, immune checkpoint blockade is not without risks. One of the most serious adverse events is immune-mediated pneumonitis, which affects 2–5% of patients and has a mortality rate of 10–15% (7). Therefore, accurate and reliable assessment of PD-L1 expression in tumor tissue is critical for predicting clinical benefit and avoiding unnecessary (8,9). However, inter- and intra-observer variability in PD-L1 scoring remains a challenge in routine pathology. To address this, digital pathology tools incorporating AI-based algorithms are increasingly being used to standardize PD-L1 quantification, thereby enhancing diagnostic reproducibility and guiding more precise treatment decisions.

NARRATIVE LITERATURE OVERVIEW

This narrative review synthesizes recent literature related to PD-L1 expression assessment in NSCLC, with a focus on diagnostic variability, antibody clone differences, cytologic challenges, and the role of AI and radiomics in digital pathology. Relevant studies published between January 2020 and June 2025 were examined for their contributions to the understanding of PD-L1 testing challenges and advancements. Rather than applying strict inclusion/exclusion criteria or systematic protocols, this overview integrates peer-reviewed studies selected for their clinical relevance, innovation, and thematic alignment. The review aims to highlight evolving practices and future directions in PD-L1 assessment, particularly in the context of limited or ambiguous samples.

1. PD-L1 Antibody Clones and Pre-Analytical Variables: Technical and Laboratory Challenges in Immunohistochemical Evaluation

Precise IHC assessment of PD-L1 expression is vital for identifying suitable candidates for ICI treatment in NSCLC. Rather than being a single standardized procedure, PD-L1 IHC comprises a range of assays that differ notably depending on the antibody clone, scoring methodology, and both pre-analytical and analytical variables affecting tissue integrity. Commonly used clones—22C3, 28-8, SP263, and SP142—exhibit significant distinctions in staining behavior, testing platforms, and targeted cell types. Notably, SP142 often demonstrates reduced tumor cell staining because it preferentially labels immune cells, which may lead to an underestimation of the tumor proportion score (TPS) in samples with limited immune infiltration (10,11). Clone selection is directly tied to therapeutic context: 22C3 is used for pembrolizumab (TPS ≥50% for monotherapy), 28-8 for nivolumab, SP263 for durvalumab (TPS-based without a fixed cutoff), and SP142 for atezolizumab (IC ≥5%). Scoring systems also differ, with 22C3 and 28-8 using TPS, SP263 incorporating both tumor and immune cells, and SP142 evaluated by immune cell positivity; interchanging clones or scoring methods without regard for the therapeutic indication risks misclassification (12).

Cytology specimens are particularly vulnerable, as alcohol-based fixatives disrupt PD-L1 epitopes and reduce staining consistency, leading to false-negative results or scoring variability (17). Analytical variables, including staining platforms, antigen retrieval, and detection chemistry, contribute to inter-laboratory variability, while SP142 frequently underperforms in tumor cell staining compared to 22C3, 28-8, and SP263 (18). Multicenter studies emphasize the need for harmonization: TPS ≥1% rates varied from 41% to 62% using the same 22C3 clone across institutions (Fusco et al., 2021), and cytology studies reported 19–23% scoring shifts with alcohol-based fixation (17,19). Interpretive variability further complicates assessment in small biopsies or borderline TPS cases, particularly with intratumoral heterogeneity (20,21). Digital pathology and AI-assisted scoring enhance reproducibility, reduce observer-dependent variability, and support standardization across institutions (22,23). Reliable PD-L1 assessment therefore depends on strict control of pre-analytical conditions, validated clone-specific protocols, involvement in external quality assurance (EQA) programs, and the integration of computational tools for harmonization (24). Figure 1 depicts the association between antibody clones, scoring systems, and therapy eligibility, while Figure 2 outlines the clinical algorithm for integrating PD-L1 testing in NSCLC across disease stages (see Figure 1, 2). These effects are particularly critical in diagnostically ambiguous TPS ranges (1–49%), where PD-L1 under- or overestimation can alter

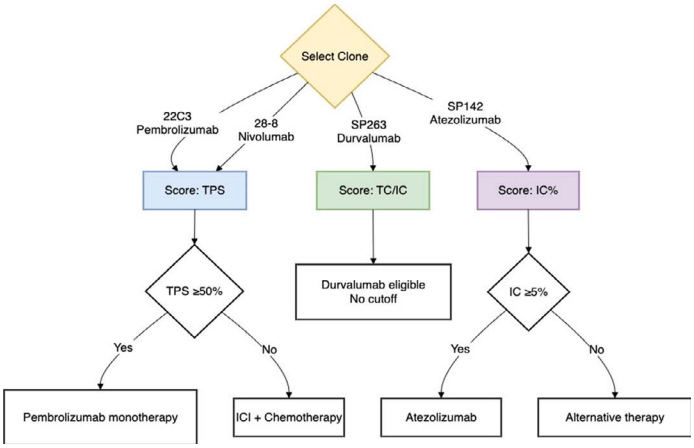

Figure 1. Pre-analytical and analytical factors influencing the accuracy of PD-L1 immunohistoche mistry.

This diagram outlines how variability in PD-L1 testing arises from both pre-analytical and analytical stages. Pre-analytical factors include specimen type (cytology vs histology), fixation method and duration, and tissue handling conditions. Analytical factors involve antibody clone selection (e.g., 22C3, SP263, SP142), staining platform compatibility, scoring algorithms such as Tumor Proportion Score (TPS) or Combined Positive Score (CPS), and interobserver consistency. Understanding and controlling these variables is essential to minimize false results and ensure reliable patient selection for immune checkpoint inhibitor (ICI) therapies.

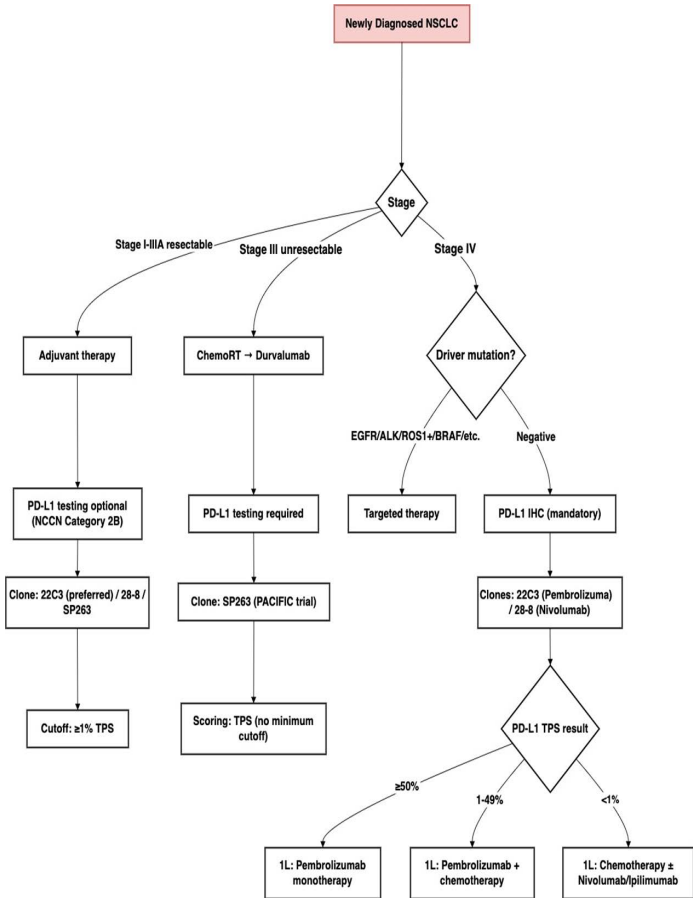

Figure 2. Clinical decision algorithm for PD-L1 testing and treatment selection across NSCLC stages.

This figure presents a stage-based approach to PD-L1 (Programmed Death-Ligand 1) testing in non-small cell lung cancer (NSCLC), aligned with current guidelines and clinical trial evidence. PD-L1 testing is not routinely recommended in early-stage, resectable tumors but becomes essential in unresectable Stage III disease and metastatic settings. Treatment selection is influenced by PD-L1 expression level (e.g., TPS ≥1%, ≥50%), mutation status (e.g., EGFR, ALK), and the availability of targeted therapies or immunotherapy options. Data are adapted from NCCN Guidelines and pivotal trials such as PACIFIC (durvalumab after chemoradiotherapy) and KEYNOTE series (pembrolizumab in 1L). Antibody clone selection (e.g., 22C3, 28-8, SP263) and standardized scoring are critical to ensure clinical consistency.

treatment decisions (38,60).

In addition to TPS, the Combined Positive Score (CPS) is another PD-L1 scoring method used in specific tumor types. CPS is calculated by dividing the number of PD-L1–positive tumor cells, lymphocytes, and macrophages by the total number of viable tumor cells, then multiplying by 100. CPS = (PD-L1–positive tumor cells + immune cells) / total tumor cells × 100. Unlike TPS, which considers only tumor cells, CPS integrates immune cell staining and is used primarily in cancers such as gastric, esophageal, and cervical cancer. In NSCLC, TPS remains the predominant scoring approach, though comparative evaluation is ongoing in select contexts.

2. Laboratory Challenges in PD-L1 Testing: Pre-analytical and Analytical Complexity

Despite the increasing reliance on PD-L1 IHC testing for patient selection in Immune Checkpoint Inhibitor (ICI) therapy, significant technical and interpretive challenges persist in routine laboratory practice. At the pre-analytical level, variables such as fixation duration, type of fixative (e.g., non-neutral buffered formalin), cold ischemia time, and tissue processing methods can substantially impact PD-L1 antigen preservation and staining intensity (25,26).

Prolonged fixation or delays in processing have been associated with epitope degradation and increased protein cross-linking, both of which impair membrane visualization and reduce PD-L1 staining intensity (27,28). Cytology specimens, in particular, pose unique challenges due to the use of alcohol-based fixatives in liquid-based preparations. These fixatives have been shown disrupt PD-L1 epitope conformation

and reduce staining consistency (17,19). From an analytical perspective, the selection and validation of antibody clones introduce another layer of complexity. Clones such as 22C3, 28-8, and SP263 generally demonstrate higher concordance in tumor cell staining, while SP142 often underperforms due to its preferential staining of immune cells rather than tumor membranes (18,25).

Switching between clones without rigorous cross-validation, particularly in settings using laboratory-developed tests (LDTs), further compromises diagnostic consistency. Even among institutions using FDA-approved assays, inter-laboratory variability remains a major obstacle. Differences in staining platforms (e.g., Dako Autostainer vs. Ventana BenchMark), incubation protocols, detection chemistry, and antigen retrieval pH can all significantly alter PD-L1 expression profiles (29,30). Even minor differences in antigen retrieval conditions or chromogen systems can lead to meaningful changes in staining intensity (31). In a multicenter study published in Current Oncology (2025), the proportion of samples with TPS ≥1% varied from 41% to 62% across five institutions using the same 22C3 clone, highlighting the importance of assay harmonization and quality assurance. Additionally, Daverio et al. (2020) reported that 19.2% of cytology specimens exhibited scoring shifts when fixed in alcohol-based media, while Tejerina et al. (2021) noted a 23% reduction in membrane-specific staining in similar samples (17,19). Interpretive variability poses further challenges, especially in small biopsies or cytology samples with limited tumor content. Subjective judgment in evaluating borderline staining can lead to over- or underestimation of PD-L1 expression, particularly in tumors with intratumoral heterogeneity (20,23). These limitations contribute to inter-observer variability and increased diagnostic burden on pathologists.

Recent advances in AI and digital pathology offer promising solutions. Whole-slide imaging (WSI) combined with AI-driven scoring has been shown to improve reproducibility and reduce observer-dependent variability (22). Studies have shown that AI-assisted platforms can improve inter-observer agreement, streamline scoring workflows, and support scalable PD-L1 assessment in Non-Small Cell Lung Cancer (NSCLC)—for instance, through digital image-based evaluation and deep learning models (32). Reliable PD-L1 assessment thus depends on strict control over pre-analytical conditions, validated assay protocols, and standardization of scoring systems. Participation in external quality assurance (EQA) schemes and continued professional training remain essential, particularly for cytopathology-based workflows lacking FDA-approved companion diagnostics (33).

3. Tumor Heterogeneity and the Reliability of PD-L1 Assessment

PD-L1 heterogeneity refers to the spatial and temporal inconsistency in PD-L1 protein expression within the same tumor or between primary and metastatic lesions. This biological variability can result in tumor areas exhibiting markedly different PD-L1 levels, potentially leading to sampling bias and diagnostic misclassification (21,34). Intratumoral heterogeneity refers to variability in PD-L1 expression across tumor regions, a challenge further amplified by intertumoral discrepancies between primary and metastatic sites. Such spatial and temporal variation can hinder diagnostic accuracy, particularly when only cytologic or small biopsy samples are available (3,34,61). These variations are especially problematic in tumors with patchy or focal PD-L1 expression, such as NSCLC and triple-negative breast cancer (11). Despite these challenges, emerging evidence suggests that small biopsies can still be reliable for PD-L1 testing when pre-analytical and analytical variables are well controlled. Several studies have reported strong concordance between biopsy and matched resection samples when using validated protocols and high-quality antibodies (35). For example, Lozano et al. (2023) reported 81.5% concordance between cytology and histology samples, dropping to 64.7% in low-cellularity cases (20). In literature found that small biopsies misclassified PD-L1 in 22% of cases (19,20).

