Derginin önceki adı: RAED Dergisi / *formerly RAED Journal*

TÜRKİYE ROMATOLOJİ DERNEĞİ

Ulusal ROMATOLOJİ Dergisi

Journal of Turkish Society for Rheumatology

ISSN: 2651-2653

www.romatolojidergisi.org

Cilt / Volume: **17** • **Sayı** / Issue: **1** • **Mart** / March **2025**

Türkiye Romatoloji Derneği'nin (TRD) bilimsel yayın organıdır.
Official Publication of Turkish Society for Rheumatology

S. Özbek, 2024

galenos yayınevi

Ulusal
ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Önceki adı: RAED Dergisi / *Formerly RAED Journal*
Türkiye Romatoloji Derneği'nin (TRD) bilimsel yayın organıdır.
Official Publication of Turkish Society for Rheumatology

Editörler Kurulu / Editorial Board

Yönetim Yeri / Administrative Office
Esentepe Mah. Kore Şehitleri Cad. No: 35/6 Şişli 34394 İstanbul, Türkiye

galenos yayınevi

Yayınevi İletişim/Publisher Contact
Adres/Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Türkiye
Telefon/Phone: +90 530 177 30 97
E-posta/E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr **Yayıncı Sertifika No:** 14521

Basım Yeri/Printing at: Son Sürat Daktilo Dijital Baskı
Merkezi Sanayi ve Ticaret Ltd. Şti.
Gayrettepe Mahallesi, Yıldızposta Caddesi, Evren Sitesi A Blok
No: 32 D: 1 - D: 3 34349 Beşiktaş, İstanbul, Türkiye
Telefon/Phone: +90 (212) 288 45 75
E-posta: info@sonsuratdaktilo.com

Basım Tarihi/Printing Date: Mart 2025/March 2025

ISSN: 2651-2653 **E-ISSN:** 2651-2661

Yılda üç kez yayımlanan süreli yayındır.
International periodical journal published three times in a year.

Ulusal
ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Derginin "Yayın Etiği" ve "Yazarlara Bilgi" konularında bilgi almak için lütfen web sayfasına **(https://www.raeddergisi.org/home)** başvurunuz.

Derginin editöryal ve yayın süreçleri ile etik kuralları ICMJE, WAME, CSE, COPE, EASE, ve NISO gibi uluslararası kuruluşların kurallarına uygun olarak şekillenmektedir. Ulusal Romatoloji Dergisi, **EBSCO, Gale, Türk Medline, Embase, J-Gate ve Tübitak Ulakbim TR Index** dizinlerde indekslenmiştir.

Dergi, asitsiz kağıda basılıp ayrıca çevrimiçi olarak yayınlanmaktadır.

Sahip: Türkiye Romatoloji Derneği

Sorumlu Yönetici: R. Haner Direskeneli

Please refer to the journal's webpage **(https://www.raeddergisi.org/)** for "Ethical Policy", "Instructions to Authors".

The editorial and publication process of the Journal of the Journal of Turkish Society for Rheumatology are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. Journal of Turkish Society for Rheumatology is indexed in **EBSCO, Gale, Türk Medline, Embase, J-Gate** and **Tübitak Ulakbim TR Index**.

The journal is printed on an acid-free paper and published online.

Owner: Turkish Society for Rheumatology

Responsible Manager: R. Haner Direskeneli

Ulusal
ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology
www.romatolojidergisi.org

İçindekiler / Contents

Orijinal Araştırmalar / Original Articles

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2024.77486
Ulus Romatol Derg 2025;17(1):1-8

Clinical significance of serum interleukin-32 levels in vasculo-Behçet's disease: A cross-sectional study

Vaskülo-Behçet hastalarında interlökin-32 düzeylerinin klinik önemi: Kesitsel bir çalışma

Serdar Kaymaz[1], Murat Yiğit[1], Aydın Demiray[2], Uğur Karasu[1], Veli Çobankara[1], Seçil Tan[3], Yavuz Dodurga[4]

[1]Pamukkale University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Denizli, Türkiye
[2]Pamukkale University Faculty of Medicine, Department of Genetics, Denizli, Türkiye
[3]Pamukkale University Institute of Medical Sciences, Department of Cancer Molecular Biology, Denizli, Türkiye
[4]Pamukkale University Faculty of Medicine, Department of Medical Biology, Denizli, Türkiye

Abstract

Objective: Interleukin-32 (IL-32) is a key mediator in various pathological processes, such as the activation of vascular smooth muscle cells, the progression of atherosclerosis, and the inflammation of endothelial cells. The objective of this study was to ascertain whether Behçet's disease (BD) patients who exhibit vascular involvement have an elevation in serum levels of IL-32. Furthermore, the study aimed to explore the correlation between disease activity and IL-32 levels and in these individuals.

Methods: This cross-sectional study involved 42 patients diagnosed with BD and 38 healthy control participants, all matched for age and sex. The patients were further categorized into two groups according to whether they had vascular involvement. Comprehensive data were collected, including demographic information, disease activity, disease duration, and ongoing medical treatments. Serum levels of IL-32, IL-6, IL-17, and tumor necrosis factor (TNF)-alpha were quantified using the Enzyme-Linked ImmunoSorbent Assay method. To evaluate disease activity, two tools were utilized: the Behçet's Disease Current Activity form (BDCAF) and the Behçet's Syndrome Activity scale (BSAS).

Results: When comparing clinical features, no significant differences were observed between BD patients who had vascular involvement and those who did not have such involvement. However, vascular involvement significantly influenced the serum levels of IL-32 and TNF-alpha. Patients with BD and vascular involvement exhibited notably higher serum levels of IL-32 and TNF-alpha than healthy controls (p=0.003 and p=0.001, respectively). Furthermore, serum levels of IL-32 were significantly elevated in BD patients with vascular involvement compared to those without (p=0.008). Despite these findings, no

Öz

Amaç: İnterlökin-32'nin (IL-32) vasküler düz kas hücresi aktivasyonunda, aterosklerozda ve endotelyal enflamasyonda rolü vardır. Bu çalışmada damar tutulumu olan Behçet hastalığında (BH) serum IL-32 düzeylerinin artıp artmadığını, ayrıca IL-32 düzeyleri ile hastalık aktivitesi arasındaki ilişkiyi inceledik.

Yöntem: Bu kesitsel çalışmada 42 BD hastası ve 38 sağlıklı birey yaş ve cinsiyete göre eşleştirildi. Behçet hastalarını damar tutulumu olup olmamasına göre iki gruba ayırdık. Hastaların demografik verileri, hastalık süreleri, hastalık aktiviteleri ve tedavileri kaydedildi. Çalışılan örneklerde tümör nekroz faktörü (TNF)-alfa, IL-6, IL-17 ve IL-32'nin serum konsantrasyonlarını belirlemek için Enzime Bağlı İmmünosorbent testi tekniği kullanıldı. Behçet Sendromu Aktivite ölçeği (BSAS) ve Behçet Hastalığı Güncel Aktivite formu (BDCAF) kullanılarak hastalık aktivitesinin değerlendirilmesi yapıldı.

Bulgular: Damar tutulumu olan ve olmayan BH'nin klinik özellikleri karşılaştırıldığında anlamlı bir fark saptanmadı. Vasküler tutulumun varlığı, TNF-alfa ve IL-32'nin serum seviyelerini etkiledi. Damar tutulumu olan BH'de serum IL-32 ve TNF-alfa düzeyleri sağlıklı kontrollere göre anlamlı derecede yüksekti (sırasıyla p=0,003; p=0,001). Damar tutulumu olan Behçet hastalarında, damar tutulumu olmayan BH'ye göre serum IL-32 düzeyleri istatistiksel olarak farklıydı (sırasıyla p=0,008). Serum IL-32 seviyeleri, dönüştürülmüş BDCAF ve BSAS aktivite ölçekleri ile hiçbir ilişki göstermedi.

Sonuç: Çalışma sonuçlarımız Behçet hastalarında serum IL-32 düzeylerinin yükseldiğini ve bunun vasküler tutulumla ilişkili olabileceğini gösterdi.

Anahtar Kelimeler: Behçet hastalığı, damar tutulumu, interlökin-32

Correspondence / İletişim:
Serdar Kaymaz MD, Pamukkale University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Denizli, Türkiye
E-mail: dr.serdarkymaz@gmail.com **ORCID ID:** orcid.org/0000-0002-6958-5436
Received / Geliş Tarihi: 22.03.2024 **Accepted / Kabul Tarihi:** 09.11.2024 **Publication Date / Yayın Tarihi:** 19.03.2025

Cite this article as / Atıf: Kaymaz S, Yiğit M, Demiray A, et al. Clinical significance of serum interleukin-32 levels in vasculo-Behçet's disease: a cross-sectional study. Ulus Romatol Derg. 2025;17(1):1-8

association was identified between disease activity and serum levels of IL-32, as measured by the BDCAF and BSAS scales.

Conclusion: The results of this study suggest that BD patients have elevated levels of serum IL-32 and such increase may be linked to the presence of vascular involvement. This highlights a potential role for IL-32 in the functional changes associated with vascular complications in BD.

Keywords: Behçet's disease, vascular involvement, interleukin-32

Introduction

Behçet's disease (BD) is characterized by a range of systemic manifestations, including persistent oral aphthous ulcers, lesions affecting the gastrointestinal system, arthritis, and complications affecting the vascular and nervous systems.[1] Among these, vascular involvement is a significant characteristic of BD, with epidemiological and clinical studies estimating its incidence to range from 6.3% to 15.3%.[2] Vascular involvement in BD is typically marked by neutrophil-predominant vasculitis, which affects all layers of the blood vessels and the vasa vasorum. In the later stages, this condition is characterized by fibrous thickening and nonspecific inflammatory infiltration.[3] Additionally, BD-associated vasculitis is closely linked to hypercoagulability, driven by excessive thrombin generation, reduced fibrinolytic activity, platelet-neutrophil aggregation, and heightened platelet activity.[4] These pathological processes collectively lead to a greater risk of thrombotic events.

Interleukin-32 (IL-32) is a cytokine involved in multiple immune processes first recognized as being secreted by natural killer (NK) cells upon IL-2 activation.[5] IL-32 is involved in regulating a range of biological activities, including cell death and cytokine production.[6-8] This cytokine is synthesized by different types of cells, including T-cells, monocytes, and NK cells. It is critical in promoting inflammation by triggering the secretion of several pro-inflammatory cytokines and chemokines, contributing to immune and inflammatory responses.[9,10] IL-32 is a key factor in driving the pro-inflammatory signaling in endothelial cells upon different stimuli, encompassing IL-1β, thrombin, lipopolysaccharides, and platelets. Under these inflammatory conditions, IL-32 levels increase significantly. According to experimental studies, silencing serum IL-32 leads to decreased synthesis of pro-inflammatory cytokines such as IL-1α, IL-6, IL-8, and intercellular adhesion molecule-1 (ICAM-1), while simultaneously enhancing the expression of thrombomodulin/CD141, an anti-inflammatory marker.[11] Additionally, IL-32 has been associated with the development of various vascular conditions. It mediates giant cell arteritis, interacts with integrins, and is a key driver of atherosclerosis progression.[12,13] Studies have further revealed that IL-32 contributes to atherosclerosis by promoting angiogenesis in endothelial cells and altering lipid profiles, thereby exacerbating disease progression.[14]

The existing literature highlights the role of cytokines in vascular endothelial injury and thrombosis formation in vasculo-BD. Inflammatory cytokines like IL-18, IL-2, IL-12, IL-6, interferon-gamma, and tumor necrosis factor (TNF)-alpha, primarily released by T helper cells, have been identified as key contributors to pathological changes in vasculo-BD. These changes include endothelial damage, systemic perivasculitis, neutrophil infiltration, and fibrinoid necrosis.[15]

However, the relationship between IL-32 and vasculo-BD has been explored in only one published study to date.[16] Building on this limited knowledge, the current study aims to examine serum levels of IL-32 in BD patients exhibiting vascular involvement. Additionally, this study seeks to establish a potential cut-off value for IL-32 that could assist in diagnosing vascular involvement in these patients.

Materials and Methods

Patients and Controls

This study had a cross-sectional design and was carried out in the Department of Rheumatology of a university hospital between January 2021 and March 2022. Sample size calculations were based on findings from Choi et al.[17]. According to their results, to achieve a statistical power of 95% and a type I error rate of 5%, at least six participants were required in each group. These calculations were based on the expected mean IL-32 levels of 1111.24 ng/mL (standard deviation = 149.59) in one group and 631.1 ng/mL (standard deviation = 120.23) in the other. For the study, 44 patients diagnosed with BD and 38 healthy controls, all matched for sex and age, were enrolled. The participants were recruited from the rheumatology outpatient clinics at the university hospital. Healthy controls were selected from blood donors registered in the hospital's blood bank, as well as university staff and their family members. All patients were diagnosed with BD referring to the most recent International Criteria for BD.[18] Following a thorough medical history assessment,

BD patients underwent a physical examination. Vasculo-BD was diagnosed in BD patients when lesions were identified in the large or small veins, aorta, or small arteries through both clinical evaluation and radiological imaging. The patients were further categorized into two groups according to whether they had involvement of vascular structures. The patterns of vascular involvement in vasculo-BD patients have been well-established in the literature.[19] All participants underwent a series of laboratory tests, including assessments of liver function, fasting plasma glucose, sedimentation rate, renal function, C-reactive protein, and complete blood count, all of which were within the normal range. The study excluded individuals with a history of antiphospholipid syndrome, high blood pressure, systemic vasculitis, blood clotting disorders, or hematological diseases.

The approval for the study was received from the local ethics committee (approval number: E-60116787-020-290434, date: 25.01.2022 - Pamukkale University Non-Interventional Clinical Research Ethics Committee). Prior to participation, all participants were informed about the study and provided written informed consent. The study adhered to the ethical guidelines set forth in the Declaration of Helsinki, ensuring the protection and rights of all BD patients participating.

Disease activity in the study was evaluated using two assessment tools: the Behçet's Syndrome Activity scale (BSAS) and the Behçet's Disease Current Activity form (BDCAF).[20,21] The BDCAF scale measures various clinical features, including oral aphthae, genital ulcers, erythema nodosum, skin pustules, diarrhea, ocular involvement, and major vessel involvement. Scores on this scale span from 0 to 12, with higher values reflecting greater disease activity. BSAS, consisting of 10 questions, quantifies the level of discomfort caused by symptoms such as mouth ulcers, genital ulcers, cutaneous lesions, and gastrointestinal, vascular, and eye involvement over the past month. Additionally, it reflects overall disease activity and the presence of current skin lesions.

Determination of Serum Cytokine Concentrations

Blood samples (3-5 milliliters) were collected from both healthy controls and patients and placed in clot activator tubes for serum separation. The samples were incubated at room temperature for 30 minutes, followed by centrifugation at 4000 rpm for 10 minutes to separate the serum. The serum samples were then stored at -80 °C for further analyses. Serum levels of TNF-alpha (Cat. no: E-EL-H0109), IL-6 (Cat. no: E-EL-H0102), IL-17 (Cat. no: E-EL-H0105), and IL-32 (Cat. no: E-EL-H0216) were determined using the Enzyme-Linked ImmunoSorbent Assay (ELISA) technique (Elabscience, USA). For cytokine quantification, the wells of the ELISA plate were prepared by adding 100 µL of standard working solution, diluted at various concentrations specified in the kit, to the first two columns of the plate. Each antibody was added in duplicate at the same concentration in both wells. After an incubation period of 90 minutes at 37 °C, 100 µL of every sample was added to the remaining wells. Following this, a biotin-labeled detection antibody solution was added to each well (100 µL per well), and the plate was left at 37 °C for 30 minutes. Following the incubation, the solution was aspirated, and the plate was washed three times with wash buffer. Next, 100 µL of working solution of horseradish peroxidase enzyme conjugate was added to each well, and the plate was incubated for an additional 30 minutes at 37 °C. The solution was aspirated again, and the plate was washed five times. Subsequently, nine microliters of substrate reagent were added to each well, and the plate was left 37 °C for 20 minutes in a dark environment. Fifty microliters of stop solution were added to each well to terminate the reaction, and the optical density of the wells was measured at 450 nm using a microplate reader. All experiments were performed in duplicate to ensure accuracy.

Statistical Analysis

Data analysis was completed with the aid of SPSS software, version 22.0, for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were employed to depict the demographic profile of the participants. The Kolmogorov-Smirnov test was employed to assess the normality of data. Non-parametric tests were applied for non-normally distributed variables. Spearman's rank correlation was performed to evaluate the relationships between non-parametric variables. Categorical variables were analyzed at baseline using the chi-square test. For intergroup comparisons, Kruskal-Wallis variance analysis was used, followed by post hoc Bonferroni correction with the Mann-Whitney U test for pairwise comparisons. In post hoc analyses, a p-value of <0.0167 was considered statistically significant, while for all other analyses, a p-value of <0.05 was set as the threshold for statistical significance.

Results

Two patients were excluded due to meeting the exclusion criteria. One of the excluded patients had a hematologic disorder, and the other had thrombophilia. The remaining 42 patients were then divided into two groups: group 1 consisted of 21 BD patients with vascular involvement, and group 2 included 21 BD patients without vascular

involvement.

Among the patients with vascular involvement, the following conditions were observed: nine (43%) had deep vein thrombosis, four (20%) had pulmonary embolism, three (15%) had thrombus formation in the jugular vein, three (15%) had thrombosis of the intracranial venous sinuses, two (10%) had occluded retinal vein, two (8%) had thrombophlebitis, one (5%) had portal vein thrombosis (Table 1).

The mean age of group 1 (patients with vascular involvement) was 36.8±5.0 years, with 8 females, while the mean age of group 2 (patients without vascular involvement) was 39.1±9.0 years, with 12 females. The mean disease duration was 4.7±8.7 years in group 1 and 4.7±5.8 years in group 2. The two groups showed no significant differences in demographic or clinical characteristics (Table 1).

Significant differences were observed in the serum levels of IL-32, TNF-alpha, and IL-6 between the three groups (p=0.012, p=0.021, p=0.037, respectively) (Figure 1, Table 2). BD patients exhibiting vascular complications had significantly lower serum IL-32 and TNF-alpha levels than healthy participants (p=0.003, p=0.001, respectively). Additionally, serum IL-32 levels were significantly higher in the patients with vascular manifestations compared to those without vascular complications (p=0.008) (Table 1).

However, the presence of vascular involvement did not significantly influence the levels of IL-17 (p>0.05) (Table 2, Figure 1). Furthermore, serum levels of IL-32 did not correlate with overall disease activity (Table 3).

Discussion

The findings of this study revealed significantly elevated serum concentrations of IL-32 in patients with vasculo-BD compared to BD patients without vascular complications and healthy controls. This suggests that IL-32 might be implicated in the vascular manifestations of this disease. However, it is noteworthy that the elevated IL-32 levels did not correlate with disease activity, indicating that IL-32 may be more closely associated with vascular involvement rather than overall disease severity. To the best of our knowledge, this study is one of the first to explore the relationship between serum IL-32 levels and vascular involvement in BD patients. While previous research has linked various cytokines with vascular damage and thrombosis in BD, the function of IL-32 in this context has not been thoroughly studied.

Few studies exploring the connection between IL-32 and vascular pathologies exist in the literature.

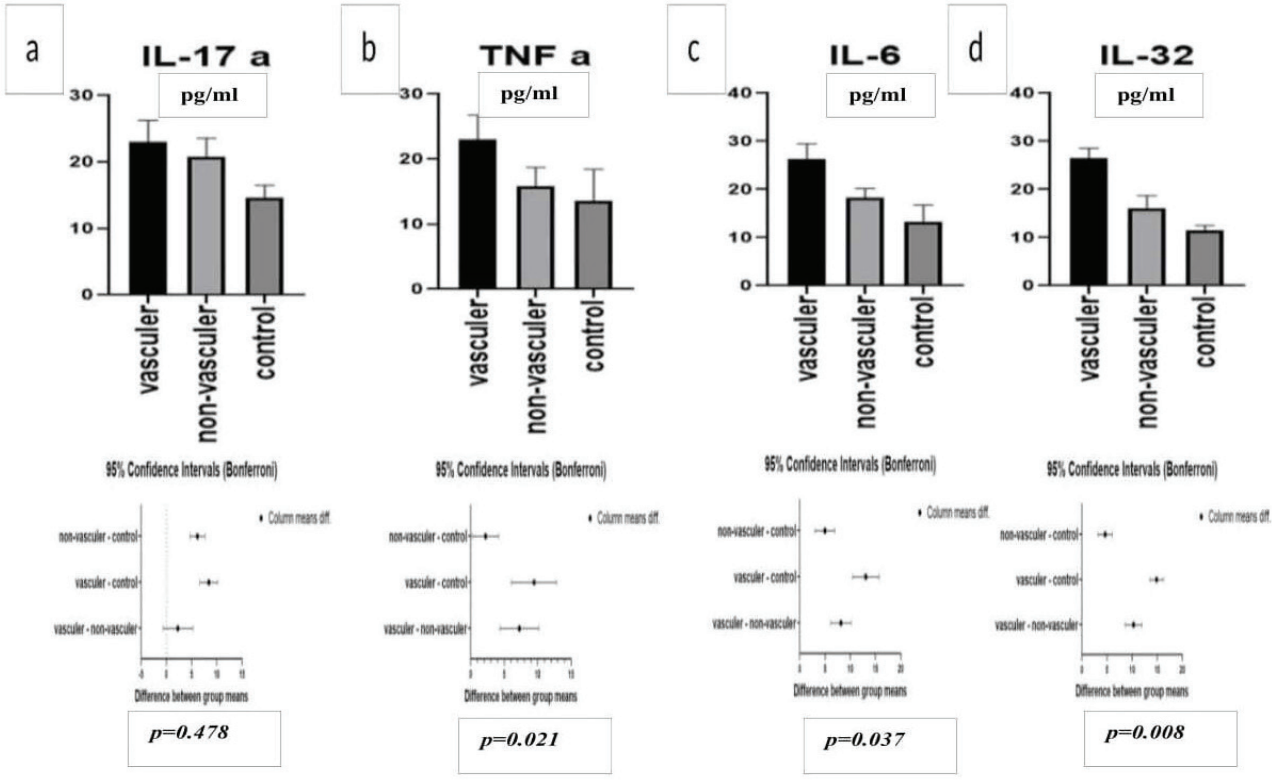

Figure 1. Serum levels of IL-32 in the study groups
IL: Interleukin, TNF: Tumor necrosis factor

Table 1. Demographic variables of participants and comparison of clinical characteristics of the groups of BD patients and medications

Mean ± SD or n (%)	Group 1 (n=21) BD with vascular involvement	Group 2 (n=21) BD without vascular involvement	Group 3 (n=38) healthy controls	p-value
Gender				
-Male	13 (62)	9 (43)	17 (45)	0.369
-Female	8 (38)	12 (57)	21 (55)	
Age (year)	36.8±5	39.1±9	37.8±6.5	0.518
Disease duration (year)	8.7±4.7	4.7±5.8	-	0.827
Laboratory findings				
-CRP	0.33±0.48	0.66±0.79		0.109
-Sedimentation	20±8.4	24±8.2	-	0.120
-HLA-51 positivity	14 (66)	16 (76)	-	0.5
Medical treatment				
-Steroid	4 (19)	5 (24)		0.799
-Colchicine	10 (48)	12 (59)		
-Azathioprine	3 (14)	4 (19)		
-Cyclosporine	5 (24)	2 (9.5)		
-Methotrexate	1 (5)	4 (19)		
-Interferon	1 (5)	1 (5)		
-Biologic agents	8 (38)	6 (28.5)		
-Anticoagulant	10 (50)	-		
Clinical lesions				
-Oral lesions	18 (86)	15 (71)	-	0.970
-Ocular	4 (20)	6 (30)	-	
-Articular	2 (10)	2 (10)	-	
-Pulmonary	1 (5)	2 (10)	-	
-Neurological	1 (5)	1 (5)		
Disease activity				
-BDCAF	0.4±0.9	0.19±0.5	-	0.224
-BSAS	1.9±1	1.9±0.7	-	0.99

-Kruskal-Wallis and Mann-Whitney U tests were used.

**: p<0.05 statistically significant, **: p<0.0167 statistically significant in the post hoc Bonferroni correction analyses, BD: Behçet's disease, BDCAF: Behcet's Disease Current Activity form, BSAS: Behçet's Syndrome Activity scale, CRP: C-reactive protein: HLA: Human leukocyte antigen, SD: Standard deviation*

Table 2. Comparison of serum levels of cytokines

Mean ± SD	Group 1 (n=21) BD with vascular involvement	Group 2 (n=21) BD without vascular involvement	Group 3 (n=38) healthy controls	p-value	Mann-Whitney U test with Bonferroni correction
TNF-alpha, pg/mL	16.0±5.2	15.3±7.6	11.7±2.3	**0.021***	Group 3<Group 2, p=0.012** Group 2=Group 1, p=0.402 Group 3<Group 1, p=0.001**
-IL-6, pg/mL	8.6±1.5	2.1±3.3	1.4±1.1	**0.037***	Group 3=Group 2, p=0.384 Group 2=Group 1, p=0.084 Group 3<Group 1, p=0.008
-1L-17, pg/mL	39.2±9.0	21.6±1.8	20.8±2.1	0.478	Group 1=Group 2, p=0.210 Group 2=Group 3, p=0.693 Group 1=Group 3, p=0.380
-1L-32, pg/mL	99.1±2.7	91.4±2.0	1.2±6.2	**0.012***	Group 1>Group 2, p=0.008** Group 2>Group 3, p=0.0160 Group 1>Group 3, p=0.003**

-Kruskal-Wallis and Mann-Whitney U tests were used.

**: p<0.05 statistically significant, **: p<0.0167 statistically significant in the post hoc Bonferroni correction analyses, BD: Behçet's disease, IL: Interleukin, SD: Standard deviation, TNF: Tumor necrosis factor*

Table 3. Correlation of serum IL-32 levels with disease activity scales and other cytokines in BD patients with vascular involvements

	IL-32	
	r	p
TNF-alpha	-0.694	0.103
IL-6	-0.112	0.481
IL-17	-0.150	0.345
BSAS	0.120	0.243
BDCF	0.075	0.637

**p<0.05, statistically significant, BD: Behçet's disease, BDCF: Behçet's Disease Current Activity form, BSAS: Behçet's Syndrome Activity scale, IL: Interleukin, TNF: Tumor necrosis factor*

Son et al.[22] demonstrated that IL-32 inhibited endothelial inflammation, atherosclerosis, and the expansion of vascular smooth muscle cells, suggesting its potential protective role in vascular health. Similarly, Kobayashi et al.[23] found that IL-32 is critical in leukocyte adhesion and endothelial inflammation. It achieves this through the enhancement of ICAM-1, vascular cell adhesion molecule, and E-selectin expression on endothelial cells, all of which are important markers of inflammation and vascular injury. These findings support the hypothesis that IL-32 might be involved in the development of vascular diseases, including vasculo-BD. The increase in inflammation and leukocyte recruitment is driven by IL-32-mediated upregulation of ICAM-1 on endothelial cells, highlighting its significance in the pathogenesis of vascular diseases such as abdominal aortic aneurysms.[24] Additionally, IL-32 has been demonstrated to regulate the functions of endothelial cells in various circulatory systems, including the aortic, pulmonary, and coronary circulations. This regulation occurs through the modulation of IL-1β and other pro-inflammatory cytokines, particularly influencing the expression of ICAM.[11]

In the current study, the significantly elevated serum concentration of IL-32 in BD patients with vascular involvement, compared to those without, may suggest that IL-32 plays a relatively peripheral role in the development of vascular pathologies in BD. However, to validate this observation and better understand the underlying mechanisms, further studies are necessary.

Despite numerous efforts over several decades, no cytokine or biomarker has demonstrated sufficient sensitivity and specificity to reliably predict vascular involvement in patients with BD. However, certain markers have shown promise. Ibrahim et al.[25] suggested that monocyte chemoattractant protein-1 and vascular endothelial growth factor (VEGF) could be valuable biomarkers for thrombosis prediction in patients presenting with BD. The same study highlighted that VEGF contributes to endothelial and tissue damage by increasing the release of free radicals through nitric oxide production, a condition that has been linked to thrombosis in BD.

In addition, other studies have identified alterations in specific biomarkers associated with vascular involvement in BD. For instance, one study reported that serum angiopoietin-1 concentrations were significantly lower in patients with BD exhibiting vascular manifestations compared to those without vascular complications, suggesting its potential role in vascular pathology.[26] These findings reinforce the need for continued exploration of biomarkers to better predict and understand vascular involvement in BD. It is well established that angiopoietin-1 indirectly influences angiogenesis through the regulation of VEGF.[27] Several cytokines like TNF-alpha, IL-32, IL-6, and IL-1 are involved in the regulation of VEGF.[25,28] This study showed significantly different IL-32 levels between BD patients with and without vascular complications. This finding suggests that IL-32 could serve as a promising biomarker for diagnosing or predicting vascular involvement in BD, offering potential clinical value.

While these results are promising and may help guide clinicians in practice, our understanding of the exact mechanisms linking IL-32 to vascular involvement remains incomplete. Further research is needed to clarify the potential of IL-32 and its interactions with other cytokines and pathways involved in vascular pathology.

The link between IL-32 and various medical treatments, inflammatory cytokines, and disease activity has been explored in several studies. For instance, it has been demonstrated that IL-32 released from pulmonary cells infected with influenza A can be inhibited by aspirin or selective COX-2 inhibitors.[29] In contrast, Kwon et al.[30] found that corticosteroid inhalers did not affect IL-32 concentrations in asthma patients. Bengts et al.[24] also reported that statins did have an effect on IL-32 concentrations.

While studies examining the relationship between TNF-alpha inhibitors and serum IL-32 levels are limited, some important findings have been reported. Specifically, a critical relationship exists between TNF-alpha, a cytokine central to the onset and progression of rheumatoid arthritis (RA), and IL-32 release.[31] Hong et al.[32] reported that the suppression of serum IL-32 led to decreased TNF-alpha levels in human macrophages, providing further evidence of the interaction between these two cytokines. These findings highlight the complex interplay between IL-32 and various inflammatory mediators, suggesting potential therapeutic implications for modulating IL-32 in inflammatory diseases. Fadaei et al.[33] reported a direct relationship between IL-32, TNF-alpha, and IL-6 in patients with Diabetes Mellitus. Similarly, another study showed that IL-32 enhances IL-

17 expression in $CD4^+$ T-cells.[34] Interestingly, the same publication indicated that these cytokines serve as predictors of coronary artery disease.[35] Based on these findings, one could hypothesize that IL-32 may play a significant role in the pathogenesis of cardiovascular diseases in individuals suffering from persistent inflammatory disorders.

However, studies specifically examining the connection between disease activity and IL-32 levels in BD patients are limited. Ha et al.[16] found only a weak relationship between BDCAF and IL-32 levels. This suggests that while IL-32 may be involved in the inflammatory processes of BD, its direct role in disease activity remains uncertain and warrants further investigation. Moreover, a relationship between disease activity and IL-32 has been observed in two published studies on RA and neuromyelitis optica.[36,37] However, the results of our study did not show any correlation between IL-32 levels and disease activity scales in BD patients. The lack of correlation in our study may be attributed to several factors, such as the small number of participants, the potential influence of medications on serum cytokine levels, and the cross-sectional design of the study. To better understand the potential impact of disease activity and medication on IL-32 levels, Future studies with expanded sample sizes are needed to corroborate these results.

There are various scales available in the literature to assess BD activation, such as BDCAF and BSAS.[38] Our study revealed no correlation between serum IL-32 concentrations and BSAS or BDCAF. This lack of correlation may be attributed to the fact that these scales evaluate a broad range of organ involvement, rather than specifically focusing on vascular involvement. Buzatu et al.[39] highlighted that the Birmingham Vasculitis Activity score, which is specifically designed to evaluate vascular involvement in BD, is more sensitive than BDCAF. Therefore, the absence of a vascular-specific scale in our study could be considered a limitation, and future studies should consider using a more targeted vascular activity scale to assess the link between IL-32 and vascular involvement in BD.

Study Limitations

Our study has three potential limitations. First, we did not exclude common conditions such as smoking and hyperlipidemia, which could also influence IL-32 levels. Second, the study's cross-sectional nature limited our capacity to determine causal relationships. While it demonstrated a relationship between vascular involvement and serum concentrations of IL-32, it could not determine if elevated IL-32 levels directly cause vascular involvement in BD patients. Third, we were unable to assess a specific cut-off value for IL-32 to diagnose vascular involvement due to the absence of an appropriate diseased control group. These limitations highlight the need for further studies with more comprehensive designs to better understand the role of IL-32 in BD and its potential as a diagnostic biomarker.

Conclusion

In conclusion, the present study indicated that serum IL-32 levels were higher in BD patients with vascular involvement. Based on these findings, IL-32 might have a subtle role in the immunopathogenesis of vascular involvement in BD. However, IL-32 was not found to be associated with disease activity. Further studies are needed to confirm these results and better understand the underlying mechanisms of IL-32 in BD, particularly in relation to vascular involvement.

Ethics

Ethics Committee Approval: The approval for the study was received from the local ethics committee (approval number: E-60116787-020-290434, date: 25.01.2022 - Pamukkale University Non-Interventional Clinical Research Ethics Committee).

Informed Consent: Prior to participation, all participants were informed about the study and provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D., Concept: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D., Design: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D., Data Collection and Processing: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D., Analysis or Interpretation: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D., Literature Search: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D., Writing: S.K., M.Y., A.D., U.K., V.Ç., S.T., Y.D.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Hatemi G, Yazici Y, Yazici H. Behçet's syndrome. Rheum Dis Clin North Am. 2013;39:245-61.
2. Ishigatsubo Y. Statement draft for clinical guidelines of vasculo-Behçet's disease. [Internet]. 2014 [cited 2018 Jun. 6] Available from: http://www.nanbyou.or.jp/upload_files/Bechet2014_4.pdf (in Japanese).

