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"Psout": The clinical intersection of psoriatic arthritis and gout

"Psout": Psoriatik artrit ve gut hastalığının klinik kesişimi

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Abstract

The coexistence of gout and psoriatic arthritis (PsA) has been recognized for many years; however, increasing awareness of their shared comorbidities and overlapping clinical phenotypes has led to more frequent identification of this association in recent clinical practice. This overlap presents several diagnostic and therapeutic challenges, particularly in terms of differential diagnosis and the need for individualized treatment strategies. Epidemiological studies have demonstrated an increased risk of developing gout in patients with both cutaneous psoriasis and PsA. Gout and PsA share common risk factors, suggesting the presence of underlying and closely interconnected pathophysiological mechanisms. This review explores the intersection between gout and PsA in the context of shared clinical features, common inflammatory pathways, and associated comorbidities. Moreover, the emerging concept of a novel "overlap syndrome" termed "Psout" is discussed. This new framework may offer meaningful contributions to clinical practice by improving diagnostic accuracy and optimizing therapeutic approaches.

Keywords: Psoriasis, psoriatic arthritis, hyperuricemia, gout, psout

Özet

Gut ve psoriatik artrit (PsA) birlikteliği uzun süredir bilinmekle birlikte, ortak komorbiditeler ve benzer klinik fenotiplere yönelik artan farkındalık nedeniyle son yıllarda klinik pratikte daha sık karşılaşılmaktadır. Bu durum, tanı sürecinde ayrıştırma güçlükleri ve tedavi stratejilerinin bireyselleştirilmesi açısından çeşitli zorluklara yol açmaktadır. Epidemiyolojik çalışmalar hem kutanöz psoriasisli hem de PsA'lı hastalarda gut gelişme riskinin arttığını göstermektedir. PsA ve gut, ortak risk faktörlerine sahip olup, bu durum altta yatan ve birbiriyle sıkı bir şekilde bağlantılı patofizyolojik mekanizmaların varlığını düşündürmektedir. Bu derlemede, gut ve PsA arasındaki örtüşme; paylaşılan klinik özellikler ortak enflamatuvar süreçler ve eşlik eden komorbiditeler bağlamında ele alınmakta ve yeni bir "örtüşen sendrom" olarak "Psout" adıyla yeni bir tanımlama tartışılmaktadır. Bu yeni yaklaşım, klinik pratiğe tanı doğruluğu ve tedavi optimizasyonu açısından anlamlı katkılar sunabilir.

Anahtar Kelimeler: Psöriasis, psöriatik artrit, hiperürisemi, gut, psout

Introduction

Although the coexistence of gout and psoriasis/psoriatic arthritis (PsA) has long been recognized, increasing awareness in recent years regarding their shared clinical features and comorbidities has led to more frequent identification of this overlap in clinical practice.[1] This has introduced various challenges in the diagnostic and therapeutic processes.

Gout and PsA are common forms of inflammatory arthritis, both of which are chronic inflammatory diseases associated with significant morbidity. Gout is the most prevalent form of inflammatory arthritis, with its prevalence varying across different geographic regions and ethnic groups. For instance, prevalence rates have been reported as 2.3% in the United Kingdom, 5.1% in the United States, and 3.7% in Canada.[2,3] The highest prevalence is observed among certain ethnic populations, such as the Indigenous peoples of Taiwan (10.4-15.2%) and the Maori population (6.1%).[4,5] PsA, on the other hand, is a seronegative chronic inflammatory arthritis that may involve axial and/or peripheral joints. While its prevalence in the general population ranges from 0.1% to 1%, it increases to 20-30% among individuals with cutaneous psoriasis.[6,7] These findings highlight PsA as one of the most common systemic comorbidities associated with psoriasis and emphasize the significant public health burden posed by both gout and PsA.

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Epidemiological studies indicate that individuals affected by both psoriasis and gout share similar demographic characteristics, lifestyle factors, and metabolic comorbidities (e.g., obesity, hypertension, dyslipidemia, type 2 diabetes).[8-10] Cross-sectional studies have shown an increased risk of developing gout among patients with psoriasis and PsA. These shared risk factors suggest the presence of underlying and potentially interconnected pathophysiological mechanisms.[11]

From clinical, pathophysiological, and radiographic perspectives, PsA and gout may exhibit overlapping features. Particularly in advanced disease stages, it may become difficult to distinguish between a gout flare and a PsA exacerbation based on clinical presentation alone. Moreover, the topographic similarities in joint involvement patterns further complicate the diagnostic process.[1] Table 1 presents the comparative features of PsA and gout. The coexistence of both diseases in a single patient is not uncommon in clinical practice. In this context, the term "Psout" was first introduced by Felten et al.[12] in 2020 as a descriptive concept for patients presenting with both PsA and gout. The authors derived this definition from a concrete case experience (Figure 1). The term "Psout" not only reflects the coexistence of these two diseases but also implies potential shared pathophysiological pathways. Therefore, in patients with concurrent PsA and gout, achieving an accurate diagnosis and developing an effective treatment plan require an integrated evaluation of both inflammatory and metabolic components. Figure 2 illustrates the general clinical and pathophysiological characteristics of Psout.

This narrative review aims to provide a comprehensive overview of "Psout", a concept representing the clinical, pathophysiological, and epidemiological intersection of gout and PsA, and to raise awareness of its clinical relevance in light of the current scientific literature.

Shared Pathogenesis Between Psoriatic Disease and Gout

There are overlapping pathophysiological mechanisms at the molecular level between PsA and gout. In both diseases, hyperuricemia acts as both a cause and a consequence of the inflammatory process. Hyperuricemia results from either increased uric acid production or decreased excretion and is closely linked to purine metabolism, intestinal transport systems, and hepatic function.[13]

Damage-associated molecular patterns, such as microbial peptides found in psoriatic plaques, keratinocyte-derived alarmins, and monosodium urate (MSU) crystals characteristic of gout, stimulate plasmacytoid dendritic cells and trigger the release of proinflammatory cytokines including interleukin (IL)-1β, IL-6, tumour necrosis factor alpha (TNF-α), and interferon (IFN)-γ. This inflammatory cascade continues with the activation of Th1 and Th17 cells via dendritic cell signaling. IL-17 and IFN-γ secreted by Th17 cells re-activate keratinocytes, leading to the establishment of a self-perpetuating autoinflammatory loop.[12,14,15] This same cytokine profile may contribute to the development of non-alcoholic fatty liver disease and elevate serum uric acid (SUA) levels due to ATP depletion in hepatocytes. Furthermore, the subclinical intestinal inflammation reported in PsA may impair uric acid homeostasis by disrupting the function of enterocytic transporters such as BCRP/ABCG2.[11,13]

In gout, phagocytosis of MSU crystals activates the NLRP3 inflammasome, which in turn enhances IL-1β production through caspase-1 activation. In addition, MSU crystals induce NETosis in neutrophils, activating innate immunity and promoting Th17 polarization through antigen presentation. Consequently, IL-17, IL-1, and other proinflammatory cytokines stimulate keratinocyte proliferation and accelerate purine metabolism, reinforcing the hyperuricemia-gout cycle.[12,15]