Nevertheless, PD-L1 scoring methods such as TPS and CPS are highly sensitive to sampling variability, and expression thresholds may shift depending on the specific tumor area analyzed (36). emphasized that small biopsies may fail to reflect the tumor's full immunological landscape, underlining the importance of recognizing sampling bias. Combined and repeated cyto-/histological PD-L1 analyses could help reduce the proportion of false negative TPS results caused by tumor heterogeneity (20). To address these limitations, recommendations include acquiring multiple biopsies from distinct tumor areas, combining histologic and cytologic evaluation, and adopting digital pathology solutions to enhance scoring reproducibility. Artificial intelligence–assisted tools have shown promising results in reducing interobserver variability by allowing objective quantification of PD-L1 across larger tissue fields (22,37) Acanfora et al. (2025), through the multicenter SAMPLING study, demonstrated moderate interobserver agreement in cytology-based PD-L1 scoring, especially in the intermediate expression range, underscoring the need for technical standardization and training (38). Understanding and accounting for PD-L1 heterogeneity is thus essential for ensuring diagnostic accuracy, improving therapy allocation, and enhancing the clinical utility of IHC-based biomarkers in immuno-oncology.

4. AI-Assisted Tumor and Immune Cell Segmentation in PD-L1 Immunohistochemistry

A central challenge in the quantification of PD-L1 IHC lies in the accurate segmentation of invasive tumor regions and the correct identification of PD-L1–stained immune cells. These processes determine the region of interest (ROI) on which scoring is based. TPS requires identification of PD-L1–positive tumor cells within invasive tumor areas, while CPS and IC scoring additionally depend on recognizing immune cell populations within and around the tumor interface. Inaccurate delineation of these regions can compromise scoring reproducibility, clinical interpretation, and ultimately, treatment decisions. Most current PD-L1 quantification algorithms operate within

pathologist-defined or pre-annotated regions, relying on expert input to define ROIs. While this approach ensures oversight, it limits automation and scalability. Efforts to automate region detection have been explored in other cancer types. For instance, Virasoft developed an H&E-based algorithm for identifying invasive areas in breast cancer; in 67% of cases, the algorithm's predictions overlapped with five pathologists' annotations at an agreement level of 81–100% (39). However, such general-purpose approaches often do not translate directly to the PD-L1 setting due to the additional complexity introduced by IHC staining and immune cell variability.

In the PD-L1 context, Arbeiten et al. proposed the DASGAN model, which utilizes cytokeratin (CK) IHC to segment epithelial tumor regions. Although this model incorporated domain-specific IHC information, its tumor cell (TC) quantification output yielded a mean absolute error (MAE) of 7.3—considered suboptimal for clinical-grade PD-L1 interpretation (40). Another attempt employed a weakly supervised learning approach to analyze WSIs directly, bypassing manual ROI input. However, its output suffered from spatial discontinuity and lacked the consistency needed for diagnostic workflows (41). These limitations have highlighted the need for fully automated, end-to-end PD-L1 assessment solutions that can detect tumor and immune cell compartments without manual intervention. One such model was recently introduced to quantify PD-L1 TPS in NSCLC using a deep learning pipeline with no manual ROI input. It showed strong concordance with pathologist scoring (Spearman $\rho = 0.925$) and effectively stratified patients by progression-free survival, especially in the ≥1% expression group (42). Separately, van Eekelen et al. developed a single-cell–level quantification pipeline that automates tumor detection, nuclear segmentation, and PD-L1 positivity scoring across NSCLC WSIs, enabling objective, scalable evaluation of spatial expression patterns (43).

The clinical impact of such technologies is multifaceted. They can minimize false positives by excluding background and stromal staining, streamline diagnostic workflows by allowing pathologists to focus on pre-defined invasive regions, and reduce inter- and intra-observer variability by applying consistent segmentation criteria. While pathologist supervision remains essential in high-stakes decisions, the incorporation of AI-based tools offers a path toward reproducible, efficient, and standardized PD-L1 interpretation in routine practice.

Box 1. Clinical Impact of AI-Based Tumor and Immune Cell Segmentation

• Reduction of false positives by excluding background and stromal staining.

• Improvement of efficiency by allowing pathologists to focus only on pre-defined invasive regions.

• Maintaining reproducibility in clinical diagnostics through optional expert validation.

5. Integrated Overview: AI in PD-L1 Evaluation, Concordance, and Remaining Challenges

Recent advances in artificial intelligence (AI) have enabled the development of multiple platforms aimed at enhancing the reproducibility and objectivity of PD-L1 evaluation in non-small cell lung cancer (NSCLC). These systems standardize TPS, CPS, and IC on WSIs stained with PD-L1 IHC. Commercial platforms such as Lunit SCOPE PD-L1 (CE-IVDD, compatible with 22C3 and SP263 clones) demonstrated Intraclass Correlation Coefficient (ICC) = 0.80 (95% CI 0.71–0.88), 84% sensitivity for TPS ≥1%, and 95% accuracy (10,44). HALO Lung PD-L1 AI (CE-IVDR) reported ICC = 0.93 and specificity >95% (45,46). While Aiforia PD-L1 (CE-IVD) provided stratified accuracy across TPS ranges. AI scoring is particularly accurate at TPS <1% (85.3%) and reduces ambiguity at the critical 1–49% range for first-line ICI therapy eligibility (47,48). Other platforms, such as PathAI AIM-PD-L1-NSCLC, Paige PD-L1, Virasoft PD-L1, and Navify DP PD-L1 (Roche), show promising performance but remain limited by research use or lack of prospective validation.

Manual interpretation of PD-L1 remains vulnerable to interobserver variability, particularly in the 1–49% TPS range and in cytology or small biopsy specimens where tumor cellularity is limited, staining is heterogeneous, and architectural context is poor (45–47). The multicenter SAMPLING study highlighted this challenge, reporting only moderate agreement ($\kappa \approx 0.47–0.49$) with particularly low concordance in intermediate TPS cases (38). AI-assisted digital pathology addresses this limitation by providing standardized, objective scoring and reducing misclassification in borderline cases. He et al. (2025) showed that AI-assisted scoring increased interobserver concordance from $\kappa = 0.47$ to $\kappa = 0.74$ and decreased misclassification by 18%, while Plass et al. (2025) demonstrated 92% accuracy and a 30% reduction in variability (10,22). Beyond analytical reproducibility, AI-derived TPS values may better correlate with clinical outcomes: in KRAS-mutant NSCLC, high PD-L1 expression (≥50%) accurately identified by algorithmic scoring was associated with longer progression-free survival under ICI therapy Hazard Ratio (HR) 0.397; $p = 0.024$). Rakaee et al., 2024) reported that algorithm-adjusted TPS predicted therapeutic benefit in cases of manual/AI score divergence (49).

Despite these advances, key challenges persist. AI models require calibration across PD-L1 antibody clones and scanner types, and they may produce overconfident predictions on out-of-distribution tissue or artifacts without flagging uncertainty. Explainability and transparency remain critical for clinical trust, as current heatmaps and overlays do not always align with pathologists' reasoning. Cytology samples, in particular, remain prone to interpretive variability due to dispersed cells, nonspecific staining, and the absence of architectural context (38). Combining manual expertise with AI-assisted PD-L1 assessment enhances diagnostic reproducibility, reduces interobserver variability, and provides a more reliable basis for patient stratification in immunotherapy. Ongoing efforts in prospective validation, cross-platform standardization, and the integration of digital decision-support tools will be essential to fully realize the potential of AI in routine clinical workflows, while continued collaboration between pathologists and algorithmic systems will help address the remaining technical and biological challenges in PD-L1 evaluation (50).

6. Cytology vs. Histology and AI-Based PD-L1 Analysis in

NSCLC

Cytological and histological specimens differ significantly in architecture, cell organization, and image complexity, which directly affects both manual and AI-assisted PD-L1 assessment. Histological sections preserve tissue architecture and tumor microenvironment, allowing clear identification of tumor margins. Cytology samples—including smears, liquid-based cytology (LBC), and cell blocks—often contain dissociated, overlapping, or poorly preserved cells, and background blood or mucus that complicate tumor cell identification and PD-L1 segmentation (48,51). Cell blocks are preferred for PD-L1 IHC because they partially mimic histologic architecture, but variability in tumor cellularity and fixation can reduce antigen preservation (33). AI algorithms trained on histology slides often underperform in cytology due to loss of architecture, background noise, and annotation challenges for crowded cells (3,22). Adapting AI to cytology requires multimodal training and robust preprocessing to handle staining and preparation differences.

Digital cytopathology and WSI offer remote consultation advantages, but 3D cell clusters can exceed the scanner depth-of-field, creating out-of-focus regions. Z-stacking improves image quality but increases scanning time and storage demand, limiting routine use (52–54). Radiomics complements tissue-based PD-L1 evaluation. PET/CT-derived features such as SUVmax, metabolic tumor volume, and heterogeneity indices correlate with PD-L1 expression and immunotherapy response, potentially reducing the need for invasive sampling (55,56). Future clinical workflows will integrate AI-based digital pathology, cytology, and radiomics in a multimodal approach. This strategy addresses PD-L1 heterogeneity, improves diagnostic reproducibility, and supports personalized immunotherapy selection in NSCLC (57,58). Looking forward, the integration of digital pathology and AI analyses with genomic and transcriptomic data will enable more precise and personalized treatment planning in lung cancer. This multimodal approach can bridge the gap between molecular profiling and clinical decision-making, enhancing the accuracy of immunotherapy selection (58,59). PD-L1 remains a pivotal biomarker for ICI eligibility, but its assessment is challenged by biological and technical variability (6,8). For AI-based PD-L1 evaluation to be clinically reliable, models must demonstrate robust performance metrics—such as 92% accuracy, 89% precision, and an Area Under the Curve (AUC) of 0.94 for Convolutional Neural Network (CNN)-based classification at ≥50% expression—while incorporating agreement measures like Cohen's kappa to ensure real-world applicability (57).

DISCUSSION

The clinical indication for immunotherapy is the primary determinant of which PD-L1 antibody clone and scoring system should be used—long before any technical or analytical considerations take place. Whether the aim is to assess eligibility for pembrolizumab monotherapy, chemo-immunotherapy, or adjuvant durvalumab, the therapeutic context dictates both the antibody clone and the scoring method (e.g., TPS, CPS, or IC). Each clone is paired with specific treatment protocols and regulatory approvals; therefore, the pathologist must understand the treatment landscape to select and apply the correct diagnostic tool. Inconsistent alignment between the clinical question and the laboratory method introduces a fundamental source of diagnostic error.

This clinical dependency is further complicated by challenges in the pre-analytical phase. Alcohol-based fixatives can alter PD-L1 epitope conformation, weaken membrane-specific staining, and lead to underestimation of TPS, an effect particularly pronounced in cytology specimens. These effects are most pronounced in the diagnostically ambiguous TPS 1–49% range, where PD-L1 expression may be either under- or overestimate (38). Analytically, the choice of antibody clone and detection platform plays a pivotal role in test performance. SP142 consistently shows lower tumor cell staining compared with 22C3 and SP263, which may result in TPS underestimation and misclassification of treatment eligibility. Differences in platform chemistry, antigen retrieval, and scoring interpretation across laboratories further exacerbate variability (10,20). Without rigorous standardization, even validated assays can generate inconsistent outcomes depending on the setting. A single sample may fail to capture the full immunologic profile of a tumor, potentially leading to false-negative or borderline results. Combining histologic and cytologic PD-L1 testing in repeated sampling may help mitigate the effects of heterogeneity on TPS accuracy.

TPS in the 1–49% range is associated with the lowest interobserver agreement and the greatest uncertainty in treatment decisions. The SAMPLING study reported only moderate agreement ($\kappa = 0.49$) among cytopathologists, highlighting the impact of subjective interpretation—especially in low-cellularity or poorly preserved specimens (10). The absence of unified scoring guides and training programs further limits reproducibility. To address these limitations, AI–based digital pathology tools have shown significant promise. WSI combined with deep learning algorithms can improve reproducibility and reduce observer variability by automating tumor region detection, cell segmentation, and clone-specific scoring (10,22). For instance, He et al. demonstrated an improvement in interobserver agreement from $\kappa = 0.47$ to $\kappa = 0.74$ using AI-based scoring (22). Similarly, Plass et al. showed an 18% reduction in borderline misclassification through AI assistance (10). While these tools are increasingly integrated into research and early-stage clinical workflows, they require rigorous validation. Most systems are trained on histological sections and may underperform in cytological preparations due to architectural differences, cell clustering, and inconsistent staining artifacts (51). Cytology-specific AI pipelines are still under development (43,54).

Beyond histopathology, radiomics has emerged as a complementary non-invasive modality. PET-based features—such as SUVmax, metabolic volume, and heterogeneity indices—have been shown to correlate with PD-L1 expression and ICI response (55,56). In patients for whom tissue acquisition is infeasible or insufficient, radiomics may serve as a surrogate

biomarker—pending further clinical validation.

In summary, ensuring reliable PD-L1 testing in NSCLC requires a multilayered approach: one that begins with clear clinical intent and extends through harmonized pre-analytical and analytical processes, observer training, and technological support. The integration of AI-assisted digital pathology and radiomics tools holds great potential to improve reproducibility, reduce ambiguity, and align pathology more closely with clinical needs. Moving forward, multimodal frameworks that combine morphology, imaging, and computational analytics may offer the most robust strategy for personalizing immunotherapy in lung cancer (21,49).

CONCLUSION

PD-L1 testing is a critical step in selecting NSCLC patients for immunotherapy, but its accuracy is hindered by expression heterogeneity, technical variability, and interpretive subjectivity. This review highlights the multifactorial challenges associated with PD-L1 IHC, including clone-specific discrepancies, scoring inconsistencies, and the unique constraints of cytologic materials. The integration of AI-powered digital pathology platforms offers a promising avenue to improve reproducibility and reduce diagnostic ambiguity, particularly in borderline TPS cases. Additionally, radiomics-based tools may serve as non-invasive complements in situations where tissue access is limited. In cytopathology practice, the development of robust, validated AI models adapted to smear and LBC formats, along with standardized interpretive frameworks, will be essential to achieving reliable PD-L1 evaluation. Ultimately, the future of PD-L1 testing lies in a multimodal, technology-integrated approach that combines pathology, imaging, and computational methods to enable more consistent, personalized, and equitable immunotherapy decision-making.

