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: **2** • **Temmuz** / July **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

Editörler Kurulu / Editorial Board

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

Sahibi / Owner

Türkiye Romatoloji Derneği adına / On behalf of the Turkish Society for Rheumatology
Ahmet Gül

Sorumlu Yazı İşleri Müdürü / Managing Editor
R. Haner Direskeneli

Editör / Editor

R. Haner Direskeneli
Marmara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul, Türkiye
ORCID ID: orcid.org/0000-0003-2598-5806

Editör Yardımcıları / Associate Editors

Umut Kalyoncu
Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye
ORCID ID: orcid.org/0000-0001-7129-2109

Ömer Karadağ
Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye
ORCID ID: orcid.org/0000-0002-3443-3117

Gülen Hatemi
İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul, Türkiye
ORCID ID: orcid.org/0000-0002-1952-1135

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: Temmuz 2025/July 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

Derleme / Review

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.32932
Ulus Romatol Derg 2025;17(2):60-67

Impact of age at disease onset on clinical manifestations and prognosis in systemic lupus erythematosus

Sistemik lupus eritematozusta hastalık başlangıç yaşının klinik belirtiler ve prognoz üzerindeki etkisi

Didem Şahin[1], Buğu Bulat[2], Emine Uslu[1], Nilgün Göveç-Gıynaş[1], Görkem Turhan[2], Mustafa Kader[2], Mehmet Levent Yüksel[1], Emine Gözde Aydemir-Gülöksüz[1], Müçteba Enes Yayla[1], Tahsin Murat Turgay[1], Gülay Kınıklı[1], Aşkın Ateş[1]

[1]*Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[2]*Ankara University Faculty of Medicine, Department of Internal Medicine, Ankara, Türkiye*

Abstract

Objective: To assess age-related differences in demographic, clinical, and treatment characteristics of systemic lupus erythematosus (SLE) patients and evaluate outcomes based on age at disease onset.

Methods: Patients diagnosed with SLE who met 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria were retrospectively evaluated. Patients were classified based on age at onset: adult-onset (18-49 years) and late-onset (≥50 years). Demographic, clinical, laboratory characteristics and outcomes of adult and late-onset groups were compared. Disease damage was evaluated with the SLICC/American College of Rheumatology damage index (SDI). To assess the effect of age on mortality, Cox regression analysis was performed with the selected variables that were causally associated with the outcome.

Results: Among 519 patients, 88.1% were female, with a mean diagnosis age of 36.6 years. Adult-onset SLE represented 82.3% of cases, while 17.7% had late-onset disease. Neurological involvement was more frequent in adult-onset SLE (25.8% *vs.* 16.3%), as was renal involvement (41.1% *vs.* 26.1%). Anti-ribonucleoprotein antibodies were more prevalent in adult-onset SLE (24.7% *vs.* 7.1%, p<0.001). Damage accrual was observed in 40.3% of patients, without significant differences in SDI scores between groups. After a median follow-up of 9.2 years, 10.8% of patients died, with a higher mortality rate in late-onset SLE (20.7% *vs.* 8.7%, p=0.001). Cox regression showed age at SLE onset was independently associated with increased mortality (hazard ratio: 1.09, 95% confidence interval: 1.06-1.11, p<0.001).

Conclusion: Age at SLE onset is associated with distinct clinical features and outcomes. Late-onset SLE patients experience higher mortality, emphasizing the need for age-specific approaches in SLE management.

Keywords: Systemic lupus eryhthematosus, age at onset, damage, mortality

Özet

Amaç: Bu çalışmanın amacı, sistemik lupus eritematozus (SLE) hastalarında yaşa bağlı demografik, klinik ve tedavi özelliklerindeki farklılıkları değerlendirmek ve hastalık başlangıç yaşına göre prognozu incelemektir.

Yöntem: 2012 Sistemik Lupus Uluslararası İşbirliği Klinikleri (SLICC) kriterlerini karşılayan SLE tanılı hastalar retrospektif olarak değerlendirildi. Hastalar, hastalık başlangıç yaşlarına göre yetişkin başlangıçlı (18-49 yaş) ve geç başlangıçlı (≥50 yaş) olmak üzere sınıflandırıldı. Yetişkin ve geç başlangıçlı grupların demografik, klinik, laboratuvar özellikleri ve sonuçları karşılaştırıldı. Hastalığa bağlı hasar, SLICC/Amerikan Romatoloji Koleji hasar indeksi (SDI) ile değerlendirildi. Yaşın mortalite üzerindeki etkisini incelemek için, sonuçla nedensel ilişkili değişkenlerin dahil edildiği Cox regresyon analizi uygulandı.

Bulgular: Toplam 519 hastanın %88,1'i kadın olup, ortalama tanı yaşı 36,6 yıl olarak belirlendi. Hastaların %82,3'ü yetişkin başlangıçlı, %17,7'si ise geç başlangıçlı SLE grubundaydı. Nörolojik tutulum yetişkin başlangıçlı SLE'de daha sık görüldü (%25,8'e karşı %16,3), aynı şekilde renal tutulum da daha yüksekti (%41,1'e karşı %26,1). Anti-ribonükleoprotein antikorları yetişkin başlangıçlı grupta daha yaygındı (%24,7'ye karşı %7,1, p<0,001). Hasar birikimi %40,3 hastada gözlenmiş olup, gruplar arasında SDI skorlarında anlamlı bir fark bulunmadı. Ortalama 9,2 yıllık takip süresi sonunda, hastaların %10,8'i hayatını kaybetti ve geç başlangıçlı SLE grubunda mortalite oranı daha yüksekti (%20,7'ye karşı %8,7, p=0,001). Cox regresyon analizi, SLE başlangıç yaşının bağımsız olarak artmış mortalite ile ilişkili olduğunu gösterdi (risk oranı: 1,09, %95 güven aralığı: 1,06-1,11, p<0,001).

Sonuç: Bu çalışmada, SLE başlangıç yaşı, klinik özellikler ve prognoz üzerinde farklılıklarla ilişkili olarak bulunmuştur. Geç başlangıçlı SLE hastalarında yüksek mortalite gözlenmiş olup, bu sonuç yaşa özgü yaklaşımların gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Sistemik lupus eritematozus, hastalık başlangıç yaşı, hasar, mortalite

Correspondence / İletişim: Didem Şahin MD,
Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
E-mail: dr.didemsa@gmail.com **ORCID ID:** orcid.org/0000-0003-3558-5400
Received / Geliş Tarihi: 26.11.2024 **Accepted / Kabul Tarihi:** 24.02.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Şahin D, Bulat B, Uslu E, et al. Impact of age at disease onset on clinical manifestations and prognosis in systemic lupus erythematosus. J Turk Soc Rheumatol. 2025;17(2):60-67

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a broad spectrum of clinical manifestations that can affect multiple organ systems.[1] The disease onset can vary significantly, occurring in individuals ranging from childhood to older adulthood. Understanding how the age at onset influences disease outcomes is crucial for optimizing management strategies and improving patient prognosis. Prior studies suggest that early-onset SLE, particularly in pediatric cases, often presents more aggressively, with higher rates of organ damage and complications, whereas late-onset SLE may exhibit distinct clinical features and outcomes.[2-7] Therefore, in this single-centre retrospective study, our objective was to assess the association between the age at SLE onset and key outcomes, including disease manifestations, cumulative damage, and survival.

Materials and Methods

In this study, we scrutinized the medical records of 579 patients who met the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE[8] and were evaluated in the adult rheumatology clinic between January 2010 and August 2021. Demographic, clinical, and treatment characteristics of all patients were retrospectively assessed, with clinical and treatment features recorded cumulatively. In contrast, for laboratory characteristics, the values at the initial evaluation or the first recorded values in our hospital data system were considered. Neurological involvement was determined based on the 1999 American College of Rheumatology (ACR) nomenclature and case definition for neuropsychiatric SLE.[9]

Patients were grouped into three different categories according to the age at onset of the disease: Childhood-onset (<18 years of age), adult-onset (18-49 years), and late-onset (≥50 years) SLE. To avoid selection bias, 60 (10.4%) patients with childhood-onset SLE were excluded from the study.

The SLICC/ACR damage index (SDI) is a widely used tool to evaluate the damage to organs in patients with SLE and captures damage resulting from both the disease process and its treatments. The SDI provides a cumulative score that reflects the extent of permanent damage.[10] It includes a variety of domains (41 items across 12 organ systems), including the renal, neuropsychiatric, cardiovascular, neurological, and musculoskeletal systems. In this study, the SDI was used to assess the long-term impact of the disease. To calculate SDI scores, only patients with a minimum follow-up period of 6 months were included, ensuring an accurate and reliable evaluation of disease progression. Follow-up time was defined as the duration from disease diagnosis to the last follow-up date or death.

We obtained approval from the Ethics Committee of Ankara University (approval number: İ9-592-21, date: 21.10.2021) and conducted the study in accordance with the Declaration of Helsinki.

Statistical Analysis

Categorical variables are presented as frequencies and percentages. In univariate of categorical variables, levels of significance were determined by means of the chi-square test or Fisher's exact probability test using contingency tables. Quantitative variables are shown as either median and 25th and 75th percentile (Q1-Q3) or as mean and standard deviation (SD). The Independent Samples t-test, or the Mann-Whitney U test as a non-parametric substitute, was used to analyse quantitative variables.

To demonstrate the association of age with overall mortality, Cox regression analyses were performed. The follow-up duration was determined as the gap-time from the diagnosis of SLE to the last visit for the survived patients and to death for the deceased patients. Based on the causal assumptions, adjustment for sex, SDI scores and immunosuppresant use was performed. A 95% confidence interval of corresponding hazard ratios (HR) which did not include a null effect was accepted as significant. Analyses were performed by using the SPSS software version 26.

Results

Characteristics of the Study Subjects

Of the 519 patients, 457 (88.1%) were female, and the mean age at SLE diagnosis was 36.6±13.4 years (31.7±8.7 and 58.9±7.4 for the adult-onset and the late-onset groups, respectively). The most common involvement was acute cutaneous lupus (57.0%), followed by hematological involvement (53.8%), synovitis (48.6%), renal involvement (38.9%), and neurological involvement (24.3%). Demographic and disease-related characteristics are shown in detail in Table 1.

The patients with adult-onset SLE comprised of 82.3% of the study cohort whereas it was 17.7% for the late-onset group. In terms of clinical phenotypes, renal and neurological involvements differed between two groups being both involvements more common in the adult-onset group. The proportions of patients with acute cutaneous lupus were similar, however, malar rash was more prevalent in the adult-onset SLE (37.2% *vs.* 26.1%, p=0.042).

Table 1. Demographic and clinical characteristics of the study population

	All cohort (n=519)	Adult-onset (n=427)	Late-onset (n=92)	p
Sex				0.726
Female, n (%)	457 (88.1)	375 (87.8)	82 (89.1)	
Male, n (%)	62 (11.9)	52 (12.2)	10 (10.9)	
Age at diagnosis, y, mean (SD)	36.6 (13.4)	31.7 (8.7)	58.9 (7.4)	<0.001
Fever, n (%)	69 (13.3)	56 (13.1)	13 (14.1)	0.795
Acute cutaneous lupus, n (%)	296 (57.0)	248 (58.1)	48 (52.2)	0.299
Photosensitivity	234 (45.1)	198 (46.4)	36 (39.1)	0.206
Malar rash	183 (35.3)	159 (37.2)	24 (26.1)	0.042
Others	17 (3.3)	14 (3.3)	3 (3.3)	1.00
Chronic cutaneous lupus, n (%)	59 (11.4)	49 (11.5)	10 (10.9)	0.868
DLE	57 (11.0)	47 (11.0)	10 (10.9)	0.969
Alopecia, n (%)	107 (20.6)	92 (21.5)	15 (16.3)	0.260
Oral or nasal ulcer, n (%)	120 (23.1)	102 (23.9)	18 (19.6)	0.372
Oral ulcer	117 (22.5)	100 (23.4)	17 (18.5)	0.304
Nasal ulcer	8 (1.5)	7 (1.6)	1 (1.1)	1.00
Synovitis, n (%)	252 (48.6)	208 (48.7)	44 (47.8)	0.877
Serositis, n (%)	92 (17.7)	76 (17.8)	16 (17.4)	0.926
Pleuritis	64 (12.3)	52 (12.2)	12 (13.0)	0.819
Pericarditis	51 (9.8)	41 (9.6)	10 (10.9)	0.711
Peritonitis	7 (1.3)	5 (1.2)	2 (2.2)	0.360
Renal involvement, n (%)	202 (38.9)	177 (41.5)	25 (27.2)	0.011
Nephrotic proteinuria	64 (12.3)	57 (13.3)	7 (7.6)	0.129
Neurological involvement, n (%)	126 (24.3)	112 (26.2)	14 (15.2)	0.025
Haematological involvement, n (%)	279 (53.8)	228 (53.4)	51 (55.4)	0.722
AIHA	94 (18.1)	78 (18.3)	16 (17.4)	0.843
Thrombocytopenia	120 (23.1)	101 (23.7)	19 (20.7)	0.536
Secondary APS, n (%)	66 (12.7)	53 (12.4)	13 (14.1)	0.654
Gestational	33 (6.4)	26 (6.1)	7 (7.6)	0.588
Vascular thrombosis	51 (9.8)	41 (9.6)	10 (10.9)	0.711
Lympadenopathy, n (%)	53 (10.2)	46 (10.8)	7 (7.6)	0.363
Livedo reticularis, n (%)	14 (2.7)	13 (3.0)	1 (1.1)	0.482
Raynaud phenomenon, n (%)	99 (19.1)	88 (20.6)	11 (12.0)	0.055
Tobacco use ever, n (%)	153/368 (41.6)	132/300 (44.0)	21/68 (30.9)	0.048
Alcohol use, n (%)	14/354 (4.0)	12/288 (4.2)	2/66 (3.0)	1.00
Follow-up ≥6 months, n (%)	498 (96.0)	412 (96.5)	86 (93.5)	0.237
Follow-up duration, y, median (Q1-Q3)	9.2 (3.9-16.9)	9.9 (4.6-17.9)	6.2 (2.3-13.7)	<0.001

AIHA: Autoimmune hemolytic anemia, APS: Antiphospholipid syndrome, DLE: Discoid lupus erythematosus, SD: Standard deviation

As for autoantibody profiles, antinuclear antibody positivity was around 95% in both groups (Table 2). Antibodies to ribonucleoprotein (anti-RNP) was detected more frequently in patients with adult-onset SLE than in patients with late-onset SLE (24.7% *vs.* 7.1%, p<0.001), whereas anti-Ro52 antibodies were more commonly seen in patients with late-onset SLE which did not reach statistical significance (16.6% *vs.* 24.7%, p=0.079).

Treatment characteristics of the cohort were demonstrated in Table 3. The rate of glucocorticoid use ever was similar in both groups; however, pulse steroids were administered more frequently to the adult-onset SLE patients (19.2% *vs.* 10.9%, p=0.058). In line with the latest finding, when glucocorticoids were grouped according to the maximum dose used during the entire follow-up, the difference reached statistical significance (Table 3). In addition, the patients with adult-onset SLE were more commonly initiated on immunosuppressive agents, which was statistically significant for cyclophosphamide, azathioprine and mycophenolic acid.

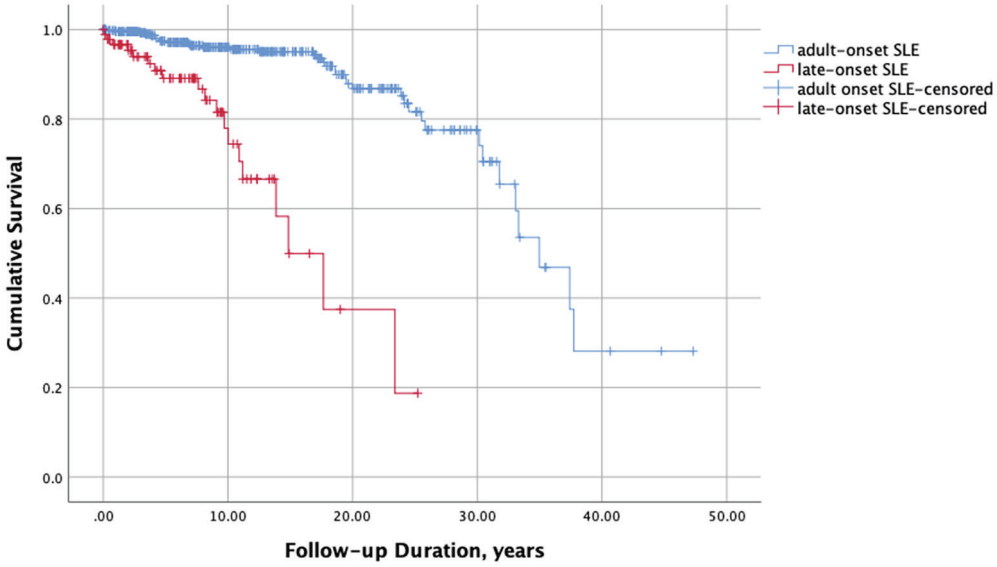

Figure 1. Kaplan-Meier curve of adult-onset and late-onset SLE patients
SLE: Systemic lupus erythematosus

Table 2. Laboratory characteristics of the study population

	All cohort (n=519)	Adult-onset (n=427)	Late-onset (n=92)	p
ANA positivity, n (%)	496/517 (95.9)	409/425 (96.2)	87/92 (94.6)	0.558
Anti-dsDNA positivity, n (%)				0.213
ULN	91/509 (17.9)	78/418 (18.7)	13/91 (14.3)	
>2xULN	234/509 (46.0)	196/418 (46.9)	38/91 (41.8)	
Anti-RNP, n (%)	97/453 (21.4)	91/368 (24.7)	6/85 (7.1)	<0.001
Anti-Sm, n (%)	111/454 (24.4)	95/369 (25.7)	16/85 (18.8)	0.181
Anti-histon, n (%)	79/453 (17.4)	62/368 (16.8)	17/85 (20.0)	0.490
Anti-SS-A, n (%)	167/453 (36.9)	135/368 (36.7)	32/85 (37.6)	0.868
Anti-SS-B, n (%)	54/453 (11.9)	40/368 (10.9)	14/85 (16.5)	0.151
Anti-Ro52, n (%)	82/453 (18.1)	61/368 (16.6)	21/85 (24.7)	0.079
Anti-nucleosome, n (%)	96/453 (21.2)	76/368 (20.7)	20/85 (23.5)	0.559
Anti-ribosomal-P, n (%)	23/453 (5.1)	20/368 (5.4)	3/85 (3.5)	0.593
APA positivity, n (%)				
Lupus anticoagulant, n (%)	97/287 (33.8)	86/245 (35.1)	11/42 (26.2)	0.259
Anti-cardiolipin	41/413 (9.9)	39/343 (11.4)	2/70 (2.9)	0.030
Anti-beta-2 glycoprotein	43/347 (12.4)	36/291 (12.4)	7/56 (12.5)	0.979
Low complement, n (%)	145/516 (28.1)	329/425 (77.4)	42/91 (46.2)	<0.001
Low C3, n (%)	330/515 (64.1)	292/424 (68.9)	38/91 (41.8)	<0.001
Low C4, n (%)	211/516 (40.9)	189/425 (44.5)	22/91 (24.2)	<0.001
Direct coombs test, n (%)	129/176 (73.3)	102/143 (71.3)	27/33 (81.8)	0.220

ANA: Antinuclear antibody, Anti-dsDNA: Anti-double stranded DNA, Anti-RNP: Anti-ribonucleoprotein, Anti-Sm: Anti-Smith, APA: Antiphospholipid antibody, C3: Low complement 3, C4: Low complement 4, ULN: Upper limit of normal

Prognosis and Mortality

The SDI was determined in 498 patients whose follow-up duration was ≥6 months. Of 498 patients, damage accrual was present in 209 (40.3%) patients after median follow-up of 9.4 years. Mean and median damage scores in the study population were 0.94 (SD: 1.51) and 0 (Q1-Q3: 0-1), respectively. There were no differences in terms of damage domains and the SDI scores between two groups (Table 4). The most common damage observed was the musculoskeletal domain (11.8%) followed by renal complications (10.6%). The percentage of malignancy was higher in the late-onset group compared to the adult-onset group (8.1% *vs.* 3.6%, respectively, p=0.081). Interestingly, as demonstrated in Table 1, tobacco use, a well-known risk

Table 3. Treatment characteristics of the study population

	All cohort (n=519)	Adult-onset (n=427)	Late-onset (n=92)	p
Glucocorticoids ever, n (%)	472 (90.9)	392 (91.8)	80 (87.0)	0.142
Pulse steroid ever, n (%)	92 (17.7)	82 (19.2)	10 (10.9)	0.058
Prednisolone dose, n (%)				<0.001
Never	48 (9.2)	35 (8.2)	13 (14.1)	
0-7.5 mg/day	74 (14.3)	53 (12.4)	21 (22.8)	
7.5-19 mg/day	106 (20.4)	84 (19.7)	22 (23.9)	
20-39 mg/day	67 (12.9)	49 (11.5)	18 (19.6)	
40-59 mg/day	78 (15.0)	72 (16.9)	6 (6.5)	
≥60 mg/day	146 (28.1)	134 (31.4)	12 (13.0)	
Antimalarials, n (%)	491 (94.6)	405 (94.8)	86 (93.5)	0.611
NSAIDs, n (%)	192 (37.0)	158 (37.0)	34 (37.0)	0.993
Immunosuppressants, n (%)	343 (66.1)	296 (69.3)	47 (51.1)	0.001
Cyclophosphamide, n (%)	108 (20.8)	101 (23.7)	7 (7.6)	0.001
Rituximab, n (%)	25 (4.8)	23 (5.4)	2 (2.2)	0.283
IVIG, n (%)	42 (8.1)	36 (8.4)	6 (6.5)	0.542
Azathioprine, n (%)	246 (47.4)	218 (51.1)	28 (30.4)	<0.001
Methotrexate, n (%)	61 (11.8)	49 (11.5)	12 (13.0)	0.672
Mycophenolic acid, n (%)	140 (27.0)	129 (30.2)	11 (12.0)	<0.001
Cyclosporin-A, n (%)	25 (4.8)	24 (5.6)	1 (1.1)	0.101
Acetylsalicylic acid, n (%)	206 (39.7)	172 (40.3)	34 (37.0)	0.554
Anticoagulation, n (%)	93 (17.9)	82 (19.2)	11 (12.0)	0.100
Statin use, n (%)	49 (9.4)	36 (8.4)	13 (14.1)	0.090

IVIG: Intravenous immunoglobulin, NSAIDs: Non-steroidal anti-inflammatory drugs

factor for malignancy development, was more common in patients with adult-onset SLE (44.0% *vs.* 30.9%, p=0.048). The most common malignancy was head and neck cancers (22.7%). Among 21 patients with less than 6-month follow-up, 3 patients died prematurely within the 6-month period after SLE diagnosis [2 patients in late-onset SLE group (haemophagocytic syndrome and acute hepatic failure) and 1 patient in adult-onset SLE group (sepsis)].

After median of 9.2 years, 56 out of 519 (10.8%) patients died; 8.7% in the adult-onset SLE and 20.7% in the late-onset SLE (p=0.001). The primary cause of death was infections, accounting for 30.4%, followed by active disease and other causes, each at 14.3%, and cardiac reasons at 5.4%. Twenty patients had an unknown cause of death. The distribution of causes was similar between both groups (data not shown). The 5-year and 10-year survival rates in the cohort were 96% and 93%, respectively. The survival differed between two groups (Log-rank<0.001, see Figure 1). Older age at SLE onset was independently associated with overall mortality in Cox regression analysis when adjusted for sex, SDI score and immunosuppressive use [HR 1.09 (1.06-1.11), p<0.001]. A model, in which smoking was also added as a covariate, HR of age was determined as 1.10 (1.05-1.52).

Discussion

This study found that most of the patients experienced disease onset between the ages of 18 and 49, as expected. The adult-onset group showed higher rates of malar rash as well as renal and neurological involvement, aligning with findings in the published literature.[4,7,11,12] As a consequence, the use of more potent immunosuppressive agents, such as cyclophosphamide, azathioprine and mycophenolate mofetil, were more frequent in patients with adult-onset SLE, which also supports the results of previous studies.[4,11]

Similar to our findings, a systematic review and meta-analysis on the neuropsychiatric manifestations of SLE found that the cumulative frequency of neurological involvement is higher in early-onset SLE patients.[13] Additionally, some studies suggest that anti-RNP antibodies may have an impact on the development of neuropsychiatric symptoms in patients, compared to those without these antibodies.[14,15] Notably, in our study, anti-RNP antibodies were more common in patients with adult-onset SLE than the late-onset SLE patients, potentially indicating a link between these antibodies and neurological involvement. Nevertheless, more research is needed to fully understand the extent of this relationship and the mechanisms through which anti-RNP antibodies influence the neurological aspects of SLE.

Table 4. The SDI domains in each group

	All cohort (n=498)	Adult-onset (n=412)	Late-onset (n=86)	p
Any damage, n (%)	209 (40.3)	171 (40.0)	38 (41.3)	0.823
Damage score, median, (Q1-Q3)	0 (0-1)	0 (0-1)	0 (0-3)	0.669
Damage score, mean (SD)	0.94 (1.51)	0.93 (1.52)	0.98 (1.46)	0.787
Ocular, n (%)	30 (6.0)	23 (5.6)	7 (8.1)	0.365
Cataract	24 (4.8)	17 (4.1)	7 (8.1)	0.160
Retinal	5 (1.0)	5 (1.2)	0 (0)	0.593
Optic atrophy	1 (0.2)	1 (0.2)	0 (0)	≥0.99
Neuropsychiatric, n (%)	25 (5.0)	21 (5.1)	4 (4.7)	≥0.99
Renal, n (%)	53 (10.6)	40 (9.7)	13 (15.1)	0.139
Pulmonary, n (%)	50 (10.0)	40 (9.7)	10 (11.6)	0.590
Cardiovascular, n (%)	48 (9.6)	39 (9.5)	9 (10.5)	0.775
Peripheral vascular, n (%)	35 (7.0)	31 (4.5)	4 (4.7)	0.343
Gastrointestinal, n (%)	21 (4.2)	16 (3.9)	5 (5.8)	0.384
Muskuloskeletal, n (%)	59 (11.8)	52 (12.6)	7 (8.1)	0.242
Muscle atrophy	2 (0.4)	2 (0.5)	0 (0)	≥0.99
Erosive arthritis	5 (1.0)	5 (1.2)	0 (0)	0.593
Osteoporosis	20 (4.0)	17 (4.1)	3 (3.5)	≥0.99
AVN	39 (7.8)	35 (8.5)	4 (4.7)	0.227
Skin, n (%)	5 (1.0)	4 (1.0)	1 (1.2)	≥0.99
Gonadal failure, n (%)	8 (1.6)	8 (1.9)	0 (0)	0.362
Diabetes, n (%)	28 (5.6)	22 (5.3)	6 (7.0)	0.605
Malignancy, n (%)	22 (4.4)	15 (3.6)	7 (8.1)	0.081
Death*, n (%)	53 (10.6)	36 (8.7)	17 (19.8)	**0.003**

**In patients with a follow-up duration ≥6 months*

ACR: American College of Rheumatology, AVN: Avascular necrosis, SD: Standard deviation, SDI: SLICC/ACR damage index, SLICC: Systemic Lupus International Collaborating Clinics

A recently published large cohort study showed that pulmonary embolism and deep vein thrombosis were more frequent in patients with late-onset SLE, where lupus anticoagulant positivity was significantly higher.[11] However, in our study, the percentages of thrombotic events were similar between the groups. Additionally, although the presence of anti-cardiolipin antibodies was statistically higher in the adult-onset group, the occurrence of antiphospholipid antibody syndrome did not differ, remaining at 12.7% in the entire study population. We also found a trend toward high frequency of Raynaud phenomenon in the adult-onset SLE, which was also demonstrated in a large population of Latin American patients with SLE.[4]

Higher SDI scores have been linked to increased rates of morbidity and mortality, and a recent systematic review and meta-analysis has reaffirmed this association.[16] Despite the availability of more targeted therapies in rheumatology and decreased rates of mortality in SLE patients over time,[17] damage still remains a significant challenge in the course of SLE. A long-term follow-up study from the UK indicated that 77% of SLE patients experienced damage accrual. [18] The SLICC inception cohort demonstrated that age, African ethnicity, high disease activity, and hypertension are factors associated with damage accrual.[19] In addition, results from the Hopkins Lupus Cohort demonstrated that the use and dosage of glucocorticoids are associated with damage accrual, and reducing the dosage may lower the estimated risk of organ damage.[20] Another retrospective multicentre European cohort study showed that patients with a disease onset at age ≥50 years had higher mean damage scores compared to pediatric and adult-onset groups.[21] It is worth noting that 40% of our study cohort showed damage and had similar SDI scores in both groups. This may be due to the shorter follow-up duration in the late-onset SLE patients or might suggest a delay in SLE diagnosis in terms of calendar days. Nevertheless, we observed higher mortality rates in the late-onset SLE patients, even after adjusting for sex, SDI scores, and immunosuppressant use, which aligns with the literature.[3,4,11]

Study Limitations

The major limitation of the current study is its retrospective design. Additionally, since we did not have disease activity scores, we were unable to incorporate them into our analyses. Furthermore, we opted to exclude the

childhood-onset group, which was necessary due to the lack of complete follow-up for all pediatric patients, including those lost to follow-up or who died before the age of 18. The absence of comprehensive data for this group could have skewed the overall analysis. Consequently, we believe the results of this study are more generalizable to patients diagnosed at 18 years or older.

Conclusion

In conclusion, this study demonstrates that age at onset significantly impacts clinical presentations and outcomes in SLE patients. Adult-onset SLE tends to present with more severe manifestations, while patients with late-onset SLE had a lower survival rate compared to those with adult-onset SLE, despite generally high survival rates across the cohort. Older age at the time of SLE diagnosis was an independent factor for worse survival, showing that age at onset is important in predicting outcomes. These findings underscore the importance of considering age of onset in disease management, which could ultimately aid in developing more targeted and effective therapeutic strategies tailored to the unique needs of each age group.

Ethics

Ethics Committee Approval: We obtained approval from the Ethics Committee of Ankara University (approval number: İ9-592-21, date: 21.10.2021) and conducted the study in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.Ş., E.U., N.G-G., M.L.Y., E.G.A-G., M.E.Y., T.M.T., G.K., A.A., Concept: T.M.T., G.K., A.A., Design: D.Ş., T.M.T., G.K., A.A., Data Collection and Processing: D.Ş., B.B., E.U., N.GG., G.T., M.K., M.L.Y., E.G.A-G., M.E.Y., Analysis or Interpretation: D.Ş., E.U., M.E.Y., T.M.T., G.K., A.A., Literature Search: D.Ş., B.B., E.U., M.E.Y., T.M.T., G.K., A.A., Writing: D.Ş., A.A.

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. Hoi A, Igel T, Mok CC, Arnaud L. Systemic lupus erythematosus. Lancet. 2024;403:2326-38.
2. Brunner HI, Gladman DD, Ibañez D, Urowitz MD, Silverman ED. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Rheum. 2008;58:556-62.
3. Lalani S, Pope J, de Leon F, Peschken C. Clinical features and prognosis of late-onset systemic lupus erythematosus: results from the 1000 faces of lupus study. J Rheumatol. 2010;37:38-44.
4. Catoggio LJ, Soriano ER, Imamura PM, et al. Late-onset systemic lupus erythematosus in latin americans: a distinct subgroup? Lupus. 2015;24:788-95.
5. Merola JF, Bermas B, Lu B, et al. Clinical manifestations and survival among adults with (SLE) according to age at diagnosis. Lupus. 2014;23:778-84.
6. Artim-Esen B, Şahin S, Çene E, et al. Comparison of disease characteristics, organ damage, and survival in patients with juvenile-onset and adult-onset systemic lupus erythematosus in a combined cohort from 2 tertiary centers in turkey. J Rheumatol. 2017;44:619-25.
7. Aljohani R, Gladman DD, Su J, Urowitz MB. Disease evolution in late-onset and early-onset systemic lupus erythematosus. Lupus. 2017;26:1190-6.
8. 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.
9. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum. 1999;42:599-608.
10. 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.
11. Riveros Frutos A, Holgado S, Sanvisens Bergé A, et al. Late-onset versus early-onset systemic lupus: Characteristics and outcome in a national multicentre register (relesser). Rheumatology (Oxford). 2021;60:1793-803.
12. Adeogun G, Camai A, Suh A, Wheless L, Barnado A. Comparison of late-onset and non-late-onset systemic lupus erythematosus individuals in a real-world electronic health record cohort. Lupus. 2024;33:525-31.
13. Pamuk ON, Raza AA, Hasni S. Neuropsychiatric lupus in late- and early-onset systemic lupus erythematosus patients: a systematic review and meta-analysis. Rheumatology (Oxford). 2024;63:8-15.
14. Sato T, Fujii T, Yokoyama T, et al. Anti-u1 rnp antibodies in cerebrospinal fluid are associated with central neuropsychiatric manifestations in systemic lupus erythematosus and mixed connective tissue disease. Arthritis Rheum. 2010;62:3730-40.
15. Katsumata Y, Kawaguchi Y, Baba S, et al. Serum antibodies against the 70k polypeptides of the U1 ribonucleoprotein complex are associated with psychiatric syndromes in systemic lupus erythematosus: a retrospective study. Mod Rheumatol. 2013;23:71-80.
16. Murimi-Worstell IB, Lin DH, Nab H, et al. Association between organ damage and mortality in systemic lupus erythematosus: a systematic review and meta-analysis. BMJ Open. 2020;10:e031850.
17. Tselios K, Gladman DD, Sheane BJ, Su J, Urowitz M. All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013). Ann Rheum Dis. 2019;78:802-6.

18. Segura BT, Bernstein BS, McDonnell T, et al. Damage accrual and mortality over long-term follow-up in 300 patients with systemic lupus erythematosus in a multi-ethnic British cohort. Rheumatology (Oxford). 2020;59:524-33.

19. Bruce IN, O'Keeffe AG, Farewell V, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the systemic lupus international collaborating clinics (slicc) inception cohort. Ann Rheum Dis. 2015;74:1706-13.

20. Al Sawah S, Zhang X, Zhu B, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the hopkins lupus cohort. Lupus Sci Med. 2015;2:e000066.

21. Cervera R, Doria A, Amoura Z, et al. Patterns of systemic lupus erythematosus expression in Europe. Autoimmun Rev. 2014;13:621-9.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.03371
Ulus Romatol Derg 2025;17(2):68-76

Patients with ANCA-associated vasculitis have low serum thiol levels, and these low levels are correlated with higher disease activity scores

ANCA ilişkili vaskülit hastaları düşük serum tiyol düzeylerine sahiptir ve düşük tiyol düzeyleri yüksek hastalık aktive skorları ile ilişkilidir

Ahmet Kor[1], Selçuk Akan[2], Esra Fırat Oğuz[3], Serdar Can Güven[4], Yüksel Maraş[5], Özcan Erel[6], Şükran Erten[7]

[1]Aksaray Training and Research Hospital, Clinic of Rheumatology, Aksaray, Türkiye
[2]Ankara Bilkent City Hospital, Clinic of Internal Medicine, Ankara, Türkiye
[3]Ministry of Health, Ankara Bilkent City Hospital, Clinic of Medical Biochemistry, Ankara, Türkiye
[4]Ministry of Health, Ankara Bilkent City Hospital, Clinic of Rheumatology, Ankara, Türkiye
[5]University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Department of Rheumatology, Ankara, Türkiye
[6]Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Department of Medical Biochemistry, Ankara, Türkiye
[7]Ankara Yıldırım Beyazıt University, Ankara Bilkent City Hospital, Department of Rheumatology, Ankara, Türkiye

Abstract

Objective: This study compared thiol/disulfide balance and ischemia-modified albumin (IMA) levels between the patients with anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) and healthy controls. Additionally, the study investigated the relationship between AAV disease activity scores, organ involvement, and levels of IMA and thiol/disulfide molecules.

Methods: Forty-six AAV patients and 45 healthy volunteers were included in the study. Birmingham vasculitis activity score (BVAS) version 3 was used for AAV disease activity. Disulfide (-SS), native thiol (-SH), and total thiol (-SH+-SS) molecule analyses were performed using an automatic spectrophotometric method, and IMA calculations were performed using the albumin-cobalt binding test. An increase in the -SS/(-SH+-SS) ratio was considered indicative of a shift towards oxidation, while an increase in the -SH/(-SH+-SS) ratio was suggested a shift towards antioxidation.

Results: The -SS/(-SH+-SS) ratio was significantly higher [β: 0.482, odds ratio (OR) confidence interval (CI) 95%: 0.618 (0.432-0.882), p=0.008] and the -SH/(-SH+-SS) ratio was lower [β: -0.242, OR (CI 95%): 1.273 (1.065-1.522), p=0.008] in the AAV group compared to the control group. A significant association was found between -SH and BVAS-3 [β: -8.202, CI 95%: -16.108- (-0.267), p=0.043].

Conclusion: Thiol/disulfide molecules are shifted towards oxidation in AAV patients compared to healthy controls. Furthermore, patients with higher BVAS-3 disease scores exhibit lower serum thiol levels.

Keywords: ANCA-associated vasculitis, thiol, IMA, BVAS-3

Özet

Amaç: Bu çalışma anti-nötrofil sitoplazmik antikor ile ilişkili vaskülit (AAV) hastaları ile sağlıklı kontroller arasında tiyol/disülfit dengesinin ve iskemi modifiye albümin (IMA) düzeylerinin karşılaştırılması amacıyla hazırlanmıştır. Ayrıca bu çalışmada AVV'nin hastalık aktivite skoru ve organ tutulumları ile IMA ve tiyol/disülfit molekülleri arasındaki ilişkiler de araştırılmıştır.

Yöntem: Çalışmaya 46 AVV hastası ile 45 sağlıklı gönüllü dahil edildi. AVV hastalık aktivitesi için Birmingham vasculitis aktivite skoru (BVAS) version-3 kullanıldı. Disülfit (-SS), doğal tiyol (-SH) ve total tiyol (-SH+-SS) moleküllerine ait analizler otomatik spektrofotometrik metod ile, IMA'ya ait hesaplamalar ise albümin-kobalt bağlanma testi ile gerçekleştirildi. -SS/(-SH+-SS) oranında artış oksidasyon lehinde kayma, -SH/(-SH+-SS) oranında artış ise antioksidasyon lehinde kayma kabul edildi.

Bulgular: AVV grubunda kontrol grubuna göre -SS/(-SH+-SS) oranı anlamlı olarak daha yüksek [β: -0,482, risk oranı (OR) güven aralığı (GA) %95: 0,618 (0,432-0,882), p=0,008], -SH/(-SH+-SS) oranı ise daha düşük [β: 0,242, OR (GA %95): 1,273 (1,065-1,522), p=0,008] saptandı. -SH ile BVAS-3 arasında anlamlı bir korelasyon ilişkisi tespit edildi [β: -8,202, GA %95: -16,108- (-0,267), p=0,043].

Sonuç: AVV hastalarında sağlık kontrollere göre tiyol/disülfit molekülleri oksidasyon yönünde kaymıştır ve yüksek BVAS-3 hastalıkları skorları olan hastalar daha düşük serum tiyol düzeylerine sahiptir.

Anahtar Kelimeler: ANCA ilişkili vaskülit, tiyol, IMA, BVAS-3

Correspondence / İletişim:
Ahmet Kor Assoc. Prof., Aksaray Training and Research Hospital, Clinic of Rheumatology, Aksaray, Türkiye
E-mail: ahmetkor_61@hotmail.com **ORCID ID:** orcid.org/0000-0002-5794-6951

Received / Geliş Tarihi: 27.11.2024 **Accepted / Kabul Tarihi:** 07.03.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Kor A, Akan S, Fırat Oğuz, et al. ANCA-associated vasculitis patients have low serum thiol levels, and low thiol levels are associated with high disease activation scores. J Turk Soc Rheumatol. 2025;17(2):68-76

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of necrotizing autoimmune vascular diseases characterized by microvascular damage, primarily affecting small vessels. These include granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis.[1] significant advances in the AAV treatment, it remains a potentially life- and organ-threatening disease entity.[2] Optimal assessment of AAV disease activity is critical in planning treatment because accurate assessment influences the physician's choice of treatment and subsequent drug therapy management.[3] The Birmingham vasculitis activity score version-3 (BVAS-3) is considered a reliable measurement score that best reflects localized or global inflammation by evaluating the disease activity of AAV. [4] However, the significant disadvantages of this index are that the measurement of BVAS-3 is complex, can cause bias among researchers, and requires considerable time for calculation. Therefore, developing objective laboratory markers that can successfully reflect inflammation and damage in AAV which are inexpensive and easy to apply is a critical necessity.