Table 1. Comparative clinical characteristics of psoriatic arthritis and gout

Feature	Psoriatic arthritis	Gout
Age/sex at onset	30-50 years, equal in males and females	>40 years, predominantly males
Pattern of joint involvement	Generally asymmetric	Generally asymmetric
Number of affected joints	Most commonly oligoarticular	Typically monoarticular or oligoarticular
Associated symptoms	Periarticular erythema is common	Periarticular erythema may occur
Cutaneous and nail manifestations	Characterized by psoriatic plaques, nail pitting, and onycholysis	Presence of tophi in chronic disease stages
Predominant sites (hands and feet)	Predominantly distal joints	Predominantly distal joints
Dactylitis (diffuse digital swelling)	A common and characteristic clinical feature	Occasionally observed
First metatarsophalangeal joint involvement	May be affected	Frequently affected and often the initial site of involvement
Axial/spinal involvement	Common; includes sacroiliitis and syndesmophyte formation	Rarely observed
Hyperuricemia	Observed in approximately 30% of patients	Common, with fluctuations during acute attacks
Monosodium urate crystal deposition (joint fluid)	Reported in ~3.3% of cases	Characteristic but variable among patients
Radiographic features	Erosions with new bone formation	"Punched-out" erosions, tophi

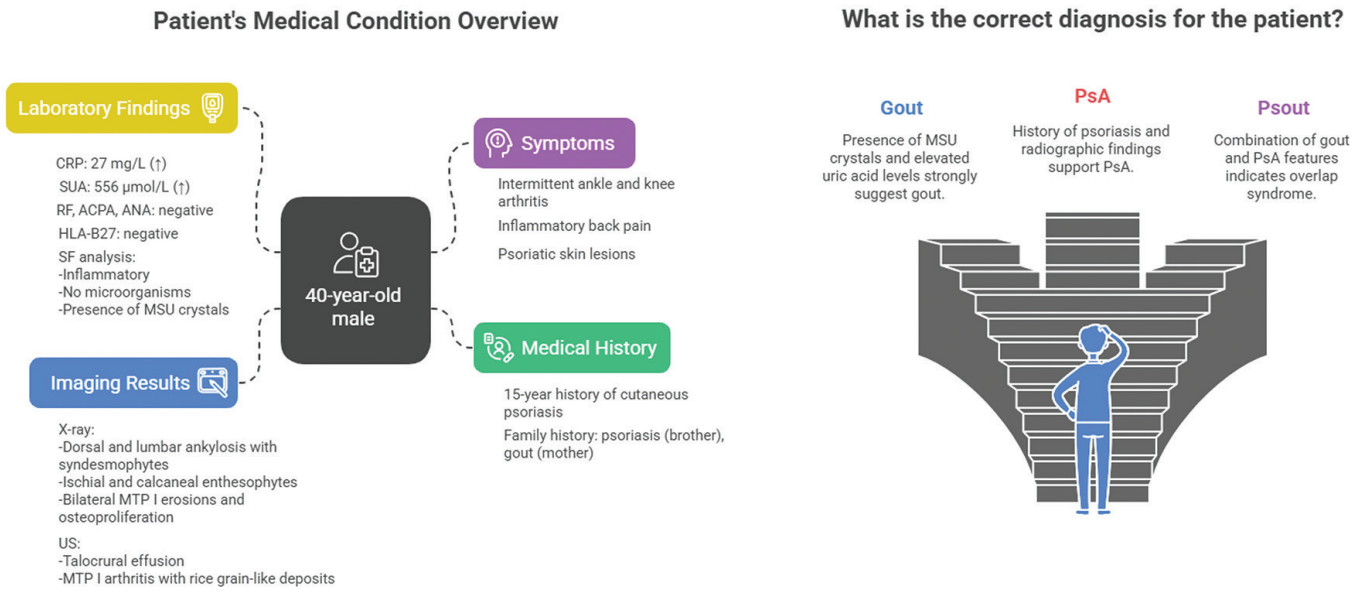

Figure 1. Diagnostic dilemma in a patient with psoriasis, arthritis, and hyperuricemia: gout, psoriatic arthritis, or the emerging overlap entity "Psout"
ACPA: Anti-citrullinated protein antibody, ANA: Antinuclear antibody, CRP: C-reactive protein, HLA: Human leukocyte antigen, MSU: Monosodium urate, MTP: Metatarsophalangeal, PsA: Psoriatic arthritis, RF: Rheumatoid factor, SF: Synovial fluid, SUA: Serum uric acid, US: Ultrasound

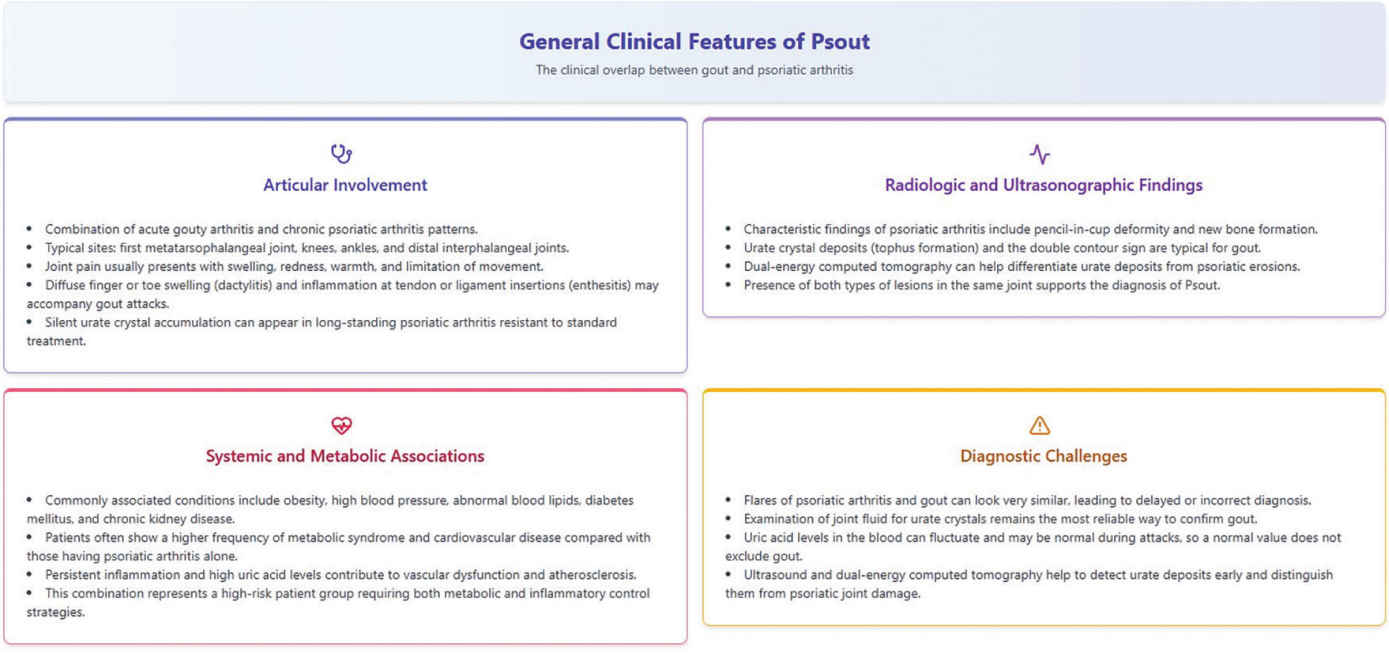

Figure 2. General clinical characteristics of Psout

In conclusion, the potential of MSU crystals to activate the IL-23/IL-17 axis and keratinocyte-T cell interactions may contribute to the emergence of "Psout." This condition is characterized by a more severe, widespread, and destructive clinical course.[1,12]