3. Seyahi E, Yurdakul S. Behçet's syndrome and thrombosis. Mediterr J Hematol Infect Dis. 2011;3:e2011026.
4. Ferrão C, Almeida I, Marinho A, Vasconcelos C, Correia JA. A nossa regra de ouro na doença de Behçet: tratar a manifestação clínica. Arq Med. 2015;29:75-9.
5. Dahl CA, Schall RP, He HL, Cairns JS. Identification of a novel gene expressed in activated natural killer cells and T cells. J Immunol. 1992;148:597-603.
6. Netea MG, Lewis EC, Azam T, et al. Interleukin-32 induces the differentiation of monocytes into macrophage-like cells. Proc Natl Acad Sci U S A. 2008;105:3515-20.
7. Kang JW, Choi SC, Cho MC, et al. A proinflammatory cytokine interleukin-32beta promotes the production of an anti-inflammatory cytokine interleukin-10. Immunology. 2009;128(1 Suppl):e532-40.
8. Khawar B, Abbasi MH, Sheikh N. A panoramic spectrum of complex interplay between the immune system and IL-32 during pathogenesis of various systemic infections and inflammation. Eur J Med Res 2015;20:7.
9. Kim SH, Han SY, Azam T, Yoon DY, Dinarello CA. Interleukin-32: a cytokine and inducer of TNFalpha. Immunity. 2005;22:131-42.
10. Netea MG, Azam T, Ferwerda G, et al. IL-32 synergizes with nucleotide oligomerization domain (NOD) 1 and NOD2 ligands for IL-1beta and IL-6 production through a caspase 1-dependent mechanism. Proc Natl Acad Sci U S A. 2005;102:16309-14.
11. Nold-Petry CA, Nold MF, Zepp JA, Kim SH, Voelkel NF, Dinarello CA. IL-32-dependent effects of IL-1beta on endothelial cell functions. Proc Natl Acad Sci U S A. 2009;106:3883-8.
12. Heinhuis B, Koenders MI, van den Berg WB, Netea MG, Dinarello CA, Joosten LA. Interleukin 32 (IL-32) contains a typical α-helix bundle structure that resembles focal adhesion targeting region of focal adhesion kinase-1. J Biol Chem. 2012;287:5733-43.
13. Ciccia F, Alessandro R, Rizzo A, et al. Expression of interleukin-32 in the inflamed arteries of patients with giant cell arteritis. Arthritis Rheum. 2011;63:2097-104.
14. Yang Z, Shi L, Xue Y, et al. Interleukin-32 increases in coronary arteries and plasma from patients with coronary artery disease. Clin Chim Acta. 2019;497:104-9.
15. de Vargas RM, da Cruz MLN, Giarllarielli MPH, et al. Vascular involvement in Behçet's disease: the immunopathological process. J Vasc Bras. 2021;20:e20200170.
16. Ha YJ, Park JS, Kang MI, Lee SK, Park YB, Lee SW. Increased serum interleukin-32 levels in patients with Behçet's disease. Int J Rheum Dis. 2018;21:2167-74.
17. Choi YS, Kim S, Oh YS, Cho S, Hoon Kim S. Elevated serum interleukin-32 levels in patients with endometriosis: a cross-sectional study. Am J Reprod Immunol. 2019;82:e13149.
18. International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28:338-47.
19. Fei Y, Li X, Lin S, et al. Major vascular involvement in Behçet's disease: a retrospective study of 796 patients. Clin Rheumatol. 2013;32:845-52.
20. Hatemi G, Merkel PA, Hamuryudan V, et al. Outcome measures used in clinical trials for Behçet syndrome: a systematic review. J Rheumatol. 2014;41:599-612.
21. Lawton G, Bhakta BB, Chamberlain MA, Tennant A. The Behcet's disease activity index. Rheumatology (Oxford). 2004;43:73-8.
22. Son DJ, Jung YY, Seo YS, et al. Interleukin-32α inhibits endothelial inflammation, vascular smooth muscle cell activation, and atherosclerosis by upregulating timp3 and reck through suppressing microRNA-205 biogenesis. Theranostics. 2017;7:2186-203.
23. Kobayashi H, Yazlovitskaya EM, Lin PC. Interleukin-32 positively regulates radiation-induced vascular inflammation. Int J Radiat Oncol Biol Phys. 2009;74:1573-9.
24. Bengts S, Shamoun L, Kunath A, et al. Altered IL-32 signaling in abdominal aortic aneurysm. J Vasc Res. 2020;57:236-44.
25. Ibrahim SE, Elshishtawy HF, HelmySamy A, Galal ZA. Role of vascular endothelial growth factor and monocyte chemoattractant protein-1 in Behçet's disease. Indian J Rheumatol. 2011;6:168-72.
26. Bassyouni IH, Sharaf M, Wali IE, Mansour HM. Clinical significance of angiopoietin-1 in Behcet's disease patients with vascular involvement. Heart Vessels. 2016;31:918-24.
27. Kanazawa H. VEGF, angiopoietin-1 and -2 in bronchial asthma: new molecular targets in airway angiogenesis and microvascular remodeling. Recent Pat Inflamm Allergy Drug Discov 2007;1:1-8.
28. Zhao WB, Wang QL, Xu YT, Xu SF, Qiu Y, Zhu F. Overexpression of interleukin-32α promotes invasion by modulating VEGF in hepatocellular carcinoma. Oncol Rep. 2018;39:1155-62.
29. Li W, Liu Y, Mukhtar MM, et al. Activation of interleukin-32 pro-inflammatory pathway in response to influenza A virus infection. PloS One. 2008;3:e1985.
30. Kwon JW, Chang HS, Heo JS, et al. Characteristics of asthmatics with detectable IL-32γ in induced sputum. Respir Med. 2017;129:85-90.
31. Damen MSMA, Schraa K, Tweehuysen L, et al. Genetic variant in IL-32 is associated with the ex vivo cytokine production of anti-TNF treated PBMCs from rheumatoid arthritis patients. Sci Rep. 2018;8:14050.
32. Hong J, Bae S, Kang Y, et al. Suppressing IL-32 in monocytes impairs the induction of the proinflammatory cytokines TNFalpha and IL-1beta. Cytokine. 2010;49:171-6.
33. Fadaei R, Bagheri N, Heidarian E, et al. Serum levels of IL-32 in patients with type 2 diabetes mellitus and its relationship with TNF-α and IL-6. Cytokine. 2020;125:154832.
34. Moon YM, Yoon BY, Her YM, et al. IL-32 and IL-17 interact and have the potential to aggravate osteoclastogenesis in rheumatoid arthritis. Arthritis Res Ther. 2012;14:R246.
35. Mohammad-Rezaei M, Ahmadi R, Rafiei A, et al. Serum levels of IL-32 in patients with coronary artery disease and its relationship with the serum levels of IL-6 and TNF-α. Mol Biol Rep. 2021;48:4263-71.
36. Gui M, Zhang H, Zhong K, Li Y, Sun J, Wang L. Clinical significance of interleukin-32 expression in patients with rheumatoid arthritis. Asian Pac J Allergy Immunol. 2013;31:73-8.
37. Wang H, Wang K, Wang C, Xu F, Qiu W, Hu X. Increased plasma interleukin-32 expression in patients with neuromyelitis optica. J Clin Immunol. 2013;33:666-70.
38. Kaymaz S, Yilmaz H, Ufuk F, et al. Ultrasonographic measurement of the vascular wall thickness and intima-media thickness in patients with Behçet's disease with symptoms or signs of vascular involvement: a cross-sectional study. Arch Rheumatol. 2021;14;36:258-66.
39. Buzatu C, Duffield S, Chadwick L, Moots RJ. THU0554 the clinical utility of two vasculitis activity scores (BVAS and BDCAF) in Behçet's Syndrome: a prospective cohort study. Ann Rheum Dis. 2019;78:567.

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.52533
Ulus Romatol Derg 2025;17(1):9-14

Evaluation of *Candida albicans* prevalence in mouth and *Stafilococcus aureus* prevalence in eye and nose in patients with Sjögren's syndrome

Sjögren sendromu hastalarında göz ile burunda *Stafilococcus aureus* ve ağızda *Candida albicans* sıklığının araştırılması

İrfan Buğday[1], Tayfun Akalın[2], Selma Karagöz[3]

[1]*Erzurum City Hospital, Clinic of Internal Medicine, Unit of Medical Oncology, Erzurum, Türkiye*
[2]*Kayseri City Hospital, Clinic of Internal Medicine, Unit of Rheumatology, Kayseri, Türkiye*
[3]*Kayseri State Hospital, Clinic of Microbiology, Kayseri, Türkiye*

Abstract

Objective: Sjögren's syndrome (SS) is a chronic, progressive and autoimmune disease characterized by the lymphocytic infiltration of the exocrine glands leading to dry eyes and dry mouth. The present study investigates the prevalence of *Staphylococcus aureus (S. aureus)* in the ophthalmic and nasal mucosa and *Candida albicans* (*C. albicans*) in the oral mucosa of patients with primary SS. Previous studies in the literature have included only a limited number of cases, while the present study includes 100 patients with primary SS patients, contributing to the achievement of more reliable results. This study aimed to show that the frequency of *S. aureus* and *C. albicans* is high in patients with SS.

Methods: This study included patients diagnosed with primary SS based on the American-European Consensus Group criteria among those who presented to the outpatient Kayseri Training and Research Hospital, Clinic of Rheumatology between February 2016 and June 2016. Healthy volunteers without chronic diseases and without regular drug use among those who presented to the outpatient Kayseri Training and Research Hospital, Clinic of Internal Medicine were included in the study as a control group. Samples were collected from the nose (medial nasal mucosa of both nostrils), the mouth (buccal mucosa at the molar tooth level), and the conjunctival sac (with four swab rotations).

Results: *C. albicans* growths were identified in 37% (n=37) and 17% (n=17) of the patient and control groups, respectively, based on oral culture evaluations. The difference between the two groups was statistically significant (p=0.001). *S. aureus* growth was identified in 12% (n=12) and 1% (n=1) of the patient and control groups, respectively, based on nasal culture evaluations, and the difference between the two groups was statistically significant (p=0.002).

Öz

Amaç: Sjögren sendromu (SS) ağız ve göz kuruluğuna sebep olan, özellikle ekzokrin bezlerin lenfositik infiltrasyonu ile karakterize kronik, ilerleyici, otoimmün bir hastalıktır. SS'de ortaya çıkan ağız ve göz kuruluğuna bağlı olarak flora etkilenmekte ve bakterilerin kolonizasyonu artmaktadır. Çalışmamızda primer SS hastalarının göz ve burun kültürlerinde *Staphylococcus aureus (S. aureus)* ve ağız kültürlerinde *Candida albicans* (*C. albicans*) sıklığının sağlıklı gönüllülere göre fazla olduğunun gösterilmesi amaçlanmıştır.

Yöntem: Çalışmaya Şubat 2016-Haziran 2016 tarihleri arasında Kayseri Eğitim ve Araştırma Hastanesi, Romatoloji Polikliniği'ne başvuran Amerika-Avrupa Konsensus Grubu kriterlerine göre primer SS tanısı almış hastalar dahil edilmiştir. Kontrol grubu olarak ise Kayseri Eğitim ve Araştırma Hastanesi, İç Hastalıkları Polikliniği'ne başvuran sağlıklı gönüllüler alınmıştır. Örnekler burundan (her iki burun deliğinin medyal burun mukozası), ağızdan (molara yakın yanak mukozası) ve konjonktival kese (dört pamuklu çubuk dönüşü ile) alınmıştır.

Bulgular: Ağız kültürlerinin değerlendirilmesinde; hasta grubunun %37'sinde (n=37) ve kontrol grubunun %17'sinde (n=17) *C. albicans* üremesi tespit edildi. İki grup arasındaki farkın istatistiksel olarak anlamlı olduğu görüldü (p=0,001). Burun kültürlerinin değerlendirilmesinde hasta grubunun %12'sinde (n=12) ve kontol grubunun %1'inde (n=1) *S. aureus* üremesi saptanmıştır. İki grup arasındaki farkın istatistiksel olarak anlamlı olduğu görüldü (p=0,002).

Sonuç: Burunda *S. aureus* ve ağızda *C. albicans* görülme sıklığının SS'li hastalarda kontrol grubuna göre artmış olduğu tespit edildi. Elde edilen bu sonuçlar SS'de meydana gelen mukozal kuruluğun normal floranın değişmesine sebep olduğunu göstermektedir. Ancak normal floradaki bu değişikliğin hastalık oluşturup oluşturmadığı net olarak ortaya konamamıştır.

Correspondence / İletişim:
İrfan Buğday MD, Erzurum City Hospital, Clinic of Internal Medicine, Unit of Medical Oncology, Erzurum, Türkiye
E-mail: drirfanbugday@gmail.com **ORCID ID:** orcid.org/0000-0002-6875-4656
Received / Geliş Tarihi: 02.05.2024 **Accepted / Kabul Tarihi:** 07.02.2025 **Publication Date / Yayın Tarihi:** 19.03.2025

Cite this article as / Atıf: Buğday İ, Akalın T, Karagöz S. Evaluation of *Candida albicans* prevalence in mouth and *Stafilococcus aureus* prevalence in eye and nose in patients with Sjögren's syndrome. Ulus Romatol Derg. 2025;17(1):9-14

Conclusion: Infections are among the main causes of morbidity and mortality in rheumatological diseases. The most common reason for hospital visits has been reported as infections associated with rheumatoid arthritis, systemic lupus erythematosus, and other rheumatological diseases. The involvement of SS in the exocrine glands leads to dysfunction and decreased secretions, resulting in dry mouth, dry eyes, and dry skin. As a result of these changes in SS, the colonization of both normal flora and unassociated pathogenic bacteria increases, contributing to a higher frequency of infections. In our study the prevalence of *S. aureus* in the nasal mucosa and *C. albicans* in the oral mucosa of primary SS patients was statistically significantly higher than in healthy controls.

Keywords: Primary Sjögren's syndrome, nasal *Staphylococcus aureus*, oral *Candida albicans*

Anahtar Kelimeler: Primer Sjögren sendromu, nazal *Stafilococcus aureus*, oral *Candida albicans*

Introduction

Sjögren's syndrome (SS) is a chronic, progressive, and autoimmune disease that characterized by the lymphocytic infiltration of the exocrine glands, leading to dry eyes and dry mouth.[1] The prevalence of SS is nine times greater in females than in males and occurs especially in the 4th and 5th decades, although it can be seen in all age groups.[2] The incidence of SS increases with age, being seven times more common in those aged 70 years or above than in those aged 40 years or above.[3] The most prominent involvement in SS is in the eye and oral mucosa, although nasal, pharyngeal, vulvar, gastric, sebaceous, sweat glands, and apocrine gland exocrine gland involvements may also be affected. Symptoms such as dry skin, dysphagia, and dyspareunia can be seen secondary to these involvements.[2] Among the extra-glandular involvements, the respiratory system may be affected on a spectrum ranging from dry cough to interstitial lung disease; musculoskeletal system involvements can vary from fatigue to myositis; and hematological system involvements can range from mild anemia to lymphoma. Additionaly, involvements of the kidneys, vessels, skin, and nerves can also be seen.[4] Symptoms depend on the affected organ and the severity of the involvement.

SS is referred to as primary when seen alone and secondary when it accompanies other connective tissue diseases, including systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, inflammatory muscle disease, autoimmune thyroiditis, and most commonly, rheumatoid arthritis.[5]

Atrophy and decreased secretion occur as a result of chronic inflammation in the exocrine glands. Protection from microorganisms diminishes as a result of the reduced exocrine gland secretions, leading to a predisposition to infections. A decreased prevalence of Candida, *Lactobacillus*, and *Streptococcus* mutans has been reported in the oral mucosa of patients with SS in previous studies.[6] In another study, the prevalence of oral candidiasis was reported as 74% and 23% were reported in patients with SS and healthy controls, respectively.[7]

The present study investigates the prevalence of *Staphylococcus aureus* (*S. aureus*) in the ophthalmic and nasal mucosa and *Candida albicans* (*C. albicans*) in the oral mucosa of patients with primary SS. Previous studies in the literature have included only a limited number of cases, while the present study includes 100 primary SS patients, contributing to more reliable results.

The prevalence of *S. aureus* is affected by factors such as age, antibiotic use, and hospitalization, although there are also variations based on the population being studied. The prevalence of *S. aureus* in the general population has been reported as 10-50%, and as high as 50-70% in healthcare professionals. Although S. aureus has been identified in the nasal mucosa of 34% of SS patients, there is a lack of studies reporting its prevalence in conjunctival cultures of SS patients to date.[8,9]

Materials and Methods

This cross-sectional study was approved by the Ethics Board of the University of Erciyes University Faculty of Medicine, and was carried out in compliance with the rules of the World Medical Association Declaration of Helsinki (approval number: 2015/581, date: 25.12.2015). Patients diagnosed with primary SS based on the American-European Consensus Group (AECG) criteria who presented the outpatient Kayseri Training and Research Hospital, Clinic of Rheumatology between February 2016 and June 2016 were included in the study.[10] Healthy volunteers without chronic diseases and without regular drug use who presented to the outpatient Kayseri Training and Research Hospital, Clinic of Internal Medicine were included as the control group.

Obtaining the Cultures

Samples were taken from the patients from the nose (medial nasal mucosa of both nostrils), the mouth (buccal

mucosa at the molar tooth level), and the conjunctival sac (with four swab rotations).

The conjunctival and nasal swab samples were harvested in a chromogenic culture medium, and the growing colonies were transported to the culture medium in accordance with a 0.5 McFarland standard with the addition of a cefoxitin disk. The samples were then identified as methicillin-resistant *staphylococcus aureus* (MRSA) and methicillin-sensitive *staphylococcus aureus* (MSSA), depending on the cefoxitin disk sensitivity after overnight incubation. The growing staphylococci were thus determined as MRSA or MSSA and recorded.

The growing *C. albicans* colonies were recorded after incubating the samples obtained from the oral mucosa in a chromogenic culture medium.

Statistical Analysis

IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.) was used for the statistical analysis of the obtained data.The normality of the distribution of the cases was evaluated using a Shapiro-Wilk test and histograms. Continuous variables were expressed as mean ± standard deviation or as median and 25^{th}-75^{th} percentiles, while categorical variables were expressed as the number of cases and percentages (%). Categorical variables were analyzed using a Pearson chi-square test or Fisher's exact chi-square test. A Mann-Whitney U test was used for the comparison of nonparametric variables, with values expressed as median and 25^{th}-75^{th} percentiles. The results were accepted as statistically significant when $p<0.05$. Age-adjusted p-values were used due to the difference in the age distribution of the patient and control groups. A logistic regression analysis was used for the calculation of the p-value. The age variable was entered into the model when the effect of the group variable on the growth was explored, and age-adjusted p-values were calculated.

Results

A total of 100 patients [97 female (97%), 3 male (3%)], diagnosed based on the AECG criteria, and 100 healthy volunteers [95 female (95%), 5 male (5%)] ($p>0.05$), were included in the study. The age range of the patients was 20-76 years, with a mean age of 50.1±11.9 years, and the age range of the control group was 18-77 years with a mean age of 38.1±13.2 years ($p<0.001$).

C. albicans growths were identified in 37% (n=37) and 17% (n=17) of the patient and control groups, respectively, based on an oral cultures evaluations. The difference between the two groups was statistically significant (p=0.001). Age-adjusted p-values were used due to the difference in the age distribution of the patient and control groups (p=0.023). Among the positive cultures in the patient group, 35 were found to be *C. albicans* positive and two to be *C. albicans* negative; while the positive cultures in the control group included 11 *C. albicans* positive and six *C. albicans* negative cultures.

S. aureus growth was identified in 12% (n=12) and 1% (n=1) of the patient and control groups, respectively based on nasal cultures. The difference between the two groups was statistically significant (p=0.002). Age-adjusted p-values were used due to the difference in the age distribution of the patient and control groups (p=0.008). Only one of the growing microorganisms was MRSA among the growing microorganisms in the patient group, and the remaining 11 were MSSA, while one MSSA growth was identified in the control group.

No growths were detected in the cultures of the samples taken from the right eye.

Only one MSSA growth was detected in the patient group in the cultures swabbed from the left eye. No growth was seen in the control group (Table 1).

No statistically significant associations were found between *C. albicans* growths in the mouth and antinuclear antibody (ANA) positivity, anti-Sjögren's syndrome A (SSA)

Table 1. Results of the cultures

	Control group (n=100)	Patient group (n=100)	p	Adjusted p*
Positive *C. albicans* growth in the mouth	17% (n=17)	37% (n=37)	**0.001**	**0.008**
Positive ***S. aureus*** growth in the nose	1% (n=1)	12% (n=12)	**0.002**	**0.023**
Positive ***S. aureus*** growth in the right eye	0% (n=0)	0% (n=0)		
Positive ***S. aureus*** growth in the left eye	0% (n=0)	1% (n=1)		

**: P-value adjusted for age, S. aureus: Stafilococcus aureus, C. albicans: Candida albicans*

positivity, anti-Sjögren's syndrome B (SSB) positivity, and rheumatoid factor (RF) positivity (Table 2).

No statistically significant associations were found between S. aureus growth in the nose and ANA positivity, Anti-SSA positivity, Anti-SSB positivity and RF positivity (Table 3).

Discussion

All mucosal membranes in the human body have mucosal barriers and defense systems that prevent the entry of microorganisms. Among these systems, saliva and its contents, in addition to contributing to the chewing, swallowing, and speaking functions, help remove bacteria from the mouth and prevent bacterial localization.[11,12] The sweat and sebaceous gland secretions from the skin are antimicrobial, while specific cells and the mucus they secrete in the respiratory tract form a defense barrier. If this barrier is defective, it facilitates the entry of microorganisms into the body and the development of infection.

Infections are among the main causes of morbidity and mortality in rheumatological diseases. The most common reason for presentation to the hospital has been reported as infections associated with rheumatoid arthritis, systemic lupus erythematosus, and other rheumatological diseases.[13]

The involvement of SS in the exocrine glands leads to dysfunction and decreased secretions, resulting in dry mouth, dry eyes, and dry skin. As a result of these changes in SS, the colonization of both normal flora and unassociated pathogenic bacteria increases, contributing to a higher frequency of infections.

Candidiasis is the most common fungal infection in the oral cavity and generally develops due to an overgrowth of Candida in the normal flora. The most common causative agent is *C. albicans*, although non-albicans species such as C. glabrata, C. tropicalis, C. krusei, and C. parapsilosis are becoming more common. Host-specific factors such as immunosuppression, inadequate nutrition, endocrine system diseases (such as diabetes mellitus and hypothyroidism), certain drug use, cancer, presence of prosthesis, changes in the amount of saliva, changed epithelial cellular layer, carbohydrate-rich nutrition, age, and inadequate oral hygiene all increase the sensitivity of a person to oral candidiasis.[14]

Table 2. Association between Candida growths and features of patients

	With Candida growth	Without Candida growth	p
Smoker	36.4% (n=8)	63.6% (n=14)	0.944
Non-smoker	37.2% (n=29)	62.8% (n=49)	
ANA positive	37.4% (n=34)	62.6% (n=57)	0.811
ANA negative	33.3% (n=3)	66.7% (n=6)	
Anti-SSA positive	41.6% (n=16)	59% (n=23)	0.505
Anti-SSA negative	34.4% (n=21)	65.6% (n=40)	
Anti-SSB positive	33.3% (n=3)	66.7% (n=6)	0.811
Anti-SSB negative	37.4% (n=34)	62.6% (n=57)	
RF positive	42.1% (n=8)	57.9% (n=11)	0.609
RF negative	35.8% (n=29)	64.2% (n=52)	

ANA: Antinuclear antibody, Anti-SSA: Sjögren syndrome antibody-A, Anti-SSB: Sjögren syndrome antibody-B, RF: Rheumatoid factor

Table 3. Association between *Stafilococcus* growths and features of patients

	With *S. aureus* growth	Without *S. aureus* growth	p
Smoker	22.7% (n=5)	77.3% (n=17)	0.080
Non-smoker	9% (n=7)	91% (n=71)	
ANA positive	12.1% (n=11)	87.9% (n=80)	0.931
ANA negative	11.1% (n=1)	88.9% (n=8)	
Anti-SSA positive	5.1% (n=2)	94.9% (n=37)	0.091
Anti-SSA negative	16.4% (n=10)	83.6% (n=51)	
RF positive	15.8% (n=3)	84.2% (n=16)	0.572
RF negative	11.1% (n=9)	88.9% (n=72)	

ANA: Antinuclear antibody, Anti-SSA: Sjögren syndrome antibody-A, Anti-SSB: Sjögren syndrome antibody-B, RF: Rheumatoid factor, S. aureus: Stafilococcus aureus

The oral mucosal culture growths of 16 patients with primary SS, 12 patients with secondary SS, and 14 patients with xerostomia were compared, revealing prevalence rates of oral *Candida* of 81.25%, 66.7%, and 71.4% in the primary SS group, secondary SS group, and xerostomia group, respectively, with no statistically significant difference found between the groups.[15] That study reported that dry mouth for any reason increased the presence of oral candida, while in the present study, oral *Candida* was identified in 37% and 17% of the primary SS patient group and the control group, respectively. This significant difference was attributed to the decreased saliva secretion and to the opportunistic overgrowth of *Candida*, normally present in the oral mucosa, due to dry mouth.

There have been few studies to date on nasal *S. aureus* carriers with primary SS. In a study comparing 57 patients with SS and 79 healthy controls, the prevalence of *S. aureus* in the nasal cultures was reported to be 20% and 12% in the primary SS group and the control group, respectively.[9] In the present study, on the other hand, the prevalence of *S. aureus* in the nasal cultures of the primary SS patients was 12%, compared to 1% in the control group. The differences in the results of the two studies may be attributable to the different growth media used. The culture samples were incubated in eosin methylene blue agar and Sabouraud dextrose agar in the previous study, whereas in the present study, samples were incubated in chromogenic agar and evaluated accordingly. The significant difference in the frequency of *S. aureus* growth in the present study in the nasal mucosa of the patient and control groups was thought to result from nasal dryness associated with primary SS and the resulting damage to the mucosal barrier.

Study Limitations

Some limitations of our study include the age difference between the patient and control groups, as healthy volunteers were included in the control group and did not have any underlying diseases.The patients in the SS group did not have other diseases that cause dry mouth, such as Graft-Versus-Host Disease or Wegener's granulomatosis. However, the age of the patient group may be a contributing factor to the dry mouth.

It is known that patients did not receive immunosuppressive treatment. However, no questions were asked to the patients about oral and dental hygiene. Additionally, the initial aim of the study did not include a comparison of demographic characteristics between the patient and control groups. For this reason, it was thought that the differences we found in the study were due to SS.

Conclusion

In conclusion, the prevalence of *S. aureus* in the nasal mucosa and *C. albicans* in the oral mucosa of primary SS patients was statistically significantly greater than in the healthy controls. One limitation of this study is its single-center design, suggesting that multi-national studies involving larger patient groups are required to accurately determine the increased prevalence of these microorganisms in the mucosa of primary SS patients.

Ethics

Ethics Committee Approval: This cross-sectional study was approved by the Ethics Board of the University of Erciyes University Faculty of Medicine, and was carried out in compliance with the rules of the World Medical Association Declaration of Helsinki (approval number: 2015/581, date: 25.12.2015).

Informed Consent: An informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.B., T.A., S.K., Concept: T.A., Design: T.A., Data Collection and Processing: İ.B., T.A., S.K., Analysis or Interpretation: İ.B., T.A., S.K., Literature Search: İ.B., Writing: İ.B.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Thanou-Stavraki A, James JA. Primary Sjögren's syndrome: current and prospective therapies. Semin Arthritis Rheum. 2008;37:273-92.
2. Roguedas AM, Misery L, Sassolas B, Le Mason G, Pennec YL, Youinou P. Cutaneous manifestations of primary Sjögren's syndrome are understimated. Clin Exp Rheumatol. 2004;22:632-6.
3. Haugen AJ, Peen E, Hulten B, et al. Estimation of the prevalence of primary Sjögren's syndrome in two age -different community-based populations using two sets of classification criteria: the Hordoland Health Study. Scand J Rheumatol. 2008;37:30-4.
4. Ramos-Casals M, Tzioufas AG, Font J. Primary Sjögren's syndrome: new clinical and therapeutic concepts. Ann Rheum Dis. 2005;64:347-54.
5. Theander E, Jacobsson LT. Relationship of Sjögren's syndrome to other connective tissue and autoimmune disorders. Rheum Dis Clin North Am. 2008;34:935-47,viii-ix.
6. Almstahl A, Kroneld U, Tarkowski A, Wikström M. Oral microbial flora in Sjögren's syndrome. J Rheumatol. 1999;26:110-4.

7. Rhodus NL, Michalowicz BS. Periodontal status and sulucular Candida albicans colonizationn in patients with primary Sjogren's syndrome. Quintessence Int. 2005;36:228-33.

8. Gül M, Çıragil P, Aral M. Kahramanmaraş Sütçü İmam Üniversitesi Tıp Fakültesi hastane personelinde burun ve el Staphylococcus aureus taşıyıcılığı. ANKEM Dergisi. 2004;18:36-9.

9. Şahin G. Sjögren sendromu'nun nazal floraya etkisi (Uzmanlık tezi). Gazi Üniversitesi İç Hastalıkları Anabilim Dalı, Ankara, 2010. [Turkish]

10. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Assessment of the European classification criteria for Sjogren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. The European Study Group On Diagnostic Criteria for Sjogren's syndrome. Ann Rheum Dis. 1996;552:116-21.

11. Mandel ID. The functions of saliva. J Dent Res. 1987;66:623-7.

12. Levine RS. Saliva. 2. Saliva and dental caries. Dent Update. 1989;16:158-65.

13. Irlapati RV, Nagaprabu VN, Suresh K, Agrawal S, Gumdal N. Infections in rheumatology practice: an experience from NIMS, Hyderabad. Indian Journal of Rheumatology. 2011;6:25-30.

14. Sherman RG, Prusinski L, Ravenel MC, Joralmon RA. Oral candidosis, Quintessence Int. 2002;33:521-32.

15. Kindelan SA, Yeoman CM, Douglas CW, Franklin C. A comparison of intraoral Candida carriage in Sjogren's syndrome patients with healthy xerostomic controls. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85:162-7.

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.61687
Ulus Romatol Derg 2025;17(1):15-19

The role of thiol-disulfide homeostasis in gouty arthropathy

Tiyol-disülfit homeostazının gut artropatisindeki rolü

Sevinç Can Sandıkçı[1], Seda Yürümez Çolak[1], Ahmet Omma[1], Salim Neşelioğlu[2], Özcan Erel[2]

[1]Ankara Numune Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
[2]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Clinical Biochemistry, Ankara, Türkiye

Abstract

Objective: Gout, the most common form of crystal-induced arthritis, is characterized by the accumulation of monosodium urate crystals within the joints. This study aimed to examine thiol-disulfide homeostasis in patients with gouty arthropathy during periods of acute attack and remission.

Methods: A novel spectrophotometric technique was employed to assess native thiol (NT) and disulfide levels in gout patients and age- and sex-matched healthy controls. A total of 90 patients and 86 healthy individuals were evaluated using clinical and laboratory data extracted from their medical records.

Results: The findings demonstrated that NT and total thiol (TT) levels in patients were significantly lower than in controls (p<0.001 for both). No significant differences in NT and TT levels were observed between acute attacks and remission periods (p>0.05).

Conclusion: Alterations in thiol-disulfide homeostasis were evident in gout patients; however, these changes did not vary between periods of acute attack and remission.

Keywords: Gout, thiol, disulfide, oxidative stress, thiol-disulfide homeostasis

Öz

Amaç: Gut, kristal artropatinin en yaygın şeklidir ve eklemlerde monosodyum ürat kristallerinin birikmesinden kaynaklanır. Bu çalışmanın amacı, gut artropatisi olan hastalarda atak veya ataksız dönemde tiyol-disülfit dengesini araştırmaktır.

Yöntem: Gut hastalarında ve yaş-cinsiyet eşleştirilmiş sağlıklı kontrol grubunda doğal tiyol (DT) ve disülfit seviyelerini ölçmek için yeni geliştirilen bir spektrofotometrik yöntem kullanıldı. Toplam 90 gut hastası ve 86 sağlıklı kontrol incelendi. Klinik ve laboratuvar verileri tıbbi kayıtlardan elde edildi.

Bulgular: Gut hastalarında DT (p<0,001) ve toplam tiyol (TT) (p<0,001) seviyeleri sağlıklı kontrollere kıyasla anlamlı derecede düşüktü. Gut hastalarında atak ve ataksız dönemlerle DT ve TT düzeyleri arasında anlamlı bir fark yoktu (p>0,05).

Sonuç: Tiyol-disülfit homeostazisi gut hastalarında değişmekte, ancak atak döneminden etkilenmemektedir.