Under physiological conditions, any of the metalic elements such as nickel, cobalt, or copper can bind to the terminal of human albumin's first amino acids. Hypoxic and ischemic events can disrupt this metal-binding capacity to albumin. This albumin, whose structure has been disrupted by the effect of hypoxia, has been defined as ischemia-modified albumin (IMA). Events resulting in ischemic reperfusion injury cause an increase in plasma IMA levels. [5,6] It has been reported that IMA may be an essential biomarker that can predict the oxidative status in processes with increased oxidative stress.[7-10] In acute coronary events, plasma IMA level can be a biomarker that accurately predicts ischemic myocardial damage.[7,11] Serum IMA levels also increase in autoimmune diseases associated with increased oxidative status, such as psoriasis, ankylosing spondylitis (AS), rheumatoid arthritis (RA), Behçet's disease, systemic sclerosis, familial Mediterranean fever (FMF), Henoch-Schönlein purpura and gout.[12-19]

Antioxidant defense systems include many enzymatic and non-enzymatic molecules, including thiols. Reactive oxygen species (ROS) formed from different reactions enable the transfer of excess electrons in the human body to thiols, thus converting thiol molecules into oxidized form. Reversible disulfide bonds formed from these reactions are converted back to thiol forms when necessary, maintaining the oxidative balance. This antioxidant protection system, called dynamic thiol/disulfide homeostasis (Dtdh), plays a role in many vital processes, such as critical enzymatic systems, apoptosis, detoxification events, intracellular signaling networks, and transcription reactions.[20-22] The structures responsible for Dtdh mainly comprise cysteine residues in the structure of albumin and other proteins.[23] Plasma thiol molecules bind ROS in an environment with increased ROS and convert it into an oxidized form. Thus, significant decreases occur in thiol molecule levels in oxidative environments.[24] Serum thiol levels are known to be decreased in rheumatological diseases such as psoriatic arthritis, RA, gout, AS, Kawasaki disease, FMF, systemic lupus erythematosus, and primary Sjögren syndrome.[25-31]

To our knowledge there is no study comparing IMA levels and Dtdh between AAV patients and healthy controls. The inadequacy of serum markers that can be used in the follow-up of disease activity in AAV patients can be pretty challenging in the management of AAV. In addition, the inadequacy of biomarkers in AAV can cause a delay in the selection of the appropriate medical treatment type. This study used a new idea to compare serum IMA and Dtdh between AAV patients and healthy controls. In addition, this study investigated how serum thiol molecules and IMA levels change according to the disease activity score, systemic organ involvement, and drugs used in AAV patients.

Materials and Methods

Study Design

This study was conducted as a case-control study between 01/06/2023 and 01/05/2024. The patient group included 46 AAV patients who were followed up and treated in the Rheumatology Department of Ankara Bilkent City Hospital. The control group included 45 healthy volunteers not previously diagnosed with rheumatological disease. The control group was selected from those with similar demographic characteristics, age, gender, and comorbidities to the patient group. Individuals with active or chronic infectious disease, malignancy, pregnancy, and non-AAV rheumatic diseases were excluded. The International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides criteria[32] was used for the classification of AAV, and the BVAS-3 (a score created by a combination of symptoms and findings involving a total of nine organ systems; score range=0 to 63)[33] was used for the follow-up of disease activity. Current data on systemic organ involvement and medical treatments in AAV patients were obtained from the hospital's online registration system or patient files. For comorbid diseases, the presence of chronic obstructive pulmonary disease, coronary artery disease, hypertension, and diabetes mellitus were taken into account. An informed voluntary consent form was obtained from all individuals participating in the study.

Analysis of Serum IMA Levels and Thiol-disulfide Molecules and Preparation of Venous Blood Samples

Venous blood samples taken from the participants in the groups for the study were centrifuged in 10 mL vacuum tubes at 1300 x g for 10 minutes. Then, the obtained sera were taken into Eppendorf tubes and stored at -80 °C until the analysis time. Analysis measurements of Dtdh parameters were carried out with the automatic spectrophotometric method previously described by Erel and Neselioglu.[34] According to this method, the calculations were briefly as follows: First, disulfide bonds were reduced with the help of sodium borohydride to form free plasma functional thiol groups. After the molecules belonging to the thiol groups reacted with 5.5'-dithiobis-2 nitrobenzoic acid, the natural thiol (-SH) and reduced thiol groups were calculated. Disulfide (-SS) levels were determined by taking the difference between total thiol (-SS+-SH) and -SH. After the determination of -SS and -SH, the percentages of native thiol/total thiol [-SH/(-SH+-SS)] and disulfide/total thiol [-SS/(-SH+-SS)] were determined. The increase in the percentage of -SS/(-SH+-SS) was considered a shift in the direction of oxidation, while the increase in the rate of -SH/(-SH+-SS) was evaluated as a shift in the direction of antioxidation.

For the calculations of IMA levels, venous blood samples were kept at room conditions for approximately 30 minutes and centrifuged at 3500 rpm for 5 minutes. Then, the samples separated into Eppendorf tubes were stored at -80 °C until the calculation day. The calculation of IMA levels was performed with an albumin-cobalt binding test (Sigma/Aldrich Chemie GmbH Riedstrasse-2, Steinheim/Germany). In this test method, serum samples obtained from the study groups were mixed with 50 mL of 0.1% cobalt (II) chloride ($CoCl_2$, $6H_2O$) solution and kept in a room for approximately 10 minutes. After this process, 50 mL of 1.5 mg/mL dithiothreitol was added to the solution to ensure cobalt binding to albumin. After a waiting period of two minutes, 1.0 mL of 0.9% sodium chloride solution was added to the solution to determine the binding capacity. Finally, absorbance measurements of the samples were carried out using a spectrophotometer with a wave sensitivity of 470 nm. The unit of IMA levels was shown as absorbance unit.[35]

Indirect immunofluorescence assay (IIA) was used to determine cytoplasmic (C)-ANCA and perinuclear (P)-ANCA. Antigen-specific tests were used for PR3-ANCA and MPO-ANCA tests. IIA was used as the initial screening test for ANCA tests.[36] Antigen-specific tests Phadia ELiA (Thermo-Fisher Scientific-Phadia-Freiburg-Germany) were used for PR3-ANCA and MPO-ANCA tests and their levels were determined using the Phadia250 analyzer. Patients with positive IIA and specific antigen tests were considered MPO-ANCA or PR3-ANCA positive.

The following methods were used in for the calculation of other biochemical analyses: C-reactive protein (CRP) nephelometric method (IMMAGE-Immunochemistry Systems-Ireland); erythrocyte sedimentation rate Westergren method (Berkhum-SDM100-Türkiye); uric acid uricase method (Siemens-Healthineers-Germany); serum creatinine modified-Jaffe method.

Ethical approval for this study was obtained from Ankara Bilkent City Hospital No. 2 Ethics Committee dated 10/05/2023 and numbered E2-23-3791.

Statistical Analysis

Version 22. 0 Statistical Packages for the Social Sciences package program was used to evaluate the statistical analyses of the study. Shapiro-Wilk or Kolmogorov-Smirnov tests, as well as histograms or probability graphs, were used to determine the normality distribution in continuous variables. The results of descriptive statistical analyses were shown in the format of mean-standard deviation (mean ± standard deviation) for variables showing normal distribution and median-interquartile range [interquartile range, (25-75%)] for variables not showing normal distribution. Statistical evaluations in pairwise comparisons were performed with Independent Samples t-test for variables with normal distribution and Mann-Whitney U test for variables not normally distributed. Correlation analyses of continuous variables were performed using Spearman correlation analysis. Bonferroni correction was first performed for multiple comparisons. Then, a One-Way ANOVA post-hoc Tukey test was performed for quantitative variables with normal distribution. Independent Samples-Kruskal-Wallis test was performed for quantitative variables that did not have a normal distribution. Fisher or chi-square analyses were used in comparative tests of categorical variables. The predictive effects of independent variables on categorical dependent variables were analyzed using multinomial or binary logistic regression tests. The predictive effects of independent variables on continuous dependent variables were evaluated using linear regression tests. P values <0.05 were considered statistically significant.

Results

Table 1 shows the results of comparing demographic characteristics and biochemical data between AAV and control groups. The median age of the AAV group was 49.2 (38.8-59.1), and the mean age of the control group was 47.2

(36.9-57.5) (p>0.05). In the AAV group, -SH (p<0.0001), -SH+-SS (p<0.0001) levels, and -SH/(-SH+-SS) ratio (p=0.003) were significantly lower, and -SS/(-SH+-SS) ratio (p=0.004) and IMA levels (p=0.039) were significantly higher compared to controls.

In binary logistic regression analysis, -SS/(-SH+-SS) [β: 0.482, odds ratio (OR) confidence interval (CI) 95%: 0.618 (0.432-0.882), p=0.008], CRP [β: 0.305, OR (CI 95%): 0.737 (0.600-0.905), p=0.004] and creatinine [β: 6.616, OR (CI 95%): 0.01 (0.00-0.056), p=0.001] levels were significantly higher, SH/(-SH+-SS) [β: -0.242, OR (CI 95%): 1.273 (1.065-1.522), p=0.008] and albumin [β: -0.272, OR (CI 95%): 1.313 (1.094-1.577), p=0.004] levels were significantly lower in the AAV group compared to controls. IMA levels were similar between the groups [β: -2.527, OR (CI 95%): 0.08 (0.006-1.044), p=0.054].

Table 2 shows the relationship between some clinical conditions or the type of medical treatment used in AAV patients and thiol parameters and IMA levels. Thiol parameters or IMA levels were similar in the presence of any systemic organ involvement in AAV or the type of medical treatment used (p>0.05).

Table 3 shows the correlation relationship between some continuous variables and thiol parameters and IMA levels in the AAV group. A significant correlation was found between -SH and creatinine (r: -0.347, p=0.018), serum albumin (r: 0.651, p<0.0001), and BVAS-3 score (r: -0.391, p=0.007). Also, a significant correlation was found between -SH+-SS and creatinine (r: -0.352 p=0.016), serum albumin (r: 0.596 p<0.0001) and BVAS-3 score (r: -0.361 p=0.014).

In linear regression analysis, a significant association was found between -SH and BVAS-3 [β: -8.202, CI 95%: -16,108- (-0.267), p=0.043] and serum albumin [β: 6.421, CI 95%: (3.537-9.306), p<0.001], but no significant association was found between -SH and creatinine [β: -7.269, CI 95%: (-18.753-4.215), p=0.209]. A significant association was found between -SH+-SS and serum albumin levels [β: 6.552, CI 95%: (3.263-9.306), p<0.001], but no significant association was found between -SH+-SS and BVAS-3 [β: -8.099, CI 95%: (-16.862-0.664), p=0.064] and creatinine [β: -8.088, CI 95%: (-20.648-4.472), p=0.201].

Table 1. Comparison of demographic characteristics and biochemical data between AAV and control groups

	ANCA	Control	p-value
n (total)	46	45	-
Age, median (IQR) (years)	49.2 (38.8-59.1)	47.2 (36.9-57.5)	0.246
Gender female/male, n	23/23	25/20	0.679
Body mass index, mean ± SD	25.4 (18.5-30.1)	26.2 (19.3-31.9)	0.407
Presence of comorbid disease			
Hypertension, n	6	5	0.777
COPD, n	4	2	0.414
Diabetes mellitus, n	5	5	0.971
CAD, n	5	2	0.250
Smoking, n (%)	6	3	0.308
Disease duration, median (IQR) [year]	1 (0.5-2)	-	-
Dialysis, n (%)	9	-	-
Creatinine, median (IQR) [mg/dL]	1.1 (0.74-1.97)	0.7 (0.6-0.7	**<0.0001**
eGFR, median (IQR) [mL/min/1.73 m²]	63 (26.5-101.25)	105 (98.5-117)	**<0.0001**
Albumin, median (IQR) [g/dL]	41.5 (37.5-45)	45 (43-47)	**<0.0001**
CRP, median (IQR) [mg/L]	6 (1.3-16.6)	1 (0-3.25)	**<0.0001**
ESR, median (IQR) [mm/h]	22.5 (6-41.75)	15 (6-19)	**0.019**
IMA, median (IQR) [ABSU]	0.79 (0.68-0.9)	0.72 (0.61-0.81	**0.039**
-SH, median (IQR) [μmol/L]	331.2 (289.4-394.4)	410.6 (382.2-435.3)	**<0.0001**
-SH+-SS, median (IQR) [μmol/L]	368 (328.2-437.6)	447.3 (416.3-472)	**<0.0001**
-SS, median (IQR) [μmol/L]	18.6 (13.7-23.4)	17.9 (16.4-19.5)	0.987
-SH/(-SH+-SS), median (IQR) [%]	90.2 (87.5-92.3)	91.8 (91-92.7)	**0.003**
-SS /(-SH+-SS), median (IQR) [%]	4.87 (3.81-6.2)	4.09 (3.63-4.49)	**0.004**
PR3 ANCA ELISA, median (IQR) [RU/mL] (n=23)	127 (45-200)	-	-
MPO ANCA ELISA, median (IQR) [RU/mL] (n=23)	128 (54.5-168.7)	-	-
BVAS-3 (version-3), median (IQR)	4 (2-7.25)	-	-

AAV: ANCA-associated vasculitis, ANCA: Anti-neutrophil cytoplasmic antibody, BVAS: Birmingham vasculitis activity score, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, eGFR: Estimated Glomerular filtration rate, ESR: Erythrocyte sedimentation rate, IMA: Ischemia modified albumin, IQR: Interquartile range, MPO: Myeloperoxidase, PR3: Proteinase 3, SD: Standard deviation, -SH: Native thiol, -SS: Disulphide, -SH+-SS: Total thiol

Table 2. Relationship between some clinical conditions or medical treatment type and thiol parameters and IMA levels in AAV patients

		n	IMA	p-value	-SS/(-SH+-SS), median (IQR) [%]	p-value	-SH/(-SH+-SS), median (IQR) [%]	p-value
ANCA type	PR3	23	0.81 (0.68-0.9)	0.878	4.9 (2.7-6.2)	0.621	90 (87.6-94.6)	0.621
	MPO	23	0.77 (0.69-0.91)		4.7 (3.9-6.4)		90.4 (87.9-95.1)	
Dialysis	Available	9	0.76 (0.70-0.88)	0.765	5.0 (3.2-7.9)	0.605	89.8 (84-0-93.5)	0.605
	No	37	0.81 (0.9-0.65)		4.7 (3.8-6.1)		90.4 (87.7-92.3)	
Nasal involvement	Available	11	0.88 (0.68-0.9)	0.410	5.9 (3.8-7.1)	0.226	88 (85.6-92.3)	0.221
	No	35	0.77 (0.69-0.087)		4.6 (3.8-6)		90.6 (87.8-92.3)	
Pulmonary involvement	Available	27	0.77 (0.68-0.9)	0.947	4.7 (3.8-6.1)	0.435	90.4 (87.8-92.3)	0.428
	No	19	0.81 (0.69-0.88)		5 (3.9-6.7)		89.8 (86.4-92.1)	
Auditory system involvement	Available	8	0.73 (0.58-0.9)	0.618	6.0 (4.2-8.3)	0.102	87.9 (83.3-91.6)	0.109
	No	38	0.81 (0.70-0.89)		4.6 (3.5-6.1)		90.6 (87.7-92.9)	
Eye involvement	Available	7	0.72 (0.63-0.87)	0.306	2.7 (2.0-6.7)	0.154	94.5 (86.4-95.8)	0.154
	No	39	0.82 (0.69-9)		4.9 (3.9-6.2)		90.0 (87.6-92.1)	
Skin involvement	Available	5	0.9 (0.68-1.07)	0.186	5.0 (2.9-6.1)	0.918	89.9 (87.6-94.1)	0.918
	No	41	0.77 (0.68-0.88)		4.7 (3.8-6.2)		90.4 (87.5-92.3)	
Neurological involvement	Available	4	0.90 (0.57-1.0)	0.315	5.5 (4.1-6.9)	0.417	88.8 (86.1-91.6)	0.439
	No	42	0.77 (0.68-0.88)		4.7 (3.7-6.2)		90.5 (87.5-92.5)	
Cardiac involvement	Available	6	0.8 (0.65-1.01)	0.667	4.8 (3.3-6.7)	0.962	90.2 (86.4-93.3)	0.987
	No	40	0.79 (0.68-0.89)		4.8 (3.8-6.1)		90.3 (87.6-92.3)	
Renal involvement	Available	30	0.79 (0.67-0.9)	0.926	4.9 (3.8-6.5)	0.454	90 (86.9-92.3)	0.460
	No	16	0.79 (0.68-89)		4.6 (3.8-5.9)		90.7 (88.2-92.3)	
GIS involvement	Available	2	0.79 (0.47-)	0.893	5.3 (3.9-)	0.773	89.3 (86.4-)	0.812
	No	44	0.79 (0.69-0.89)		4.8 (3.8-6.1)		90.2 (87.6-92.3)	
Hemoptysis	Available	6	0.75 (0.67-0.8)	0.397	5.6 (3.6-6.8)	0.555	88.6 (86.3-92.6)	0.555
	No	40	0.82 (0.68-9)		4.7 (3.8-6.1)		90.5 (87.6-92.3)	
Pulmonary tomography findings	Normal	19	0.85 (0.75-0.92)	0.063	5.0 (3.9-6.4)	0.953	89.9 (87.1-92.1)	0.950
	Nodule	14	0.77 (0.59-0.87)		4.5 (3.5-6.3)		90.8 (87.2-92.9)	
	Cavity	8	0.80 (0.70-0.92)		5.0 (3.8-6.0)		89.9 (87.8-92.2)	
	Hemorrhage	5	0.72 (0.49-0.74)		4.3 (2.1-7.8)		91.3 (84.2-95.6)	
Corticosteroids	Available	36	0.72 (0.67-0.79)	0.804	4.4 (4.1-4.8)	.585	90.1 (88.1-92.6)	0.520
	No	10	0.73 (0.69-0.85)		4.2 (3.8-4.6)		91.4 (89.7-92.8)	
Methotrexate	Available	16	0.75 (0.66-0.87)	0.703	4.5 (4.2-4.6)	0.506	90.7 (90.1-91.5)	0.774
	No	30	0.73(0.63-0.84)		4.3 (3.6-4.4)		91.0 (90.4-91.9)	
Rituximab	Available	10	0.78 (0.67-0.85)	0.632	4.1 (3.6-4.6)	0.472	90.2 (88.2-92.6)	0.685
	No	36	0.74 (0.63-0.81)		4.4 (4.5-5.3)		91.1 (89.4-93.1)	
Cyclophosphamide	Available	8	0.72 (0.67-0.79)	0.798	4.0 (3.6-4.5)	0.421	90.2 (89.0-91.8)	0.495
	No	38	0.74 (0.68-0.83)		4.3 (4.1-4.8)		91.6 (90.4-92.9)	
Azathioprine	Available	7	0.70 (0.67-0.84)	0.781	4.6 (3.9-5.1)	0.503	90.4 (87.5-91.8)	0.234
	No	39	0.72 (0.70-0.87)		4.4 (3.7-4.8)		92.6 (91.6-92.2)	
Mycophenolate mofetil	Available	5	0.72 (0.57-0.85)	0.767	4.1 (3.6-4.7)	0.622	92.0 (90.2-96)	0.408
	No	41	0.74 (0.71-0.83)		4.2 (3.8-5.0)		91.4 (89.4-91.9)	

AAV: ANCA-associated vasculitis, ANCA: Anti-neutrophil cytoplasmic antibody, GIS: Gastrointestinal system, IMA: Ischemia modified albumin, IQR: Interquartile range, MPO: Myeloperoxidase, PR3: Proteinase 3, -SH: Native thiol, -SS: Disulphide, -SH+-SS: Total thiol

Discussion

In this study, we compared IMA levels and Dtdh between AAV patients and healthy people and evaluated the correlation relationship between these molecules and the disease activity score used in AAV. In our study, it was found that -SH/(-SH+-SS) median values were significantly lower and -SS/(-SH+-SS) median values were higher in the AAV group compared to healthy controls. We also found that there was a significant negative correlation between BVAS-3, one of the indicators of AAV disease activity, and serum -SH levels in linear regression analysis. These data showed that Dtdh shifted in the oxidative direction in AAV patients compared to healthy people and in those with high AAV disease activity. Serum IMA levels were similar between

Table 3. Correlation analyses between some continuous variables and thiol parameters and IMA levels in the AAV group

r (p)	Age	Creatinine	BVAS-3	Serum albumin	CRP	ESR
-SS	-0.189 (0.208)	-0.196 (0.192)	-0.055 (0.715)	0.180 (0.242)	0.162 (0.281)	-0.021 (0.889)
-SH	-0.249 (0.095)	**-0.347 (0.018)**	**-0.391 (0.007)**	**0.651 (<0.0001)**	-0.079 (0.604)	-0.250 (0.094)
-SH+-SS	-0.286 (0.076)	**-0.352 (0.016)**	**-0.361 (0.014)**	**0.596 (<0.0001)**	-0.016 (0.917)	-0.201 (0.180)
-SS/(-SH+-SS)	-0.052 (0.732)	-0.055 (0.714)	0.221 (0.141)	-0.223 (0.145)	0.275 (0.069)	0.195 (0.193)
-SH/(-SH+-SS)	0.051 (0.738)	0.055 (0.714)	-0.219 (0.143)	0.244 (0.144)	-0.278 (0.065)	-0.196 (0.191)
IMA	-0.095 (0.529)	-0.136 (0.369)	0.012 (0.935)	-0.139 (0.369)	0.236 (0.114)	0.046 (0.760)

AAV: ANCA-associated vasculitis, BVAS: Birmingham vasculitis activity score, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IMA: Ischemia modified albumin, -SH: Native thiol, -SS: Disulphide, -SH+-SS: Total thiol, r: Correlation coefficient

the AAV and control groups. It was determined that thiol/disulfide and IMA levels did not change in the presence of any organ involvement or the types of medical treatment used in AAV.

In the present study, the median values of -SH/(-SH+-SS) were found to be lower and the median values of -SS/(-SH+-SS) were found to be higher in the AAV group compared to the controls. In addition, a negative significant correlation was found between BVAS-3, one of the AAV disease activity indicators, and -SH in our study. Dtdh has not been evaluated before between AAV patients and healthy controls, and our study is the first to demonstrate that Dtdh changes to the oxidative direction in AAV patients and those with high AAV disease activity. The role of oxidative damage in the pathogenesis of some subtypes of small vessel vasculitis has been evaluated in some clinical studies.[37,38] Possible mechanisms of this pathogenesis include activation of inflammatory cells by polymorphic nuclear leukocytes, monocytes, and macrophages due to immune complex accumulation in small vessels, increased oxidative stress triggering lipid peroxidation, and ultimately increased ROS production.[39] Under physiological conditions, the amount of ROS increases during oxygen metabolism, and the antioxidant system removes these ROS from the body. Increased ROS causes tissue damage due to disruption of the oxidant-antioxidant system balance.[39,40] It has been previously shown that myeloperoxidase (MPO) antibodies in AAV trigger oxidative bursts in neutrophils and hypochlorous acid (HOCl) production associated with increased oxidative stress and ultimately play a critical role in the development of endothelial damage and vasculitis.[41,42] Increased ROS and decreased antioxidant levels caused by oxidative stress have been shown to contribute to processes such as inflammation and fibroblast proliferation[43] that play a role in fibrosis in tumoral or systemic sclerosis[44-47] and in AAV-associated pulmonary fibrosis.[48] Interestingly, thiol compounds reduce tissue damage by suppressing leukocyte margination[49,50] and reverse the effects of MPO and HOCl through chloramine scavenging.[51,52] In our study, serum thiol levels were significantly lower in patients with AAV compared to healthy controls and those with high AAV disease activity. Although further studies are needed in this area, our study results suggest that thiols may constitute a physiological defense mechanism against vascular inflammation and tissue damage that play a role in AAV pathogenesis and AAV-related complications.

In our study, serum IMA levels were similar between the AAV and control groups. In addition, no significant correlation was observed between BVAS-3 score and serum IMA levels. Studies have shown that serum IMA levels may be a helpful biomarker reflecting the oxidative status. IMA may be essential in treating inflammatory and vascular endothelial dysfunction diseases.[13,53-55] Serum IMA levels have not been previously compared between AAV patients and healthy controls. However, in a prospective study, serum IMA levels were similar in active and remission AAV patients. In addition, this study found no significant correlation between serum IMA levels and BVAS-3 scores.[56] IMA levels were not affected by AAV disease activity in our study because of the relatively small number of subjects in the study group or the possible effects of drugs used in medical treatment on serum IMA levels. However, considering the close relationship of IMA with diseases that progress with inflammatory processes, numerous and more advanced studies are needed to understand its possible roles in AAV pathophysiology better.

In our study, although a significant relationship was found between AAV disease activity score BVAS-3 and -SH, it was found that thiol parameters and IMA levels did not change in any organ involvement of AAV or the types of medical treatment used. Except for one study in which thiol levels were measured with the old method and their relationship with the presence of AAV renal crescent was evaluated,[57] neither Dtdh and IMA levels nor the types of medical treatment used have not been previously evaluated in AAV patients. In this study in which thiol levels were measured with the old method, serum thiol levels were lower in those with active crescent than those without. The authors of this study suggested that high thiol levels may be protective against renal damage caused by vasculitis.[57] In this study,

in which we evaluated serum thiol levels according to AAV systemic organ involvement with the new method, we did not find a significant relationship between organ damage and thiol levels, but further studies are needed to understand better the possible roles of thiol and IMA molecules in the pathophysiology of AAV organ damage.

Study Limitations

The limitations of this study include the possible effects of medical treatments used in the treatment of AVV on IMA levels and Dtdh, and the fact that it was a cross-sectional study.

Conclusion

Dtdh was shifted in favor of oxidation in AAV patients compared to controls, and patients with higher AAV disease scores had lower serum thiol levels. Thiol molecules may be a potential candidate for understanding AAV disease pathophysiology and predicting disease activity.

Acknowledgments

We would like to thank the medical biochemistry and rheumatology department staff of Ankara Bilkent City Hospital, who contributed to the preparation of this study but whose names are not included in this article.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from Ankara Bilkent City Hospital No. 2 Ethics Committee dated 10/05/2023 and numbered E2-23-3791.

Informed Consent: Informed consent forms were obtained from all participants of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., Ö.E., Concept: A.K., E.F.O., S.C.G., Y.M., Ş.E., Design: A.K., E.F.O., S.C.G., Ş.E., Data Collection and Processing: A.K., S.A., E.F.O., S.C.G., Y.M., Ö.E., Analysis or Interpretation: A.K., S.A., E.F.O., Ö.E., Literature Search: A.K., S.A., Writing: A.K.

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. Yates M, Watts RA, Bajema I, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis. 2016;75:1583-94.
2. Koening CL, von Hennigs I. Antineutrophil cytoplasmic antibody (ANCA) vasculitis: pathophysiology, diagnosis, and the evolving treatment landscape. Am J Manag Care. 2021;27(15 Suppl):S267-76.
3. Hellmich B, Flossmann O, Gross WL, et al. EULAR recommendations for conducting clinical studies and/or clinical trials in systemic vasculitis: focus on anti-neutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2007;66:605-17.
4. Yates M, Watts R. ANCA-associated vasculitis. Clin Med (Lond). 2017;17:60-4.
5. Borderie D, Allanore Y, Meune C, Devaux JY, Ekindjian OG, Kahan A. High ischemia-modified albumin concentration reflects oxidative stress but not myocardial involvement in systemic sclerosis. Clin Chem. 2004;50:2190-3.
6. Apple FS, Quist HE, Otto AP, Mathews WE, Murakami MM. Release characteristics of cardiac biomarkers and ischemia-modified albumin as measured by the albumin cobalt-binding test after a marathon race. Clin Chem. 2002;48:1097-100.
7. Bhagavan NV, Lai EM, Rios PA, et al. Evaluation of human serum albumin cobalt binding assay for the assessment of myocardial ischemia and myocardial infarction. Clin Chem. 2003;49:581-5.
8. Piva SJ, Duarte MM, Da Cruz IB, et al. Ischemia-modified albumin as an oxidative stress biomarker in obesity. Clinical Biochem. 2011;44:345-7.
9. Caglar GS, Oztas E, Karadag D, Pabuccu R, Demirtas S. Ischemia-modified albumin and cardiovascular risk markers in polycystic ovary syndrome with or without insulin resistance. Fertil Steril. 2011;95:310-3.
10. Duarte MM, Rocha JB, Moresco RN, et al. Association between ischemia-modified albumin, lipids and inflammation biomarkers in patients with hypercholesterolemia. Clin Biochem. 2009;42:666-71.
11. Bonorino NF, Lunardelli A, Oliveira JR. Use of ischemia modified albumin for the diagnosis of myocardial infarction. J Bras Patol Med Lab. 2015;51:383-8.
12. Leitemperguer MR, Tatsch E, Kober H, De Carvalho J, Moresco RN, Da Silva J. Assessment of ischemia-modified albumin levels in patients with rheumatoid arthritis. Clin Lab. 2014;60:1065-70.
13. Özdemir M, Kiyici A, Balevi A, Mevlitoğlu I, Peru C. Assessment of ischaemia-modified albumin level in patients with psoriasis. Clin Exp Dermatol. 2012;37:610-4.
14. Türkön H, Gökmen F, Çakir DÜ, Sehitoğlu MH, Reşorlu H, Döner D, et al. Increased levels of serum ischemia modified albumin in patients with ankylosing spondylitis. Clin Lab. 2016;62:645-9.
15. Kor A, Maraş Y, Atalar E, Oğuz EF, Gök K, Erel Ö. Ischemia-modified albumin levels are elevated, and thiol/disulfite homeostasis is impaired in Behçet's disease. J Turk Soc Rheumatol. 2022;14:15-22.
16. Kucuk A, Uslu AU, Arslan S, et al. Ischemia-modified albumin and atherosclerosis in patients with familial Mediterranean fever. Angiology. 2016;67:456-60.
17. Balik AR, Omma A, Sandikci SC, et al. Evaluation of oxidative stress in gout disease; thiol-disulfide homeostasis and ischemia-modified albumin levels. Int J Med Biochem. 2022;5:109-15.

18. Montagnana M, Lippi G, Volpe A, et al. Evaluation of cardiac laboratory markers in patients with systemic sclerosis. Clin Biochem. 2006;39:913-7.

19. Omma A, Colak S, Can Sandikci S, et al. Serum neopterin and ischemia modified albumin levels are associated with the disease activity of adult immunoglobulin A vasculitis (Henoch-Schönlein purpura). Int J Rheum Dis. 2019;22:1920-5.

20. Dickinson DA, Forman HJ. Cellular glutathione and thiols metabolism. Biochem Pharmacol. 2002;64:1019-26.

21. Cuozzo JW, Kaiser CA. Competition between glutathione and protein thiols for disulphide-bond formation. Nat Cell Biol. 1999;1:130-5.

22. Deneke SM. Thiol-based antioxidants. Curr Top Cell Regul. 2001;36:151-80.

23. Lushchak VI. Glutathione homeostasis and functions: potential targets for medical interventions. J Amino Acids. 2012;2012:736837.

24. Rossi R, Giustarini D, Milzani A, Dalle-Donne I. Cysteinylation and homocysteinylation of plasma protein thiols during ageing of healthy human beings. J Cell Mol Med. 2009;13:3131-40.

25. Kor A, Akan S, Oğuz EF, Maraş Y, Neşelioğlu S, Erten Ş. The thiol/disulfide balance is shifted towards oxidation in psoriatic arthritis compared to controls and is associated with higher disease activity. Lab Med. 2024:lmae014.

26. Polat YH, Erten Ş, Kor A, et al. Evaluation of thiol/disulfide homeostasis in rheumatoid arthritis and disease activity. Clin Biochem. 2023;111:81-6.

27. Baykara RA, Tuzcu A, Omma A, et al. Evaluation of serum thiol/disulfide homeostasis in patients with ankylosing spondylitis by a novel method. North Clin Istanb. 2019;6.

28. 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.

29. Kaman A, Aydın Teke T, Gayretli Aydın ZG, et al. Dynamic thiol/disulphide homeostasis and pathogenesis of Kawasaki disease. Pediatr Int. 2019;61:913-8.

30. Yilmaz CN, Gemcioglu E, Baser S, Erten S, Erel O. Thiol/disulfide homeostasis impaired in patients with primary Sjögren's syndrome. J Med Biochem. 2021;40:270.

31. Lalwani P, de Souza GKBB, de Lima DSN, Passos LFS, Boechat AL, Lima ES. Serum thiols as a biomarker of disease activity in lupus nephritis. PLoS One. 2015;10:e0119947.

32. Jennette JC. Overview of the 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Clin Exp Nephrol. 2013;17:603-6.

33. 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.

34. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326-32.

35. Bar–Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia—a preliminary report. J Emerg Med. 2000;19:311-5.

36. Bossuyt X, Cohen Tervaert J-W, Arimura Y, et al. Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13:683-92.

37. Ece A, Kelekçi S, Kocamaz H, et al. Antioxidant enzyme activities, lipid peroxidation, and total antioxidant status in children with Henoch–Schönlein purpura. Clin Rheumatol. 2008;27:163-9.

38. Demircin G, öuner A, Ünver Y, Bülbül M, Erdoĝan Ö. Erythrocyte superoxide dismutase activity and plasma malondialdehyde levels in children with Henoch Schönlein purpura. Acta Pædiatr. 1998;87:848-52.

39. Buyan N, Erbaş D, Akkök N, Öz E, Biberoğlu G, Hasanoğlu E. Role of free oxygen radicals and prostanoids in the pathogenesis of Henoch-Schönlein purpura. Prostaglandins Leukot Essent Fatty Acids. 1998;59:181-4.

40. Keskin N, Civilibal M, Elevli M, Koldas M, Duru NS, Ozturk H. Elevated plasma advanced oxidation protein products in children with Henoch–Schonlein purpura. Pediatr Nephrol. 2011;26:1989-93.

41. Guilpain P, Servettaz A, Goulvestre C, et al. Pathogenic effects of antimyeloperoxidase antibodies in patients with microscopic polyangiitis. Arthritis Rheum. 2007;56:2455-63.

42. Witko-Sarsat V, Friedlander M, Capeillère-Blandin C, et al. Advanced oxidation protein products as a novel marker of oxidative stress in uremia. Kidney Int. 1996;49:1304-13.

43. Okamura DM, Himmelfarb J. Tipping the redox balance of oxidative stress in fibrogenic pathways in chronic kidney disease. Pediatr Nephrol. 2009;24:2309-19.

44. Laurent A, Nicco C, Chéreau C, et al. Controlling tumor growth by modulating endogenous production of reactive oxygen species. Cancer Res. 2005;65:948-56.

45. Maria AT, Toupet K, Bony C, et al. Antifibrotic, antioxidant, and immunomodulatory effects of mesenchymal stem cells in HOCl induced systemic sclerosis. Arthritis Rheumatol. 2016;68:1013-25.

46. Poli G, Parola M. Oxidative damage and fibrogenesis. Free Radic Biol Med. 1997;22:287-305.

47. Servettaz A, Guilpain P, Goulvestre C, et al. Radical oxygen species production induced by advanced oxidation protein products predicts clinical evolution and response to treatment in systemic sclerosis. Ann Rheum Dis. 2007;66:1202-9.

48. Guilpain P, Chéreau C, Goulvestre C, et al. The oxidation induced by anti-MPO antibodies triggers fibrosis in microscopic polyangiitis. Eur Respir J. 2010;37:1503-13.

49. Atalay M, Marnila P, Lilius E-M, Hänninen O, Sen CK. Glutathione-dependent modulation of exhausting exercise-induced changes in neutrophil function of rats. Eur J Appl Physiol Occup Physiol. 1996;74:342-7.

50. Sen CK, Packer L. Thiol homeostasis and supplements in physical exercise. Am J Clin Nutr. 2000;72:653S-69S.

51. Van Antwerpen P, Boudjeltia KZ, Babar S, et al. Thiol-containing molecules interact with the myeloperoxidase/H2O2/chloride system to inhibit LDL oxidation. Biochem Biophys Res Commun. 2005;337:82-8.

52. Vasu VT, De Cruz SJ, Houghton JS, Hayakawa KA, Morrissey BM, Cross CE, et al. Evaluation of thiol-based antioxidant therapeutics in cystic fibrosis sputum: focus on myeloperoxidase. Free Radic Res. 2011;45:165-76.

53. Kadioğlu H, Ömür D, Bozkurt S, et al. Ischemia modified albumin can predict necrosis at incarcerated hernias. Dis Markers. 2013;35:807-10.

54. Valle Gottlieb MG, da Cruz IBMn, Duarte MM, et al. Associations among metabolic syndrome, ischemia, inflammatory, oxidatives, and lipids biomarkers. J Clin Endocrinol Metab. 2010;95:586-91.

55. Dominguez-Rodriguez A, Abreu-Gonzalez P. Current role of ischemia-modified albumin in routine clinical practice. Biomarkers. 2010;15:655-62.

56. Ahn SS, Yoon T, Song JJ, Park Y-B, Lee S-W. Serum albumin, prealbumin, and ischemia-modified albumin levels in patients with ANCA-associated vasculitis: a prospective cohort study. PloS One. 2022;17:e0271055.

57. Hilhorst M, Maria AT, Kavian N, Batteux F, et al. Impact of MPO-ANCA-mediated oxidative imbalance on renal vasculitis. Am J Physiol Renal Physiol. 2018;315:F1769-76.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.92300
Ulus Romatol Derg 2025;17(2):77-84

Flow mediated dilation in association with hyperuricemia as predictors of subclinical atherosclerosis in patients with systemic lupus erythematosus

Sistemik lupus eritematozuslu hastalarda subklinik aterosklerozun tahmin edicileri olarak hiperürisemi ile birlikte akımla aracılık edilen dilatasyon

Eman Mohammed Ibrahem[1], Refaat Fathy Abdel Alaal[1], Lobna Ahmed Hassan[1], Sara Hassanein[2]

[1]Assiut University Faculty of Medicine, Department of Internal Medicine, Assiut, Egypt
[2]Assiut University Faculty of Medicine, Department of Diagnostic Radiology, Assiut, Egypt

Abstract

Objective: Reduced flow mediated dilation (FMD) in systemic lupus erythematosus (SLE) patients indicates impaired endothelial function while elevated uric acid contributes to increased oxidative stress. These factors can synergistically promote the development of atherosclerosis. This study aimed to estimate subclinical atherosclerosis through measuring carotid intima media thickness (CIMT) and brachial artery FMD in SLE patients, correlating these measurements with uric acid levels.

Methods: This study included 60 SLE patients who were divided into two groups based on their FMD results. All patients underwent a comprehensive medical evaluation. CIMT was measured using carotid Doppler ultrasound, and brachial artery FMD was assessed with ultrasound. Serum uric acid levels were also measured. We investigated various factors that may influence FMD in patients with SLE by comparing the characteristics of the two groups.

Results: Patients with abnormal FMD exhibited higher disease activity based on modified SLE disease activity index 2000 (p=0.002) and significantly elevated uric acid levels compared to those with normal FMD (p=0.012). Mean CIMT was significantly higher in patients with abnormal FMD (0.64±0.17 mm) compared to those with normal FMD (0.51±0.11 mm). Regression analysis revealed that increased CIMT, representive of subclinical atherosclerosis, was primarily associated with higher disease activity index, abnormal FMD, and hyperuricemia.

Conclusion: Our findings highlight that FMD and uric acid can serve as potential markers of subclinical atherosclerosis in SLE patients. The association with increased CIMT emphasizes the importance of addressing these factors to reduce cardiovascular risk.

Keywords: Systemic lupus erythematosus, subclinical atherosclerosis, endothelial dysfunction, flow-mediated dilation, carotid intima-media thickness, hyperuricemia

Özet

Amaç: Bu çalışma, sistemik lupus eritematozus (SLE) hastalarında karotis intima media kalınlığı (CİMK) ve brakiyal arter akımla aracılık edilen dilatasyonu (FMD) kullanarak subklinik aterosklerozu değerlendirmeyi ve bu ölçümleri ürik asit düzeyleri ile ilişkilendirmeyi amaçlamıştır.

Yöntem: Bu çalışma, FMD sonuçlarına göre iki gruba ayrılan 60 SLE hastasını dahil etmiştir. Tüm hastalar kapsamlı bir tıbbi değerlendirmeden geçirilmiştir. CİMK, karotis Doppler ultrasonografi ile ölçülmüş ve brakiyal arter FMD'si ultrasonografi ile değerlendirilmiştir. Serum ürik asit düzeyleri de ölçülmüştür. İki grubun özelliklerini karşılaştırarak SLE'li hastalarda FMD'yi etkileyebilecek çeşitli faktörler araştırılmıştır.