Hyperuricemia in PsA

Hyperuricemia is approximately three times more prevalent in patients with PsA compared to the general population.[16] In PsA, accelerated cutaneous cell turnover and chronic systemic inflammation may contribute to elevated SUA levels. The global prevalence of hyperuricemia in patients with psoriasis and/or PsA has been reported to range between 13% and 40.7%.[9,11] Although the potential association between psoriasis and hyperuricemia was first described by Walker in 1958, subsequent studies have yielded inconsistent results.[17] A meta-analysis including 14 studies and a total of 29.416 participants revealed

that the association between hyperuricemia and psoriasis varies according to ethnicity and geographic region. While a significant positive correlation was found in Western Europe, similar associations were not observed in Asian or Middle Eastern populations. These discrepancies are thought to be attributable to differences in study design, characteristics of the target populations, the presence of concomitant PsA, and varying levels of disease severity.[18]

Several studies have demonstrated a significant association between hyperuricemia and psoriasis, and some have shown that SUA levels increase in parallel with the extent of skin involvement. Hyperuricemia is proposed not only as a metabolic abnormality but also as a potential independent risk factor for the development of PsA.[13,19] Supporting this hypothesis, a retrospective case-control study conducted in Japan analyzed data from 331 patients and found that the prevalence of hyperuricemia was significantly higher in patients with PsA compared to those with psoriasis alone (22% vs. 9%). Regression analysis further identified hyperuricemia as an independent predictor for the development of PsA [odds ratio (OR) 4.18, 95% confidence interval (CI) 1.60-10.96]. These findings underscore the potential role of hyperuricemia within the psoriatic disease spectrum.[20]

PsA and Gout

The reported prevalence of gout among patients with PsA varies significantly across studies. In a Canadian cohort of 265 patients followed for six years, the incidence was 0.8%, whereas in another cohort predominantly composed of white males, this rate increased to 8.6% over a median follow-up of 19.5 years.[21,22] Retrospective case-control data from France also confirmed a notably higher prevalence of gout in male PsA patients (6.2%) compared to the general population (0.9%).[23] Compared to normouricemic cases, hyperuricemic PsA patients had significantly higher proportions of male sex (72.6% vs. 39.1%), higher body mass index (BMI) (30.9 vs. 28.7 kg/m²), and greater comorbidity burden (Charlson index 2.6 vs. 1.8). Multivariate analyses revealed that hyperuricemia was independently associated with male sex, hypertension, moderate-to-severe chronic kidney disease, prior PUVA therapy, peripheral joint involvement, and poor treatment response. Hyperuricemia was found to triple the risk of peripheral PsA (OR 2.98, 95% CI: 1.15-7.75) and significantly reduce the likelihood of good therapeutic response (OR 0.35, 95% CI: 0.15-0.87). A ten-year retrospective French dataset demonstrated that hyperuricemia was associated with a more polyarticular and destructive PsA phenotype, with erosions observed more frequently in hyperuricemic patients (43.7% vs. 28%), particularly when SUA levels exceeded 300 µmol/L. However, it was suggested that this association might be partially exaggerated due to more frequent SUA testing in treatment-resistant cases. Furthermore, hyperuricemic PsA patients tended to be older, predominantly male, and had later disease onset.

In a Canadian prospective cohort study, 1019 patients with psoriasis and/or PsA were followed for 6 to 12 months to assess the impact of hyperuricemia on disease characteristics and comorbidities. Hyperuricemia was detected in 325 patients (35.9%), yet only 11 (3.4%) developed gout. Hyperuricemic patients had significantly longer PsA disease duration, and higher Psoriasis Area and Severity Index (PASI) scores compared to normouricemic individuals, although no significant differences were observed in tender or swollen joint counts. In a parallel case-control analysis of 318 hyperuricemic PsA patients matched for age, sex, and disease duration with 318 normouricemic PsA patients, hyperuricemia was associated with increased prevalence of cardiovascular and metabolic diseases, nephrolithiasis, and higher serum creatinine levels.[24] Persistent hyperuricemia during follow-up was found to significantly increase the incidence of myocardial infarction, heart failure, and renal dysfunction, underscoring its potential role not only in joint disease but also in systemic cardio-renal morbidity in PsA.

A large-scale Taiwanese cohort study including 114.623 individuals with gout and 114.623 controls demonstrated a strong association between gout and PsA (adjusted OR=2.50; 95% CI: 1.95-3.22), while the association between gout and psoriasis alone was weaker (adjusted OR=1.30; 95% CI: 1.20-1.42).[19] Prospective data from the US-based Health Professionals Follow-Up Study and Nurses' Health Study cohorts support these findings, showing that physician-diagnosed psoriasis and PsA independently increased the risk of incident gout [multivariable hazard ratio (HR) for psoriasis=1.71; 95% CI: 1.36-2.15; for PsA=4.95; 95% CI: 2.72-9.01].[25] Gout diagnoses were confirmed using the 1977 American College of Rheumatology classification criteria. In sex-stratified analyses, psoriasis alone conferred a higher risk of gout in men than in women (HR=2.72; 95% CI: 1.75-4.25); however, this difference was no longer significant when PsA was present, likely due to the comparable prevalence of PsA between sexes and the shared inflammatory/metabolic burden equalizing the risk.

Another population-based cohort study from Taiwan revealed that individuals with both psoriasis and gout had a significantly higher risk of cardiovascular disease compared to those with psoriasis alone (relative risk=2.39), highlighting the substantial cardiovascular burden associated with gout as a comorbidity within the psoriatic disease spectrum.[26]

MSU Crystals in PsA

Even in patients without a clinical diagnosis of gout, MSU crystals can be frequently detected in synovial fluid (SF), supporting the possibility of a biological overlap between PsA

and gout. In a large-scale analysis of 5,020 SF samples, MSU crystals were identified in 3.34% of PsA cases, compared to 0.30% in rheumatoid arthritis, 0.70% in other spondylarthritis, and 0.80% in calcium pyrophosphate deposition disease.[27] Galozzi et al.[28] reported that MSU crystals, rather than hyperuricemia, may be a stronger trigger for the PsA-gout overlap (Psout). In their initial study analyzing seven categories of arthritis, the prevalence of MSU crystals was found to be 83.3% in gout and 10% in PsA. A subsequent, broader study involving ten arthritis categories confirmed these findings, with MSU crystal prevalence rates of 97.96% in gout and 3.34% in PsA.[29]

In another case-control series, MSU crystals were found in 68.6% of PsA patients, with crystal-positive cases being more frequently associated with metabolic comorbidities such as obesity, diabetes, ischemic heart disease, and dyslipidemia. Moreover, the presence of crystals was strongly correlated with disease activity (OR: 15.96; 95% CI: 5.76-44.23).[30] Age and sex distributions were similar between crystal-positive and crystal-negative PsA subgroups, emphasizing the potential role of MSU crystals in PsA pathophysiology and the importance of considering metabolic risk profiles in clinical management.