Anahtar Kelimeler: Gut, tiyol, disülfit, oksidan stres, tiyol-disülfit homeostazı

Introduction

Gout is a persistent inflammatory condition characterized by heightened uric acid levels and the saturation of monosodium urate (MSU) crystals in the patient's joints and adjacent tissues. This condition represents the most prevalent form of inflammatory arthritis among adults, particularly males, and its prevalence is surging worldwide, ranging from 1% to 3%.[1] In instances where the serum urate concentration surpasses 6.8 mg/dL, the precipitation of urate within joints and other tissues becomes a possibility. The accumulation of MSU in the intra-articular space activates inflammatory cytokines, which, in turn, results in the accumulation of macrophages and neutrophils. This series of events ultimately leads to the development of gouty arthritis.[2,3]

Correspondence / İletişim:
Assoc. Prof. Sevinç Can Sandıkçı, Ankara Numune Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
E-mail: scsandikci@gmail.com **ORCID ID:** orcid.org/0000-0001-5921-8029
Received / Geliş Tarihi: 12.06.2024 **Accepted / Kabul Tarihi:** 22.01.2025 **Publication Date / Yayın Tarihi:** 19.03.2025

Cite this article as / Atıf: Can Sandıkçı S, Yürümez Çolak S, Omma A, Neşelioğlu S, Erel Ö. The role of thiol-disulfide homeostasis in gouty arthropathy. Ulus Romatol Derg. 2025;17(1):15-19

Beyond the inflammatory process, the earliest event linked with gout may be oxidative stress (OS), which involves an imbalance between reactive oxygen species (ROS) and antioxidant mechanisms.[4] The oxidative state is induced by the generation of ROS and pro-inflammatory cytokines.[5] Previous *in vivo* research showed that elevated uric acid levels have the capacity to trigger endothelial dysfunction, manifesting in anti-proliferative effects on endothelial cells and impaired nitric oxide bioavailability.[6,7] The pivotal enzyme in this process, xanthine oxidase (XO), is key to ROS production, and the inhibition of XO with allopurinol has been demonstrated to enhance cardiovascular function.[8,9]

Dynamic thiol-disulfide homeostasis is key to antioxidant protection, detoxification, signal transduction, apoptosis, enzymatic activity, regulation of transcription factors, and cellular signaling mechanisms.[10,11] Thiols are functional groups found in the structure of major proteins, with the highest thiol levels in blood plasma found in albumin and other proteins. Thiols react with reactive oxygen radicals to oxidize and scavenge these radicals, thereby preventing tissue damage. Subsequent to this oxidation, disulfide bonds are formed.[12,13] It should be noted that these structures can be converted back to thiols. The measurement of thiol-disulfide levels offers an indirect indication of OS levels. Erel and Neselioglu[14] have recently introduced a novel spectrophotometric approach for measuring thiol-disulfide, characterized by its simplicity and cost-effectiveness. The method involves the quantification of native thiol (NT), total thiol (TT), and disulfide levels and the calculation of the relative proportions of these molecules [e.g., disulfide/native thiol (DNT), disulfide/total thiol (DTT), and native thiol/total thiol (NTT)].

The present study attempts to examine the thiol-disulfide equilibrium in patients with gout arthropathy during periods of acute attack and remission.

Materials and Methods

Sample

For this cross-sectional study, we considered data from 90 patients (77 males, 13 females) and 86 healthy subjects (73 males, 13 females). The patient group consisted of individuals diagnosed with gouty arthritis according to the 2015 ACR/EULAR gout classification criteria in our rheumatology clinic.[15] Patients who had not experienced a gout attack for at least six months were considered to be in remission. The control group comprised age- and sex-matched healthy individuals with no known chronic conditions.

Patients with the following conditions were excluded from the study: acute kidney problems, cardiovascular events, stroke, uncontrolled hypertension, malignancy, any infectious disease, and urgent medical conditions (e.g., respiratory failure due to interstitial disease) on the day of their evaluation at the outpatient clinic.

Blood Sampling

Blood samples were obtained from patients and controls after a 12-hour fast during the attack-free period. A similar protocol was applied to patients within the first 24 hours of an acute attack. We utilized 10 mL plain tubes containing ethylenediaminetetraacetic acid (EDTA) and 2 mL vacuum tubes for sampling. The samples were centrifuged at 1,500 g for 10 minutes.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured within 3 hours of collection. Serum samples intended for thiol and disulfide analyses were meticulously stored at -80 °C until analysis. The same serum samples were used in the same session to measure NT, TT, and disulfide levels.

Biochemical Analysis

Serum NT, TT, and disulfide levels (µmol/L) were measured using a novel, affordable spectrophotometric technique.[14] Briefly, NT levels were initially assessed after the serum reacted with 5,5-dithiobis-2-nitrobenzoic acid (DTNB) without any procedural modifications. Dynamic disulfide bonds in the samples were then reduced using sodium borohydride ($NaBH_4$) to measure TT levels, releasing free functional thiol groups. Formaldehyde was used to eliminate any unused $NaBH_4$, and reduced and native TT groups were measured following the reaction with DTNB.

The difference between NT and TT levels was calculated, and the amount of disulfide bonds was determined by subtracting NT from TT and dividing the result by two. Additionally, we calculated the ratios of DNT, DTT, and NTT.

For CRP measurements, we used the immunoturbidimetric method with the Beckman Coulter AU5800 clinical chemistry system (reference CRP <5 mg/L, Beckman Coulter, Inc., Brea, CA, USA). ESR levels were measured using the Alifax ESR analyzer system with the modified Westergren method (reference ESR <20 mm/h, Alifax, Polverara, Italy).

Statistical Analysis

We analyzed the data using SPSS version 18.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was employed to assess the normality of data distribution. Data are presented as mean (M), standard deviation, number (n), percentage (%), and range (minimum-maximum).

An independent samples t-test was used for parametric data, while the Mann-Whitney U test was applied for non-parametric data. Categorical variables were compared using chi-square analysis. Pearson's and Spearman's correlation analyses were used to assess relationships between continuous variables. A p-value <0.05 was considered statistically significant.

Ethics Statement

The protocol for this prospective case-control study was approved by the Institutional Review Board for Human Research of Ankara Numune Training and Research Hospital. All participants provided written informed consent before participating in the study.

Results

Age (55.2±13.8 years *vs.* 53.1±13.1 years, p>0.05) and gender distribution (M/F, n=77/13 *vs.* 72/14, p>0.05) were statistically similar between the groups. Table 1 presents the clinical and demographic characteristics of the patient group.

Table 1. Patients' demographic and clinical characteristics

Characteristics	Values
Gender (male/female)	77/13
Age, years	55.2±13.8 (24-82)
Disease duration, months	53.3±59.8 (0-480)
Number of attacks, annual	3.01±1.99 (0-8)
Patients with attack (n, %)	37 (41.1)
Subcutaneous tophi (n, %)	6 (6.7)
Medication	
Allopurinol	50 (55.6)
Febuxostat	4 (4.4)
Colchicine	16 (17.7)
Steroid	10 (11.1)
Colchicine + steroid	10 (11.1)
Urate lowering therapy (n, %)	54 (60%)

The findings revealed that NT, TT, and NTT levels were significantly lower in the patient group compared to control subjects. DNT, DTT, CRP, and ESR levels were significantly higher in patients. Although disulfide levels were elevated in patients, this increase did not reach statistical significance (p>0.05; Table 2).

Table 3 presents a comparative analysis of TT, NT, CRP, ESR, and disulfide levels in patients based on attack status. No significant differences were found in NT, TT, or disulfide levels between attack and remission periods (p>0.05). However, CRP and ESR levels were significantly higher in patients experiencing acute attacks compared to those in remission.

Correlation analyses showed that age was negatively correlated with NT levels (r=-0.341, p=0.000), TT levels (r=-0.336, p=0.000), and NTT (r=-0.188, p=0.013), but positively correlated with DNT (r=0.188, p=0.013) and DTT (r=0.188, p=0.013). No significant correlation was found between age and disulfide levels.

CRP levels were inversely correlated with NT (r=-0.252, p=0.017), TT (r=-0.233, p=0.027), and NTT (r=-0.213, p=0.044), while showing a positive correlation with DNT (r=0.213, p=0.044) and DTT (r=0.213, p=0.044). However, CRP levels did not significantly correlate with disulfide levels.

Additionally, disulfide parameters were not associated with disease duration, colchicine dose, allopurinol dose, ESR levels, or thiol levels.

Discussion

Gouty arthritis is an inflammatory condition arising from the deposition of MSU crystals within the joints. The secretion of various cytokines, prostanoids, chemotactic factors, and other proteins is induced by MSU crystals. This inflammatory mechanism is amplified through several pathways, including the recruitment of inflammatory cells, upregulation of adhesion molecules, and stimulation of the acute phase response.[16,17] Persistent, chronic inflammation

Table 2. Laboratory results of the patient and control group

Variables	Gout (n=90)	Control (n=86)	p-value
NT, µmol/L	239.9±65.3	457.2±54.6	0.00
TT, µmol/L	281.4±67	494.8±54.2	0.00
Disulfide, pmol/L	20.7±6.3	18.7±7.6	0.054
NTTx100	84.4±5.7	92.3±3	0.00
DNTx100	9.5±4.4	4.2±1.7	0.00
DTTx100	7.7±2.8	3.8±1.5	0.00
ESR, mm/h	22.7±14.5	7.52±4.29	0.00
CRP, mg/L	19.8±30.6	2.75±1.67	0.00

CRP: C-reactive protein, DNT: Disulfide/native thiol, DTT: Disulfide/total thiol, ESR: Erythrocyte sedimentation rate, NT: Native thiol, NTT: Native thiol/total thiol, TT: Total thiol

Table 3. Laboratory results of gout patients by attack status

Variables	Attack (n=53)	Attack-free (n=37)	p-value
NT, µmol/L	230.4±81.7	246.4±50.6	0.694
TT, µmol/L	270.5±84.2	289.1±51.3	0.715
Disulfide, pmol/L	20±6.2	21.3±6.4	0.463
NTTx100	83.6±6.9	84.9±4.7	0.468
DNTx100	10.2±5.5	9±3.4	0.468
DTTx100	8.1±3.4	7.5±2.3	0.468
ESR, mm/h	30.5±16.7	17.2±9.7	0.00
CRP, mg/L	38.6±40.4	6.7±6.5	0.00

CRP: C-reactive protein, DNT: Disulfide/native thiol, DTT: Disulfide/total thiol, ESR: Erythrocyte sedimentation rate, NT: Native thiol, NTT: Native thiol/total thiol, TT: Total thiol

eventually leads to OS and oxidative tissue damage.[18] A previous study highlighted the significance of OS and ROS in stimulating leucine-rich repeat and pyrin domain-containing protein inflammasomes induced by MSU crystals.[19]

Thiols are critical mediators in mitigating OS, with the capacity to safeguard against cellular damage by forming disulfide bridges that act as covalent bonds.[20] Consequently, thiol levels are considered significant markers of antioxidant capacity within the metabolic system. Thiol biochemistry has seen substantial growth in both fundamental and applied biological sciences, and since 1979, the assessment of sulfhydryl groups has commonly utilized DTNB as a standard protocol.[21] In this context, we aimed to evaluate serum thiol-disulfide homeostasis in gout patients using the spectrophotometric technique developed by Erel and Neselioglu.[14] Consistent with recent findings, our results showed that serum TT and NT levels were diminished in gout patients compared to healthy controls. Although disulfide levels correlated with CRP levels, they did not show an association with ESR or leukocyte counts.

A growing body of research has explored the interplay between chronic diseases (e.g., rheumatological conditions) and OS. However, there is limited literature on thiol-disulfide homeostasis in gout patients during periods of acute attack and remission. The study by Dogru et al.[22] made a notable contribution by demonstrating significantly reduced TT levels in ankylosing spondylitis (AS) patients. Similarly, Arpa et al.[23] observed significantly diminished TT and NT levels, alongside increased disulfide levels, in AS patients compared to controls. In both groups, ESR was negatively correlated with NT and TT levels, and high-sensitivity CRP (hs-CRP) levels showed similar negative correlations in patients with highly active AS. Serdaroğlu et al.[24] also reported significantly lower NT and TT levels in rheumatoid arthritis patients compared to healthy controls.

In another study, Omma et al.[25] found that dynamic thiol-disulfide homeostasis shifted towards disulfide formation due to thiol oxidation in patients with Familial Mediterranean fever. Additionally, juvenile idiopathic arthritis (JIA) patients demonstrated reduced plasma thiol levels, particularly during active disease periods. The researchers suggested that decreased thiol levels might play a critical role in the pathogenesis of JIA and that inflammatory diseases negatively impact antioxidant systems during heightened disease activity.[26]

In clinical practice, the severity of inflammation in various inflammatory conditions is typically assessed by measuring CRP and ESR levels. However, there is a lack of specific biomarkers for disease activity in gout. While serum uric acid is not a reliable predictor of flares or a diagnostic biomarker for gout, CRP remains a widely accepted marker of inflammation during gout flares. These findings underscore the role of OS in the inflammatory response in gout patients. Moreover, our results suggest that thiol-disulfide homeostasis could serve as a promising new biomarker for gout, though further studies are necessary to validate its cost-effectiveness in clinical settings.

Patients with gouty arthritis may benefit from adjuvant antioxidant-rich diets or treatments to enhance their antioxidant status. However, these findings require confirmation in larger cohorts of gout patients.

Study Limitations

This study has certain limitations. Its cross-sectional design and relatively small sample size (n=90) restrict the generalizability of the results. Additionally, OS levels can be influenced by several factors, such as lifestyle and dietary habits, which were not addressed in this study. Despite these limitations, this research offers valuable insights by examining thiol as a distinct biomarker of OS in gout patients.

Conclusion

This study demonstrates that thiol-disulfide homeostasis is disrupted in gout patients, with no significant changes observed between acute attack and remission periods.

Ethics

Ethics Committee Approval: The protocol for this prospective case-control study was approved by the Institutional Review Board for Human Research of Ankara Numune Training and Research Hospital.

Informed Consent: All participants provided written informed consent before participating in the study.

Footnotes

Authorship Contributions

Concept: S.C.S., A.O., Ö.E., Design: S.C.S., A.O., S.N., Data Collection and Processing: S.C.S., S.Y.Ç., S.N., Ö.E., Analysis or Interpretation: S.C.S., A.O., S.N., Ö.E., Literature Search: S.C.S., S.Y.Ç., A.O., Writing: S.C.S., S.Y.Ç.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the national health and nutrition examination survey 2007–2008. Arthritis Rheum. 2011;63:3136-41.
2. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440:237-41.
3. Martillo MA, Nazzal L, Crittenden DB. The crystallization of monosodium urate. Curr Rheumatol Rep. 2014;16:400.
4. Afonso V, Champy R, Mitrovic D, Collin P, Lomri A. Reactive oxygen species and superoxide dismutases: role in joint diseases. Joint Bone Spine. 2007;74:324-9.
5. Peng YJ, Lee CH, Wang CC, Salter DM, Lee HS. Pycnogenol attenuates the inflammatory and nitrosative stress on joint inflammation induced by urate crystals. Free Radic Biol Med. 2012;52:765-74.
6. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. J Hypertens. 2008;26:269-75.
7. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol. 2005;25:39-42.
8. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. Lancet. 2010;375:2161-7.
9. Rekhraj S, Gandy SJ, Szwejkowski BR, et al. High-dose allopurinol reduces left ventricular mass in patients with ischemic heart disease. J Am Coll Cardiol. 2013:61:926-32.
10. Biswas S, Chida AS, Rahman I. Redox modifications of protein-thiols: emergingroles in cellsignaling. Biochem Pharmacol. 2006;71:551-64.
11. Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, andapoptosis. Free Radic Biol Med. 2010:48:749-62.
12. Yuksel M, Ates I, Kaplan M, et al. The dynamic thiol/disulphide homeostasis in inflammatory bowel disease and its relation with disease activity and pathogenesis. Int J Colorectal Dis. 2016;31:1229-31.
13. Kundi H, Ates I, Kiziltunc E, et al. A novel oxidative stress marker in acute myocardial infarction; thiol/disulphide homeostasis. Am J Emerg Med. 2015;33:1567-71.
14. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326-32.
15. Neogi T, Jansen T, Dalbeth N, et al. 2015 gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74:1789-98.
16. Dalbeth N, Haskard DO. Mechanisms of inflammation in gout. Rheumatology (Oxford). 2005;44:1090-6.
17. Scanu A, Oliviero F, Ramonda R, Frallonardo P, Dayer JM, Punzi L. Cytokine levels in human synovial fluid during the different stages of acute gout: role of transforming growth factor β1 in the resolution phase. Ann Rheum Dis. 2012;71:621-4.
18. Lagnoux D, Darbre T, Schmitz ML, Reymond JL. Inhibition of mitosis by glycopeptide dendrimer conjugates of colchicine. Chemistry. 2005;11:3941-50.
19. Punzi L, Scanu A, Ramonda R, Oliviero F. Gout as autoinflammatory disease: new mechanisms for more appropriated treatment targets. Autoimmun Rev. 2012;12:66-71.
20. Itani HA, Dikalova AE, McMaster WG, et al. Mitochondrial cyclophilin D in vascular oxidative stress and hypertension. Hypertension. 2016;67:1218-27.
21. Ellman G, Lysko H. A precise method for the determination of whole blood and plasma sulfhydryl groups. Anal Biochem. 1979;93:98-102.
22. Dogru A, Balkarli A, Cetin GY, et al. Thiol/disulfide homeostasis in patients with ankylosing spondylitis. Bosn J Basic Med Sci. 2016;16:187-92.
23. Arpa M, Şen B, Beyazal MS, Erel O. Evaluation of thiol-disulfide homeostasis in active ankylosing spondylitis patients. Reumatol Clin (Engl Ed). 2021;17:S1699-258X(21)00118-2.
24. Serdaroglu Beyazal M, Arpa M, Devrimsel G, Yıldırım M, Erel O, Erdogan T. Thiol/disulphide homeostasis in patients with rheumatoid arthritis: a potential link between disease activity and preclinical atherosclerosis. Acta Reumatol Port. 2021;46:23-31.
25. Omma A, Sandikci SC, Kücüksahin O, Alisik M, Erel O. Can the thiol/disulfide imbalance be a predictor of colchicine resistance in familial mediterranean fever? J Korean Med Sci. 2017;32:1588-94.
26. Altinel Acoglu E, Erel O, Yazilitas F, et al. Changes in thiol/disulfide homeostasis in juvenile idiopathic arthritis. Pediatr Int. 2018;60:593-6.

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.27247
Ulus Romatol Derg 2025;17(1):20-29

Frequency and clinical implications of metabolic syndrome in different rheumatic diseases: Relationship with disease activity and severity

Metabolik sendromun romatizmal hastalıklar üzerindeki klinik etkileri: Hastalık aktivitesi ve şiddetiyle ilişkisi

Suzan Sadek Al-Adle, Passant Nabil El-Husseiny, Nahla Naeem Eesa, Tamer A Gheita

Cairo University Faculty of Medicine, Department of Rheumatology, Cairo, Egypt

Abstract

Objective: To assess the frequency of metabolic syndrome (MetS) in various rheumatic diseases and to depict its association with disease characteristics, activity, and/or severity.

Methods: Two hundred fifty-seven patients [47 rheumatoid arthritis (RA), 100 systemic lupus erythematosus (SLE), 49 systemic sclerosis (SSc), 33 axial spondyloarthritis (axSpA), and 28 vasculitis (21 with primary vasculitis and 7 with Behçet's disease (BD)] and 70 controls were recruited, with a suitable number of controls matched for each corresponding disease. Demographic data, body mass index, waist circumference, comorbidities, and clinical and laboratory data were collected. Disease activity and/or severity were determined. MetS was defined according to the Adult Treatment Panel criteria.

Results: In RA, MetS was comparable to the control group with no significant association to the disease activity score (p=0.33), but there was a significant difference according to the activity grading (p=0.007). In SLE, MetS was significantly more frequent (42%) versus the control (14.9%) (p=0.001) and was significantly related to disease activity (p=0.001). In SSc, axSpA, and vasculitis, the frequency of MetS was comparable to their corresponding controls (p=0.24, p=0.4, p=0.08) and was not related to their disease activity scores (p=0.7, p=0.4, p=0.97; respectively), as well as p=0.45 and p=0.14 for BD activity and damage. When comparing the different rheumatic diseases, MetS was significantly more frequent in SLE (p=0.04). Regarding MetS components, there was a significantly higher frequency of hypertension (p<0.0001) and significantly higher triglycerides (p=0.004) in SLE versus the other rheumatic diseases. No significant association was found between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio with MetS in RA (p=0.4, p=0.4), SLE (p=0.35, p=0.73), SSc (p=0.46, p=0.14), axSpA (p=0.35, p=0.45) and vasculitis (p=0.72, p=0.29).

Conclusion: MetS is frequently associated with rheumatic diseases, being significantly more frequent in SLE, and could be related to disease activity.

Keywords: Rheumatic diseases, metabolic syndrome (MetS), disease activity, severity

Öz

Amaç: Bu çalışmanın amacı farklı romatizmal hastalıklarda metabolik sendromun (MetS) sıklığını değerlendirmek ve hastalık özellikleri, aktivitesi ve/veya şiddetiyle ilişkisini incelemektir.

Yöntem: İki yüz elli yedi hasta [47 romatoid artrit (RA), 100 sistemik lupus eritematozus (SLE), 49 sistemik skleroz (SSc), 33 aksiyel spondiloartrit (axSpA) ve 28 vaskülit (21'i primer vaskülit ve 7'si Behçet hastalığı (BH)] ve 70 kontrol, ilgili her hastalık için uygun sayıda kontrol eşleştirilerek alınmıştır. Demografik veriler, vücut kitle indeksi, bel çevresi, komorbiditeler ve klinik ve laboratuvar verileri toplanmıştır. Hastalık aktivitesi ve/veya şiddeti belirlenmiştir. MetS, Yetişkin Tedavi Paneli kriterlerine göre tanımlanmıştır.

Bulgular: RA'da MetS, hastalık aktivite skoru ile anlamlı bir ilişkisi olmayan kontrol grubu ile karşılaştırılabilir düzeydeydi (p=0,33), ancak aktivite derecelendirmesine göre anlamlı bir fark vardı (p=0,007). SLE'de MetS, kontrol grubuna (%14,9) kıyasla anlamlı derecede daha sık (%42) görülmüş (p=0,001) ve hastalık aktivitesiyle anlamlı derecede ilişkili bulunmuştur (p=0,001). SSc, axSpA ve vaskülitte, MetS sıklığı karşılık gelen kontrollerle karşılaştırılabilirdi (p=0,24, p=0,4, p=0,08) ve hastalık aktivite skorlarıyla ilişkili değildi (sırasıyla p=0,7, p=0,4, p=0,97); ayrıca BH aktivitesi ve hasarı için p=0,45 ve p=0,14 idi. Farklı romatizmal hastalıklar karşılaştırıldığında, MetS SLE'de anlamlı olarak daha sık görülmüştür (p=0,04). MetS bileşenleri açısından, SLE'de diğer romatizmal hastalıklara kıyasla anlamlı derecede daha yüksek hipertansiyon (p<0,0001) ve anlamlı derecede daha yüksek trigliserit (p=0,004) sıklığı vardı. Nötrofil-lenfosit oranı ve trombosit-lenfosit oranı ile MetS arasında RA (p=0,4, p=0,4), SLE (p=0,35, p=0,73), SSc (p=0,46, p=0,14), axSpA (p=0,35, p=0,45) ve vaskülitte (p=0,72, p=0,29) anlamlı bir ilişki bulunmamıştır.

Sonuç: MetS, romatizmal hastalıklarla sıklıkla ilişkilidir, SLE'de önemli ölçüde daha sık görülür ve hastalık aktivitesi ile ilişkili olabilir.

Anahtar Kelimeler: Romatizmal hastalıklar, metabolik sendrom (MetS), hastalık aktivitesi, şiddet

Correspondence / İletişim:
Assist. Lecturer M.Sc. Passant Nabil El-Husseiny, Cairo University Faculty of Medicine, Department of Rheumatology, Cairo, Egypt
E-mail: passantnabil94@gmail.com **ORCID ID:** orcid.org/0000-0002-1503-7071
Received / Geliş Tarihi: 14.08.2024 **Accepted / Kabul Tarihi:** 22.01.2025 **Publication Date / Yayın Tarihi:** 19.03.2025

Cite this article as / Atıf: Al-Adle SS, El-Husseiny PN, Eesa NN, Gheita TA. Frequency and clinical implications of metabolic syndrome in different rheumatic diseases: relationship with disease activity and severity. Ulus Romatol Derg. 2025;17(1):20-29

Introduction

Metabolic syndrome (MetS) is marked by the presence of several components, including dyslipidemia, insulin insensitivity, hypertension, hyperglycemia, and central obesity, which together form a constellation of cardiovascular disease (CVD) risk factors.[1] There are several definitions of MetS, with the Adult Treatment Panel (ATP III) criteria being one of the most commonly used.[2] There is evidence that inflammation contributes to the pathogenesis of MetS, with pro-inflammatory cytokines playing a significant role in insulin resistance.[3] Moreover, heightened inflammation is associated with dysregulated lipid parameters, such as decreased high-density lipoprotein (HDL) and elevated triglycerides (TG).[4]

Rheumatic diseases (RDs) have been associated with an increased risk of CVDs.[5] MetS has been reported in several RDs, including rheumatoid arthritis (RA),[6] systemic sclerosis (SSc),[7] and primary vasculitis.[8] Inflammatory mediators, such as interleukin-6, can induce insulin resistance through various mechanisms,[9] suggesting a possible explanation for the link between chronic inflammatory conditions like RDs and MetS.

Inflammatory indices, such as the neutrophil-lymphocyte ratio (NLR), can predict the risk of CVDs.[10] Furthermore, NLR has been a common inflammatory marker in RDs,[11] indicating its potential as a predictor of systemic inflammation. MetS has been correlated with disease activity and severity in several RDs,[8,12,13] implying that chronic inflammation may contribute to the pathogenesis of MetS and subsequent metabolic and vascular complications.

This study aimed to investigate the frequency of MetS in various RDs and assess its relationship with disease characteristics, activity, and/or severity.

Materials and Methods

The study included 257 adult patients with different RDs. Exclusion criteria included subjects diagnosed with hypothyroidism, liver impairment, Cushing syndrome, malignancy, or infection, as well as those who had been on drugs altering the lipid profile in the past 3 months. Patients with a history of smoking and alcohol consumption were also excluded. Seventy age- and sex-matched healthy control subjects were enrolled, with a suitable number of controls for each corresponding RD: 50/70 for RA, 50/70 for systemic lupus erythematosus (SLE), 50/70 for SSc, 30/70 for axial spondyloarthritis (axSpA), and 30/70 for vasculitis patients.

Patients underwent full history taking and physical examination, including measurements of body mass index and waist circumference (cm). Complete blood count with differential was recorded. A lipid profile was performed for all patients after 12-14 hours of fasting, including total cholesterol (TC), HDL, TG, low-density lipoprotein (LDL), and very LDL. MetS was diagnosed in accordance with the ATP III criteria.[2] Disease activity was assessed using the disease activity score (DAS-28)[14] for RA, the SLE disease activity index (SLEDAI)[15] for SLE, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[16] for axSpA, the Birmingham Vasculitis Activity Score[17] for primary vasculitis, and the Arabic version of the Behçet's Disease Current Activity Form (Ar-BDCAF)[18] for BD. Disease severity/damage was evaluated using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index[19] for SLE, the modified Rodnan Skin Score (mRss)[20] for SSc, the vasculitis damage index (VDI)[21] for primary vasculitis, and the Behçet's Disease Damage Index (BDI)[22] for BD patients.

Statistical Analysis

Data were statistically described as mean ± standard deviation, median and range, or frequencies and percentages. Numerical data were tested for normality using the Kolmogorov-Smirnov test. Comparisons of numerical variables between two study groups were conducted using the Mann-Whitney U test, while the Kruskal-Wallis test was applied for comparisons among more than two groups. The chi-square (χ^2) test was performed to compare categorical data. The exact test was used when the expected frequency was less than 5. Results were adjusted for missing variable values. Two-sided p-values <0.05 were considered statistically significant.

For numerical data, effect size was represented by Cohen's d for differences between two groups and eta-squared (η^2) for differences among more than two groups. For qualitative data, effect size was expressed as odds ratio (OR) and 95% confidence interval (CI). Cohen's d standards were 0.2, 0.5, and 0.8 for small, medium, and large effect sizes, respectively. For eta-squared, the standards were 0.01, 0.059, and 0.138 for small, medium, and large effect sizes, respectively. If the generated two-tailed 95% CIs for qualitative data did not cross 1, the results were considered statistically significant.

Multivariate logistic regression analysis was conducted to estimate independent risk modifiers for the occurrence of MetS among different diseases. Risk factors included in the model were those with significant results in univariate analysis. IBM SPSS (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY, USA), version 22 for Microsoft Windows, was used for statistical analysis.

The patients provided informed consent, and the study was approved by the Scientific Research and Ethical Committee in accordance with the 1964 Helsinki Declaration.

The members of the Scientific Research and Ethics Committee of the Rheumatology and Rehabilitation Department, Cairo University (SReC-RCU) have reviewed and approved the aforementioned M.Sc. protocol (approval number: 40-SReC-RCU2021, date: 20.03.2021).

Results

The current study included 47 subjects with RA, 100 with SLE, 49 with SSc, 33 with axial spondyloarthritis (axSpA), and 28 with vasculitis [21 with primary vasculitis and 7 with Behçet's disease (BD)]. All participants were recruited from the Rheumatology Department and met the corresponding classification criteria for RA,[23] SLE,[24] SSc,[25] and axSpA.[26]

Twenty-one patients with primary vasculitic syndromes were included: 5 with Takayasu arteritis, 3 with granulomatosis with polyangiitis, 1 with microscopic polyangiitis, 1 with eosinophilic granulomatosis with polyangiitis (Churg-Strauss), 2 with polyarteritis nodosa, 2 with Cogan syndrome, 1 with urticarial vasculitis, 1 with cryoglobulinemic vasculitis, and 5 with undifferentiated vasculitis, classified according to the 2012 Chapel Hill Consensus.[27] Additionally, 7 patients with BD were included.[28]

The characteristics of the RD patients are illustrated in Table 1. The matched control group for RA and SSc patients included 6 males (12%) and 44 females (88%) (p>0.05), with ages ranging from 18-60 years and a mean age of 40.8±11.6 years (p>0.05). The matched control group for SLE patients comprised 8 males (16%) and 42 females (84%) (p>0.05) with ages ranging from 16-55 years and a

Table 1. Characteristics of the studied rheumatic diseases

Mean ± SD or n (%)	RA (n=47)	SLE (n=100)	SSc (n=49)	axSpA (n=33)	Vasculitis (n=28)		p
					PV (n=21)	BD (n=7)	
Age (years)	44.3±13.7 (21-75)	33.8±10.3 (18-63)	43.3±13.7 (18-79)	40.7±10 (17-62)	40.4±15.8 (19-77)	34.4±6.6 (29-44)	**<0.0001**
Gender							
Male	4 (8.5)	7 (7)	7 (14.3)	24 (72.7)	10 (47.6)	6 (85.7)	**<0.0001**
Female	43 (91.5)	93 (93)	42 (85.7)	9 (27.3)	11 (52.4)	1 (14.3)	
Disease duration	12.3±7.4 (1-27)	8.9±7.02 (1-27)	7.4±5.6 (1-24)	12.4±8.1 (1-35)	6.1±6.1 (1-22)	8±8.4 (1-25)	**<0.0001**
Age at onset	31.9±13.02	24.6±10.9	36.1±12.5	28.2±10.9	34.3±16.2	26.4±3	**<0.0001**
BMI	29.4±5.6 (19.7-45.2)	27.9±6 (15.1-48.9)	25.8±5.9 (14.6-46)	28±3.3 (23.4-35.9)	28.7±8.1 (15.6-51)	26.5±3.8 (22.7-32.7)	**0.04**
MetS components							
DM	7 (14.9)	11 (11)	3 (6.1)	2 (6.1)	3 (14.3)	1 (14.3)	0.68
Hypertension	9 (19.1)	47 (47)	8 (16.3)	1 (3)	12 (57.1)	1 (14.3)	**<0.0001**
WC (cm)	100.2±16.4 (46-130)	98.9±13.7 (70-137)	96.6±11.6 (70-123)	103.1±11.8 (80-127)	100±14.1 (68-133)	102.8±14 (90-125)	0.36
TG (mg/dL)	121.4±54.3	167.9±91.6	125.1±67.5	130.9±72.7	135.5±99.9	122.7±62.3	**0.004**
HDL (mg/dL)	53±17.6	48.7±19.4	46.3±11.9	47.4±17.7	52.8±13.9	51.4±15.6	0.3
MetS	11 (23.4)	45 (42)	14 (28.6)	5 (15.2)	7 (33)	1 (14.3)	**0.04**
NLR	3.7±3.9	4.4±3.3	3.2±2.7	1.8±0.97	4.3±3.6	4.4±1.99	**<0.0001**
PLR	217.4±165.3	257.3±186.9	178.8±101.9	138.7±50.2	286.7±484.9	209.5±115.2	**0.004**
TC (mg/dL)	188.5±37.1	204.5±59.3	183.6±34.9	191.7±36	200±48.2	199.6±56.4	0.4
LDL (mg/dL)	113.8±30.8	124.7±52.3	113.4±30.3	116±26.5	126.9±40.7	132±44.1	0.7
VLDL (mg/dL)	24.2±10.8	34±18.5	25±13.7	25.7±14.7	26.1±19.9	26.2±13.4	**0.002**
Disease activity and/or severity	**DAS-28** 5.2±2.27 (0-8.5)	**SLEDAI** 8.3±5.9 (0-29)		**BASDAI** 4.9±1.8 (2.1-8)	**BVAS** 5±3.9 (0-12)	**BDCAF** 5.14±2.7 (1-10)	–
		SLICC-DI 0.45±0.79 (0-4)	**mRss** 22.9±8.3 (2-43)		**VDI** 1.9±2.3 (0-6)	**BDI** 3.2±2.9 (0-7)	–

axSpA: Axial spondyloarthritis, BD: Behçet's disease, BASDAI: Bath ankylosing spondylitis disease activity index, BDCAF: BD current activity form, BDI: Behçet damage index, BMI: Body mass index, BVAS: Birmingham vasculitis activity score, DAS-28: Disease activity score-28, DM: Diabetes mellitus, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MetS: Metabolic syndrome, mRss: Modified Rodnan skin score, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, PV: Primary vasculitis, RA: Rheumatoid arthritis, SD: Standard deviation, SLE: Systemic lupus erythematosus, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinic-damage index, SSc: Systemic sclerosis, TC: Total cholesterol, TG: Triglycerides, WC: Waist circumference, VDI: Vasculitis damage index, VLDL: Very-low density lipoprotein. Statistically significant p-values are in bold. Significant effect sizes were found for comparison of the characteristics of RDs; age (0.19), age at disease onset (0.2), disease duration (0.1), BMI (0.5), WC (0.2), NLR (0.7), PLR (0.97), TC (0.5), HDL (0.4), LDL (0.5), TGs (0.6) and VLDL (0.3)

mean of 36.7±9.3 years (p>0.05). The matched control group for axSpA and vasculitis patients included 19 males (63.3%) and 11 females (36.7%) (p>0.05) with ages ranging from 16-83 years and a mean of 44.8±14.7 years (p>0.05).