Bulgular: Anormal FMD'li hastalar, modifiye edilmiş SLE hastalığı aktivite indeksi 2000'e göre daha yüksek hastalık aktivitesi (p=0,002) ve normal FMD'ye sahip olanlara göre anlamlı derecede yüksek ürik asit düzeyleri göstermiştir (p=0,012). Ortalama CİMK, normal FMD'ye sahip olanlara göre anormal FMD'li hastalarda anlamlı derecede daha yüksektir (0,51±0,11 mm vs. 0,64±0,17 mm, p=0.001). Regresyon analizi, subklinik aterosklerozu temsil eden artmış CİMK'nin öncelikle daha yüksek hastalık aktivite indeksi, anormal FMD ve hiperürisemi ile ilişkili olduğunu ortaya koymuştur.

Sonuç: Bulgularımız, SLE hastalarında subklinik ateroskleroz belirteçleri olarak FMD ve ürik asidin potansiyelini vurgulamaktadır. Artmış CİMK ile olan ilişki, kardiyovasküler riski azaltmak için bu faktörlerin ele alınmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Sistemik lupus eritematozus, subklinik ateroskleroz, endotel disfonksiyonu, akımla aracılık edilen dilatasyon, karotis intima-media kalınlığı, hiperürisemi

Correspondence / İletişim:
Eman Mohammed Ibrahem MD, Assiut University Faculty of Medicine, Department of Internal Medicine, Assiut, Egypt
E-mail: emanmibrahem@gmail.com **ORCID ID:** orcid.org/0000-0003-0672-6630
Received / Geliş Tarihi: 20.01.2025 **Accepted / Kabul Tarihi:** 20.05.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Ibrahem EM, Alaal RFA, Hassan LA, Hassanein S. Flow mediated dilation in association with hyperuricemia as predictors of subclinical atherosclerosis in patients with systemic lupus erythematosus. J Turk Soc Rheumatol. 2025;17(2):77-84

Introduction

Systemic lupus erythematosus (SLE) is closely tied to accelerated atherosclerosis and increased cardiovascular risk. Traditional risk factors alone cannot fully explain this association, suggesting a complex interplay of factors.[1] Subclinical atherosclerosis is a significant predictor of cardiovascular risk and an early finding in patients with SLE.[2] Atherosclerosis is now known to have immunologic aspects. Inflammation plays a pivotal role in atherosclerosis development.[3]

SLE impacts repair mechanisms and the integrity of endothelial cells via deposition of circulating immune complexes and binding of antibodies directly to endothelial cells.[4] Endothelial dysfunction (ED) is thought to be the first step in the pathogenesis of atherosclerosis.[5]

A number of non-invasive imaging surrogate measures have been employed to assess functional and morphological alterations in the arterial wall and ED. Carotid intima media thickness (CIMT) is a dependable and non-invasive indicator of subclinical atherosclerosis that effectively predicts future cardiovascular events.[6] Additionally, brachial artery reactivity testing is a non-invasive technique employed to assess endothelial function through the responsiveness to reactive hyperemia or flow mediated dilation (FMD). FMD quantifies the vasodilatory capacity of the brachial artery in response to an increase in blood flow, primarily mediated by nitric oxide release. A diminished FMD response signifies impaired endothelium-dependent vasodilation, indicative of ED.[7]

Uric acid (UA) is an established independent risk factor for cardiovascular disease (CVD).[8] The elevated prevalence of hyperuricemia in SLE patients is likely multifactorial, stemming from various endogenous and exogenous factors, including inflammation, hypertension, and renal involvement, which are common manifestations of the disease.[9]

This study aims to highlight the role of FMD as a non-invasive marker of ED in SLE patients and to investigate factors affecting it. Additionally, we will explore the association between serum UA levels and the risk of CVD in this population. By elucidating these relationships, we seek to identify potential targets for early intervention and improved CVD management in SLE patients.

Materials and Methods

Study Setting and Design

This is a cross sectional study carried out at the Rheumatology & Clinical Immunology Unit in the Department of Internal Medicine at Assiut University Hospitals. Sixty SLE patients from Outpatient Clinics or admitted to the Rheumatology & Clinical Immunology Unit were enrolled. It was carried out between June 2022 and June 2023. Registered in clinicalTrials.gov (NCT05342285).

Selection Criteria

Patients aged ≥18 years meeting the 2019 the American College of Rheumatology/the European League Against Rheumatism classification criteria for SLE.[10] Exclusion criteria included: History of cardiac disease [primarily ischemic heart disease or coronary heart disease defined as a documented previous myocardial infarction or coronary artery revascularization (including percutaneous coronary interventions or coronary artery bypass grafting, additionally, patients with history of typical angina or already on anti-ischemic drugs were excluded], end-stage renal disease, and/or other autoimmune diseases.

Ethics Approval and Consent to Participate

The study received ethical clearance from the Faculty of Medicine's Institutional Review Board, Assiut University (approval number: 17101668, date: 07.03.2022). The study adhered to the ethical principles outlined in the Declaration of Helsinki. Prior to enrollment, all subjects provided written informed consent.

Data Collection

- Comprehensive medical history including demographics, course of the disease, comorbidities, and medications.
- Clinical evaluation and disease activity assessment using modified version of the SLE disease activity index (SLEDAI-2K).[11] Activity levels were categorized as follows: no activity (SLEDAI-2K=0), mild (SLEDAI-2K=1-5), moderate (SLEDAI-2K=6-10), high (SLEDAI-2K=11-19), and very high (≥20).

Laboratory Tests

Complete Blood Count with Reticulocytes: Performed using a Sysmex XN 1000 System (Siemens, Germany).

Liver Function Tests: Including alanine transaminase, Aspartate transaminase, total protein, and serum albumin which were measured using an Advia 1800 System (Siemens, Germany).

Kidney Function Tests: Included blood urea, serum creatinine, albumin-to-creatinine ratio, 24-hour urinary proteins, and glomerular filtration rate performed using an Advia 1800 System (Siemens, Germany).

C-reactive protein (CRP): Measured using an Advia 1800 System (Siemens, Germany).

Erythrocyte Sedimentation Rate: Assessed via the Westergren method.

Complement Levels (C3 and C4): Assessed using an indirect immunofluorescence method with a Kallestad kit.

Random Blood Sugar and Glycosylated Hemoglobin: Measured using a Sysmex CA 1500 System (Siemens, Germany).

Serum Uric Acid: Measured using a Pars Azmoon kit.

Urine Analysis: Included evaluation of active urinary sediments.

Lipid Profile: Cholesterol level, low-density lipoproteins (LDL), high-density lipoproteins (HDL), and triglycerides were measured in mg/dL using an enzymatic colorimetric assay by STANBIO (USA).

Antiphospholipid antibodies: Lupus anticoagulants (LA), detected by *in vitro* clotting tests, anticardiolipin antibodies immunoglobulin G (IgG), IgM and β_2-glycoprotein I IgG, IgM detected by solid-phase enzyme-linked immunosorbent assays.

Cardiovascular Assessments

Electrocardiogram (ECG): A baseline 12-lead ECG was performed on all participants (150 Hz low pass filter, 25 mm/s paper speed, 10 mm/mv voltage).

Echocardiography: Two-dimensional echocardiography was carried out with a 2.5 MHz transducer using an ACUSON scanner (Siemens, Germany). Left ventricular volumes and ejection fraction were calculated.

Carotid Duplex Examination: CIMT was estimated via high-resolution B-mode ultrasonography utilizing a 10 MHz transducer. Measurements were obtained from both the near and far walls of the right and left common carotid arteries, the carotid bifurcations, and the proximal internal carotid arteries. CIMT corresponds to the distance between the lumen-intima interface and the media-adventitia interface. A mean CIMT value of less than 0.80 mm was considered within the normal range.[12]

Brachial Artery Diameter and FMD: FMD measures the increase in brachial artery diameter after a brief period of blood flow restriction. This dilation reflects the artery's ability to respond to increased blood flow. Reduced dilation indicates vascular dysfunction.

FMD was assessed using a 10 MHz linear array ultrasound transducer (UNEXEF18G, Unex Co., Ltd., Nagoya, Japan). The right brachial artery was examined after an 8-hour fast and 12 hours of refraining from caffeine or exercise. Patients rested for 10-15 minutes before the procedure. Baseline measurements of artery diameter and blood flow velocity were obtained. Subsequently, an occlusion cuff was inflated around the upper arm for approximately 5 minutes, temporarily halting blood flow to the forearm. This period of ischemia induces vasodilation in the vessels below the cuff, leading to a decrease in vascular resistance. Upon cuff deflation, the reduced resistance facilitates a significant increase in blood flow to the forearm. FMD is the difference between the baseline arterial diameter and the maximum diameter achieved following cuff release. FMD was calculated as the percentage increase in arterial diameter following reactive hyperemia using the equation FMD = (peak flow diameter/baseline diameter) × 100. A normal FMD value ranges from 8-15%.[13]

Statistical Analysis

All data were analyzed using SPSS version 26 (IBM SPSS Inc, Chicago, IL, USA). Categorical variables were presented using frequencies and percentages. The normality of numerical variables were assessed using the Shapiro-Wilk test. Data were presented as mean and standard deviation or as median and range based on data distribution. The independent Sample t-test or Mann-Whitney U test was employed to compare mean or median difference between normal and abnormal FMD. The chi-square/Fisher's exact tests were used to compare proportions between normal and abnormal FMD. Pearson/Spearman correlations were used to identify correlation between percentage of FMD, carotid intimal media thickness, UA and other variables. Predictors of abnormal CIMT were determined by logistic regression analysis. Statistical significance was defined as a p-value <0.05.

Results

The study included 60 participants with SLE, divided into two groups based on FMD:

- Normal FMD Group: Thirty women with SLE and normal FMD (8-15%). The mean percentage of FMD in this group was 11.20±2.20 with a range between 9-16.
- Abnormal FMD Group: Thirty women with SLE and reduced FMD (<8%). The mean percentage of FMD in this group was 5.20±1.37 with a range between 4-7.

Demographic and Clinical Characteristics of the Participants in Each Group (Table 1)

No statistically significant differences were observed between the study groups, in mean age, body mass index, or comorbidities. Both groups of patients had similar frequencies of diabetes mellitus and other recorded

comorbidities. However, patients with abnormal FMD had higher SLEDAI-2K scores indicating greater disease activity [median (range) 9.0 (0.0-32.0) in patients with normal FMD vs. 17.50 (0.0-46.0) in patients with abnormal FMD p<0.001].

All patients received hydroxychloroquine (HCQ) at a dose of 400 mg daily. Prednisolone was administered orally to 53 patients (88.3%). Among these, 26 (86.7%) had normal FMD, and 27 (90.0%) had abnormal FMD. There was no significant difference in the mean dose of corticosteroids between the two groups. Other demographic and clinical data are detailed in Table 1.

Laboratory Data Among the Studied Groups (Table 2)

Among our patient population, no cases met the clinical criteria for antiphospholipid syndrome. However, based on the presence of antiphospholipid antibodies using common clinical thresholds (LA 44 sec, anti-cardiolipin IgG >12, anticardiolipin IgM >12 MPL U/mL, β_2-glycoprotein I IgM >20, β_2-glycoprotein I IgG >20 U/mL), the estimated rate of seropositive patients having at least one positive antibody is 3.6%. There was no significant difference in the mean levels of antiphospholipid antibodies between the two groups. Detailed data are presented in Table 2.

Table 1. Baseline demographic and clinical characteristics of the study population

	Total (n=60)	Normal FMD (n=30)	Abnormal FMD (n=30)	p-value
Age (years)	28.20±8.47 (18-55)	26.57±8.29 (18-55)	29.83±8.46 (18-44)	0.137
Disease duration (years)	6.37±3.15 (1-15)	6.13 (2.89)	6.60 (3.43)	0.571
Body mass index (kg/m²)	25.52±3.53 (19-32)	25.63±3.52 (20-31)	25.40±3.60 (19-32)	0.801
Blood pressure (mm/hg)				
Systolic	135.67±28.76 (90-190)	133.67±27.94 (10-190)	137.67±29.90 (90-180)	0.595
Diastolic	78.58±14.05 (50-100)	77.17±14.89 (50-100)	80.00±13.26 (60-100)	0.440
Mean BP	96.40±17.25 (66.0-126.0)	93.22±15.04 (66-116)	99.57±18.92 (70-126)	0.156
Manifestations				
Articular manifestations	31 (51.7%)	18 (60.0%)	13 (43.3%)	0.196
Mucocutaneous manifestations	25 (41.7%)	12 (40.0%)	13 (43.3%)	0.793
Serositis	11 (18.3%)	4 (13.3%)	7 (23.3%)	0.506
Pulmonary manifestations	9 (15.0%)	6 (20.0%)	3 (10.0%)	0.472
Hematological affection	11 (18.3%)	6 (20.0%)	5 (16.7%)	0.739
Lupus nephritis	21 (35.0%)	8 (26.7%)	13 (43.3%)	0.176
Neuropsychiatric manifestations	8 (13.3%)	3 (10.0%)	5 (16.7%)	0.706
Presence of comorbidities				
Diabetes mellitus	13 (21.7%)	6 (20.0%)	7 (23.3%)	0.754
Hypertension	10 (16.7%)	6 (20.0%)	4 (13.3%)	0.488
Chronic kidney disease	6 (10.0%)	3 (10.0%)	3 (10.0%)	1.000
SLEDAI_ 2K categories				
Remission	8 (13.3%)	6 (20.0%)	2 (6.7%)	
Mild disease activity	7 (11.7%)	6 (20.0%)	1 (3.3%)	
Moderate disease activity	14 (23.3%)	9 (30.0%)	5 (16.7%)	**0.013**
High disease activity	14 (23.3%)	3 (10.0%)	11 (36.7%)	
Very high disease activity	17 (28.3%)	6 (20.0%)	11 (36.7%)	
SLEDAI-2K value (median (range)	11.50 (0.0-46.0)	9.0 (0.0-32.0)	17.50 (0.0-46.0)	**0.002**
Drugs:				
Corticosteroid (n%)	53 (88.3%)	26 (86.7%)	27 (90.0%)	
Dose (mg)	22.54±13.49 (5-60)	21.05±12.65 (5-60)	23.98±14.34 (5-60)	0.436
Corticosteroid duration (in years)	6 (1-10)	5.73 (2.57)	5.92 (2.61)	0.785
Azathioprine	8 (13.3%)	3 (10.0%)	5 (16.7%)	
Cyclophosphamide	7 (11.7%)	4 (13.3%)	3 (10.0%)	
Mycophenolate mofetil	9 (15.0%)	5 (16.7%)	4 (13.3%)	
Cyclosporine	4 (6.7%)	3 (10.0%)	1 (3.3%)	

FMD: Flow mediated dilation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000. Data were expressed as frequency and %, mean ± standard deviation or median and range as appropriate.

Chi-square/Fisher's exact test compares proportion between normal and abnormal FMD.

Independent Sample U test/Mann-Whitney U test compares mean/median difference between normal and abnormal FMD

The serum UA levels were significantly different between patients with normal FMD (4.0±1.7 mg/dL, range 1.7-9.0) and those with abnormal FMD (5.25±1.7 mg/dL, range 1.7-10.0) (p=0.012). A detailed comparison of laboratory investigations between the two groups is presented in Table 2.

Echocardiographic Findings and Intima Media Thickness in the Studied Groups

No significant differences were observed between the two groups regarding echocardiography and ECG findings. Mean pulmonary artery systolic pressure was 32.77±10.47 mmHg in patients with normal FMD and 33.73±8.68 mmHg in patients with abnormal FMD (p=0.699). Ejection fraction was 61.03±3.77% in patients with normal FMD and 61.00±4.23% in patients with abnormal FMD (p=0.974). Meanwhile, patients with abnormal FMD exhibited significantly higher CIMT (0.64±0.17 mm) compared to those with normal FMD (0.51±0.11 mm) (p=0.001).

Correlation of FMD, CIMT and Uric Acid with Other Variables (Table 3)

A significant negative correlation was observed between FMD and the SLEDAI-2K score (r=-0.402, p=0.001), indicating that higher disease activity was associated with lower FMD values. A strong negative correlation was found between FMD and CIMT (r=-0.709, p<0.001), suggesting an inverse relationship between endothelial function and arterial stiffness. A significant negative correlation was observed between FMD and serum UA levels (r=-0.343, p=0.007).

Serum UA levels showed a positive correlation with the presence of hypertension (r=0.260, p=0.045) and chronic

Table 2. Difference between patients with normal and abnormal FMD regarding laboratory investigations

	Normal FMD (n=30)	Abnormal FMD (n=30)	p-value
Complete blood count			
White blood cells (10^3/uL)	6.377±2.16 (2.8-12.0)	6.733±2.07 (2.4-11.4)	0.518
Hemoglobin (g/dL)	10.07±1.75 (5.80-13.00)	10.44±1.64 (6.40- 14.00)	0.397
Platelets (10^3/uL)	279.50±87.26 (90-453)	253.07±76.39 (30-437)	0.217
Random blood glucose (mmol/L):	4.43±0.93 (2.9-7.3)	4.80±1.14 (2.6-7.3)	0.171
Inflammatory markers			
Erythrocyte sedimentation rate 1st hr (mm/hr)	70.00 (12-112)	87.50 (10-112)	0.107
C-reactive protein (mg/dL)	4.35 (0.4-41.0)	6.00 (0.8-52.0)	0.058
Kidney function tests			
Urea (mmol/L)	4.65 (2.70-54.00)	4.05 (2.40-6.50)	0.091
Creatinine (umol/L)	70.0 (42-435)	72.50 (38-421)	0.762
Albumin/creatinine ratio (mg/g)	300 (25-1890)	140 (50-2300)	0.900
Uric acid (mg/dL)	4.0 (1.7-9.0)	5.25 (1.7-10.0)	**0.012**
Liver function tests			
Total protein (g/L)	71.77±6.40 (58.0-84.0)	74.46±5.54 (59.0-82.1)	0.087
Albumin (g/L)	38.40±4.54 (26.0-44.3)	40.20±3.38 (32.0-45.1)	0.088
Alanine transaminase (u/L)	22.71±9.42 (6.0-41.0)	19.29±7.49 (7.5-36.0)	0.125
Aspartate transaminase (u/L)	24.17±10.07 (7.8-54.0)	21.42±8.66 (8.6-36.4)	0.262
Lipid profile			
Cholesterol (mg/dL)	196.23±50.85 (100-287)	187.50±41.27 (109-270)	0.468
Low density lipoproteins (mg/dL)	115.67±36.76 (49-220)	113.63±29.79 (56-175)	0.815
High density lipoproteins (mg/dL)	41.53±8.01 (26-53)	41.53±12.61 (27-94)	0.999
Triglycerides (mg/dL)	180.00 (58-530)	131.50 (57-373)	0.071
Antiphospholipid antibodies			
Lupus anticoagulant (sec.)	30.17±9.89 (17-60)	30.23±9.68 (17-58)	0.979
Anticardiolipin IgG (MPL U/mL)	8 (IQR:3) (3-40)	7 (IQR:5) (2-44)	0.330
Anticardiolipin IgM (MPL U/mL)	6.87±2.46 (3-11)	7.23±2.74 (2-11)	0.587
β_2-glycoprotein I IgG (U/mL)	11.97±3.70 (6-19)	12.10±4.05 (6-19)	0.894
β_2-glycoprotein I IgM (U/mL)	11.73±3.59 (5-19)	11.63±3.44 (5-18)	0.913

Data were expressed as mean ± standard deviation or median (IQR) and range as appropriate.
Independent Sample U test/Mann-Whitney U test compares mean/median difference between normal and abnormal FMD.
FMD: Flow mediated dilation, Ig: Immunoglobulin, IQR: Interquartile range

kidney disease (r=0.368, p=0.004). A strong positive correlation was also observed between serum UA and lupus nephritis (r=0.430, p=0.001). Correlations between FMD, CIMT, and serum UA with other variables are detailed in Table 3.

Regression Analysis for Predictors of Abnormal CIMT in Patients with SLE (Table 4)

Significant variables associated with occurrence of abnormal CIMT in bivariate analysis were entered in multivariate logistic regression model adjusted with age and the significant predictors associated with occurrence of increased CIMT, a marker of subclinical atherosclerosis, in multivariate logistic regression were: abnormal FMD [odds ratio (OR)= 3.98, confidence interval (CI)=2.23-8.02, p-value <0.001], increase in serum UA level (OR=1.76, CI=1.11-3.01, p-value=0.01), and increase SLEDAI-2K score (OR=1.56, CI=1.33-2.98, p-value=0.01).

Discussion

FMD represents a non-invasive technique to assess endothelial function. Reduced FMD often indicates ED, which can lead to vascular inflammation and atherosclerotic plaque formation. ED, an early indicator of atherosclerosis, is linked to a heightened risk of future cardiovascular events, even in individuals with normal coronary angiograms. Unlike established atherosclerosis, ED is often reversible.[14] While imaging techniques can identify signs of atherosclerosis, such as thickened carotid intima, these changes often manifest late in the disease process.

Table 3. Correlations between percentage of FMD, CIMT, uric acid and other variables

	FMD (percentage %)		CIMT (mm)		Uric acid (mg/dL)	
	r	p-value	r	p-value	r	p-value
FMD (percentage %)			**-0.709**	**<0.001**	**-0.343**	**0.007**
CIMT (mm)	**-0.709**	**<0.001**			**0.431**	**0.022**
Uric acid (mg/dL)	**-0.343**	**0.007**	-0.070	0.593		
Age (years)	-0.091	0.490	-0.077	0.558	0.046	0.728
Body mass index	0.061	0.642	-0.138	0.291	0.050	0.706
Disease duration (years)	0.044	0.739	-0.085	0.520	0.131	0.318
Investigations						
Erythrocyte sedimentation rate 1st hr. (mm/hr)	-0.236	0.069	0.103	0.434	0.417	0.054
C-reactive protein	-0.327	0.056	0.089	0.498	0.161	0.220
Low density lipoproteins (mg/dL)	0.014	0.914	0.056	0.670	-0.108	0.410
High density lipoproteins (mg/dL)	0.105	0.426	-0.182	0.164	-0.100	0.445
Triglycerides (mg/dL)	0.230	0.077	-0.046	0.729	**-0.312**	**0.015**
Cholesterol (mg/dL)	0.154	0.241	-0.154	0.241	-0.098	0.456
SLEDAI-2K score	**-0.402**	**0.001**	0.236	0.069	0.069	0.602
Comorbidities						
Diabetes mellitus	-0.061	0.643	0.013	0.922	0.245	0.059
Hypertension	0.080	0.541	-0.021	0.875	**0.260**	**0.045**
Chronic kidney disease	-0.063	0.633	0.184	0.160	**0.368**	**0.004**
Lupus nephritis	-0.188	0.151	0.037	0.782	**0.430**	**0.001**
Corticosteroid dose	-0.179	0.198	0.169	0.226	0.333	0.151

CIMT: Carotid intimal media thickness, FMD: Flow mediated dilation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000.
r (correlation coefficient), Pearson/Spearman correlation as appropriate

Table 4. Multivariate logistic regression analysis for factors associated with occurrence of increased carotid intimal media thickness

	AOR	95% confidence interval	p-value
Age	0.71	0.32-1.65	0.22
Body mass index	1.14	0.50-2.22	0.09
Steroid therapy	0.89	0.11-1.09	0.55
SLEDAI-2K	1.56	1.33-2.98	**0.01**
Abnormal FMD	3.98	2.23-8.02	**<0.001**
Hyperuricemia	1.76	1.11-3.01	**0.01**

Logistic regression analysis
AOR: Adjusted odds ratio, FMD: Flow mediated dilation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000

SLE patients frequently exhibit elevated UA levels through different mechanisms. Elevated levels of serum UA have been linked to increased oxidative stress and inflammation. These factors can contribute to ED and accelerate atherosclerosis progression.[15]

Here, in the current study we aimed to assess applicability of brachial FMD and serum UA as non-invasive tools for early prediction of subclinical atherosclerosis, detected by measuring CIMT, in female patients with SLE.

Our findings demonstrate that patients with abnormal FMD had significantly higher disease activity as assessed by SLEDAI-2K, emphasizing the clinical value of FMD as a non-invasive biomarker. This observation aligns with the study by Diószegi et al.,[16] which reported reduced FMD in SLE patients with higher disease activity. Higher SLEDAI-2K scores exhibit a greater risk of organ damage and adverse outcomes in SLE patients. Thus, effective management of SLE disease activity can help minimize the risk of cardiovascular complications.

We could not find a strong link between CRP levels and ED, despite previous studies reporting such a correlation in other autoimmune diseases, such as rheumatoid arthritis. This may be partly explained by the limited reliability of CRP as a marker of disease activity in SLE. Unlike in other inflammatory conditions, many patients with active SLE do not exhibit a significant elevation in CRP levels.

Significantly higher serum UA levels were observed in SLE patients with HTN, CKD, and lupus nephritis. These conditions can contribute to elevated UA levels, which in turn may exacerbate systemic inflammation, worsen hypertension, and impair renal function creating a vicious cycle. Another key finding in our study was the strong association between both abnormal FMD and elevated serum UA with subclinical atherosclerosis in female SLE patients. Our findings revealed that patients with abnormal FMD had significantly higher UA compared to those with normal FMD. These results align with those of previous research.[17,18]

One of the primary findings of this study was that mean CIMT was significantly elevated in patients with abnormal FMD compared to those with normal FMD. Consistent with these findings, previous research has reported elevated CIMT in patients with SLE compared to controls.[14,19] Additionally, a previous study observed decreased FMD in SLE patients with arterial stiffness as measured by IMT.[20]

Our analysis identified SLEDAI-2K, abnormal FMD, and hyperuricemia as predictors of increased CIMT, an early marker of CVD in SLE patients.

Medications used in the management of SLE can also impact the cardiovascular system. Corticosteroids, while effective in controlling lupus activity, are associated with various metabolic side effects. Prednisone has been linked to changes in blood pressure, glucose intolerance, increased body mass index, elevated total cholesterol and levels of LDL-C accompanied by reduced HDL-C levels collectively contribute to a heightened risk of CVD.[21] However, this association was not observed in our study, as the proportion of patients using corticosteroids was similar between the two groups, with no significant difference in the mean corticosteroid dosage. Nonetheless, long-term corticosteroid therapy necessitates regular monitoring and careful dose management.

Studies have demonstrated that HCQ contributes to reductions in blood glucose levels, serum cholesterol, carotid plaque formation, and overall vascular damage in patients with lupus. By minimizing disease flare-ups and helping to maintain remission, this antimalarial agent exerts both immunomodulatory and atheroprotective effects.[22] HCQ is now considered a cornerstone of long-term SLE management and is recommended for all patients, except in cases of contraindications or significant side effects.[23] In line with these guidelines, all patients in our study were prescribed HCQ.

Non-pharmacological interventions, including a healthy diet, regular physical activity, and smoking cessation, play a significant role in cardiovascular protection for patients with SLE. Consequently, optimal disease management alongside lifestyle modifications is essential for lowering cardiovascular risk in this population.

Study Limitations

Key limitations of this study include the relatively small sample size and its single-center design. Furthermore, the lack of long-term follow-up data for all participants. Yet, the study was considered the first study that enrolled the role of FMD and UA in early atherosclerosis in patients with SLE.

Conclusion

Based on the evidence presented, it is evident that SLE patients are at an elevated risk of CVD. The increased CIMT and decreased FMD observed in our study are strong indicators of early atherosclerotic changes. Additionally, the positive association between disease activity, UA levels, and subclinical atherosclerosis further emphasizes the need for vigilant monitoring and management of CVD in SLE patients. FMD and serum UA could potentially serve as valuable tools for early identification of patients at risk for subclinical atherosclerosis and guide targeted interventions. Incorporating FMD and UA into risk stratification models could help clinicians identify patients who require more aggressive management strategies. Early identification of ED

in SLE patients offers a valuable window for implementing primary preventive strategies to delay CVD progression.

Therefore, future research should focus on validating these findings in larger, longitudinal studies and evaluating the effectiveness of interventions targeting FMD and UA.

Ethics

Ethics Committee Approval: The study received ethical clearance from the Faculty of Medicine's Institutional Review Board, Assiut University (approval number: 17101668, date: 07.03.2022). The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Informed Consent: Prior to enrollment, all subjects provided written informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.M.I., R.F.A.A., L.A.H., S.H., Concept: R.F.A.A., Design: E.M.I., R.F.A.A., Data Collection and Processing: L.A.H., S.H., Analysis or Interpretation: L.A.H., Literature Search: S.H., Writing: E.M.I.

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. Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. Arthritis Rheum. 2001;44:2331-7.
2. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. N Engl J Med. 2003;349:2399-406.
3. Libby P. Inflammation in atherosclerosis. Nature. 2002;19-26;420:868-74.
4. Prechl J, Czirják L. The endothelial deprotection hypothesis for lupus pathogenesis: the dual role of C1q as a mediator of clearance and regulator of endothelial permeability. F1000Res. 2015;4:24.
5. Charakida M, Masi S, Lüscher TF, Kastelein JJ, Deanfield JE. Assessment of atherosclerosis: the role of flow-mediated dilatation. Eur Heart J. 2010;31:2854-61.
6. O'Leary DH, Polak JF. Intima–media thickness: a tool for atherosclerosis imaging and event prediction. Am J Cardiol. 2002;90:18-21L.
7. Dos Santos M, Veronese FV, Moresco RN. Uric acid and kidney damage in systemic lupus erythematosus. Clin Chim Acta. 2020;508:197-205.
8. Shahin L, Patel KM, Heydari MK, Kesselman MM. Hyperuricemia and cardiovascular risk. Cureus. 2021;13:e14855.
9. Singh G, Lingala B, Mithal A. Gout and hyperuricaemia in the USA: prevalence and trends. Rheumatology (Oxford). 2019;58:2177-80.
10. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78:1151-9.
11. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29:288-91.
12. Stein JH, Korcarz CE, Hurst RT, et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21:93-111; quiz 189-90.
13. Weissgerber TL. Flow-mediated dilation: can new approaches provide greater mechanistic insight into vascular dysfunction in preeclampsia and other diseases? Curr Hypertens Rep. 2014;16:487.
14. Mak A, Kow NY, Schwarz H, Gong L, Tay S, Ling L. Endothelial dysfunction in systemic lupus erythematosus – a case-control study and an updated meta-analysis and meta-regression. Sci Rep. 7.2017;7320.
15. Elera-Fitzcarrald C, Reátegui-Sokolova C, Gamboa-Cardenas RV, et al. Serum uric acid is associated with damage in patients with systemic lupus erythematosus. Lupus Sci Med. 2020;7:e000366.
16. Diószegi Á, Lőrincz H, Kaáli E, Harangi M, Tarr T. Investigation of flow-mediated dilatation, carotid artery intima-media thickness and arterial stiffness in systemic lupus erythematosus patients. Atherosclerosis. 2023;379:S152.
17. Supratip K, Vishal P, Sayantan R, et al. Predicting flow-mediated dilation of brachial artery in systemic lupus erythematosus patients by reproducible and operator-independent inflammatory and immunologic markers and development of a novel score. Indian Journal of Rheumatology. 2015;10:202-7.
18. Tang J, Liu K, Eshak ES, et al. Association between serum uric acid and impaired endothelial function: the circulatory risk in communities study. J Atheroscler Thromb. 2022;29:1534-46.
19. Asmaa A, Mohammed H, Ali A, Essam A, Sahar E. Carotid intima-media thickness as an indicator of subclinical atherosclerosis in systemic lupus erythematosus patients. Al-Azhar Assiut Medical Journal. 2021;19:36-45.
20. Ammar W, Taha M, Baligh E, Osama D. Assessment of vascular stiffness using different modalities in patients with systemic lupus erythematosus: a case control study. Egypt Heart J. 2020;72:24.
21. Pesqueda-Cendejas K, Rivera-Escoto M, Meza-Meza MR, et al. Nutritional approaches to modulate cardiovascular disease risk in systemic lupus erythematosus: a literature review. Nutrients. 2023;15:1036.
22. McMahon M, Hahn BH, Skaggs BJ. Systemic lupus erythematosus and cardiovascular disease: prediction and potential for therapeutic intervention. Expert Rev Clin Immunol. 2011;7:227-41.
23. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797-808.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.37450
Ulus Romatol Derg 2025;17(2):85-91

The relationship between disease activity, quality of life, and psychological status in patients with rheumatoid arthritis: A cross-sectional study

Romatoid artritli hastalarda hastalık aktivitesi, yaşam kalitesi ve psikolojik durum arasındaki ilişki: Kesitsel bir çalışma

Özlem Karakaş[1], Melda Ağır[2], Abdulsamet Erden[3]

[1]Kırıkkale University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kırıkkale, Türkiye
[2]İskenderun State Hospital, Clinic of Internal Medicine, Hatay, Türkiye
[3]Gazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye

Abstract

Objective: Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disorder predominantly affecting peripheral joints. Beyond its articular involvement, RA imposes substantial physical limitations and emotional challenges, adversely impacting patients' quality of life and contributing to a significant socioeconomic burden. This study was conducted to investigate the associations among disease activity, pain intensity, psychological well-being, and quality of life in individuals diagnosed with RA.

Methods: In this retrospective cross-sectional study, 64 patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA were included. Disease activity was quantified using the disease activity score-28, and pain was assessed through the visual analog scale (VAS). Health-related quality of life was evaluated using the short form-12 (SF-12), which generates physical component summary (PCS) and mental component summary (MCS) scores. Participants were categorized based on disease activity levels, and the impact of both treatment modality and clinical response on quality of life was examined.

Results: The average age of the study population was 56.1 years (standard deviation ±11.82). Most patients (71.9%) were receiving conventional disease-modifying antirheumatic drugs, while 18.8% were treated with biological agents. Patients with moderate to high disease activity exhibited significantly lower SF-12 PCS and MCS scores (p<0.001). VAS pain scores were substantially elevated in those with higher disease activity levels (p<0.001). Furthermore, a strong correlation was observed between psychological status, pain severity, and overall quality of life (p<0.001).

Özet

Amaç: Romatoid artrit (RA), genellikle periferik eklemleri etkileyen, enflamatuvar, kronik ve ilerleyici bir hastalıktır. Prevalansı dünya genelinde %0,25 ile %1 arasında değişmekte olup, kadınlar erkeklere göre 2-3 kat daha fazla etkilenmektedir. RA, önemli fiziksel ve duygusal engellerle ilişkilidir ve yaşam kalitesinde azalmaya yol açarak yüksek sosyoekonomik yük oluşturur. Erken tedavi edilmezse geri dönüşümsüz hasarlara neden olabilir. Bu çalışma, RA hastalarında hastalık aktivitesi, ağrı, psikolojik durum ve yaşam kalitesi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Yöntem: Bu kesitsel çalışma, 2010 Amerikan Romatoloji Koleji/Romatizmaya Karşı Avrupa Birliği tanı kriterlerine göre RA tanısı almış 64 hastayı içermektedir. Hastalık aktivitesi, hastalık aktivite skoru-28 ile, ağrı ise görsel analog ölçeği (GAÖ) ile ölçüldü. Yaşam kalitesi değerlendirilmesi için kısa form-12 (SF-12) ile hem fiziksel bileşen özeti (PCS) hem de zihinsel bileşen özeti (MCS) elde edildi. Hastalar hastalık aktivitelerine göre gruplandırarak tedavi ve hastalık yanıtlarının yaşam kalitesine etkileri analiz edildi.

Bulgular: Katılımcıların ortalama yaşı 57,5 yıl (minimum: 22, maksimum: 82) olup, hastaların %76,6'sı kadındı ve %23,4'ü erkekti. Hastaların çoğu (%71,9) hastalığı modifiye eden ajanlar kullanırken, %18,8'i biyolojik tedavi alıyordu. Yaşam kalitesi, SF-12 ile değerlendirildiğinde, orta ve yüksek hastalık aktivitesine sahip hastalarda (p<0,001) fiziksel ve zihinsel sağlık skorları anlamlı derecede düşük bulundu. GAÖ ile ölçülen ağrı, hastalık aktivitesi yüksek olan hastalarda belirgin şekilde daha yüksekti (p<0,001). Psikolojik durum, ağrı ve genel yaşam kalitesi ile güçlü bir şekilde ilişkiliydi (p<0,001).

Correspondence / İletişim:
Dr. Özlem Karakaş, Kırıkkale University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Kırıkkale, Türkiye
E-mail: ozlem01us@yahoo.com **ORCID ID:** orcid.org/0000-0002-3031-3353
Received / Geliş Tarihi: 21.04.2025 **Accepted / Kabul Tarihi:** 07.07.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Karakaş Ö, Ağır M, Erden A. The relationship between disease activity, quality of life, and psychological status in patients with rheumatoid arthritis: a cross-sectional study. J Turk Soc Rheumatol. 2025;17(2):85-91

Abstract

Conclusion: These findings underscore the importance of addressing both pain and psychological well-being in RA management. Improving quality of life requires more than symptom control-it necessitates a comprehensive and multidisciplinary therapeutic approach tailored to the physical and emotional needs of patients.

Keywords: Rheumatoid arthritis, quality of life, disease activity, SF-12, VAS

Öz

Sonuç: Çalışmamız, RA hastalarının yaşam kalitesini iyileştirmede ağrı yönetimi ve psikolojik desteğin kritik bir rol oynadığını ortaya koymaktadır. Sonuçlar, hastalık aktivitesinin yalnızca fiziksel semptomların kontrol altına alınmasıyla iyileşemeyeceğini, bütüncül bir tedavi yaklaşımının gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Romatoid artrit, yaşam kalitesi, hastalık aktivitesi, SF-12, VAS

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune condition that primarily targets the peripheral joints.[1] The global prevalence of RA exhibits notable variability, ranging from approximately 0.25% to 1%.[2] Although it is more frequently observed in individuals over 40 years of age, the disease can manifest at any age. Women are disproportionately affected, with incidence rates reported to be two to three times higher than in men.[3]

RA is marked by both articular involvement and systemic manifestations, which are thought to result from a complex interaction of genetic predisposition and environmental influences. Clinically, it typically presents as a symmetrical, erosive polyarthritis, predominantly involving the small joints of the hands and feet. Key features often include morning stiffness exceeding one hour, rest-related joint pain, visible swelling, deformities, reduced mobility, and consequently, a decline in quality of life (QoL).[1] In the absence of effective treatment, up to 80-85% of patients may develop chronic joint pain, structural damage, and systemic complications. This progression is commonly associated with increased morbidity, reduced life expectancy, and substantial socioeconomic consequences.[4]

According to the World Health Organization, health-related QoL (HRQoL) reflects an individual's perceived position in life, contextualized by their cultural setting, value system, goals, expectations, and social environment. This multidimensional concept encompasses physical health, psychological well-being, functional independence, interpersonal relationships, spiritual beliefs, and environmental factors.[4] The general negative impacts of RA significantly affect patients' QoL.[5] Studies have shown that RA has substantial effects on both physical and mental health, affirming that QoL should be a critical goal in RA management.[6]

The short form-12 (SF-12) health survey is a widely utilized, abridged instrument for assessing health status, offering physical and mental health summary scores. As a streamlined version of the SF-36, it allows for more efficient health evaluations in clinical and research settings.[7] The visual analog scale (VAS), on the other hand, is employed to quantify subjective symptoms such as pain and discomfort.

For optimal treatment guidance in RA, the use of standardized composite indices is preferred over isolated clinical judgments or single variables. The disease activity score-28 (DAS-28) and clinical disease activity index are the primary tools recommended by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for routine practice.[8] DAS-28 integrates tender and swollen joint counts, acute phase reactants, and patient global health assessments into a continuous metric of disease activity.

The present study aims to examine the influence of disease activity on both QoL and psychological status in individuals with RA. For this purpose, disease activity will be assessed using the DAS-28, while general well-being will be evaluated through SF-12 and VAS scores. Additionally, the study seeks to explore the relationship between disease control, treatment response, and daily functional capacity.

Materials and Methods

Study Design and Patient Selection

This study utilized a retrospective cross-sectional design. Individuals aged 18 years and older who had been diagnosed with RA and were under follow-up at the rheumatology outpatient clinic were evaluated. A total of 64 patients who agreed to participate and completed the questionnaire during face-to-face interviews with the rheumatology specialist were included in the final analysis. Data regarding comorbidities such as hypertension (HT), diabetes mellitus (DM), asthma, and coronary artery disease were extracted from patient medical records and assessed accordingly.