It can be challenging to distinguish acute monoarthritis flares in PsA from crystal-induced gout attacks. Although the presence of pathogenic crystals and data on SF inflammation can help reduce misclassification, they may still be insufficient to determine the exact etiology of acute joint swelling.[31] In a retrospective Italian series of 213 PsA patients, the overall prevalence of MSU crystals was 2.4%, increasing to 10.5% in the hyperuricemic subgroup. Hyperuricemic patients were typically older and predominantly male.[29] However, hyperuricemia was not significantly associated with SF inflammatory features (white blood cell counts <2,000, 2,000-5,000, or 5,000-50,000/mm^3), and crystals were mostly observed in specimens with low-grade inflammation. The presence of MSU crystals in normouricemic patients may reflect transient SUA reductions during acute gout attacks. As the study only included patients presenting with joint swelling and lacked SUA measurements, PsA flares or hyperuricemia may have been underdiagnosed. Indeed, three crystal-positive patients were normouricemic but had high percentages of polymorphonuclear leukocytes in the SF (50-90%).

In a retrospective case-control study, 156 PsA patients and 50 gonarthrosis (GoA) controls were compared using pain (visual analog scale), disease activity (disease activity in psoriatic arthritis, PASI, modified composite psoriatic disease activity index), and functional limitation (health assessment questionnaire - disability index) measures. SF crystal analysis revealed that 23.7% of PsA patients had detectable crystals, while none were identified in the GoA group ($p<0.001$). Among PsA patients, 67.6% of the crystals were MSU and 21.6% were calcium pyrophosphate. Crystal-positive PsA patients had higher prevalence of ischemic heart disease and hyperuricemia, and crystal presence was significantly associated with increased disease activity, severe pain, and marked functional impairment. Notably, the OR for severe pain associated with crystal presence was 157.25 (95% CI: 39.50-625.94). These findings suggest that synovial crystals may be linked to heightened inflammatory burden and reduced quality of life in PsA and support the consideration of SF analysis and urate-lowering therapy in patients with active disease.[30]

Differentiating Gout and PsA Using Imaging Modalities

The 2016 The European Alliance of Associations for Rheumatology guidelines emphasized the identification of MSU crystals in SF as the gold standard for the diagnosis of gout. The 2018 update highlighted the diagnostic value of joint ultrasonography (US) in cases where joint aspiration is not feasible, and the clinical presentation is atypical. Indeed, subclinical MSU crystal deposits detectable by US have been reported in 15-25% of individuals with asymptomatic hyperuricemia.[11] In a single-center, cross-sectional observational study conducted in patients followed with a diagnosis of PsA, coexisting gout was identified in approximately 10% of cases, and it was demonstrated that SUA measurement combined with US screening may help predict gout risk in PsA patients.[32] Moreover, the association of concomitant gout with increased cardiovascular morbidity in PsA underscores the critical importance of early gout screening and personalized treatment strategies in disease management.

Classical radiographic features of PsA—such as periarticular and diaphyseal periostitis, “pencil-in-cup” deformities due to osteolysis, acro-osteolysis, ankylosis, and spondylitis—offer important clues for differentiating chronic PsA from chronic gouty arthritis. However, in rare cases of spinal gout, sacroiliitis may develop, mimicking axial involvement seen in PsA.[33] In advanced gout arthritis, bone erosions and complete joint ankylosis may be observed, and intraosseous peripheral tophi may resemble the marginal erosions typical of PsA (Figure 3). Additionally, both conditions may present with enthesopathy or tophus formation in the Achilles tendon and plantar fascia, further complicating the clinical distinction. The characteristic bone proliferation and distal interphalangeal joint involvement in PsA facilitate differentiation from rheumatoid arthritis, while the marginal erosions in PsA—often associated with periostitis—contrast with the central erosions seen in erosive osteoarthritis (Figure 4). These marginal erosions can form sharp protrusions resembling “mouse ears”, producing the so-called “Mickey Mouse” sign in imaging.[12]

US can provide information on both synovitis and crystal deposition by identifying features such as the double contour sign, MSU aggregates, and tophi. In contrast, dual-energy computed tomography (DECT) directly visualizes crystal deposits.

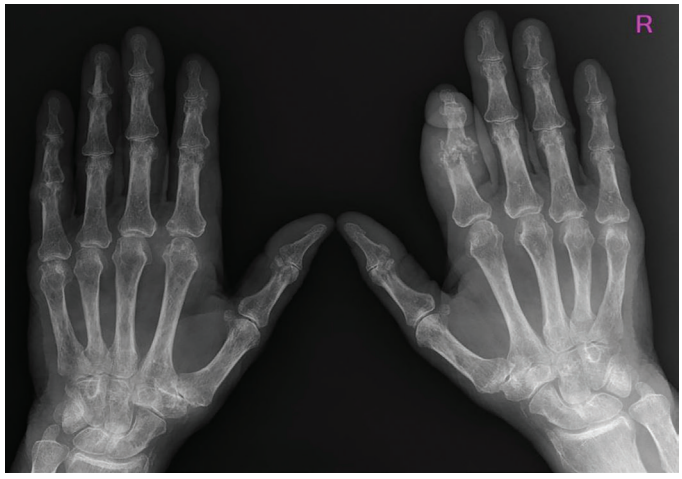

Figure 3. Radiographic features of gout showing bone erosions, ankylosis, and intraosseous tophi mimicking psoriatic marginal erosions (from the authors' collection)

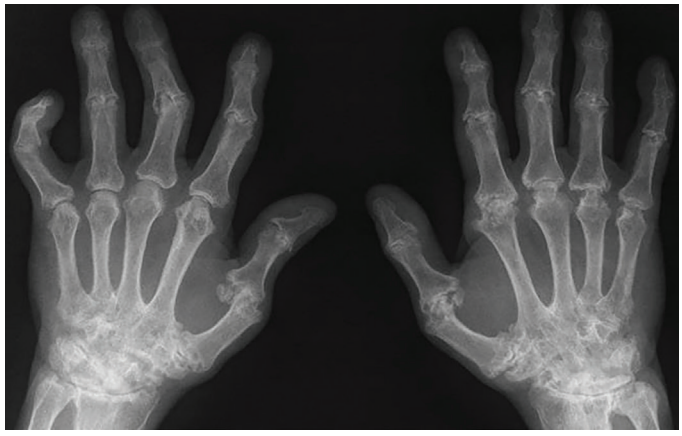

Figure 4. Radiographic features of psoriatic arthritis showing periostitis, bone proliferation, and distal interphalangeal joint involvement (from the authors' collection)

[34,35] Although US findings are considered more characteristic for gout arthritis, their specificity is limited; for instance, the double contour sign can also be observed in calcium pyrophosphate deposition disease and asymptomatic hyperuricemia.