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OPEN REVIEW

Safety of Biologic Agents in the Treatment of Psoriasis Vulgaris: An Integrated Review of Clinical Trials and Real-World Evidence

Psoriasis Vulgaris Tedavisinde Biyolojik Ajanların Güvenliliği: Klinik Çalışmalar ve Gerçek Yaşam Verilerinin Derlemesi

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ABSTRACT
Psoriasis vulgaris is a chronic, immune-mediated inflammatory disease in which dysregulation of the TNF-α and IL-23/Th17 axes drives keratinocyte hyperproliferation and systemic comorbidities. Targeted biologic drugs-TNF-α inhibitors, the IL-12/23 p40 inhibitor ustekinumab, IL-23 p19 inhibitors, and IL-17 pathway inhibitors-successfully control the disease. Network meta-analyses (NMA) demonstrate that these drugs show high efficacy in the short term and are generally well tolerated. Long-term use, however, raises concerns about serious infection, tuberculosis (TB) and hepatitis B virus (HBV) reactivation, malignancy, inflammatory bowel disease (IBD), major adverse cardiovascular events (MACE), and rare paradoxical reactions. This review integrates randomized trial data, long-term extensions, pharmacovigilance signals and real-world cohorts to appraise the safety of biologic agents in psoriasis vulgaris. TNF-α inhibitors carry class-typical risks of serious infection and opportunistic mycoses, particularly in older or comorbid patients, but large registries demonstrate stable long-term profiles when screening and prophylaxis are optimized. Ustekinumab and IL-23 inhibitors show low serious-infection and TB-reactivation rates, reassuring data in patients with prior TB or cancer, and neutral MACE signals. IL-17-pathway inhibitors are associated with predictable, mostly mild mucocutaneous candidiasis and rare IBD onset or exacerbation, with very high skin-clearance rates and durable safety in trials and real-world studies. Observational data suggest that age, baseline comorbidity and concomitant immunosuppression drive absolute risk more strongly than molecule choice. When agents are selected according to comorbidity profile, supported by structured screening, vaccination and close monitoring, modern biologics for psoriasis vulgaris appear broadly safe, with rare but important class-specific adverse events that require proactive counselling and early recognition.

Keywords: Biologics, psoriasis, safety

ÖZET
Psoriasis vulgaris, TNF-α ve IL-23/Th17 yolaklarındaki regülasyonun bozulması sonrası keratinosit hiperproliferasyonuna ve sistemik komorbiditelere yol açan kronik, immün aracılı bir inflamatuar hastalıktır. Biyolojik ajanlar — TNF-α inhibitörleri, IL-12/23 p40 inhibitörü, IL-23 p19 inhibitörleri ve IL-17 yolak inhibitörleri — hastalığı başarılı bir şekilde kontrol eder. Meta-analizler, bu ilaçların kısa vadede yüksek etkinlik gösterdiğini ve genel olarak iyi tolere edildiğini ortaya koymaktadır. Ancak uzun süreli kullanım, ciddi enfeksiyon, tüberküloz (TB) ve hepatit B virüsü (HBV) reaktivasyonu, malignite, inflamatuar bağırsak hastalığı (IBD), majör advers kardiyovasküler olaylar (MACE) ve nadir paradoksal reaksiyonlar konusunda endişelere yol açmaktadır. Bu derleme, psoriasis vulgaris'te biyolojik ajanların güvenliğini değerlendirmek için randomize çalışma verilerini, uzun vadeli uzatma çalışmalarını, farmakovijilans sinyallerini ve gerçek yaşam verilerini bir araya getirmektedir. TNF-α inhibitörleri, özellikle yaşlı veya komorbid hastalarda, ciddi enfeksiyon ve fırsatçı mikozlar gibi sınıfa özgü riskler taşır, ancak büyük kayıtlar, tarama ve profilaksi ile uzun vadede stabil bir profile sahip olduğunu göstermektedir. Ustekinumab ve IL-23 inhibitörleri, düşük ciddi enfeksiyon ve TB reaktivasyon oranları, önceden TB veya kanser öyküsü olan hastalarda güven verici veriler ve nötr MACE sinyalleri göstermektedir. IL-17 yolak inhibitörleri, öngörülebilir, çoğunlukla hafif mukokutanöz kandidiyazis ve nadir IBD başlangıcı veya alevlenmesi ile ilişkilidir ve klinik çalışmalar ve gerçek yaşam çalışmalarında çok yüksek deri temizlenme oranları ve kalıcı güvenlik göstermiştir. Gözlemsel veriler, yaş, başlangıçtaki komorbidite ve eşlik eden immünosupresyonun, molekül seçiminden daha güçlü bir şekilde mutlak riski etkilediğini göstermektedir. Komorbidite profiline göre, yapılandırılmış tarama, aşılama ve yakın izlem ile desteklenen ajanlar seçildiğinde, psoriasis vulgaris için biyolojik ilaçlar genel olarak güvenli görünmektedir, ancak proaktif danışmanlık ve erken tanı gerektiren nadir ancak önemli sınıfa özgü advers olaylar mevcuttur.

Anahtar Kelimeler: Biyolojikler, psoriasis, güvenlilik

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INTRODUCTION

Psoriasis vulgaris is a chronic, immune-mediated dermatosis characterized by dysregulated TNF-α and IL-23/Th17 signalling (1). This inflammatory cascade drives keratinocyte proliferation and a systemic inflammatory milieu that underlies cardiometabolic, hepatic and psychological comorbidities (2). Targeted biologic therapies have reshaped the management of moderate-to-severe disease, achieving rapid and durable PASI 90–100 responses in many patients who previously had refractory disease or unacceptable toxicity on conventional systemic agents.

Randomized trials and network meta-analyses consistently show that IL-17 and IL-23 inhibitors achieve the highest short-term clearance rates, with TNF-α inhibitors and ustekinumab somewhat less efficacious but still superior to traditional systemic treatments (3-5). However, trial populations are relatively young, carefully screened and followed for limited periods. Contemporary practice extends biologic treatment to older, multimorbid patients with long-standing systemic inflammation, prior malignancy or chronic viral infections—populations in whom long-term safety is a central concern (6-8).

Key safety questions:

- How do biologic classes differ regarding serious infection, opportunistic mycoses and viral reactivation (HBV, TB)?
- Is there a meaningful difference in MACE or cerebrovascular risk between classes or individual agents?
- What is the real-world risk of IBD, paradoxical reactions or rarely seen adverse events such as bullous pemphigoid?
- If biologics may be safely prescribed in patients with previous malignancy, chronic viral hepatitis, TB or HIV infection, or in paediatric and elderly populations?

This review synthesizes randomized trials and real-world evidence across biologic classes used in psoriasis vulgaris. Within each class, we summarize class-level safety themes and then highlight drug-specific data, with a particular focus on long-term extensions, pharmacovigilance analyses and special populations.

TUMOUR NECROSIS FACTOR-ALPHA (TNF-α) INHIBITORS

Class overview

TNF-α is a critical pro-inflammatory cytokine for host defence against intracellular pathogens and a central driver of many autoimmune and autoinflammatory diseases, which makes TNF-α inhibitors cornerstone therapies in several difficult-to-treat conditions but also links their use to an increased risk of infections (9). A systematic review and meta-analysis of 29 randomized controlled trials (RCTs) also including psoriasis patients found that treatment with TNF-α antagonists nearly doubles the risk of active tuberculosis compared with placebo or standard care, with particularly elevated risk in rheumatoid arthritis and in high TB-incidence regions (10). A systematic review of fungal infections associated with TNF-α inhibitors identified invasive and opportunistic mycoses-particularly histoplasmosis, coccidioidomycosis and cryptococcosis—occurring predominantly in patients treated with infliximab and adalimumab, often in endemic areas or in the presence of additional immunosuppressive drugs (9).

TNF-α inhibitors are the most-studied biologics regarding HBV reactivation. In psoriasis and other IMID cohorts, HBsAg-positive patients exposed to anti-TNF without antiviral prophylaxis have reported reactivation rates around 14–63%, whereas HBsAg-negative/anti-HBc-positive patients carry a lower 3–5% risk that is usually manageable with close monitoring (11). In older adults with psoriatic disease, a large population-based cohort found similar rates of serious infection with TNF inhibitors compared with methotrexate and other traditional systemics, while IL-12/23 and IL-23/17 biologics were associated with lower rates of serious infection; in contrast, the JAK inhibitor tofacitinib carried the highest infection risk (8). TNF-α inhibitors have a complex relationship with congestive heart failure (CHF). In a pivotal RCT of infliximab in patients with advanced CHF (NYHA III–IV, LVEF <35%), high-dose infliximab (10 mg/kg) increased the risk of hospitalization or death versus placebo. Multiple case reports across infliximab, adalimumab and certolizumab pegol describe new-onset or worsening CHF and, rarely, sudden death temporally related to treatment, whereas small studies with etanercept have suggested possible improvements in ventricular function and symptoms. In practice, TNF inhibitors are generally contraindicated in patients with NYHA III–IV CHF or LVEF <50%, and baseline echocardiography plus cardiology input is advised before considering TNF blockade in those with milder (NYHA I–II) heart failure (12).

Beyond heart failure, TNF-α inhibitors may modestly increase MACE. In a large network meta-analysis of 40 comparative studies (126,961 patients), anti-TNF agents were associated with a higher MACE risk versus placebo (13). With respect to malignancy, long-term TNF-α blockade raises theoretical concerns because of impaired immune surveillance and the complex role of TNF-α in tumorigenesis, but current clinical data are largely reassuring. The most consistent signal is a modestly increased risk of non-melanoma skin cancer, whereas a recent large patient-level meta-analysis of 45 interventional and 10 observational studies across all approved TNF inhibitors did not demonstrate a statistically significant increase in overall cancer risk (excluding NMSC), although a trend with longer exposure and possible lymphoma excess was noted and confounded by underlying disease and co-medication (14). Paradoxical immune-mediated events are a distinctive feature of the TNF-α inhibitor class. The most frequent are psoriasiform paradoxical reactions, with an estimated incidence of about 3.8–10.7% among treated patients. Infliximab accounts for roughly half of reported cases, followed by adalimumab and etanercept, whereas certolizumab and golimumab are rarely implicated. Reactions may present as de novo psoriasis, flares or phenotype switches in patients treated for psoriasis, and typically mimic plaque or palmoplantar pustular disease, although guttate, inverse, generalized pustular and alopecic variants are also described. Onset is highly variable (from <1

month to >10 years; mean ≈16 months), and most eruptions improve or resolve after TNF-α inhibitor withdrawal, with milder cases sometimes manageable using topical therapy or switching to another biologic class (15).

Less common but clinically important paradoxical events include lupus-like and sarcoidosis-like syndromes and other granulomatous eruptions. Lupus-like reactions have low incidence (≈0.06–0.18% depending on the agent) and are most often linked to infliximab, adalimumab and etanercept; they range from isolated cutaneous lupus to full systemic lupus erythematosus, usually with ANA positivity and onset around 1–1.5 years after starting therapy, and generally regress after drug discontinuation, though some patients require ongoing lupus-directed treatment. Sarcoidosis-like disease is still rare (≈0.04%), occurs predominantly with etanercept, and may involve skin, lungs and, less often, heart; most cases show at least partial improvement after stopping the TNF-α inhibitor and initiating corticosteroids (15). TNF-α inhibitors have been linked to demyelinating disease. In a phase I infliximab trial in rapidly progressive multiple sclerosis (MS), cerebrospinal fluid leukocytes and immunoglobulins rose after treatment, suggesting TNF neutralization exacerbated disease activity. Multiple case reports describe new-onset or worsening MS in patients receiving etanercept, infliximab or adalimumab for psoriasis or psoriatic arthritis, with neurological symptoms often improving after drug withdrawal. On this basis, TNF-α inhibitors are generally avoided in patients with established demyelinating disease and used with great caution in those with suggestive neurological histories (12).

Adalimumab

Among TNF-α inhibitors, adalimumab remains one of the most widely used biologics in dermatology, and available real-world data support a safety profile broadly consistent with the TNF class. A retrospective single-centre cohort from Italy including both paediatric and elderly patients with psoriasis treated with originator adalimumab and its biosimilar SB5, as well as etanercept biosimilar SB4, showed that these agents were effective and generally well tolerated across age groups, with no new safety signals emerging over follow-up; adverse events were mostly mild and led to few discontinuations (16). Beyond psoriasis, a large series of hidradenitis suppurativa cases from a Turkish dermatology clinic specifically evaluated the risks of hepatitis B and tuberculosis reactivation during adalimumab treatment: Among patients at risk for HBV or TB reactivation who received appropriate antiviral (entecavir or tenofovir) or isoniazid prophylaxis, no cases of HBV or TB reactivation were observed during treatment. This highlights the importance of systematic baseline screening and prophylaxis (17).

A nationwide retrospective cohort study using Taiwan's National Health Insurance database compared the risk of herpes zoster across multiple biologics and traditional systemic treatments; in this analysis, adalimumab was associated with a significantly increased risk of herpes zoster relative to traditional systemic therapies (18). A recent systematic review and meta-analysis of randomised psoriasis trials found no significant increase in MACEs with TNF-α inhibitors, IL-17, IL-12/23 or IL-23 inhibitors compared with placebo, suggesting that cardiovascular risk under adalimumab is driven primarily by traditional risk factors rather than the biologic itself (19).