Inclusion criteria comprised patients fulfilling the 2010 classification criteria of the ACR and the EULAR for RA,[9] who had been receiving regular treatment and follow-up care for at least six months, and who provided informed consent to complete the survey. Exclusion criteria involved patients who did not meet the 2010 ACR/EULAR criteria, those diagnosed with concomitant autoimmune conditions (e.g.,

overlap syndromes, primary Sjögren's syndrome, systemic sclerosis, inflammatory myopathies), individuals under the age of 18, those who refused to participate in the survey, and those with severe cognitive or psychiatric disorders that could impair their ability to respond. Additionally, patients with active infections, malignancies, or severe organ dysfunction (e.g., advanced heart failure or end-stage renal disease) were excluded from the study.

The study received ethical approval from the Ethics Committee of Kırıkkale University (approval number: 19, dated: 09.04.2025) and was conducted in compliance with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent revisions.

Data Collection

Demographic and clinical information was obtained through structured face-to-face interviews and a review of patient medical records. Recorded variables included age, sex, comorbid conditions, disease duration, and perceived overall QoL.

Disease activity was evaluated using the DAS-28, while pain intensity over the preceding week was assessed via the VAS. HRQoL was measured using the SF-12 questionnaire, which provides both a mental component score (SF-12 mental) and a physical component score (SF-12 physical).

Considering the potential influence of disease activity on QoL, participants were stratified into two groups based on DAS-28 scores. Group 1 comprised patients in remission or with low disease activity (DAS-28 ≤3.2), whereas group 2 included those exhibiting moderate to high disease activity (DAS-28 >3.2). This classification facilitated the comparison of clinical and QoL outcomes across disease activity levels.

Statistical Analysis

All statistical procedures were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). The distributional characteristics of continuous variables were examined through the Shapiro-Wilk test, complemented by visual assessments including histograms and Q-Q plots. As the distributions of DAS-28, SF-12 mental, and SF-12 physical scores deviated from normality, non-parametric statistical methods were employed for subsequent analyses.

Descriptive statistical methods were applied to summarize the demographic profiles and clinical characteristics of the study population. Categorical variables -such as sex, presence of comorbidities, and types of pharmacological treatment- were presented as frequencies and percentages. Continuous variables, including age and disease duration, were reported using measures of central tendency and dispersion, such as means, medians, ranges, and standard deviations.

To evaluate the association between treatment modalities and disease activity categories (based on DAS-28 scores), the chi-square (χ^2) test was utilized. Given the non-normal distribution of disease activity data, the Mann-Whitney U test was applied to compare DAS-28 scores across different treatment groups.

The relationship between disease duration and disease activity was examined using Spearman's rank-order correlation, owing to the ordinal characteristics of the variables involved. Additionally, comparisons of QoL scores (SF-12 physical and mental components) between DAS-28-defined activity groups were performed using the Mann-Whitney U test, as the data did not meet normality assumptions.

The association between VAS pain scores and disease activity was analyzed using Spearman's rank-order correlation. Similarly, the relationship between age and QoL was examined using Spearman's correlation, based on the distributional properties of the variables.

The effects of gender and employment status on QoL scores were evaluated using independent samples t-tests when normality assumptions were met, and Mann-Whitney U tests when data deviated from normal distribution.

Patient satisfaction with treatment and their psychological status were also assessed. For categorical variables such as satisfaction levels and psychological well-being, descriptive statistics -namely frequencies and percentages- were reported. The correlation between psychological well-being and VAS pain scores was further analyzed using Spearman's correlation, in accordance with the distribution of the data.

All analyses were performed using SPSS software (version 22), and statistical significance was defined as $p<0.05$.

Results

Demographic Characteristics

A total of 64 patients were included, with a mean age of 56.1 years (standard deviation ±11.82). Of the patients, 49 (76.6%) were female and 15 (23.4%) were male. Patients were categorized into four groups based on disease duration. Accordingly, 12 patients (18.8%) had been diagnosed with RA within the past year, 19 patients (29.7%) had a disease duration between 1 and 5 years, 7 patients (10.9%) had a duration between 5 and 10 years, and 26 patients (40.6%) had been diagnosed more than 10 years ago. A family history of rheumatic diseases was present in 22 patients (34.4%). At least one

comorbidity was identified in 34 patients (53.1%) (Table 1). The most common comorbid condition was HT, present in 20 patients (58.8% of those with comorbidity), followed by DM in 12 patients (35.3%), asthma in 9 patients (26.5%), and coronary artery disease in 5 patients (14.7%).

Disease Characteristics and Quality of Life

An evaluation of the pharmacological treatments currently administered revealed that 46 patients (71.9%) were being treated exclusively with conventional disease-modifying antirheumatic drugs (DMARDs). A total of 12 patients (18.8%) were receiving biological therapies, which included agents targeting CD20, tumor necrosis factor-alpha, interleukin-6, or Janus kinase pathways. Four individuals (6.3%) were undergoing combination therapy involving both conventional DMARDs and biologic agents. Notably, two patients (3.1%) were not receiving any form of pharmacological treatment at the time of evaluation.

Participants were stratified into two categories according to disease activity levels: Remission or low disease activity [group 1 (n=47)] and moderate to high disease activity [group 2 (n=17)]. When treatment regimens were analyzed in relation to disease activity, 33 patients (71.7%) receiving DMARD monotherapy and 9 patients (75%) treated exclusively with biologic agents were classified within group 1. Statistical analysis revealed no significant association between DAS-28-defined disease activity groups and the type of pharmacological treatment administered (p=1.000).

Table 1. Demographic characteristics of RA patients

Mean age (years)	56.1±11.82
Gender, n, %	
Female	49 (76.6%)
Male	15 (23.4%)
Disease duration, n, %	
<1 year	12 (18.8%)
1-5 years	19 (29.7%)
5-10 years	7 (10.9%)
>10 years	26 (40.6%)
Family history of rheumatic disease, n, %	22 (34.4%)
At least one comorbidity, n, %	34 (53.1%)
HT	20 (58.8%)
DM	12 (35.3%)
Asthma	9 (26.5%)
Coronary artery disease	5 (14.7%)
Treatment, n, %	
DMARDs only	46 (71.9%)
Biologic therapy only	12 (18.8%)
Combination therapy	4 (6.3%)
No current treatment	2 (3.1%)

DM: Diabetes mellitus, DMARDs: Disease-modifying antirheumatic drugs, HT: Hypertension, RA: Rheumatoid arthritis

Likewise, no significant correlations were observed between treatment type and SF-12 mental component (p=0.68) or physical component (p=0.08) scores.

Patients were grouped into four categories according to disease duration: ≤1 year (n=12, 18.8%), 1-5 years (n=19, 29.7%), 5-10 years (n=7, 10.9%), and >10 years (n=26, 40.6%). Analysis of the relationship between disease duration and disease activity revealed no significant correlation, indicating that disease duration did not have a measurable effect on DAS-28 scores (Spearman's rho=-0.008, p=0.949). Similarly, no statistically significant associations were identified between disease duration and SF-12 mental component (p=0.64) or physical component (p=0.95) scores.

When QoL was compared between the DAS-28 disease activity groups, both SF-12 mental and physical scores were significantly lower in patients with moderate to high disease activity (group 2) (p<0.001) (Figure 1). Furthermore, evaluation of VAS pain scores in relation to DAS-28 categories showed that individuals in group 2 exhibited substantially higher VAS scores compared to those in group 1 (Spearman's rho=0.816, p<0.001) (Figure 2).

The effect of age on patients' QoL was examined, and no significant relationship was found between age and SF-12 mental scores (Spearman's rho=-0.196, p=0.124) or SF-12 physical scores (Spearman's rho=0.000, p=1.000). When evaluating the impact of gender on QoL, no significant difference was observed between groups in terms of SF-12 physical scores (p=0.054). However, SF-12 mental scores were found to be worse in males, with a statistically significant difference between male and female groups (p=0.027).

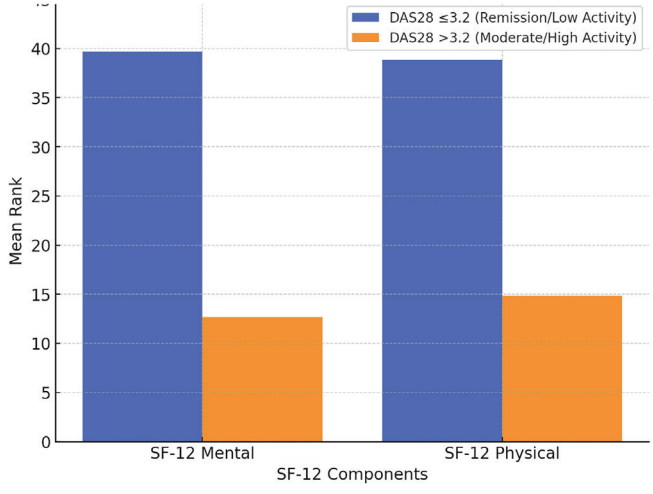

Figure 1. Comparison of SF-12 mental and SF-12 physical scores by DAS-28 groups This visualization shows that patients in the remission/low activity group (DAS-28 ≤3.2) have significantly higher SF-12 mental and physical scores than those in the moderate/high activity group (DAS-28 >3.2)
DAS-28: Disease activity score-28, SF-12: Short form-12

The impact of employment status on QoL was also evaluated. Accordingly, individuals who were not employed had significantly better SF-12 physical health scores compared to those who were employed (p=0.030). However, no significant difference was observed between the two groups in terms of SF-12 mental scores.

When evaluating patients' treatment satisfaction, 43 patients (67.2%) reported being satisfied with their current treatment, while 7 patients (10.9%) stated they were not satisfied. When treatment satisfaction was analyzed based on the type of medication, patients using conventional DMARDs were found to be more satisfied with their treatment compared to those receiving biological therapy (p=0.012).

16 patients (25%) stated that their disease did not affect their lives at all, whereas the remaining 48 patients (75%) reported that the disease affected their daily lives to some extent. Additionally, 27 patients (42.2%) reported that their overall QoL was high. 28 patients (43.8%) stated that there had been no changes in their participation in social activities.

A total of 37 participants (57.8%) reported experiencing a satisfactory level of psychological well-being. In contrast, 13 individuals (20.3%) indicated poor psychological status, while 14 participants (21.9%) expressed ambivalence regarding their psychological state. A statistically significant and strong positive correlation was identified between psychological distress and VAS pain scores (p<0.001), indicating that individuals who reported feeling psychologically unwell also exhibited higher levels of pain (Figure 3). In other words, as psychological well-being deteriorated, perceived pain severity increased. Moreover, a similarly strong and statistically significant positive association was observed between psychological well-being and overall QoL (p<0.001). Participants with poorer psychological status tended to report markedly reduced QoL.

Discussion

In our study, we evaluated the relationships between demographic characteristics, treatment types, disease activity, pain levels, psychological status, and QoL parameters in patients with RA. Our findings revealed that patients with moderate to high disease activity had significantly lower physical and mental health scores (p<0.001). Similarly, VAS pain scores were notably higher in patients with higher disease activity (p<0.001). In line with these findings, psychological status was found to be strongly associated with both pain and overall QoL (p<0.001).

Our findings were consistent with data in the literature. The most significant factors determining QoL in RA patients were pain perception (VAS score), DAS-28 disease activity indices, and psychological status. In contrast, age, disease duration, and the type of treatment used did not have a significant impact.[9,10]

RA is frequently associated with symptoms such as pain, fatigue, reduced physical function, and emotional distress. In the absence of timely and effective treatment, the disease may progress to cause irreversible structural and functional impairments. These consequences not only diminish patients' HRQoL but also contribute to a substantial economic burden at the societal level.[11] Accordingly, the primary aim of treatment should extend beyond achieving clinical remission to include improvements in HRQoL and

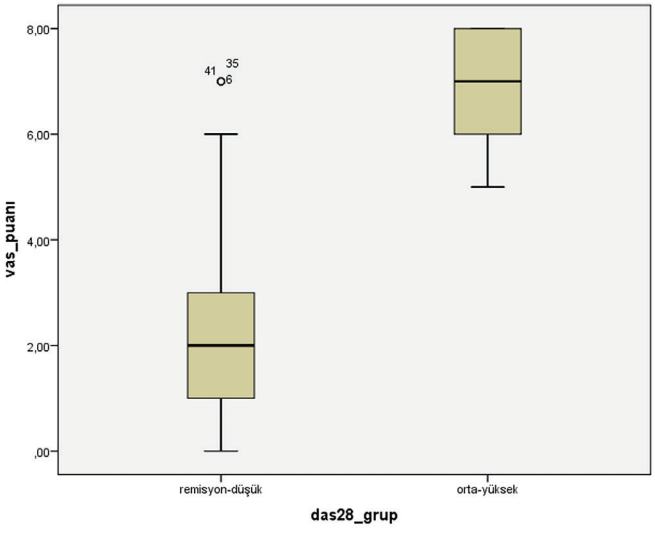

Figure 2. Distribution of VAS scores according to DAS-28 disease activity groups As disease activity increases, patients' pain levels (VAS) also increase
DAS-28: Disease activity score-28, VAS: Visual analog scale

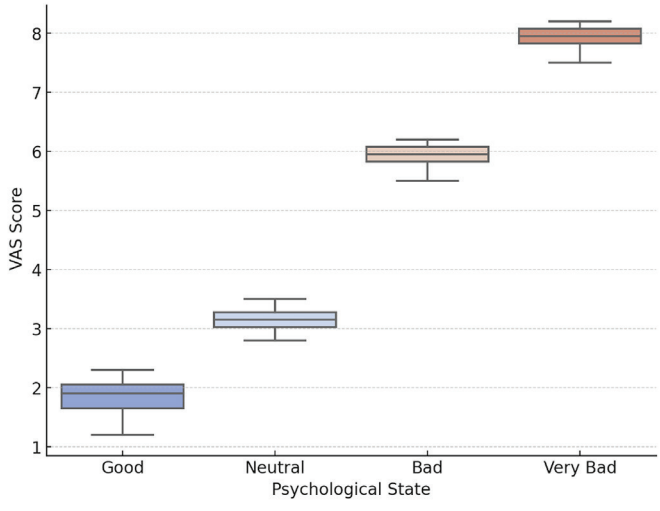

Figure 3. VAS scores by psychological state Accordingly, patients who felt psychologically well had low VAS scores, while patients who felt bad or very bad had high VAS scores
VAS: Visual analog scale

physical capabilities, thereby reducing the overall impact of RA on both individuals and the healthcare system.

Clinical and laboratory markers are commonly used to assess disease activity. However, the patient's own perspective on disease worsening or flares is a highly important metric. [9] Since data such as the impact of the disease on daily life can only be obtained directly from the patient, some researchers consider patient-reported outcomes to be even more important than clinician-reported measures. [12] The SF-12 is a 12-item questionnaire derived from the SF-36, used to calculate physical component summary and mental component summary scores.[13] SF-12 has been studied in various patient populations and has shown strong correlations with SF-36.[14,15] Therefore, it is widely used for assessing QoL in various rheumatic diseases.[16,17]

Similarly, a study by Rosa-Gonçalves et al.[9] emphasized that higher disease activity negatively affects HRQoL and functional capacity, with an interesting finding that SF-36 showed stronger correlations with measures of disability and pain (such as HAQ and VAS-P) than with traditional disease process indicators like erythrocyte sedimentation rate, C-reactive protein, and joint count.

The findings obtained from our QoL assessment using the SF-12 indicate that the factors affecting QoL in RA patients are not limited to disease activity alone; pain and psychological well-being also play significant roles. A recent systematic review investigating HRQoL determinants in RA patients identified disease duration, disease activity, and physical function as the most frequently evaluated factors. [18] The review found that higher disease activity and poorer physical function were consistently associated with worse HRQoL, whereas the association between longer disease duration and HRQoL was inconsistent. Additionally, psychosocial factors such as anxiety and depression showed strong negative associations with HRQoL. These findings are consistent with the present study, which also demonstrated that disease activity and pain were major contributors to reduced QoL. This highlights that disease management requires more than just controlling physical symptoms. To improve patients' QoL, it is essential to incorporate multidimensional approaches such as pain management and psychological support into treatment plans. Furthermore, the significantly lower physical and mental health scores observed in patients with high disease activity underscore that these individuals may not benefit adequately from treatments targeting disease activity alone, emphasizing the need for a multidisciplinary treatment strategy. These findings suggest that a more comprehensive approach should be adopted in the management of RA.

Study Limitations

Our study has several limitations. The main limitations of our study are the lack of a control group. Another limitation of our study is the small number of samples. The study design is cross-sectional, which prevents us from assessing changes in QoL as the disease progresses and the factors impacting these changes. Additionally, it is not possible to establish the directionality of interpretation, meaning it is unclear whether the group of patients in remission and with low disease activity showed better SF-12 scores compared to when they presented higher levels of disease activity. A further limitation is that the joint damage was not assessed.

Conclusion

Although clinical practice often focuses on disease activity, our findings highlight that pain management and psychological support are also critical for improving QoL. The significantly lower physical and mental health scores observed in patients with moderate to high disease activity indicate that controlling disease activity alone is not sufficient. This emphasizes the need for a holistic treatment approach. Therefore, in the management of RA, comprehensive strategies should be developed that address not only inflammation but also pain perception and mental health.

Ethics

Ethics Committee Approval: The study received ethical approval from the Ethics Committee of Kırıkkale University (approval number: 19, dated: 09.04.2025) and was conducted in compliance with the ethical principles outlined in the 1964 Declaration of Helsinki and its subsequent revisions.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K., Concept: Ö.K., A.E., Design: M.A., Data Collection and Processing: M.A., Analysis or Interpretation: Ö.K., Literature Search: M.A., A.E., Writing: Ö.K., A.E.

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. Martinec R, Pinjatela R, Balen D. Quality of life in patients with rheumatoid arthritis - a preliminary study. Acta Clin Croat. 2019;58:157-66.
2. Finckh A, Gilbert B, Hodkinson B, et al. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol. 2022;18:591-602.
3. Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. Lancet. 2023;402:2019-33.
4. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA. 2018;320:1360-72.
5. Salaffi F, Carotti M, Gasparini S, Intorcia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. Health Qual Life Outcomes. 2009;7:25.
6. Hendrikx J, de Jonge MJ, Fransen J, Kievit W, van Riel PL. Systematic review of patient-reported outcome measures (PROMs) for assessing disease activity in rheumatoid arthritis. RMD Open. 2016;2:e000202.
7. Lin Y, Yu Y, Zeng J, Zhao X, Wan C. Comparing the reliability and validity of the SF-36 and SF-12 in measuring quality of life among adolescents in China: a large sample cross-sectional study. Health Qual Life Outcomes. 2020;18:360.
8. England BR, Tiong BK, Bergman MJ, et al. 2019 update of the American College of Rheumatology recommended rheumatoid arthritis disease activity measures. Arthritis Care Res (Hoboken). 2019;71:1540-55.
9. Rosa-Gonçalves D, Bernardes M, Costa L. Quality of life and functional capacity in patients with rheumatoid arthritis - cross-sectional study. Reumatol Clin (Engl Ed). 2018;14:360-6. English, Spanish.
10. Cruz-Castillo Y, Montero N, Salazar-Ponce R, Villacís-Tamayo R. Quality of life in ecuadorian patients with rheumatoid arthritis: a cross-sectional study. Reumatol Clin (Engl Ed). 2019;15:296-300. English, Spanish.
11. Lee DMWM. Rheumatoid arthritis. Lancet. 2001;358:903-11.
12. Berthelot J-M, De Bandt M, Morel J, et al. A tool to identify recent or present rheumatoid arthritis flare from both patient and physician perspectives: the 'FLARE'instrument. Ann Rheum Dis. 2012;71:1110-6.
13. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220-33.
14. Riddle DL, Lee KT, Stratford PW. Use of SF-36 and SF-12 health status measures: a quantitative comparison for groups versus individual patients. Med Care. 2001;39:867-78.
15. Kiely JM, Brasel KJ, Guse CE, Weigelt JA. Correlation of SF-12 and SF-36 in a trauma population. J Surg Res. 2006;132:214-8.
16. Hurst N, Ruta D, Kind P. Comparison of the MOS short form-12 (SF12) health status questionnaire with the SF36 in patients with rheumatoid arthritis. Br J Rheumatol. 1998;37:862-9.
17. Dritsaki M, Petrou S, Williams M, Lamb SE. An empirical evaluation of the SF-12, SF-6D, EQ-5D and Michigan Hand Outcome Questionnaire in patients with rheumatoid arthritis of the hand. Health Qual Life Outcomes. 2017;15:20.
18. Hassen N, Moolooghy K, Kopec J, Xie H, Khan KM, Lacaille D. Determinants of health-related quality of life in adults living with rheumatoid arthritis: a systematic review. Semin Arthritis Rheum. 2025;73:152717.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.63935
Ulus Romatol Derg 2025;17(2):92-101

The effects of disease activity on sleep disorders in ankylosing spondylitis patients

Ankilozan spondilitli hastalarda hastalık aktivitesinin uyku bozukluklarına etkisi

Ali Karataş[1], Tahsin Murat Turgay[2], Orhan Küçükşahin[3]

[1]Ankara University Faculty of Medicine, Department of Internal Medicine, Ankara, Türkiye
[2]Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
[3]Ankara Yıldırım Beyazıt University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye

Abstract

Objective: Sleep disorders in patients diagnosed with ankylosing spondylitis are frequently associated with back pain, depression, chronic disease, and anxiety. This study analyzed the correlations between sleep quality, disease activity, and functional scores.

Methods: This study used the Pittsburgh sleep quality index (PSQI) with 143 patients and 143 healthy volunteers who visited the Rheumatology Clinic of the Faculty of Medicine at Ankara University. The Bath ankylosing spondylitis disease activity index (BASDAI) scores, Bath ankylosing spondylitis functional index (BASFI) functional scores, and C-reactive protein biochemical parameters were extracted from the patients' records.

Results: There were no significant differences between the groups in terms of age or sex. However, the control group showed significantly better outcomes in subjective sleep quality, sleep latency, sleep disturbances, daytime functioning, and total PSQI scores. In the patient group, a significant positive correlation was observed between PSQI scores and BASDAI, BASFI demonstrating that poorer sleep quality was associated with increased disease activity, reduced functional status, and elevated inflammation.

Conclusion: The data indicated a direct correlation between sleep disorders, disease activity, and other parameters. Notably, sleep disorders are less prevalent among patients receiving treatment with anti-tumor necrosis factor antibodies.

Keywords: Ankylosing spondylitis, sleep disorders, PSQI, disease activity, anti-TNF

Özet

Amaç: Ankilozan spondilit tanısı almış hastalarda uyku bozuklukları sıklıkla bel ağrısı, depresyon, kronik hastalıklar ve anksiyete ile ilişkilidir. Bu çalışma, uyku kalitesi ile hastalık aktivitesi ve fonksiyonel skorlar arasındaki korelasyonları analiz etmeyi amaçlamıştır.

Yöntem: Bu çalışmada, Ankara Üniversitesi Tıp Fakültesi, Romatoloji Polikliniği'ne başvuran 143 ankilozan spondilit hastası ve 143 sağlıklı gönüllüye Pittsburgh uyku kalitesi indeksi (PUKİ) uygulanmıştır. Hastalık aktivitesi Bath ankilozan spondilit hastalık aktivite indeksi (BASDAI) ile, fonksiyonel durum Bath ankilozan spondilit fonksiyonel indeksi (BASFI) ile değerlendirilmiş; C-reaktif protein düzeyleri hasta dosyalarından elde edilmiştir.

Bulgular: Yaş ve cinsiyet açısından hasta ve kontrol grupları arasında anlamlı fark saptanmamıştır. Ancak, kontrol grubu; öznel uyku kalitesi, uykuya dalma süresi, uyku bozukluğu, gündüz işlevselliği ve toplam PUKİ skorları açısından anlamlı derecede daha iyi sonuçlar göstermiştir. Hasta grubunda PUKİ skorları ile BASDAI, BASFI ve C-reaktif protein düzeyleri arasında anlamlı pozitif korelasyon saptanmıştır. Bu durum, artan hastalık aktivitesi, azalan fonksiyonel kapasite ve yükselen enflamasyonun kötüleşmiş uyku kalitesi ile ilişkili olduğunu göstermektedir.

Sonuç: Elde edilen veriler, uyku bozukluklarının hastalık aktivitesi ve diğer klinik parametrelerle doğrudan ilişkili olduğunu ortaya koymaktadır. Özellikle, anti-tümör nekroz faktörü tedavisi alan hastalarda uyku bozukluklarının daha düşük oranda görüldüğü gözlemlenmiştir.

Anahtar Kelimeler: Ankilozan spondilit, uyku bozuklukları, PUKİ, hastalık aktivitesi, anti-TNF

Correspondence / İletişim: Dr. Ali Karataş,
Ankara University Faculty of Medicine, Department of Internal Medicine, Ankara, Türkiye
E-mail: akaratas85@hotmail.com **ORCID ID:** orcid.org/0000-0002-2464-1975
Received / Geliş Tarihi: 29.04.2025 **Accepted / Kabul Tarihi:** 26.06.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Karataş A, Turgay TM, Küçükşahin O. The effects of disease activity on sleep disorders in ankylosing spondylitis patients. J Turk Soc Rheumatol. 2025;17(2):92-101

Introduction

Research indicates that rheumatological diseases are often accompanied by pain, fatigue, depression, and sleep disorders. Sleep disorders are particularly prevalent in this group, with certain sleep issues being unique to these conditions. Clinicians treating rheumatological diseases should possess a fundamental understanding of sleep physiology, cycles, and disorders. Addressing sleep disorders can enhance patients' functional status, pain severity, and quality of life. Similarly, appropriate treatment for rheumatological diseases can improve the patients' quality of life, functional capacity, sleep quality, and pain severity.

Physicians may observe sleep disorders in patients with rheumatologic diseases, whether related or unrelated to the underlying disease. It is undeniable that accurate diagnosis and appropriate treatment of rheumatologic conditions are crucial in alleviating pain, fatigue, and sleep disorders associated with the disease. Both animal and clinical studies have demonstrated that effective pain management not only enhances sleep quality but also that improved sleep quality can help patients experience less pain.[1-4]

The central nervous system is directly impacted by cytokines and immune functions, which play a role in regulating the brain's sleep/wake homeostasis and behavior.[5,6] Tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) play a regulatory role in the body's sleep-wake cycle and various other physiological processes.[6] Proinflammatory cytokine activity may lead to symptoms such as fatigue, pain, and depression.[7,8]

Sleep disorders in individuals with ankylosing spondylitis (AS) exhibit a prevalence ranging from 15.4% to 80%, contingent upon the specific sleep assessment employed. These disturbances may present in various forms, including non-restorative sleep, extended morning stiffness, difficulties in awakening, and the onset of obstructive sleep apnea syndrome.[9-11] Ankylosis, restricted thoracic mobility, and increased body weight are factors that may contribute to the development of obstructive sleep apnea syndrome.[12,13] Axial pain, nocturnal stiffness occurring in the latter half of the night, and inflammatory back pain are significant contributors to sleep disorders in patients.[14] A Canadian study employing the Pittsburgh sleep quality index (PSQI) found that 69% of individuals with spondyloarthropathy experienced poor sleep quality. These issues were mainly associated with reduced sleep duration, challenges in falling asleep, and diminished sleep quality.[15]

Individuals with AS frequently report sleep problems, often associated with back pain, depression, chronic conditions, and anxiety. This study examined the relationship between sleep quality and disease activity scores, specifically the Bath ankylosing spondylitis disease activity index (BASDAI), as well as functional scores, namely the Bath ankylosing spondylitis functional index (BASFI). Various scales can be employed to assess sleep quality, with patient-evaluated tests offering cost-effectiveness and greater adaptability. These tests include the PSQI, insomnia severity index, Pittsburgh sleep diary, and medical outcomes study. In our study, we utilized the PSQI as a subjective measure of sleep quality over the past month. Therefore, sleep quality may reflect the effectiveness of treatment. This study aimed to evaluate the relationship between disease activity and sleep quality in patients with AS using the PSQI.

Materials and Methods

Data Collection

This study examined the correlation between the PSQI scores and parameters of disease activity (BASDAI) and functional scoring (BASFI) in patients with ankylosing spondylitis. These patients were assessed and monitored at the Internal Medicine and Rheumatology Department of the Faculty of Medicine at Ankara University during their routine hospital visits between October 2014 and January 2015.

Initially, 200 patients were enrolled in the study; however, 41 were excluded due to insufficient treatment duration, and 16 were excluded due to incomplete data, resulting in a final cohort of 143 patients for analysis. The BASDAI and BASFI scores were calculated for these 143 patients with ankylosing spondylitis, all of whom had been receiving treatment for at least six months and were diagnosed according to the Assessment of SpondyloArthritis International Society (ASAS) and New York criteria. Participants were queried regarding their smoking habits, marital status, and caffeine consumption history. Following the acquisition of informed consent, the Turkish-adapted PSQI was administered. This study aimed to evaluate whether sleep quality could serve as an indirect indicator of treatment effectiveness. In the control group, 143 age- and sex-matched healthy adults, who did not have any chronic diseases and provided informed consent. These individuals were administered the PSQI. This study was conducted on healthy volunteers who presented to the hospital for a check-up, among individuals with no comorbid conditions, matched for age and gender. Matching by age and sex minimized their potential confounding effects, thereby demonstrating the difference in sleep quality. Demographic and clinical parameters, including age, sex, human leukocyte antigen (HLA)-B27 status, erythrocyte sedimentation rate, and C-reactive protein (CRP) levels, were extracted from patient medical records.

Inclusion criteria: The study encompassed individuals aged 18 to 65 who provided informed consent and were diagnosed with AS in accordance with the 1984 Modified New York Criteria and the 2009 ASAS Classification Criteria, alongside age- and sex-matched healthy controls.

Exclusion criteria: Children, individuals with another active systemic disease [malignancy (cancer), acute or chronic infection, hypertension, diabetes mellitus, hypothyroidism, liver cirrhosis, hyperthyroidism, hepatitis, etc.].

Method of Analysis

The BASDAI was used to determine the patient's disease activity, while the BASFI was used to determine their functional capacities.

The PSQI, initially developed by Buysse et al.[16] and later validated for Turkish use by Ağargün et al.[17], is a self-administered questionnaire aimed at assessing sleep quality and disturbances over the past month. It comprises 19 items, each rated on a scale from 0 to 3, and encompasses seven components: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The total score is derived by summing the component scores, resulting in a range from 0 to 21. A global PSQI score exceeding 5 indicates poor sleep quality, with a reported sensitivity of 89.6% and specificity of 86.5%. Scores above this threshold suggests either significant impairment in at least two components or moderate disruption in three or more domains. Hypnotic use was based solely on participants' self-reported information.

The sedimentation and CRP values of the patients at the time of surveying and their previous records of HLA-B27 and disease duration in their files were obtained.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara University (decision no: 17-728-14, date: 27.10.2014).

Statistical Analysis

Statistical analyses were conducted utilizing SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables exhibiting a normal distribution are presented as mean ± standard deviation, while those not conforming to a normal distribution are summarized as median and range (minimum–maximum). Prior to descriptive or inferential testing, the distribution of each continuous variable was examined for normality using the Shapiro-Wilk test; for sample sizes greater than 50, results were cross-checked with the Kolmogorov-Smirnov (Lilliefors corrected) test and inspection of Q-Q plots. Categorical variables are reported as counts and percentages.

Group comparisons were performed using the independent samples t-test for variables with a normal distribution and the Mann-Whitney U test for non-parametric data. Associations between categorical variables were assessed using Pearson's chi-square test or Fisher's exact test, as appropriate.

To evaluate the relationships between continuous variables, Pearson's correlation was used for data that followed a normal distribution, while Spearman's rank correlation was applied to data that did not. In order to identify independent predictors of poor sleep quality in patients with ankylosing spondylitis, a hierarchical multivariable regression analysis was conducted. Predictors of poor sleep quality (PSQI >5) were examined using hierarchical multivariable logistic regression, first entering demographic and inflammatory parameters (Model 1) and subsequently adding disease activity/functional scores (Model 2) to quantify their incremental explanatory power. Variables with p-values less than 0.05 were deemed statistically significant.

Results

Table 1 details the demographic and clinical characteristics of the study participants, encompassing mean age, sex distribution, disease duration, HLA-B27 positivity, anti-TNF treatment status, erythrocyte sedimentation rate (ESR) and CRP levels, marital status, smoking and caffeine consumption habits, as well as BASDAI and BASFI scores.

The patient cohort comprised 143 individuals, with 88 males and 55 females, mirroring the gender distribution of the control group. The median age in the patient group was 40 years (range: 22-69), while the control group had a median age of 39 years (range: 22-69). There were no significant differences between the groups regarding age or sex. Upon comparing the components of the PSQI, it was observed that the control group demonstrated significantly superior scores in subjective sleep quality, sleep latency, sleep disturbances, daytime functioning, and overall PSQI scores. Notably, the patient group exhibited a longer sleep duration. These differences were statistically significant.

As shown in Table 2, significant differences were observed between patients and controls in subjective sleep quality, sleep latency, sleep duration, sleep disturbance, and total sleep scores, while other demographic and sleep efficiency measures were comparable.

Table 1. Patient group characteristics

Variable	Values (mean ± SD)
Age	40.19±10.067
Gender (male, %)	61.5
Disease duration	5.83±5.4 (min. 1, max. 30)
HLA-B27 (positive, %)	68.5
Receiving anti-TNF treatment (%)	64.3
ESR (mm/hour)	17.36±16 (min. 1, max. 84)
CRP (mg/dL)	10.83±13.9 (min. 0.7, max. 103)
Marital status (married, %)	79.7
Smoking (positive, %)	49.0
Caffeine intake (positive, %)	21.7
BASDAI	3.01±2.07
BASFI	2.09±1.76

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HLA: Human leukocyte antigen, min.: Minimum, max: Maximum, SD: Standard deviation, TNF: Tumor necrosis factor

Table 2. Comparison of PSQI components between the patient and control groups (mean ± SD)

	Patients (n=143)	Control (n=143)	p-value
Age (years)	40.29±10.18	40.19±10.06	0.933
Gender (male, %)	61.5	61.5	1
BMI	25.1±6.3	24.8±6.6	0.9
Subjective sleep quality (1)	1.23±0.68	0.94±0.61	**<0.001**
Sleep latency (2)	1.17±1.09	0.80±1.03	**0.003**
Sleep duration (3)	0.71±0.86	0.94±0.71	**0.014**
Sleep efficiency (4)	0.14±0.36	0.10±0.38	0.362
Sleep disturbance (5)	1.01±0.51	0.56±0.52	**<0.001**
Medication (6)	0.03±0.07	0.06±0.11	0.637
Daytime functions (7)	0.85±0.94	0.69±0.92	0.089
Total score	5.15±3.178	4.04±2.55	**0.005**

BMI: Body mass index, PSQI: Pittsburgh sleep quality index, SD: Standard deviation

In a comparative analysis of sleep disorders between patient and control groups, defined by total scores exceeding 5, the incidence of sleep disorders was observed to be 19.6% in the control group, whereas it was 36.4% in the patient group. The Pearson's chi-square analysis yielded a p-value of 0.002, indicating a statistically significant difference. The estimated relative risk was calculated as 2.34 [confidence interval (CI) 95%; 1.34-4.09].

When patient characteristics were compared using the Mann-Whitney U test, a significant relationship was found between the presence of sleep disorders, namely, PSQI scores higher than 5, and the parameters of BASDAI, BASFI, and CRP. The chi-squared test revealed that having PSQI scores above 5 was significantly associated with being female, not receiving anti-TNF treatment, and being married, as indicated in Table 3.

The chi-square test results, as presented in Table 4, indicate significant differences among the treatment groups (p=0.007). When categorized into classical disease-modifying antirheumatic drug (DMARD), non-steroidal anti-inflammatory drug (NSAID), and anti-TNF (infliximab, etanercept, golimumab, and adalimumab) groups, the anti-TNF group showed notably superior outcomes in sleep quality (p=0.004), sleep latency (p=0.003), sleep duration (p=0.04), sleep disturbance (p<0.001), and total PSQI scores (p=0.001).

In the Spearman correlation analysis, a weak correlation was identified when Spearman's rho was less than 0.3, a moderate correlation when Spearman's rho ranged from 0.3 to 0.5, and a strong correlation when Spearman's rho exceeded 0.5. As indicated in Table 5, the Spearman correlation analysis revealed a strong correlation between sleep disorders and the components and parameters of the BASDAI and BASFI.

Table 3. Comparison of patient characteristics between those PSQI ≤5 and PSQI >5

Variable	PSQI ≤5	PSQI >5	p
Age	39.27±10.64	42±9.15	0.068
Year of disease	5.98±4.68	5.58±6.5	0.135
ESR (mm/hour)	15.54±13.84	20.54±18.91	0.195
CRP (mg/dL)	9.54±14.44	13.10±12.74	**0.026**
BASDAI	1.87±1.06	5.01±1.88	**<0.001**
BASFI	1.32±1.16	3.44±1.85	**<0.001**
Sex (male, female) (%)	76.1%, 43.6%	23.9%, 56.4%	**<0.001**
HLA-B27 (-, +) (%)	64.4%, 63.3%	35.6%, 36.7%	0.892
Receiving anti-TNF (-, +) (%)	41.2%, 76.1%	58.8%, 23.9%	**<0.001**
Being married (-, +) (%)	82.8%, 58.8%	17.2%, 41.2%	**0.017**
Smoking (-, +) (%)	61.6%, 65.7%	38.4%, 34.3%	0.613
Caffeine (-, +) (%)	67.9%, 48.4%	32.1%, 51.6%	**0.046**

BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HLA: Human leukocyte antigen, PSQI: Pittsburgh sleep quality index, TNF: Tumor necrosis factor

Table 4. Mean PSQI scores based on the treatments received by the patients

Treatment	N	Mean PSQI score	p-value
Classical DMARD and/or NSAID	51	6.41±3.383	-
Adalimumab	23	4.13±3.020	**0.027**
Infliximab	40	4.23±2.636	**0.019**
Etanercept	20	5.40±3.393	1
Golimumab	9	4.11±1.616	0.857
Anti-TNF	92	4.00±2.841	**0.001**
Total	143	5.15±3.178	-

**In the paired comparisons of the treatments, the differences between infliximab and classical DMARD and NSAID (p=0.019), adalimumab and classical DMARD and NSAID (p=0.027), and DMARD and NSAID and Anti-TNF (0.001) were found to be significant. No statistically significant differences were observed in the other paired comparisons. DMARD: Disease-modifying antirheumatic drug, NSAID: Non-steroidal anti-inflammatory drug, PSQI: Pittsburgh sleep quality index, TNF: Tumor necrosis factor*

Table 5. Spearman correlation analyses (Spearman's rho) of PSQI scores based on the patients' clinical characteristics

Variable	PSQI total	Subjective sleep quality (1)	Sleep latency (2)	Sleep duration (3)	Sleep efficiency (4)	Sleep disturbance (5)	Medication (6)	Daytime functions (7)
BASDAI	0.689**	0.578**	0.496**	0.386**	0.313**	0.391**	0.201*	0.516**
BASFI	0.646**	0.631**	0.429**	0.370**	0.342**	0.242**	0.125*	0.507**
ESR	0.124	0.035	0.067	0.102	0.067	0.183*	0.061	0.062
CRP	0.223**	0.193*	0.095	0.111	0.053	0.093	0.013	0.178*

**: p<0.05, **: p<0.001. BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, PSQI: Pittsburgh sleep quality index*

Hierarchical Multivariable Regression Analysis

Objective and Outcome

• Both models aim to identify independent predictors of poor sleep quality, defined dichotomously as PSQI >5 (1=poor sleep, 0=good sleep).

Modelling Strategy

• We adopted a hierarchical multivariable logistic-regression approach to evaluate the incremental contribution of clinical variables beyond basic demographics and inflammation markers.

• Model 1 (baseline block) included only demographic and inflammatory covariates:

- Age (continuous, years)
- Gender (reference = male)
- Disease duration (continuous, years)
- Treatment category (reference = anti-TNF; comparator = classical DMARD ± NSAID)
- ESR (continuous, mm h^{-1})
- CRP (continuous, mg dL^{-1})

• Model 2 (expanded block) retained all Model 1 covariates and added disease-specific activity/functional indices:

- BASDAI (continuous, 0-10)

- BASFI (continuous, 0-10)

Variable Selection and Multicollinearity Control

• All covariates were chosen a priori based on biological plausibility and prior literature; no data-driven stepwise elimination was performed.

• Variance-inflation factors (VIFs) were inspected; all VIF <2, confirming negligible multicollinearity.

Model Diagnostics

• Goodness-of-fit was assessed with the Hosmer-Lemeshow test (Model 1 p=0.74; Model 2 p=0.68).