DECT evaluates tissue absorption and chemical composition using two different energy levels (80 and 140 kVp). It can be employed for diagnosing gout, monitoring therapeutic response, and assessing disease progression. However, its routine use is limited by cost and accessibility.[36] Nevertheless, DECT may be considered in PsA patients with persistent joint flares despite treatment and inconclusive SF/US findings. Additionally, DECT can be useful in PsA patients with axial involvement who respond poorly to standard non-steroidal anti-inflammatory drugs (NSAIDs) or biologic therapies and who have risk factors for gout. Still, crystal deposition detected by DECT or US in asymptomatic individuals is not a reliable predictor of future flares.[11]

Clinical Implications of Hyperuricemia in PsA

Gout and PsA are two distinct types of inflammatory arthritis that can share overlapping clinical features. Both conditions commonly affect similar peripheral joints—including the metatarsophalangeal joints, feet, ankles, and knees—and may present in an asymmetric monoarticular or oligoarticular pattern. Findings such as synovitis and dactylitis—characterized by localized erythema, swelling, and tenderness—can be observed in both diseases.[11,12] However, axial involvement and sacroiliitis are rarely seen in gout, whereas they are more frequently encountered in PsA. Genetic markers also play a key role in distinguishing the two; for instance, the HLA-B27 allele is found in only 8-10% of gout patients but in up to 50% of those with PsA.[12,37]

A prospective cohort study from Canada found that hyperuricemia was common among patients with psoriasis and PsA and was associated with an increased risk of developing gout. Hyperuricemic individuals had longer PsA disease duration and more severe skin involvement, as reflected by higher PASI scores. However, hyperuricemia did not correlate with increased joint activity, as the number of tender and swollen joints was similar between hyperuricemic and normouricemic patients.[24]

Conversely, a 10-year retrospective case-control study from France revealed that hyperuricemia was associated with a more destructive pattern of joint involvement in PsA. Multivariable analyses demonstrated a significant relationship between hyperuricemia and inadequate therapeutic response. In this study, hyperuricemic PsA patients exhibited less frequent axial involvement but had a more widespread (polyarticular) and destructive disease course. Joint erosions were also more commonly observed in hyperuricemic individuals compared to normouricemic patients (43.7% vs. 28%). This increased frequency of erosions was particularly noted in cases where SUA levels exceeded 300 µmol/L. Demographically, hyperuricemic PsA patients were found to be older, more frequently male, and to have a later age of PsA onset than normouricemic counterparts.[23]

Hyperuricemia in PsA has also been associated with renal and cardiovascular comorbidities.[38] The literature reports increased prevalence of hypertension, angina, diabetes mellitus, elevated liver enzymes, elevated inflammatory markers, increased serum creatinine, and nephrolithiasis in hyperuricemic individuals.[11,39] Particularly, the presence of persistent hyperuricemia—defined as elevated SUA levels over two consecutive clinical visits—has been significantly associated with higher prevalence of myocardial infarction and congestive heart failure. Multivariate analyses have shown that in PsA patients, persistent hyperuricemia correlates significantly with disease duration (OR: 4.430), BMI (OR: 1.176), and a history of kidney stones (OR: 4.430). In contrast, no significant correlation was found between PASI score and hyperuricemia.[40] However, some studies have reported conflicting findings. For example, a study from Korea demonstrated a significant association between SUA levels and both PASI score and BMI. These discrepancies may stem from differences in population characteristics and methodological approaches.[41]

Therapeutic Approaches at the Intersection of Psoriatic Disease and Hyperuricemia

Studies investigating the impact of PsA or psoriasis treatment on SUA levels remain limited. Nevertheless, current literature suggests that PsA patients are at a significantly increased risk for developing hyperuricemia and gout. Furthermore, hyperuricemic PsA patients have been reported to exhibit lower treatment responses and more pronounced peripheral and destructive joint damage.[23] A comprehensive post-hoc analysis using data from 2504 patients enrolled in phase 3 trials (FUTURE 2-5 and MAXIMISE) compared hyperuricemic patients (SUA ≥360 µmol/L) to normouricemic patients (SUA <360 µmol/L). Evaluations based on joint, skin, and nail involvement, radiographic progression, and quality of life indicated that hyperuricemia may adversely influence the clinical course of PsA.[42] These findings suggest that hyperuricemia could represent an important biomarker to consider in PsA management.

There is currently no direct clinical evidence regarding the effects of gout or hyperuricemia treatment on disease activity in PsA or psoriasis. However, a limited number of studies have shown that urate-lowering therapies such as allopurinol and febuxostat significantly reduce proinflammatory cytokines, including TNF-α, IL-6, and IL-17.[43-45] These reductions have been correlated with decreases in SUA levels. Such findings imply that uric acid may play a role in the pathogenesis of psoriasis and that treatment of hyperuricemia could potentially contribute to clinical improvement in PsA by attenuating inflammatory activity.

To date, only one diagnostic and treatment algorithm has been proposed for Psout—the coexistence of PsA and gout. Widawski et al.[23] outlined a series of criteria aimed at guiding a structured diagnostic and therapeutic approach to this clinical phenotype: (1) thorough documentation of any history of gout; (2) assessment and control of SUA levels ≥360 µmol/L; (3) monitoring the response to urate-lowering therapy; (4) evaluating the response to concomitant PsA treatment; (5) confirmation of MSU crystal presence via SF analysis or DECT; and (6) assessment of family history of gout. An illustrative figure regarding the management of Psout has been presented (Figure 5). These recommendations underscore the need for a comprehensive evaluation of both inflammatory and metabolic components in diagnosing Psout and advocate for a personalized treatment approach.

Discussion

While the association between gout and psoriasis/PsA has long been acknowledged, growing recognition of their common comorbidities and similar clinical presentations has contributed to the increasing identification of this overlap in routine clinical

Figure 5. Proposed management approach for Psout
DECT: Dual-energy computed tomography, MSU: Monosodium urate, PsA: Psoriatic arthritis, SF: Synovial fluid, SUA: Serum uric acid, ULT: Urate-lowering therapy

settings. The simultaneous presence of gout and PsA in the same patient is not uncommon and was first termed "Psout" by Felten et al.[12] in 2020. This review summarizes the current literature on the Psout concept; however, it should be noted that Psout is not yet a clinically validated entity.

The association between gout and PsA was first described in 1982, and elevated SUA levels have been reported in patients with psoriasis ± PsA even in the absence of clinical manifestations of gout. Epidemiological data suggest that shared pathophysiological mechanisms may underlie this relationship, supporting the concept of a distinct "Psout" syndrome.[1,11] However, most existing studies are retrospective or cross-sectional in nature, limiting the ability to establish temporal associations or causal outcomes. This overlap may be at least partially explained by the high prevalence of metabolic syndrome in both disease populations.