Etanercept

The OBSERVE-5 post-marketing registry followed 2510 psoriasis patients on etanercept for up to five years, observing cumulative incidences of 6.5% for serious infection and 3.2% for malignancy excluding non-melanoma skin cancer, with event rates comparable to administrative claims data and no new safety signals (20). Psoriasis severity and quality of life improved and remained stable. In a 30-month prospective cohort directly comparing adalimumab, infliximab, etanercept, secukinumab and ustekinumab, etanercept was associated with musculoskeletal and reproductive adverse events (e.g. menstrual disorders) but did not show higher serious adverse event or discontinuation rates; overall, ustekinumab had the most favourable safety profile, while infliximab and adalimumab had more frequent adverse events (AEs) (21).

Infliximab

Infliximab provides rapid disease control but has distinct safety considerations. A detailed review of infliximab and its biosimilars in psoriasis and other indications emphasized infusion reactions, immunogenicity and loss of response as key long-term challenges (22). The same 30-month observational cohort noted higher rates of asymptomatic liver enzyme elevation, fatigue and respiratory infections with infliximab compared with other biologics (21). These findings underscore the need for early vigilance, careful patient selection and reconsideration of long-term infliximab therapy when safer alternatives are available.

Certolizumab pegol

Certolizumab pegol, a pegylated Fab fragment lacking the Fc region, has minimal placental transfer and is generally preferred in women planning pregnancy and breastfeeding. A prospective, non-interventional 1-year real-world study (CIMREAL) in 399 plaque psoriasis patients reported PASI75 and PASI90 response rates of 77% and 56.5% at 12 months, with marked DLQI improvement; 30.6% experienced AEs and 9.3% serious AEs, but no new safety signals emerged (23). Pharmacovigilance analyses in pregnant women with psoriasis suggest broadly similar maternal and neonatal outcomes across TNF inhibitors, with spontaneous abortion the most common event; certolizumab's safety profile overlapped with other TNF inhibitors, emphasizing that current pregnancy recommendations—largely based on preclinical data—should be continually updated using real-world evidence (24). FAERS-based analyses of certolizumab confirm expected infection and musculoskeletal AEs and identify rare unexpected events such as pemphigus and basal cell carcinoma, warranting continued surveillance but not altering its general safety profile (25).

IL-12/23 (p40) Inhibition

Ustekinumab

Ustekinumab targets the p40 subunit shared by IL-12 and IL-23, modulating both Th1 and Th17 pathways. Network meta-analyses place ustekinumab among biologics with

high short-term efficacy and favourable tolerability (3,4). In an updated network meta-analysis of 62. RCTs including 11 biologics, ustekinumab clustered with agents combining high PASI90 rates and low withdrawal due to AEs (4). The observational cohort comparing TNF inhibitors, secukinumab and ustekinumab found that ustekinumab had the lowest incidence of adverse events overall, reinforcing its reputation as a "steady and safe" option, especially in patients with multiple comorbidities (21).

Bullous pemphigoid induced by biologics (BIBP) is a rare but serious dermatologic adverse event. A systematic review identified 15 cases of BIBP in psoriasis patients, with ustekinumab accounting for six, mostly in individuals previously exposed to TNF inhibitors. Latency tended to be longer with ustekinumab than with TNF blockers, and causality assessments rated most cases as "probable". Awareness of this entity and baseline history of bullous disease are important when selecting therapy and managing new blistering eruptions (26)

IL-23 (P19) INHIBITORS

Class overview

IL-23 p19 inhibitors selectively modulate the Th17 axis while sparing IL-12, potentially preserving some host defence and antitumour surveillance. Trials and real-world studies consistently report low rates of serious infection, TB reactivation and malignancy, including in patients with prior TB infection (27-29). A monocentric study of 16 psoriasis patients with prior TB infection (positive Quantiferon) treated with guselkumab, risankizumab or tildrakizumab found that all achieved at least PASI75, most PASI100, and none developed TB reactivation over a median 18.8-month follow-up, regardless of whether they received isoniazid prophylaxis (27). These findings support IL-23 inhibitors as preferred options in patients with TB infection when anti-TNF therapy is relatively contraindicated. Real-world data on HBV reactivation with IL-23 (p19) inhibitors are still limited but currently reassuring. In a retrospective cohort of 219 psoriasis patients treated with newer biologics (including guselkumab and risankizumab), 21% were anti-HBc IgG–positive and thus at risk, yet among the 40 who received antiviral prophylaxis no HBV reactivation or clinically relevant ALT/AST elevation occurred during follow-up (30).

Real-world data suggest a potentially favorable cardiovascular profile for IL-23 (p19) inhibitors. In a large TriNetX cohort of >12,000 biologic-treated psoriasis patients, biologics overall were associated with a lower 5-year risk of MACEs compared with oral systemic therapies. Within class-specific analyses, patients receiving only anti-IL-23 agents also showed a significantly reduced risk of any cardiovascular disease versus oral drugs, supporting the hypothesis that effective IL-23 blockade may attenuate systemic vascular inflammation (31). Across placebo-controlled trials and long-term extension studies, IL-23 (p19) inhibitors have not been associated with an increased risk of malignancy. In a large meta-analysis, short-term randomized data showed no excess malignancy with IL-23 blockers compared with placebo (RR ≈0.87), and pooled long-term exposure-adjusted incidence rates remained low, around 0.40/100 patient-years for non-melanoma skin cancer and 0.43/100 patient-years for malignancies excluding non-melanoma skin cancer, without evidence of a time-dependent increase. Overall, current data support a favorable malignancy profile for guselkumab, risankizumab and tildrakizumab, although continued pharmacovigilance and age- and risk-appropriate cancer screening remain advisable (32).

Case series in HIV-positive patients showed good disease control without deterioration in viral load or CD4 counts under guselkumab or risankizumab, suggesting that IL-23 inhibitors may be appropriate with infectious-disease oversight (33). Drug-survival reviews highlight IL-23 inhibitors as the class with the highest long-term persistence, likely reflecting a combination of high efficacy, convenient dosing and favourable safety (34).

Guselkumab

Real-world cohorts in Asia confirm guselkumab's sustained efficacy and quiet safety profile. In a Chinese single-centre study (mean follow-up ~72 weeks, n=37), over 80% of patients achieved PASI90–100 between weeks 60–92 with no serious AEs; abnormal HBV markers were common but no HBV or TB reactivation occurred (28). A 20-week interim analysis of a 52-week Japanese post-marketing surveillance program (n=411) reported adverse drug reactions(ADRs) in 6.6% and serious ADRs in 2.2% of patients, mostly infections such as nasopharyngitis, with significant early PASI improvement (29). Switching studies provide further reassurance. A three-year Italian multicentre study of 169 patients who partially responded to ustekinumab and switched to guselkumab found PASI75/90/100 rates of 88.4%, 55.8% and 32.6%, respectively, at three years, with no severe AEs (35). Another two-year real-life study of 61 patients who had failed at least one IL-17 inhibitor showed that guselkumab maintained high PASI90/100 rates and improved difficult-to-treat areas, again without severe AEs (36).

Risankizumab

Risankizumab has robust long-term data. The LIMMitless phase 3 open-label extension followed psoriasis patients for up to six years, showing sustained PASI90/100 responses and low, stable rates of serious infection, malignancy and MACE (37). Real-world 24-week and longer-term series confirm high effectiveness and a reassuring safety profile across naive and biologic-experienced patients, including those with cardiometabolic comorbidities (38-40). In three-year retrospective study (n=333), risankizumab efficacy and AE rates were similar in patients with and without cardiometabolic disease, with no major safety concerns (40). In very severe psoriasis (baseline PASI ≥30, difficult areas), the VESPA real-life study demonstrated that risankizumab achieved sustained PASI75/90/100 and DLQI improvement up to 104 weeks without new safety signals (39). Post-marketing pharmacovigilance has generated important-but as yet unconfirmed-signals. A FAERS disproportionality analysis suggested a potential cerebrovascular accident (CVA) signal for risankizumab compared with other psoriasis therapeutics (41). Further

FAERS mining identified unexpected AEs such as myocardial infarction, pancreatitis, diabetes and nephrolithiasis, but most signals were weak and tended to occur early in treatment (42). EudraVigilance data highlight serious reports mainly in the categories of infections, malignancy, nervous-system and cardiac disorders, aligning with known risks and underlining the need for continued surveillance (43).

These hypotheses have been challenged by letters emphasizing the limitations of spontaneous reporting, lack of a plausible mechanism linking IL-23 blockade to CVA and reassuring long-term trial event rates compared with epidemiologic benchmarks (44). A retrospective study of coagulation parameters in patients treated with risankizumab or guselkumab found no evidence of hypercoagulability, whereas secukinumab modestly shortened PT, the clinical significance of which remains uncertain (45).

Tildrakizumab

In elderly psoriasis patients with difficult areas, the ESTER multicentre real-life study (n=49, mean age 73 years) found that 77.5%, 60% and 45.2% achieved PASI75/90/100 at week 28, with substantial improvement in scalp, genital and palmoplantar disease and no geriatric-specific safety signal (46). A phase 4 open-label real-world trial up to 64 weeks reported PASI75/90/100 rates of 87/56.5/32.6% at week 52, with no tildrakizumab-related serious AEs (47). A phase 3b RCT in scalp psoriasis confirmed sustained efficacy through week 52 with no treatment-related serious AEs (48).

IL-17-PATHWAY INHIBITORS

Class overview

IL-17 inhibitors are highly effective biologic agents that target the IL-23/Th17 axis, a central pathway in the pathogenesis of psoriasis, by blocking IL-17A, IL-17A/F, or the IL-17 receptor. Agents such as secukinumab, ixekizumab, bimekizumab, and brodalumab provide rapid and sustained skin and joint clearance and are now widely used for moderate-to-severe disease. Short-term NMAs consistently rank them among the most efficacious agents, albeit with somewhat higher AE rates than IL-23 inhibitors (3,4). A Polish real-world comparison of bimekizumab, secukinumab and ixekizumab in 98 patients showed that all three improved PASI rapidly and all agents showing favourable safety with no serious AEs (49). A large multicentre retrospective study of 405 psoriasis patients with latent TB infection treated with IL-17 or IL-23 inhibitors found only one case of active TB, in a patient on ixekizumab who had not received chemoprophylaxis; no reactivations occurred in the remaining patients during a mean follow-up of about 33 months. The overall TB reactivation rate was 0.46% for IL-17 inhibitors and 0% for IL-23 inhibitors, with no significant difference between the two classes (50).

A recent systematic review and meta-analysis of patients with PsA showed that IL-17 inhibitors carry a measurable but overall low risk of HBV reactivation, with a pooled reactivation rate around 4% across HBV serotypes and no clear difference from other targeted agents. Reactivation risk is strongly driven by HBV status: in chronic HBV infection, rates reached roughly 20–30% when IL-17 inhibitors (especially secukinumab) were used without antiviral prophylaxis, whereas no reactivations were observed in chronic carriers who received concomitant antiviral prophylaxis (51). Experimental data suggest that IL-17A has a complex role in atherosclerosis: blockade of IL-17A reduces plaque burden and vascular inflammation in mouse models, implying a pro-atherogenic effect, whereas other studies indicate, potentially plaque-stabilising actions. Clinically, however, a systematic review and meta-analysis of nine RCTs found no significant change in MACE risk with IL-17 inhibitors overall, nor in secukinumab or ixekizumab subgroups, and no dose-response signal (52).

Current evidence suggests that IL-17 inhibitors have a very favorable malignancy profile, with overall cancer rates similar to or even lower than those of the general population and anti-TNF–treated patients. Large cohorts and meta-analyses report very low incidence rates of melanoma and non-melanoma skin cancer, without a consistent signal for increased internal malignancies. Some population-based data even suggest a reduced risk of certain tumors, including non-Hodgkin lymphoma, colorectal, hepatobiliary, ovarian cancers, melanoma and basal cell carcinoma in patients receiving IL-17 inhibitors, although follow-up remains relatively short and ongoing surveillance is warranted (53). IL-17 is crucial for mucocutaneous antifungal immunity. A large multi-source observational study (WHO and EMA safety databases, national prescription registry, psoriasis cohort) demonstrated a strong association between IL-17 inhibitors and candidiasis, especially oropharyngeal and esophageal disease; risk was 2–42-fold higher compared with TNF inhibitors, though most cases were non-invasive and managed effectively with antifungals (54).

IL-17 inhibition has also been linked to potential IBD new onset or exacerbation. A systematic review and meta-analysis of IL inhibitors in psoriasis found no significant increase in new-onset IBD with most agents, but ixekizumab was associated with a small but statistically significant excess risk, prompting calls for heightened vigilance in high-risk patients (55). Paradoxical eczema is an emerging safety issue across IL-17 inhibitors. In a series of 595 IL-17-treated psoriasis patients, 25 (4.2%) developed paradoxical eczema-most commonly atopic dermatitis-like-often in patients with atopic background and elevated IgE. Eczematous reactions were milder with secukinumab and more severe with bimekizumab; IL-17 inhibition was withdrawn in all cases requiring specific treatment. Severe cases responded rapidly to short courses of oral JAK inhibitors (upadacitinib or abrocitinib), after which patients were switched successfully to IL-23 inhibitors without relapse (56).

Secukinumab

Secukinumab and ixekizumab selectively inhibit IL-17A. Real-world data suggest that secukinumab can be used safely in patients with latent TB when proper screening and, often, prophylaxis are applied. In a multicentre Italian cohort of 59 psoriasis patients with latent TB, ten (17%) patients did not undergo prophylaxis before starting secukinumab, 83.1% received isoniazid ± rifampicin prophylaxis; after a mean of

84 weeks of secukinumab, no TB reactivation or unexpected safety signals were observed (57). Another case documented simultaneous HBV reactivation and hair discoloration under secukinumab in a patient with anti-HBcIgG positivity; HBV DNA became detectable despite normal transaminases and negative HBsAg, and entecavir therapy cleared viremia while hair discoloration persisted. The authors stressed serial HBV DNA monitoring in anti-HBcIgG-positive patients lacking prophylaxis (58).