• Nagelkerke pseudo-R^2 rose from 0.21 (Model 1) to 0.36 (Model 2), indicating that adding BASDAI/BASFI explained an additional 15% of variance in sleep disturbance.

• Discriminatory capacity improved: area under the receiver operating characteristic curve increased from 0.74 to 0.83.

Interpretation of Key Coefficients

• Model 1:

- Female sex → odds ratio (OR) = 2.62 (95 % CI: 1.17-5.86, p=0.018)

- Classical DMARD therapy → OR = 3.04 (95 % CI: 1.35-6.82, p=0.007)

• Model 2:

- Female sex → OR = 4.08 (95 % CI: 1.28-12.97, p=0.017)

- BASDAI (per one-point increase) → OR = 3.66 (95 % CI: 2.45-5.54, p<0.001)

- Treatment effect attenuated once BASDAI was included, suggesting disease activity partly mediates the therapy-sleep relationship.

Why Two Models?

• Separating the analyses clarifies whether disease activity indices (BASDAI/BASFI) independently predict poor sleep above and beyond demographics, inflammatory markers, and treatment.

• The hierarchical design also demonstrates how effect estimates (e.g., treatment category) shift once activity scores are introduced, highlighting possible mediation or confounding.

Multivariate regression analysis was conducted for Models 1 and 2. In Model 1, the independent variables included age, sex, duration of disease, treatment received, ESR, and CRP. Regarding the occurrence of sleep disorders, specifically PSQI total scores exceeding 5, being female increased the relative risk by 2.62 times (CI: 95%; 1.17-5.861; p=0.018). Additionally, undergoing classical DMARD treatment raised the relative risk by 3.04 times (CI: 95%; 1.35-6.82; p=0.007).

In Model 2, the independent variables included age, sex, duration of the disease, treatment received, CRP, ESR, BASDAI, and BASFI. Regarding sleep disorders, being female increased the relative risk by 4.08 times (CI: 95%; 1.28-12.97; *p*=0.017), while a high BASDAI score raised the relative risk by 3.66 times (CI: 95%; 2.45-5.54).

Discussion

The present study underscores three principal contributions. First, we show that deteriorating disease activity is closely coupled with impaired sleep: PSQI scores rose in parallel with both BASDAI and BASFI indices, yielding robust correlations (p=0.65-0.69). Second, compared with an age- and sex-matched cohort of 143 healthy controls, patients with AS exhibited more than a two-fold higher prevalence of poor sleep quality (36.4% vs. 19.6%; relative risk=2.34), and this deficit tracked positively with systemic inflammation (CRP). Finally, anti-TNF therapy emerged as a protective factor; multivariable logistic regression identified treatment as independently associated with lower global PSQI scores and consistent improvement across all sub-components. The large sample size, the inclusion of a rigorously matched control group, and the stratified analyses by treatment status collectively strengthen the clinical relevance and novelty of these findings. Using a hierarchical multivariable logistic-regression framework, we show for the first time in a Turkish cohort that BASDAI remains an independent predictor of poor sleep even after accounting for age, sex, systemic inflammation (CRP/ESR) and treatment category, while anti-TNF therapy confers a protective effect.

The pathogenesis of sleep disorders in AS remains incompletely elucidated. This study examined the correlation between sleep quality and disease activity scores (BASDAI) as well as functional scores (BASFI). Various scales can be employed to assess sleep quality. Patient self-assessment of sleep quality is not only cost-effective but also offers greater adaptability. In our study, we utilized the PSQI as a subjective measure of sleep quality over the preceding month. Disturbances in sleep quality, or the absence thereof, indirectly reflect the therapeutic efficacy of the treatments administered.

Previous research has identified the male-to-female ratio among patients as 2-3:1.[18] Gunal et al.[19] reported a male-to-female ratio of 1.8 in a study conducted in Türkiye. In our study, 61.5% of the AS patients were male, a proportion comparable to that observed by Gunal et al.[19] In a study by Hultgren et al.[9] involving 43 male and 27 female patients with ankylosing

spondylitis, a comparison was made with another study of 3558 individuals from the general population. The findings revealed that sleep disorders were prevalent in 80.8% of women and 50.0% of men with AS. In contrast, these prevalence rates were 28.8% in women and 21.8% in men in the reference group.[9]

Gunal et al.[19] conducted a study in Türkiye that examined the prevalence of HLA-B27 in patients with AS. They found that 70% of the patients were HLA-B27 positive. Whereas the recent multicenter study by Bulut Gökten et al.[20] documented a lower rate of 59.4% in 488 patients from the Thrace region; compared to 68.5% in our patient group.

Although sleep disorders have become more common in the general population, their increased occurrence among individuals with AS is attributed to persistent pain and restricted joint mobility. In our research, we found that 36.4% of the patients had poor sleep quality, indicated by PSQI scores exceeding 5, compared to 19.6% of the healthy participants. This highlights the significantly higher incidence of sleep disorders in AS. For instance, Batmaz et al.[21] reported a prevalence of 50%, whereas Li et al.[22] reported it as 35.4%. A 2023 systematic review and meta-analysis, which combined data from 18 studies, found a pooled prevalence of poor sleep (PSQI >5) at 53% (95% CI: 44.9-61) among individuals with AS.[23] In our cohort, this figure was 36.4%, still significantly higher than in matched healthy controls (~20%), yet somewhat lower than the global average. The meta-analysis observed a slight reduction in prevalence over time, which may indicate the increased use of biologics and more comprehensive management strategies. Previous studies reported that the prevalence of sleep disorders in the general population ranged from 15-35%, which was comparable to the 19.6% rate found in our study's control group.[24-26]

Our finding of poorer sleep quality among female patients aligns with broader population-based studies showing similar sex-related disparities in sleep outcomes.[27] Fluctuations in oestrogen and progesterone across the menstrual cycle, pregnancy and menopause can alter sleep architecture, pain perception and thermoregulation; concomitantly, lower nocturnal melatonin and higher prolactin levels in women appear to promote lighter, more fragmented sleep, and chronic inflammation may interact bidirectionally with sex-hormone modulation of cytokine release. Beyond these physiological mechanisms, sociocultural dynamics in Türkiye -such as women's disproportionate overnight caregiving for children or older relatives, the higher prevalence of mood disorders, and greater domestic workload- further curtail sleep duration and increase night-time awakenings, collectively explaining why female sex emerged as an independent predictor of poor sleep quality in our cohort.[28,29] In our study, we observed a decline in sleep quality among married individuals. Subgroup analysis demonstrated that the antiTNFtoDMARD utilization ratio in unmarried patients (1.8) was virtually indistinguishable from that of the entire cohort (1.9). However, the married-to-single ratio was 3.3 among men and 5.2 overall. This disparity can be attributed to the fact that the majority of women in the study were married.

An intriguing finding among both patients and controls was the limited use of hypnotics in Türkiye, despite the increased prevalence of sleep disorders. Specifically, recorded solely from participants' self-reported information, the usage rate was 4% in the patient group and 2% in the control group. This phenomenon may be attributed to the prevalent belief among patients that such medications could lead to addiction and tolerance.

Consistent with prior research, the prevalence of poor sleep quality was observed to be associated with the BASDAI and BASFI.[20,22,30-32] The correlation coefficients for BASDAI (p=0.69) and BASFI (p=0.65) in relation to PSQI are consistent with findings from a substantial Korean multicenter cohort, where elevated BASDAI independently predicted poor sleep.[33]

ESR was not associated with sleep disorders, as also reported by Batmaz et al.[21] In contrast, significant associations were identified by Karadağ et al.[31] and Li et al.[22] This discrepancy might be due to ESR being a late-recovering acute-phase reactant.

Recent studies have shed more light on the prevalence and impact of sleep disorders in AS. Wu et al.[34] found that sleep disorders in AS patients were significantly linked to elevated inflammatory markers, such as CRP and IL-6, supporting our finding of a positive correlation between CRP levels and sleep disorders. Similarly, Wang et al.[35] confirmed that elevated CRP, IL-6, and TNFα serve as independent predictors of disordered sleep in AS.

Treatments that facilitate recovery from the disease may also improve patients' sleep status, alongside their clinical condition. In our study, anti-TNF treatment demonstrated superiority over classical DMARD and/or NSAID use in terms of subjective sleep quality, sleep latency, sleep disturbance, and total PSQI scores. The finding that anti-TNF therapy enhances sleep quality is consistent with the results of Druce et al.[36], who reported that TNF inhibitors not only reduce disease activity but also improve sleep quality and overall well-being in AS patients. Although our finding that anti-TNF therapy improves sleep contradicts the results of Karadağ et al.[31], it is mechanistically plausible, as TNF-α is known to regulate sleep. This suggests a complex relationship that may differ based on study populations or methodologies.[37,38] Recent literature has highlighted a significant finding regarding the impact of

biologic therapies on sleep outcomes in patients with AS. Ayyıldız et al.[39] demonstrated that patients undergoing anti-TNF therapy, in combination with aerobic exercise, experienced notable enhancements in sleep quality and overall physical function.This observation aligns with our findings that patients treated with anti-TNF exhibited better PSQI scores compared to those on non-biologic disease-modifying antirheumatic drugs. Furthermore, a study by Cai et al.[40] highlighted that emotional distress and sleep disorders were significantly alleviated following biologic therapy, underscoring the importance of targeted treatment in addressing sleep dysfunction in AS. Mounting evidence indicates that sleep and systemic inflammation operate in a reciprocal, self-reinforcing loop. Acute elevations of IL-6 and TNF-α deepen non-REM sleep, yet chronic overproduction fragments sleep architecture and shortens total sleep time; likewise, even a single night of curtailed or disrupted sleep stimulates sympathetic outflow and up-regulates IL-6 and TNF-α gene expression, fuelling further inflammation.[41,42]

In the subgroup analysis of anti-TNF treatment, it was found that infliximab and adalimumab were more effective than etanercept and golimumab. The relatively small number of patients treated with etanercept and golimumab may have influenced the statistical significance. Conducting a similar study with a larger patient cohort would be appropriate for further comparison of this issue. The efficacy of golimumab in enhancing sleep quality may vary, with some studies indicating benefits comparable to those of infliximab and adalimumab. The superior performance of infliximab and adalimumab observed in our subgroup analysis may be attributed to their potent suppression of TNF-α, a cytokine involved in sleep regulation, as noted by Chennaoui et al.[37] However, the limited sample size for etanercept and golimumab in our study necessitates further investigation to confirm these differences.

Our data consequently revealed a direct relationship between sleep disorders and disease activity, along with other related parameters. Anti-TNF treatments not only addressed the patients' sleep issues but also alleviated other problems. It is crucial to thoroughly assess sleep disorders in cases of ankylosing spondylitis. Improved disease management can reduce sleep disorders and significantly enhance patients' quality of life. Furthermore, better sleep quality was a predictor of treatment response.

Study Limitations

This study has several limitations that warrant consideration. First, its cross-sectional design precludes causal inference between disease activity and sleep outcomes. Second, all key variables including PSQI components and hypnotic use were assessed by self-report, introducing the possibility of recall and social-desirability bias. Third, although we adjusted for age, sex, disease duration, inflammatory markers, and anti-TNF treatment, several potentially important lifestyle and psychosocial covariates were not captured: habitual exercise level, which can independently improve sleep quality; employment status and work-schedule characteristics, which influence circadian regularity; and current antidepressant use, given the bidirectional links between mood, medication, and sleep. The absence of these data may have led to residual confounding. Finally, the sample was drawn from a single tertiary rheumatology center, limiting generalizability to community settings or other geographic regions. Future longitudinal studies incorporating objective sleep measures and a broader set of behavioural and pharmacologic variables are needed to confirm and extend our findings.

Future Research Should Aim to:

- Longitudinal studies: Should be conducted to comprehensively elucidate the causal relationship between disease activity and sleep disorders.
- Mechanistic insights: Examine the biological mechanisms that interconnect inflammation, pain, and poor sleep quality in patients with AS.
- Broader treatment spectrum: Investigate the impact of other biological agents, such as IL-17 inhibitors and JAK inhibitors, on sleep quality to uncover additional therapeutic options.
- Management of comorbidities: Investigate further the impact of managing comorbid conditions on enhancing sleep outcomes for patients with AS.

Clinical Implications

This research underscores the importance of a holistic strategy for managing AS, which includes the routine evaluation and treatment of sleep disorders. Healthcare providers should be proactive in identifying sleep issues and consider the advantages of anti-TNF therapy in enhancing sleep quality. Incorporating sleep management techniques such as cognitive-behavioral therapy for insomnia and lifestyle changes can also prove advantageous.

Conclusion

The management of disease activity in AS is essential not only for the control of inflammation and pain but also for the enhancement of sleep quality. By addressing both disease activity and sleep disorders, healthcare providers can significantly improve the overall quality of life for patients with AS.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Ankara University (decision no: 17-728-14, date: 27.10.2014).

Informed Consent: Informed consent was obtained from all the subjects involved in the study.

Footnotes

Authorship Contributions

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

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. Moldofsky H. The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes. Joint Bone Spine. 2008;75:397-402.
2. Silva A, Andersen ML, Tufik S. Sleep pattern in an experimental model of osteoarthritis. Pain. 2008;140:446-55.
3. Wei H, Ma A, Wang YX, Pertovaara A. Role of spinal 5-HT receptors in cutaneous hypersensitivity induced by REM sleep deprivation. Pharmacol Res. 2008;57:469-75.
4. Moldofsky H. Rheumatic manifestations of sleep disorders. Curr Opin Rheumatol. 2010;22:59-63.
5. Moldofsky H, Luk W-P, Dickstein J. Sleep, health and immunocompetence. Neuroimmune Biol. 2001;1:255-68.
6. Krueger JM. The role of cytokines in sleep regulation. Curr Pharm Des. 2008;14:3408-16.
7. Khairova RA, Machado-Vieira R, Du J, Manji HK. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int J Neuropsychopharmacol. 2009;12:561-78.
8. Schäfers M, Sommer C, Geis C, Hagenacker T, Vandenabeele P, Sorkin LS. Selective stimulation of either tumor necrosis factor receptor differentially induces pain behavior in vivo and ectopic activity in sensory neurons in vitro. Neuroscience. 2008;157:414-23.
9. Hultgren S, Broman JE, Gudbjörnsson B, Hetta J, Lindqvist U. Sleep disturbances in outpatients with ankylosing spondylitisa questionnaire study with gender implications. Scand J Rheumatol. 2000;29:365-9.
10. Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. Sleep Med Rev. 2008;12:211-28.
11. Jones SD, Koh WH, Steiner A, Garrett SL, Calin A. Fatigue in ankylosing spondylitis: its prevalence and relationship to disease activity, sleep, and other factors. J Rheumatol. 1996;23:487-90.
12. Ortancil O, Sarikaya S, Sapmaz P, Basaran A, Ozdolap S. The effect(s) of a six-week home-based exercise program on the respiratory muscle and functional status in ankylosing spondylitis. J Clin Rheumatol. 2009;15:68-70.
13. Solak O, Fidan F, Dündar U, et al. The prevalence of obstructive sleep apnoea syndrome in ankylosing spondylitis patients. Rheumatology (Oxford). 2009;48:433-5.
14. Da Costa D, Zummer M, Fitzcharles MA. Determinants of sleep problems in patients with spondyloarthropathy. Musculoskeletal Care. 2009;7:143-61.
15. Rudwaleit M, Metter A, Listing J, Sieper J, Braun J. Inflammatory back pain in ankylosing spondylitis: a reassessment of the clinical history for application as classification and diagnostic criteria. Arthritis Rheum. 2006;54:569-78.
16. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193-213.
17. Ağargün MY, Kara H, Anlar O. Pittsburgh uyku kalitesi indeksinin gecerligi ve guvenirligi. Turk Psikiyatri Dergisi. 1996;7:107-15.
18. Slobodin G, Rosner I, Rimar D, Boulman N, Rozenbaum M, Odeh M. Ankylosing spondylitis: field in progress. Isr Med Assoc J. 2012;14:763-7.
19. Gunal EK, Sarvan FO, Kamali S, et al. Low frequency of HLA-B27 in ankylosing spondylitis patients from Turkey. Joint Bone Spine. 2008;75:299-302.
20. Bulut Gökten D, Mercan R, Kurtuldu B, Tozkır H. Low frequency of HLA-B27 in ankylosing spondylitis patients from Turkey: insights from the thrace region. Med Sci Monit. 2025;31:e948449.
21. Batmaz İ, Sarıyıldız MA, Dilek B, Bez Y, Karakoç M, Çevik R. Sleep quality and associated factors in ankylosing spondylitis: relationship with disease parameters, psychological status and quality of life. Rheumatol Int. 2013;33:1039-45.
22. Li Y, Zhang S, Zhu J, Du X, Huang F. Sleep disturbances are associated with increased pain, disease activity, depression, and anxiety in ankylosing spondylitis: a case-control study. Arthritis Res Ther. 2012;14:R215.
23. Salari N, Sadeghi N, Hosseinian-Far A, et al. Prevalence of sleep disturbance in patients with ankylosing spondylitis: a systematic review and meta-analysis. Adv Rheumatol. 2023;63:33.
24. Rajput V, Bromley SM. Chronic insomnia: a practical review. Am Fam Physician. 1999;60:1431-8; discussion 1441-2.
25. Eddy M, Walbroehl GS. Insomnia. Am Fam Physician. 1999;59:1911-6, 1918.
26. Insomnia: assessment and management in primary care. National Heart, Lung, and Blood Institute Working Group on Insomnia. Am Fam Physician. 1999;59:3029-38.
27. Ford DE, Cooper-Patrick L. Sleep disturbances and mood disorders: an epidemiologic perspective. Depress Anxiety. 2001;14:3-6.

28. Salari N, Hasheminezhad R, Hosseinian-Far A, et al. Global prevalence of sleep disorders during menopause: a meta-analysis. Sleep Breath. 2023;27:1883-97.

29. Perger E, Silvestri R, Bonanni E, et al. Gender medicine and sleep disorders: from basic science to clinical research. Front Neurol. 2024;15:1392489.

30. Günaydin R, Göksel Karatepe A, Ceşmeli N, Kaya T. Fatigue in patients with ankylosing spondylitis: relationships with disease-specific variables, depression, and sleep disturbance. Clin Rheumatol. 2009;28:1045-51.

31. Karadağ O, Nakas D, Kalyoncu U, Akdoğan A, Kiraz S, Ertenli I. Effect of anti-TNF treatment on sleep problems in ankylosing spondylitis. Rheumatol Int. 2012;32:1909-13.

32. Chu P, Ju YS, Hinze AM, Kim AHJ. Measures of sleep in rheumatologic diseases: sleep quality patient-reported outcomes in rheumatologic diseases. Arthritis Care Res (Hoboken). 2020;72(Suppl 10):410-30.

33. Song BW, Jeong HJ, Kim BY, et al. Disease activity and sleep quality in a Korean ankylosing spondylitis cohort. J Rheum Dis. 2021;28:143-9.

34. Wu X, Wu J, Li X, et al. The clinical characteristics of other HLA-B Types in chinese ankylosing spondylitis patients. Front Med (Lausanne). 2021;7:568790.

35. Wang H, Sun JY, Zhang Y. Effects of serum inflammatory factors and disease activity on sleep disorder in ankylosing spondylitis. World J Psychiatry. 2024;14:866-75.

36. Druce KL, Jones GT, Macfarlane GJ, Basu N. Patients receiving anti-TNF therapies experience clinically important improvements in RA-related fatigue: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology (Oxford). 2015;54:964-71.

37. Chennaoui M, Sauvet F, Drogou C, et al. Effect of one night of sleep loss on changes in tumor necrosis factor alpha (TNF-α) levels in healthy men. Cytokine. 2011;56:318-24.

38. Shearer WT, Reuben JM, Mullington JM, et al. Soluble TNF-alpha receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. J Allergy Clin Immunol. 2001;107:165-70.

39. Ayyıldız A, İnceoğlu SÇ, Çoban NA. Effect of anti-tumor necrosis factor therapy on the efficacy of aerobic exercise in patients with ankylosing spondylitis. Magna Scientia Advanced Research and Reviews. 2024;10:131-7.

40. Cai Y, Chen J, Dou J, et al. Relationships between emotional state, sleep disturbance and health-related quality of life in patients with axial spondyloarthritis. Clin Rheumatol. 2025;44:267-76.

41. Besedovsky L, Lange T, Haack M. The sleep-immune crosstalk in health and disease. Physiol Rev. 2019;99:1325-80.

42. Irwin MR, Opp MR. Sleep health: reciprocal regulation of sleep and innate immunity. Neuropsychopharmacology. 2017;42:129-55.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.97269
Ulus Romatol Derg 2025;17(2):102-106

Educational and skill development needs of early-career rheumatologists in Türkiye

Türkiye'de çalışmakta olan kariyerinin başındaki romatologların eğitim ve beceri geliştirme ihtiyaçları

Mert Öztaş[1], Gizem Ayan[2], Emre Bilgin[3], Ertuğrul Çağrı Bölek[4], Ufuk İlgen[5]

[1]Acıbadem University, Atakent Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
[2]Ankara Training and Research Hospital, Clinic of Internal Medicine, Ankara, Türkiye
[3]Sakarya University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Sakarya, Türkiye
[4]Gazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
[5]Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Abstract

Objective: Several previous reports from Europe have disclosed the educational needs of early-career rheumatologists on an international scale. We aimed to identify and characterize the current clinical and academic educational needs of early-career rheumatologists in Türkiye.

Methods: This cross-sectional study was conducted via an online survey distributed to rheumatology fellows in training and consultants working in Türkiye. The survey, distributed by SurveyMonkey, was sent to all Turkish Society of Rheumatology (TSR) member trainees and consultants. The questionnaire included sections on demographics, current professional status, academic interests, and awareness of various TSR programs. Clinical and academic domains were assessed separately using a 7-point scale, with 1 indicating the highest need.

Results: The survey was sent to all rheumatology trainees and consultants who are members of the TSR (n=190), and data from 113 participants (59.4%) were analyzed. Most of the respondents (68.1%) were rheumatology trainees, while the remaining were consultant rheumatologists. In the clinical domain, the most needed skill for both trainees (2.6±1.7) and consultants (2.9±1.8) was musculoskeletal ultrasonography. This was followed by X-ray interpretation among trainees (4±1.6) and magnetic resonance imaging interpretation (3.6±1.3) among consultants. In the academic domain, trainees primarily expressed a need for training in scientific writing (2.8±1.6), while consultants prioritized statistical education (2.7±1.4). Research methodology was the second most frequently requested topic in both groups. Awareness of the educational and academic opportunities provided by the TSR varied greatly among participants.

Conclusion: Musculoskeletal ultrasound emerged as the most reported clinical skill need, emphasizing its relevance and the necessity of incorporating it into routine clinical practice. While the educational programs offered by the TSR are relatively well-known and widely attended, awareness and utilization of academic support mechanisms remain limited.

Keywords: Rheumatology, education, survey, Turkish Society of Rheumatology

Özet

Amaç: Kariyerinin başındaki romatologların eğitim ihtiyaçlarını uluslararası ölçekte gösteren çalışmalar mevcuttur. Bu çalışmada, Türkiye'deki genç romatologların mevcut klinik ve akademik eğitim ihtiyaçlarını belirlemeyi amaçladık.

Yöntem: Bu kesitsel çalışma, Türkiye'de çalışan romatoloji yan dal asistanları ve uzmanlarına yönelik çevrim içi bir anket yoluyla gerçekleştirildi. SurveyMonkey ile dağıtılan anket, Türk Romatoloji Derneği (TRD) üyesi tüm asistan ve uzman hekimlere gönderildi. Anket; demografik bilgiler, mevcut mesleki durum, akademik ilgi alanları ve TRD'nin çeşitli programlarına dair farkındalığı içeren bölümlerden oluşmaktaydı. Klinik ve akademik alanlar ayrı ayrı değerlendirilmiş olup, 1 en yüksek ihtiyacı gösterecek şekilde 7 puanlık bir ölçek kullanılmıştır.

Bulgular: Anket TRD üyesi tüm asistan ve uzmanlara (n=190) gönderildi, 113 kişinin (%59,4) verisi analiz edildi. Katılımcıların çoğunluğu (%68,1) romatoloji asistanı iken, kalanlar uzman romatologlardı. Klinik alanda en fazla ihtiyaç duyulan beceri hem asistan (2,6±1,7) hem de uzman hekimlerde (2,9±1,8) kas-iskelet ultrasonografisiydi bunu asistanlarda grafi okuma becerisi (4±1,6) izlerken asistanlarda manyetik rezonans görüntüleme okuma becerisi (3,6±1,3) izledi. Akademik alanda ise asistanların ilk tercihi makale yazma becerileri (2,8±1,6) iken uzmanlar istatistik eğitimini (2,7±1,4) tercih etmişlerdi. Araştırma metodolojisi her iki grupta da ikinci en sık talep edilen konuydu. TRD'nin sunduğu eğitim ve akademik olanaklara dair farkındalık ise oldukça değişkendi.

Sonuç: Kas-iskelet ultrasonografisi en çok ihtiyaç duyulan klinik beceri olarak ön plana çıkmakta olup, bu alanın rutin klinik uygulamalara entegrasyonunun önemini vurgulamaktadır. TRD'nin sunduğu eğitim programları genel olarak bilinir ve katılım görece yüksek olsa da, akademik destek mekanizmalarına dair farkındalık ve kullanım halen sınırlıdır.

Anahtar Kelimeler: Romatoloji, eğitim, anket, Türkiye Romatoloji Derneği

Correspondence / İletişim:
Mert Öztaş MD, Acıbadem University, Atakent Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
E-mail: dr.mertoztas@gmail.com **ORCID ID:** orcid.org/0000-0002-4077-1374
Received / Geliş Tarihi: 20.05.2025 **Accepted / Kabul Tarihi:** 08.07.2025 **Publication Date/Yayın Tarihi :** 31.07.2025

Cite this article as / Atıf: Öztaş M, Ayan G, Bilgin E, Bölek EÇ, İlgen U. Educational and skill development needs of early-career rheumatologists in Türkiye. J Turk Soc Rheumatol. 2025;17(2):102-106

Introduction

Training early-career rheumatologists is essential for advancing rheumatology, a field evolving with developments in immunology, imaging, and targeted therapies. As clinical care becomes more complex, the need for well-structured, competency-based education has become more obvious.[1,2]

National and international rheumatology societies provide a range of educational and academic resources to support the development of young professionals including workshops, digital platforms, research grants, and mentorship programs.[2-5] Despite the increasing number of these programs, it is not fully known to what extent they meet the needs of early rheumatologists. Understanding the educational needs of early-career rheumatologists is important for optimizing national and international training programs.

Several previous reports from Europe disclosed the educational needs of early-career rheumatologists on an international scale.[6-8] There is still a lack of country-specific evidence, and no similar studies have been conducted from Türkiye to date.

We aimed to identify and characterize the current clinical and academic educational needs of early-career rheumatologists in Türkiye.

Materials and Methods

This cross-sectional study was conducted via an online survey distributed to rheumatology trainees and consultants working in Türkiye. The survey, distributed by SurveyMonkey, was sent to all Turkish Society of Rheumatology (TSR) member trainees and consultants. Consultants working as assistant professors were excluded from the present study. The questionnaire included sections on demographics, current professional status, academic interests, and awareness of various TSR programs. We evaluated current clinical and academic knowledge and skill needs of young rheumatologists, based on a 7-point scale where 1 indicates the highest level of need. Data were collected between May 2022 and November 2022. The study was approved by the Ethical Committee of the İstanbul Research and Training Hospital (approval number: 154, date: 20.05.2022).

Statistical Analysis

Statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as percentages.

Results

The survey was sent to all TSR member trainees and consultants (n=190), and 116 (61%) completed the questionnaire. Three consultants who were holding assistant professor positions were excluded from the study and 113 (59.4%) were included for the data analysis.

Demographics

Of the 113 participants, 66.3% were between the ages of 30-35, and a slightly over half of the respondents were female (53.1%). Most of the respondents (68.1%) were rheumatology trainees, while the remaining were consultant rheumatologists. The majority were working in university hospitals (57.5%). The most represented geographic region was Central Anatolia (36.3%), followed by the Marmara Region (20.4%). Internal Medicine was the primary specialty of origin for 88.5% of participants. Slightly less than a quarter (23.9%) had been working as rheumatologists for over four years, while nearly half (46.9%) had not yet completed two years in the rheumatology field. Participants indicated the mean ± SD hours per week for their clinical and academic work was 40.1±8.9 and 5.8±6 respectively. Thirteen (11.5%) participants stated that they could not dedicate any time to academic activities. While 40.7% had not yet chosen an academic focus, the most reported interests included connective tissue disorders (19.5%) and spondylarthritis (14.2%). Demographics of the participants were depicted at Table 1.

Current Clinical and Academic Knowledge and Skill Needs

In the clinical domain, the most prominent skill need for both trainees (2.6±1.7) and consultants (2.9±1.8) was musculoskeletal ultrasound. Among trainees, this was followed by a need for improvement in X-ray interpretation (4±1.6), whereas consultants expressed a greater need for improvement in MR interpretation (3.6±1.3). The remaining clinical skill needs -physical examination skills, interventional approaches, laboratory evaluation and capillaroscopy- were similar in both groups.

In the academic domain, trainees' top preference was writing skills (2.8±1.6), whereas consultants prioritized statistics (2.7±1.4). Research methodology was the second most frequently requested topic in both groups. The remaining academic skill needs were similar between the two groups, including presentation skills, poster preparation, and ethics committee application processes. Current clinical and academic knowledge and skill needs were depicted in Table 2.

Awareness and Participation in Current Educational and Academic Programs

Participation in recent conferences was relatively high, with 63.7% had attended the National Rheumatology Congress in 2021 and 54.8% attended the 2022 Fellows' Congress. Awareness and participation levels in the TSR's educational and academic programs were comparable. Among digital educational initiatives, Romatoscope is the most well recognized, with more than 70% of the respondents reported active participation. Furthermore, TSR-digital and RODY had quite similar participation rates with slightly less than 60%. Awareness is notably lower for the academic opportunities. More than half of the respondents were unaware of the publication support program and research funding opportunities. Less than 5% of the respondents were applied for them previously. The bursary for research abroad was better known, 63.8% of the participants had heard the program while less than 10% had previously applied. Awareness and participation in current educational and academic programs are depicted in Table 3.

Table 1. Demographics of the participants

Characteristics	n (%)	Total response (%)
Age, years		
30-35	75 (66.3)	113 (100)
35-40	38 (33.7)	
Gender, n (%)		
Female	60 (53.1)	113 (100)
Male	53 (46.9)	
Region of residence		
Aegean	22 (19)	113 (100)
Black sea	4 (3.5)	
Central Anatolian	41 (36.3)	
Eastern Anatolia	7 (6)	
Marmara	23 (20.4)	
Mediterranean	12 (10.5)	
Southeastern Anatolia	4 (3.5)	
Current position		
Trainee in rheumatology	77 (68.1)	113 (100)
Consultant physician	36 (31.9)	
Current workplace		
University hospital	65 (57.5)	113 (100)
Research and training hospital	30 (25.9)	
Public hospital	7 (6)	
City hospital	6 (5.2)	
Private hospital	5 (4.3)	
Years in rheumatology		
1st	27 (23.3)	113 (100)
2nd	26 (22.5)	
3rd	18 (15.5)	
4th	15 (12.9)	
>4 years	37 (23.9)	
Primary specialty		
Internal Medicine	100 (88.5)	113 (100)
Physical therapy and rehabilitation	13 (11.5)	
Academic subject of interest		
Autoinflammatory disorders	4 (3.5)	113 (100)
Behçet's syndrome	9 (8)	
Connective tissue disorders	22 (19.5)	
Spondylarthritis	16 (14.2)	
Vasculitis	11 (9.7)	
Has not yet been decided	46 (40.7)	
Other	5 (4.4)	

Discussion

Most of the survey respondents (68,1%) were young clinicians currently in rheumatology training. The most frequently reported clinical training need was musculoskeletal ultrasound in both trainees and consultants, which was followed by X-ray interpretation among trainees and magnetic resonance interpretation among consultants. These findings are in line with previous European surveys.[6,7] In terms of academic development, trainees highlighted academic writing while consultants preferred statistics. Research methodology was also a key area where both groups needed support. This pattern is also consistent with an earlier study.[6] These findings disclose that early-career rheumatologists in different countries share similar educational and skill needs.

More than half of the participants were aware of the digital educational offers of TSR. This finding was also consistent with the general awareness of European League Against Rheumatism educational offerings among the same target audience in a previous report,[9] reflecting that such resources have become an integral part of rheumatology education in the post-COVID era.[10,11]

Despite high awareness of the educational offers, awareness of academic support programs was quite low. Nearly one third of the participants had never heard of TSR bursary for research abroad and more than half have never heard of the research funding and publication support program. Fewer than 10% of the participants had applied for such opportunities before. This points to the need for better visibility and promotion of these academic resources.

Conclusion

Musculoskeletal ultrasound emerged as the most reported clinical skill need, emphasizing its relevance and the necessity of incorporating it into routine clinical practice. While the educational programs offered by the TSR are relatively well-known and widely attended, awareness and

Table 2. Current clinical and academic knowledge and skill needs

Domains*			
Clinical	Trainees, mean ± SD	Consultants, mean ± SD	Total, mean ± SD
Ultrasound	2.6±1.7	2.9±1.8	2.8±1.8
X-ray interpretation	4±1.6	3.9±1.7	3.9±1.7
Physical exam	4±2.6	4.1±2.7	4±2.6
MR interpretation	4.4±1.7	3.6±1.3	4.1±1.6
Interventional approaches	4.1±1.9	4.3±2.2	4.1±2
Laboratory evaluation	4.2±1.9	4.4±2	4.2±2
Capillaroscopy	4.7±1.7	4.7±1.7	4.7±1.7
Academic			
Writing skills	2.8±1.6	2.9±1.6	2.8±1.6
Research methodology	2.8±1.6	3±1.7	2.9±1.6
Statistics	3.1±1.7	2.7±1.4	3±1.6
Literature research	3.1±1.7	3.3±1.8	3.2±1.7
Presentation skills	4.8±1.3	4.6±1.7	4.7±1.4
Poster presentation skills	5.4±1.5	5.5±1.2	5.4±1.4
Ethical committee application	6±1.6	5.9±1.7	6±1.6

*Participants were asked to rate their needs for clinical and academic knowledge and skills on a1 to 7 scale. 1 indicates the highest level of need and 7 indicates the lowest, MR: Magnetic resonance, SD: Standard deviation

Table 3. Awareness of the existing educational and academic offers of the Turkish Society of Rheumatology

Characteristic			
Educational	Have never heard of it n (%)	Heard but did not participate n (%)	Participated n (%)
TRD-Digital	15 (13.2)	31 (27.4)	67 (59.4)
Romatoscope	3 (2.7)	26 (23)	84 (74.3)
RODY	5 (4.4)	39 (34.5)	69 (56.6)
Academic	Have never heard of it	Heard but did not apply	Applied
Bursary for research abroad	41 (36.2)	63 (55.8)	9 (8)
Research funding	59 (52.2)	51 (45.1)	3 (2.7)
Publication support	76 (67.3)	33 (29.2)	4 (3.5)

utilization of academic support mechanisms remain limited. The Turkish Young Rheumatologists Group could help close this gap by connecting early-career rheumatologists with the TSR.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Committee of the İstanbul Research and Training Hospital (approval number: 154, date: 20.05.2022).

Informed Consent: Not necessary.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ö., G.A., E.B., E.Ç.B., U.İ., Concept: M.Ö., G.A., E.B., E.Ç.B., U.İ., Design: M.Ö., G.A., E.B., E.Ç.B., U.İ., Data Collection and Processing: M.Ö., G.A., E.B., E.Ç.B., U.İ., Analysis or Interpretation: M.Ö., G.A., E.B., E.Ç.B., U.İ., Literature Search: M.Ö., G.A., E.B., E.Ç.B., U.İ., Writing: M.Ö., G.A., E.B., E.Ç.B., U.İ.

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. Alunno A, Avcin T, Haines C, et al. Points to consider: EULAR-UEMS standards for the training of European rheumatologists. Ann Rheum Dis. 2023;82:1107-13. Erratum in: Ann Rheum Dis. 2023;82:e226.
2. Liebowitz JE, Torralba KD, Kolfenbach J, et al. Rheumatology Milestones 2.0: A Roadmap for Competency-Based Medical Training of Rheumatology Fellows in the 21st Century. Arthritis Care Res (Hoboken). 2022;74:675-685.
3. Turkish Society of Rheumatology. Eğitim ve Akademik Destek Programları. [Online]. Available from: https://www.TSR.org.tr

4. EULAR. Education and training. [Online]. Available from: https://www.eular.org/education.cfm

5. American College of Rheumatology. Available from: https://rheumatology.org/online-education

6. Beyer C, Ramiro S, Sivera F, et al. Educational needs and preferences of young European clinicians and physician researchers working in the field of rheumatology. RMD Open. 2016;2:e000240.

7. Bandinelli F, Bijlsma JW, Ramiro MS, et al. Rheumatology education in Europe: results of a survey of young rheumatologists. Clin Exp Rheumatol. 2011;29:843-5.

8. Gupta L, Khan H, Sinha M, et al. Rheumatology education in India: a survey-based cross sectional study. Rheumatol Int. 2021;41:1773-83.

9. Oztas M, Ayan G, Bilgin E, et al. AB1709 awareness of educational and research offerings of eular and emeunet among young rheumatologists working in Türkiye. Annals of the Rheumatic Diseases. 2023;82:2091-2.

10. Ahmed S, Zimba O, Gasparyan AY. Moving towards online rheumatology education in the era of COVID-19. Clin Rheumatol. 2020;39:3215-22.

11. Dua AB, Kilian A, Grainger R, et al. Challenges, collaboration, and innovation in rheumatology education during the COVID-19 pandemic: leveraging new ways to teach. Clin Rheumatol. 2020;39:3535-41.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.29494
Ulus Romatol Derg 2025;17(2):107-119

Fatigue and kinesiophobia in axial spondyloarthritis: Exploring the role of disease activity, functional impairment, and psychological factors

Aksiyel spondiloartritte yorgunluk ve kinezyofobi: Hastalık aktivitesi, fonksiyonel bozulma ve psikolojik faktörlerin rolünün incelenmesi

Gülay Alp[1], Fulden Sari[2]

[1]Uşak University Faculty of Medicine, Department of Internal Medicine, Uşak, Türkiye
[2]Bingöl University Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Bingöl, Türkiye

Abstract

Objective: Fatigue and kinesiophobia are common in axial spondyloarthritis (axSpA) and may be influenced by disease activity, functional impairment, quality of life (QoL), and psychological factors. This study aimed to determine the prevalence of fatigue and kinesiophobia in patients with axSpA and to evaluate their associations with disease activity, functional status, QoL, and psychological variables.

Methods: This cross-sectional study involved 134 patients with axSpA. Fatigue was assessed using the fatigue severity scale, and kinesiophobia was evaluated with the tampa kinesiophobia scale (TKS). At the same time, anxiety and depression were assessed using the hospital anxiety and depression scale. Structural equation modeling (SEM) was used to evaluate the mediating role of fatigue in the effect of anxiety and depression on kinesiophobia.

Results: The mean age of the 134 patients was 38.3±10.4 years. Fatigue was observed in 60.6% of patients and kinesiophobia in 53.3%. Fatigue was more common among women, patients with higher body mass index, comorbidities, and those on non-steroidal anti-inflammatory drugs (NSAIDs). Patients with fatigue had higher disease activity, worse functional status, and reduced spinal mobility compared to those without fatigue. In multivariate analysis, QoL [odds ratio (OR)=1.36, 95% confidence interval (CI): 1.20-1.53] and erythrocyte sedimentation rate (OR=1.12, 95% CI: 1.00-1.26) were identified as independent predictors of fatigue. TKS score were moderately correlated with several measures of disease activity, functional impairment, and QoL. In multivariate analysis, QoL, anxiety, and NSAIDs use were independent predictors of kinesiophobia. SEM analysis showed that fatigue partially mediated the effects of anxiety on kinesiophobia, highlighting the contribution of psychological distress in movement-avoidance behavior.

Özet

Amaç: Yorgunluk ve kinezyofobi, aksiyel spondiloartrit (axSpA) hastalarında yaygın olup ve hastalık aktivitesi, fonksiyonel bozulma, yaşam kalitesi ve psikolojik faktörlerden etkilenebilir. Bu çalışmanın amacı, axSpA'lı hastalarda yorgunluk ve kinezyofobi sıklığını belirlemek ve bu durumların hastalık aktivitesi, fonksiyonel durum, yaşam kalitesi ve psikolojik faktörlerle ilişkisini değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya 134 axSpA hastası dahil edildi. Yorgunluk, yorgunluk şiddeti ölçeği ile ölçüldü ve kinezyofobi tampa kinezyofobi ölçeği (TKS) ile değerlendirildi. Aynı zamanda, anksiyete ve depresyon düzeyleri de hastane anksiyete ve depresyon ölçeği ile değerlendirildi. Anksiyete ve depresyonun kinezyofobi üzerindeki etkisinde yorgunluğun aracılık rolünü değerlendirmek için yapısal eşitlik modeli (SEM) kullanılmıştır.