Given the pathogenic role of MSU crystals in triggering inflammation, urate-lowering therapies such as allopurinol and febuxostat may represent potential treatment options for controlling psoriatic disease activity, especially in refractory cases.[12,23] This therapeutic approach aims to reduce SUA levels, thereby limiting crystal formation and suppressing associated inflammatory responses. The Psout concept—defined by the coexistence of PsA and gout—highlights the importance of personalized treatment strategies that address both metabolic and inflammatory components. In this context, therapeutic interventions targeting hyperuricemia in PsA may reduce disease activity and improve clinical outcomes.

While biologic agents such as TNF-α and IL-17 inhibitors remain central in PsA management, some conventional disease-modifying antirheumatic drugs like leflunomide have demonstrated mild hypouricemic effects, potentially offering additional benefits in hyperuricemic patients.[11,46] Considering the strong association between hyperuricemia/gout and cardiovascular-metabolic comorbidities, treatment planning should incorporate lifestyle modifications and cardiovascular risk management. Furthermore, the widespread use of NSAIDs should be carefully evaluated in this patient population due to their potential to exacerbate cardiovascular risk. Despite these insights, randomized controlled trials assessing the direct efficacy of urate-lowering therapies in PsA patients are still lacking. Therefore, advanced clinical studies are needed to define optimal treatment strategies for this subgroup.

Conclusion

In conclusion, growing evidence supports the existence of a clinical and pathophysiological intersection between PsA and gout, conceptualized as "Psout". Although it is not yet formally recognized as a distinct disease entity, Psout highlights the need for heightened clinical awareness and comprehensive evaluation strategies that integrate both inflammatory and metabolic components. Future prospective studies and randomized controlled trials are warranted to elucidate its pathogenesis, refine diagnostic criteria, and develop targeted treatment protocols. Recognizing and addressing this overlap may ultimately improve clinical outcomes and quality of life in a specific subset of patients within the psoriatic disease spectrum.

Footnotes

Author Contributions

Concept: S.U., Ö.S.G., T.P., Design: S.U., Ö.S.G., T.P., Data Collection or Processing: S.U., Ö.S.G., T.P., Analysis or Interpretation: S.U., Ö.S.G., T.P., Literature Search: S.U., Ö.S.G., T.P., Writing: S.U., Ö.S.G., T.P.

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References

1. Sherri A, Mortada MM, Makowska J, Sokolowska M, Lewandowska-Polak A. Understanding the interplay between psoriatic arthritis and gout: "Psout". Rheumatol Int. 2024;44:2699-709.
2. Yokose C, McCormick N, Lu N, et al. Trends in prevalence of gout among US Asian adults, 2011-2018. JAMA Netw Open. 2023;6:e239501.
3. Rai SK, Aviña-Zubieta JA, McCormick N, et al. The rising prevalence and incidence of gout in British Columbia, Canada: population-based trends from 2000 to 2012. Semin Arthritis Rheum. 2017;46:451-6.
4. Tu F-Y, Lin G-T, Lee S-S, Tung Y-C, Tu H-P, Chiang H-C. Prevalence of gout with comorbidity aggregations in southern Taiwan. Joint Bone Spine. 2015;82:45-51.
5. Winnard D, Wright C, Taylor WJ, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. Rheumatology (Oxford). 2012;51:901-9.
6. Mease PJ, Karki C, Palmer JB, et al. Clinical characteristics, disease activity, and patient-reported outcomes in psoriatic arthritis patients with dactylitis or enthesitis: results from the corrona psoriatic arthritis/spondyloarthritis registry. Arthritis Care Res (Hoboken). 2017;69:1692-9.
7. Haddad A, Elkayam PC, Stein N, et al. Epidemiological trends in psoriatic arthritis: a comprehensive population-based study. Arthritis Res Ther. 2024;26:108.
8. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007-2008. Am J Med. 2012;125:679-87.e1.
9. Lai TL, Yim CW, Wong PY, Leung MC, Ng WL. Hyperuricemia in Asian psoriatic arthritis patients. Int J Rheum Dis. 2018;21:843-9.
10. Merola JF, Wu S, Han J, Choi HK, Qureshi AA. Psoriasis, psoriatic arthritis and risk of gout in US men and women. Ann Rheum Dis. 2015;74:1495-500.
11. Chandratre P, Sabido-Sauri R, Zhao SS, Abhishek A. Gout, hyperuricemia and psoriatic arthritis: an evolving conundrum. Curr Rheumatol Rep. 2025;27:22.

12. Felten R, Duret P-M, Gottenberg J-E, Spielmann L, Messer L. At the crossroads of gout and psoriatic arthritis: "psout". Clin Rheumatol. 2020;39:1405-13.

13. Tripolino C, Ciaffi J, Ruscitti P, Giacomelli R, Meliconi R, Ursini F. Hyperuricemia in psoriatic arthritis: epidemiology, pathophysiology, and clinical implications. Front Med. 2021;8:737573.

14. Eleftheriadis T, Pissas G, Sounidaki M, et al. Urate crystals directly activate the T-cell receptor complex and induce T-cell proliferation. Biomed Reports. 2017;7:365-9.

15. Schauer C, Janko C, Munoz LE, et al. Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Nat Med. 2014;20:511-7.

16. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med. 2005;143:499-516.

17. Lea WAJ, Curtis AC, Bernstein IA. Serum uric acid levels in psoriasis. J Invest Dermatol. 1958;31:269-71.

18. Li X, Miao X, Wang H, et al. Association of serum uric acid levels in psoriasis: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95:e3676.

19. Hu SC-S, Lin C-L, Tu H-P. Association between psoriasis, psoriatic arthritis and gout: a nationwide population-based study. J Eur Acad Dermatol Venereol. 2019;33:560-7.

20. Tsuruta N, Imafuku S, Narisawa Y. Hyperuricemia is an independent risk factor for psoriatic arthritis in psoriatic patients. J Dermatol. 2017;44:1349-52.

21. Bruce IN, Schentag CT, Gladman DD. Hyperuricemia in psoriatic arthritis: prevalence and associated features. J Clin Rheumatol. 2000;6:6-9.

22. Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC. Incidence and risk factors for gout in white men. JAMA. 1991;266:3004-7.

23. Widawski L, Fabacher T, Spielmann L, et al. Psoriatic arthritis with hyperuricemia: more peripheral, destructive, and challenging to treat. Clin Rheumatol. 2022;41:1421-9.

24. AlJohani R, Polachek A, Ye JY, Chandran V, Gladman DD. Characteristic and outcome of psoriatic arthritis patients with hyperuricemia. J Rheumatol. 2018;45:213-7.

25. Dominguez PL, Assarpour A, Kuo H, Holt EW, Tyler S, Qureshi AA. Development and pilot-testing of a psoriasis screening tool. Br J Dermatol. 2009;161:778-84.

26. Chen Z, Xu Y, Chen M, et al. Gout augments the risk of cardiovascular disease in patients with psoriasis: a population-based cohort study. Front Immunol. 2021;12:703119.

27. Oliviero F, Scanu A, Galozzi P, et al. Prevalence of calcium pyrophosphate and monosodium urate crystals in synovial fluid of patients with previously diagnosed joint diseases. Joint Bone Spine. 2013;80:287-90.