Paradoxical phenomena such as Behçet-like disease can be seen with IL-17 inhibitors. A case report plus literature review described a psoriasis patient who developed Behçet-like disease (oral/genital ulcers, nodular lesions) after secukinumab, with resolution after drug discontinuation and highlighting similar cases across IL-17 inhibitors (59).

Overall, secukinumab remains a highly effective agent whose infectious and paradoxical risks are largely manageable with appropriate pre-treatment assessment and multidisciplinary follow-up.

Ixekizumab

Long-term real-world data for ixekizumab have recently expanded and strongly support its durability of response and reassuring safety profile. In the large IL PSO multicentre retrospective study, 1096 patients with moderate-to-severe plaque psoriasis treated with ixekizumab for at least one year achieved PASI 90 and PASI 100 responses of 85.0% and 69.1% at week 52; among the 145 patients completing five years of therapy, PASI 90 and complete skin clearance were maintained without the emergence of new safety signals (60). These findings confirm that the high clearance rates seen in randomized trials can be sustained over many years in routine practice, including in patients with prior biologic exposure and challenging disease distributions. The class-typical risk of mucocutaneous candidiasis with IL-17 blockade has been quantified in an integrated safety analysis of 25 ixekizumab clinical studies across psoriasis, psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA) (61). Candida infections occurred at low incidence rates—1.9, 2.0 and 1.2 per 100 patient-years in PsO, PsA and axSpA, respectively—and were predominantly single, mild-to-moderate episodes affecting the oral or genital mucosa. Most events resolved with topical antifungals or even without specific therapy, and virtually none led to treatment discontinuation, indicating that candidiasis with ixekizumab is usually manageable and non-invasive. Importantly, no unexpected invasive fungal patterns emerged despite extensive cumulative exposure.

A recent systematic literature review, which complements these datasets and includes 118 real-world publications, reported that ixekizumab is consistently effective in psoriasis, PsA, and axSpA, achieving high drug survival rates and meaningful improvements in the Dermatology Quality of Life Index. It also reported that ixekizumab frequently outperformed comparator biologics in achieving DLQI 0/1 and that no unexpected safety signals were identified (62). Across studies, the safety profile remained aligned with clinical-trial experience, with no new serious-event signals identified. Taken together, these real-world data position ixekizumab as a high-efficacy IL-17A inhibitor with durable responses, low rates of mostly mild mucocutaneous candidiasis and a stable long-term safety profile that is comparable to, or in some domains favourable over, other agents within the IL-17 class.

Brodalumab

Brodalumab, an IL-17 receptor A antagonist, initially raised concern due to imbalances in suicidal ideation/behaviour (SIB) in early trials. A recent synthesis of open-label and real-world studies, however, found that most AEs mirrored the package insert (upper respiratory tract infection, injection-site reactions), serious infections were rare, and there was no clear excess of completed suicides versus background psoriasis risk (63). Several studies comparing brodalumab with other biologics reported no increase in MACE or serious fungal infections (63). Current practice emphasises routine mood screening and psychiatric collaboration where indicated, rather than blanket avoidance.

Bimekizumab

Bimekizumab neutralizes both IL-17A and IL-17F. Network meta-analyses and head-to-head trials show that it can induce PASI100 more frequently than IL-17A-only inhibitors and some IL-23 inhibitors in the short term (64). Longer-term data are now available. In the BE RADIANT phase IIIb trial, bimekizumab was superior to secukinumab for PASI100 at year 1; over three years, PASI100 responses were maintained in ~69% of patients initially randomised to bimekizumab, and in those switched from secukinumab, with stable rates of nasopharyngitis, oral candidiasis and upper respiratory tract infection and no increase in serious infections, IBD or suicidality over time (65). A safety-focused narrative review of bimekizumab concluded that although mucocutaneous candidiasis is more frequent than with other IL-17 inhibitors, events are typically mild to moderate, respond to azoles and rarely require discontinuation; serious infections, malignancies and MACE have been uncommon in trials and extensions (66).

CROSS-CLASS SAFETY THEMES AND SPECIAL POPULATIONS

HBV and TB reactivation

Multiple studies converge on a key principle: risk is highest with TNF inhibitors but can be mitigated by systematic screening and prophylaxis. HBV reactivation risk under IL-17 and IL-23 inhibitors appears low but not negligible in anti-HBcIgG-positive patients without prophylaxis, as illustrated by the secukinumab-related case (58) and dermatology HBV cohorts in psoriasis and HS (17,30). IL-23 inhibitors have reassuring data in TB-infected patients, with no reactivation seen across clinical trials and real-world cohorts when active disease is excluded and prophylaxis used selectively (27-29).

Malignancy and oncologic patients

Retrospective series of psoriasis patients with prior or concomitant malignancy treated with biologics suggest that IL-23 and IL-17 inhibitors—followed by ustekinumab—can be used safely with oncology input, without obvious increases in recurrence or new cancer events during follow-up (6,7). IL-23 and IL-17 blockade may be less broadly immunosuppressive

than TNF inhibition, although definitive comparative oncologic safety data are lacking. Current practice favours IL-23 or IL-12/23 agents when comorbid psoriasis emerges as an immune-related adverse event during checkpoint inhibitor therapy, as they allow continued oncologic treatment (6).

Cardiovascular events

Psoriasis is associated with increased rates of ischemic heart disease and heart failure, so cardiovascular status should be systematically assessed before and during biological therapy. A comprehensive meta-analysis of 43 RCTs involving TNF, IL-17, IL-12/23 and IL-23 inhibitors found no significant increase in MACE risk for any biologic class compared with placebo (19). In contrast, TNF inhibitors have been linked to new-onset or worsening congestive heart failure, particularly in patients with NYHA class III–IV disease, and are generally avoided in this setting, with a preference for alternative biologic classes. For patients with stable ischemic heart disease or compensated heart failure, biologics, including TNF inhibitors, can usually be used, but treatment should be individualized with cardiology consultation, optimization of traditional cardiovascular risk factors, and regular follow-up as part of comprehensive psoriasis management.

Inflammatory bowel disease and gastrointestinal safety

A systematic review/meta-analysis of new-onset IBD in psoriasis patients receiving IL inhibitors (bimekizumab, ixekizumab, secukinumab, brodalumab, ustekinumab) across 21 RCTs identified 22 IBD cases in active-treatment arms versus one in controls; only ixekizumab showed a statistically significant risk difference. For bimekizumab, secukinumab, brodalumab and ustekinumab, the data did not support a significantly increased risk compared with placebo or non-IL biologics (55). Clinically, IL-23 inhibitors are generally preferred in patients with pre-existing IBD, while IL-17 inhibitors can still be considered in carefully selected cases with gastroenterology oversight.

Paediatric and elderly patients

Biologics are increasingly used in paediatric psoriasis. A structured review of biologics in children found encouraging efficacy and favourable short-term safety across TNF, IL-12/23 and IL-17 agents, with signals that IL-12/23 and IL-17A inhibitors may be more efficacious than TNF inhibitors, though long-term paediatric safety data remain limited (67). Anti-TNF biosimilar experience in children and older adults similarly suggests good tolerability with careful monitoring (16). In older adults, the Ontario cohort showed that IL-12/23, IL-23 and IL-17 biologics were associated with a lower rate of serious infection than traditional systemic agents, whereas TNF inhibitors had similar infection rates to methotrexate (8). IL-23 inhibitors such as tildrakizumab and guselkumab have especially reassuring geriatric data (28,46).

Rarely seen adverse events

IL-17 inhibitors may cause paradoxical eczema, Behçet-like disease, and rarely vasculitic phenomena; in most cases, discontinuation of the drug is sufficient, and paradoxical eczema responds to short-term systemic immunomodulatory therapy such as JAK inhibitors, after which switching to IL-23 is usually successful. (56,59). Bullous pemphigoid induced by biologics, most commonly ustekinumab and TNF inhibitors, is rare but important (26).

Herpes zoster risk may differ between agents, with adalimumab carrying higher risk and ustekinumab/guselkumab possibly lower compared with traditional systemics, though vaccination with recombinant zoster vaccine remains advisable for most patients initiating biologic therapy (18).

CONCLUSION

Taken together, randomized trials, long-term extensions, pharmacovigilance analyses and real-world cohorts provide a broadly reassuring picture of biologic safety in psoriasis vulgaris. TNF inhibitors retain a central role but require the greatest vigilance for TB, HBV and opportunistic mycoses. Ustekinumab offers steady long-term tolerability, while IL-23 inhibitors combine excellent efficacy with low serious-infection and TB-reactivation rates, neutral MACE signals and good performance in cancer survivors, TB-exposed and elderly patients. IL-17-pathway inhibitors deliver very rapid, deep skin clearance at the cost of predictable mucocutaneous candidiasis and rare paradoxical or IBD-related events, which are usually manageable with early recognition and appropriate switching.

Ultimately, absolute risk is driven more by age, comorbidities and concomitant immunosuppression than by any single biologic agent. Aligning drug choice with each patient's risk profile, supported by structured screening, vaccination and close monitoring, allows clinicians to exploit the remarkable efficacy of modern biologics while minimizing preventable harm (Table 1-2).

Table 1. Practical Prevention and Monitoring

Pre-treatment screening	IGRA/TST with chest imaging as indicated; HBV/HCV serology (with hepatology input for anti-HBcIgG-positive or HBsAg-positive patients); HIV testing where risk factors exist; baseline cancer and IBD history.
Vaccination	Update influenza, pneumococcal and recombinant zoster vaccines before or early during therapy; avoid live vaccines during active biologic treatment.
On-treatment monitoring	Regular clinical review, targeted lab monitoring (liver function, HBV DNA where relevant), vigilance for signs of infection, new GI symptoms, neurologic deficits, unexplained lymphadenopathy or blistering eruptions.

IGRA: Interferon Gamma Release Assay, TST: Tuberculin skin test, IBD: Inflammatory bowel disease, GI: Gastrointestinal,

Table 2. Class selection by comorbidity

Prior TB infection	Consider IL-23 or IL-12/23 inhibitors over TNF inhibitors (27).
Chronic HBV	Any biologic requires hepatology-supervised prophylaxis; case data suggest IL-17 and IL-23 inhibitors are reasonable with entecavir/tenofovir in at-risk patients (17,30,58).
IBD	Consider IL-23 or TNF inhibitors; avoid IL-17 inhibitors in active IBD when alternatives exist (55).
Prior malignancy	In patients with a current or recent (≤5-year) history of malignancy, IL-17 or IL-23 inhibitors should generally be preferred as first-line biologics, while TNF-α inhibitors and ustekinumab may be considered on an individual basis in close collaboration with oncology.
Pregnancy/lactation	Consider certolizumab when TNF inhibition suffices (23,24).

IL: Interleukin, TNF: Tumour Necrosis Factor, IBD: Inflammatory bowel disease,

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CASE REPORT

Endometriosis of the Appendix: Two Rarely Encountered Cases and Review of the Literature

Apendiks Endometriozisi: Nadir Karşılaşılan İki Olgu ve Literatürün Gözden Geçirilmesi

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ABSTRACT
Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity and musculature. Appendiceal endometriosis was first described in 1860 by von Rokitansky. The pathogenesis of endometriosis is based on three main theories: Retrograde menstruation with implantation and failure of immunologic clearance, coelomic metaplasia, and hematologic or lymphatic metastasis. A 26-year-old female patient presenting with abdominal pain no known medical history and a 50-year-old female patient presenting with menstrual irregularity without any known medical problems are presented. Histopathological examination of their appendectomy specimens revealed foci of endometriosis. Appendiceal endometriosis, while relatively uncommon in patients with endometriosis, is rare in the general population. It not only may cause symptoms of acute and chronic appendicitis but is also known to cause cyclic and chronic right lower quadrant pain, melena, lower intestinal hemorrhage, and cecal intussusception. Appendicitis should be considered in the differential diagnosis. Recognition of this benign entity is essential to avoid misdiagnosis and unnecessary aggressive management.

Keywords: Endometriosis, appendix, appendectomy, pelvic pain

ÖZET
Endometriozis, endometriyal bezlerin ve stromanın uterusun duvarı ve kavitesi dışında varlığı olarak tanımlanır. Apendiks endometriozisi ilk olarak 1860 yılında von Rokitansky tarafından tanımlanmıştır. Apendiks endometriozisi oldukça nadir görülen bir durumdur ve gastrointestinal sistem endometriozis olgularının çok küçük bir kısmını oluşturur. Endometriozisin patogenezine ilişkin üç ana teori vardır: implantasyon ve retrograd menstrüasyon, çölomik metaplazi ve hematolojik veya lenfatik metastaz. Bilinen bir tıbbi öyküsü olmayan, karın ağrısı ile başvuran 26 yaşında kadın hasta ve adet düzensizliği ile başvuran, herhangi bir bilinen tıbbi sorunu olmayan 50 yaşında kadın hasta sunulmuştur. Apendektomi örneklerinin histopatolojik incelemelerinde endometriozis odakları tespit edilmiştir. Apendiks endometriozisi, endometriozisli hastalarda nispeten nadir olmakla birlikte, genel popülasyonda daha da nadirdir. Sadece akut ve kronik apendisit semptomlarına neden olmakla kalmaz, aynı zamanda döngüsel ve kronik sağ alt kadran ağrısı, melena, alt bağırsak kanaması, çekum invajinasyonuna neden olduğu bilinmektedir. Apendisit ayırıcı tanısında düşünülmelidir. Bu benign durumun tanınması, yanlış tanı ve gereksiz agresif tedavilerin önlenmesi açısından önemlidir.