When comparing the RD patients to their corresponding controls, the occurrence of MetS was comparable (p>0.05) except for SLE patients (42%) versus their controls (14.9%) (p=0.001) (Figure 1). In terms of effect size, MetS was significantly more frequent in SLE (OR 4.5, 95% CI: 1.8-10.9) and vasculitis patients (OR 5.6, 95% CI: 1.1-29.2) compared to their controls. The frequency of MetS in RA (OR 1.6, 95% CI: 0.9-4.4), SSc (OR 1.8, 95% CI: 0.7-4.72), and axSpA (OR 2.5, 95% CI: 0.5-13.9) was not significantly different from their controls.

Tables 2 and 3 summarize the comparison between RA, SLE, SSc, and vasculitis patients with and without MetS.

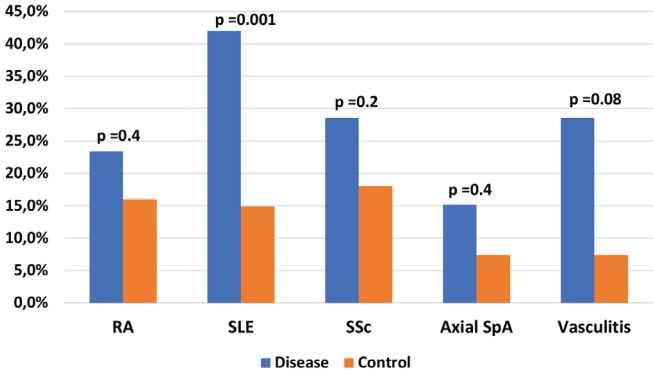

Figure 1. Frequency of metabolic syndrome among different rheumatic diseases and their corresponding control
RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, SSc: Systemic sclerosis, axSpA: Axial spondyloarthritis

Table 2. Comparison between RA and SSc patients with and without metabolic syndrome

Variable Mean ± SD or n (%)	Metabolic syndrome in RA patients (n=47)			Metabolic syndrome in SSc patients (n=49)		
	With (n=11)	Without (n=36)	p	With (n=14)	Without (n=35)	p
Age (years)*	55.6±11.7	40.8±12.4	**0.003**	45.2±9.5	42.5±15.1	0.49
Gender						
Male[t] Female	2 (18.2) 9 (81.8)	2 (5.6) 34 (94.4)	0.23	0 (0) 14 (100)	7 (20) 28 (80)	0.17
Disease duration (years)*	13.5±7.7	11.97±7.4	0.53	8.1±6.9	7.1±5.1	0.79
Neutrophils (%)	69.5±11.4	63.6±13.6	0.38	63.2±11.6	60±12.5	0.53
Lymphocytes (%)	22.7±9	25.8±10.7	0.67	28.8±10.5	27.4±11.4	0.39
NLR*	4.9±6.3	3.3±2.6	0.44	2.9±2.35	3.3±2.8	0.46
PLR*	199.8±143.2	223.2±173.5	0.44	146.1±91.9	193.1±104.1	0.14
ESR (mm/hour)*	51.5±39.8	44.4±28.3	0.72	56.7±38	40.4±27.2	0.19
Uric acid (mg/dL)	4.2±1.4	3.7±1.1	0.41	4.8±1.5	4.3±1.2	0.36
Creatinine (mg/dL)	0.76±0.4	0.66±0.19	0.71	1.2±1.5	0.7±0.3	0.66
Positive RF	5/6 (83.8)	13/18 (72.2)	1	-	-	-
Positive anti-CCP	2/2 (100)	9/11 (81.1)	1	-	-	-
Positive ANA	-	-	-	8/10 (80)	28/31 (90.3)	0.58
DAS-28* Active (≥2.6)[t] Remission (<2.6)[t]	4.6±1.8 7 (63.6) 4 (36.4)	5.4±2.4 28 (80) 7 (20)	0.33 0.42	-	-	-
High disease activity[t] Moderate disease activity[t] Low disease activity	2 (28.6) 5 (71.4) 0 (0)	19 (67.9) 4 (14.3) 5 (17.9)	**0.007**	-	-	-
mRss*	-	-	-	23.8±7.3	22.5±8.7	0.7
Current steroid dose*	9±6.3 (0-20)	6.5±3.7 (0-18)	0.24	8.9±11.9 (0-40)	6.6±7.5 (0-25)	0.67
Leflunomide[t]	4 (40)	17 (47.2)	0.74	0 (0)	3 (8.6)	-

Table 2. Continued

Variable Mean ± SD or n (%)	Metabolic syndrome in RA patients (n=47)			Metabolic syndrome in SSc patients (n=49)		
	With (n=11)	Without (n=36)	p	With (n=14)	Without (n=35)	p
Biologics[t]	3 (27.3)	13 (36.1)	0.73	0 (0)	1 (2.9)	-
Methotrexate[t]	4 (36.4)	10 (27.8)	0.71	1 (7.1)	6 (17.1)	0.66
Hydroxychloroquine[t]	1 (9.1)	8 (22.2)	0.66	1 (7.1)	4 (11.4)	1
Sulfasalazine	0 (0)	2 (5.6)	-			
Cyclophosphamide[t]	1 (9.1)	0 (0)	-	1 (7.1)	6 (17.1)	0.66
AZA[t]	-	-	-	1 (7.1)	2 (5.7)	1

*ANA: Antinuclear antibodies, Anti-CCP: Anti-cyclic citrullinated peptide, AZA: Azathioprine, CI: Confidence interval, DAS-28: Disease activity score-28, ESR: Erythrocyte sedimentation rate, mRss: Modified Rodnan skin score, NLR: Neutrophil-lymphocyte ratio, OR: Odds ratio, PLR: Platelet-lymphocyte ratio, RA: Rheumatoid arthritis, RF: Rheumatoid factor, SSc: Systemic sclerosis. Statistically significant p-values are in bold. *Effect sizes (Cohen's d) in RA: age (1.2), disease duration (0.2), NLR (0.4), PLR (0.1), ESR (0.2), DAS-28 (0.4) and current steroid dose (0.6). *: Effect sizes (Cohen's d) in SSc: Age (0.2), disease duration (0.2), NLR (0.2), PLR (0.5), ESR (0.5), mRss (0.2) and current steroid dose (0.3). t: Effect sizes (OR, 95% CI) in RA: Gender (OR 3.8, 95% CI: 0.5-30.6), DAS-28 (active) (OR 0.5, 95% CI: 0.1-2.2), DAS-28 (remission) (OR 2.4, 95% CI: 0.5-10.4), high disease activity (OR 0.2, 95% CI: 0.04-1.1), moderate disease activity (OR 6.7, 95% CI: 1.4-32.3), leflunomide (OR 0.6, 95% CI: 0.2-2.6), biologics (OR 0.7, 95% CI: 0.2-2.9), methotrexate (OR 1.5, 95% CI: 0.4-6.2) and hydroxychloroquine (OR 0.4, 95% CI: 0.04-3.2). t: Effect sizes (OR, 95% CI) in SSc: Methotrexate (OR 0.4, 95% CI: 0.04-3.4), hydroxychloroquine (OR 0.6, 95% CI: 0.06-5.9), cyclophosphamide (OR 0.4, 95% CI: 0.04-3.4) and AZA (OR 1.3, 95% CI: 0.1-15.2)*

Table 3. Comparison between SLE and vasculitis patients with and without metabolic syndrome

Variable Mean ± SD (range) or n (%)	Metabolic syndrome in SLE patients (n=100)			Metabolic syndrome in vasculitis patients (n=28)		
	With (n=42)	Without (n=58)	p	With (n=8)	Without (n=20)	p
Age (years)*	33.1±9.9	34.3±10.6	0.62	45.6±10.4	36.2±14.8	**0.04**
Gender						
Male[t] Female	3 (7.1) 39 (92.9)	4 (6.9) 54 (93.1)	1	5 (62.5) 3 (37.5)	11 (55) 9 (45)	1
Disease duration (years)*	10.14±7.2	7.98±6.8	0.08	7.1±9.2	6.3±5.6	0.66
Neutrophils (%)	72.4±10.3	66.9±14.6	0.09	69.88±11.1	68.85±12.5	1
Lymphocytes (%)	16.9±7.2	23.9±13.3	0.34	21.38±12.2	22.85±11.4	0.74
NLR*	4.77±3.57	4.03±2.99	0.35	4.8±4.159	4.146±2.8	0.72
PLR*	241.1±162	269.2±203.9	0.73	162.9±96.89	309.18±493.4	0.29
ESR (mm/1st hour)*	73.1±30.1	56±37.9	**0.02**	50.3±49.1	40.6±29.8	0.87
Uric acid (mg/dL)*	6.4±2.2	5.4±2.6	**0.03**	5.6±1.5	4.8±1.48	0.39
Urea (mg/dL)*	67.1±43.3	44.4±39	**<0.0001**	30.5±6.7	28.3±10.1	0.48
Creatinine (mg/dL)*	1.8±2.9	0.98±1.2	**0.001**	0.9±0.39	0.815±0.2	0.39
24 hours urinary proteins (gm/dL)*	2.5±2.2	1.25±1.6	**0.001**	-	-	-
Consumed C3[t]	16/24 (66.7)	13/24 (54.2)	0.38	-	-	-
Consumed C4[t]	5/22 (22.7)	10/24 (41.7)	0.2	-	-	-
Positive ANA	36/38 (94.7)	57/57 (100)	0.16	-	-	-
SLEDAI*	10.8±5.7	6.5±5.4	**0.001**	-	-	-
SLICC-DI*	0.6±0.98	0.33±0.6	0.15	-	-	-
Primary vasculitis BVAS* VDI* BD: BDCAF* BDI*	- -	- -	- -	5±3.7 0.6±1.1 6±0 (6-6) 7±0 (7-7)	5±4.2 2.5±2.4 5±2.96 2.4±2.5	0.97 0.07 0.45 0.14
Current steroid dose (mg/day)*	24.8±12.5 (5-50)	20.5±12.1 (5-50)	0.08	26.3±13 (0-40)	22.5±11.6 (0-40)	0.39
AZA[t]	15 (35.7)	23 (39.7)	0.7	1 (12.5)	5 (25)	0.64
Hydroxychloroquine[t]	28 (66.7)	41 (70.7)	0.67	1 (12.5)	0 (0)	-
Biologics[t]	2 (4.8)	1 (1.7)	0.57	0 (0)	2 (10)	-
MMF[t]	9 (21.2)	10 (17.2)	0.6	0 (0)	1 (5)	-
Cyclophosphamide[t]	9 (21.4)	5 (8.6)	0.07	4 (50)	6 (30)	0.4

Table 3. Continued

Variable Mean ± SD (range) or n (%)	Metabolic syndrome in SLE patients (n=100)			Metabolic syndrome in vasculitis patients (n=28)		
	With (n=42)	Without (n=58)	p	With (n=8)	Without (n=20)	p
Methotrexate[t]	1 (2.4)	2 (3.4)	1	1 (12.5)	0 (0)	-
Leflunomide	0 (0)	1 (1.7)	-	-	-	-
Cyclosporine	-	-	-	0 (0)	2 (10)	-

*ANA: Antinuclear antibodies, c-ANCA: Cytoplasmic ANCA, AZA: Azathioprine, BD: Behçet's disease, BDCAF: Behçet's disease current activity form, BDI: Behçet's disease damage index, BVAS: Birmingham vasculitis activity score, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, MMF: Mycophenolate mofetil, NLR: Neutrophil-lymphocyte ratio, OR: Odds ratio, PLR: Platelet-lymphocyte ratio, SD: Standard deviation, SLE: Systemic lupus erythematosus, SLEDAI: Systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaboration Clinics-damage index, VDI: Vasculitis damage index. Statistically significant p-values are in bold. *: Effect sizes (Cohen's d) in SLE: Age (0.1), disease duration (0.3), NLR (0.2), PLR (0.2), ESR (0.5), uric acid (0.4), urea (0.7), creatinine (0.4), 24-hours urinary proteins (0.7), SLEDAI (0.8), SLICC-DI (0.4) and current steroid dose (0.4). *: Effect sizes (Cohen's d) in vasculitis: Age (0.7), disease duration (0.1), NLR (0.2), PLR (0.3), ESR (0.3), BVAS (0), VDI (0.9), BDCAF (0.4), BDI (2.2) and current steroid dose (0.3). t: Effect sizes (OR, 95% CI) in SLE: Gender (OR 1, 95% CI: 0.2-4.9), consumed C3 (OR 1.7, 95% CI: 0.5-5.4), consumed C4 (OR 0.4, 95% CI: 0.1-1.5), AZA (OR 0.9, 95% CI: 0.4-1.9), hydroxychloroquine (OR 0.8, 95% CI: 0.4-2), biologics (OR 2.9, 95% CI: 0.3-32.5), MMF (OR 1.3, 95% CI: 0.5-3.6), cyclophosphamide (OR 2.8, 95% CI: 0.9-9.4) and methotrexate (OR 0.7, 95% CI: 0.1-7.8). t: Effect sizes (OR, 95% CI) in vasculitis: Gender (OR 1.4, 95% CI: 0.3-7.3), AZA (OR 0.4, 95% CI: 0.04-4.4) and cyclophosphamide (OR 2.3, 95% CI: 0.4-12.6)*

None of the recruited patients with different RDs had chronic kidney disease.[29] The clinical characteristics of SLE patients with and without MetS were not significantly different (p>0.05) except for nephritis, which was more frequent among patients with MetS (83.3%) compared to those without (48.3%) (OR 5.4, 95% CI: 2.1-14.1, p<0.0001). In SSc, no significant differences were observed (p>0.05) except for myositis, which was reported in 28.6% of patients with MetS compared to 2.9% of those without (OR 13.6, 95% CI: 1.4-135.9, p=0.02). Table 4 presents the comparison between axSpA patients with and without MetS.

In regression analysis, age was independently associated with MetS (B=0.2, p=0.02) in RA patients, while the association between DAS-28 disease activity grading and MetS was not significant (B=-0.2, p=0.8). In SLE, nephritis, SLEDAI, and creatinine were associated with MetS (B=2.6, p=0.01; B=0.2, p=0.01; and B=3.2, p=0.03, respectively). The associations of erythrocyte sedimentation rate (ESR), urea, 24-hour urinary proteins, and serum uric acid with MetS were not significant (B=0.02, p=0.1; B=-0.02, p=0.5; B=-0.2, p=0.5; and B=-0.3, p=0.2, respectively).

Discussion

Inflammation contributes significantly to the pathogenesis of MetS.[3] Moreover, hematological indices have been strongly associated with multiple metabolic conditions, such as CVDs[30] and diabetes,[31] and have been correlated with pro-inflammatory cytokines.[32] In this study, MetS was found in 23.4% of RA patients, with no significant difference compared to controls. MetS has been reported in 30-42% of RA patients,[6] however, lower frequencies, such as 19%, have also been reported.[33]

Regarding DAS-28, no significant association was found with MetS in this study, but a significant difference was observed based on DAS-28 activity grading, where a higher disease activity grade was noted in RA patients without MetS. A statistically significant difference was observed in DAS-28 grading (moderate disease activity) between RA patients with and without MetS (OR 6.7, 95% CI: 1.4-32.3). Similarly, a significant difference was found regarding the current steroid dose (effect size, 0.6). In line with these findings, some studies reported no association between DAS-28 and MetS,[34,35] whereas others found a significant increase in DAS-28 among RA patients with MetS compared to those without.[12]

MetS was present in 42% of SLE patients, significantly higher than in controls (p=0.001). This aligns with previous studies, which reported MetS in 32.4% of SLE patients.[36] In this study, SLEDAI and ESR were significantly higher in SLE patients with MetS, while the damage index did not differ significantly. Regression analysis revealed that SLEDAI was independently associated with MetS, supporting earlier findings,[13] though some studies reported no such association.[37]

Nephritis was significantly more frequent in SLE patients with MetS (83.3%) compared to those without (48.3%) (OR 5.4, 95% CI: 2.1-14.1, p<0.0001). Urea, creatinine, serum uric acid and 24 hour-urinary proteins were also significantly higher in SLE patients with MetS. Regression analysis showed that nephritis and creatinine were independently associated with MetS. Dyslipidemia has been linked to SLE nephritis, with elevated TC, TG, and LDL levels, along with reduced HDL.[38] Dyslipidemia can contribute to renal disease progression in SLE by damaging the endothelium, glomerular filtration barrier, and causing tubular-interstitial lipid deposition.[39] In line, dyslipidemia was significantly associated with proteinuria in SLE nephritis patients.[40] Consistent with previous findings, hyperuricemia was significantly associated with dyslipidemia,[41] though some

Table 4. Comparison between axSpA patients with and without metabolic syndrome

Variable Mean ± SD or n (%)	Metabolic syndrome in axSpA patients (n=33)		
	With (n=5)	Without (n=28)	p
Age (years)*	47.6±10.4	39.5±9.6	0.15
Gender			
Male[ŧ] Female	4 (80) 1 (20)	20 (71.4) 8 (28.6)	1
Disease duration (years)*	10±1.9	12.9±8.7	0.63
Neutrophils (%)	51.6±2.96	55.2±10.96	0.49
Lymphocytes (%)	35.2±5.2	33.6±10.2	0.48
NLR*	1.5±0.3	1.9±1.04	0.35
PLR*	119.2±34.1	142.4±50.4	0.45
ESR (mm/hour)*	31±15.6	26.6±19.6	0.35
Uric acid (mg/dL)	5.5±0.7	4.7±1.6	0.33
Creatinine (mg/dL)	0.8±0.3	0.8±0.3	0.88
BASDAI*	5.6±1.3	4.8±1.9	0.4
Psoriasis	2 (40)	5 (17.9)	0.28
Pyoderma gangrenosum	0 (0)	1 (3.6)	-
Peripheral arthritis	1 (20)	4 (14.3)	1
Uveitis	0 (0)	2 (7.1)	-
IBD	0 (0)	3 (10.7)	-
Enthesitis	0 (0)	1 (3.6)	-
Dactylitis	0 (0)	1 (3.6)	-
Current steroid dose	0.5±1.1 (0-3)	0.6±2.9 (0-15)	0.19
Biologics	2 (40)	17 (60.7)	0.63
Methotrexate	1 (20)	4 (14.3)	1
Sulfasalazine	0 (0)	2 (7.1)	-

*axSpA: Axial spondyloarthritis, BASDAI: Bath ankylosing spondylitis disease activity index, CI: Confidence interval, ESR: Erythrocyte sedimentation rate, IBD: Inflammatory bowel disease, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, OR: Odds ratio, SD: Standard deviation. Statistically significant p-values are in bold. *: Effect sizes (Cohen's d): Age (0.8), disease duration (0.4), NLR (0.4), PLR (0.5), ESR (0.2) and BASDAI (0.4). ŧ: Effect sizes (OR, 95% CI): Gender (OR 1.6, 95% CI: 0.2-16.6)*

studies found no significant difference in uric acid levels between SLE patients with and without MetS.[13]

Interestingly, corticosteroid use was not significantly associated with MetS in this SLE cohort, potentially due to the predominance of young female patients. However, since cumulative steroid doses were not analyzed, the impact of corticosteroids on MetS development remains unclear.

In SSc, MetS was present in 28.6% of patients, comparable to controls. This is consistent with previous findings reporting MetS in 20% of SSc patients versus 14.3% in controls.[42] No significant differences were observed between SSc patients with and without MetS regarding age, disease duration, gender, ESR, mRss, or current steroid dose. However, myositis was significantly more frequent in SSc patients with MetS (28.6%) compared to those without (2.9%) (OR 13.6, 95% CI: 1.4-135.9, p=0.02).

In axSpA, MetS prevalence was 15.2%, similar to controls. While some studies reported higher MetS prevalence in ankylosing spondylitis patients compared to controls,[43] this study found no significant association between BASDAI scores and MetS, consistent with prior findings.[43] A small effect size (0.4) was, however, noted when comparing BASDAI scores in axSpA patients with and without MetS.

In vasculitis, MetS was found in 28.6% of patients, comparable to controls. This contrasts with studies showing significantly higher MetS prevalence in ANCA-associated vasculitis patients.[8,44] In BD patients, MetS prevalence was also similar to controls, with no significant difference in BDCAF scores between patients with and without MetS.[45] Notably, large effect sizes were observed for the VDI and BDI in primary vasculitis and BD patients, respectively.

This study is one of the first to assess the association of NLR and platelet-lymphocyte ratio (PLR) with MetS across different RDs. No significant associations were found, although a medium effect size was noted for PLR in axSpA patients. Some studies have reported increased platelet counts in MetS patients compared to controls, though PLR was not significantly different.[46] In contrast, other studies

have shown significant associations between NLR and MetS and correlations with its components.[47,48]

The current study had a few limitations. Being a cross-sectional design, we cannot delineate a causal relationship between disease characteristics and MetS. Moreover, we did not record data on treatment duration and compliance, limiting our ability to estimate the effect of these factors on MetS development. The relatively small number of cases may warrant future larger-scale, and even prospective, studies to better assess the impact of anti-rheumatic medications on MetS diagnosis. Additionally, given the small sample size, interpreting results solely based on p-values is not recommended;[49] however, estimating effect sizes and their respective uncertainty might provide better insight into the magnitude of the observed differences.

There were many variations between patient groups in the current study; therefore, a simple correlation analysis between variables provided limited strength to the results. Accordingly, logistic regression analysis was conducted, adjusting for one or two confounding variables, especially those related to lipid metabolism. Other confounders for MetS, including physical activity and dietary habits, were not available in the current study cohort. Nonetheless, by adjusting for several confounding variables, this analysis offers insights for future larger-scale longitudinal studies.

The clinical relevance of the current study is strengthened by the fact that it is among the few studies assessing the frequency of MetS and its components across different RDs, including rare diseases such as primary vasculitis. RDs are considered a diverse array of conditions that, despite their differences, share overlapping features, the use of common non-specific therapies, and the potential for progression from one disease to another, suggesting common pathogenic mechanisms.[50] In this study, MetS was frequently associated with various RDs, with a significantly higher prevalence in SLE patients compared to controls, potentially related to disease activity. When comparing different RDs, MetS was significantly more frequent in SLE (42%) than in other RDs. Regarding MetS components, there was a significantly higher frequency of hypertension and elevated TG in SLE patients compared to those with other RDs. In contrast, no significant difference in MetS diagnosis was reported among RA, SLE, and SSc patients.[51] However, lower HDL levels and increased abdominal circumference have been reported in SLE and RA patients, respectively.[51]

Conclusion

The current study delves into the complex relationship between metabolic alterations, inflammation, and disease activity in a group of RDs. Encompassing different RDs in the same setting was one of the objectives of this analysis, aiming to determine which disease warrants the most attention. Moreover, this study is among the first to assess the association of NLR and PLR with MetS across different RDs. Investigating NLR and PLR in this context may provide insights into the link between inflammation, MetS, and atherosclerotic CVDs in RD patients. Given the heightened frequency of MetS among SLE patients, larger-scale prospective studies are warranted to explore the impact of MetS on atherogenesis and CVDs in RDs.

Ethics

Ethics Committee Approval: The members of the Scientific Research and Ethics Committee of the Rheumatology and Rehabilitation Department, Cairo University (SReC-RCU) have reviewed and approved the aforementioned M.Sc. protocol (approval number: 40-SReC-RCU2021, date: 20.03.2021).

Informed Consent: An informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Concept: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Design: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Data Collection and Processing: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Analysis or Interpretation: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Literature Search: S.S.A-A., P.N.E-H., N.N.E., T.A.G., Writing: S.S.A-A., P.N.E-H., N.N.E., T.A.G.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? Circulation. 2003;108:1546-51.
2. National cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults; Third report of the national cholesterol education program expert panel (NCEP) on detection, evaluation and treatment of high blood choleaterol in adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.
3. Nilsson J, Jovinge S, Niemann A, Reneland R, Lithell H. Relation between plasma tumor necrosis factor-alpha and insulin sensitivity in elderly men with non-insulin-dependent diabetes mellitus. ArterioscIerThrombVasc Biol. 1998;18:1199-202.
4. Piché ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein,

interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. Am J Cardiol. 2005;96:92-7.

5. Schattner A, Liang MH. The cardiovascular burden of lupus: a complex challenge. Arch Intern Med. 2003;163:1507-10.
6. Chung CP, Oeser A, Solus JF, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis. 2008;196:756-63.
7. Peralta-Amaro AL, Cruz-Domínguez Mdel P, Olvera-Acevedo A, Vera-Lastra OL. Prevalence of metabolic syndrome and insulin resistance in system sclerosis. Rev Med Inst Mex Seguro Soc. 2015;53:476-83.
8. Petermann Smits DR, Wilde B, KianersiAdegani M, de Jongh H, van Paassen P, Cohen Tervaert JW. Metabolic syndrome in ANCA-associated vasculitis. Rheumatology (Oxford). 2013;52:197-203.
9. Senn JJ, Klover PJ, Nowak IA, Mooney RA. Interleukin-6 induces cellular insulin resistance in hepatocytes. Diabetes. 2002;51:3391-9.
10. Balta S, Celik T, Mikhailidis DP, et al. The relation between atherosclerosis and the neutrophil-lymphocyte ratio. Clin Appl Thromb. 2016;22:405-11.
11. Hao X, Li D, Wu D, Zhang N. The relationship between hematological indices and autoimmune rheumatic diseases (ARDs), a meta-analysis. Sci Rep. 2017;7:1-9.
12. Karvounaris SA, Sidiropoulos PI, Papadakis JA, et al. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis. 2007;66:28-33.
13. Hammam N, Rashad SM, Mohamed AAA. Metabolic syndrome in systemic lupus erythematosus patients. Zeitschrift für Rheumatologie. 2018;77:938-45.
14. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44-8.
15. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. Arthritis Rheum. 1992;35:630-40.
16. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath ankylosing spondylitis disease activity index. J Rheumatol. 1994;21:2286-91.
17. Mukhtyar C, Lee R, Brown D, et al. Modification and validation of the Birmingham vasculitis activity score (version 3). Ann Rheum Dis. 2009;68:1827-32.
18. Gheita TA, Fathi HM, Eesa NN, et al. Development of an Arabic version of the Behçet's disease current activity form (Ar-BDCAF): cross-cultural adaptation and validation initiative in Egypt. Clin Rheumatol. 2021;40:4609-18.
19. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum. 1996;39:363-9.
20. Clements P, Lachenbruch P, Siebold J, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol. 1995;22:1281-5.
21. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997;40:371-80.
22. Gheita TA, Hammam N, Fawzy SM, et al. Development and validation of a Behçet's disease damage index for adults with BD: an explicit, composite and rated (ECR) tool. Int J Rheum Dis. 2021;24:1071-9.
23. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
24. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677-86.
25. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65:2737-47.
26. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68:777-83.
27. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of vasculitides. Arthritis Rheum. 2013;65:1-11.
28. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet. 1990;335:1078-80.
29. Chen YC, Chen CY, Tien YC, Fang JT, Huang CC. Organ system failures prediction model in intensive care patients with acute renal failure treated with dialysis. Ren Fail. 2001;23:207-15.
30. Saliba W, Barnett-Griness O, Elias M, Rennert G. Neutrophil to lymphocyte ratio and risk of a first episode of stroke in patients with atrial fibrillation: a cohort study. J ThrombHaemost. 2015;13:1971-9.
31. Khandare SA, Chittawar S, Nahar N, Dubey TN, Qureshi Z. Study of neutrophil-lymphocyte ratio as novel marker for diabetic nephropathy in type 2 diabetes. Indian J Endocrinol Metab. 2017;21:387-92.
32. Turkmen K, Erdur FM, Ozcicek F, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17:391-6.
33. Dessein PH, Tobias M, Veller MG. Metabolic syndrome and subclinical atherosclerosis in rheumatoid arthritis. J Rheumatol. 2006;33:2425-32.
34. Ghazaly AH, El-Moez KM, El Shorbagy MS, El-Nahrery EM. Angiopoietin-2 as a biomarker for metabolic syndrome and disease activity in rheumatoid arthritis patients. The Egyptian Rheumatol. 2016;38:9-13.
35. Eldin AB, ElBakry SA, Morad CS, Abd-El-Samie AM. The impact of metabolic syndrome on rheumatoid arthritis in a cohort of Egyptian patients. Egyptian Rheumatol. 2018;40:7-10.

36. Baraka E, El Dein M, Farouk H, El Moutaz Y. Hyperhomocysteinemia and metabolic syndrome are risk factors for sub-clinical atherosclerosis in women with systemic lupus erythematosus. Egyptian Rheumatol. 2015;37:67-74.

37. El-Hady A, Sennara S, Mosaad Y, Mahmoud N. Serum ferritin, transferrin and metabolic syndrome are risk factors for subclinical atherosclerosis in Egyptian women with systemic lupus erythematosus (SLE). The Egyptian Rheumatol. 2019;41:35-40.

38. Liu L, Zhang T, Ye Y, Zhang S, Chen L. [Analysis of traditional cardiovascular risk factors in patients with systemic lupus erythematosus]. Zhonghua Xin Xue Guan Bing Za Zhi. 2014;42:753-8.

39. Luzar B, Ferluga D. Role of lipids in the progression of renal disease in systemic lupus erythematosus patients. Wien KlinWochenschr. 2000;112:716-21.

40. Mirghani HO, Alyoussef AAK, Mohammed OS, Amirthalingam P. The relationship between dyslipidemia and lupus nephritis in systemic lupus erythematosus patients attending a Saudi Rheumatic Center, Tabuk. Sudan Journal of Medical Sciences. 2020;15:10-9.

41. Chen S, Yang H, Chen Y, et al. Association between serum uric acid levels and dyslipidemia in Chinese adults: a cross-sectional study and further meta-analysis. Medicine (Baltimore). 2020;99:e19088.

42. Lee SG, Kim JM, Lee SH, et al. Frequency of metabolic syndrome in female patients with systemic sclerosis: a preliminary report. J Rheum Dis. 2012;19:262-9.

43. Malesci D, Niglio A, Mennillo GA, Buono R, Valentini G, La Montagna G. High prevalence of metabolic syndrome in patients with ankylosing spondylitis. Clin Rheumatol. 2007;26:710-4.

44. Atas DB, Atas H, İzgi TN, et al. The prevalence of metabolic syndrome is increased in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. Int Urol Nephrol. 2021;53:1427-34.

45. El-Gazzar I, El-Dakrony AH, Sayed S, et al. Clinical significance of metabolic syndrome and carotid intima-media thickness in Behçet's disease patients: relation to disease activity. Egyptian Rheumatol. 2017;39:171-4.

46. Jialal G, Adams-Huet B, Jialal I. Both the platelet count and the platelet: lymphocyte ratio are not increased in nascent metabolic syndrome. Platelets. 2019;30:1057-8.

47. Hashemi Moghanjoughi P, Neshat S, Rezaei A, Heshmat-Ghahdarijani K. Is the neutrophil-to-lymphocyte ratio an exceptional indicator for metabolic syndrome disease and outcomes? Endocr Pract. 2022;28:342-8.

48. Gaafar A, Aly HM, Amer A. Metabolic syndrome, hematological markers of inflammation and disease activity in rheumatoid arthritis. Int J Clin Rheumatol. 2021;16:052-8.

49. Wasserstein RL, Schirm, AL, Lazar NA. Moving to a World Beyond "p<0.05". The American Statistician. 2019;73 (Sup 1):1-19.

50. Moutsopoulos HM. Autoimmune rheumatic diseases: one or many diseases? J TranslAutoimmun. 2021;4:100129.

51. Paats A, Valinotti V, Acosta R, et al. SAT0085 metabolic syndrome and its association with rheumatic diseases in Paraguayan patients. Ann Rheum Dis. 2020;79:976.

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2024.46330
Ulus Romatol Derg 2025;17(1):30-44

Unveiling malignancy patterns among rheumatology patients: Insights from a retrospective study

Romatoloji hastalarında malignite: Retrospektif bir çalışmadan değerlendirmeler

Senem Tekeoğlu

Haliç University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye

Abstract

Objective: Malignancy is a significant comorbidity in patients with rheumatic diseases. This study investigates the incidence, prevalence, and risk factors of malignancies among patients with rheumatic diseases and non-inflammatory conditions in a rheumatology clinic.