28. Galozzi P, Oliviero F, Frallonardo P, et al. The prevalence of monosodium urate and calcium pyrophosphate crystals in synovial fluid from wrist and finger joints. Rheumatol Int. 2016;36:443-6.

29. Galozzi P, Oliviero F, Scanu A, et al. Acute joint swelling in psoriatic arthritis: flare or "psout"-a 10-year-monocentric study on synovial fluid. Exp Biol Med (Maywood). 2022;247:1650-6.

30. Geneva-Popova M, Popova-Belova S, Popova V, Stoilov N. Assessment of crystals in the synovial fluid of psoriatic arthritis patients in relation to disease activity. Diagnostics (Basel, Switzerland). 2022;12.

31. Chen-Xu M, Yokose C, Rai SK, Pillinger MH, Choi HK. Contemporary prevalence of gout and hyperuricemia in the united states and decadal trends: the national health and nutrition examination survey, 2007-2016. Arthritis Rheumatol (Hoboken, NJ). 2019;71:991-9.

32. Moukarzel V, Doussière M, Barbier V, et al. Interest in daily clinical practice of screening for gouty disease in patients with psoriatic arthritis. Rheumatol Adv Pract. 2024;8:rkae069.

33. Ory PA, Gladman DD, Mease PJ. Psoriatic arthritis and imaging. Ann Rheum Dis. 2005;64(Suppl 2):ii55-7.

34. Stewart S, Dalbeth N, Vandal AC, Allen B, Miranda R, Rome K. Are ultrasound features at the first metatarsophalangeal joint associated with clinically-assessed pain and function? A study of people with gout, asymptomatic hyperuricaemia and normouricaemia. J Foot Ankle Res. 2017;10:22.

35. Breuer GS, Bogot N, Nesher G. Dual-energy computed tomography as a diagnostic tool for gout during intercritical periods. Int J Rheum Dis. 2016;19:1337-41.

36. Hu H-J, Liao M-Y, Xu L-Y. Clinical utility of dual-energy CT for gout diagnosis. Clin Imaging. 2015;39:880-5.

37. Tsai Y-G, Chang D-M, Kuo S-Y, Wang W-M, Chen Y-C, Lai J-H. Relationship between human lymphocyte antigen-B27 and clinical features of psoriatic arthritis. J Microbiol Immunol Infect. 2003;36:101-4.

38. Polachek A, Touma Z, Anderson M, Eder L. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2017;69:67-74.

39. Gupta S, Syrimi Z, Hughes DM, Zhao SS. Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. Rheumatol Int. 2021;41:275-84.

40. Kwon HH, Kwon IH, Choi JW, Youn JI. Cross-sectional study on the correlation of serum uric acid with disease severity in Korean patients with psoriasis. Clin Exp Dermatol. 2011;36:473-8.

41. Wu C, He C, Wang H, Wang W, Jin H. Impact of IL-17A inhibitors on serum uric acid levels in psoriatic patients with hyperuricemia: a prospective observational study. Psoriasis (Auckland, NZ). 2024;14:153-66.

42. Felten R, Widawski L, Spielmann L, et al. Impact of hyperuricaemia on patients with psoriatic arthritis treated with secukinumab in the FUTURE 2-5 and MAXIMISE studies. RMD Open. 2023;9.

43. Luis-Rodríguez D, Donate-Correa J, Martín-Núñez E, et al. Serum urate is related to subclinical inflammation in asymptomatic hyperuricaemia. Rheumatology (Oxford). 2021;60:371-9.

44. Huang Y-Y, Ye Z, Gu S-W, Jiang Z-Y, Zhao L. The efficacy and tolerability of febuxostat treatment in a cohort of Chinese Han population with history of gout. J Int Med Res. 2020;48:300060520902950.

45. Hao G, Duan W, Sun J, Liu J, Peng B. Effects of febuxostat on serum cytokines IL-1, IL-4, IL-6, IL-8, TNF-α and COX-2. Exp Ther Med. 2019;17:812-6.

46. Arida D, Silva L, Skare TL. The hypouricemiant effect of leflunomide. Jt. bone spine. France; 2014. p. 273-4.

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The 2025 Turkish Society for Rheumatology management recommendations for ANCA-associated vasculitides

Türkiye Romatoloji Derneği ANCA ilişkili (asosiye) vaskülitler hastalık yönetimi kılavuzu

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) manifest with involvement of the ear, nose, and throat; the skin; and the nervous system, together with constitutional symptoms, and can also be potentially life-threatening with cardiac renal, and pulmonary involvement leading to organ dysfunction. Early diagnosis is critical, necessitating increased awareness among clinicians. In patients presenting with systemic features suggestive of AAV, such as cutaneous vasculitis, chronic upper and lower respiratory tract diseases, rapidly progressive renal impairment, or peripheral neuropathy, high-quality antigen-specific assays for proteinase-3

Özet

Anti-nötrofil sitoplazmik antikor (ANCA) asosiye vaskülitlerde (AAV), üst solunum yolu, deri, nörolojik sistem ve konstitüsyonel bulgularla birlikte kardiyak, renal ve pulmoner sistemleri tutan ve organ fonksiyon kaybı ya da yaşamı tehdit eden klinik tablolar gelişebilir. Bu nedenle erken tanı için hekimler arasında farkındalığın artırılması gerekmektedir. AAV şüphesi bulunan ve kutanöz vaskülit, kronik üst ve alt solunum yolu hastalıkları, hızlı ilerleyen böbrek fonksiyon bozukluğu, periferik nöropati gibi AAV tanısını düşündüren sistemik bulguları olan hastalarda, birincil tanı yöntemi olarak yüksek kaliteli antijen-spesifik yöntemle proteinaz-3 ANCA ve

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Abstract

and myeloperoxidase should be performed as primary diagnostic tests. Management by multidisciplinary teams experienced in the management of vasculitis is recommended. Advances in technology have facilitated the use of various laboratory, imaging, and interventional methods for diagnosis, differential diagnosis, and disease monitoring; composite indices are employed to assess disease activity and organ damage. AAV treatment is divided into remission induction and maintenance phases; induction therapy for organ- or life-threatening disease typically includes glucocorticoids combined with rituximab- or cyclophosphamide-based regimens. Maintenance therapy, often with rituximab, follows remission to prevent relapse. While glucocorticoids remain a cornerstone of induction therapy, studies demonstrate that reduced-dose steroid regimens offer comparable efficacy to standard doses, with a lower risk of infection. Additionally, the introduction of biologics such as rituximab and mepolizumab has significantly decreased treatment-related damage associated with glucocorticoids and other immunosuppressants. During follow-up, patients should be monitored regularly for treatment-related adverse effects and comorbidities, including hypertension, osteoporosis, and cardiovascular disease-and appropriate lifestyle modifications should be recommended to optimize long-term outcomes.