Anahtar Kelimeler: Endometriozis, apendiks, apendektomi, pelvik ağrı

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INTRODUCTION

Endometriosis is a disease characterized by the presence of endometrial glands and stroma outside the uterine cavity and muscular layer, and is estimated to affect approximately 4–50% of women of reproductive age. Up to 50% of affected patients experience pelvic pain and infertility. Clinical manifestations vary depending on the location of the lesions. In addition to pelvic involvement, gastrointestinal tract involvement represents an important clinical manifestation of the disease. Gastrointestinal endometriosis is reported to occur in 3–34% of patients with endometriosis and may cause a wide spectrum of symptoms (1). Appendiceal endometriosis (AE) was first described by von Rokitansky in 1860. The reported prevalence of AE in the literature ranges from 0.8% to 22%. While the prevalence of AE among patients with endometriosis is approximately 2.8%, it is considerably lower in the general population, estimated at around 0.4% (1). Cecal and appendiceal involvement is rare and may mimic malignancy by presenting with anemia. The incidence is highest in women of childbearing age. Clinical presentation varies according to lesion location and may include tenesmus, hematochezia, iron deficiency anemia, epigastric pain, and even pneumothorax. This

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broad clinical spectrum further complicates the diagnosis of endometriosis (2). From a clinical perspective, most cases of gastrointestinal endometriosis are asymptomatic. The disease predominantly involves the serosal layer and therefore often lacks overt clinical signs. Moreover, cecal pathologies usually present with delayed and nonspecific symptoms, further challenging timely diagnosis (2).

Appendicitis is one of the most common causes of abdominal pain, with a lifetime risk of 8.6% in males and 6.7% in females, and the majority of appendectomies are performed for this diagnosis. Luminal obstruction is the most common etiological factor of appendicitis, particularly in the pediatric population. Three main theories have been proposed to explain the pathogenesis of endometriosis: retrograde menstruation with implantation, coelomic metaplasia, and hematogenous or lymphatic dissemination (3).

Although endometriosis is more prevalent in women of reproductive age, its sequelae may also be observed in the postmenopausal period and may present solely with gastrointestinal manifestations (4). In this study, we report two cases of appendiceal endometriosis and review the relevant literature.

CASE REPORTS

Case-1:

A 26-year-old female patient with no known medical history was admitted to Konya Numune Hospital with right lower quadrant abdominal pain. Physical examination revealed right lower quadrant tenderness. Abdominal ultrasonography demonstrated a dirty mesentery, and the appendix could not be clearly visualized, and further clinical evaluation for acute appendicitis was recommended. Laboratory examination revealed significantly elevated inflammatory markers: C-reactive protein (CRP) was 81.36 mg/L (reference range: 0–5), white blood cell (WBC) count was 19.43 $\times 10^9$/L (reference range: 4.0–9.75), and neutrophil percentage was 88.5% (reference range: 42–73). Hemoglobin level was near the lower limit of normal (10.5 g/dL; reference range: 10.3–15.4), mean corpuscular volume (MCV) was low (74 fL; reference range: 75–98), and hematocrit was reduced (31.3%; reference range: 32.7–46.6). Based on the combined evaluation of clinical, laboratory, and imaging findings, an appendectomy was performed with a presumptive diagnosis of acute appendicitis. Intraoperatively, the appendix was found to be minimally enlarged and was resected.

Gross pathological examination showed a slightly enlarged appendix. Histopathological evaluation revealed neutrophil-rich inflammation involving the appendix wall and serosa. Additionally, endometrial glandular structures of varying sizes accompanied by a cellular stroma measuring approximately 0.6 cm in diameter were observed within the muscular layer of the appendix (Figure 1). Immunohistochemical analysis demonstrated CD10 positivity in the stromal component, supporting the diagnosis of endometrial stroma. Vimentin expression was also positive in the glandular structures, consistent with endometrial tissue. Considering the histopathological and immunohistochemical findings together, the final diagnosis was endometriosis externa associated with acute appendicitis.

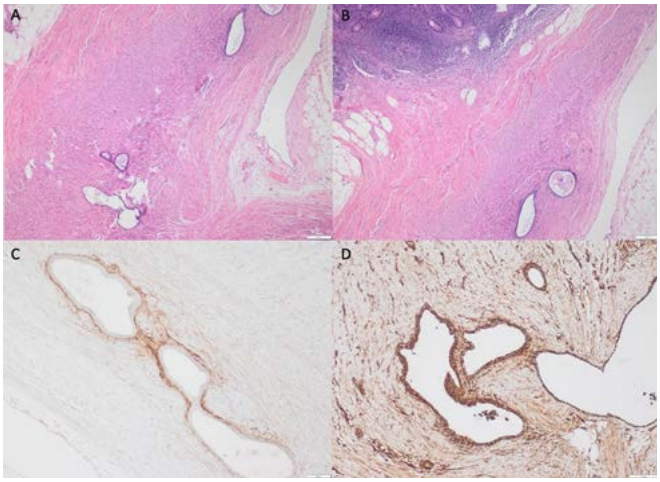

Figure 1. Histopathological appearance and immunohistochemical staining pattern of the primary lesion. A: In hematoxylin and eosin staining, sparse benign glandular structures within the muscular tissue of the appendix wall (x40). B: In hematoxylin staining, benign glandular structures within the muscular layer as well as the appendix mucosa (x40). C: Immunohistochemical CD10 staining showing (+) expression in the narrow stroma surrounding the glands (x100). D: Immunohistochemical Vimentin staining showing (+) expression in glandular epithelia (x100).

Case-2:

A 50-year-old female patient with no known comorbidities presented with a complaint of heavy menstrual bleeding. Transabdominal ultrasonography revealed multiple uterine fibroids, the largest measuring 7.5 cm in diameter. A total hysterectomy was planned. During surgery, a separate appendectomy was also performed due to suspicion of adhesion of the appendix to the surrounding tissues. No endometriotic foci were detected in the uterus, ovaries, or fallopian tubes.

Histopathological examination of the appendix revealed endometrial stromal and glandular structures measuring approximately 0.5 cm in diameter within the muscular layer at the tip of the appendix, similar to the findings observed in Case 1 (Figure 2). In this region, immunohistochemical staining demonstrated CD10 (+), Vimentin (+), and Estrogen Receptor (ER) (+) expression, consistent with endometrial tissue. Based on these findings, the final pathological diagnosis was endometriosis externa, and reactive lymphoid hyperplasia. Informed consent forms were obtained from both cases.

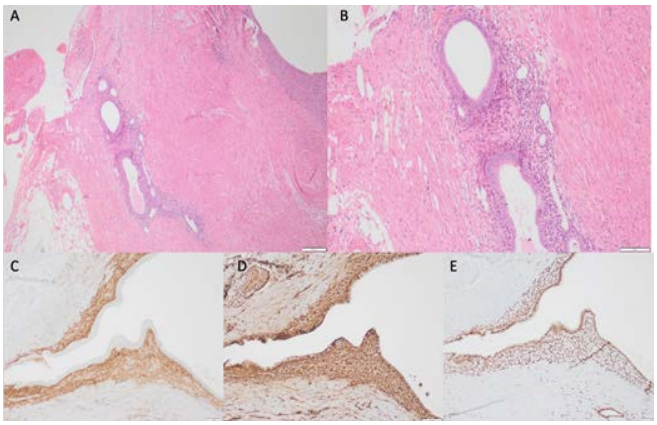

Figure 2. Histopathological appearance and immunohistochemical staining pattern of the second specimen. A: In hematoxylin and eosin staining, sparse benign glandular structures within the muscular tissue of the appendix wall and cellular stroma surrounding them (x40).
B: Benign glandular structures within the muscular layer on hematoxylin and eosin staining, stroma (x100). C: Immunohistochemical CD10 staining showing (+) expression in the narrow stroma surrounding the glands (x100). D: Immunohistochemical Vimentin staining showing positive expression in glandular epithelia (x100). E: Immunohistochemical Estrogen receptor staining showing positive expression in both stroma and glandular epithelia (x100).

DISCUSSION

Appendiceal endometriosis is known to cause both acute appendicitis–like symptoms and cyclic right lower quadrant pain. It may also present with lower gastrointestinal bleeding, cecal intussusception, and perforation. Since right lower quadrant pain is commonly observed in women with endometriosis, the detection of AE is particularly important in patients with chronic pelvic pain undergoing laparoscopy (1). Colonic neoplasms, whether malignant or benign, typically present as a mass lesion in the colon. However, several other conditions may also lead to a colonic mass, including infectious and inflammatory bowel diseases. Additional causes include endometriosis, schwannoma, diverticular disease resulting in mass-like inflammatory changes, and even foreign bodies (2).

Atypical endometriosis can occur at extrapelvic sites, with the gastrointestinal tract being one of the most frequently involved locations. Within the gastrointestinal system, endometriosis most commonly affects the rectosigmoid colon. In contrast, cecal and appendiceal involvement are exceedingly rare, accounting for only a small proportion (approximately 5%) of gastrointestinal endometriosis cases (2). Laparoscopy remains the gold standard for the diagnosis of endometriosis, although non-invasive imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) are frequently used. Once the diagnosis is established, first-line treatment consists of non-steroidal anti-inflammatory drugs and hormonal therapies. Surgical intervention should be considered in patients with contraindications to medical therapy or in those who fail to respond adequately. Although malignancy must always be considered as the primary diagnosis, alternative etiologies, including endometriosis, should also be taken into account, particularly in patients without clear risk factors for colorectal cancer (2).

Malignancy is another important cause of appendicitis, with an incidence ranging from 5.9% to 12% in patients presenting with an appendiceal mass. The most common primary appendiceal malignancies are neuroendocrine tumors, which are typically located at the tip of the appendix (3). According to the study by Feldhaus et al., appendiceal endometriosis is detected in less than 1% of women undergoing appendectomy. Other studies have reported an AE prevalence of 0.4% in the general population. Therefore, AE should be included in the differential diagnosis of appendicitis in female patients (3). The number, ages, and clinical presentations of AE cases in the articles we used as references are detailed in the table (Table 1). In a 12-year study by Mabrouk et al., AE was detected in 2.6% of patients with endometriosis who underwent surgery. AE was associated with adenomyosis, endometrioma, bladder endometriosis, and ileocecal involvement (5). Similarly, Centini

Table 1. Number, ages, and clinical presentations of appendiceal endometriosis cases in the references

References	Appendicial Endometriosis (n)	Age/ Gender	Symptom
Gustofson et al. (1)	4/ 120	18–45 years	Right lower quadrant pain
Togra et al. (2)	1	50-year-old female	Symptomatic anemia
Hale et al. (3)	1	49-year-old female	Incidental finding on computed tomography
Sooklal et al. (4)	1	51-year-old female	Asymptomatic, a colonoscopy for colorectal cancer screening
Mabrouk et al. (5)	50 / 1935	Not specified	Not specified
Centini et al. (6)	13 / 460	Not specified	Not specified
Ross et al. (7)	23 / 300	22–52 years	Patients undergoing coincidental appendectomy at the time of a primary gynecologic procedure.
Gupta et al. (8)	1	36-year-old female	Acute abdominal pain
Uwaezuoke et al. (9)	1	29-year-old female	Right iliac fossa pain

et al. reported a significant association between appendiceal, ovarian, and bladder endometriosis, suggesting that disease spread may occur via the dissemination of endometrioma fluid (6).

Ross et al. demonstrated that appendectomies performed for gynecological indications are associated with higher rates of endometriosis and abnormal pathological findings. Endometriosis was identified in 7.7% of routine pathological examinations (7). The mechanism by which endometriosis develops within the muscularis propria of the appendix in patients without a prior history of endometriosis remains unclear. This observation challenges the theory of retrograde menstruation, as direct seeding cannot occur without serosal involvement. Since both the appendix and the cecum originate from mesodermal tissue, the transformation of the intestinal wall supports the theory of coelomic metaplasia (8). In our cases, neither patient had a known history of endometriosis, yet endometriotic foci were detected within the muscular layer of the appendix.

Although acute symptoms generally resolve after appendectomy, lower abdominal pain may recur. This recurrence is most likely attributable to concomitant pelvic (particularly ovarian) endometriosis. Previous studies have shown that 56% of appendiceal endometriosis cases involve the body of the appendix, while 44% involve the tip, with no reported involvement of the appendiceal base. In our patients, endometrial tissue was localized at the tip of the appendix with involvement of the muscularis propria, while the mucosa and serosa were not affected (9). With increasing awareness and accumulated data, more effective screening tools for appendiceal masses and pathologies may be developed. In conclusion, as demonstrated in our case report, AE should be considered as an important and rare cause of appendicitis. This report highlights the clinical significance of recognizing appendiceal endometriosis as an underlying etiology of appendiceal mass lesions.

DECLARATIONS

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OPEN

CASE REPORT

A Case of Late-Onset Trichotillomania with Coexisting Dysthymiaand Substance Use

Geç Başlangıçlı Trikotilomani ve Eşlik Eden Distimi ve Madde Kullanımı Olgusu

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ABSTRACT

Trichotillomania is a compulsive disorder characterized by recurrent hair-pulling, typically beginning in adolescence and showing a marked female predominance. Late-onset cases are rare and frequently associated with psychiatric comorbidity. We report a 62-year-old woman referred from dermatology with a two-year history of scalp itching and repetitive hair-pulling that began shortly after she realized she had used expired hair dye. Despite multiple dermatological consultations, no organic pathology was identified. Psychiatric evaluation revealed a three-year history of persistent low mood, worsening over the preceding two months, along with relapse of alcohol use 20 days prior to presentation after 25 years of abstinence. Psychosocial stressors were significant, and biological and social functioning were impaired. Examination showed patchy alopecia, while dermatoscopy demonstrated broken hairs and perifollicular hemorrhage. Mental status examination revealed agitation, preoccupation with scalp discomfort, and depressive cognitions. She was diagnosed with dysthymia, a current moderate depressive episode with somatic syndrome, and trichotillomania; alcohol use did not meet criteria for dependence. Laboratory investigations and brain MRI were normal. Treatment with escitalopram, short-term anxiolytics, and behavioral interventions resulted in an approximately 25% reduction in symptom severity at six-week follow-up. This case underscores the importance of recognizing psychiatric morbidity underlying persistent dermatological complaints and highlights the need for a multidisciplinary approach in late-onset trichotillomania.