Methods: A retrospective analysis was conducted on 2,600 patients between January 2021 and January 2024. Data collected included patient demographics, rheumatic disease types, non-inflammatory conditions, treatments, and cancer history. Statistical analyses included chi-square tests, Fisher's exact tests, Mann-Whitney U tests, logistic regression, and standard incidence ratio (SIR) calculations.

Results: Of the 2,600 patients, 100 had a cancer history, with a median age of 66 years, higher than those without cancer (p<0.001). Breast cancer was the most common malignancy (29%), followed by gynecologic and respiratory cancers. Cancer prevalence was higher among rheumatoid arthritis (RA) and osteoarthritis patients and lower in ankylosing spondylitis and fibromyalgia patients. Twenty-six patients received a cancer diagnosis after the onset of a rheumatic or non-inflammatory condition. In female patients, gynecologic cancers [SIR=3.76, 95% confidence interval (CI)=1.2-8.7, p=0.005] and lymphoma (SIR=8.14, CI=1.6-23.7, p=0.001) were more common. In male patients, the total number of cancers was significantly higher (SIR=381, CI=182.7-700.8, p<0.001). Moreover, two patients treated with nivolumab developed new-onset RA and psoriatic arthritis, while one patient treated with ribociclib developed systemic sclerosis. Logistic regression identified age [odds ratio (OR)=1.03], male gender (OR=2.16), the presence of inflammatory diseases (OR=4.52), and Charlson Comorbidity index score (OR=5.65) as significant predictors of cancer diagnosis.

Conclusion: This study highlights the need for vigilant cancer screening in rheumatic disease patients, especially the elderly. Future research should focus on prospective studies to develop targeted cancer prevention and management strategies for this population.

Keywords: Neoplasms, lymphoma, rheumatoid arthritis, autoimmune diseases

Öz

Amaç: Malignite romatizmal hastalıklarda önemli bir komorbiditedir. Bu çalışmada bir romatoloji kliniğinde takip edilen romatizmal ve non-enflamatuvar hastalıkları olan bireylerde maligniteleri insidansı, prevalansı ve risk faktörleri araştırılmaktadır.

Yöntem: Ocak 2021 ile Ocak 2024 arasında takip edilen 2.600 hasta üzerinde retrospektif bir analiz yapıldı. Toplanan veriler arasında hastaların demografik özellikleri, romatizmal hastalık türleri, enflamatuvar olmayan durumlar, tedaviler ve kanser geçmişine yer verildi. İstatistiksel analizlerden ki-kare, Fisher kesin olasılık ve Mann-Whitney U testleri, lojistik regresyon analizi ve standart insidans oranı (SIR) hesaplamaları kullanıldı.

Bulgular: 2.600 hastanın 100'ünde kanser öyküsü saptandı. Ortalama yaş 66 olup malignite öyküsü olanlarda olmayanlara göre daha yüksekti (p<0,001). Meme kanseri en sık görülen malignite (%29) olup, bunu jinekolojik ve solunum sistemi kanserleri takip etmekteydi. Kanser prevalansı romatoid artrit (RA) ve osteoartrit hastalarında daha yüksek, ankilozan spondilit ve fibromiyalji hastalarında ise daha düşüktü. Yirmi altı hastaya romatizmal veya enflamatuvar olmayan bir durumun başlangıcından sonra kanser tanısı konuldu. Kadın hastalarda jinekolojik kanserler [SIR=3,76, %95 güven aralığı (GA)=1,2-8,7, p=0,005] ve lenfoma (SIR=8,14, GA=1,6-23,7, p=0,001) daha sık görüldü. Erkek hastalarda toplam kanser sayısı anlamlı derecede yüksekti (SIR=381, GA=182,7-700,8, p<0,001). Ayrıca, nivolumab ile tedavi edilen iki hastada yeni başlayan RA ve psoriatik artrit gelişirken, ribosiklib ile tedavi edilen bir hastada sistemik skleroz gelişti. Lojistik regresyonda yaş [odds oranı (OR)=1,06], erkek cinsiyet (OR=2,16), enflamatuvar hastalık öyküsü (OR=4,52) ve Charlson komorbidite indeks skorunun (OR=5,65) kanser gelişiminde önemli belirleyiciler olduğunu saptandı.

Sonuç: Bu çalışma romatizmal hastalığı olan özellikle yaşlı bireylerde kanser taramasının gerekliliğini vurgulamaktadır. Bu hastalar için hedefe yönelik kanser önleme ve yönetim stratejileri geliştirme odaklı prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Neoplazmalar, lenfoma, romatoid artrit, otoimmün hastalıklar

Correspondence / İletişim:
Senem Tekeoğlu Asst. Prof., Haliç University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
E-mail: senemtekeoglu@gmail.com **ORCID ID:** orcid.org/0000-0001-5539-8755
Received / Geliş Tarihi: 13.08.2024 **Accepted / Kabul Tarihi:** 08.12.2024 **Publication Date / Yayın Tarihi:** 19.03.2025

Cite this article as / Atıf: Tekeoğlu S. Unveiling malignancy patterns among rheumatology patients: insights from a retrospective study. Ulus Romatol Derg. 2025;17(1):30-44

Introduction

Malignancies are a significant comorbidity in patients with rheumatic diseases, posing unique challenges in their management.[1] This increased risk arises from both the underlying autoimmune processes and potential side effects of treatments such as immunosuppressants. Shared environmental factors, like smoking, further amplify this risk.[2]

Chronic inflammation in rheumatic diseases fosters a pro-tumorigenic environment through cytokine-mediated DNA damage, angiogenesis, and immune dysregulation.[3,4] Notably, conditions like primary Sjögren's syndrome and systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) are associated with higher risks of lymphoma,[5-7] emphasizing the need for vigilance.

The impact of antirheumatic treatments on cancer risk remains debated.[8,9] While a 2019 systematic review found no increased cancer risk with biological disease-modifying antirheumatic drugs,[10] high doses of cyclophosphamide have been associated with lymphoproliferative and bladder cancers,[11] and prolonged azathioprine use may increase the risk of skin cancers and cervical atypia.[12]

Additionally, the relationship between autoimmunity and cancer is bidirectional.[13] Immune responses against tumors can target self-tissues, leading to paraneoplastic syndromes. Moreover, cancer therapies, including chemotherapy and immune-checkpoint inhibitors, can trigger immune-related adverse events.[14,15]

While existing studies often focus on individual rheumatic conditions, comprehensive analyses across multiple diseases are scarce, especially in Turkish cohorts.[16-18] This study aims to bridge this gap by examining the incidence, prevalence, and risk factors for malignancies in patients with rheumatic and non-inflammatory diseases over a three-year period.

Materials and Methods

The electronic medical records of all 2,600 consecutive patients who visited the two rheumatology clinics of a private hospital between January 2021 and January 2024 were retrospectively evaluated. This private hospital in Istanbul provides care to both Turkish and international patients, treating individuals aged 16 and above for rheumatic diseases and non-inflammatory conditions.

Patient Selection

All 2,600 patients who visited the outpatient clinics during the study period were included, regardless of their final diagnosis. While many patients had confirmed inflammatory rheumatic diseases based on established diagnostic criteria, some presented with non-inflammatory conditions or non-specific complaints.

Inclusion Criteria

Inflammatory Diseases

Patients were included if they met the diagnostic or classification criteria for inflammatory diseases, such as:

- RA[19]

- Spondyloarthritis (SpA),[20] comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA),[21] enteropathic arthritis, and reactive arthritis

- Connective tissue diseases (CTDs), such as SLE,[22] Sjögren's syndrome,[23] systemic sclerosis, myositis, and undifferentiated CTDs

- Polymyalgia rheumatica (PMR),[24] gout[25]

- Vasculitis, including Behçet's disease[26] and other systemic vasculitides.[27-29]

Non-inflammatory Conditions

Patients without a confirmed inflammatory diagnosis were included in the study for completeness, but their data were analyzed separately. Osteoarthritis,[30] and fibromyalgia[31] were diagnosed according to criteria. The remaining non-inflammatory conditions included cases such as isolated autoantibody positivity without clinical manifestations of autoimmune disease, elevated acute-phase reactants, non-specific musculoskeletal pain, or referrals for different complaints, such as headaches or mucocutaneous symptoms.

Data Collection

Data collected included age, gender, smoking status, type of rheumatic disease, and non-inflammatory conditions and treatments. Comorbidities were documented using the Charlson Comorbidity index (CCI) for each patient. Patients aged 65 and older at their last clinic visit were classified as geriatric patients. Survival information for Turkish citizens was obtained from the national registry, though specific times and causes of death were not available. This information was not available for international patients.

Malignancy Data

The type and onset of malignancies were recorded relative to the onset of rheumatic disease. Cancers were categorized as follows:

- Gastrointestinal cancers (C15-26): esophageal (C15), stomach (C16), colorectal (C18-20), pancreatic (C25) cancers

- Respiratory system cancers (C30-38): laryngeal (C32), lung (C34) cancers

- Skin cancers: melanoma (C43) and non-melanoma skin cancers (NMSC) (C44)

- Gynecologic cancers (C51-58): cervical (C53), endometrium (C54), ovarian (C56) cancers

- Male reproductive system cancers (C60-63): prostate (C61), testicular (C62) cancers

- Urinary tract cancers (C64-68): renal cell carcinoma (C64), bladder cancer (C67)

- Hematologic cancers (C81-96): lymphoma (C81-85), multiple myeloma (C90), chronic lymphocytic leukemia (C91.1)

- Sarcoma (C49), thyroid cancer (C73), carcinoma of unknown primary (C80.1).

Statistical Analysis

Data analysis was performed using SPSS version 26 and R version 4.2.2. Qualitative variables, such as the prevalences of rheumatic diseases and cancers, were presented as absolute and relative frequencies. Comparisons between groups for gender, smoking history, geriatric status, and prevalences of rheumatic diseases and cancers were conducted using the chi-square test. Fisher's exact test was utilized when expected frequencies were less than 5. Age differences among groups were assessed with the Mann-Whitney U test, and values were expressed as medians ± interquartile ranges (IQRs) due to the non-normal distribution of these variables. Logistic regression analysis was performed to determine the influence of variables on cancer history.

For newly diagnosed cancer cases during the study period, the standard incidence ratio (SIR), 95% confidence intervals (CIs), and p-values were calculated using the R program and the epiR package. The SIR was determined by dividing the number of observed cases by the expected cases. Observed cases refer to patients with a new cancer diagnosis during the follow-up period. Expected cases were calculated as person-years of follow-up multiplied by the incidence rate of each cancer in the general population. For patients without cancer, person-years of follow-up were calculated from their first to their last visit during the study period. For patients diagnosed with cancer after the onset of rheumatic disease, person-years of follow-up were calculated from the date of rheumatic disease diagnosis to the date of cancer diagnosis. The incidence rates of specific cancers in the Turkish population were obtained from 2018 public health records.[32]

Statistical significance was set at a p-value of less than 0.05.

The study was approved by the local ethics committee (Memorial Bahçelievler Hospital Ethics Committee – approval number: 133, date: 11.06.2024).

Results

General Demographics

The study included a total of 2,600 patients, with a median age of 49 years (IQR=26) and a female-to-male ratio of 7:3. Among all patients, 45.8% had inflammatory diseases, with RA (33.7%), SpA (31.2%), CTDs (11.5%), and crystalline arthropathies (11.1%) being the most common diagnoses. Osteoarthritis (18.1%) and fibromyalgia syndrome (14.8%) were among the most common non-inflammatory conditions leading to admission. Other musculoskeletal complaints (35.1%) and back pain (12.2%) accounted for the majority of the remaining cases (Table 1).

Cancer Prevalence and Demographics

Out of the 2,600 patients, 100 had a history of cancer. The female-to-male ratio was comparable between those with and without a history of cancer (p=0.13). However, the median age of patients with a history of cancer was 66 (IQR=16.5), while those without such a history were younger, with a median age of 48 (IQR=25) (Table 1).

In total, 41 patients (3.4%) with inflammatory diseases and 59 patients (4.2%) with non-inflammatory conditions had a history of cancer (Table 2). When comparing all patients with inflammatory diseases to those with non-inflammatory conditions (e.g., osteoarthritis, fibromyalgia, non-specific musculoskeletal pain), the prevalence of malignancy was not significantly different between the two groups in univariate analysis (p=0.32). However, when other parameters were taken into account in multivariate logistic regression, the difference became significant (p<0.001).

Further analysis of individual disease types revealed that patients with AS, SpA and fibromyalgia had a lower prevalence of cancer compared to other groups (p=0.005 for AS and SpA and p=0.01 for fibromyalgia). In contrast, osteoarthritis was associated with a higher prevalence of cancer (p=0.01) (Table 1).

By the end of the study, 39 patients were known to have died, accounting for 1.6% of known cases. Of these, 10 patients (10.1%) were from the cancer group, while 29 patients (1.2%) were from the non-cancer group (Table 1).

Table 1. Demographics, rheumatic diseases, and non-inflammatory conditions in patients with and without cancer

	Total	Cancer present	Cancer absent	p	OR	CI
	n=2,600	n=100 (%)	n=2,500 (%)			
Age				**<0.001**		
Median (IQR)	49 (26)	66 (16.5)	48 (25)			
Min-max	16-88	28-88	16-88			
Gender				0.13		
Female	1862 (71.6)	65 (3.5)	1797 (96.5)			
Male	738 (28.4)	35 (4.7)	703 (95.3)			
Smoking ever	684 (26.3)	31 (31.0)	653 (26.1)	0.27		
No	1916 (73.7)	69 (69.0)	1847 (73.9)			
Yes	548 (21.1)	22 (22.0)	526 (21.0)			
Previous	136 (5.2)	9 (9.0)	127 (5.1)			
CCI (mean ± SD)	0.82±0.95	3.0±1.1	0.74±0.82	**<0.001**		
Mortality						
Yes	39 (1.6%)	10 (25.6%)	29 (74.4%)	**<0.001**	9.48	4.47-20.13
No	2282	80	2202			
Unknown	279	10	269			
Inflammatory diseases	1193 (45.8)	43 (3.6)	1150 (96.4)	0.55		
Rheumatoid arthritis	403 (15.5)	17 (4.2)	386 (95.8)	0.67		
Connective tissue diseases	138 (5.3)	9 (6.5)	129 (93.5)	0.09		
Systemic lupus erythematosus	52 (2.0)	1 (1.9)	51 (98.1)	0.72		
Sjögren's syndrome	37 (1.4)	3 (8.1)	34 (91.9)	0.16		
Others	49 (1.8)	5	44			
Spondyloarthropathies	373 (14.3)	5 (1.3)	368 (98.7)	**0.005**	0.30	0.12-0.76
Ankylosing spondylitis	255 (9.8)	2 (0.8)	253 (99.2)	**0.005**	0.18	0.04-0.74
Psoriatic arthritis	105 (4.0)	2 (1.9)	103 (98.1)	0.43		
Enteropatic and reactive arthritis	13	1 (7.6)	12 (92.3)			
Vasculitis	27 (1.0)	1 (3.7)	26 (96.3)	0.72		
Behcet's disease	30 (1.2)	0	30 (100)	0.62		
Polymyalgia rheumatica	30 (1.2)	1 (3.7)	29 (96.7)	0.67		
Familial Mediterranean fever	76 (2.9)	1 (1.3)	75 (98.7)	0.36		
Cryrstalline arthropathies	133 (5.1)	9 (6.8)	124 (93.2)	0.07		
Osteoarthritis	255 (9.8)	17 (6.7)	238 (93.3)	**0.01**	1.98	1.10-3.56
Fibromyalgia syndrome	209 (8.0)	2 (1.0)	207 (99.0)	**0.01**	0.20	0.04-0.83
Autoantibody positivity	85 (3.3)	2 (2.4)	83 (97.6)	0.57		
High acute phase reactants	46 (1.8)	3 (6.5)	43 (93.5)	0.42		
Other complaints	864 (33.2)	35	829			
Musculoskeletal	494 (19.0)	24	470			
Back pain	172 (6.6)	2	170			
Mucocutaneous	102 (3.9)	6	96			
Headache	3 (0.1)	1	2			
Pulmonary	13 (0.5)	1	12			
Thrombosis	9 (0.3)	1	8			

CCI: Charlson Comorbidity index, CI: Confidence interval, IQR: Interquartile range, Min-max: Minimum-maximum, OR: Odds ratio, SD: Standard deviation

Table 2. Comparison of cancer types and demographics in patients with inflammatory *vs.* non-inflammatory diseases

	All patients	Inflammatuary group	Non-inflammatuary group	p
	n=100	n=43 (%)	n=57 (%)	
Age				0.13
Median (IQR)	66 (16.5)	67.5 (13.5)	66 (18)	
Min-max	28-88	40-88	28-85	
Gender				0.65
Female	65	29 (67.4)	36 (63.2)	
Male	35	14 (32.6)	21 (36.8)	
Geriatric	57	28 (65.1)	29 (50.9)	0.15
Smoking ever	31	13 (30.2)	18 (31.6)	0.88
No	69	29 (69)	40 (69)	
Yes	22	7 (16.7)	15 (25.9)	
Previous	9	6 (14.3)	3 (5.2)	
Mortality				
Yes	10	6 (13.9)	4 (7.0)	0.30
No	80	31 (72.0)	49 (85.9)	
Unknown	10	5 (11.6)	5 (8.7)	
CCI (mean ± SD)	3.06±1.11	3.56±1.16	2.7±0.94	p<0.001
Breast cancer	29	12 (27.9)	17 (29.8)	0.83
Gynecologic cancers	10	5 (11.6)	5 (8.8)	0.63
Ovarian cancer	4	2 (4.7)	2 (3.5)	0.57
Endometrium cancer	3	2 (4.7)	1 (1.8)	0.57
Cervix cancer	3	1 (2.3)	2 (3.5)	0.60
Male reproductive cancers	10	5 (11.6)	5 (8.8)	0.63
Prostate cancer	9	5 (11.6)	4 (7.0)	0.49
Testicular cancer	1	0	1 (1.8)	0.57
Urological cancers	9	5 (11.6)	4 (7.0)	0.49
Renal cell carcinoma	4	2 (4.7)	2 (3.5)	0.57
Bladder cancer	5	3 (7.0)	2 (3.5)	0.64
Gastrointestinal cancers	12	7 (16.3)	5 (8.8)	0.25
Esophageal cancer	1	1 (2.3)	0	0.43
Stomach cancer	5	3 (7.0)	2 (3.5)	0.64
Colorectal cancer	5	2 (4.7)	3 (5.3)	0.63
Pancreatic cancer	2	1 (2.3)	1 (1.8)	0.67
Respiratory system cancers	10	4 (9.3)	6 (10.5)	0.55
Laryngeal cancer	3	2 (4.7)	1 (1.8)	0.57
Lung cancer	7	2 (4.7)	5 (8.8)	0.69
Thyroid cancer	10	4 (9.3)	6 (10.5)	0.55
Hematologic cancers	9	2 (4.7)	7 (12.3)	0.29
Lymphoma	4	2 (4.7)	2 (3.5)	0.57
Chronic lymphocytic leukemia	1	0	1 (1.8)	0.57
Multiple myeloma	4	0	4 (7.0)	0.13
Skin cancers	5	3 (7.0)	2 (3.5)	0.64
Non-melanoma skin cancer	2	0	2 (3.5)	0.50
Melanoma	3	3 (7.0)	0	0.07
Sarcoma	1	0	1 (1.8)	0.57
Carcinoma of unknown primary	1	0	1 (1.8)	0.57

CCI: Charlson Comorbidity index, IQR: Interquartile range, SD: Standard deviation

Analysis of Specific Cancers

Among the 100 cancer patients, the most prevalent cancer type was breast cancer, affecting 29 patients (Figure 1). Details of specific cancers are presented in Table 2. Five patients had multiple primary cancers: one patient had prostate and laryngeal cancer; one patient had prostate and lung cancer; one patient had prostate cancer and NMSC; one patient had stomach cancer and melanoma; and one patient had breast cancer, renal cell carcinoma, and melanoma. A smoking history was reported in 31 patients.

Gender-based and Age Stratified Differences in Cancer Prevalence

The detailed subgroup comparisons, including gender-based and age-stratified differences, are presented in Supplementary Tables. Smoking history was significantly higher in males (p=0.005). Among female patients (n=65), breast cancer (44.6%), gynecologic cancers (15.4%), and thyroid cancer (13.8%) were the most common. Among male patients (n=35), prostate cancer (25.7%) was the most prevalent, followed by respiratory system cancers (22.9%) and gastrointestinal cancers (17.1%). When comparing female and male patients, respiratory system cancers were more prevalent among males (p=0.003). Mortality was higher in the geriatric group (p=0.04), with nine patients known to have died compared to one patient in the non-geriatric group. In the non-geriatric group, the most common cancers were breast cancer (27.9%), thyroid cancer (20.9%), gynecologic cancers (11.6%), and hematologic cancers (11.6%). In the geriatric group, the most common cancers were breast cancer (29.8%), gastrointestinal cancers (17.5%), respiratory system cancers (15.8%), and prostate cancer (12.3%). Thyroid cancers were significantly more prevalent in the non-geriatric group (p=0.002).

Cancer Types Based on Rheumatic Diseases and Treatments

Among the 100 patients with a history of cancer, an analysis was conducted based on their rheumatic disease history. Of the 43 patients with an inflammatory diagnosis, the most prevalent rheumatic disease was RA, accounting for 17 cases (Figure 2). These patients represented 4.2% of all RA patients. The most common cancers among RA patients were breast cancer (23.5%), gastrointestinal cancers (23.5%), and gynecological cancers (17.6%). One-third of these patients had a history of smoking. Thirteen patients were treated with steroids. Methotrexate was used by 9 patients, hydroxychloroquine by 7 patients, and leflunomide by 2 patients. Adalimumab was the biological treatment used by only one patient. Nine patients with CTDs, nine patients with crystalline arthropathies, two patients with AS, and two patients with PsA had cancer. Detailed information on the rheumatic diseases and treatments received by the patients is presented in Table 3.

Non-inflammatory conditions accounted for 57 patients, with the most common reasons for admission being non-specific musculoskeletal complaints (24 patients) and primary osteoarthritis (17 patients). Additionally, 2 patients were referred to our clinics due to positive autoantibodies, and 3 patients were referred for elevated acute phase reactants.

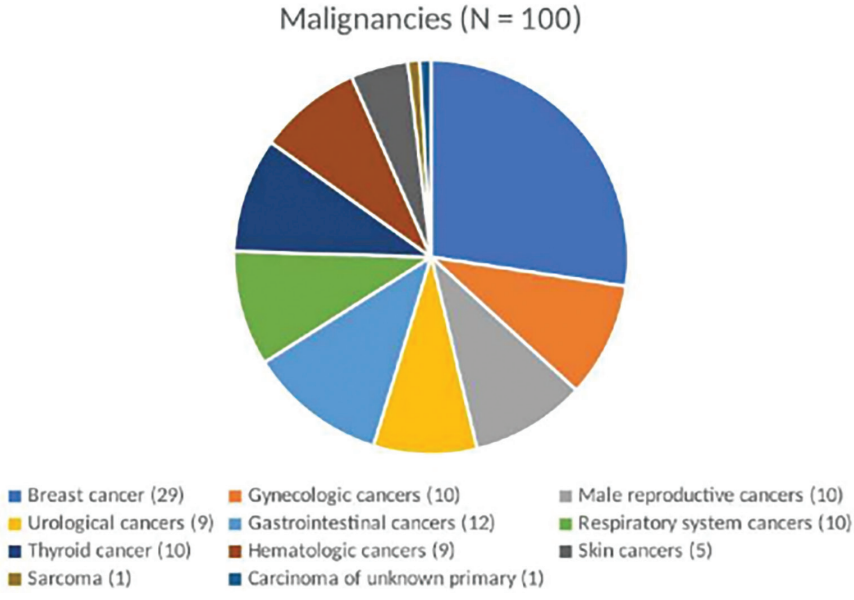

Figure 1. Types of malignancies

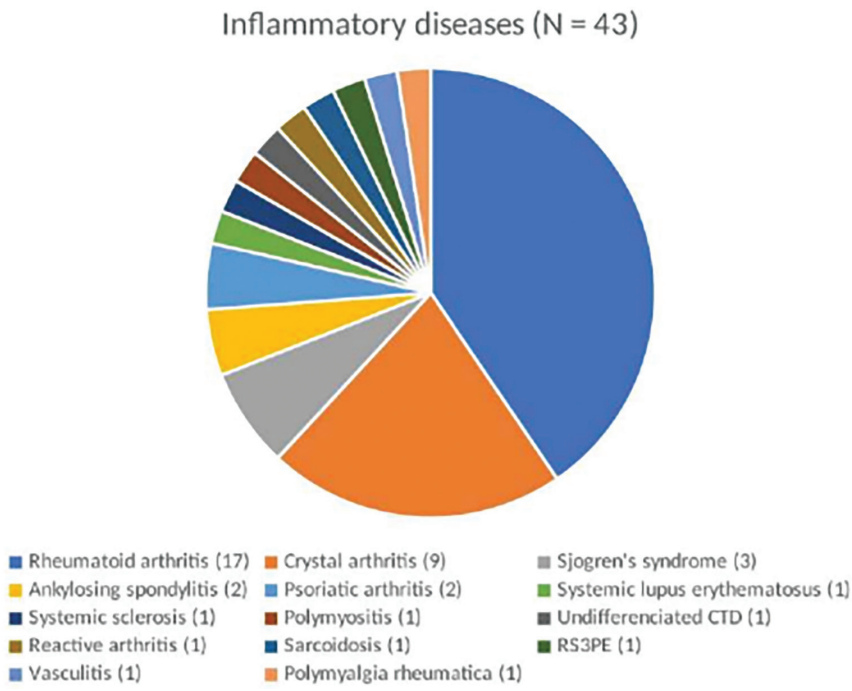

Figure 2. Inflammatory diseases with malignancy diagnosis

CTD: Connective tissue disease, RS3PE: Remitting seronegative symmetrical synovitis with pitting edema

Timing of Cancer Diagnosis Relative to Rheumatic Disease

Patients with cancer history were analyzed according to timing of the cancer history relative to the onset of rheumatic disease or non-inflammatory condition (Figure 3). Among 100 patients with cancer history, 74 patients had cancer diagnosis earlier than the rheumatic disease or non-inflammatory condition. Within these patients, 47 had non-inflammatory conditions and 27 had rheumatic diseases later on. In the latter group, 10 patients experienced the onset of rheumatic disease more than 10 years after their cancer diagnosis. Seven patients developed rheumatic disease between 5 and 10 years after their cancer diagnosis, six patients between 1 and 5 years, and four patients within the same year as their cancer diagnosis. Specific cases in the last group include: SLE onset following cervical cancer; systemic sclerosis onset after a breast cancer relapse; relapsing seronegative symmetrical synovitis with pitting edema following laryngeal cancer; and vasculitis following melanoma. The patient with a breast cancer relapse developed systemic sclerosis within three months of starting the kinase inhibitor ribociclib. In two patients treated with the immune checkpoint inhibitor nivolumab, one developed RA two years after an esophageal cancer diagnosis, and the other developed PsA three years after a melanoma diagnosis.

Sixteen patients with rheumatic diseases and 10 patients with non-inflammatory complaints had a later cancer diagnosis. This group comprised 17 females and 9 males, with a mean age of 66.4±9.7 years. Seven patients had a history of smoking. The detailed diagnoses of these patients are presented in Table 4A. These patients' specific cancer diagnoses, stratified by gender, number of observed and expected cases, and SIRs, are presented in Table 4B. In female patients, gynecologic cancers (p=0.005, CI=1.2-8.7), hematologic cancers (p=0.002, CI=1.4-13.5), and lymphoma (p=0.001, CI=1.6-23.7) were particularly more common.

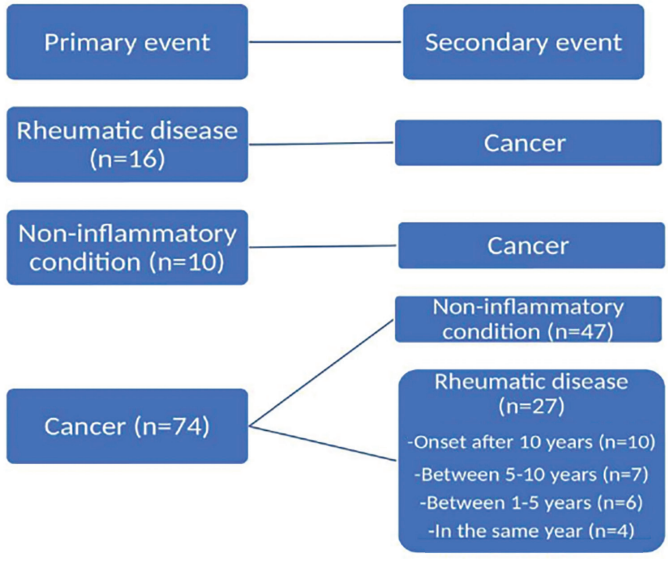

Figure 3. Temporal relationship between the onset of cancer and rheumatic or non-inflammatory diseases. The total number of patients with a history of both rheumatic diseases and cancer is 43

Table 3. Treatments administered and types of malignancies in patients with specific inflammatory diseases

Inflammatory diseases (n=43)	Treatments	Malignancies
Rheumatoid arthritis (n=17)	Steroid (n=13)	Breast (n=4)
	Methotrexate (n=9)	Stomach (n=2)
	Leflunomide (n=2)	Endometrial (n=2)
	Hydroxychloroquine (n=7)	Lung (n=2)
	Adalimumab (n=1)	Bladder (n=2)
		Prostate (n=2)
		Esophageal (n=1)
		Colorectal (n=1)
		Lymphoma (n=1)
Sjögren's syndrome (n=3)	Hydroxychloroquine (n=3)	Breast (n=3)
Systemic lupus erythematosus (n=1)	Steroid (n=1)	Cervix (n=1)
	Hydroxychloroquine (n=1)	
Systemic sclerosis (n=1)	Nifedipine (n=1)	Breast (n=1)
	Acetylsalicylic acid (n=1)	
Polymyositis (n=1)	Steroid (n=1)	Ovarian (n=1)
UCTD (n=1)	Nifedipine (n=1)	Lymphoma (n=1)
	Acetylsalicylic acid	
Ankylosing spondylitis (n=2)	NSAID (n=2)	Renal cell carcinoma (n=1)
	Etanercept (n=2)	Bladder (n=1)
Psoriatic arthritis (n=2)	Steroid (n=1)	Thyroid (n=1)
	Methotrexate (n=1)	Melanoma (n=1)
	Leflunomide (n=1)	
	Adalimumab (n=1)	
Reactive arthritis (n=1)	NSAID (n=1)	Thyroid (n=1)
Familial Mediterranean fever (n=1)	Colchicine (n=1)	Thyroid (n=1)
Sarcoidosis (n=1)	Steroid (n=1)	Thyroid (n=1)
RS3PE (n=1)	Steroid (n=1)	Larengeal (n=1)
Polymyalgia rheumatica (n=1)	Steroid (n=1)	Prostate (n=1)
	Leflunomide (n=1)	
Vasculitis (n=1)	Steroid (n=1)	Breast (n=1)
		Renal cell carcinoma (n=1)
		Melanoma (n=1)
Crystal arthritis (n=9)	Steroid (n=6)	Breast (n=3)
	Allopurinol (n=6)	Prostate (n=2)
	Colchicine (n=4)	Stomach (n=1)
		Colorectal (n=1)
		Pancreatic (n=1)
		Larengeal (n=1)
		Melanoma (n=1)

NSAID: Non-steroidal anti-inflammatory drug, RS3PE: Remitting seronegative symmetrical synovitis with pitting edema, UCTD: Undifferentiated connective tissue disease

In male patients, the total number of all cancers was significantly higher (p<0.001, CI=182.7-700.8), although no specific cancer type reached statistical significance.

Logistic regression analysis was performed to assess the effects of age, gender, smoking history, comorbidities, various rheumatic diseases, and treatments on the likelihood of cancer. The analysis identified significant associations between cancer diagnosis and age (p=0.002), male gender (p=0.02), the presence of inflammatory diseases (p<0.001), and CCI score (p<0.001) (Table 5). However, individual rheumatic diseases did not demonstrate statistical significance.