Bulgular: Çalışmaya dahil edilen 134 axSpA hastasının ortalama yaşı 38,3±10,4 yıldı. Hastaların %60,6'sında yorgunluk, %53,3'ünde ise kinezyofobi gözlendi. Yorgunluk, kadınlarda, vücut kitle indeksi daha yüksek olanlarda, ek hastalığı (komorbiditesi) bulunanlarda ve non-steroid anti-enflamatuvar ilaç (NSAİİ) kullananlarda daha sık görüldü. Yorgunluk bildiren hastalar, bildirmeyenlere kıyasla daha yüksek hastalık aktivitesi, daha kötü fonksiyonel durum ve azalmış spinal mobilite gösteriyordu. Çok değişkenli analizde, yaşam kalitesi [olasılık oranı (OR)=1,36; %95 güven aralığı (GA): 1,20-1,53] ve eritrosit sedimentasyon hızı (OR=1,12; %95 GA: 1,00-1,26) yorgunluğun bağımsız belirleyicileri olarak saptandı. TKS puanı, hastalık aktivitesi, fonksiyonel bozulma ve yaşam kalitesi ile orta düzeyde koreleydi. Çok değişkenli analizde, yaşam kalitesi, anksiyete ve NSAİİ kullanımı kinezyofobinin bağımsız belirleyicileri olarak kaldı. SEM analizi, yorgunluğun anksiyete ile kinezyofobi arasındaki ilişkiyi kısmen aracıladığını ortaya koydu.

Correspondence / İletişim:
Asst. Prof. Dr. Gülay Alp, Uşak University Faculty of Medicine, Department of Internal Medicine, Uşak, Türkiye
E-mail: gulay_alp88@hotmail.com **ORCID ID:** orcid.org/0000-0003-1908-8439
Received / Geliş Tarihi: 30.05.2025 **Accepted / Kabul Tarihi:** 14.07.2025 **Publication Date / Yayın Tarihi:** 31.07.2025

Cite this article as / Atıf: Alp G, Sari F. Fatigue and kinesiophobia in axial spondyloarthritis: exploring the role of disease activity, functional impairment, and psychological factors. J Turk Soc Rheumatol. 2025;17(2):107-119

Abstract

Conclusion: Fatigue and kinesiophobia are highly prevalent in axSpA and are closely linked to disease burden and emotional distress. These findings underscore the importance of addressing psychological factors to improve functional outcomes in axSpA.

Keywords: Axial spondyloarthritis, anxiety, depression, fatigue, quality of life, kinesiophobia

Öz

Sonuç: Yorgunluk ve kinezyofobi, axSpA'da oldukça yaygındır ve hastalık yükü ile duygusal sıkıntı ile yakından ilişkilidir. Bulgularımız, yalnızca inflamasyonun kontrol altına alınmasının yeterli olmadığını ve axSpA'da yorgunluk ile kinezyofobiyi azaltmak için psikolojik sıkıntıların da ele alınmasının gerekli olduğunu vurgulamaktadır.

Anahtar Kelimeler: Aksiyel spondiloartrit, anksiyete, depresyon, yorgunluk, yaşam kalitesi, kinezyofobi

Introduction

Axial spondyloarthritis (axSpA) is a common inflammatory rheumatic disease that primarily affects the axial skeleton, leading to inflammatory lower back pain and structural and functional impairments, substantially reducing the quality of life (QoL). AxSpA significantly affects both physical and psychological well-being. In patients with axSpA, increased fear of movement (kinesiophobia) secondary to pain and secondary mood disorders cause pain to be felt more. These psychological conditions can intensify the perception of pain, creating a vicious cycle of physical and mental distress. Cluster analyses reveal that depression is one of the most common comorbidities in axSpA, alongside anxiety, both of which correlate with poorer health outcomes and more severe disease symptoms.[1] More than half of patients with axSpA experience fatigue, with poorer QoL being associated with more fatigue.[2]

To assess disease activity and functional impairment in axSpA, the bath ankylosing spondylitis disease activity index (BASDAI) and the bath ankylosing spondylitis functional index (BASFI) are widely used.[3] These indices, however, include subjective measures such as morning stiffness, pain, and fatigue symptoms that psychological factors like anxiety and depression can heavily influence. Fatigue, in particular, is a critical component of the BASDAI and has been shown to significantly affect disease activity scores and influence treatment decisions. It is one of the most debilitating symptoms reported by axSpA patients, often persisting despite therapeutic advances. Reddy et al.[4] found that nearly one-third of axSpA patients exhibit clinically significant anxiety and depression, with younger age at disease onset, higher disease activity, sleep disturbances, fatigue, lower QoL, and reduced work productivity being significant contributing factors.

Psychological factors, such as anxiety and depression, can further exacerbate the disease burden in axSpA, influencing both the perception of pain and overall disease progression. The relationship between fatigue and psychological factors in axSpA has been highlighted in several studies. Fatigue is often linked to demographic factors such as age, female gender, ethnicity, higher body mass index (BMI), and lower socioeconomic status.[5-7] While the introduction of biological treatments such as tumor necrosis factor-alpha (TNF-α) inhibitors has led to significant improvements in disease management, including reductions in inflammation and pain, the persistence of fatigue in a substantial proportion of patients remains a challenge. Bedaiwi et al.[8] demonstrated that although TNF-α inhibitors effectively reduce fatigue in many patients, many continue to experience severe fatigue post-treatment. Similarly, Bixio et al.[9] found that 44.5% of axSpA patients reported fatigue despite being on effective treatment.

Given these complexities, the 2023 European Alliance of Associations for Rheumatology recommendations for managing axSpA emphasize a comprehensive approach that integrates pharmacological treatments with physical and psychoeducational interventions. These guidelines suggest the use of anti-inflammatory therapies, such as non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs, and biologics, including TNF-α inhibitors, interleukin-17, and Janus tyrosine kinase inhibitors, in combination with tailored non-pharmacological interventions. Addressing psychological factors, particularly anxiety and depression, is critical for breaking the cycle of physical and emotional suffering in axSpA patients.[10]

The primary objective of this cross-sectional study was to assess the prevalence of fatigue and kinesiophobia in patients with axSpA and their association with disease activity and QoL. The secondary objective was to explore the relationship between psychological factors, particularly anxiety and depression, with fatigue and kinesiophobia.

Materials and Methods

Study Design and Participants

This observational cross-sectional study was conducted at the rheumatology outpatient clinic between March 2024 and June 2024. Patients between the ages of 18 and 65 years diagnosed with ankylosing spondylitis (AS) according to the modified New York Criteria[11] and axSpA meeting

the Assessment of SpondyloArthritis International Society classification criteria were included in the study.[12] A total of 134 patients with axSpA participated in the study. All questionnaires were self-administered by patients in a quiet, private setting at the clinic. To ensure data accuracy, patients were instructed to complete each questionnaire, and staff members verified the completeness of responses before submission. Trained staff were available to assist patients if needed. Completed questionnaires were reviewed for missing or inconsistent responses, and any discrepancies were resolved through direct communication with the patient. The timing of all assessments (clinical evaluations, laboratory measurements, and psychological assessments) was synchronized to occur at a single visit.

Data Collection

Disease activity was assessed using the BASDAI and AS disease activity score with C-reactive protein (ASDAS-CRP), functional status using the BASFI, spinal mobility using the Bath AS metrology index (BASMI), and QoL using the AS quality of life questionnaire (ASQoL). Weight and height were measured, and BMI was calculated. Duration of disease (years), symptom duration, age of diagnosis, acute phase reactants [the erythrocyte sedimentation rate (ESR), CRP mg/dL], and human leukocyte antigen (HLA)-B27 status were recorded.[13]

Comorbidity data and current medication were collected through a combination of medical history review and patient reported questionnaires. Fibromyalgia was diagnosed based on the 2016 revision of the American College of Rheumatology criteria, which requires the presence of generalized pain in at least four offive regions, a symptom severity score, and symptoms persisting for at least three months.[14]

Leeds enthesitis index (LEI) score was used for enthesial involvement. The LEI was initially developed to assess enthesitis in psoriatic arthritis. However, its application has been extended to other forms of spondyloarthritis, including axSpA, due to its simplicity and relevance to commonly affected enthesitis sites in axSpA.[15] Scores greater than or equal to one enthesitis were considered present. The BASMI was used to assess spinal mobility in patients with AS. It consists of five physical measurements: cervical rotation, tragus-to-wall distance, lateral lumbar flexion, modified Schober's test, and intermalleolar distance. Cervical rotation measures the degree of neck rotation, while tragus-to-wall distance assesses the distance between the ear tragus and the wall when standing. Lateral lumbar flexion measures the bending distance at the waist, modified Schober's test reflects lumbar spine flexibility during forward flexion, and intermalleolar distance measures the distance between the ankles during maximal hip abduction. For cervical rotation, lumbar side flexion, and tragus-to-wall distance, the mean of the left and right measurements was taken, and all scores were converted according to the BASMI 10 scoring system.[16] Each test is scored from 0 to 10, with higher scores indicating more significant mobility impairment. The overall BASMI score is the average of the five individual scores.[17]

ASDAS-CRP score was calculated. The interpretation of the cut-off values for these two measures is <1.3 for "inactive disease", 1.3 to 2 for "low activity", 2.1 to 3.5 for "high activity", and >3.5 for "very high activity".[18] ASQoL is a validated and reliable tool widely used to measure patients' QoL with AS. It consists of 18 questions covering several aspects of daily life, such as mobility, self-care, and social participation.[19]

Psychological Assessment Protocols

Anxiety and depression were assessed using the hospital anxiety and depression scale (HADS), a tool that measures both anxiety and depression symptoms. Symptoms of anxiety and depression were categorized as moderate-severe (≥11), mild (8-10), and none (<8).[20] The fatigue severity scale (FSS) indices were used for fatigue assessment. This scale is designed to measure the severity of fatigue and its impact on daily activities. The FSS is a validated and reliable tool with nine items rated on a 7-point scale. The total FSS score ranges from 9 to 63, but the final score is expressed as the mean (1 to 7) of all items. Higher scores indicate more severe fatigue and a score of ≥4 suggests the presence of fatigue.[21]

The tampa scale for kinesiophobia (TSK) was used to assess kinesiophobia in patients. This scale consists of 17 items, with a four-point Likert scale ranging from 1 (I fully disagree) to 4 (I fully agree). Higher scores reflect greater levels of kinesiophobia. A score of >37 was classified as high kinesiophobia. In contrast, a score of ≤37 was classified as low kinesiophobia.[22] The Turkish versions of the FSS, TKS, and HADS used in this study have been previously validated for reliability and cultural relevance in the Turkish population.[21-23]

Statistical Analysis

The statistical analysis was conducted using both SPSS version 25 and lavaan in R to support a combination of traditional statistical tests and structural equation modeling (SEM). The normality of quantitative variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Variables with a normal distribution are presented as mean ± standard deviation (SD), while those with a non-normal

distribution are presented as median [interquartile range (IQR)]. The Mann-Whitney U test was used for comparisons between two groups of continuous variables, and the chi-square or Fisher's exact test was performed to compare categorical variables. The relationships between different variables were analyzed using the Spearman correlation test. Backward stepwise regression analyses were conducted to investigate which factors are associated with fatigue and kinesiophobia.

Subsequently, SEM was used to evaluate mediation pathways between anxiety, depression, fatigue, and kinesiophobia. The SEM model was built with maximum likelihood (ML) estimation. Indirect effects were calculated, and total effects were assessed for both anxiety and depression.

Post-hoc power analysis for the study's sample size was performed using G*Power 3.1.9.2 software. Fatigue was chosen for post-hoc analysis using the independent samples t-test. The study's power was sufficient (1-β>95%, α=0.05; d=1.20; df=130).

Ethical Approval

The Bingöl University Health Sciences Scientific Research and Publication Ethics Committee obtained the study's ethical approval (date of approval: 07.05.2024, number: 24/10). Written informed consent was obtained from all participants before study enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

A total of 134 patients with axSpA were included in the study. The mean age was 38.3±10.4 years, and the mean BMI was 26.6±4.3 kg/m². The median symptom duration was 7 years (IQR 8), and the median disease duration was 6 years (IQR 8). Of the participants, 50.7% were male, and 42.5% were current smokers. At least one comorbidity was present in 28.4% of patients, with depression being the most common comorbidity (16%), followed by hypertension (5.2%) and thyroid disease (4.5%). The median ESR was 8 mm/h (IQR 6), and the median CRP level was 4.2 mg/L (IQR 6.9). The mean hemoglobin level was 14.2±1.7 g/dL (Table 1).

Patients receiving biological therapy (50.7%) were older, had longer disease duration, and were more likely to have radiographic axSpA and HLA-B27 positivity compared to those not receiving biologics. Current smoking was less common among biologic users, and anterior uveitis was observed exclusively in this group. Despite these differences, there were no significant between-group differences in disease activity (BASDAI), functional status (BASFI), anxiety, depression, or kinesiophobia. However, fatigue prevalence was slightly higher among patients not receiving biological therapy (68.2% vs. 51.5%, p=0.049).

Fatigue Analysis

Clinically relevant fatigue (FSS ≥4) was observed in 60.6% of axSpA patients. Fatigue was more common in women (76.5%) than in men (42.4%) (p<0.001). The patients with fatigue had a higher mean BMI (27.6±5.1 vs.

Table 1 . Demographic, clinical and disease activity characteristics of axSpA patients

Variables	n=134	Variables	n=134
Sex, male, n (%)	68 (50.7)	ESR mm/h, median (IQR)	8 (6)
Age, years, mean ± SD	38.3 (10.4)	CRP mg/L, median (IQR)	4.2 (6.9)
Current smoker, n (%)	57 (42.5)	Hb mg/L, mean ± SD	14.2 (1.7)
Currently employed, n (%)	74 (55.6)	History of anterior uveitis, n (%)	9 (6.7)
Symptom duration, years, median (IQR)	7 (8)	BASDAI, mean ± SD	4.3 (2.1)
Disease duration, years, median (IQR)	6 (8)	BASFI, mean ± SD	2.9 (2.3)
AxSpA type, r-axSpA, n (%)	81 (60.4)	ASDAS-CRP, mean ± SD	2.6 (0.9)
HLA-B27 positive, n (%)	45 (47.4)	ASQoL, mean ± SD	7.9 (5.4)
BMI, kg/m², mean ± SD	26.6±4.3	LEI ≥1, n (%)	40 (30.3)
Comorbidity, at least one, n (%)	38 (28.4)	BASMI, median (IQR)	3.29 (1.45)
Fibromyalgia, n (%)	12 (9)	Fatigue, n (%)	80 (59.7)
Spondyloarthritis family history, n (%)	40 (29.9)	Kinesiophobia, n (%)	65 (53.3)
NSAID, n (%)	101 (75.4)	HADS anxiety, n (%)	27 (20.1)
Biological therapy, n (%)	68 (50.7)	HADS depression, n (%)	22 (16.4)

AxSpA: Axial spondyloarthritis, ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, cm: Centimeters, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, HLA: Human leukocyte antigen, IQR: Interquartile range, LEI: Leeds enthesitis index, r-axSpA: Radiographic axial spondyloarthritis, SD: Standard deviation

25.2±3.3, p=0.002) and more frequent comorbidities (37.5% vs. 14.8%, p=0.004). Fibromyalgia was more common in patients with fatigue (13.8% vs. 1.9%, p=0.027), and they had significantly lower hemoglobin levels (13.8±1.74 g/dL vs. 14.7±1.47 g/dL, p=0.001). ESR was higher in patients with fatigue (median 9 mm/h vs. 7.5 mm/h, p=0.010), whereas CRP levels were similar between the two groups. No significant differences were observed in symptom duration, disease duration, or HLA-B27 positivity between patients with and without fatigue. Fatigue was more prevalent in without biological therapy and less frequent in patients on biological therapy, though the difference was not statistically significant (p=0.066). No significant differences were found in peripheral arthritis, uveitis, enthesitis, family SpA history, or joint limitations. Anxiety (30% vs. 5.6%, p=0.001) and depression (26.3% vs. 1.9%, p=0.009) were significantly more prevalent in patients with fatigue (Table 2).

The patients with fatigue also exhibited higher disease activity and worse functional impairment. BASMI scores indicated reduced spinal mobility in patients with fatigue (median 3.4 vs. 3, p=0.030). FSS scores showed moderate to strong correlations with disease activity, functional impairment, and quality of life. Specifically, significant correlations were observed with BASDAI (r=0.592), BASFI (r=0.631), ASQoL (r=0.701), and ASDAS-CRP (r=0.455), all p-values <0.001. Weak but significant correlations were noted with BASMI total scores (r=0.271, p=0.002) and lateral lumbar flexion (r=0.234, p=0.009). Additionally, FSS scores were weakly correlated with BMI (r=0.231, p=0.007) and hemoglobin levels (r=-0.255, p=0.003), while no significant correlation was found with ESR or CRP. Strong correlations with HADS anxiety (r=0.552) and HADS depression (r=0.457) further highlight the psychological impact on fatigue (p-values <0.001) (Figure 1).

In the univariate analysis, several factors were significantly associated with fatigue, including sex, BMI, ASQoL, BASDAI, BASFI, fibromyalgia, ESR, and the presence of anxiety, depression, and kinesiophobia. In the multivariate analysis, ASQoL (OR=1.406, 95% CI: 1.233-1.604, p<0.001) and ESR (OR=1.117, 95% CI: 1.001-1.264, p=0.048) were identified as independent factors associated with fatigue (Table 3).

Kinesiophobia Analysis

Kinesiophobia analysis was based on 122 patients for whom complete TSK data were available. Among them, 65 (53.3%) were classified as having kinesiophobia. Patients with kinesiophobia had significantly higher disease activity and worse functional outcomes. BASMI scores were marginally higher in patients with kinesiophobia. Anxiety, depression, and fatigue were also significantly more prevalent in patients with kinesiophobia (Table 4). TKS scores showed moderate significant correlations with BASDAI (r=0.367), ASDAS-CRP (r=0.368), BASFI (r=0.364), and ASQoL (r=0.519), all p-values <0.001. Weak but significant correlations were noted between kinesiophobia and BASMI scores (r=0.186, p=0.048), lateral lumbar flexion (r=-0.257, p=0.006), and intermalleolar distance (r=-0.268, p=0.004) (Figure 1).

Table 2. Comparison of disease characteristics, activity, functionality, comorbidity, depression, and anxiety in axSpA patients with and without fatigue

Variables	With fatigue (n=80)	Without fatigue (n=54)	p-value
Sex, female, n (%)	52 (65)	16 (29.6)	**<0.001**
Age, years, mean ± SD	39.9 (11.5)	37 (8.7)	0.096
Current smoker, n (%)	37 (46.3)	20 (37)	0.290
Currently employed, n (%)	36 (45)	38 (71.7)	**0.002**
Marital status, married, n (%)	62 (79.5)	36 (66.7)	0.158
Symptom duration, years, median (IQR)	6 (8)	10 (7)	0.141
Disease duration, years, median (IQR)	4 (7)	6 (10)	0.201
AxSpA type, r-axSpA, n (%)	45 (56.3)	36 (66.7)	0.226
HLA-B27 positive, n (%)	22 (40)	23 (57.5)	0.092
BMI, kg/m^2, mean ± SD	27.6±5.1	25.2±3.3	**0.002**
At least one comorbidity, n (%)	30 (37.5)	8 (14.8)	**0.004**
Fibromyalgia, n (%)	11 (13.8)	1 (1.9)	**0.027**
Spondyloarthritis family history, n (%)	25 (31.3)	15 (27.8)	0.667
NSAID, n (%)	66 (82.5)	35 (64.8)	**0.020**
Biological therapy, n (%)	35 (44.9)	33 (63.1)	0.066
Swollen joint count, (0-66) median (IQR)	0 (0)	0 (0)	0.094
Tender joint count, (0-68) median (IQR)	0 (2)	0 (1)	0.019
LEI ≥1, n (%)	28 (35.9)	12 (22.2)	0.093
ESR mm/h, median (IQR)	9 (7)	7.5 (4)	**0.010**
CRP mg/L, median (IQR)	3.9 (7.2)	3.93 (6.8)	0.235
Hb mg/L, mean ± SD	13.8±1.74	14.7±1.47	0.001
ASQoL, median (IQR)	2.98 (0.9)	2.27 (0.8)	<**0.001**
BASDAI, mean ± SD	5.19±1.9	3.12±1.9	<**0.001**
ASDAS-CRP, mean ± SD	2.9±0.9	2.2±0.8	<**0.001**
BASFI, mean ± SD	4.01±2.2	1.58±1.7	<**0.001**
BASMI, median (IQR)	3.4 (1.2)	3 (1.6)	**0.030**
Kinesiophobia, n (%)	49 (65.3)	16 (34)	**0.001**
HADS anxiety, n (%)	24 (30)	3 (5.6)	**0.001**
HADS depression, n (%)	21 (26.3)	1 (1.9)	**0.009**

AxSpA: Axial spondyloarthritis, ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, cm: Centimeters, ESR: Erythrocyte sedimentation rate, HADS: Hospital anxiety and depression scale, Hb: Hemoglobin, HLA: Human leukocyte antigen, LEI: Leeds enthesitis index, SD: Standard deviation, NSAID: Non-steroidal anti-inflammatory drugs, r-axSpA: Radiographic axial spondyloarthritis, TKS: Tampa kinesiophobia scale

Table 3. Evaluation of factors affecting fatigue in unadjusted and multivariable analysis

	Unadjusted analysis			Multivariable analysis (backward stepwise regression)			
Variables	OR	Lower-upper 95% CI	p-value	Odds ratio	Lower 95% CI	Upper 95% CI	p-value
Age, years	1.028	0.993-1.064	0.117				
Sex, female, n (%)	4.441	2.098-9.274	<0.001				
Disease duration, years	0.964	0.910-1.020	0.206				
Body mass index, kg/m²	1.132	1.037-1.236	0.006				
ASQol	1.398	1.252-1.561	<0.001	1.361	1.208	1.533	**<0.001**
BASDAI, active disease	6.988	3.231-15.112	<0.001				
BASFI	1.841	1.456-2.329	<0.001				
BASMI	1.248	0.959-1.624	0.099				
ASDAS, active disease	3.678	1.693-7.792	0.001				
ESR, mm/h	1.131	1.042-1.227	0.003	1.117	1.001	1.264	**0.048**
CRP, mg/L	1.041	0.985-1.099	0.151				
Hb, mg/L	0.693	0.550-0.874	0.002				
Depression, present	18.864	2.453-145.092	0.005	8.731	.887	85.986	0.063
Anxiety, present	7.286	2.069-25.653	0.002				
Kinesiophobia, present	3.651	1.694-7.872	0.001				
At least one comorbidity	3.450	1.436-8.290	0.006				
Fibromyalgia, present	8.449	1.057-67.509	0.044				
NSAID, yes/no	2.559	1.147-5.712	0.022				
Biological therapy, yes/no	0.495	0.245-1.000	0.050				

ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, CI: Confidence interval, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HADS: Hospital anxiety and depression scale, Hb: Hemoglobin, NSAID: Non-steroidal anti-inflammatory drugs, OR: Odds ratio

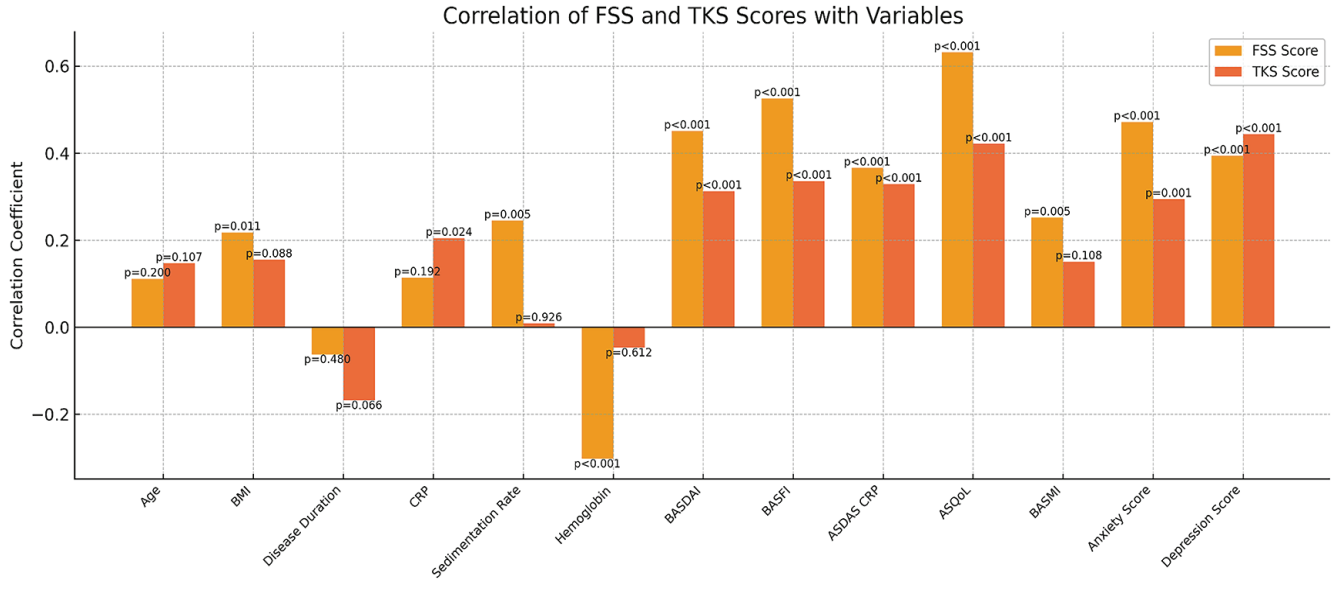

Figure 1. Pearson correlation analysis between FSS and TSK scores and clinical variables in axial spondyloarthritis
This heatmap illustrates the strength and direction of correlations between fatigue (FSS) and kinesiophobia (TSK) scores and a range of clinical and psychosocial parameters, including disease activity indices (BASDAI, ASDAS-CRP), functional impairment (BASFI), spinal mobility (BASMI), quality of life (ASQoL), acute phase reactants (CRP, ESR), hemoglobin levels, body mass index (BMI), anxiety, and depression scores (HADS). Significant associations (p<0.05) are visually indicated

ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, FSS: Fatigue severity scale, HADS: Hospital anxiety and depression scale, TSK: Tampa scale for kinesiophobia

For kinesiophobia, the univariate analysis identified disease duration, BASDAI, BASFI, ASQoL, depression, anxiety, and NSAID use as significant factors. In the multivariate analysis, ASQoL (OR=1.130, 95% CI: 1.022-1.250, p=0.017), anxiety (OR=7.139, 95% CI: 1.538-33.132, p=0.012), and NSAID use (OR=3.204, 95% CI: 1.029-9.981, p=0.045) were identified as independent factors associated with kinesiophobia (Table 5).

Table 4. Comparison of disease characteristics, activity, functionality, comorbidity, depression, and anxiety in axSpA patients with and without kinesiophobia

Variables	With kinesiophobia (n=65)	Without kinesiophobia (n=57)	p
Sex, female, n (%)	34 (52.3)	28 (49.1)	0.726
Age, years, mean ± SD	40.5±11.8	37.1±8.7	0.070
Current smoker, n (%)	30 (46.2)	24 (42.1)	0.653
Symptom duration, years, median (IQR)	6 (6)	8 (8)	0.254
Disease duration, years, median (IQR)	4 (7)	6 (8)	0.276
AS type, r-axSpA, n (%)	36 (55.4)	37 (64.9)	0.284
BMI, kg/m^2, mean ± SD	27.4±5.1	25.9±4.3	0.096
At least one comorbidity, n (%)	23 (35)	12 (21.1)	0.081
NSAID n (%)	57 (87.7)	35 (61.4)	**0.001**
Biological therapy, n (%)	31 (47.7)	30 (52.6)	0.586
Swollen joint count, (0-66) median (IQR)	0 (0)	0 (0)	0.096
Tender joint count, (0-68) median (IQR)	0 (2)	0 (1)	0.126
LEI >1, n (%)	27 (35.5)	12 (22.2)	0.103
ESR mm/h, median (IQR)	9 (7)	8.5 (6)	0.961
CRP mg/L, median (IQR)	5.2 (8.8)	3.58 (5.9)	0.100
Hb mg/L, mean ± SD	13.9±1.7	14.8±1.5	0.588
ASQoL, median (IQR)	10 (9)	4 (8)	<**0.001**
BASDAI, mean ± SD	5.13±1.9	3.12±1.9	**0.001**
ASDAS-CRP, mean ± SD	3.01±0.9	2.37±0.9	**0.001**
BASFI, mean ± SD	3.96±2.2	1.55±1.7	**0.002**
BASMI, median (IQR)	3.3 (1.2)	3.1 (1.7)	**0.038**
Cervical rotation, cm, mean ± SD	64.3±14.2	65.1±17.5	0.778
Tragus-to-wall distance, cm, mean ± SD	16.6±3.2	17.1±5.3	0.635
Lateral lumbar flexion, cm, mean ± SD	13.9±5.2	16.2±10.1	0.123
Modified Schober's test, cm, mean ± SD	4.3±1.4	4.3±1.8	0.974
Intermalleolar distance, cm, mean ± SD	94.2±15.9	100.4±18.3	0.056
Fatigue, n (%)	49 (75.4)	26 (45.6)	**0.001**
HADS anxiety, n (%)	21 (32.3)	4 (7)	**0.001**
HADS depression, n (%)	17 (26.2)	4 (7)	**0.005**

ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath Ankylosing spondylitis metrology index, BMI: Body mass index, CRP: C-reactive protein, HADS: Hospital anxiety and depression scale, Hb: Hemoglobin, IQR: Interquartile range, LEI: Leeds enthesitis index, NSAID: Non-steroidal anti-inflammatory drugs, ESR: Erythrocyte sedimentation rate, r-axSpA: Radiographic axial spondyloarthritis, SD: Standard deviation

Anxiety and Depression

Patients with anxiety or depression showed significantly worse clinical and functional outcomes compared to those without these symptoms. Anxiety and depression were more frequent in patients with higher disease activity, worse functional impairment, lower quality of life, and more significant physical and psychological symptom burden, including fatigue and kinesiophobia. Depression was linked to higher BMI, more comorbidities, and NSAID use (Supplementary Tables 1 and 2).

A mediation analysis was conducted using SEM with the ML estimator on a sample of 120 participants. The model demonstrated an excellent fit to the data. The parameter estimates showed that anxiety had a significant effect on fatigue (β=1.844, SE=0.390, p<0.001), while depression had a marginal effect (β=0.795, SE=0.426, p=0.062). Fatigue, in turn, had a strong direct effect on kinesiophobia (β=0.151, SE=0.042, p<0.001). Depression also directly influenced kinesiophobia with a substantial effect (β=0.703, SE=0.198, p<0.001), whereas anxiety's direct effect on kinesiophobia was not significant (β=0.078, SE=0.194, p=0.689). The analysis further revealed a significant indirect effect of anxiety on kinesiophobia through fatigue (β=0.278, SE=0.097, p=0.004), while the indirect effect of depression on kinesiophobia was not statistically significant (β=0.120, SE=0.072, p=0.098). The total effect of anxiety on kinesiophobia was marginally significant (β=0.356, SE=0.188, p=0.058), whereas the total effect of depression was strongly significant (β=0.823, SE=0.205, p<0.001).

The model explained 31.2% of the variance in fatigue and 33.6% of the variance in kinesiophobia, suggesting that psychological factors such as anxiety and depression play a crucial role in shaping physical outcomes. These findings highlight the mediating role of fatigue in the relationship between psychological distress and movement-related fear, emphasizing the interconnected nature of mental and physical health (Figure 2).

Discussion

Our study highlights the complex and multifaceted nature of fatigue and kinesiophobia in axSpA, emphasizing their strong associations with both physical and psychological factors. Fatigue was present in 60.6% of patients, with multivariate analysis identifying ASQoL and ESR as independent predictors. Patients experiencing fatigue exhibited higher disease activity, greater functional impairment, elevated BMI, increased ESR, more frequent

Table 5. Evaluation of factors affecting kinesiophobia in multivariable analysis

	Unadjusted analysis				Multivariable analysis (backward stepwise regression)			
Variables	OR	Lower 95% CI	Upper 95% CI	p	OR	Lower 95% CI	Upper 95% CI	p
Age, years	1.033	0.997	1070	0.730	1.046	0.998	1.097	0.062
Sex, female vs. male	1.136	0.558	2.315	0.726	0.422	0.151	1.077	0.099
Body mass index, kg/m^2	1.069	0.997	1.106	0.100				
Disease duration, years	0.947	0.888	1.009	0.096				
BASDAI-active disease	1.354	1.131	1.620	0.001				
BASFI	1.278	1.085	1.505	0.003				
ASQoL	1.187	1.1098	1.282	<0.001	1.130	1.022	1.250	**0.017**
BASMI	1.083	0.838	1.400	0.543				
ASDAS- active disease	3.212	1.418	7.278	0.005				
ESR, mm/h	0.992	0.950	1.035	0.700				
CRP, mg/L	1.060	0.998	1.126	0.058				
Hemoglobin, mg/L	0.941	0.757	1.170	0.585				
Depression, present	4.693	1.475	14.926	0.009				
Anxiety, present	6.324	2.019	19.803	0.002	6.641	1.492	29.551	**0.013**
At least one comorbidity	2.054	0.090	4.639	0.083				
NSAID, yes/no	4.479	1.799	11.150	0.001	4.449	1.489	13.412	**0.008**
Biological therapy, yes/no	1.219	0.598	2.484	0.586				

ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, CI: Confidence interval, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, NSAID: Non-steroidal anti-inflammatory drugs, OR: Odds ratio

comorbidities, and lower hemoglobin levels. The association between fatigue and elevated ESR may be partly explained by coexisting anemia and low grade chronic inflammation, both of which contribute to systemic fatigue burden more accurately reflected by ESR than CRP.[8] Furthermore, psychological distress, including anxiety, depression, and kinesiophobia, was significantly more common in fatigued patients, underscoring the need for a comprehensive, multidisciplinary approach to management. Similarly, kinesiophobia was observed in 53.3% of patients and was strongly linked to higher disease activity, worse functional outcomes, and increased psychological distress. Multivariate analysis identified ASQoL, anxiety, and NSAID therapy as independent predictors of kinesiophobia, reinforcing the interplay between disease burden and emotional well-being in axSpA. These findings underscore the necessity of addressing both physical and psychological aspects in clinical care to optimize patient outcomes.

Bixio et al.[9] also highlighted the psychological dimension of fatigue, showing that patients with higher fatigue levels had significantly elevated HADS-D scores alongside higher ASDAS, BASFI, and HAQ scores. Their study identified HADS-D as a significant predictor of fatigue. This supports our findings that psychological distress, especially depression, plays a crucial role in contributing to fatigue in patients with axSpA.[7] Although fibromyalgia was associated with fatigue and kinesiophobia in univariate analysis, it did not remain significant in the multivariate model. This may be due to shared pathways with depression and pain-related disease impact. Further studies with larger samples and subgroup analyses are needed to elucidate its independent contribution to fatigue in axSpA.

Effective fatigue management in axSpA should not only aim at controlling disease activity but also prioritize interventions addressing mental health, particularly depression. A study conducted in France found that fatigue was strongly correlated with increased disease activity, which is consistent with our results.[5] The relationship between activity and fatigue may be because our measures of disease activity include fatigue. Increased inflammatory states may also exacerbate fatigue symptoms, possibly through increased cytokine production and immune dysregulation.

A meta-analysis evaluating fatigue in patients with axSpA from different geographies found a pooled prevalence of 56%, and poor QoL was associated with increased fatigue.[2] This relationship between poor QoL and a similar prevalence of fatigue was also found in our study. While previous studies have reported a high prevalence of fatigue in axSpA, our findings add novelty by identifying ESR as an independent predictor. This suggests that persistent inflammatory activity plays a critical role in fatigue, even in patients undergoing advanced treatment. Despite improvements in disease control with biologics, the persistence of fatigue highlights unmet clinical needs.[9]

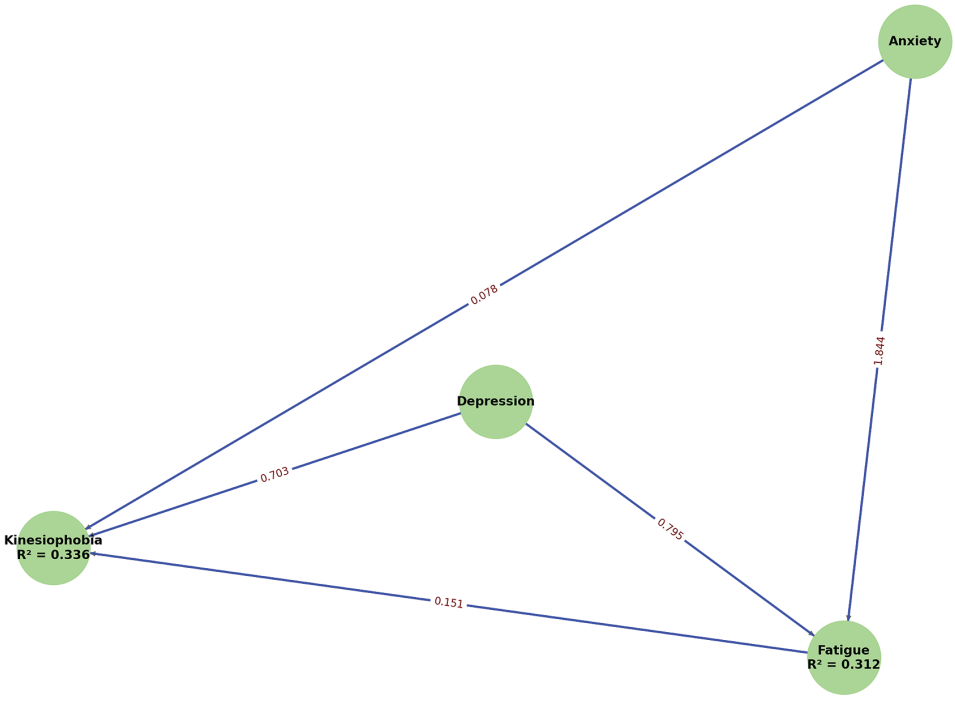

Figure 2. Structural equation model showing the mediating role of fatigue in the relationship between anxiety and kinesiophobia in axial spondyloarthritis The model depicts standardized path coefficients between anxiety, depression, fatigue, and kinesiophobia. Fatigue is shown to partially mediate the relationship between anxiety and kinesiophobia. R^2 values inside each construct represent the proportion of variance explained. Solid arrows represent significant paths ($p<0.05$), and dashed lines represent non-significant associations

Anxiety → Fatigue	(β=1.844, SE=0.390, p<0.001)
Depression → Fatigue	(β=0.795, SE=0.426, p=0.062)
Fatigue → Kinesiophobia	(β=0.151, SE=0.042, p<0.001)
Depression → Kinesiophobia	(β=0.703, SE=0.198, p<0.001)
Anxiety → Kinesiophobia	(β=0.078, SE=0.194, p=0.689)

Reddy et al.[4] reported a high prevalence of anxiety (38%) and depression (36%) among patients with axSpA, with these conditions correlating strongly with younger age at disease onset, elevated disease activity, sleep disturbances, fatigue, and diminished QoL. Similarly, in our study, we found that in patients with anxiety and depression, disease activity, fatigue, and kinesiophobia scores were high, and QoL was poor. Taken together, these findings highlight the intertwined relationship between psychological distress, disease activity, and physical limitations in axSpA, supporting the need for treatment of both psychological and physical symptoms to manage fatigue in these patients.

In a study conducted on AS patients, moderate correlations were observed between kinesiophobia and depression, body awareness and pain catastrophizing and depression, and pain catastrophizing and disease activity.[24] Previous studies, such as those by Oskay et al.,[25] have demonstrated that kinesiophobia negatively impacts QoL in axSpA. Our findings are consistent, highlighting significant correlations between TKS scores, disease activity, QoL, anxiety, and depression. We observed worse disease activity and functional impairment in patients with higher levels of kinesiophobia, though BASMI total scores were higher. However, in another study, no statistically significant relationship was reported between kinesiophobia scores and BASDAI, but there was a weak correlation with BASFI.[25] However, we observed only weak correlations between kinesiophobia and spinal mobility measures, such as BASMI scores and lateral lumbar flexion, contrasting with the stronger associations reported by Er and Angın.[26] These differences may be due to variations in study populations or methodologies. Nevertheless, our results suggest that psychological factors play a more prominent role in kinesiophobia than physical limitations alone.