Keywords: Trichotillomania, late-onset trichotillomania, psychiatric morbidity in trichotillomania, bodily focused repetitive behaviours

ÖZET

Trikotillomani, yineleyici saç yolma davranışı ile karakterize, genellikle ergenlik döneminde başlayan ve kadınlarda belirgin olarak daha sık görülen kompulsif bir bozukluktur. Geç başlangıçlı olgular nadir olup sıklıkla psikiyatrik eş tanılarla ilişkilidir. Bu yazıda, süresi geçmiş saç boyası kullandığını fark etmesinden kısa süre sonra başlayan ve iki yıldır devam eden saçlı deride kaşıntı ve tekrarlayıcı saç yolma yakınmaları nedeniyle dermatoloji kliniğinden yönlendirilen 62 yaşındaki bir kadın olgu sunulmaktadır. Çok sayıda dermatolojik değerlendirmeye rağmen organik bir patoloji saptanmamıştır. Psikiyatrik değerlendirmede üç yıldır süregelen düşük duygu durum, son iki ayda belirgin kötüleşme ve 25 yıllık yoksunluk sonrası başvurudan 20 gün önce yeniden başlayan alkol kullanımı saptanmıştır. Belirgin psikososyal stresörler mevcut olup biyolojik ve sosyal işlevsellik etkilenmiştir. Muayenede yamalı alopesi alanları izlenmiş, dermatoskopide kırık saç telleri ve perifoliküler hemoraji görülmüştür. Ruhsal durum muayenesinde ajitasyon, saçlı deriye yönelik yoğun uğraş ve depresif bilişler dikkati çekmiştir. Hastaya distimi zemininde mevcut somatik sendromlu orta şiddette depresif epizod ve trikotillomani tanısı kondu; alkol kullanımı bağımlılık ölçütlerini karşılamamaktaydı. Laboratuvar incelemeleri ve beyin MRG normal bulunmuştur. Escitalopram, kısa süreli anksiyolitik tedavi ve davranışçı müdahaleler sonrası altıncı haftada semptom şiddetinde yaklaşık %25 azalma izlenmiştir. Bu olgu, dirençli dermatolojik yakınmaların altta yatan psikiyatrik morbiditeyi maskeleyebileceğini ve geç başlangıçlı trikotillomanide multidisipliner yaklaşımın önemini vurgulamaktadır.

Anahtar Kelimeler: Trikotillomani, geç başlangıçlı trikotillomani, trikotillomanide psikiyatrik morbidite, vücut odaklı tekrarlayıcı davranışlar

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INTRODUCTION

Trichotillomania, derived from the Greek terms trich (hair) and till (to pull), is a psychiatric condition where there are repetitive, irresistible compulsions to pull out one's own hair. This leads to overt hair loss, distress and impairment in functioning. Lifetime prevalence is approximated to be 1–3% of the general population. There is a marked female predominance (approximately 10:1). The disorder typically starts in early adolescence (1). Although paediatric and adolescent-onset trichotillomania is fairly well established, late-onset trichotillomania in geriatric patients is rare and only a few cases have been reported worldwide (2). Its appearance in the elderly population is thus clinically relevant because it could be easily missed or mistakenly attributed to dermatological and neurological disorders. Late-onset

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trichotillomania usually co-occurs with mood or anxiety disorders. Evaluation of trichotillomania in this age group is crucial, as it underscores the intricate interplay between psychiatric comorbidity, psychosocial stressors and unusual clinical presentations in later life.

CASE

A 62-year-old female patient was referred from the Department of Dermatology with the complaint of itching over her scalp and hair plucking since two years, 1 week after she became anxious on finding out that the hair dye that she had used had expired. Although she consulted dermatologists on multiple occasions, underwent repeated clinical evaluations and was reassured consistently that there was no dermatological pathology and no medical harm from the expired dye, she remained unconvinced and anxious. The worry gradually progressed to an extreme preoccupation with her scalp, followed by subjective feelings of itching and discomfort, ascribed to the previous application of the dye. She had a tendency of plucking and pulling her scalp hair every time the feeling became overwhelming. When family members attempted to stop her from the constant pulling, she described a feeling of unbearable restlessness, anger and anxiety, which forced her back into the act. Over a period of time, the hair-pulling led to large, patchy areas of baldness accompanied by broken hairs and overt scalp lesions (Figure 1). The family was worried about the unsightly appearance of these patches and, on two occasions, tonsured her head entirely. This however, did not bring the hair-pulling to an end. On comprehensive psychiatric assessment, it was seen that she had been persistently feeling sad, was irritable, had crying spells and tiredness from almost three years, features consistent with dysthymia. There was worsening of the above symptoms in the last two months. Her son was physically abusive, actively involved in polysubstance abuse and legal issues. Her husband was emotionally distant and did not provide for the family. This led to frequent arguments at home. The exacerbation was temporally related to multiple psychosocial stressors. This was characterized by further worsening in her biological functioning, such as disrupted sleep and decreased appetite. She stopped doing the household chores and there was reduced self-care. Of particular concern was the resumption of alcohol use approximately 20 days prior to presentation after nearly 25 years of abstinence. Initially limited to small amounts (60 mL weekly), consumption escalated under interpersonal stress to 180–270 mL, 2–3 times per week. No withdrawal symptoms were observed, and criteria for dependence were not met. She had a history of hypothyroidism on stable replacement therapy. Premorbidly, she was described as dominant and the primary decision-maker in the family.

On mental status exam, patient was restless, agitated and was preoccupied with her scalp itch during the entire interview. She was speaking coherently. Her affect was anxious and was congruent with her self-report of low mood and worrying. She had depressive thoughts, hopelessness, ruminations concerning her dermatological issues, constant worry about the psychosocial stressors and preoccupation with the fear of long-term consequences of the use of expired hair dye. There were no psychotic symptoms. Her cognitive functions were normal with impaired personal, social judgement and preserved insight. Mini Mental Status Examination score was 27. Massachusetts General Hospital Hair Pulling scale (MGH-HPS) was administered – showed a score of 26. Dermatoscopy showed broken multiple hairs of different length, patchy hair loss, comma sign, black dot and perifollicular haemorrhage, features indicative of trichotillomania (Figure 2). Routine laboratory investigations and MRI brain were within normal

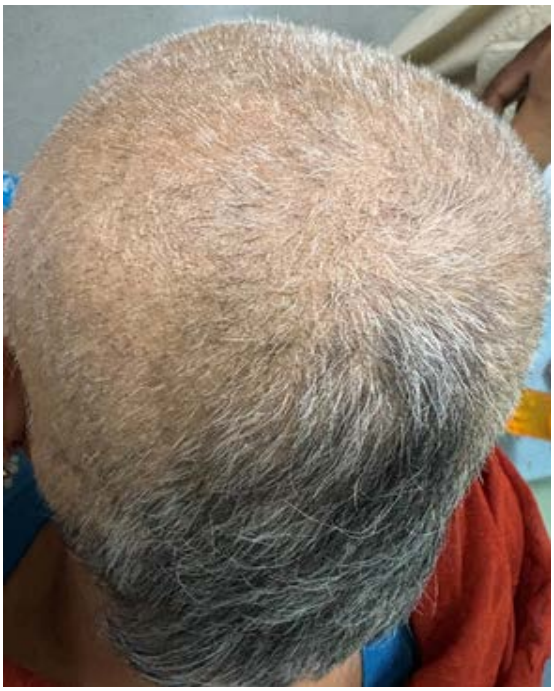

Figure 1. Large patchy areas of hair loss

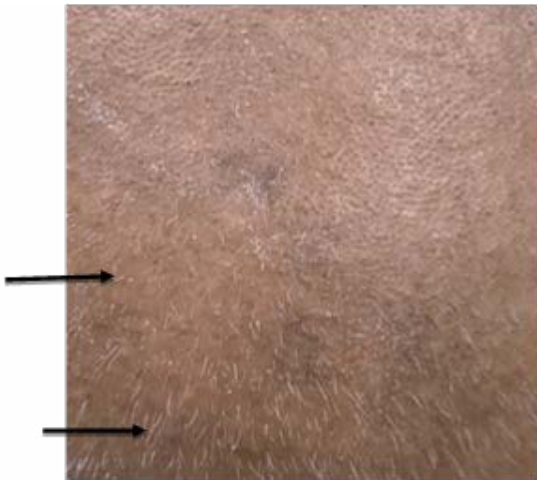

Figure 2. Broken hair, black-dot haemorrhages

limits. Given the egosyntonic nature of the symptoms and preserved insight, obsessive–compulsive disorder and delusional disorder were excluded. Based on ICD-10 criteria, she was diagnosed with dysthymia (F34.1), a current moderate depressive episode with somatic syndrome (F32.11), trichotillomania (F63.3), and alcohol use not meeting criteria for dependence.

She was started on escitalopram 10 mg/day for her symptoms. A combination of etizolam 0.5 mg and propranolol 20 mg was given to treat acute anxiety which was tapered and stopped during follow-up visits. Quetiapine 25 mg was started in view of disturbed sleep. Patient and her family were psycho-educated regarding the nature of her condition, with special emphasis on the contribution of psycho-social factors, the vicious cycle of hair pulling and the significance of supportive management. Relaxation strategies, such as guided breathing and progressive muscle relaxation, were taught. Multiple sessions on habit reversal therapy sessions were conducted. Weekly supportive psychotherapy was initiated with an emphasis on rapport building, coping skill augmentation and reinforcement of adaptive behaviour. Family therapy sessions were conducted to decrease critical remarks, increase understanding of the disorder and reinforce supportive feedback.

At the six-week follow-up, the patient reported improvement, with an approximately 25% reduction in symptom severity. (Massachusetts General Hospital Hair Pulling Scale score dropped to 19 after 6 weeks) She reported less preoccupation with her scalp and a decrease in the frequency of hair-pulling episodes. There was improvement in her mood and sleep. She was better able to participate in daily activities. The family also decreased their hostile response. Informed consent was obtained from the patient.

DISCUSSION

Late-onset trichotillomania is uncommon. Adult cohort analyses suggest that only a small minority (around 4%) develop symptoms after adolescence (4). Reports of late-life onset are therefore considered clinically significant and are frequently associated with comorbid mood or anxiety disorders, psychosocial stressors, or medical vulnerability, highlighting the need for careful psychiatric evaluation when new-onset hair-pulling behavior emerges in older adults (2,3). The primary precipitating factor in our case was anxiety about the perceived harmful effects of using an expired hair dye in the background of low mood resulting in itching and compulsive hair-pulling. This in turn presented as non-response or minimal response to dermatological treatment. The presence of co-occurring mood disturbance and alcohol use also made the presentation more complex. Chronic dermatologic complaints often mask an underlying psychiatric disorder leading to underdiagnosis of the same.

Pharmacological treatments have shown variable efficacy. The FDA has not approved any medication for trichotillomania. A double-blind randomized trial of N-acetylcysteine (NAC) in adults reported significant symptom reduction, with ≈56% reporting improvement suggesting potential benefit through glutamatergic modulation. Clomipramine, NAC and olanzapine have some evidence in managing trichotillomania (6). However, SSRIs retain an important therapeutic role in the presence of comorbid depressive or anxiety disorders, where they effectively reduce affective distress, rumination, and anxiety, which may inturn decrease suggesting the urge to pull hair and improves overall functioning (6).

Randomized and controlled clinical trials have demonstrated that behavioural interventions, particularly habit reversal training (HRT)–based cognitive-behavioural therapy (≈64% responders) have superior efficacy over pharmacotherapy (≈9% responders) (5).

Our case highlights the complex presentation of late onset trichotillomania and the need for early screening for psychiatric morbidity in such patients.

DECLARATIONS

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OPEN

CASE REPORT

Intratesticular Leiomyoma Associated with Polyorchidism: A Rare Case Report

Poliorşidizm ile Birlikte Görülen İntratestiküler Leiomyom: Nadir Bir Olgu Sunumu

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ABSTRACT
Polyorchidism is an exceptionally rare congenital urogenital anomaly characterized by the presence of three or more testes, whereas testicular leiomyomas are uncommon benign tumors originating from smooth muscle cells and typically demonstrating slow growth. We report the case of a 74-year-old man with congenital polyorchidism who presented with suspected testicular malignancy. The patient was admitted with a complaint of firmness in the left scrotum. Physical examination revealed two normally palpable testes; however, a well-circumscribed, firm mass measuring approximately 3–4 cm in diameter was detected distal to the left inguinal canal. Serum tumor markers were within normal limits. Left inguinal exploration performed under spinal anesthesia demonstrated a normal left testis as well as a separate mass originating from the testicular base and terminating in an additional spermatic cord structure, which was subsequently excised. Histopathological examination confirmed the diagnosis of an intratesticular leiomyoma arising from a supernumerary testis containing a spermatic cord structure. Because intratesticular leiomyomas are rare and may clinically mimic malignant testicular tumors, definitive diagnosis relies solely on histopathological evaluation, often leading to radical orchiectomy in suspected cases. Polyorchidism has been reported in only a limited number of cases in the literature, and to the best of our knowledge, no tumor arising from a third testis has previously been described.