Discussion

This study aimed to analyze the incidence, prevalence and characteristics of cancer among patients with rheumatic diseases and non-inflammatory conditions. The results

Table 4A. Comparison of patients diagnosed with cancer after inflammatory disease (n=16) onset or non-inflammatory conditions (n=10)

Inflammatory diseases (n=16)		Non-inflammatory conditions (n=10)	
Age (mean ± SD)	65.4±13.4	Age (mean ± SD)	65.4±9.5
Female/male	11:5	Female/male	6:4
Smoking ever	3	Smoking ever	4
Spesific diseases	**Malignancies**	**Spesific conditions**	**Malignancies**
Rheumatoid arthritis (n=9)	Breast (n=2)	Osteoarthritis (n=6)	Breast (n=1)
	Endometrial (n=2)		Ovarian (n=1)
	Stomach (n=1)		Prostate (n=2)
	Colorectal (n=1)		Pancreas (n=1)
	Lung (n=1)		Lymphoma (n=1)
	Bladder (n=1)		Multiple myeloma (n=1)
	Lymphoma (n=1)	Back pain (n=1)	Renal cell carcinoma (n=1)
Cryrstalline arthropathies (n=3)	Prostate (n=2)	Positive autoantibodies (n=1)	Lung (n=1)
	Stomach (n=1)*	Increased acute phase reactants (n=2)	Cervix (n=1)
	Melanoma (n=1)*		Multiple myeloma (n=1)
Ankylosing spondylitis (n=1)	Renal cell carcinoma (n=1)		
Sjogren syndrome (n=1)	Breast (n=1)		
Polymyositis (n=1)	Ovarian (n=1)		
UCTD (n=1)	Lymphoma (n=1)		

SD: Standard deviation, UCTD: Undifferentiated connective tissue disease

Table 4B. Specific diagnosis, observed and expected cases, and SIRs for malignancies, stratified by gender

	Female Observed	Expected	SIR	p	CI (95%)	Male Observed	Expected	SIR	p	CI (95%)
All cancers (C00-96)	17	10.5	1.62	0.044	0.9-2.5	10	0.03	381.10	**<0.001**	182.7-700.8
Breast cancer (C50)	4	2.7	1.47	0.279	0.4-3.7					
Gynecologic cancers (C51-58)	5	1.33	3.76	**0.005**	1.2-8.7					
Ovarian cancer (C56)	2	0.36	5.51	0.012	0.6-19.9					
Endometrium cancer (C54)	2	0.62	3.23	0.050	0.3-11.6					
Cervix cancer (C53)	1	0.23	4.26	0.047	0.1-23.7					
Male reproductive system cancers (C60-63)						3	1.04	2.88	0.043	0.5-8.4
Prostate cancer (C61)						3	0.94	3.20	0.031	0.6-9.3
Urinary tract cancers (C64-68)	2	0.36	5.51	0.012	0.6-19.9	1	0.65	1.53	0.280	0.04-8.5
Renal cell carcinoma (C64)	1	0.19	5.27	0.032	0.1-29.3	1	0.17	5.73	0.027	0.1-31.9
Bladder cancer (C67)	1	0.16	6.17	0.024	0.1-34.3	0				
Gastrointestinal cancers (C15-26)	1	1.64	0.61	0.977	0.02-3.3	3	1.25	2.39	0.077	0.4-6.9
Stomach cancer (C16)	1	0.36	2.75	0.104	0.07-15.3	1	0.33	3.05	0.087	0.08-16.9
Colorectal cancer (C18-20)						1	0.58	1.73	0.229	0.04-9.6
Pancreatic cancer (C25)						1	0.13	7.67	0.016	0.1-42.7
Respiratory system cancers (C30-38)	1	0.67	1.49	0.291	0.04-8.3	1	1.46	0.69	0.856	0.02-3.8
Lung cancer (C34)	1	0.61	1.64	0.250	0.04-9.1	1	1.29	0.77	0.741	0.02-4.3
Hematologic cancers (C81-96)	4	0.75	5.30	**0.002**	1.4-13.5	1	0.44	2.27	0.145	0.06-12.6
Lymphoma (C81-85)	3	0.37	8.14	**0.001**	1.6-23.7	0				
Multiple myeloma (C90)	1	0.12	8.52	0.013	0.2-47.5	1	0.07	14.32	0.005	0.3-79.7
Skin cancers (C43-44)	0					1	0.61	1.63	0.252	0.04-9.1
Melanoma (C43)	0					1	0.04	23.86	0.002	0.6-132.9

CI: Confidence interval, SD: Standard deviation

Table 5. Logistic regression analysis for malignancy

	p	Odds ratio	Confidence interval
Age	0.002	1.03	1.01-1.06
Male gender	0.026	2.16	1.09-4.28
Inflammatory disease history	<0.001	4.52	2.16-9.45
Charlson Comorbidity index	<0.001	5.65	2.87-11.13

revealed several noteworthy findings that align with and contribute to the current understanding of cancer risk in these patient populations.

Firstly, the overall prevalence of cancer in this cohort was 3.8%, with a higher median age among cancer patients compared to those without cancer. This aligns with existing literature suggesting that cancer incidence increases with age.[33] Interestingly, our study found a lower prevalence of cancer in patients with SpA, AS, and fibromyalgia, whereas those with osteoarthritis exhibited a higher prevalence. Studies have shown that the prevalence of cancer in patients with AS is not significantly elevated compared to the general population.[34]

In this study, although male sex (p<0.001) and a history of smoking-a known carcinogen- (p<0.001) were more common in AS patients, these patients were generally younger (p<0.001, mean: 38.8±10.6 years) and had lower CCI scores (p<0.001, 0.6±0.7), which may partly explain the reduced cancer prevalence observed in this group. On the other hand, fibromyalgia patients were predominantly female (p<0.001) and had lower CCI scores (p<0.001, 0.5±0.6), although age (p=0.33) and smoking history (p=0.49) did not differ between those with and without the condition.

In contrast, patients with osteoarthritis showed an increased risk of cancer, which may be linked to shared risk factors, particularly advanced age.[35] In our study, osteoarthritis patients were predominantly female (p<0.001), and smoking was less common among them (p<0.001). However, these patients were older (p<0.001, mean: 66.7±9.5 years) and had higher CCI scores (p=0.004, 0.97±1.1). These findings suggest that age and comorbidity status may have a greater influence on cancer risk in this cohort than factors such as sex or smoking history, particularly in patients with osteoarthritis.

The analysis of cancer prevalence with aging revealed that geriatric patients had a higher mortality rate, and a different distribution of cancer types compared to non-geriatric patients. Thyroid cancers were significantly more prevalent in the non-geriatric group, which might reflect differences in cancer biology and detection rates between age groups.[36] Although lung, gastrointestinal, and prostate cancers were more common in geriatric patients, these differences did not reach statistical significance. This suggests that while there are observable trends in cancer type distribution between age groups, the sample size or variability may limit the statistical power to detect significant differences.

In terms of rheumatic disease, RA was the most prevalent inflammatory disease in patients with cancer, with 17 RA patients in total. Most of the RA patients in this study were female (p<0.001), with a similar smoking history compared to those without RA (p=0.12). However, RA patients had higher CCI scores (p<0.001, 1.2±0.9) and were older (p<0.001, 57.4±15.1 years). Although the frequency of cancer did not reach statistical significance in this group, RA remained the most common inflammatory diagnosis among patients with a history of cancer, which may be attributed to the relatively small sample size. Consequently, it was not possible to draw definitive conclusions about the effects of different treatments on cancer incidence in this cohort.

The analysis of specific cancer types revealed that breast cancer was the most common malignancy in this cohort, accounting for 29% of cancer cases. This finding is consistent with global cancer statistics, which identify breast cancer as the most prevalent cancer among women.[37] Additionally, this study identified sex-based disparities in cancer types, with thyroid cancers being more common in females and respiratory system and gastrointestinal cancers being more frequent in males. The higher prevalence of respiratory system cancers in males may be linked to the significantly higher smoking history observed in this group.[38]

An important aspect of this study was the timing of cancer diagnosis relative to the onset of rheumatic disease, which provided insights into potential causal relationships. In some cases, rheumatic diseases preceded the onset of cancer, while in others, rheumatic diseases developed after a cancer diagnosis. This bidirectional relationship suggests that chronic inflammation and immune dysregulation may play a role in the development of both conditions.[13] Among the 16 female patients with newly diagnosed cancers during follow-up, gynecologic cancers and lymphoma were significantly more common when SIRs were calculated based on the latest incidence rates in the Turkish population. In the 10 male patients with newly diagnosed cancers during follow-up, the total number of cancers was significantly higher. Moreover, the occurrence of rheumatic diseases following cancer treatment with immune checkpoint inhibitors and kinase inhibitors highlights the impact of these therapies on immune regulation, which was observed in three of our

patients.[39]

Rheumatologists may encounter malignancy in various contexts during routine clinical practice. Patients with rheumatic diseases might receive a new cancer diagnosis, requiring adjustments to their treatment plans. Additionally, patients presenting with symptoms commonly associated with rheumatic conditions, such as an elevated sedimentation rate, positive autoantibodies, or back pain, may have an underlying malignancy. In some cases, newly diagnosed seronegative arthritis may represent a paraneoplastic syndrome, though these diagnoses are often challenging to confirm. In this study, four patients were diagnosed with both rheumatic disease and cancer within the same year, suggesting a potential paraneoplastic relationship. The recognition of paraneoplastic syndromes is clinically significant, as they often mimic primary rheumatic diseases and can complicate the diagnosis and management of both conditions.

The results of the logistic regression analysis further elucidate the factors associated with cancer risk in this cohort. Age, male sex, the presence of inflammatory diseases, and higher CCI scores were all significantly associated with a higher likelihood of cancer. These findings align with the broader literature on cancer risk factors, emphasizing the role of age, comorbidity burden, and gender in determining cancer susceptibility. The lack of statistical significance for individual rheumatic diseases in the regression analysis may be attributed to the low number of cancer cases within each specific disease group. These results reinforce the need for comprehensive cancer risk assessments in patients with rheumatic diseases, especially those with multiple comorbidities or higher inflammatory disease activity.

In comparing our findings with previous Turkish studies on malignancy risk in rheumatic diseases, several similarities emerge. Similar to our study, research on patients with anti-neutrophil cytoplasmic autoantibody-associated vasculitis and primary Sjögren syndrome demonstrated an increased cancer risk compared to the general Turkish population. For instance, in the vasculitis cohort, the cancer risk was 2.1 times higher than in the general population, particularly for lung and head-neck cancers.[16] Likewise, the study on primary Sjögren syndrome reported an overall increased risk for both solid and hematologic malignancies (SIR=2.45), with ovarian and non-Hodgkin lymphoma cancers being notably more prevalent, underscoring the need for vigilant cancer monitoring across different rheumatic diseases.[17] Similarly, studies on systemic sclerosis also identified an elevated malignancy risk, particularly for breast and lung cancers.[18] In our study, RA was the most common rheumatic disease associated with a history of cancer, and breast cancer emerged as the most frequent malignancy.

Study Limitations

There is conflicting information regarding the incidence and prevalence of cancer in patients with rheumatic diseases, primarily due to methodological challenges in this research area.[40] Cancer risk is not constant or easily modeled over time.[41] Besides autoimmunity, other factors, such as genetics and smoking, also contribute to cancer risk. On the other hand, the risk of cancer development in patients with rheumatic disease is very low, estimated as 2-5 cases per 1000 patients treated annually.[42] Many studies are limited by short observation periods and small sample sizes, which hinder statistical significance.

This study has several limitations that may introduce bias and affect the interpretation of our findings. The retrospective design is a key limitation, as it relies on existing medical records, which are subject to missing data. This could lead to misclassification of both rheumatic diseases and cancer diagnoses, particularly in cases where detailed clinical histories or follow-up data were unavailable. Furthermore, the lack of detailed information on cancer staging, treatment responses, and disease progression limits our ability to assess cancer outcomes comprehensively.

Selection bias may also be present, as only patients followed at our center were included. This could result in the exclusion of patients with milder forms of disease who may not require frequent hospital visits, or those who sought care at other facilities. As a result, the patient population may not be fully representative of the broader rheumatic disease population, affecting the generalizability of our findings.

Additionally, survival bias is a potential issue, as patients with more severe cancer or advanced rheumatic diseases may have had limited follow-up, leading to an underestimation of cancer prevalence in our study. Patients who succumbed to cancer early in the disease course or those with poor health may have been less likely to be captured in the study, skewing the cancer incidence rates lower.

Finally, conducting the study at a single private hospital limits the external validity of our results, as patient demographics and healthcare practices may differ across other regions or healthcare systems. This could mean that our findings are not fully applicable to other populations, particularly in terms of cancer screening and treatment practices.

Conclusion

Despite these limitations, the large sample size and comprehensive analysis in this study provide valuable insights

into the prevalence and characteristics of cancer in patients with rheumatic diseases. The findings highlight the need for vigilant cancer screening and monitoring in this population, particularly considering the influence of age, gender, and specific rheumatic conditions. Future research should focus on well-designed, prospective, multicenter studies with longer follow-up periods and larger cohorts to further elucidate the complex relationship between rheumatic diseases and cancer and to develop targeted strategies for cancer prevention and management in these patients.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (Memorial Bahçelievler Hospital Ethics Committee - approval number: 133, date: 11.06.2024).

Informed Consent: Retrospective study.

Footnotes

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

Financial Disclosure: The author declares that they have no relevant financial disclosures.

References

1. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther. 2008;10:R45.
2. Kallberg H. Rheumatoid arthritis and lung cancer: you probably heard it before. J Rheumatol. 2008;35:1695-6.
3. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001;357:539-45.
4. Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev. 2017;16:1049-57.
5. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med. 2005;165:2337-44.
6. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non- Hodgkin's lymphoma by subtype. J Natl Cancer Inst. 2006;98:51-60.
7. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54:692-701.
8. Ramiro S, Gaujoux-Viala C, Nam JL, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2014;73:529-35.
9. Mercer LK, Davies R, Galloway JB, et al. C. British Society for Rheumatology biologics register control centre, risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology (Oxford). 2013;52:91-8.
10. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020;79:760-70.
11. Monach PA, Arnold LM, Merkel PA. Incidence and prevention of bladder toxicity from cyclophosphamide in the treatment of rheumatic diseases: a data-driven review. Arthritis Rheum. 2010;62:9-21.
12. van den Reek JM, van Lümig PP, Janssen M, et al. Increased incidence of squamous cell carcinoma of the skin after long-term treatment with azathioprine in patients with auto-immune inflammatory rheumatic diseases. J Eur Acad Dermatol Venereol. 2014;28:27-33.
13. Masetti R, Tiri A, Tignanelli A, et al. Autoimmunity and cancer. Autoimmun Rev. 2021;20:102882.
14. Xie W, Huang H, Xiao S, Fan Y, Deng X, Zhang Z. Immune checkpoint inhibitors therapies in patients with cancer and preexisting autoimmune diseases: a meta-analysis of observational studies. Autoimmun Rev. 2020;19:102687.
15. Roberts J, Ennis D, Hudson M, et al. Rheumatic immune-related adverse events associated with cancer immunotherapy: a nationwide multi-center cohort. Autoimmun Rev. 2020;19:102595.
16. Bilgin E, Yildirim DT, Ozdemir BU, et al. Unveiling cancer risk in ANCA-associated vasculitis: result from the Turkish Vasculitis Study Group (TRVaS) Intern Emerg Med. 2024;19:1025-34.
17. Aslan B, Ogut TS, Erbasan F, et al. The risk of cancer in patients with primary Sjögren syndrome; a single-center study from Türkiye. Turk J Med Sci. 2022;52:587-95.
18. Karadag DT, Gonul B, Isik OO, Tekeoglu S, Yazici A, Cefle A. Malignancy and risk factors in systemic sclerosis patients. J Turk Soc Rheumatol. 2020;12:71-5.
19. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012;51(Suppl 6):vi5-9.
20. Rudwaleit M, van der Heijde D, Landewe R, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70:25-31.
21. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73.
22. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1400-12.
23. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2017;69:35-45.
24. Dasgupta B, Cimmino MA, Maradit-Kremers H, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2017;71:484-92.
25. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout classification

criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2015;74:1789-98.

26. Criteria for diagnosis of Behçet's disease. International study group for Behçet's disease. Lancet. 1990;335:1078-80.
27. Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis. 2022;74:1881-89.
28. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. Ann Rheum Dis. 2022;81:1654-60.
29. Robson JC, Grayson PC, Ponte C, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81:315-20.
30. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum. 1990;33:1601-10.
31. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken). 2010;62:600-10.
32. General directorate of public health. National cancer statistics 2018. Available from: https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/Dokumanlar/Istatistikler/Kanser_Rapor_2018.pdf Accessed August 1, 2024.
33. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. Am J Prev Med. 2014;46(3 Suppl 1):S7-15.
34. Bittar M, Merjanah S, Alkilany R, Magrey M. Malignancy in ankylosing spondylitis: a cross-sectional analysis of a large population database. BMC Rheumatol. 2022;6:44.
35. Ward MM, Alehashemi S. Risks of solid cancers in elderly persons with osteoarthritis or ankylosing spondylitis. Rheumatology (Oxford). 2020;59:3817-25.
36. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.
37. O'Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SAE. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. BMJ Open. 2018;8:e021611.
38. National Cancer Institute. SEER cancer statistics review, 1975-2017. Available from: https://seer.cancer.gov/csr/1975_2017/ Accessed August 1, 2024.
39. Kostine M, Rouxel L, Barnetche T, et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann Rheum Dis. 2018;77:393-8.
40. Jeziorski K. Cancer and rheumatic diseases. Methodological and clinical pitfalls in searching links between these diseases. Nowotwory Journal of Oncology 2022;72:190-4.
41. Turesson C, Matteson EL. Malignancy as a comorbidity in rheumatic diseases. Rheumatology (Oxford). 2013;52:5-14.
42. Davis JM 3rd. Overview of the associations between cancer and rheumatic disease. Rheum Dis Clin North Am. 2020;46:417-27.

Supplementary Table 1. Specific cancer types according to gender

	All patients	Female	Male	p	OR	CI
	n=100	n=65 (%)	n=35 (%)			
Age				0.22		
Median (IQR)	66 (16.5)	65 (15)	69 (13.5)			
Mean (SD)	63.7 (12.3)	62.6 (12.1)	65.8 (12.6)			
Min-max	28-88	28-88	33-85			
Gender						
Female	65					
Male	35					
Geriatric patients	57	32 (49.2)	25 (71.4)	**0.03**	2.5	1.06-6.2
Smoking	31	14 (21.5)	17 (48.6)	**0.005**	3.4	1.4-8.3
No	69	51 (78.5)	18 (51.4)			
Yes	22	11 (16.9)	11 (31.4)			
Previous	9	3 (4.6)	6 (17.1)			
Mortality				0.35		
Yes	10	5 (7.7)	5 (14.3)			
No	80	52 (80)	28 (80)			
Unknown	10	8 (12.3)	2 (5.7)			
Breast cancer (C50)	29	29 (44.6)	0			
Gynecologic cancers (C51-58)	10	10 (15.4)	0			
Ovarian cancer (C56)	4	4 (6.2)	0			
Endometrium cancer (C54)	3	3 (4.6)	0			
Cervix cancer (C53)	3	3 (4.6)	0			
Male reproductive system cancers (C60-63)	10	0	10 (28.6)			
Prostate cancer (C61)	9	0	9 (25.7)			
Testicular cancer (C62)	1	0	1 (2.9)			
Urinary tract cancers (C64-68)	9	4 (6.2)	5 (14.3)	0.27		
Renal cell carcinoma (C64)	4	2 (3.1)	2 (5.7)	0.61		
Bladder cancer (C67)	5	2 (3.1)	3 (8.6)	0.34		
Gastrointestinal cancers (C15-26)	12	6 (9.2)	6 (17.1)	0.24		
Esophageal cancer (C15)	1	1 (1.5)	0	0.65		
Stomach cancer (C16)	5	2 (3.1)	3 (8.6)	0.34		
Colorectal cancer (C18-20)	5	2 (3.1)	3 (8.6)	0.34		
Pancreatic cancer (C25)	2	1 (1.5)	1 (2.9)	0.58		
Respiratory system cancers (C30-38)	10	2 (3.1)	8 (22.9)	**0.003**	9.3	1.8-46.8
Laryngeal cancer (C32)	3	0	3 (8.6)	0.04	1.09	0.9-1.2
Lung cancer (C34)	7	2 (3.1)	5 (14.3)	0.04	5.2	0.9-28.6
Thyroid cancer (C73)	10	9 (13.8)	1 (2.9)	0.15		
Hematologic cancers (C81-96)	9	5 (7.7)	4 (11.4)	0.71		
Lymphoma (C81-85)	4	3 (4.6)	1 (2.9)	0.56		
Chronic lymphocytic leukemia (C91.1)	1	0	1 (2.9)	0.35		
Multiple myeloma (C90)	4	2 (3.1)	2 (5.7)	0.61		
Skin cancers (C43-44)	5	1 (1.5)	4 (11.4)	0.05		
Non-melanoma skin cancer (C44)	2	0	2 (5.7)	0.12		
Melanoma (C43)	3	1 (1.5)	2 (5.7)	0.28		
Sarcoma (C49)	1	0	1 (2.9)	0.35		
Carcinoma of unknown primary (C80.1)	1	1 (1.5)	0	0.65		

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio, SD: Standard deviation

Supplementary Table 2. Specific cancer types according to geriatric status

	All patients	Non-geriatric	Geriatric	p	OR	CI
	n=100	n=43 (%)	n=57 (%)			
Age				**<0.001**		
Median (IQR)	66 (16.5)	52 (13.5)	70 (9)			
Mean (SD)	63.7 (12.3)	52.5 (9.2)	72.2 (5.8)			
Min-max	28-88	28-64	65-88			
Gender				**0.03**	2.5	1.06-6.2
Female	65	33 (76.7)	32 (56.1)			
Male	35	10 (23.3)	25 (43.9)			
Geriatric patients	57					
Smoking	31	12 (27.9)	19 (33.3)	0.56		
No	69	31 (72.1)	38 (66.7)			
Yes	22	8 (18.6)	14 (24.6)			
Previous	9	4 (9.3)	5 (8.8)			
Mortality				**0.04**		
Yes	10	1 (2.3)	9 (15.8)			
No	80	37 (86)	43 (75.4)			
Unknown	10	5 (11.6)	5 (8.8)			
Breast cancer (C50)	29	12 (27.9)	17 (29.8)	0.83		
Gynecologic cancers (C51-58)	10	5 (11.6)	5 (8.8)	0.63		
Ovarian cancer (C56)	4	2 (4.7)	2 (3.5)	0.57		
Endometrium cancer (C54)	3	1 (2.3)	2 (3.5)	0.60		
Cervix cancer (C53)	3	2 (4.7)	1 (1.8)	0.57		
Male reproductive system cancers (C60-63)	10	3 (7.0)	7 (12.3)	0.50		
Prostate cancer (C61)	9	2 (4.7)	7 (12.3)	0.29		
Testicular cancer (C62)	1	1 (2.3)	0	0.43		
Urinary tract cancers (C64-68)	9	5 (11.6)	4 (7.0)	0.49		
Renal cell carcinoma (C64)	4	3 (7.0)	1 (1.8)	0.31		
Bladder cancer (C67)	5	2 (4.7)	3 (5.3)	0.63		
Gastrointestinal cancers (C15-26)	12	2 (4.7)	10 (17.5)	0.06		
Esophageal cancer (C15)	1	1 (2.3)	0	0.43		
Stomach cancer (C16)	5	0	5 (8.8)	0.06		
Colorectal cancer (C18-20)	5	1 (2.3)	4 (7.0)	0.38		
Pancreatic cancer (C25)	2	0	2 (3.5)	0.05		
Respiratory system cancers (C30-38)	10	1 (2.3)	9 (15.8)	0.04	7.8	0.9-64.7
Laryngeal cancer (C32)	3	0	3 (5.3)	0.25		
Lung cancer (C34)	7	1 (2.3)	6 (10.5)	0.23		
Thyroid cancer (C73)	10	9 (20.9)	1 (1.8)	**0.002**	0.06	0.008-0.5
Hematologic cancers (C81-96)	9	5 (11.6)	4 (7.0)	0.49		
Lymphoma (C81-85)	4	3 (7.0)	1 (1.8)	0.31		
Chronic lymphocytic leukemia (C91.1)	1	0	1 (1.8)	0.57		
Multiple myeloma (C90)	4	2 (4.7)	2 (3.5)	0.57		
Skin cancers (C43-44)	5	1 (2.3)	4 (7.0)	0.38		
Non-melanoma skin cancer (C44)	2	1 (2.3)	1 (1.8)	0.67		
Melanoma (C43)	3	0	3 (5.3)	0.25		
Sarcoma (C49)	1	0	1 (1.8)	0.57		
Carcinoma of unknown primary (C80.1)	1	1 (2.3)	0	0.43		

CI: Confidence interval, IQR: Interquartile range, OR: Odds ratio, SD: Standard deviation

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2024.39200
Ulus Romatol Derg 2025;17(1):45-52

Sleep problems in elderly patients with rheumatoid arthritis: Contributing factors and quality of life implications

Romatoid artritli yaşlı hastalarda uyku bozuklukları: Etkileyen faktörler ve yaşam kalitesine yansımaları

Neslihan Kayahan Satış[1], Hasan Satış[2]

[1]University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology RTraining and Research, Hospital, Clinic of Geriatrics, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye

Abstract

Objective: Sleep-related problems are common in rheumatoid arthritis (RA) patients of advanced age. This study aimed to identify factors contributing to poor sleep quality in elderly RA patients and assess their impact on quality of life.

Methods: This study included RA patients aged ≥65 years, admitted to a rheumatology clinic between May and September 2024, using a cross-sectional design. The Pittsburgh Sleep Quality index (PSQI) was used to evaluate sleep, while RA activity was measured via disease activity score 28-C-reactive protein (DAS28-CRP), and quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30. A multivariate regression analysis was used to identify factors associated with poor sleep quality.

Results: The study included 77 elderly RA patients (mean age 70.8±4.9 years, 59.8% female). The median DAS28-CRP score was 4.3, and 75.3% were not in remission. A total of 50.65% of the patients had poor sleep quality (PSQI >5). In the multivariate analysis, age ≥75 years [odds ratio (OR)=8.23, 95% confidence interval (CI) (1.51-44.77), p=0.015], being single [OR=4.63, 95% CI (1.17-18.36), p=0.029], active RA [OR=5.65, 95% CI (1.44-19.99), p=0.035] and depression [OR=5.04, 95% CI (1.17-21.73), p=0.030] were associated with poor sleep quality. Physical, emotional, and role function scores as well as fatigue, pain, and insomnia symptoms were observed at worse levels in the group with poor sleep quality.

Conclusion: Our study emphasizes the significance of managing sleep disorders in elderly RA patients. Disease activity and psychosocial

Öz

Amaç: Romatoid artritli (RA) yaşlı hastalarda uyku ilişkili problemlere sık rastlanmaktadır. Bu çalışmanın amacı, yaşlı RA hastalarında kötü uyku kalitesine katkıda bulunan faktörleri belirlemek ve uyku kalitesiyle yaşam kaliteleri arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya Mayıs ve Eylül 2024 arasında ayaktan bir üçüncü basamak romatoloji polikliniğinde değerlendirilen ≥65 yaş RA hastaları dahil edildi. Uyku kalitesi Pittsburgh Uyku Kalitesi indeksi (PSQI), RA hastalık aktivitesi hastalık aktivite skoru 28-C-reaktif protein (DAS28-CRP) ve yaşam kalitesi European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 ölçeği ile değerlendirildi. Kötü uyku kalitesiyle ilişkili faktörleri belirlemek için çok değişkenli regresyon analizi kullanıldı.

Bulgular: Çalışmaya ortalama yaşı 70,8 (±4,9) ve %59,8'i (n=46) kadın olan toplam 77 yaşlı RA hastası dahil edildi. Ortanca DAS28-CRP skoru 4,3'tü ve hastaların %75,3'ü remisyonda değildi. Hastaların %50,65'i kötü uyku kalitesine (PSQI >5) sahipti. Çok değişkenli analizde, ≥75 yaş [risk oranı (RO)=8,23, %95 güven aralığı (GA) (1,51-44,77), p=0,015], bekar olmak [RO=4,63, %95 GA (1,17-18,36), p=0,029], aktif RA [RO=5,65, %95 GA (1,44-19,99), p=0,035] ve depresyon [RO=5,04, %95 GA (1,17-21,73), p=0,030] kötü uyku kalitesiyle ilişkili olarak bulunmuştur. Fiziksel, duygusal ve rol fonksiyon skorları ile yorgunluk, ağrı ve insomnia semptomları kötü uyku kalitesine sahip grupta daha kötü düzeyde izlenmiştir.

Sonuç: Sonuçlarımız, yaşlı RA hastalarında uyku bozukluklarının yönetiminin önemini ortaya koymaktadır. Uyku sorunları, artan hastalık aktivitesi ve psikososyal durumla yakından bağlantılı olup,

Correspondence / İletişim:
Neslihan Kayahan Satış MD, University of Health Sciences Türkiye, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Clinic of Geriatrics, Ankara, Türkiye
E-mail: neslihan-kayahan@hotmail.com **ORCID ID:** orcid.org/0000-0002-6802-7926
Received / Geliş Tarihi: 11.10.2024 **Accepted / Kabul Tarihi:** 08.12.2024 **Publication Date / Yayın Tarihi:** 19.03.2025

Cite this article as / Atıf: Kayahan Satış N, Satış H. Sleep problems in elderly patients with rheumatoid arthritis: contributing factors and quality of life implications. Ulus Romatol Derg. 2025;17(1):45-52

factors are closely linked to sleep problems, which can be addressed to improve sleep quality and overall quality of life.

Keywords: Rheumatoid arthritis, sleep quality, quality of life, disease activity, elderly patients

bu faktörlerin hasta değerlendirmelerinde dikkate alınması hem uyku kalitesini hem de genel yaşam kalitesini olumlu yönde etkileyebilir.

Anahtar Kelimeler: Romatoid artrit, uyku kalitesi, yaşam kalitesi, hastalık aktivitesi, yaşlı hastalar

Introduction

Rheumatoid arthritis (RA) is an autoimmune disorder arising from a complex interaction of genetic, hormonal, and environmental factors, leading to joint inflammation and damage.[1] Although RA's prevalence varies between 0.5% and 1%, it is observed to increase even more in the aging population. The pathophysiology of RA involves abnormal immune system activation that causes inflammation and damage to the joints. At the same time, the exacerbation of symptoms has often been associated with triggers such as infections, smoking, and hormonal changes.[2] The impact of these inflammatory processes on quality of life is particularly noticeable in elderly patients.

The immune system's optimal functioning and regulation of inflammatory responses are greatly influenced by sleep. It is common for RA, an inflammatory disease, to cause sleep disorders.[3] Signaling activation and cellular inflammasome expression may be inhibited in the presence of RA. Dysregulation of sleep-wake activity is caused by a disrupted inflammatory profile in RA patients, resulting in excessive inflammation and increased pain sensitivity.[4] Sleep disorders such as insomnia and restless legs syndrome are common in RA patients and can complicate disease management.[5,6]

Sleep disorders in RA patients can be caused by many factors, including disease activity, neuropsychiatric diseases, comorbidities, and medication use.[7] In particular, chronic pain, which is a feature of RA, has been shown to disrupt sleep continuity and reduce restorative sleep, contributing to a decrease in quality of life.[8] RA patients are increasingly experiencing psychological problems such as depression and anxiety, which can shorten of sleep duration, cause sleep disruptions, and complicate treatment processes.[9] In addition, while multiple drug use is known to be associated with sleep disorders, drugs used in the treatment of RA can also have negative effects on sleep. Corticosteroids can cause insomnia and restlessness, while biological agents can affect inflammatory processes and change sleep patterns.[10,11]

In conclusion, considering that sleep disorders in RA patients are multifactorial, the management of these disorders should be considered part of disease control. Improving the quality of life for RA patients can be achieved through awareness and appropriate approaches to this issue. This study aimed to evaluate the factors that influence sleep disorders in RA patients and the connection between sleep disorders and quality of life to emphasize the importance of considering these factors in managing the disease.

Materials and Methods

Study Design and Participants

This observational study was designed to evaluate the factors affecting sleep disorders in RA patients. This cross-sectional study included 109 RA patients aged ≥65 years who applied to the rheumatology outpatient clinic of a tertiary healthcare institution between May and September 2024. Twenty-eight individuals were excluded due to terminal diseases or acute intervention, use of assistive devices, staying in nursing homes, having auditory or visual sensory impairment, and communication disability. In addition, the mini-mental state assessment was applied for the cognitive evaluation of the patients, and 4 individuals who were evaluated as "cognitively impaired" with a score below 24 points were not included in the study. The participants were given written informed consent, and the study, which was conducted in accordance with the Declaration of Helsinki, was approved by the appropriate ethics committee. The study was approved by Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee IRB (no.: 2024-05/64, date: 23.05.2024).

Clinical Features Associated with RA

RA diagnosis was determined and/or confirmed by a rheumatologist according to the criteria established by the American College of Rheumatology/European Association of Rheumatology.[12] The patient's history and electronic records were used to record their RA diagnosis and follow-up periods. Disease activity of RA was reviewed by disease activity score 28-C-reactive protein (DAS28-CRP), where a score of <2.6 is considered remission, while ≥2.6 is called active disease.[13] Furthermore, the drugs utilized by the patients in RA treatment have been analyzed in-depth and categorized as biological and conventional synthetic disease-modifying antirheumatic drugs and corticosteroids.

Evaluating the Characteristics of Sleep

All patients were asked in detail about their sleep difficulties. The Pittsburgh Sleep Quality index (PSQI) was chosen for sleep disturbance evaluation.[14] The PSQI scale

has 24 questions, 19 of which are self-assessment questions that examine the severity of certain sleep-related problems. The 18 items included in the scoring are grouped into 7 areas as "subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping pills, and daytime dysfunction" and a maximum of 21 points can be obtained from the test, with a score between 0-3 in these areas. A PSQI score of >5 is evaluated as "poor sleep quality".[14] A high index score indicates worse sleep quality.[14] Insomnia severity was determined by using the Insomnia Severity index (ISI). ISI is a scale that evaluates the severity of insomnia in 7 separate items out of a total of 28 points. Clinically insignificant insomnia ranges from 0-7 points, while lower threshold insomnia ranges from 8-14 points, and moderate clinical insomnia ranges from 15-21 points.