Our findings demonstrate, for the first time in axSpA, that fatigue mediates the relationship between anxiety and kinesiophobia, reinforcing the hypothesis that psychological distress may amplify physical avoidance behaviors. In our

SEM model, fatigue partially mediated the association between anxiety and kinesiophobia, supporting the role of psychological distress in physical avoidance behaviors. Similarly, Medrado et al.[27] reported that kinesiophobia mediates the relationship between pain and physical dysfunction in inflammatory arthritis, underscoring the psychological dimension. While their study focused on broader inflammatory arthritis, our model provides specific insights into these interactions within the axSpA population, supported by acceptable fit statistics. Our SEM findings emphasize that fatigue and kinesiophobia in axSpA are shaped not only by inflammatory processes but also by psychological distress. These findings support the clinical utility of integrating brief psychological screening (e.g., HADS) into routine care and tailoring interventions such as cognitive-behavioral therapy and physical rehabilitation to address these psychosocial contributors.

In contrast, our multivariate analysis identified ASQoL, anxiety, and NSAID use as independent predictors, suggesting that kinesiophobia in axSpA is not solely driven by physical limitations but also by psychological and treatment-related factors. This highlights the role of fear-avoidance behavior, where anxiety amplifies movement related fears due to pain or disease progression concerns. The association with NSAID use may reflect heightened pain perception or disease activity.These findings underscore the importance of comprehensive management, including gradual physical activity, education on movement safety, and psychological support to address underlying fears and improve functional outcomes. Although NSAID use is not a known driver of fatigue or kinesiophobia, its association in our study may reflect ongoing symptoms in patients who rely solely on NSAIDs due to limited access to or delay in initiating biologic therapy. While biologics are effective in suppressing inflammation, they may not fully address fatigue and kinesiophobia, particularly in patients with irreversible structural damage or comorbid fibromyalgia. These residual symptoms highlight the need for comprehensive symptom management beyond inflammation control.

Study Limitations

Our study has several limitations. First, its cross-sectional design limits our ability to infer causality between fatigue, kinesiophobia, and disease-related factors, underscoring the need for longitudinal research. Second, while our sample size was sufficient for primary analyses, it may have been underpowered to detect smaller associations in specific subgroups. Third, although self-reported measures are essential for capturing subjective experiences such as anxiety, depression, and kinesiophobia, we acknowledge that these tools provide only a screening, not a clinical diagnosis. The absence of formal psychiatric evaluations is a limitation, as definitive diagnoses of anxiety and depression require clinical assessment. Lastly, the lack of a control group restricts our ability to draw broader comparisons with other populations or disease groups.

Conclusion

In conclusion, fatigue and kinesiophobia in axSpA reflect complex interactions between physical and psychological domains. Addressing disease activity, comorbidities, and mental health—especially anxiety and depression may improve outcomes. Multidisciplinary approaches, including psychological support and physical rehabilitation, are essential for managing these burdensome symptoms.

Ethics

Ethics Committee Approval: The Bingöl University Health Sciences Scientific Research and Publication Ethics Committee obtained the study's ethical approval (date of approval: 07.05.2024, number: 24/10).

Informed Consent: Written informed consent was obtained from all participants before study enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., Concept: G.A., F.S., Design: G.A., F.S., Data Collection and Processing: G.A., F.S., Analysis or Interpretation: G.A., Literature Search: G.A., Writing: G.A.

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. Zhao SS, Radner H, Siebert S, et al. Comorbidity burden in axial spondyloarthritis: a cluster analysis. Rheumatology (Oxford). 2019;58:1746-54.
2. Tang H, Singh BSM, Fong W. Prevalence and factors associated with fatigue in patients with axial spondyloarthritis: a systematic review and meta-analysis. Rheumatol Adv Pract. 2023;7:rkad084.
3. Zochling J. Measures of symptoms and disease status in ankylosing spondylitis: ankylosing spondylitis disease activity score (ASDAS), ankylosing spondylitis quality of life scale (ASQoL), bath ankylosing spondylitis disease activity index (BASDAI), bath ankylosing spondylitis functional index (BASFI), bath ankylosing spondylitis global score (BAS-G), bath ankylosing spondylitis metrology index (BASMI), dougados functional index (DFI), and health assessment questionnaire for the spondylarthropathies

(HAQ-S). Arthritis Care Res (Hoboken). 2011;63(Suppl 11):S47-58.

4. Reddy KN, Sabu N, Pandey N, Raut A, Joag K, Patil P. Anxiety and depression among patients with axial spondyloarthritis. Eur J Rheumatol. 2022;9:8-13.
5. Gossec L, Dougados M, D'Agostino MA, Fautrel B. Fatigue in early axial spondyloarthritis. Results from the French DESIR cohort. Joint Bone Spine. 2016;83:427-31.
6. Roussou E, Kennedy LG, Garrett S, Calin A. Socioeconomic status in ankylosing spondylitis: relationship between occupation and disease activity. J Rheumatol. 1997;24:908-11.
7. Zhou W, Guo J, He M, et al. Fatigue and contributing factors in Chinese patients with ankylosing spondylitis. Clin Rheumatol. 2020;39:2337-44.
8. Bedaiwi M, Sari I, Thavaneswaran A, Ayearst R, Haroon N, Inman RD. Fatigue in ankylosing spondylitis and nonradiographic axial spondyloarthritis: analysis from a longitudinal observation cohort. J Rheumatol. 2015;42:2354-60.
9. Bixio R, Bonetto C, Fracassi E, et al. Depression as a possible determinant of fatigue in patients with axial spondyloarthritis. Clin Exp Rheumatol. 2024;42:1015-9.
10. Dures E, Farisoğulları B, Santos EJF, et al. 2023 EULAR recommendations for the management of fatigue in people with inflammatory rheumatic and musculoskeletal diseases. Ann Rheum Dis. 2024;83:1260-7.
11. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.
12. 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.
13. Lukas C, Landewé R, Sieper J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24.
14. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46:319-29.
15. Palominos PE, de Campos APB, Ribeiro SLE, et al. Correlation of enthesitis indices with disease activity and function in axial and peripheral spondyloarthritis: a cross-sectional study comparing MASES, SPARCC and LEI. Adv Rheumatol. 2019;59:23.
16. Haywood KL, Garratt AM, Jordan K, Dziedzic K, Dawes PT. Spinal mobility in ankylosing spondylitis: reliability, validity and responsiveness. Rheumatology (Oxford). 2004;43:750-7.
17. Castro MP, Stebbings SM, Milosavljevic S, Bussey MD. Construct validity of clinical spinal mobility tests in ankylosing spondylitis: a systematic review and meta-analysis. Clin Rheumatol. 2016;35:1777-87.
18. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:1811-8.
19. Doward LC, Spoorenberg A, Cook SA, et al. Development of the ASQoL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis. 2003;62:20-6.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361-70.
21. Armutlu K, Korkmaz NC, Keser I, et al. The validity and reliability of the Fatigue severity scale in Turkish multiple sclerosis patients. Int J Rehabil Res. 2007;30:81-5.
22. Yilmaz ÖT, Yakut Y, Uygur F, Ulug N. Turkish version of the tampa scale for kinesiophobia and its test-retest reliability. Accessed January 23, 2024. https://www.researchgate.net/publication/287009550_Turkish_version_of_the_tampa_scale_for_kinesiophobia_and_its_test-retest_reliability
23. Düzce Keleş E, Birtane M, Ekuklu G, et al. Validity and reliability of the Turkish version of the central sensitization inventory. Arch Rheumatol. 2021;36:518-26.
24. Karaca NB, Arin-Bal G, Sezer S, et al. Physical activity, kinesiophobia, pain catastrophizing, body awareness, depression and disease activity in patients with ankylosing spondylitis and rheumatoid arthritis: a cross-sectional explorative study. Musculoskeletal Care. 2024;22.
25. Oskay D, Tuna Z, Düzgün İ, Elbasan B, Yakut Y, Tufan A. Relationship between kinesiophobia and pain, quality of life, functional status, disease activity, mobility, and depression in patients with ankylosing spondylitis. Turk J Med Sci. 2017;47:1340-7.
26. Er G, Angın E. Determining the relationship of kinesiophobia with respiratory functions and functional capacity in ankylosing spondylitis. Medicine (Baltimore). 2017;96:e7486.
27. Medrado LN, Oliveira-Junior SA, Martinez PF. The mediating role of kinesiophobia in pain intensity, physical function, and physical activity level in inflammatory arthritis. Int J Rehabil Res. 2024;47:252-9.

Supplementary Table 1. Demographic, clinical and disease activity characteristics of axSpA patients with and without anxiety

Variables	With anxiety (n=27)	Without anxiety (n=107)	p-value
Sex, male, n (%)	17 (63)	51 (47.7)	0.155
Age, years, mean ± SD	35.1 (9.6)	39.6 (10.6)	0.053
Current smoker, n (%)	13 (48.1)	44 (44.1)	0.509
Currently employed, n (%)	10 (37)	64 (60.4)	**0.029**
Marital status, married, n (%)	62 (79.5)	36 (66.7)	0.158
Symptom duration, years, median (IQR)	6 (7)	8 (8)	0.263
Disease duration, years, median (IQR)	6 (7)	6 (8)	0.984
AxSpA type, r-axSpA, n (%)	12 (44.4)	69 (64.5)	0.057
HLA-B27 positive, n (%)	8 (40)	37 (49.3)	0.458
BMI, kg/m , mean ± SD	28.3±5.4	26.3±4.4	0.091
At least one comorbidity, n (%)	10 (37)	28 (26.2)	0.263
Fibromyalgia, n (%)	7 (25.9)	5 (4.7)	**0.003**
Spondyloarthritis family history, n (%)	7 (25.9)	33 (30.8)	0.618
NSAID, n (%)	22 (81.5)	79 (73.8)	0.410
Biological therapy, n (%)	12 (44.4)	56 (52.3)	0.464
Swollen joint count, (0-66) median (IQR)	0 (0)	0 (0)	0.932
Tender joint count, (0-68) median (IQR)	0 (3)	0 (1)	0.431
LEI ≥1, n (%)	28 (35.9)	12 (22.2)	0.093
ASQoL, median (IQR)	11.9 (4.5)	7.1 (5.3)	<**0.001**
BASDAI, mean ± SD	5.9 (1.9)	3.9 (2.1)	<**0.001**
ASDAS-CRP, mean ± SD	3.3 (0.9)	2.5 (0.9)	<**0.001**
BASFI, mean ± SD	4.01 (2.2)	1.58 (1.7)	<**0.001**
BASMI, median (IQR)	3.1 (1.5)	3 (1.6)	0.223
Kinesiophobia, n (%) n=122	21 (84)	44 (45.4)	**0.001**
Fatigue, n (%)	24 (88.9)	56 (52.3)	**0.001**
HADS depression, n (%)	13 (48.1)	9 (8.4)	<**0.001**

ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, HADS: Hospital anxiety and depression scale, Hb: Hemoglobin, HLA: Human leukocyte antigen, IQR: Interquartile range, LEI: Leeds enthesitis index, r-axSpA: Radiographic axial spondyloarthritis, SD: Standard deviation

Supplementary Table 2. Demographic, clinical and disease activity characteristics of axSpA patients with and without depression

Variables	With depression (n=22)	Without depression (n=112)	p-value
Sex, male, n (%)	13 (59.1)	55 (49.1)	0.392
Age, years, mean ± SD	40.6 (10.8)	38.4 (10.4)	0.336
Current smoker, n (%)	10 (45)	47 (42)	0.762
Currently employed, n (%)	10 (45.5)	64 (57.7)	0.293
Marital status, married, n (%)	62 (79.5)	36 (66.7)	0.158
Symptom duration, years, median (IQR)	8 (13)	7 (8)	0.697
Disease duration, years, median (IQR)	6 (12)	6 (6)	0.581
AxSpA type, r-axSpA, n (%)	10 (45.4)	71 (63.4)	0.116
HLA-B27 positive, n (%)	5 (3.3)	40 (50)	0.235
BMI, kg/m^2, mean ± SD	28.9±6.7	26.2±4.4	**0.011**
At least one comorbidity, n (%)	11 (50)	27 (24.1)	**0.014**
Fibromyalgia, n (%)	4 (18.2)	8 (7.1)	0.097
Spondyloarthritis family history, n (%)	7 (31.8)	33 (29.5)	0.825
NSAID, n (%)	21 (95.5)	80 (71.4)	**0.017**
Biological therapy, n (%)	10 (45.5)	58 (51.8)	0.587
Swollen joint count, (0-66) median (IQR)	0 (0)	0 (0)	0.902
Tender joint count, (0-68) median (IQR)	0 (3)	0 (1)	0.431
LEI ≥1, n (%)	28 (35.9)	12 (22.2)	0.093
ASQoL, median (IQR)	11.9 (4.5)	7.1 (5.3)	0.001
BASDAI, mean ± SD	5.6 (2.3)	4.1 (2.1)	<**0.001**
ASDAS-CRP, mean ± SD	2.57 (0.9)	3.34 (0.9)	**0.001**
BASFI, mean ± SD	4.37 (2.4)	2.77 (2.2)	**0.004**
BASMI, median (IQR)	3.4 (1.5)	2.9 (1.6)	0.241
Kinesiophobia, n (%) n=122	17 (81)	48 (47.5)	**0.005**
Fatigue, n (%)	21 (95.5)	59 (52.7)	**0.001**
HADS Anxiety, n (%)	13 (59.1)	14 (12.5)	<**0.001**

ASDAS-CRP: Ankylosing spondylitis disease activity score with C-reactive protein, ASQoL: Ankylosing spondylitis quality of life questionnaire, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BASMI: Bath ankylosing spondylitis metrology index, BMI: Body mass index, ESR: Erythrocyte sedimentation rate, HADS: Hospital anxiety and depression scale, Hb: Hemoglobin, HLA: Human leukocyte antigen, IQR: Interquartile range, LEI: Leeds enthesitis index, r-axSpA: Radiographic axial spondyloarthritis, SD: Standard deviation

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

Derleme / Review

DOI: 10.4274/raed.galenos.2025.69672
Ulus Romatol Derg 2025;17(2):120-130

Sistemik lupus eritematozusta acil durumlar

Emergencies in systemic lupus erythematosus

Senem Tekeoğlu[1], Gökhan Keser[2]

[1]Haliç Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul, Türkiye
[2]Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir, Türkiye

Özet

Sistemik lupus eritematozus (SLE), çoklu organ tutulumu ile seyreden kronik otoimmün bir hastalıktır. Hastalık remisyon ve alevlenmelerle dalgalı bir seyir gösterebilirken, ağır tutulumlar ve immünosupresif tedavilere bağlı komplikasyonlar acil servise başvuruların önemli nedenleri arasındadır. Nefrolojik, nörolojik, pulmoner ve hematolojik tutulumlar acil müdahale gerektirebilir. Lupus nefriti, trombotik mikroanjiyopati ve antifosfolipid sendromu gibi durumlar, renal disfonksiyon ile seyrederek ciddi sonuçlar doğurabilir. Nörolojik komplikasyonlar arasında inme, nöbetler, nöropsikiyatrik lupus ve santral sinir sistemi vasküliti yer alır. Pulmoner aciller arasında akut lupus pnömoniti, diffüz alveolar hemoraji ve pulmoner emboli öne çıkarken, kardiyak tutulumda perikardit, miyokardit ve hızlanmış ateroskleroz görülebilir. Ayrıca otoimmün hemolitik anemi, trombositopeni ve makrofaj aktivasyon sendromu gibi hematolojik komplikasyonlar, yüksek mortalite ile ilişkilidir. Enfeksiyonlar, immünosupresyon altındaki hastalarda sık görülür ve hastalık alevlenmesi ile karışabilir. Gebelikte ise preeklampsi, Hemoliz, Yüksek Karaciğer enzimleri, Düşük Trombositler (*Hemolysis, Elevated Liver enzymes, Low Platelets*) sendromu, neonatal lupus ve antifosfolipid sendromuna bağlı komplikasyonlar gelişebilir. SLE'ye bağlı acil durumların yönetimi multidisipliner bir yaklaşım gerektirir. Güncel kılavuzlara uygun bireyselleştirilmiş tedavi ve erken müdahale, mortaliteyi azaltmak için kritik öneme sahiptir.

Anahtar Kelimeler: Sistemik lupus eritematozus, acil tedavi, çoklu organ yetmezliği

Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multi-organ involvement, characterized by periods of remission and flares. Severe disease manifestations and complications of immunosuppressive therapy are common reasons for emergency department visits. Nephrological, neurological, pulmonary, and hematological involvement may require urgent intervention. Lupus nephritis, thrombotic microangiopathy, and antiphospholipid syndrome can cause significant renal dysfunction. Neurological complications include stroke, seizures, neuropsychiatric lupus, and central nervous system vasculitis. Pulmonary emergencies such as acute lupus pneumonitis, diffuse alveolar hemorrhage, and pulmonary embolism are life-threatening, while cardiac involvement includes pericarditis, myocarditis, and accelerated atherosclerosis. Hematologic complications, including autoimmune hemolytic anemia, thrombocytopenia, and macrophage activation syndrome, are associated with high mortality. Infections are common in immunosuppressed patients and can mimic disease flares. During pregnancy, complications such as preeclampsia, Hemolysis, Elevated Liver enzymes, Low Platelets syndrome, neonatal lupus, and antiphospholipid syndrome-related thrombosis may arise. The management of SLE emergencies requires a multidisciplinary approach. Individualized treatment strategies following current guidelines and early intervention are crucial in reducing mortality.

Keywords: Systemic lupus erythematosus, emergency treatment, multiple organ failure

Giriş

Sistemik lupus eritematozus (SLE), genetik yatkınlık, çevresel faktörler ve hormonal etmenlerin karmaşık etkileşimi sonucunda gelişen, otoantikor aracılı doku hasarı ile karakterize kronik otoimmün bir hastalıktır. Deri, böbrekler, sinir sistemi ve akciğerler başta olmak üzere çok sayıda organı etkileyerek geniş bir klinik spektrum sergiler. SLE'de acil durumların yönetimi, hastalığın ağır atakları, ciddi organ tutulumları veya kullanılan immünosupresif tedavilerin komplikasyonları hayati risk taşıdığı için kritik öneme sahiptir.[1,2] Lupus nefriti (LN), santral sinir sistemi (SSS) tutulumu ve pulmoner komplikasyonlar, hızlı müdahale gerektiren başlıca klinik durumlar arasında yer alırken, immünosupresyon altındaki hastalarda enfeksiyon riski artarak hastalığın yönetimini daha da karmaşık hale getirmektedir.[3,4]

İletişim / Correspondence:
Doç. Dr. Senem Tekeoğlu, Haliç Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul, Türkiye
E-posta: senemtekeoglu@gmail.com **ORCID ID:** orcid.org/0000-0001-5539-8755
Geliş Tarihi / Received: 26.02.2025 **Kabul Tarihi / Accepted:** 20.05.2025 **Yayın Tarihi / Publication Date:** 31.07.2025

Atıf / Cite this article as: Tekeoğlu S, Keser G. Emergencies in systemic lupus erythematosus. J Turk Soc Rheumatol. 2025;17(2):120-130

Acil servis başvurularının sıklığı ve nedenleri, SLE hastalarının genel sağlık durumu ve hastalığın yönetimi hakkında önemli ipuçları sağlar. Çoğu başvuru, enfeksiyonlar ve komorbiditelere bağlı olup, doğrudan hastalık alevlenmesi nedeniyle acil servise gelen hasta oranı nispeten düşüktür. Nitekim, yapılan bir çalışmada acil başvuruların yalnızca %8,9'unun doğrudan SLE alevlenmesi ile ilişkili olduğu gösterilmiştir.[5] İmmünosupresif tedavi alan hastalarda enfeksiyon riski belirgin şekilde artmakta ve bu durum, sık acil servis başvurularının en yaygın nedenlerinden biri olarak öne çıkmaktadır. Enfeksiyon ve hastalık alevlenmesinin klinik olarak birbirinden ayırt edilmesi çoğu zaman güçtür; ayrıca, her iki durumun aynı anda ortaya çıkabileceği de unutulmamalıdır. Bu nedenle, SLE hastalarının acil yönetiminde enfeksiyonlar öncelikli olarak değerlendirilirken, hastalık alevlenmesinin ayırıcı tanısı da dikkatle yapılmalıdır.[6]

Bunun yanı sıra, hipertansiyon, kronik böbrek hastalığı (KBH) ve kalp yetmezliği gibi komorbiditeler de SLE hastalarının acil başvurularında önemli rol oynar. Özellikle KBH, hastaneye yatış gereksiniminin en güçlü belirleyicilerinden biri olarak öne çıkmaktadır. Sık acil servis başvurusu yapan hastalarda daha yüksek hastalık aktivitesi, son üç ay içinde geçirilmiş alevlenme öyküsü ve kötü genel sağlık durumu gibi faktörlerin daha yaygın olduğu bildirilmiştir. Bu bulgular, SLE yönetiminde enfeksiyon kontrolü ve komorbiditelerin etkin tedavisini içeren multidisipliner bir yaklaşımın gerekliliğini vurgulamaktadır.[7]

Bu derlemede, SLE'ye bağlı acil durumların klinik yönetimi ve tedavi yaklaşımları ele alınacak; güncel literatür bilgileri ışığında pratik öneriler sunulacaktır.[8]

1. Nefrolojik Aciller

Nefrolojik tutulum, genellikle LN ile karakterize edilse de, trombotik mikroanjiyopati (TMA) ve antifosfolipid sendromuna (AFS) bağlı böbrek tutulumları gibi ciddi durumları da içerebilir. Bu komplikasyonlar, hızlı tanı ve tedavi gerektiren yaşamı tehdit edici tablolardır.

1.A. Lupus Nefriti

LN, SLE'nin en ciddi organ tutulumlarından biri olup genellikle akut veya subakut böbrek yetmezliği ile seyreder. Hematüri, proteinüri, hipertansiyon ve böbrek fonksiyon bozukluğu tanıda önemli bulgulardır.[9-11] Serum kreatinin seviyesindeki artış, glomerüler filtrasyon hızında (GFR) azalma, mikroskobik hematüri ve proteinüri varlığı tanıyı destekler. Yüksek anti-dsDNA antikorları ve düşük serum C3/C4 seviyeleri LN için önemli belirteçlerdir; ancak kesin tanı böbrek biyopsisi ile konulur.[12,13]

Aktif proliferatif LN olan hastalar, kortikosteroid (KS) tedavisi ile birlikte [intravenöz (iv) metilprednizolon (MP)] mikofenolat veya düşük doz iv siklofosfamid (CP) (EuroLupus rejimi) tedavisi almalıdır. Uygun hastalarda CP veya mikofenolat ile kombine belimumab tedavisi ya da özellikle mikofenolat ile birlikte kullanılan kalsinörin inhibitörleri (voklosporin veya takrolimus) tercih edilebilir.[8,14] İdame tedavide azatioprin (AZA) veya mikofenolat, daha düşük dozlarda uzun dönem kontrol için kullanılırken, KS kademeli olarak azaltılır veya uygun hastalarda kesilir.[15,16] Dirençli olgularda ise rituksimab (RTX) ve plazmaferez (*therapeutic plasma exchange* - TPE) önerilmiştir.[8] Bu tedavi yaklaşımları, hastaların klinik ve laboratuvar bulguları dikkate alınarak bireyselleştirilmelidir. Tedavi süresince hastaların düzenli olarak izlenmesi ve olası yan etkilerin yönetimi önem taşımaktadır.

1.B. Trombotik Mikroanjiyopati

TMA, endotel hasarı, mikroanjiyopatik hemolitik anemi (MAHA) ve trombositopeni ile karakterize bir patolojidir. SLE hastalarında TMA, sıklıkla LN, sepsis veya AFS gibi durumlarla ilişkilendirilir. Renal tutulumunda, glomerüler kapillerlerde trombüs oluşumu ve fibrin birikimi gözlenir. Klinik olarak, hipertansiyon, proteinüri, akut böbrek yetmezliği ve anemi ile kendini gösterir. Periferik yaymada şistositlerin görülmesi ve laktat dehidrojenaz (LDH) düzeylerinde artış TMA tanısında önemli kriterlerdir.

Böbrek biyopsisi, TMA tanısının doğrulanmasında altın standart yöntemdir. Biyopside, trombotik lezyonlar, glomerüler kapillerlerde endotel proliferasyonu ve fibrin birikimi saptanır. TMA'nın ayırıcı tanısında ADAMTS13 düzeylerinin değerlendirilmesi de önemlidir. Özellikle SLE hastalarında TMA, LN ile karışabileceğinden ayırıcı tanı dikkatle yapılmalıdır.[17]

Tedavide, TPE, KS ve ekulizumab gibi kompleman inhibitörleri önemli rol oynar. TPE, dolaşımdaki otoantikorların ve enflamatuvar mediyatörlerin uzaklaştırılmasını sağlar. Şiddetli olgularda RTX gibi biyolojik tedaviler uygulanabilir. Ek olarak, hipertansiyonun etkin kontrolü ve renal replasman tedavisi (örneğin hemodiyaliz) gerekebilir.[18]

1.C. Antifosfolipid Sendromu ve Renal Tutulum

SLE hastalarında sık görülen AFS, tromboz ve gebelik komplikasyonları ile karakterize otoimmün bir hastalıktır. Böbrek tutulumu geliştiğinde, bu durum antifosfolipid sendromu nefropatisi (AFSN) olarak adlandırılır.

Hipertansiyon, proteinüri, hematüri ve renal fonksiyon bozukluğu AFSN'nin tipik klinik belirtileridir. Laboratuvar testlerinde antifosfolipid antikorlarının (aFL; lupus

antikoagülanı, antikardiyolipin ve anti-beta2 glikoprotein I antikorları) pozitifliği tanıyı destekler. Böbrek biyopsisinde akut veya kronik vasküler lezyonlar saptanabilir. Akut lezyonlar arasında TMA, glomerüler kapillerlerde fibrin trombüsleri yer alırken, kronik lezyonlar glomerüloskleroz ve arteriyel intima proliferasyonu ile karakterizedir.

AFS'nin tedavisinde, uzun süreli düşük doz aspirin, düşük molekül ağırlıklı heparin ya da oral antikoagülanlar (örneğin; varfarin) temel ajanlardır. Bazı hastalarda KS ve RTX komplikasyonların kontrol altına alınmasında etkili olabilir. Dirençli olgularda ise ekulizumab kullanılabilir. Hipertansiyonun kontrolü ve proteinüriyi azaltmak için anjiyotensin dönüştürücü enzim inhibitörleri veya anjiyotensin reseptör blokerleri kullanılabilir.[19,20]

2. Nörolojik Aciller

SLE'nin nörolojik tutulumları, tanı ve tedavi sürecinde en karmaşık ve zorlu klinik tablolar arasında yer alır. SSS ve periferik sinir sistemi (PSS) tutulumu, hem enflamatuvar hem de iskemik mekanizmalarla ortaya çıkabilir. Klinik spektrumda inme, nöbet ve dural sinüs trombozu gibi santral komplikasyonların yanı sıra periferik nöropatiler ve nöropsikiyatrik durumlar yer alır. Bu tutulumlar genellikle acil müdahale gerektirir. SLE'de nörolojik tutulum çok çeşitli olmakla birlikte aşağıda en sık görülenler özetlenmiştir.

2.A. Santral Sinir Sistemi Tutulumu

SLE hastalarında inme insidansı genel popülasyona kıyasla yüksektir. Bu durum, aFL varlığına bağlı hiperkoagülabilite ve endotel disfonksiyonu ile ilişkilidir. Belirtiler ani başlangıçlı hemiparezi, konuşma bozukluğu veya görme kaybını içerebilir. Tanıda manyetik rezonans görüntüleme (MRG) ve özellikle difüzyon ağırlıklı görüntüleme kullanılır. Tedavide, AFS varlığında uzun süreli oral antikoagülanlar (örneğin; varfarin) önerilirken, akut inmede, trombolitik tedavi uygun hastalarda düşünülebilir.[21]

Dural sinüs trombozu, SLE hastalarında görülen nadir ancak ciddi bir nörolojik komplikasyondur. Çoğunlukla aFL varlığına bağlı olarak gelişir. Klinik olarak baş ağrısı, bulantı-kusma, görme bozuklukları ile kendini gösterir. Tanıda kontrastlı MR venografi altın standarttır. Tedavi antikoagülanlarla sağlanır; gerekirse trombolitik tedavi uygulanabilir.[22]

Nöbetler, SLE'nin SSS tutulumunda sık görülür ve genellikle hastalık aktivitesi ile ilişkilidir. Serebral vaskülit ve immün kompleks birikimi, kortikal irritabiliteye yol açarak nöbetlerin ortaya çıkmasına neden olur. Tedavide antiepileptik ilaçlar ve hastalık aktivitesinin kontrolü için immünosupresif tedavi birlikte kullanılır.[23]

SSS vasküliti, SLE'nin nadir ancak ciddi tutulumlarındandır. Endotel hasarı ve enflamatuvar süreçler, serebral iskemik ataklar ve hemorajilere neden olabilir. Klinik belirtiler arasında baş ağrısı, nöbetler ve bilişsel bozukluklar yer alır. Tanıda anjiyografi ve beyin biyopsisi yardımcıdır. Tedavide genellikle yüksek doz KS ve CP kullanılır.[24]

Transvers miyelit, SLE hastalarında görülebilen, spinal kord enflamasyonu ile karakterize ciddi bir nörolojik komplikasyondur. Klinik olarak ani başlangıçlı alt ekstremite güçsüzlüğü, duyu kaybı ve mesane/bağırsak disfonksiyonu ile kendini gösterebilir. Tanıda MRG'de longitudinal tutulum sıkça görülür. Tedavi yüksek doz iv MP, CP veya RTX ile sağlanır. Bazı olgularda iv immünoglobulin (IVIG) veya TPE kullanılabilir.[25]

2.B. Periferik Sinir Sistemi Tutulumu

SLE hastalarında PSS tutulumu sıklıkla vaskülite bağlı gelişir. Mononöritis multipleks, periferik sinirlerde asimetrik güçsüzlük, duyu kaybı ve nöropatik ağrı ile seyreden vaskülitik tutulumudur. Tanıda elektromiyografi kullanılır. Tedavi KS ve immünosupresif ajanlarla sağlanır.[26]

Optik nörit, SLE hastalarında görülebilen bir diğer PSS tutulumudur. Optik sinirin enflamasyonu sonucu ani görme kaybı ve göz hareketleriyle artan ağrı ile karakterizedir. Genellikle hastalığın aktif dönemlerinde ortaya çıkar, erken tanı ve tedavi görme fonksiyonunun korunması açısından kritik öneme sahiptir. Yüksek doz iv MP ve immünosupresif ajanlarla tedavi edilir.[27]

2.C. Nöropsikiyatrik SLE

SLE, nöropsikiyatrik belirtilerle de seyredebilir ve bu durum nöropsikiyatrik SLE olarak adlandırılır. Psikoz, bu tabloların en ağırlarından biridir ve genellikle otoantikorların doğrudan etkisi, serebral vaskülit veya metabolik disfonksiyonlarla ilişkilidir. Halüsinasyonlar, paranoya ve düşünce bozuklukları ile kendini gösterir. Psikoz genellikle hastalık aktivitesinin yüksek olduğu dönemlerde ortaya çıkar. Tanıda nöropsikolojik değerlendirme ve MRG kullanılır. Tedavi yüksek doz KS, CP ve gerektiğinde antipsikotik ajanları içerir.[28]

Akut konfüzyon durumu (deliryum), SLE hastalarında enfeksiyon, hastalık alevlenmesi, böbrek yetmezliği veya kullanılan ilaçların yan etkileri sonucu gelişebilir. Ani bilinç değişiklikleri, oryantasyon kaybı ve ajitasyon ile karakterizedir. Tanıda serum elektrolitleri, renal fonksiyon testleri ve enfeksiyon parametreleri değerlendirilir. Tedavi, nedenin hızlıca belirlenmesi ve düzeltilmesiyle sağlanır. Semptomatik tedavi için antipsikotik ajanlar kullanılabilir.[28]

Kognitif bozukluklar, hastalık aktivitesi arttığında sıkça görülür ve yaşam kalitesini ciddi şekilde etkileyebilir. Hafıza kaybı, dikkat eksikliği ve üst düzey bilişsel işlevlerde bozukluk sıkça gözlenir. Mikrotrombozlar, serebral hipoperfüzyon ve nöroenflamasyon, bu bozuklukların temel mekanizmalarıdır. Tanı nöropsikolojik testler ile desteklenir. Tedavi, immünosupresif ilaçlar ve kognitif rehabilitasyon yöntemlerini içerir.[28]

Baş ağrısı ve migren, SLE hastalarında sık görülen, otoimmün süreçlerle ilişkili semptomlardır. Trigeminal sinir yolundaki nöroenflamasyon bu durumun gelişiminde rol oynayabilir. Akut baş ağrısı durumlarında triptanlar ve nonsteroid anti-enflamatuvar ilaçlar (NSAİİ) kullanılır. Sık tekrarlayan ataklarda ise profilaktik tedavi tercih edilir.[29]

3. Pulmoner Aciller

SLE'de pulmoner aciller, yaşamı tehdit eden ve acil müdahale gerektiren klinik durumlardır. En sık karşılaşılan tablolar arasında akut lupus pnömoniti, pulmoner emboli ve diffüz alveolar hemoraji (DAH) bulunur. Patagonezde genellikle enflamasyon, vasküler disfonksiyon ve aFL birlikte rol oynar.

Akut lupus pnömoniti, SLE'de nadir görülmekle birlikte ciddi komplikasyonlara yol açabilir. Dispne, ateş, göğüs ağrısı ve hipoksemi gibi belirtilerle aniden ortaya çıkar. Alveoller içinde enflamasyon ve immün kompleks birikimi temel patofizyolojik mekanizmalardır. Akciğer röntgeni ve toraks bilgisayarlı tomografisinde (BT) bilateral alveolar infiltratlar ve konsolidasyon saptanır. Ancak, bu bulgular enfeksiyon, pulmoner emboli ve kalp yetmezliği gibi durumlarla benzerlik gösterebilir. Ayırıcı tanı için bronkoalveolar lavaj (BAL) yapılması ve enfeksiyonların dışlanması önemlidir. Tedaviye genellikle yüksek doz iv KS ile başlanır. Ciddi olgularda CP gibi immünosupresif ajanlar kullanılır. Hipoksemi gelişen hastalarda oksijen desteği ve gerektiğinde mekanik ventilasyon gerekebilir.[30]

Pulmoner emboli, AFS tanısı olan SLE hastalarında daha sık görülür. Klinik olarak ani başlangıçlı dispne, göğüs ağrısı ve taşikardi görülür. D-dimer testi tarama amaçlı kullanılırken pulmoner BT anjiyografi, tanıda altın standarttır. Ayırıcı tanıda lupus pnömoniti, enfeksiyonlar ve akut solunum sıkıntısı sendromu göz önünde bulundurulmalıdır. Tedavide akut dönemde anfraksiyone veya düşük molekül ağırlıklı heparin başlanır; uzun vadede ise warfarin gibi oral antikoagülanlarla devam edilir. Hemodinamik instabilite durumlarında trombolitik tedavi düşünülebilir, ancak SLE hastalarında bu tedavinin komplikasyon riski nedeniyle dikkatle değerlendirilmesi gerekir.[31]

DAH, SLE'de nadir görülen ancak mortalitesi yüksek bir komplikasyondur. Kapiller endotel hasarına bağlı olarak alveollere masif kanama gelişir. Klinik olarak hemoptizi, dispne, hipoksemi ve hızlı kötüleşen solunum sıkıntısı ile karakterizedir. Radyolojik incelemelerde bilateral alveolar infiltratlar sıkça görülür, ancak bu bulgular enfeksiyon ve pulmoner ödem ile karışabilir. Tanıda BAL, hemorajiyi doğrulamak ve enfeksiyonu dışlamak için önemlidir. Tedaviye, yüksek doz iv KS ile başlanır ve ciddi olgularda CP veya RTX eklenir. Şiddetli solunum yetmezliği olan hastalarda TPE ve destekleyici tedavi (örneğin; oksijen veya mekanik ventilasyon) gerekebilir. Ekstrakorporeal membran oksijenasyonu, dirençli olgularda hayat kurtarıcı bir seçenek olabilir.[32,33]

4. Kardiyak Aciller

SLE hastalarında kardiyak komplikasyonlar, yüksek morbidite ve mortalite riski taşır. Enflamatuvar süreçler, vasküler disfonksiyon ve otoimmün mekanizmalar, bu komplikasyonların temelinde yer alır. Perikardit ve tamponad, miyokardit, koroner arter hastalığı ve Libman-Sacks endokarditi, SLE'ye bağlı önemli kardiyak aciller arasındadır.

Perikardit, SLE'nin en sık kardiyak tutulumlarındandır. Genellikle göğüs ağrısı, dispne, ateş şikayeti olan hastalarda muayenede perikardiyal sürtünme sesi duyulur. Küçük efüzyonlar çoğunlukla asemptomatik olurken, büyük ve hızlı gelişen efüzyonlar tamponada yol açabilir. Muayenede hipotansiyon, pulsus paradoksus ve juguler venöz distansiyon gibi klasik bulgular gözlenir. Tanıda ekokardiyografi (EKO) en değerli yöntemdir ve perikardiyal efüzyonun boyutunu ve hemodinamik etkisini değerlendirmek için kullanılır. Perikardit tedavisinde NSAİİ'ler ilk basamak tedavi olarak kullanılırken, şiddetli durumlarda KS tercih edilir. Tamponad geliştiğinde perikardiyosentez hayat kurtarıcıdır.[34]

Miyokardit, SLE'nin nadir ancak ağır seyreden bir komplikasyonudur. Semptomlar arasında dispne, taşikardi, göğüs ağrısı ve efor kapasitesinde azalma vardır. Troponin seviyelerindeki artış, enflamasyon sonucu gelişen miyokard hasarını biyokimyasal olarak gösterir. Kardiyak MRG ise, anatomik olarak enflamatuvar tutulumun görüntülenmesine olanak tanır. Tedavide KS ve immünosupresif ajanlar (örneğin; CP, mikofenolat mofetil) kullanılır. Şiddetli olgularda RTX eklenebilir. Kalp yetmezliği gelişen hastalarda mekanik dolaşım desteği (örneğin; intraaortik balon pompası veya ventriküler destek cihazları) gerekebilir. Tedavide geç kalınması durumunda kalp yetmezliği ve kardiyojenik şok riski artar.[35]

Koroner arter hastalığı, SLE hastalarında enflamasyon, endotel disfonksiyonu ve aFL antikorlarına bağlı tromboz

nedeniyle daha sık görülür. Kronik enflamasyonun neden olduğu hızlanmış ateroskleroz, koroner arterlerin daralmasına yol açarak klinik olarak stabil angina pektoris, akut koroner sendrom veya ani kardiyak ölüm şeklinde ortaya çıkabilir. Tanıda konvansiyonel koroner anjiyografi veya non-invaziv yöntemler (örneğin; koroner BT anjiyografi) kullanılır. Medikal tedavi, aspirin, statinler ve antikoagülanları içerir. Gerektiğinde, perkütan koroner girişim veya koroner arter bypass grefti uygulanabilir. AFS varlığında uzun süreli antikoagülasyon tedavisi gereklidir. Bu durumdaki hastalarda erken tanı ve agresif statin tedavisi önemlidir.[36]

Libman-Sacks endokarditi, SLE hastalarında görülen enfektif olmayan endokardit formudur ve genellikle aFL'ye bağlı olarak gelişir. Mitral ve aort kapaklarının her iki yüzeyinde steril vejetasyonlarla karakterizedir. Klinik olarak genellikle asemptomatik olmasına rağmen, kopan vejetasyonların embolizasyonu ciddi komplikasyonlara neden olabilir. Serebral ve renal embolik enfarktlar gözlenebilir. EKO, özellikle transözofageal EKO, tanıda en duyarlı yöntemdir. Antikoagülan tedavi, emboli riskini azaltmak için esastır. Şiddetli kapak disfonksiyonu veya tekrarlayan embolik olaylar durumunda cerrahi müdahale gerekebilir. Libman-Sacks endokarditi, uzun dönem morbidite açısından dikkatle izlenmesi gereken bir durumdur.[37]

5. Hematolojik Aciller

SLE hastalarında hematolojik tutulumlar, hastalığın klinik spektrumunun önemli bir parçasını oluşturur ve bazı durumlarda yaşamı tehdit edici olabilir. Bu komplikasyonlar, otoimmün mekanizmalar veya immünosupresif tedavilerin yan etkileri nedeniyle ortaya çıkabilir. Sık karşılaşılan hematolojik anormallikler arasında otoimmün hemolitik anemi (OIHA), ciddi trombositopeni, pansitopeni, TMA ve makrofaj aktivasyon sendromu (MAS) yer alır.