Keywords: Polyorchidism, testicular tumor, triorchidism, leiomyoma

ÖZET
Poliorşidizm, üç veya daha fazla testisin bulunmasıyla karakterize, oldukça nadir görülen konjenital bir ürogenital anomalidir; testiküler leiomyomlar ise düz kas hücrelerinden köken alan, yavaş büyüme eğilimi gösteren ve benign karakterde seyreden nadir tümörlerdir. Bu çalışmada, doğuştan üç testisi bulunan ve testiküler malignite şüphesiyle başvuran 74 yaşındaki bir erkek olgu sunulmaktadır. Sol skrotumda sertlik yakınmasıyla başvuran hastanın fizik muayenesinde iki testis normal olarak palpe edilirken, sol inguinal kanal distalinde yaklaşık 3–4 cm çapında, sınırlı ve sert bir kitle saptandı; tümör belirteçleri normal sınırlarda idi. Spinal anestezi altında gerçekleştirilen sol inguinal eksplorasyonda sol testisin normal olduğu, ayrıca testis tabanından kaynaklanan ve ikinci bir spermatik kord yapısı ile sonlanan ayrı bir kitlenin bulunduğu gözlendi ve lezyon eksize edildi. Histopatolojik incelemede spermatik kord yapısı içeren ikinci testise ait intratestiküler leiomyom tanısı konuldu. İntratestiküler leiomyomlar nadir görülmeleri ve klinik olarak malign testis tümörlerini taklit edebilmeleri nedeniyle kesin tanısı yalnızca histopatolojik değerlendirme ile konulabilen lezyonlar olup, bu şüphe nedeniyle çoğu olguda radikal orşiektomi uygulanmaktadır. Poliorşidizm ise literatürde son derece sınırlı sayıda bildirilmiş olup, üçüncü testisten köken alan tümör varlığına ilişkin bugüne kadar bildirilmiş bir olgu bulunmamaktadır.

Anahtar Kelimeler: Poliorşidizm, testis tümörü, üç testis, leiomyom

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INTRODUCTION

Polyorchidism is a rare congenital condition defined by the presence of more than two testicles. Since its first description in the late nineteenth century, fewer than a few hundred cases have been reported, highlighting its exceptional rarity (1). The embryological origin of polyorchidism has not been fully elucidated; however, several theories have been proposed. The most widely accepted hypothesis suggests abnormal division of the genital ridge during early embryogenesis, occurring before or during differentiation of the primordial gonads. Depending on the timing and extent of this division, the supernumerary testis may or may not have an associated epididymis or vas deferens. Alternative theories include transverse or longitudinal duplication of the genital ridge and incomplete degeneration of mesonephric tissue, all of which may contribute to the wide anatomical variability observed in reported cases.The most frequent form is triorchidism, in which the supernumerary testis is usually located

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within the scrotum. From an anatomical and functional standpoint, polyorchidism demonstrates considerable heterogeneity. The supernumerary testis may be located within the scrotum, inguinal canal, or abdomen, with scrotal localization being the most common. Classification systems have been proposed based on reproductive potential and anatomical connections to the epididymis and vas deferens, as these features have implications for fertility preservation and management strategies. Testicular positioning is reported to be scrotal in 75% of cases, inguinal in 20%, and abdominal in 5% (2,3). Supernumerary testes may be unilateral or bilateral, with over half of reported cases involving the left side (4).

While the majority of testicular tumors are malignant, benign masses may also occur. These include epidermoid cysts, lipomas, benign teratomas, and sex cord–stromal tumors (5). Testicular leiomyomas are particularly rare and arise from smooth muscle proliferation, typically exhibiting slow growth (6,7). In this report, we present a case of triorchidism with leiomyoma arising from the third testis following complaints of scrotal firmness.

CASE

A 74-year-old male patient presented to our clinic with complaints of firmness in the left scrotum. On examination, both testicles were normal in size and consistency. However, a firm, well-circumscribed mass measuring approximately 3–4 cm was palpated in the distal left inguinal canal at the level of the spermatic cord. Scrotal ultrasonography confirmed the presence of a 3 cm well-defined lesion in the same region. Tumor markers were as follows: Lactate Dehydrogenase (LDH): 186 U/L (normal: 125–220 U/L), Alpha-fetoprotein (AFP): 1.34 ng/mL (normal: 0–10 ng/mL), and β-Human Chorionic Gonadotropin (β-HCG): <0.2 U/L (normal: 0–2 U/L).

Based on these findings, surgical exploration was planned. Under spinal anesthesia, a left inguinal incision was performed. The testicle and the mass were exposed, revealing two separate spermatic cord structures. The left testicle appeared normal, while the second cord terminated in a mass arising from the base of an accessory testis (Figure 1). The mass was completely excised. The patient was discharged on the first postoperative day without complications. A follow-up scrotal ultrasound showed no additional pathology, and the patient remained asymptomatic at the 6-month postoperative follow-up.

Histopathological evaluation revealed a 3 × 2.5 × 2.5 cm well-circumscribed mass with a smooth external surface and an associated 3 × 0.8 cm segment of spermatic duct. The lesion consisted of spindle-shaped smooth muscle cells with focal nuclear atypia but no mitotic figures or necrosis, consistent with leiomyoma (Figures 2–3). Written informed consent was obtained from the patient prior to surgery.

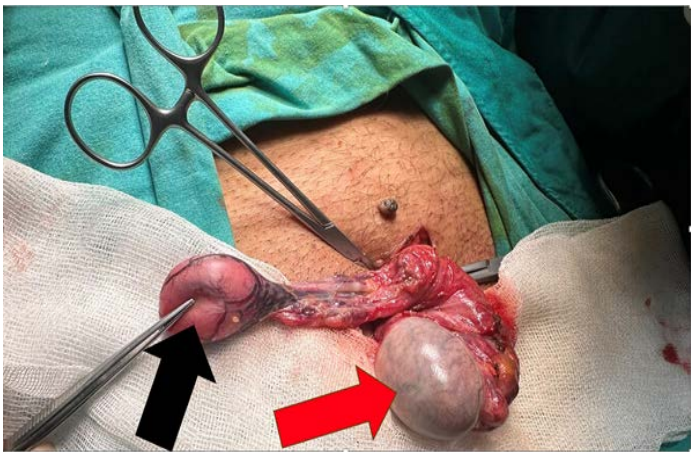

Figure 1. Macroscopic image of the mass detected after a left inguinal incision during surgery and the left testicle. Red arrow: left testicle, Black arrow: leiomyoma of the 3rd testicle.

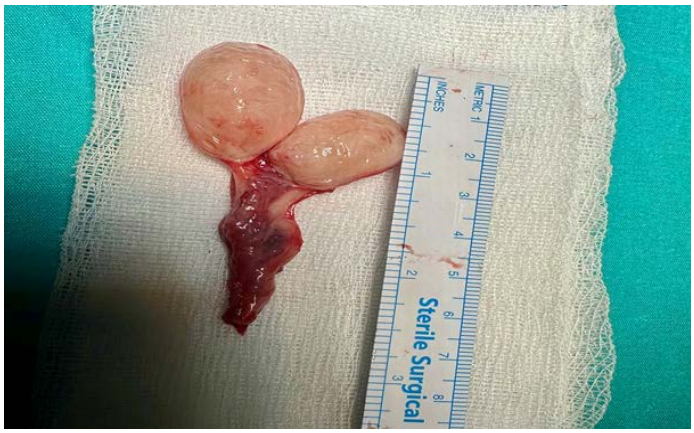

Figure 2. Postoperative macroscopic image of a specimen taken after mass excision. The mass is approximately 3 cm in size and appears to have smooth borders.

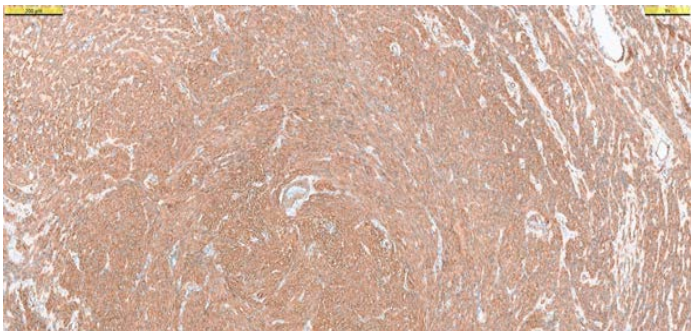

Figure 3. Microscopic examination reveals a well-defined, encapsulated mass of smooth muscle tissue organized into interwoven bundles. The cells have long, spindle-shaped nuclei with rounded ends, heterogeneous chromatin, thin nucleoli, and eosinophilic cytoplasm with indistinct cytoplasmic boundaries. Extensive staining with smooth muscle actin (SMA) stain is observed.

DISCUSSION

Leiomyomas are benign tumors originating from smooth muscle cells. Although they are most commonly found in the renal pelvis, they may also arise in the bladder, spermatic cord, epididymis, prostate, glans penis, or scrotal structures (8). These tumors are generally observed in individuals older than 50 years. Previous reports have described leiomyomas in locations such as the tunica vaginalis, tunica albuginea, epididymis, spermatic cord, and even the testicular parenchyma (9). Scrotal leiomyomas typically present as slow-growing masses. Due to their indolent course, the interval between initial detection and hospital admission can range from 2 to 20 years (10). On physical examination, they usually appear as firm, non-tender nodules, often localized to the pole of the testis. Their mean size is approximately 3 cm, although reported sizes range from 1 to 8 cm (11). A wide variety of differential diagnoses should be considered, including fibroma, supernumerary testis, and sebaceous cyst (12). Painful schwannomas associated with scrotal ulcerations may clinically mimic squamous cell carcinoma, particularly when preceded by trauma (13). Tumor markers are usually within normal limits, as observed in our patient.

Pathological evaluation of leiomyomas relies on several criteria, including tumor size greater than 5 cm, irregular margins, more than 10 mitotic figures per 10 high-power fields, and significant cytological atypia. A lesion demonstrating one of these features may be classified as a leiomyoma; two features suggest an atypical leiomyoma, while three or more are indicative of leiomyosarcoma (14). In the present case, the mass was well-demarcated, measured less than 5 cm, and showed no mitotic activity or necrosis, supporting the diagnosis of benign leiomyoma. From a management perspective, a recent systematic review of epididymal leiomyomas demonstrated that testis-sparing surgical approaches are both feasible and safe, with reported procedures ranging from simple lesion excision to epididymectomy. Importantly, no recurrences were documented during follow-up. These findings support organ-preserving strategies when tumor markers are negative, imaging does not suggest invasive disease, and intraoperative findings are consistent with a benign, well-circumscribed paratesticular lesion (15).

Polyorchidism is an uncommon congenital condition, most frequently involving a supernumerary testis on the left side (16). Rare cases of bilateral or triplicated testes have also been reported. Although its etiology remains speculative, polyorchidism is generally thought to result from abnormal division of the genital ridge, with or without involvement of the Wolffian duct (17). A supernumerary testis may mimic other scrotal pathologies, including tumors, spermatoceles, varicoceles, or hydroceles, and may also be incidentally detected during surgery for undescended testes (18). Therefore, physical examination alone is insufficient for diagnosis. Imaging modalities—particularly Doppler ultrasonography supplemented by magnetic resonance imaging (MRI)—play a crucial role in evaluation (19). A recent systematic review reported that imaging-based diagnosis was common, and while observation was frequently chosen, surgical intervention was preferred when the supernumerary testis was ectopic or when features raised concern for neoplastic transformation (20). In the present case, the third testis was identified intraoperatively by the presence of two distinct spermatic cords and ductus deferens structures. Bergholz et al. proposed a classification system for polyorchidism (16):

- Type A: Testis with drainage via the vas deferens
  - A1: Own epididymis and vas deferens
  - A2: Own epididymis but shared vas deferens
  - A3: Shared epididymis and duct
- Type B: Testis without drainage
  - B1: With epididymis
  - B2: Without epididymis; isolated testicular tissue

Our case is consistent with Type A1 polyorchidism, as the supernumerary testis possessed its own ductal structures. The optimal management of polyorchidism remains controversial. The balance between the potential risk of malignancy and the reproductive contribution of the supernumerary testis presents a clinical dilemma. While most authors advocate preservation of the supernumerary testis, orchiectomy is recommended when malignancy is suspected (16). The coexistence of polyorchidism and leiomyoma is particularly challenging, as polyorchidism itself may present as an "additional mass," and the presence of a solid paratesticular lesion may further increase suspicion of malignancy, potentially leading to overtreatment. This is especially relevant because imaging findings may not reliably distinguish benign from malignant paratesticular tumors. Recent imaging-focused studies emphasize that accurate preoperative identification of benign extratesticular lesions is essential to avoid unnecessary orchiectomy, and that MRI can be valuable in clarifying lesion origin and anatomical relationships (21).

The unique contribution of this report lies in highlighting a rare but clinically relevant scenario in which a congenital anatomical variant (polyorchidism) coexists with a benign paratesticular smooth muscle tumor (leiomyoma). This combination increases diagnostic uncertainty and the risk of unnecessary radical surgery. Our case underscores the importance of differentiating diagnostic pitfalls related to polyorchidism—such as misinterpretation of accessory testicular tissue—from those related to leiomyoma, which may closely mimic malignant disease. In carefully selected patients with reassuring tumor markers and non-aggressive imaging findings, a personalized, testis-sparing surgical approach with definitive histopathological confirmation can achieve oncological safety while minimizing morbidity.

CONCLUSION

Polyorchidism is a rare congenital anomaly that can complicate the evaluation of scrotal masses, particularly when associated with paratesticular tumors. This case illustrates the uncommon coexistence of a supernumerary testis and a paratesticular leiomyoma, a benign entity that may closely mimic testicular malignancy. Given the limitations of imaging in such rare anatomical settings, careful clinical judgment

is essential. In selected patients with a low suspicion of malignancy, testis-sparing surgery represents a reasonable and effective approach, with definitive diagnosis established by histopathological examination.

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