Data Collection and Other Measurements

Patients' socio-demographics (age, gender, marital status, education level, living partner, smoking status) and anthropometric data were recorded. The participants were assessed for other chronic diseases, and the burden of comorbidity was determined by using the Charlson Comorbidity index.[15] The medications used at the time of admission were examined in detail, and the use of 5 or more medications was defined as polypharmacy.[16]

To evaluate the patients' physical independence status, the 6-item Katz Activities of Daily Living scale for basic living activities and the 8-item Lawton-Brody Instrumental Activities of Daily Living scale for instrumental activities of daily living were used.[17,18] The Clinical Frailty scale (CFS) 24 was utilized to determine the frailty status of the individuals. Individuals with a CFS score of ≥4 were defined as "frail". The Global Pain scale and visual analog scale (VAS) was used to determine pain intensity, and the scores were recorded with two separate questions "global" and "joint".[19]

The 15-item Geriatric Depression scale 15 (GDS-15) was used for mood assesment.[20] A GDS-15 ≥6 was defined as "depression". The Generalized Anxiety Disorder-7 (GAD-7) scales was used to asses the anxiety.[21] A score of <5 is defined as minimal anxiety on this scale, while 5-9 is defined as mild, 10-14 as moderate, and ≥15 as severe anxiety. In our study, we defined those with a GAD-7 score of ≥5 as "anxiety". Furthermore, the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) scale was utilized to measure quality of life. Evaluation was made in 3 categories: global health status, functional scales and symptom scales. Twenty-eight of the 30 questions were based on a four-point Likert-type scale, while the remaining two questions assessed global health status. The higher the score for functional scales and global health status, and the lower the score for symptom scales, the better the health status.[1]

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 24 (IBM SPSS Inc., Chicago, USA) was used to analyze all the data. The comparison of patients was made based on their PSQI status (≤5 *vs.* >5). Means, standard deviation, median, minimum, and maximum values were used to present numerical variables; while frequency and percentage were used to report categorical data. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to assess data distribution. Parametric tests were preferred for data that followed a normal distribution, while non-parametric tests were used for data that did not. Numerical data were compared between groups using an independent sample t-test or Mann-Whitney U test. Independent sample t-test was used to compare numerical variables that followed normal distribution; while the Mann-Whitney U test was used to compare numerical variables that did not. Comparison of categorical data conducted through chi-square or Fisher's exact test. A multivariate regression analysis was performed to identify parameters associated with poor sleep, using variables (age, sex, marital status, RA disease activity, frailty, anxiety and depression) selected based on statistical significance (p=0.05) in univariate analysis. The Hosmer-Lemeshow test was used to assess the model's fit. Hazard ratios and their 95% confidence intervals (CI) were reported from the models in all evaluations, and statistical significance was accepted as $p<0.05$.

Results

Baseline Characteristics

A total of 77 patients aged ≥65 years with RA diagnosis (mean age 70.8±4.9 years), participated in our study. Of these, 59.7% of the patients were women, and 53.2% of the population were married. The mean duration of RA diagnosis was 4 years (2-30 years). The median DAS28-CRP score was 4.3 (2.0-7.1), and 75.3% of the patients were not in remission. Hypertension (46.3%), diabetes mellitus (19.5%), and cardiovascular disease (19.5%) were the three most common comorbidities. Polypharmacy was observed in 31 patients (40.3%). The most commonly used RA treatment agents were methotrexate (42.9%) and leflunomide (33.8%). The median overall VAS score was 3 (1-7), while 11.7% of the participants were assessed as frail. In terms of sleep disorder severity, more than half of the patients (59.7%) had "no clinically significant insomnia",

while only 3 patients (3.9%) had severe clinical insomnia. Anxiety was detected in 15 (19.5%) patients, and depression was detected in 25 (32.4%) (Table 1).

Evaluation of Sleep Quality

When evaluated with PSQI, the rate of patients with poor sleep quality (PSQI >5) was found to be 50.65% (n=39). The median PSQI score was 8 (6-14) in the (PSQI >5) group, while it was 3 (1-5) in the PSQI ≤5 group. According to ISI, moderate and severe insomnia were detected only in the PSQI >5 group. Those with poor sleep demonstrated significantly elevated DAS28-CRP scores (5.2 *vs.* 3.0, p<0.001), and a larger percentage were not in remission (92.3% *vs.* 57.9%, p<0.001). In addition, VAS, GAD-7, and GDS-15 scores were observed to be worse in this group than in the other group (p<0.001). A detailed evaluation of sleep quality is provided in Table 1. When adjusted for age, gender, marital status, RA disease activity, frailty, anxiety, and depression in multivariate regression analysis; age ≥75 years [odds ratio (OR)=8.23, 95% CI (1.51-44.77), p=0.015], being single [OR=4.63, CI (1.17-18.36), p=0.029], active RA [OR=5.65, CI (1.44-19.99), p=0.035], and depression [OR=5.04, CI (1.17-21.73), p=0.030] were associated with poor sleep quality (Figure 1).

Quality of Life Assessment

The quality-of-life data assessed with EORTC QLQ-C30 are given in Table 2. The average global health status score for the patients was 75 (16.7-100). The functional parameters most frequently affected were role function [66.7 (16.7-100)] and physical function [80.0 (13.3-100)], while the most frequently recorded symptoms were pain [33.3 (0-100)] and insomnia [33.3 (0-100)]. When compared according to sleep quality, physical, emotional, and role function scores were worse in the PSQI >5 group. Fatigue, pain, and insomnia were observed at higher levels in this group. No difference was found in terms of global health status and other quality of life subparameters.

Discussion

This cross-sectional study examined the factors that affect sleep quality in elderly RA patients and the effects of this condition on quality of life. Our study showed that 75.3% of patients had active RA, while 50.65% had impaired sleep quality. DAS28-CRP scores were found to be significantly higher in the PSQI >5 group as well. Multivariate regression indicated that poor sleep quality was independently associated with advanced age (≥75 years), being single, heightened disease activity, and depression. Patients with poor sleep quality had worse physical, emotional, and role functioning and more symptoms of fatigue, pain, and insomnia based on quality-of-life assessments. These findings emphasize that sleep quality and the factors that may affect it should be taken into consideration in the management of RA patients and that these may be related to quality of life.

The frequency of sleep disorders in RA patients and their relationship with remission status have been demostrated in previous studies in the literature.[22-25] Brahem et al.[22] found the frequency of sleep disorders measured with PSQI to be 51%, similar to ours, and this was found to be related to disease activity. In another study on RA, sleep disorders were detected in 65.3% of the total population, and a moderate correlation was found between disease activity and PSQI scores in this group.[23] Previous large-scale population studies have shown that, insomnia is common in RA patients, similar to our findings. In addition, improvement in sleep quality has been reported to have positive effects on quality of life.[7,24] In our study, RA disease activity was found to be independently associated with sleep disturbance at a rate of 5.65 (1.44-19.99) times. Chronic pain, fatigue, and discomfort resulting from chronic pain and ongoing inflammatory processes in RA, which can seriously impair sleep quality. Sleep problems may arise from increased levels of proinflammatory cytokines [tumor necrosis factor-alpha, interleukin (IL)-6, and IL-1] in the central nervous system. The sleep-wake cycle is directly affected by the activation of the hypothalamic-pituitary-adrenal axis by these inflammatory processes, which in turn increase cortisol levels and make it difficult to fall asleep. Sleep quality can be negatively impacted by the reduced mobility that occurs with increasing disease activity in RA patients. As a result, failure to achieve remission in RA patients is pivotal in the pathophysiology of sleep disorders, which can significantly reduce the life quality.

The relationship between RA patients and depression is influenced by the chronic nature of the disease and its associated challenges. The rate of depression detected in 32.4% of our patients is consistent with findings in the literature evaluating other elderly RA patients.[25,26] Depression risk may be elevated by specific medications used in the treatment of RA, such as corticosteroids. Furthermore, patients' mental health can be negatively impacted by long-term treatment, side effects, and the need for constant monitoring. The development of depression can be facilitated by the unpredictable and fluctuating course of RA, as well as the uncertainty and loss of control it causes in patients. Disease progression can result in a decline in patients' self-sufficiency and a fear of losing independence, which can lead to psychological pressure and depression. According to our research, depression was independently associated with sleep

Table 1. Sociodemographic and disease characteristics in terms of PSQI score

Characteristic	Overall (n=77)	PSQI ≤5 (n=38)	PSQI >5 (n=39)	p-value
Age, years, mean (SD)	70.8 (4.9)	70.8 (4.9)	70.8 (5.0)	0.980
65-74 years	59 (76.6)	28 (73.7)	31 (79.5)	0.547
≥75 years	18 (23.4)	10 (26.3)	8 (20.5)	
Gender, female, n (%)	46 (59.7)	21 (55.3)	25 (64.1)	0.429
Marital status, married, n (%)	41 (53.2)	29 (76.3)	12 (30.8)	**<0.001**
Education time, <5 years, n (%)	59 (76.6)	32 (84.2)	27 (69.2)	0.120
Living alone, n (%)	15 (19.5)	5 (13.2)	10 (25.6)	0.167
Current smokers, n (%)	9 (11.7)	3 (7.9)	6 (15.4)	0.306
BMI, kg/m^2, mean (SD)	25.9 (3.4)	25.7 (2.9)	26.2 (3.8)	0.527
Duration of RA, years, median (range)	4 (1-30)	4 (1-30)	4 (1-30)	0.939
DAS28-CRP, score, median (range)	4.3 (2.0-7.1)	3.0 (2.0-5.9)	5.2 (2.1-7.1)	**<0.001**
Active disease, n (%)	58 (75.3)	22 (57.9)	36 (92.3)	**<0.001**
Comorbidities, n (%)				
Hypertension	36 (46.8)	17 (44.7)	19 (48.7)	0.447
Diabetes mellitus	15 (19.5)	8 (21.5)	7 (18.4)	0.817
Cardiovascular disease	16 (19.5)	8 (21.5)	8 (20.5)	0.978
Cerebrovascular disease	4 (5.2)	3 (7.9)	1 (2.6)	0.292
Chronic obstructive pulmonary disease	9 (11.7)	3 (7.9)	6 (15.4)	0.306
Benign prostatic hyperplasia	14 (18.2)	7 (18.4)	7 (17.9)	0.957
CCI, score, median (range)	3 (2-7)	3 (2-4)	3 (2-7)	0.120
Number of drugs, median (range)	4 (2-8)	4 (2-8)	4 (2-8)	0.666
Polypharmacy, n (%)	31 (40.3)	15 (39.5)	16 (41.0)	0.890
RA treatment, n (%)				
csDMARDs				
Methotrexate	33 (42.9)	14 (36.8)	19 (48.7)	0.292
Leflunamide	26 (33.8)	15 (39.5)	11 (28.2)	0.296
Sulfsalazine	12 (15.6)	8 (21.1)	4 (10.3)	0.192
Hydroxychloroquine	10 (13.0)	5 (13.2)	5 (12.8)	0.965
bDMARDs	12 (15.6)	4 (10.5)	8 (20.5)	0.227
Corticosteroids	49 (63.6)	26 (68.4)	23 (59.0)	0.389
VAS, general score, median (range)	3 (1-7)	2 (1-6)	4 (1-7)	<0.001
VAS, joint score, median (range)	3 (1-9)	2 (1-7)	6 (1-9)	<0.001
ADL, median (range)	6 (4-6)	2 (4-6)	2 (4-6)	0.465
IADL, median (range)	5 (4-8)	5 (4-8)	5 (4-8)	0.484
CFS, median, (range)	2 (1-7)	3 (1-4)	6 (1-7)	0.001
Frail, CFS ≥4, n (%)	9 (11.7)	1 (2.6)	8 (20.5)	0.029
PSQI, score, median (range)	6 (1-14)	3 (1-5)	8 (6-14)	**<0.001**
ISI, score, median (range)	5 (0-24)	2.5 (0-10)	9 (2-24)	**<0.001**
Insomnia severity, n (%)				
No clinically significant insomnia	46 (59.7)	37 (97.4)	9 (23.1)	<0.001
Subthreshold insomnia	25 (32.5)	1 (2.6)	24 (61.5)	
Clinical insomnia (moderate)	3 (3.9)	-	3 (7.7)	
Clinical insomnia (severe)	3 (3.9)	-	3 (7.7)	
MMSE, score, mean (SD)	28.1 (1.9)	28.3 (1.7)	27.9 (2.2)	0.915
GAD-7, score, median (range)	2 (0-13)	1 (0-5)	3 (0-13)	**<0.001**
Anxiety, GAD-7 ≥5, n (%)	15 (19.5)	2 (5.3)	13 (33.3)	**0.002**
GDS-15, median (range)	3 (0-10)	2 (0-9)	4 (0-9)	**<0.001**
Depression, GDS-15 ≥6, n (%)	25 (32.4)	5 (13.2)	20 (51.3)	**<0.001**

ADL: Activities of daily living, BMI: Body mass index, CCI: Charlson Comorbidity index, CFS: Clinical Frailty scale, DAS28-CRP: Disease activity score 28-C-reactive protein, DMARDs: Disease-modifying antirheumatic drugs, GDS: Geriatric Depression scale, IADL: Instrumental activities of daily living, MMSE: Mini-Mental State Assessment, PSQI: Pittsburgh Sleep Quality index, SD: Standard deviation, VAS: Visual analogue scale

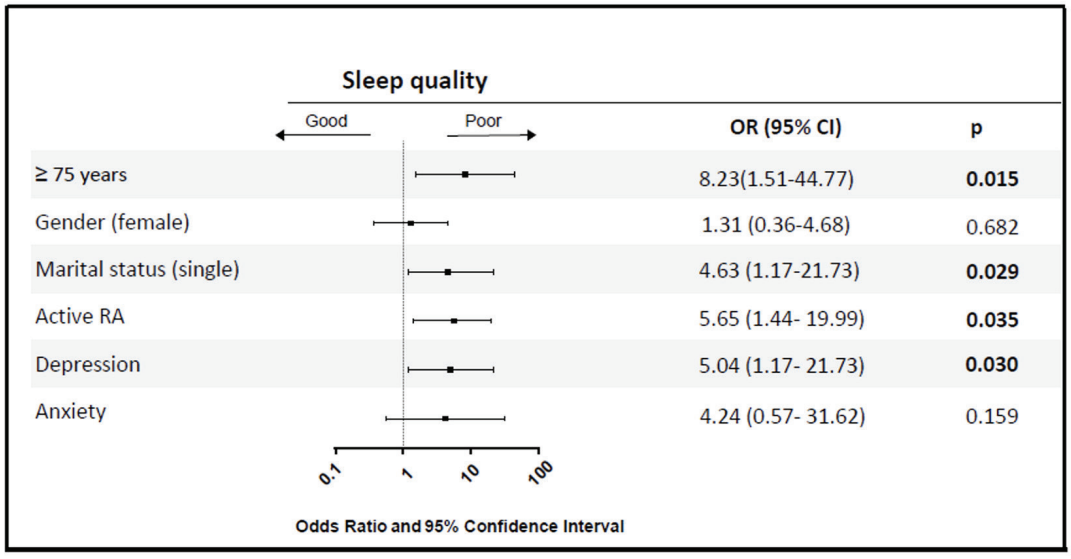

Figure 1. Forest plot of regression analysis on factors affecting sleep quality
Active RA: Patients with DAS score ≥2.6
Depression: Geriatric Depression scale-15 (GDS-15) was used for mood-related examination and a score ≥6 was defined as "depression".
Anxiety: Generalized anxiety disorder-7 (GAD-7) scales were used for anxiety examination. Those with a GAD-7 score of ≥5 defined as anxiety
CI: Confidence interval, DAS: Disease activity score, OR: Odds ratio, RA: Rheumatoid arthritis

Table 2. Comparison of EORTC subscales in terms of PSQI score

EORTC QLQ-30 parameters	Overall (n=77)	PSQI ≤5 (n=38)	PSQI >5 (n=39)	p-value
Global health status, median (range)	75.0 (16.7-100)	83.3 (16.7-100)	66.6 (16.7-100)	0.102
Functional scales, median (range)				
Physical function	80.0 (13.3-100)	80.0 (33.3-100)	73.3 (13.3-86.7)	**0.005**
Emotional function	83.3 (16.7-100)	87.5 (16.7-100)	75.0 (41.7-100)	**0.050**
Cognitive function	83.3 (33-100)	93 (50.0-100)	83.3 (33,3-100)	0.064
Role function	66.7 (16.7-100)	83.3 (16.7-100)	66.7 (16.7-100)	**<0.001**
Social function	83.3 (0-100)	100 (0-100)	83.3 (0-100)	0.081
Symptoms scales, median (range)				
Fatigue	22.2 (0-66.7)	11.1 (0-66.7)	22.2 (0-66.7)	**0.047**
Pain	33.3 (0-100)	33.3 (0-100)	66.7 (0-83.3)	**0.002**
Nausea and vomiting	0 (0-100)	0 (0-50.0)	0 (0-50.0)	0.430
Dyspnea	0 (0-100)	0 (0-66.7)	0 (0-100)	0.177
Loss of appetite	0 (0-33.3)	0 (0-33.3)	0 (0-33.3)	0.443
İnsomnia	33.3 (0-100)	0 (0-66.7)	66.7 (33.3-100)	**<0.001**
Diarrhea	0 (0-66.7)	0 (0-66.7)	0 (0-66.7)	0.257
Constipation	0 (0-33.3)	0 (0-33.3)	0 (0-33.3)	0.642
Financial difficulties	0 (0-66.7)	0 (0-33.3)	0 (0-66.7)	0.128

EORTC QLQ-30: European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30, PSQI: Pittsburgh Sleep Quality index

disorders at a rate of 5.04 (1.17-21.73) times. Depression is known to cause disruptions in sleep architecture, making it hard to fall asleep and negatively affecting sleep continuity.[27] Sleep disorders are exacerbated by imbalances in the serotonergic and dopaminergic neurotransmitter systems, which are linked to this condition. In the management of elderly RA patients, it is crucial to evaluate depressive symptoms as they have a significant impact on sleep quality through both biological and psychological mechanisms.

Aging plays a significant role in natural physiological that increase the likelihood of sleep disorders. Sleep quality may decline in older individuals due to disruptions in their circadian rhythm, decreased melatonin production, and increased physical discomfort. In addition, aging causes a decrease in sleep duration, shortened deep sleep stages, and increased night awakenings.[28,29] In our study, aging was independently associated with sleep disorders in the multivariate regression analysis, consistent with findings

reported in the literature. Additionally, it is noteworthy that single individuals are more prone to sleep disorders. According to the literature, married individuals have stronger social and emotional support, which are crucial for stress management.[30,31] Sleep patterns can be negatively impacted by social isolation and loneliness, which increase psychological stress and anxiety levels.

In our study, some notable differences were observed between the groups with and without sleep disorders in terms of the quality of life assessment of elderly RA patients using EORTC QLQ-C30. Contrary to expectations, no significant difference was observed regarding general health status. This may be due to patients' tendency to view their overall health perception from a broader perspective rather than focusing solely on symptoms. The patient's overall health perception may not always be directly affected by specific symptoms, as it may be thought. However, physical, emotional, and role functioning were significantly worse in patients with poor sleep quality. The deterioration in physical functionality can be explained by the negative effects of joint pain and movement restrictions on sleep quality. Increased pain at night and morning stiffness can disrupt patients' sleep patterns and negatively affect their daytime functions.[11] The deterioration in emotional functionality may be associated with high levels of depression and anxiety. The reduction in role functionality could be attributed to the fact that patients who struggle to meet their daily responsibilities may experience the effects of sleep disorders more profoundly. In symptom scales, significant differences were detected in the parameters "fatigue", "pain" and "insomnia" according to sleep disorder status. These findings are expected since these are parameters that have a significant effect on sleep disorders, especially within the symptomatic burden of RA.

Study Limitations

This study has some limitations. The cross-sectional design limits the ability to determine causality. The generalizability of the results is restricted by the small sample size and the study being conducted in a single center. Objective sleep measurements were not utilized, and sleep disturbances were assessed solely through subjective methods. In addition, since the scale used to assess quality of life was not specific to RA, it was not possible to examine all the symptoms specific to the disease in detail. Our study involved subjective assessment of sleep quality in RA patients. The use of objective methods such as polysomnography or actigraphy could increase the strength of the study's results. However, our study also has notable strengths. Quality of life and sleep disturbances in elderly RA patients were evaluated comprehensively, and the effects of sleep disturbances on the functional status and symptoms of the patients were examined in detail. Moreover, multivariate analyses revealed independent relationships between sleep disturbances. In this context, our study provides important findings that contribute to the literature.

Conclusion

This study is important in terms for identifying the factors affecting sleep quality in elderly RA patients and highlighting the effects of these disorders on the patients' quality of life. Managing disease activity alongside psychosocial and functional support can improve both sleep and quality of life outcomes. Incorporating specific strategies, like cognitive-behavioral therapy for insomnia and lifestyle modifications, such as establishing proper sleep hygiene practices, can alleviate insomnia and enhance sleep quality, resulting in better health outcomes. These findings indicate that sleep management in RA patients is a crucial component of disease management strategies.

Ethics

Ethics Committee Approval: The study was approved by Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Ethics Committee IRB (no.: 2024-05/64, date: 23.05.2024).

Informed Consent: An informed consent form was obtained from all participants in the study.

Footnotes

Authorship Contributions

Concept: N.K.S., Design: N.K.S, H.S., Data Collection and Processing: N.K.S, H.S., Analysis or Interpretation: N.K.S, H.S., Literature Search: N.K.S, H.S., Writing: N.K.S.

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

Financial Disclosure: The authors declare that they have no relevant financial disclosures.

References

1. Sun Y, Liu J, Xin L, et al. Factors influencing the Sharp score of 1057 patients with rheumatoid arthritis and anemia: a retrospective study. J Int Med Res. 2022;50:03000605221088560.
2. Bozzalla-Cassione E, Grignaschi S, Xoxi B, et al. Insights into the concept of rheumatoid arthritis flare. J Front Med (Lausanne). 2022;9:852220.
3. Grabovac I, Haider S, Berner C, et al. Sleep quality in patients with rheumatoid arthritis and associations with pain, disability, disease duration, and activity. J Clin Med. 2018;7:336.

4. Irwin MR, Straub RH, Smith MT. Heat of the night: sleep disturbance activates inflammatory mechanisms and induces pain in rheumatoid arthritis. Nat Rev Rheumatol. 2023;19:545-59.

5. Ucar U, Duruoz MT. Assessment of sleep quality in patients with rheumatoid arthritis. Paper presented at: 2012 ACR/ARHP Annual Meeting.

6. Salih A, Gray R, Mills K, Webley M. A clinical, serological and neurophysiological study of restless legs syndrome in rheumatoid arthritis. Br J Rheumatol. 1994;33:60-3.

7. Juárez-Rojop IE, Fresán A, Genis-Mendoza AD, et al. Prevalence of poor sleep quality and associated factors in individuals with rheumatoid arthritis: a cross-sectional study. Medicina (Kaunas). 2023;59:1633.

8. Lee YC, Chibnik LB, Lu B, et al. The relationship between disease activity, sleep, psychiatric distress and pain sensitivity in rheumatoid arthritis: a cross-sectional study. Arthritis Res Ther. 2009;11:R160.

9. Cakirbay H, Bilici M, Kavaçi O, et al. Sleep quality and immune functions in rheumatoid arthritis patients with and without major depression. Int J Neurosci. 2004;114:245-56.

10. Cole JL. Steroid-induced sleep disturbance and delirium: a focused review for critically ill patients. Fed Pract. 2020;37:260.

11. Ditmer M, Gabryelska A, Turkiewicz S, Białasiewicz P, Małecka-Wojciesko E, Sochal M. Sleep problems in chronic inflammatory diseases: prevalence, treatment, and new perspectives: a narrative review. J Clin Med. 2021;11:67.

12. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford). 2012;51(Suppl 6):vi5-9.

13. Canhão H, Rodrigues AM, Gregório MJ, et al. Common evaluations of disease activity in rheumatoid arthritis reach discordant classifications across different populations. Front Med (Lausanne). 2018;5:40.

14. Buysse D. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.

15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.

16. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:1-10.

17. Katz S. The index of ADL: a standardized measure of biological and psychosocial function. JAMA. 1963;185:914-9.

18. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9:179-86.

19. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38:633-8.

20. Ja Y. Development and validation of a geriatric depression screening scale; a preliminary report. J Psychiatr Res. 1983;39:37-49.

21. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166:1092-7.

22. Brahem M, Chebil A, Abid H, et al. Sleep disorders in rheumatoid arthritis patients. The Egyptian Rheumatologist. 2024;46:107-11.

23. Azzam AI. The impact of sleep problems on rheumatoid arthritis disease activity. Sleep Med Res. 2024;15:106-12.

24. McBeth J, Dixon WG, Moore SM, et al. Sleep disturbance and quality of life in rheumatoid arthritis: prospective mHealth study. J Med Internet Res. 2022;24:e32825.

25. Wright GE, Parker JC, Smarr KL, Johnson JC, Hewett JE, Walker SE. Age, depressive symptoms, and rheumatoid arthritis. Arthritis Rheum. 1998;41:298-305.

26. Fakra E, Marotte H. Rheumatoid arthritis and depression. Joint Bone Spine. 2021;88:105200.

27. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neuroscience. 2008;10:329-36.

28. Myers BL, Badia P. Changes in circadian rhythms and sleep quality with aging: mechanisms and interventions. Neurosci Biobehav Rev. 1995;19:553-71.

29. Bulut SD. Yaşlılarda uyku bozuklukları ve tedavisi. Turkiye Klinikleri Psychiatry-Special Topics. 2016;9:33-41.

30. Gamsizkan Z, Aslan S. Birinci basamakta insomnia sıklığı ve ilişkili inanç ve tutumların değerlendirilmesi. JCBPR. 2014;3:156-61.

31. Algın D, Akdağ G, Erdinç O. Kaliteli uyku ve uyku bozuklukları Quality sleep and sleep disorders. Osmangazi Tıp Dergisi. 2016;38:29-34.

Ulusal ROMATOLOJİ Dergisi
Journal of Turkish Society for Rheumatology www.romatolojidergisi.org

Orijinal Araştırma / Original Article

DOI: 10.4274/raed.galenos.2025.22043
Ulus Romatol Derg 2025;17(1):53-59

Biyolojik DMARD kullanan veya başlanacak olan seropozitif ve seronegatif romatoid artrit hastalarının karşılaştırılması

Comparison of seropositive and seronegative rheumatoid arthritis patients using or about to be initiated with biological DMARDS

Zehra Özsoy, Şerife Asya Germe, Gizem Ayan, Güllü Sandal Uzun, Mustafa Ekici, Erdinç Ünaldı, Levent Kılıç, Ali Akdoğan, Şule Apras Bilgen, Sedat Kiraz, Ali İhsan Ertenli

Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye

Öz

Amaç: Romatoid artrit (RA) etiyolojisi net olarak bilinmeyen, dünya nüfusunun %0,5-1'ini etkileyen enflamatuvar, otoimmün sistemik bir hastalıktır. Bu çalışmada biyolojik tedavi alan veya yeni başlanan seronegatif (SN) ve seropozitif (SP) RA hastalarının demografik, klinik özelliklerinin, tedavi seçimlerinin ve tedaviye yanıtlarının karşılaştırılması hedeflenmiştir.

Yöntem: 2010-2024 tarihleri arasında biyolojik hastalık modifiye edici antiromatizmal ilaçlar (b-DMARD) kullanması planlanan ve kullanan RA tanılı Hacettepe Üniversitesi Biyolojik Veri Tabanı'na kayıtlı hastanın dosyaları ve kayıtları otomasyon sisteminden tarandı. RA hastaları SPRA ve SNRA olarak iki gruba ayrıldı. Çalışmaya dahil edilen RA hastalarının demografik özellikleri, hastalık süresi, b-DMARD kullanım takip süresi, komorbiditeleri, RA ekstraartiküler bulguları, fomatoid faktör ve anti-siklik sitrulinlenmiş peptid antikoru sonuçları, biyolojik tedavi başlangıcı ve kontrollerde hastalık aktivasyon ölçümleri, görsel analog ölçek (GAÖ) global, GAÖ ağrı, GAÖ yorgunluk, Sağlık Değerlendirme Anketi-Engellilik indeksine kaydedildi.

Bulgular: Çalışmaya 2.559 hasta dahil edildi. Hastaların yaş ortanca değeri 55 idi ve 2.034'ü kadındı. Hastalık süresi ortanca değeri 14 yıldı. Hastaların %75'i SPRA, %25'i SNRA idi. Hastalık aktivite skoru (DAS-28), iki grup arasında karşılaştırıldığında istatistiksel anlamlı fark oluşturmasa da düşük hastalık aktivitesinde olan hasta oranı SNRA grupta daha fazla iken, SPRA grupta ise orta ve yüksek hastalık aktivitesindeki hasta oranı daha fazlaydı. B-DMARD tedavisi sonrası hastalar DAS-28 hastalık aktivite skoruna göre değerlendirildiğinde remisyon veya düşük hastalık aktivitesine ulaşan hasta oranı SNRA grupta, orta ve yüksek hastalık aktivitesinde kalan hasta oranı SPRA grupta istatistiksel anlamlı fark oluşturmasa da daha fazla idi. Ekstraartiküler bulgulardan interstisyel akciğer hastalığı sıklığı ve sikka semptomları SPRA grupta daha fazla idi.

Sonuç: SPRA ve SNRA klinik özellikleri, ekstraartiküler tutulum bulguları, hastalık aktiviteleri, tedavi seçimleri ve tedavi yanıtları farklılıklar gösteren RA'nın iki ayrı alt tipi olarak düşünülebilir.

Anahtar Kelimeler: Romatoid artrit, seropozitif, seronegatif, b-DMARD

Abstract

Objective: Rheumatoid arthritis (RA) is an inflammatory, autoimmune systemic disease. This study aimed to compare the demographic, clinical characteristics, treatment choices, and treatment responses of seronegative (SN) and seropositive (SP) RA patients who were receiving or newly started biological treatment.

Methods: The files and records of patients registered with Hacettepe University Biological Database with RA diagnosis who were planned to use biological disease-modifying antirheumatic drugs (b-DMARDs) between 2010-2024 were scanned. RA patients were divided into two groups as SPRA and SNRA. Demographic characteristics, disease duration, bDMARD use follow-up period, comorbidities, RA extra-articular findings, visual analog scale (VAS) global, VAS pain, VAS fatigue, Health Assessment Questionnaire-Disability index were recorded for RA patients included in the study.

Results: Two thousand five hundred and fifty-nine patients were included in the study. Median age of the patients was 55 years and 2034 of them were female. 75% of the patients were SPRA, 25% were SNRA. Although the DAS-28 score did not create a statistically significant difference when compared between the two groups, the rate of patients with low disease activity was higher in the seronegative group, while the rate of patients with moderate and high disease activity was higher in the SPRA group. When patients were evaluated according to the disease activity score (DAS-28) disease activity score after b-DMARD treatment, the proportion of patients who achieved remission or low disease activity was higher in the seronegative group. Among extra-articular findings, the frequency of interstitial lung disease and sicca symptoms were higher in the SPRA group.

Conclusion: SPRA and SNRA can be considered as two separate subtypes of RA with differences in clinical features, extra-articular involvement findings, disease activities, treatment choices and treatment responses.

Keywords: Rheumatoid arthritis, seropositive, seronegative, b-DMARD

İletişim / Correspondence:
Dr. Zehra Özsoy, Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye
E-posta: dr.zehraduman@hotmail.com **ORCID ID:** orcid.org/0000-0002-4534-4929
Geliş Tarihi / Received: 21.01.2025 **Kabul Tarihi / Accepted:** 28.02.2025 **Yayın Tarihi / Publication Date:**19.03.2025

Atıf / Cite this article as: Özsoy Z, Germe ŞA, Ayan G, et al. Comparison of seropositive and seronegative rheumatoid arthritis patients using or about to be initiated with biological DMARDS. Ulus Romatol Derg. 2025;17(1):53-59

Giriş

Romatoid artrit (RA) etiyolojisi net olarak bilinmeyen, enflamatuvar, simetrik periferik poliartrittir.[1] Dünya nüfusunun %0,5-1'ini etkileyen, otoimmün sistemik bir hastalıktır.[2-4] Tedavi edilmez ise başta el ve ayak küçük eklemleri olmak üzere sinoviyal pek çok eklemde, kıkırdak-kemik harabiyetine, deformitelere ve fiziksel işlev kaybına neden olur.[5] Sistemik enflamasyona bağlı olarak akciğer fibrozisi, sklerit, lenfoproliferatif hastalık gibi diğer organ tutulumlarına da yol açabileceği gibi inme, miyokard enfarktüsü ile sonuçlanabilecek aterosklerozu hızlandırabilir.[6]

Anti-siklik sitrulinlenmiş peptid antikoru (ACPA), romatoid faktör (RF) gibi RA tanısında kullanılan bir otoantikor olmakla birlikte, prognozun tahmin edilmesinde de değerli bir belirteçtir.[7] RF kadar duyarlı olmakla birlikte RF'den çok daha spesifiktir.[8] RF ve ACPA gibi RA ile ilişkili otoantikorların varlığı hastalığın otoimmün doğasını destekler.[9,10] ve eklem hasarı, ekstraartiküler bulgular, mortalite ile ilişkilidirler.[11,12] Önceki Amerikan Romatizma Derneği (*American College of Rheumatism* - ACR) 1987 kriterleri, ACPA henüz geliştirilmediğinden yalnızca RF'yi içeriyordu.[13] Bu otoantikorlar, ACR/Avrupa Romatizmayla Mücadele Birliği (*the European Alliance of Associations for Rheumatology* - EULAR) 2010 RA tanı kriterlerine dahil edilmiştir.[14] Otoantikor pozitifliği olan hastalar "seropozitif RA" (SPRA) olarak adlandırılırken, RA'nın klinik belirtilerini gösteren ancak antikor pozitifliği olmayanlar ise "seronegatif RA" (SNRA) olarak tanımlanır.[14]

RA farklı klinik fenotipleri ve tedaviye değişken yanıtları olan bir sendrom olarak kabul edilmektedir.[6,15] RF ve özellikle ACPA'nın tanımlanması, belirli genetik ve çevresel risk faktörlerine sahip, homojen bir hasta alt grubunun ve ayrıca hastalığın daha şiddetli seyrinin tanınmasına olanak sağlamıştır.[12]

Bu çalışmada biyolojik tedavi alan veya yeni başlanan SNRA ve SPRA hastalarının demografik, klinik özelliklerinin, tedavi seçimlerinin ve tedaviye yanıtlarının karşılaştırılması hedeflenmiştir.