5.A. Otoimmün Hemolitik Anemi

OIHA, SLE'nin en önemli hematolojik komplikasyonlarından biridir. Çoğunlukla IgG sınıfından sıcak otoantikorlar eritrositlere bağlanarak retiküloendotelyal sistem tarafından hızla yıkılmalarına neden olur. Bu durum, hemolitik krize yol açarak derin anemiye sebep olabilir. Hastalar sıklıkla halsizlik, yorgunluk, çarpıntı ve sarılık gibi semptomlarla başvurur. Akut hemolitik krizlerde dispne, taşikardi ve hipotansiyon gelişebilir. Periferik yaymada sferositler ve retikülositoz gözlenir. Hemoliz göstergeleri arasında artmış LDH, indirekt bilirubin ve azalmış haptoglobulin yer alır. Pozitif Coombs testi (direkt antiglobulin testi) tanıyı doğrular.

İlk basamak tedavi yüksek doz KS'dir (örneğin; prednizon 1 mg/kg/gün). KS tedavisine dirençli hastalarda RTX veya splenektomi düşünülebilir. Hemoglobin seviyesinin kritik düzeylere düştüğü hastalarda kan transfüzyonu yapılabilir, ancak transfüzyon öncesinde aktif hemolizin kontrol altına alınması gerekir.[38-40]

5.B. Otoimmün Trombositopeni

SLE hastalarında trombositopeni, antitrombosit antikorlarına bağlı olarak trombositlerin yıkımının artması ve kemik iliği supresyonu nedeniyle gelişebilir. Trombosit sayısı 20.000/μL'nin altına düştüğünde peteşi, purpura ve diş eti kanamaları, menoraji gibi mukozal kanamalar görülebilir. Hastalar genellikle peteşi, purpura ve mukozal kanama semptomlarıyla başvururlar. Periferik yaymada trombosit azlığı ve megakaryositlerin varlığı, immün aracılı trombositopeniyi destekler. Diğer nedenlerin dışlanması için kemik iliği biyopsisi ve enfeksiyon taramaları yapılmalıdır.

İlk basamak tedavi yüksek doz KS'dir (örneğin; MP iv 1 g/gün, 3 gün). Ağır kanama varlığında IVIG hızlı bir yanıt sağlayabilir. Tedaviye dirençli olgularda RTX veya trombopoetin reseptör agonistleri kullanılabilir. Splenektomi, nadiren tercih edilmekle birlikte, refrakter durumlarda tek seçenek olabilir.[41,42]

5.C. Kemik İliği Supresyonu ve Pansitopeni

Pansitopeni, SLE'de tüm hücre serilerinin immün mekanizmalar veya ilaç etkileri sebebiyle baskılanması ile karakterizedir. Progenitör hücrelere karşı gelişmiş otoantikorlar ya da immünosupresif tedaviler (örneğin; CP ve mikofenolat mofetil), hemopoetik hücrelerin üretimini azaltabilir. Hastalar halsizlik, yorgunluk, mukokütanöz kanamalar ve sık enfeksiyon geçirme öyküsü ile başvurabilir. Periferik yaymada tüm hücre serilerinde azalma ve kemik iliği biyopsisinde, hiposelüler kemik iliği saptanabilir. Ayırıcı tanıda B12, folik asit, demir eksiklikleri ve akut viral enfeksiyonlar değerlendirilmelidir.

Tedavi, altta yatan nedene yönelik planlanır. İmmünosupresif tedaviye bağlı pansitopeni durumunda ilaçların kesilmesi veya dozun azaltılması gerekebilir. Ciddi olgularda hematopoetik büyüme faktörleri (örneğin; eritropoetin, granülosit koloni stimulan faktör) veya kan transfüzyonu uygulanabilir. Hastalıkla ilişkili aplastik anemi durumunda KS'ye ek olarak, RTX veya anti-timosit globülin tedaviye eklenebilir.[43]

5.D. Trombotik Mikroanjiyopati

TMA, MAHA, trombositopeni ve organ iskemisi ile karakterize, nadir ancak yaşamı tehdit eden bir durumdur. Endotel hasarı ve mikrotromboz oluşumu, kapiller ve

küçük arteriyollerde trombosit-fibrin birikimine yol açarak organlarda iskemik hasara neden olur. SLE hastalarında TMA sıklıkla LN, AFS veya enfeksiyon gibi tetikleyici faktörlerle ilişkilidir. Renal tutulum TMA'nın en sık klinik bulgularındandır ve hipertansiyon, akut böbrek yetmezliği ile kendini gösterebilir. Nörolojik bulgular arasında baş ağrısı, konfüzyon ve nöbetler yer alır. Tanıda periferik yaymada şistositlerin varlığı ve artmış LDH, indirekt bilirubin, azalmış haptoglobulin seviyeleri intravasküler hemoliz için tipiktir. Böbrek tutulumunun derecesini belirlemek için serum kreatinin değerleri ve GFR değerlendirilir. ADAMTS13 enzimi düzeyi, TMA ile trombotik trombositopenik purpura ayrımında önemlidir.

Tedavide TPE, dolaşımdaki otoantikorları ve toksik maddeleri uzaklaştırarak hızlı klinik düzelme sağlayabilir. Yüksek doz KS, otoimmün yanıtı kontrol altına almak için yaygın olarak kullanılır. Refrakter olgularda RTX etkili bulunmuştur. Özellikle kompleman sistemi disfonksiyonu olan hastalarda, ekulizumab tedaviye eklenebilir. Hipertansiyonun kontrolü ve elektrolit dengesinin sağlanması, destekleyici tedavinin temel bileşenleridir. Şiddetli böbrek yetmezliği gelişen hastalarda hemodiyaliz, gerekebilir.[44]

5.E. Makrofaj Aktivasyon Sendromu

MAS, SLE'nin nadir ancak ölümcül seyredebilen komplikasyonlarından biridir. Kontrolsüz enflamatuvar yanıt ve aşırı makrofaj aktivasyonu sonucu gelişir. Sitokin fırtınası ile karakterizedir ve interlökin-1 (IL-1), IL-6 ve tümör nekroz faktör-alfa gibi proenflamatuvar sitokinlerin aşırı salınımı görülür. Enfeksiyonlar ve hastalık alevlenmeleri tetikleyici olabilir. SLE hastalarında MAS'nin klinik belirtileri, yüksek ateş, pansitopeni, hepatosplenomegali ve yaygın enflamasyon bulgularını içerir. Ek olarak, dissemine intravasküler koagülasyon benzeri bir tablo da gelişebilir ve bu durum kanama eğilimi ile kendini gösterebilir. MAS'nin laboratuvar bulguları, genellikle 10.000 ng/mL'nin üzerinde ferritin, düşük fibrinojen düzeyleri, hipertrigliseridemi ve karaciğer fonksiyon testlerinde yükseklik ile karakterizedir. Tanı, klinik özelliklerin ve laboratuvar bulgularının birlikte değerlendirilmesiyle konur.

Tedavide, enflamasyonu hızlı bir şekilde kontrol altına almak için yüksek doz iv KS ilk seçenek olarak kullanılır. Anakinra ve tosilizumab sitokin fırtınasını baskılamada etkili ajanlardır. Şiddetli olgularda, CP gibi immünosupresif ajanlar veya IVIG tedavisi gerekebilir. Kan transfüzyonları ve koagülopati yönetimi gibi destekleyici tedaviler sıklıkla gereklidir. MAS tedavisinde erken tanı ve agresif yönetim, mortaliteyi azaltmada kritik öneme sahiptir.[45,46]

6. Avasküler Nekroz

Avasküler nekroz (AVN), SLE hastalarında önemli bir morbidite kaynağıdır ve genellikle KS tedavisinin yan etkisi olarak ortaya çıkar. KS, intraossöz basıncı artırarak ve mikrovasküler dolaşımı bozarak kemik dokusunda iskemiye neden olur. Bu süreç, kemik hücrelerinin ölümüne ve çevre dokularda yıkıcı değişikliklere neden olur. SLE'de görülen AVN, KS'ye ek olarak, aFL aracılı hiperkoagülabilite ve vaskülit gibi mekanizmalarla da ilişkilidir. Bu nedenle, AVN genellikle multifaktöriyel bir etiyolojiye sahiptir. En sık femur başında görülmekle birlikte, diz, omuz, ayak bileği ve el bileği gibi diğer eklemler de etkilenebilir.[47,48]

AVN'nin klinik belirtileri genellikle sinsi başlangıçlıdır ve erken evrelerde spesifik olmayan semptomlarla kendini gösterir. En yaygın belirti, yük taşımakla artan ve ilerleyen dönemde dinlenme sırasında da hissedilen derin eklem ağrısıdır. İlerlemiş olgularda, eklemde deformite ve ciddi hareket kısıtlılığı görülebilir. Tanı genellikle klinik değerlendirme ve görüntüleme yöntemleri ile konur. Radyografiler, ileri evrelerde kemik çökmesi ve eklem aralığında daralma gibi bulgular gösterebilir. Ancak, AVN'nin erken evrelerinde direk radyoloji genellikle yetersizdir. MRG, AVN tanısında altın standart olarak kabul edilir ve kemik ödemi ile nekrozun erken belirtilerini gösterebilir.

Tedavi yaklaşımları, hastalığın evresine ve semptomların şiddetine göre değişiklik gösterir. Erken evrelerde konservatif tedavi yöntemleri tercih edilir. Ağrı yönetimi için NSAİİ'ler yaygın olarak kullanılırken, ekleme binen yükün azaltılması ve fizik tedavi verilmesi semptomların hafifletilmesine katkıda bulunur. Ayrıca, bifosfonatlar gibi ilaçlar, kemik yıkımını azaltarak hastalığın ilerlemesini yavaşlatabilir. İleri evrelerde, cerrahi müdahale genellikle gerekli hale gelir. Dekompresyon cerrahisi, erken evrede uygulanabilen ve intraosseöz basıncı azaltarak kan dolaşımını artıran bir yöntemdir. Daha ileri evrelerde, total eklem protezi, özellikle femur başı nekrozunda en etkili tedavi yöntemidir. Bunun yanı sıra, vaskülarize kemik greftleri gibi cerrahi teknikler de uygun olgularda kullanılabilir.[49,50]

SLE hastalarında AVN'nin önlenmesi ve yönetiminde, KS tedavisinin dikkatli bir şekilde planlanması önem taşır. KS kullanımını en aza indirgemek ve gerektiğinde immünosupresif tedavilerle desteklemek, AVN riskini azaltabilir. AVN her ne kadar doğrudan bir acil durum olmasa da, hızlı progresyon gösteren olgularda şiddetli ağrı ve hareket kısıtlılığı acil servis başvurusunu gerekli kılabilir. Bu nedenle, erken farkındalık ve multidisipliner bir yaklaşım, SLE hastalarında AVN'nin etkili yönetimi için kritik öneme sahiptir.

7. Enfeksiyonlar ve Sepsis

Enfeksiyonlar, SLE hastalarının en sık acil servis başvuru nedenleri arasındadır. İmmünolojik disfonksiyon ve immünosupresif tedavilerin etkisiyle enfeksiyon riski artar. Özellikle pnömoni, piyelonefrit, septik artrit ve sepsis gibi ciddi enfeksiyonlar acil müdahale gerektirir ve zamanında tedavi edilmezse organ yetmezliği veya ölümle sonuçlanabilir. Bu nedenle erken tanı ve uygun tedavi hayati önem taşır.[51,52]

SLE'de enfeksiyon riskini artıran temel faktörler, immünolojik disfonksiyon ve immünosupresif tedavilerin kullanımıdır. KS, CP, mikofenolat ve RTX gibi ajanlar, hastalığın enflamatuvar etkilerini baskılamak için kullanılırken, bağışıklık sisteminin enfeksiyonlara karşı savunmasını da zayıflatır. Ayrıca, SLE'nin seyrinde sıkça görülen hipokomplementemi, fagositoz ve opsonizasyon mekanizmalarını bozarak enfeksiyon riskini daha da artırır.

Pnömoni, SLE hastalarında en sık karşılaşılan ciddi enfeksiyonlardan biridir. *Streptococcus pneumoniae* ve *Haemophilus influenzae* gibi toplum kaynaklı patojenlerin yanı sıra, *Pneumocystis jirovecii* ve *Mycobacterium tuberculosis* gibi fırsatçı patojenler da pnömoniye yol açabilir. Klinik olarak öksürük, dispne, ateş ve hipoksemi görülür. Tedaviye erken dönemde geniş spektrumlu antibiyotiklerle başlanmalı ve fırsatçı enfeksiyonlardan şüpheleniliyorsa özgün ajanlar eklenmelidir. Şiddetli olgularda oksijen desteği ve mekanik ventilasyon gerekebilir.[53]

Piyelonefrit, özellikle LN öyküsü olan hastalarda daha sık görülür. En yaygın patojen *Escherichia coli* olup, hastalar genellikle ateş, yan ağrısı ve dizüri ile başvurur. Bu hastalarda, bakteriyemi ve sepsis riski artar. Tedavide geniş spektrumlu antibiyotikler kullanılır ve renal fonksiyon bozukluğu olan hastalarda hastaneye yatış gerekebilir.[54]

Septik artrit, eklemde ağrı, şişlik ve ısı artışı ile kendini gösteren ciddi bir enfeksiyondur. En sık etken *Staphylococcus aureus*'tur. Tanı için eklem aspirasyonu ve mikrobiyolojik inceleme gereklidir. Tedavi, iv antibiyotikler ve bazı durumlarda cerrahi drenajı içerir. İmmünosupresif tedavi alan hastalarda daha şiddetli seyreder ve komplikasyon riski yüksektir.[55]

Sepsis ve septik şok, SLE hastalarında enfeksiyonun en ciddi komplikasyonlarındandır. Bu durum genellikle kontrol altına alınmamış bir enfeksiyonun sistemik enflamatuvar yanıtı tetiklemesi sonucu ortaya çıkar. Sepsis, çoklu organ yetmezliğine yol açabilir ve erken müdahale edilmediğinde mortalite oranı yüksektir. Sepsisin yönetimi, geniş spektrumlu antibiyotik tedavisine hızlı bir şekilde başlanması, sıvı resüsitasyonu ve hemodinamik desteği içerir. Yoğun bakım takibi genellikle gereklidir ve mekanik ventilasyon, renal replasman tedavisi gibi destekleyici tedaviler sıklıkla uygulanır.[56]

Yoğun bakım gerektiren diğer enfeksiyonlar arasında yaygın fungal enfeksiyonlar (örneğin; *Aspergillus*, *Candida*) ve sitomegalovirüs reaktivasyonu gibi viral enfeksiyonlar yer alır. Bu hastalarda enfeksiyonların yönetimi, kapsamlı bir multidisipliner yaklaşım gerektirir. Enfeksiyonun kontrolü için immünosupresif tedavinin geçici olarak azaltılması veya kesilmesi önemlidir.[57]

Sonuç olarak, SLE hastalarında enfeksiyonlar önemli bir morbidite ve mortalite nedenidir. Pnömoni, piyelonefrit, septik artrit ve sepsis gibi durumlar acil müdahale gerektirir. Erken tanı ve uygun tedavi, prognozu iyileştirmede kritik rol oynar. Ayrıca, immünosupresif tedavilerin dikkatli yönetimi ve düzenli enfeksiyon taramaları, enfeksiyon riskini azaltmada etkili stratejiler arasındadır.

8. SLE ve Gebelikte Acil Durumlar

SLE tanılı gebelerde acil durumlar, hem maternal hem de fetal sağlığı ciddi şekilde tehdit edebilir. Çoğu gebelik başarılı seyretse de, SLE hastalarında maternal ve fetal komplikasyon riski belirgin şekilde artmıştır. Gebelik planlaması öncesinde en az altı ay boyunca hastalığın kontrol altında olması önerilir. Aksi takdirde, gebelik sırasında hastalık aktivitesinde artış ve acil müdahale gerektiren preeklampsi gibi obstetrik komplikasyonlar görülebilir. Bu nedenle, gebelik sürecinin yakından takip edilmesi ve risklerin etkin yönetilmesi, morbidite ve mortalite oranlarını düşürmede kritik öneme sahiptir.[58]

8.A. Hastalık Alevlenmesi

SLE tanılı hastaların yaklaşık dörtte birinde gebelik süresince hastalık aktivitesi artabilir. Ancak bu alevlenmelerin çoğu hafif seyirli olup, genellikle yalnızca KS dozunun artırılmasıyla kontrol altına alınabilir. Ciddi alevlenmeler ise daha nadir olup, bazen erken doğum gerektirebilir. Bu nedenle güncel kılavuzlar, gebelikle ilişkili komplikasyon riskini en aza indirmek için, hastaların gebelik öncesi dönemde en az altı ay boyunca remisyonda olmalarını önermektedir.[58]

Gebelik sırasında LN alevlenmesi, SLE tanılı hastalarda yaygın bir komplikasyondur ve preeklampsi ile benzer klinik bulgular sergileyebilir. Klinik olarak hipertansiyon, proteinüri ve serum kreatinin artışı ile karakterizedir. Gebelikte LN alevlenmesi, erken doğum ve intrauterin büyüme geriliği (IUBG) riskini artırır. Tedavi planı hastalığın şiddetine göre belirlenir. Hafif olgularda düşük doz KS kullanılırken, ciddi olgularda iv MP ve AZA gibi immünosupresif ajanlar tedaviye eklenebilir.[59,60]

8.B. Preeklampsi

Preeklampsi, gebeliğin 20. haftasından sonra ortaya çıkan, hipertansiyon ve proteinüri ile karakterize edilen ciddi bir klinik tablodur. Görme bozukluğu, baş ağrısı, trombositopeni ve karaciğer fonksiyon bozukluğu gibi sistemik belirtiler eşlik edebilir. İleri evrelerinde pulmoner ödem, böbrek yetmezliği ve eklampsi gibi yaşamı tehdit eden komplikasyonlar gelişebilir. Fetal riskler arasında oligohidramniyos, IUBG, prematürite ve ölü doğum bulunmaktadır.

Tedavinin temel amacı, kan basıncının düzenlenmesi ve gebelik haftasına göre doğum zamanlamasının planlanmasıdır. Otuz dördüncü gebelik haftasından önce gelişen preeklampsi olgularında, fetal akciğer maturasyonunu desteklemek amacıyla KS tedavisi uygulanır. Şiddetli preeklampsi varlığında ise anne ve fetüsün durumu değerlendirilerek, erken doğum kararı alınabilir.[61]

8.C. HELLP Sendromu

HELLP sendromu (*Hemolysis*, *Elevated Liver enzymes*, *Low Platelets*), gebelik sırasında veya doğum sonrası gelişebilen, hemoliz, karaciğer enzimlerinde yükselme ve trombositopeni ile tanımlanan ciddi bir durumdur. Klinik belirtileri arasında sağ üst kadran ağrısı, yorgunluk, bulantı, kusma ve hipertansiyon yer alır. Tanı için periferik yaymada şistositlerin varlığı, karaciğer enzimlerinde yükseklik ve trombositopeni anlamlıdır.

Bu sendromun kesin tedavisi acil doğumdur. Gebelik haftasına bağlı olarak, 34. haftadan sonra veya şiddetli komplikasyonlar geliştiğinde doğum hemen gerçekleştirilmelidir. Otuz dördüncü haftadan önce ise, maternal durum stabilse, KS tedavisi için 48 saatlik gecikme düşünülebilir. Ancak, ağır komplikasyonlar (hepatik kanama, akut böbrek hasarı, pulmoner ödem, nöbet, fetal distres) gelişmişse, gebeliğin sürdürülmesi anne açısından risk oluşturabileceğinden, acil doğum kaçınılmaz hale gelebilir.[62]

8.D. Antifosfolipid Sendromu İlişkili Komplikasyonlar

AFS, SLE'li gebelerde venöz ve arteriyel tromboz, tekrarlayan gebelik kayıpları ve IUBG gibi ciddi komplikasyonlara yol açabilir. AFS'nin en ciddi komplikasyonlarından biri olan katastrofik AFS'de hızlı hastalık seyri, çoklu organ tutulumu, büyük damar trombozu ve mikrovasküler trombozlar birlikte bulunur. Gebelik döneminde HELLP sendromu ile ayırıcı tanısı zor olabilir ve iki hastalık bir arada bulunabilir.

Tedavisinde heparin ve aspirin ile antikoagülasyon, yüksek doz KS, seçilmiş olgularda TPE ve/veya IVIG uygulanmaktadır. Refrakter olgularda RTX veya ekulizumab tedavi seçenekleri arasındadır.[63]

8.E. Fetüsle İlgili Durumlar

SLE tanılı gebelerde fetal komplikasyonlar, transplasental antikor geçişi, plasental disfonksiyon ve maternal hastalık aktivitesine bağlı olarak gelişebilir. Bu komplikasyonlar arasında IUBG, prematürite, düşük doğum ağırlığı ve konjenital kalp bloğu yer alır.

Preeklampsi, fetüs açısından ciddi sonuçlar doğurabilir. Erken başlangıçlı preeklampside, uteroplasental kan akımının yetersiz olması nedeniyle IUBG, oligohidramniyos ve perinatal mortalite riski yükselir. Fetal ultrasonografi ve Doppler incelemeleri, uterin arter direnci ve umbilikal arter akımındaki değişiklikleri değerlendirmede yardımcı olabilir. Plasental damar direncinin artması, kötü fetal prognoz ile ilişkilidir.[64]

AFS'de bulunan aFL antikorları, uteroplasental dolaşımı bozarak fetal büyümeyi olumsuz etkileyebilir. Prematürite ve düşük doğum ağırlığı, bu hastalarda yaygındır. Plasental yetmezlik nedeniyle fetal distres gelişen olgularda, erken doğum planlanabilir.

Anti-SSA/Ro ve anti-SSB/La antikorları pozitif SLE hastalarında, bu antikorların transplasental geçişi nedeniyle 18-24. gebelik haftasından itibaren neonatal lupus sendromu gelişebilir. Bu durum, fetüsün kardiyak ileti sisteminde enflamasyon ve fibrozise yol açarak konjenital kalp bloğuna neden olabilir. Tanı ve takip için fetal EKO kullanılır. Tedavi, atriyoventriküler blok derecesine göre belirlenir. Birinci derece blok olguları genellikle yalnızca izlemle yönetilirken, ikinci ve üçüncü derece bloklarda acil girişimler gerekebilir. Fetal kardiyak dokudaki enflamasyonu baskılamak amacıyla anneye yüksek dozda, plasentayı geçme özelliği olan deksametazon verilebilir. Dirençli olgularda IVIG eklenebilir. Üçüncü derece kalp bloğunda ise doğum sonrası kalıcı kalp pili implantasyonu dışında bir tedavi seçeneği bulunmamaktadır. Erken tanı ve multidisipliner yaklaşım, hem maternal, hem de fetal sağ kalımı artırmada kritik öneme sahiptir.[65]

Sonuç

SLE, çoklu organ tutulumu gösteren kronik otoimmün bir hastalık olup, klinik seyri remisyon ve alevlenmelerle değişkenlik gösterebilir. Hastalığın yönetimi, erken tanı, düzenli takip ve immünosupresif tedavilerin etkin kullanımı ile sağlanırken, akut tablolar hastaların morbidite ve mortalitesini önemli ölçüde artırmaktadır. Özellikle hastalık

alevlenmeleri, organ yetmezlikleri ve immünosupresyonun neden olduğu komplikasyonlar, acil servise başvuruların en sık nedenleri arasındadır. Bu nedenle, SLE hastalarının acil durum yönetiminde hem hastalığın kendisi hem de tedavi sürecine bağlı komplikasyonlar dikkatle değerlendirilmelidir.

SLE'de acil servis başvuruları genellikle nörolojik, nefrolojik, pulmoner ve hematolojik tutulumlar ile ilişkilidir. Hastalık alevlenmelerine ek olarak, immünosupresif tedavi altındaki hastalarda sepsis ve diğer enfeksiyonlar önemli bir morbidite kaynağıdır. Gebelik ise hastalığın doğal seyrini etkileyebilen bir faktör olup, özellikle preeklampsi, HELLP ve neonatal lupus sendromu gibi ciddi obstetrik komplikasyonlarla ilişkili olabilir. Bu komplikasyonlar, hem maternal hem de fetal sağlığı tehdit eden acil müdahale gerektiren tablolar olarak öne çıkmaktadır. Ayrıca, AFS varlığında trombotik komplikasyonlar daha sık görülmekte ve gebelik kaybı riski artmaktadır.

SLE'nin acil durumlarında yönetim, multidisipliner bir yaklaşım gerektirir. Klinik tablonun ayırıcı tanısı dikkatle yapılmalı ve hastalık alevlenmesi ile enfeksiyon gibi diğer durumların ayrımı hızlıca sağlanmalıdır (Tablo 1). Güncel kılavuzlar doğrultusunda bireyselleştirilmiş tedavi stratejileri belirlenmeli ve hastaların uzun dönem prognozunu iyileştirmek için takip süreçleri düzenlenmelidir.[8] Acil servise başvuran SLE hastalarında erken müdahale, komplikasyonların önlenmesi ve uygun tedavi yaklaşımlarının benimsenmesi, hasta sağ kalımını artırmada kritik rol oynamaktadır.

Tablo 1. Sistemik lupus eritematozusda acil durumların yönetimi

	Acil durum	Klinik belirtiler	Tanı	Tedavi
Nefrolojik tutulum	LN, TMA, AFSN, ATN	Proteinüri, hematüri, hipertansiyon, akut böbrek yetmezliği, oligüri	İdrar tahlili, serum kreatinin düzeyi, GFR, Anti-dsDNA, C3/C4, böbrek biyopsisi	Kortikosteroidler, siklofosfamid veya mikofenolat, plazmaferez (TMA), diüretik ve antihipertansifler
Nörolojik tutulum	İnme, nöbet, dural sinüs trombozu, transvers miyelit, mononöritis mültipleks, optik nörit, deliryum, psikoz	Fokal nörolojik defisit, nöbet, bilinç değişikliği, şiddetli baş ağrısı, görme kaybı	MRG/BT, kranial anjiyografi, lomber ponksiyon, EMG	Antikoagülan tedavi, kortikosteroidler, siklofosfamid veya mikofenolat, antiepileptik ve antipsikotikler
Pulmoner tutulum	Akut lupus pnömoniti, pulmoner emboli, diffüz alveolar hemoraji	Dispne, hemoptizi, hipoksemi, ateş, göğüs ağrısı	Toraks BT, bronkoskopi (alveolar hemoraji şüphesinde), D-dimer, pulmoner anjiyografi	Oksijen desteği, immünosupresif tedavi (kortikosteroid veya rituksimab), antikoagülan tedavi
Kardiyak tutulum	Perikardit, myokardit, Libman-Sacks endokarditi, akut koroner sendrom	Göğüs ağrısı, emboli bulguları	EKG, EKO, kardiyak enzim düzeyleri, kardiyak MRG	NSAİİ (perikardit), yüksek doz kortikosteroid (miyokardit), Libman-Sacks endokarditinde antibiyotik ve cerrahi konsültasyon
Hematolojik tutulum	Otoimmün hemolitik anemi, trombositopeni, pansitopeni, MAS	Anemi, peteşi, ekimoz, splenomegali, sitokin fırtınası bulguları	Kan sayımı, periferik yayma, LDH, bilirubin, direkt Coombs testi, ferritin, haptoglobulin, trigliserid, fibrinogen, ADAMTS13 düzeyleri, kemik iliği biyopsisi	Kortikosteroid, siklofosfamid, rituksimab, IVIG, plazmaferez (MAS)
Enfeksiyonlar	Pnömoni, pyelonefrit, septik artrit, viral ve fungal enfeksiyonlar, sepsis	Öksürük, balgam, yan ağrısı, akut artrit, yüksek ateş, taşikardi, hipotansiyon, bilinç bulanıklığı	Balgam, idrar ve kan kültürleri, akciğer grafisi, toraks BT, üriner USG, eklem sıvısı kültürleri	Geniş spektrumlu antibiyotikler, sıvı resüsitasyonu, yoğun bakım desteği
Gebelikte aciller	Preeklampsi, HELLP sendromu, AFS, konjenital kalp bloğu, IUBG	Hipertansiyon, proteinüri, fetal bradikardi, epigastrik ağrı, karaciğer enzim yüksekliği	Fetal EKO, Doppler USG, plasental kan akımı ölçümü	Yüksek doz steroid, IVIG (konjenital kalp bloğu), antikoagülan tedavi, preeklampsi ve HELLP'de doğum planlaması, acil sezaryen (fetal distres)

AFSN: Antifosfolipid sendromu nefropatisi, ATN: Akut tubuler nekroz, BT: Bilgisayarlı tomografi, EKG: Elektrokardiyografi, EKO: Ekokardiyografi, EMG: Elektromiyografi, GFR: Glomeruler filtrasyon hızı, HELLP: Hemolysis, Elevated Liver enzymes, Low Platelets, IUGR: İntrauterin büyüme geriliği, IVIG: İntravenöz immünoglobulin, LN: Lupus nefriti, MAS: Makrofaj aktivasyon sendromu, MRG: Manyetik rezonans görüntüleme, NSAİİ: Non-steroid anti-enflamatuvar ilaç, TMA: Trombotik mikroanjiyopati, USG: Ultrasonografi

Dipnotlar

Yazarlık Katkıları

Konsept: S.T., G.K., Dizayn: S.T., G.K., Veri Toplama veya İşleme: S.T., Analiz veya Yorumlama: S.T., G.K., Literatür Arama: S.T., Yazan: S.T., G.K.

Çıkar Çatışması: Yazarlar tarafından çıkar çatışması bildirilmemiştir.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021;80:14-25.
2. Kaul A, Gordon C, Crow MK, Hughes GC, Kolfenbach JR, Costenbader KH. Systemic lupus erythematosus. Nat Rev Dis Primers. 2016;2:16039.
3. Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet. 2019;393:2344-58.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100:S1-276.
5. Nagai Y, Yokogawa N, Shimada K, Sugii S. Characteristics and risk factors of an emergency department visit in patients with systemic lupus erythematosus. Rheumatol Int. 2019;39:1567-73.
6. Dhital R, Pokharel A, Karageorgiou I, Poudel DR, Guma M, Kalunian K. Epidemiology and outcomes of emergency department visits in systemic lupus erythematosus: Insights from the nationwide emergency department sample (NEDS). Lupus. 2023;32:1646-55.
7. Panopalis P, Gillis JZ, Yazdany J, Schmajuk G, MacLean CH, Trupin L. Frequent use of the emergency department among persons with systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010;62:401-8.
8. Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024;83:15-29.
9. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110-21.
10. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358:929-39.
11. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004;65:521-30.
12. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:721-31.
13. Mok CC. Biomarkers for lupus nephritis: a critical appraisal. J Biomed Biotechnol. 2010;2010:638413.
14. Gordon C, Amissah-Arthur MB, Gayed M, et al. The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. Rheumatology (Oxford). 2018;57:e1-e45.
15. Saxena A, Sorrento C, Izmirly P, et al. Low versus high initial oral glucocorticoid dose for lupus nephritis: a pooled analysis of randomised controlled clinical trials. Lupus Sci Med. 2025;12:e001351.
16. Bandhan IH, Islam MN, Ahmad HI, Ahmedullah AK. Outcome of low-dose prednisolone use for the induction of remission in lupus nephritis patients. Int J Rheum Dis. 2022;25:121-30.
17. Zhou XJ, Chen M, Wang SX, Zhou FD, Zhao MH. A 3-year follow-up of a patient with acute renal failure caused by thrombotic microangiopathy related to antiphospholipid syndrome: case report. Lupus. 2017;26:777-82.
18. Kotzen ES, Roy S, Jain K. Antiphospholipid syndrome nephropathy and other thrombotic microangiopathies among patients with systemic lupus erythematosus. Adv Chronic Kidney Dis. 2019;26:376-86.
19. Bienaimé F, Legendre C, Terzi F, Canaud G. Antiphospholipid syndrome and kidney disease. Kidney Int. 2017;91:34-44.
20. Scheen M, Adedjouma A, Esteve E, et al. Kidney disease in antiphospholipid antibody syndrome: risk factors, pathophysiology and management. Autoimmun Rev. 2022;21:103072.
21. Lvovich S, Goldsmith DP. Neurological complications of rheumatic disease. Semin Pediatr Neurol. 2017;24:54-9.
22. Wang L, Chen H, Zhang Y, et al. Clinical characteristics of cerebral venous sinus thrombosis in patients with systemic lupus erythematosus: a single-centre experience in China. J Immunol Res. 2015;2015:540738.
23. Rodriguez-Hernandez A, Ortiz-Orendain J, Alvarez-Palazuelos LE, Gonzalez-Lopez L, Gamez-Nava JI, Zavala-Cerna MG. Seizures in systemic lupus erythematosus: a scoping review. Seizure. 2021;86:161-7.
24. Rodrigues M, Galego O, Costa C, et al. Central nervous system vasculitis in systemic lupus erythematosus: a case series report in a tertiary referral centre. Lupus. 2017;26:1440-7.
25. Jain S, Khormi A, Sangle SR, D'Cruz DP. Transverse myelitis associated with systemic lupus erythematosus (SLE-TM): a review article. Lupus. 2023;32:1033-42.
26. Andreoli M, Hollenhorst CN, Malavia T, et al. A case report of systemic lupus erythematosus presenting as ısolated mononeuropathy multiplex. Neurohospitalist. Published online September 23, 2024.
27. Sayeed SKJB, Khan AH, Moniruzzaman M, Mahmud R, Rahman MM. Systemic lupus erythematosus with acute ischemic optic neuropathy complicated with neuromyelitis optica: a case report. J Med Case Rep. 2023;17:21.
28. Sarwar S, Mohamed AS, Rogers S, et al. Neuropsychiatric systemic lupus erythematosus: a 2021 update on diagnosis, management, and current challenges. Cureus. 2021;13:e17969.
29. de Oliveira I, Sampaio Rocha-Filho PA. Headache and systemic lupus erythematosus: a narrative review. Headache. 2023;63:461-71.
30. Cantero C, Vongthilath R, Plojoux J. Acute lupus pneumonitis as the initial presentation of systemic lupus erythematosus. BMJ Case Rep. 2020;13:e234638.
31. Jiménez-Zarazúa O, Vélez-Ramírez LN, Ramírez-Casillas CA, Mondragón JD. Pulmonary thromboembolism and alveolar hemorrhage as initial manifestations of systemic lupus erythematosus. Lupus. 2022;31:116-24.

32. Al-Adhoubi NK, Bystrom J. Systemic lupus erythematosus and diffuse alveolar hemorrhage, etiology and novel treatment strategies. Lupus. 2020;29:355-63.

33. Andrade C, Mendonça T, Farinha F, et al. Alveolar hemorrhage in systemic lupus erythematosus: a cohort review. Lupus. 2016;25:75-80.

34. Dein E, Douglas H, Petri M, Law G, Timlin H. Pericarditis in lupus. Cureus. 2019;11:e4166.

35. du Toit R, Karamchand S, Doubell AF, Reuter H, Herbst PG. Lupus myocarditis: review of current diagnostic modalities and their application in clinical practice. Rheumatology (Oxford). 2023;62:523-34.

36. Melano-Carranza E, Zambrano-Zambrano A, Valle-Uitzil W, et al. Coronary artery disease in systemic lupus erythematosus: what do the facts say? Cureus. 2023;15:e33449.

37. Sanaka K, Mathew J, Hoque AR, Xu B. Outcomes and predictors of inpatient mortality for marantic endocarditis complicating systemic lupus erythematosus: contemporary nationwide study from the United States. Angiology. Published online September 26, 2024.

38. Hill QA, Stamps R, Massey E, et al. The diagnosis and management of primary autoimmune haemolytic anaemia. Br J Haematol. 2017;176:395-411.

39. Santacruz JC, Mantilla MJ, Rueda I, Pulido S, Rodriguez-Salas G, Londono J. A practical perspective of the hematologic manifestations of systemic lupus erythematosus. Cureus. 2022;14:e22938.

40. Jäger U, Barcellini W, Broome CM, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020;41:100648.

41. Lambert MP, Gernsheimer TB. Clinical updates in adult immune thrombocytopenia. Blood. 2017;129:2829-35.

42. Rodeghiero F. A critical appraisal of the evidence for the role of splenectomy in adults and children with ITP. Br J Haematol. 2018;181:183-95.

43. Means RT Jr. Pure red cell aplasia. Blood. 2016;128:2504-9.

44. El-Husseini A, Hannan S, Awad A, Jennings S, Cornea V, Sawaya BP. Thrombotic microangiopathy in systemic lupus erythematosus: efficacy of eculizumab. Am J Kidney Dis. 2015;65:127-30.

45. Poudel P, Swe T, Rayancha S. A rare case of macrophage activation syndrome presenting as the first manifestation of systemic lupus erythematosus. J Investig Med High Impact Case Rep. 2018;6:2324709618812196.

46. Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. Hematology Am Soc Hematol Educ Program. 2013;2013:605-11.

47. Gladman DD, Dhillon N, Su J, Urowitz MB. Osteonecrosis in SLE: prevalence, patterns, outcomes and predictors. Lupus. 2018;27:76-81.

48. Shaharir SS, Chua SH, Mohd R, et al. Risk factors for symptomatic avascular necrosis (AVN) in a multi-ethnic systemic lupus erythematosus (SLE) cohort. *PLoS One.* 2021;16:e0248845.

49. Sodhi N, Acuna A, Etcheson J, et al. Management of osteonecrosis of the femoral head. Bone Joint J. 2020;102-B(7_Supple_B):122-8.

50. Zhao D, Zhang F, Wang B, et al. Guidelines for clinical diagnosis and treatment of osteonecrosis of the femoral head in adults (2019 version). *J Orthop Translat.* 2020;21:100-10.

51. Yin P, Li J, Wen Q, et al. Infection-related hospitalization after intensive immunosuppressive therapy among lupus nephritis and ANCA glomerulonephritis patients. Ren Fail. 2020;42:474-82.

52. Singh JA, Cleveland JD. Hospitalized infections in lupus: a nationwide study of types of infections, time trends, health care utilization, and in-hospital mortality. Arthritis Rheumatol. 2021;73:617-30.

53. García-Guevara G, Ríos-Corzo R, Díaz-Mora A, et al. Pneumonia in patients with systemic lupus erythematosus: epidemiology, microbiology and outcomes. Lupus. 2018;27:1953-9.

54. Barber MRW, Clarke AE. Systemic lupus erythematosus and risk of infection. Expert Rev Clin Immunol. 2020;16:527-38.

55. Nguyen Y, Costedoat-Chalumeau N. Serious infections in patients with systemic lupus erythematosus: how can we prevent them? Lancet Rheumatol. 2023;5:e245-6.

56. Oud L, Garza J. The association of systemic lupus erythematosus with short-term mortality in sepsis: a population-level analysis. J Investig Med. 2023;71:419-28.

57. Suárez-Avellaneda A, Quintana JH, Aragón CC, et al. Systemic lupus erythematosus in the intensive care unit: a systematic review. Lupus. 2020;29:1364-76.

58. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis. 2017;76:476-85.

59. Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5:2060-8.

60. Gholizadeh Ghozloujeh Z, Singh T, Jhaveri KD, et al. Lupus nephritis: management challenges during pregnancy. Front Nephrol. 2024;4:1390783.

61. Muñoz CM, Goulden B, Ahmed K, Alijotas-Reig J, Giles I. Risk of adverse pregnancy outcomes prior to the onset of an autoimmune rheumatic disease: a systematic review. Rheumatology (Oxford). 2023;62:497-511.

62. Tufano A, Coppola A, Maruotti GM, Martinelli P, Cerbone AM, Di Minno G. HELLP syndrome and its relation with the antiphospholipid syndrome. Blood Transfus. 2014;12:114-8.

63. Arachchillage DRJ, Laffan M. Pathogenesis and management of antiphospholipid syndrome. Br J Haematol. 2017;178:181-95.

64. de Ganzo Suárez T, de Paco Matallana C, Plasencia W. Spiral, uterine artery doppler and placental ultrasound in relation to preeclampsia. Best Pract Res Clin Obstet Gynaecol. 2024;92:102426.

65. Bankole A, Nwaonu J. A review of neonatal lupus syndrome. Sci Prog. 2024;107:368504241278476.