Gereç ve Yöntemler

Hasta Seçimi

2010-2024 tarihleri arasında bDMARD kullanması planlanan ve kullanan 2010 ACR/EULAR RA tanı kriterlerini[14] sağlayan RA tanılı Hacettepe Üniversitesi Biyolojik Veri Tabanı'na (HÜR-BİO) kayıtlı 2559 hastanın dosyaları ve kayıtları otomasyon sisteminden tarandı. HÜR-BİO 2005 yılında kurulan, biyolojik hastalık modifiye edici antiromatizmal ilaçlar (b-DMARD) tedavisi başlanacak olan romatolojik hastalığa sahip hastaların kayıt ve takip edildiği tek merkezli veri tabanıdır.[16] Hastalar tek kaynaktan seçilmiştir. Kontrol grubu olmayan, tek merkezli, retrospektif, tanımlayıcı bir çalışmadır.

Çalışma Parametreleri

Çalışmaya dahil edilen RA hastalarının yaş, cinsiyet, eğitim durumu gibi demografik özellikleri, hastalık süresi, b-DMARD kullanım takip süresi, komorbiditeleri [diabetes mellitus (DM), hipertansiyon (HT), kronik böbrek hastalığı (KBH), koroner arter hastalığı (KAH), astım, malignite], RA ekstraartiküler bulguları [romatoid nodül, amiloidoz, karpal tünel sendromu, intertisyel akciğer hastalığı (İAH), pulmoner nodül, sikka semptomları], sigara kullanımı, kullanıyor ise sigara paket yılı, vücut kitle indeksleri, RF ve ACPA sonuçları, kan eritrosit sedimentasyon hızı, C-reaktif protein (CRP) değerleri, geçmiş ve kullanmakta oldukları tedavileri (cDMARD: sulfasalazin, methotreksat, leflunomid, plaquenil; steroid), [bDMARD'lar (infliximab, adalimumab, etanercept, sertolizumab, golimumab gibi anti-TNF ilaçlar; tofacitinib, baricitinib, upadacitinib gibi Janus kinase (JAK) inhibitörleri; rituximab gibi anti-CD20 monoklonal antikoru; abatacept gibi T-hücre inhibitörü; tocilizumab gibi interlökin-6 reseptörü monoklonal antikoru)], biyolojik tedavi başlangıcı ve kontrollerde hastalık aktivasyon ölçümleri hastalık aktivite skoru (DAS-28),[17] görsel analog ölçeği (GAÖ) global,[18] GAÖ ağrı,[18] GAÖ yorgunluk,[18] Sağlık Değerlendirme Anketi-Engellilik indeksi (*Health Assessment Questionnaire-Disability index* - HAQ-DI)[19] kaydedildi. Hastalar 6 ayda bir kontrol vizitlerde hastalık aktivite parametreleri açısından değerlendirildi. Tedaviye cevap, b-DMARD kullanmaya başladığı ilk ve hastayı en son değerlendirdiğimiz son vizit hastalık aktivite parametrelerindeki değişim olarak kabul edildi.

RF (<20 IU/mL) ve ACPA (0-5 RU/mL) normal olarak sınıflandırıldı. Normal üst seviyenin üç katına kadar "düşük seviyeli seropozitiflik" ve üst normal seviyenin üç katının üzerinde "kuvvetli (yüksek seviyeli) seropozitiflik" olarak adlandırıldı.

RA hastaları RF ve/veya ACPA pozitifliğine göre SPRA ve SNRA olarak iki gruba ayrıldı. Bu hasta gruplarının demografik verileri, hastalık süreleri, b-DMARD kullanım takip süreleri, komorbiditeleri, ekstraartiküler tutulumları, sigara kullanma durumları, vücut kitle indeksleri, kan sedimentasyon ve CRP değerleri, başlangıç ve kontrol hastalık aktivasyonları, b-DMARD seçimleri ve tedaviye yanıtları karşılaştırıldı.

Etik Değerlendirme

Çalışmamız Helsinki bildirgesinin 2013 yılındaki değişikliğine uygun olup Hacettepe Üniversitesi Kurumsal Etik Kurulu'ndan (karar no: KA: 2022/13-19 - 22005, tarih: 23.08.2022) etik onayı alınmıştır. Tüm katılımcılar yazılı muvafakatname verdi.

İstatistiksel Analiz

Veriler SPSS İstatistikleri Windows, Sürüm 23.0 (IBM SPSS İstatistikleri Windows, Sürüm 23.0. Armonk, NY: IBM Corp) kullanılarak analiz edildi. Sayısal değişkenlerin normal dağılımına uygun olup olmadığı görsel (histogram ve olasılık grafikleri) ve analitik yöntemlerle (Kolmogorov-Smirnov ve Shapiro-Wilk testleri) araştırıldı. Tanımlayıcı analizler, normal dağılım göstermeyen sayısal değişkenler için medyan ve çeyrekler arası aralık ile gösterildi. Bağımsız gruplarda kategorik verilerin ve oranların analizinde ki-kare veya Fisher testleri kullanıldı. Bağımsız grupların normal dağılmayan verilerinin medyanlarının değerlendirilmesinde Mann-Whitney U testi kullanıldı. P<0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular

Demografik Bulgular

Çalışmaya 2.559 hasta dahil edildi. Hastaların yaş ortanca [minimum-maksimum (min-maks)] değeri: 55 (17-89) idi ve 2034'ü (%79,5) kadındı. Hastalık süresi ortanca (min-maks) değeri: 14 (0-56) yıldı. b-DMARD kullanım takip süresi ortanca (min-maks) değeri: 35,6 (0-286) aydı. Hastaların %75'i SPRA, %25'i SNRA idi.

Seropozitif ve Seronegatif RA Hastalarının Özellikleri

SPRA grupta 1.730 (%90,3) hastada RF pozitifliği, 1.253 (%65,4) hastada ACPA pozitifliği, 1.067 (%55,6) hastada hem RF hem ACPA pozitifliği mevcuttu. SPRA hastaların 679'unda (%35,4) RF kuvvetli pozitif iken, 614'ünde (%32) ACPA kuvvetli pozitif idi. Her iki grup daha sıklıkla kadındı. SPRA grup daha ileri yaştaydı (p≤0,001), hastalık (p≤0,001) ve b-DMARD kullanım (p=0,01) takip süreleri daha uzundu ve daha fazla sigara içicisiydiler (p=0,01) (Tablo 1). b-DMARD başlama sırasında SPRA hasta grubunun hassas eklem (p=0,02), şiş eklem (p=0,004), DAS-28 skoru (p≤0,001) daha yüksek idi (Tablo 1). DAS-28 skoru iki grup arasında karşılaştırıldığında istatistiksel anlamlı fark oluşturmasa da düşük hastalık aktivitesinde olan hasta oranı SNRA grupta daha fazla iken [48 (%12,4) vs. 120 (%9,7) (p=0,12)], SPRA grupta ise orta ve yüksek hastalık aktivitesindeki hasta oranı daha fazla idi [1.114 (%90,3) vs. 338 (%87,6) (p=0,12)]. SNRA grubun lise ve üzeri eğitim seviyesi diğer gruba göre daha yüksek idi [314 (%54,5) vs. 702 (%42,4) (p≤0,001)]. SPRA olan gruptaki hastalarda HT [641 (%36,2) vs. 178 (%30,5) (p=0,01)] ve astım [151 (%8,5) vs. 34 (%5,8) (p=0,03)] sıklığı daha fazla iken, diğer komorbidite oranları (DM, KBH, KAH, malignite) benzerdi. Ekstraartiküler bulgulardan İAH

Tablo 1. Seropozitif ve seronegatif RA hastalarının özelliklerinin ve biyolojik tedavi öncesi hastalık aktivite parametrelerinin karşılaştırılması

			Seropozitif RA sayı (%): 1916 (74,9)	Seronegatif RA sayı (%): 643 (25,1)	p-değeri
Cinsiyet, kadın, sayı (%)			1531 (79,9)	503 (78,2)	0,36
Yaş, ortanca (min-maks)			57 (19-89)	50 (17-88)	<0,001
Hastalık Süresi (yıl), ortanca (min-maks)			15 (0-56)	13 (0-56)	<0,001
b-DMARD takip süresi (ay), ortanca (min-maks)			37,6 (0-286)	29,7 (0-242)	0,01
Vücut kitle indeksi, ortanca (min-maks)			28,4 (3-58)	27,9 (13-58)	0,33
Sigara, sayı (%)		Hiç içmemiş	1003 (55)	370 (60,5)	
İçmiş		821 (45)	242 (39,5)		0,01
ESR (mm/h), ortanca (min-maks)			31,5 (2-123)	24 (1-120)	<0,001
CRP (mg/dL), ortanca (min-maks)			1,44 (0,1-37,4)	1,38 (0,05-85,6)	0,2
Hastalık aktivite parametreleri ortanca (min-maks)	Hassas eklem		6 (0-28)	4 (0-28)	0,02
	Şiş eklem		2 (0-24)	2 (0-22)	0,004
	DAS-28		4,9 (1-8,2)	4,5 (1,5-7,7)	<0,001
	HAQ-DI		1 (0-3)	0,95 (0-2,9)	0,202
	GAÖ global		70 (0-100)	70 (0-100)	0,902
	GAÖ ağrı		70 (0-100)	70 (0-100)	0,262
	GAÖ yorgunluk		70 (0-100)	70 (0-100)	0,361

b-DMARD: Biyolojik hastalık modifiye edici antiromatizmal ilaçlar, CRP: C-reaktif protein, DAS-28: Hastalık aktivite skoru, ESR: Eritrosit sedimentasyon hızı, GAÖ: Görsel analog ölçeği, HAQ-DI: Sağlık Değerlendirme Anketi-Engellilik indeksi, min-maks: Minimum-maksimum, RA: Romatoid artrit

sıklığı SPRA grupta istatistiksel anlamlı fark olacak şekilde daha fazla iken [57 (%27) vs. 3 (%9,4) (p=0,03)]; pulmoner nodül [73 (%42,2) vs. 13 (%46,4) (p=0,67)] sıklığı benzerdi. Amiloidoz [12 (%0,7) vs. 2 (%0,3) (p=0,36)] ve romatoid nodül [17 (%9,8) vs. 1 (%3,6) (p=0,28)] sıklığı her iki grupta benzerdi. Sikka semptomları SPRA grupta daha fazla idi [81 (%4,6) vs. 13 (%2,2) (p=0,01)]. Ayrıca her iki grupta diz ve kalça protezi, omurga cerrahisi ve karpal tünel sendromu oranları benzerdi.

Seropozitif ve Seronegatif RA Hastalarının DMARD Tedavileri

SNRA hasta grubunda anti-tümör nekroz faktörü (TNF) tedaviler ilk başlanan b-DMARD olarak daha fazla tercih edilmiş iken; SPRA grubunda Ritüksimab, Abatecept, Tocilizumab, JAK inhibitörleri kullanılmıştır. İzlem sürecinde kullanılan b-DMARD tedaviler incelendiğinde SPRA grupta SNRA gruba göre tüm b-DMARD'ların daha fazla kullanıldığı görülmüştür. Biyolojik tedavi öncesi kullanılan c-DMARD tedaviler açısından hastalar değerlendirildiğinde SPRA grupta daha fazla uygulandıkları saptanmıştır. Hasta gruplarının tedavileri ayrıntılı olarak Tablo 2'de verilmiştir.

Seropozitif ve Seronegatif RA Hastaların b-DMARD Tedavi Yanıtları

b-DMARD tedavisi sonrası hastalar DAS-28 hastalık aktivite skoruna göre değerlendirildiğinde remisyon veya düşük hastalık aktivitesine ulaşan hasta oranı SNRA grupta [280 (%51,3) vs. 792 (%47) (p=0,08)]; orta ve yüksek hastalık aktivitesinde kalan hasta oranı SPRA grupta [892 (%53) vs. 266 (48,7) (p=0,08)] istatistiksel anlamlı fark oluşturmasa da daha fazla idi. SPRA hasta grubundaki hastaların kullanılan tedaviler sonrası SNRA gruptaki hastalara göre hassas, şiş eklem ve DAS-28 hastalık aktivite skorlarının istatistiksel olarak anlamlı fark yaratacak şekilde daha fazla gerilediği görülmüş iken; GAÖ global, Ağrı ve HAQ-DI değişimlerinin de daha iyi olduğu görüldü. Hasta gruplarının b-DMARD tedavileri sonrası tedaviye yanıt hastalık aktivite skorlarındaki değişimin karşılaştırılması ayrıntılı olarak Tablo 3'te verilmiştir.

Kullanılan b-DMARD tedaviler ayrı ayrı incelendiğinde; DAS-28 skorunda düşüş Anti-TNF [ortanca (min-maks) (-1,32 (-7,3, 2,76) vs. -0,67 (-6,3, 6,3), p=0,01)], Ritüksimab [ortanca (min-maks) (-1,61 (-5,5, 4,5) vs. -0,65 (-4,1, 2,2), p=0,02)], Tosilizumab [(min-maks) (-1,5 (-5,5, 2,3) vs. -0,4 (-3,9, 1,5), p=0,01)] tedavisi sonrası SPRA grupta SNRA

Tablo 2. Seropozitif ve seronegatif RA hasta gruplarının biyolojik tedavi öncesi kullanmış oldukları c-DMARD, ilk başlanan ve takip boyunca kullanılan b-DMARD tedavilerinin karşılaştırılması

		Seropozitif RA	Seronegatif RA	p-değeri
İlk başlanan b-DMARD sayı (%)	Adalimumab	431 (22,5)	174 (27,1)	0,01
	Etanercept	357 (18,6)	159 (24,7)	0,001
	Infliximab	107 (5,6)	51 (7,9)	0,03
	Golimumab	64 (3,3)	27 (4,2)	0,3
	Sertolizumab	106 (5,5)	53 (8,2)	0,01
	Ritüksimab	261 (13,6)	43 (6,7)	0,001
	Abatacept	338 (17,6)	82 (12,8)	0,004
	Tocilizumab	2 (0,1)	0 (0)	1
	Janus kinaz inhibitörleri	250 (13)	54 (8,4)	0,002
İzlem sürecinde kullanılan b-DMARD sayı (%)	Adalimumab	684 (72,5)	260 (27,5)	0,03
	Etanercept	529 (70,2)	225 (29,8)	<0,001
	Infliximab	247 (73,5)	89 (26,5)	0,53
	Golimumab	96 (68,6)	44 (31,4)	0,07
	Sertolizumab	209 (67,4)	101 (32,6)	0,001
	Ritüksimab	428 (86,8)	65 (13,2)	<0,001
	Abatacept	444 (80,9)	105 (19,1)	<0,001
	Tosilizumab	323 (78,2)	90 (21,8)	0,08
	Janus kinaz inhibitörleri	462 (79)	123 (21)	0,009
Biyolojik tedavi öncesi kullanılan c-DMARD sayı (%)	Methotreksat	1512 (85,5)	484 (83,3)	0,2
	Leflunomid	1098 (62,1)	268 (46,1)	<0,001
	Sulfasalazin	1069 (60,4)	321 (55,2)	0,02
	Hidroksiklorokin	1420 (80,3)	367 (63,2)	<0,001
	Glukokortikoid	1589 (89,8)	499 (85,9)	0,009

b-DMARD: Biyolojik hastalık modifiye edici antiromatizmal ilaçlar, RA: Romatoid artrit

Tablo 3. Seropozitif ve seronegatif RA hasta gruplarında kullanılan b-DMARD tedavisine başlamadan önceki ve takip sonundaki hastalık aktivite parametrelerindeki değişimin karşılaştırılması

Hastalık aktivite parametreleri ortanca (min-maks)	Seropozitif RA	Seronegatif RA	p-değeri
Hassas eklem	-3 (-25; 18)	-1 (-27; 15)	<0,001
Şiş eklem	-1 (-24; 10)	0 (-21; 13)	0,002
DAS-28	-1,37 (-7,3; 4,5)	-0,67 (-6,3; 6,3)	<0,001
HAQ-DI	-0,1 (-2,4; 1,9)	0 (-2,1; 1,8)	0,88
GAÖ global	-10 (-100; 80)	-2,5 (-100; 40)	0,21
GAÖ ağrı	-10 (-100; 100)	0 (-100; 70)	0,2
GAÖ yorgunluk	0 (-100; 100)	0 (-100; 80)	0,71

b-DMARD: Biyolojik hastalık modifiye edici antiromatizmal ilaçlar, DAS-28: Hastalık aktivite skoru, GAÖ: Görsel analog ölçeği, HAQ-DI: Sağlık Değerlendirme Anketi-Engellilik indeksi, min-maks: Minimum-maksimum, RA: Romatoid artrit

gruba göre daha fazlaydı. Abatacept, Janus Kinaz İnhibitörleri kullanımı ile gruplar arasında fark yoktu. Bununla birlikte SNRA hastalarında b-DMARD tedavi ajanları arasında tedavi yanıtları arasında anlamlı fark saptanmadı.

Tartışma

Çalışmamızda hastaların %75'i SPRA idi. SPRA grup daha ileri yaştaydı ve daha fazla sigara içicisiydiler. Hastalık ve b-DMARD kullanım takip süreleri daha uzundu. b-DMARD başlama sırasında hassas eklem, şiş eklem, DAS-28 skoru SPRA grupta daha yüksekti. Sikka semptomları ve İAH sıklığı SPRA grupta daha fazlaydı. Anti-TNF tedaviler ilk başlanan b-DMARD olarak SNRA hastalarında daha fazla tercih edilmiş iken; diğer biyolojik ajanlar SPRA grubunda daha çok kullanılmıştı. İzlem sürecinde SPRA grupta SNRA gruba göre tüm b-DMARD'lar daha fazla kullanılmıştı. SPRA hastaların kullanılan tedaviler sonrası hassas, şiş eklem ve DAS-28 hastalık aktivite skorlarının daha fazla gerilemekle birlikte daha çok orta ve yüksek hastalık aktivitesinde kaldıkları görüldü.

SNRA'nın daha iyi huylu doğasına ilişkin yaygın inanç, bu hastalık alt grubunun doğru şekilde anlaşılmasını büyük ölçüde engellemiştir. SPRA'nın tedavisinde kaydedilen ilerlemelerin SNRA hastalarda aynı derecede anlamlı iyileşmelere yol açmadığının anlaşılması,[20] otoantikor pozitifliğine dayanan analizlerin yapılmasını zorunlu kılmaktadır. RF ve ACPA RA patogenezinde önemli rol oynar ve radyografik ilerlemeyle önemli ölçüde ilişkili bulunmuş,[21] kötü prognostik belirteçler olarak kabul edilmiş ve SPRA hastalarında daha yoğun tedavi verilmesi gerektiği öne sürülmüştür.[22] Çalışmalar, bizim çalışmamızı destekler nitelikte, SPRA hastalarında hem hastalığın ortaya çıkışı sırasında hem de DMARD tedavi sonrasında hastalığın ciddiyetinin ve fonksiyon bozukluğunun daha fazla olduğunu göstermektedirler.[23-26] Çalışmamızda SPRA hastaları, özellikle başlangıçta hastalık aktivitesi yüksek olanlar, SNRA hastalarına kıyasla hassas, şiş eklem, DAS-28 değerlerinde daha büyük bir düşüşle tedaviye daha iyi yanıt gösterdi.

SPRA'da çok nadir görülen ilaçsız sürekli remisyon, SNRA hastaların %40'a varan bir kısmında elde edilebilmektedir.[27] Çalışmamızda da SPRA tedavi sonrası orta ve yüksek hastalık aktivitesinde kalır iken; SNRA düşük hastalık aktivitesini sağlayabilmiştir. 2022'de yayınlanan 41 çalışmayı içeren sistematik bir literatür taramasında, RF ile ACPA ve anti-TNF'ye yanıt arasında bir ilişki gösterilemedi.[28] Bununla birlikte bazı çalışmalarda SPRA TNF'lere daha kötü yanıt için bir risk faktörü olarak görülmüştür.[29] Ritüksimabın SPRA'da SNRA'ya göre daha etkili olduğu gösterilmiştir.[30] Norris-Gray ve ark.[31] otoantikor negatifliğinin, ritüksimabın kesilmesinde bağımsız bir belirleyiciydi. Benzer şekilde, Shipa ve ark.'nın[32] çalışması rituksimab ile tedavi edilen RA hastalarında sadece otoantikorların varlığında uzun süre ilaçta kalım görüldü. Alten ve ark.[33], Abatacept SubcutaneOus çalışmasında 2892 RA hastasının RF ve/veya ACPA pozitifliği olan hastalarda abataseptte kalımın daha yüksek olduğu görüldü. Beş randomize kontrollü çalışmanın tek bir post-hoc analizi, 3 ayda SPRA hastalarında SNRA hastalara kıyasla tofasitinib yanıtının daha yüksek olduğunu göstermiştir.[34] Benzer bir sonuçlar başka çalışmalarda da gösterilmiştir.[35] Bununla birlikte Jin ve ark.[36] tarafından yapılan bir çalışmada[36] biyolojik DMARD'ların ve JAK inhibitörlerinin etkinliğini 4000 SNRA ve 7000 SPRA arasında karşılaştırılmıştır ve tedaviye başladıktan 12 ay sonra değerlendirilen klinik etkinliğin iki grup arasında anlamlı farklılık göstermediğini bulmuşlardır. Bizim çalışmamızda da literatürle uyumlu bir şekilde anti-TNF tedaviler ilk başlanan b-DMARD olarak SNRA'da, ritüksimab, tosilizumab, abatacept ve JAK inhibitörleri SPRA grubunda daha çok tercih edilmişti.

Literatürde SNRA'nın prevalansına ilişkin güncel bir metaanalizde RA'lı hastaların %20-30'unun SNRA olduğunu bildirilmektedir.[37] Bununla birlikte, bu tahminlerin kayıtlardan elde edildiği göz önüne alındığında, bazı yazarlar SNRA'nın gerçek prevalansının belirsizliğini

koruduğunu ileri sürmektedir.[38] Literatürle uyumlu bir şekilde çalışmamızdaki hastaların %25'i SNRA idi. RA'nın eklem dışı belirtilerinin de SPRA ve SNRA hastalar arasında farklılık gösterdiği bulunmuştur; örneğin sklerit ve romatoid nodüllerin SPRA'da mevcut olma olasılığı daha yüksektir.[39] Benzer şekilde, bir meta-analiz İAH'nın daha yüksek ACPA antikor titreleri ile ilişkili olduğunu bildirmiştir.[40] Çalışmamızda da İAH SPRA'da daha fazla görülmüştür. Finlandiya'da 1980-2000'de[41] ve Pima Kızılderili popülasyonunda[42] ve daha yakın zamanda ABD'deki büyük bir çalışmada[43] RF pozitif RA olgusunda azalma sigarayı bırakmayı da içeren halk sağlığı önlemlerine bağlandı. Bizim çalışmamızda da bunu destekler nitelikte SPRA grubunda sigara içme oranı daha fazla idi.

Çalışmanın Kısıtlılıtları

Çalışmamızın kısıtlılıkları retrospektif olmasıdır. Çalışmamızın bir diğer kısıtlılığı 3. basamak bir sağlık kuruluşunda gerçekleşmiş olmasıdır ki bu daha alt basamak hastanelerde çözülemeyen daha ağır bir hastalık profili demektir. Ayrıca atlanan seronegatif hastalara tanı konulması açısından bir avantajdır. İkincisi, RA'da SNRA'nın düşük oranı nedeniyle SNRA'lı hasta sayısı nispeten azdı. Ancak, bu çalışmadaki RA hastaları arasında SNRA'lı hastaların oranı genel olarak SNRA'lı hastalara benzerdi; bu da bu çalışmanın gerçek dünya verisini yansıttığını düşündürmektedir. Bununla birlikte tek merkez olması hasta sayısı ve ayrıca farklı tanı ve tedavi yaklaşımları açısından çok merkezli çalışmalara göre kısıtlılık oluşturmaktadır. Ayrıca hastaların Sharp van der Heijde skoru gibi standart değerlendirme araçları için gerekli olan tanı ve takip radyografileri eksikti.

Sonuç

Sonuç olarak SPRA ve SNRA klinik özellikleri, ekstraartiküler tutulum bulguları, hastalık aktiviteleri, tedavi seçimleri ve tedavi yanıtları farklılıklar gösteren RA'nın iki ayrı alt tipi olarak düşünülebilir. Klinisyen klinik pratikte bu durumu göz önünde bulundurmalıdır.

Etik

Etik Kurul Onayı: Çalışmamız Helsinki bildirgesinin 2013 yılındaki değişikliğine uygun olup Hacettepe Üniversitesi Kurumsal Etik Kurulu'ndan (karar no: KA: 2022/13-19 - 22005, tarih: 23.08.2022) etik onayı alınmıştır.

Hasta Onayı: Tüm katılımcılar yazılı muvafakatname verdi.

Dipnotlar

Yazarlık Katkıları

Konsept: Z.Ö., A.İ.E., Dizayn: G.S.U., M.E., Veri Toplama veya İşleme: Z.Ö., Ş.A.G., Analiz veya Yorumlama: Ş.A.G., Ş.A.B., S.K., Literatür Arama: Z.Ö., G.A., E.Ü., A.A., L.K., Yazan: Z.Ö.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Guidelines for the management of rheumatoid arthritis. American college of rheumatology ad hoc committee on clinical guidelines. Rheum. 2002;46:328-46.
2. Hochberg MC. Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. Epidemiol Rev. 1981;3:27-44.
3. Buch M, Emery P. The etiology and pathogenesis of rheumatoid arthritis. Hosp Pharm 2002;9:5-10.
4. Weissmann G. Pathogenesis of rheumatoid arthritis. J Clin Rheumatol. 2004;10(3 Suppl):S26-31.
5. Semble EL. Rheumatoid arthritis: new approaches for its evaluation andmanagement. Arch Phys Med Rehabil .1995;76:190-201.
6. Gravallese EM, Firestein GS. Rheumatoid arthritis - common origins, divergent mechanisms. N Engl J Med. 2023;388:529-42.
7. Whiting PF, Smidt N, Sterne JA, et al. Systematic review: accuracy of anti-citrullinated peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med. 2010;152:456-64.
8. Finckh A, Liang MH. Anti-cyclic citrullinated peptide antibodies in the diagnosis of rheumatoid arthritis; bayes cleaers the haze. Ann Intern Med. 2007;146:816-7.
9. Volkov M, van Schie KA, van der Woude D. Autoantibodies and B cells: the ABC of rheumatoid arthritis pathophysiology. Immunol Rev. 2020;294:148-63.
10. Sokolova MV, Schett G, Steffen U. Autoantibodies in rheumatoid arthritis: his- torical background and novel findings. Clin Rev Allergy Immunol. 2022;63:138-51.
11. Bugatti S, Manzo A, Montecucco C, Caporali R. The clinical value of autoantibodies in rheumatoid arthritis. Front Med (Lausanne). 2018;5:339.
12. Willemze A, Trouw LA, Toes RE, Huizinga TW. The influence of ACPA status and characteristics on the course of RA. Nat Rev Rheumatol. 2012;8:144-52.
13. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
14. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
15. Lin CMA, Cooles FAH, Isaacs JD. Precision medicine: the precision gap in rheumatic disease. Nat Rev Rheumatol. 2022;18:725-33.

16. Nikiphorou E, Buch MH, Hyrich KL. Biologics registers in RA: methodological aspects, current role and future applications. Nat Rev Rheumatol. 2017;13:503-10.

17. Aletaha D, Landewe R, Karonitsch T, et al. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. Arthritis Rheum. 2008;59:1371-7.

18. Miller MD, Ferris DG. Measurement of subjective phenomena in primary care research: the visual analogue scale. Fam Pract Res J. 1993;13:15-24.

19. Küçükdeveci AA, Sahin H, Ataman S, Griffiths B, Tennant A. Issues in cross-cultural validity: example from the adaptation, reliability, and validity testing of a Turkish version of the Stanford Health Assessment Questionnaire. Arthritis Rheum. 2004;51:14-9.

20. Matthijssen XME, Niemantsverdriet E, Huizinga TWJ, Van Der Helm-Van Mil AHM. Enhanced treatment strategies and distinct disease outcomes among autoanti- body-positive and -negative rheumatoid ar- thritis patients over 25 years: a longitudinal cohort study in the Netherlands. PLoS Med. 2020;17:e1003296.

21. Meyer O, Labarre C, Dougados M, et al. anticitrullinated protein/pep- tide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. Ann Rheum Dis. 2003;62:120-6.

22. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying anti- rheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492-509.

23. Farragher TM, Lunt M, Plant D, Bunn DK, Barton A, Symmons DP. Benefit of early treatment in inflam- matory polyarthritis patients with anti-cyclic citrullinated peptide antibodies versus those without anti- bodies. Arthritis Care Res (Hoboken). 2010;62:664-75.

24. Katchamat W, Koolvisoot A, Aromdee E, Chiowchanwesawakit P, Muengchan C. Associations of rheu- matoid factor and anti-citrullinated peptide antibody with disease progression and treatment outcomes in patients with rheumatoid arthritis. Rheumatol Int. 2015;35:1693-9.

25. Kastbom A, Strandberg G, Lindroos A, Skogh T. Anti-CCP antibody test predicts the disease ourse dur- ing 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis. 2004;63:1085-9.

26. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B, BARFOT Study Group. Prediction of radio- logical outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis. 2004;63:1090-5.

27. D'Onofrio B, van der Helm-van Mil A, W J Huizinga T, van Mulligen E. Inducibility or predestination? Queries and concepts around drug-free remission in rheumatoid arthritis. Expert Rev Clin Immunol. 2023;19:217-25.

28. Wientjes MHM, den Broeder AA, Welsing PMJ, Verhoef LM, van den Bemt BJF. Prediction of response to anti-TNF treatment using laboratory biomarkers in patients with rheumatoid arthritis: a systematic review. RMD Open. 2022;8:e002570.

29. Hambardzumyan K, Hermanrud C, Marits P, et al. Association of female sex and positive rheumatoid factor with low serum infliximab and anti-drug antibodies, related to treatment failure in early rheumatoid arthritis: results from the SWEFOT trial population. Scand J Rheumatol. 2019;48:362-6.

30. Isaacs JD, Cohen SB, Emery P, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. Ann Rheum Dis. 2013;72:329-36.

31. Norris-Grey C, Cambridge G, Moore S, Reddy V, Leandro M. Long-term persistence of rituximab in patients with rheumatoid arthritis: an evaluation of the UCL cohort from 1998 to 2020. Rheumatology (Oxford). 2022;61:591-6.

32. Shipa MRA, Di Cicco M, Balogh E, et al. Drug-survival profiling of second-line biologic therapy in rheumatoid arthritis: choice of another tumour necrosis factor inhibitor or a biologic of different mode of action? Mod Rheumatol. 2023;33:700-7.

33. Alten R, Mariette X, Flipo RM, et al. Retention of subcutaneous abatacept for the treatment of rheumatoid arthritis: real-world results from the ASCORE study: an international 2-year observational study. Clin Rheumatol. 2022;41:2361-73.

34. Bird P, Hall S, Nash P, et al. Treatment outcomes in patients with seropositive versus seronegative rheumatoid arthritis in phase III randomised clinical trials of tofacitinib. RMD Open. 2019;5:e000742.

35. Sugawara M, Fujieda Y, Noguchi A, et al. Prediction of the intolerance or non-responder to Janus kinase inhibitors in patients with rheumatoid arthritis: a preliminary retrospective study with integrative cluster analysis. Clin Exp Rheumatol. 2022;40:1674-80.

36. Jin Y, Liu J, Desai RJ, Kim SC. Real-world treatment effectiveness of disease-modifying antirheumatic drugs by serostatus among patients with rheumatoid arthritis. ACR Open Rheumatol. 2023;5:571-80.

37. De Stefano L, Bugatti S, Mazzucchelli I, et al. Synovial and serum B cell signature of autoantibody-negative rheumatoid arthritis vs autoantibody-positive rheumatoid arthritis and psoriatic arthritis. Rheumatology (Oxford). 2024;63:1322-31.

38. De Stefano L, D'Onofrio B, Gandolfo S, et al. Seronegative rheumatoid arthritis: one year in review 2023. Clin Exp Rheumatol. 2023;41:554-64.

39. Koslow M, Young JR, Yi ES, et al. Rheumatoid pulmonary nodules: clinical and imaging features compared with malignancy. Eur Radiol. 2019;29:1684-92.

40. Kamiya H, Panlaqui OM. Systematic review and meta-analysis of the risk of rheumatoid arthritis-associated interstitial lung disease related to anti-cyclic citrullinated peptide (CCP) antibody. BMJ Open. 2021;11:e040465.

41. Kaipiainen-Seppanen O, Kautiainen H. Declining trend in the incidence of rheumatoid factor-positive rheumatoid arthritis in Finland 1980-2000. J Rheumatol. 2006;33:2132-8.

42. Enzer I, Dunn G, Jacobsson L, Bennett PH, Knowler WC, Silman A. An epidemiologic study of trends in prevalence of rheumatoid factor seropositivity in Pima Indians: evidence of a decline due to both secular and birth-cohort influences. Arthritis Rheum. 2002;46:1729-34.

43. Myasoedova E, Davis J, Matteson EL, Crowson CS. Is the epidemiology of rheumatoid arthritis changing? Results from a population-based incidence study, 1985-2014. Ann Rheum Dis. 2020;79:440-4.