Keywords: Vasculitis, granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), immunosuppressive therapy, cyclophosphamide, rituximab, plasma exchange, glucocorticoids, infections

Özet

miyeloperoksidaz ANCA bakılmalıdır. AAV hastalarının vaskülitler konusunda deneyimli merkezler tarafından multidisipliner bir ekiple değerlendirilmesi akılcı yaklaşımdır. Teknolojik gelişmelerle birlikte tanı, ayırıcı tanı ve hastalık süresinin izleminde çeşitli laboratuvar, görüntüleme teknikleri ve girişimsel yöntemler kullanılmaktadır. Hastalık aktivitesinin ve organ hasarının değerlendirilmesinde çeşitli hastalık kompozit indekslerinden yararlanılmaktadır. AAV tedavisi, remisyon indüksiyonu ve idame tedavisi olmak üzere iki aşamada planlanmaktadır. Organ veya yaşamı tehdit eden olgularda, indüksiyon tedavisinde glukokortikoidlere ek olarak rituksimab veya siklofosfamid temelli rejimler önerilmektedir. Remisyon sağlandıktan sonra, nüksleri önlemek amacıyla idame tedavisine geçilir ve bu dönemde en sık tercih edilen ajan rituksimabdır. Glukokortikoidler, indüksiyon tedavisinin temel bileşenlerinden biri olmasına karşın, yapılan çalışmalar düşük doz glukokortikoid rejimlerinin standart dozlara benzer etkinlik gösterdiğini ve daha düşük enfeksiyon riski ile ilişkili olduğunu ortaya koymuştur. Ayrıca, rituksimab ve mepolizumab gibi biyolojik ilaçların kullanımıyla birlikte glukokortikoidler ve diğer immünsüpresiflere bağlı gelişen hasar gelişimi önemli oranda azalmıştır. Hastalar takipleri sırasında tedavi ilişkili yan etkiler ve komorbiditeler (hipertansiyon, osteoporoz, kardiyovasküler hastalıklar) açısından periyodik olarak taranmalı ve hastalara gerekli yaşam tarzı değişiklikleri önerilmelidir.

Anahtar Kelimeler: Vaskülit, granülomatöz polianjiitis (GPA), eozinofilik granülomatöz polianjiitis (EGPA), mikroskopik polianjiitis (MPA), immünosüpresif tedavi, siklofosfamid, rituksimab, plazma değişimi, glukokortikoid, komorbidite, enfeksiyonlar

Introduction and Objectives

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are rare, heterogeneous, and potentially llife-threatening diseases. Therefore, these diseases should be managed by a multidisciplinary team in centers with vasculitis expertise or with ready access to such expertise. Patients diagnosed with AAV should receive optimal and individualized care through shared decision-making between patients and physicians, taking into account efficacy, safety, and cost considerations. Disease activity and organ damage should be assessed using validated composite disease indices. Furthermore, patients should undergo regular monitoring for treatment-related adverse effects and comorbid conditions, with appropriate preventive measures implemented as needed. This guideline on AAV has been developed primarily for rheumatologists and is also intended for internists, nephrologists, pulmonologists, and otorhinolaryngologists who may be involved in the diagnosis or follow-up of such patients in secondary and tertiary care settings. The development process of this guideline was primarily informed by current scientific literature and expert consensus. In addition, recommendations from international organizations such as the European Alliance of Associations for Rheumatology (EULAR), Kidney Disease: Improving Global Outcomes, and the American College of Rheumatology (ACR) were incorporated.

Epidemiology

The annual incidence of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) varies by country and ethnicity, ranging from 0.4 to 11.9 per 1,000,000 for GPA, 0.5 to 24 per 1,000,000 for MPA, and 0.5 to 2.3 per 1,000,000 for EGPA. The prevalence of GPA has been reported to range from 2.3 to 146 per 1,000,000 individuals, whereas those of MPA and EGPA range from 9 to 94 and 2 to 22.3 per 1,000,000 individuals, respectively.[1] The age at disease onset ranges from 45 to 65 years for GPA, 55 to 75 years for MPA, and 38 to 54 years for EGPA, with an overall male-to-female ratio of approximately 1:1. According to data collected in our country by the Turkish Vasculitis Study Group (TRVaS), the age of onset of AAV tends to fall at the lower end of these ranges and does not exhibit a significant sex-based difference.[2]

Symptoms, Signs, and Characteristics of AAV-specific Disease Involvement

Patients with AAV may present with a wide spectrum of symptoms because of heterogeneous clinical manifestations and multisystem involvement. Supplementary Table 1 summarizes the frequency of organ and tissue involvement in patients with AAV at the time of diagnosis. The data presented in this table are derived from the international Diagnostic and Classification Criteria in Vasculitis Study and the TRVaS Prospective Database.[2,3]

GPA is typically characterized by an insidious onset and granulomatous inflammation affecting both the upper and lower respiratory tracts. In contrast, MPA usually presents with renal and pulmonary involvement accompanied by systemic vasculitic features and is often associated with a more acute clinical

course. EGPA, on the other hand, is defined by eosinophilia and granulomatous inflammation that develop during the disease course in patients with a history of asthma.

• Patients may present with constitutional symptoms such as fever, fatigue, and weight loss, which are nonspecific and often precede organ-specific manifestations.

• Skin lesions may include palpable purpura, livedoid changes, papules, nodules, urticarial lesions, and less commonly ulcers. These may occur concomitantly with systemic symptoms or represent the initial manifestation of the disease.

• Treatment-resistant oral ulcers and red, exophytic gingival hypertrophy (commonly referred to as strawberry gingivitis) may occur in cases of oral mucosal involvement.

• Patients may experience arthralgia, arthritis, or myalgia. Ear, nose, and throat (ENT) manifestations include epistaxis, nasal crusting, nasal polyps, septal perforation, saddle-nose deformity, chronic sinusitis, subglottic stenosis, hoarseness, and ear fullness.

• Symptoms may include hearing loss, otorrhea, otalgia, tinnitus, and dizziness, along with skull base involvement manifesting as facial nerve paralysis and hypertrophic pachymeningitis.

• Pulmonary involvement in AAV encompasses tracheobronchial inflammation and structural abnormalities, as well as parenchymal lesions such as nodules, masses, or cavitations. Severe complications may include diffuse alveolar hemorrhage (DAH) and interstitial lung disease (ILD).

• Acute kidney injury is common in patients with rapidly progressive glomerulonephritis (RPGN) secondary to AAV. Hematuria, proteinuria, edema, and hypertension are frequently observed.

• Ocular involvement may present as conjunctivitis, uveitis, proptosis, episcleritis/scleritis, or peripheral ulcerative keratitis. Less commonly, retinitis, optic neuritis, and vision loss may develop.

• The peripheral nervous system is most often affected, manifesting as mononeuritis multiplex, sensory neuropathy, or

Table 1. 2022 ACR/EULAR Classification Criteria for GPA, MPA, and EGPA

Entry criterion: A confirmed diagnosis of small- or medium-vessel vasculitis is required, and other medical conditions that may mimic vasculitis must be excluded.

	GPA	MPA	EGPA
Clinical criteria			
• Nasal involvement (bloody discharge, ulcers, crusting, congestion, obstruction, or septal defect/perforation)	+3	-3	
• Cartilaginous involvement (auricular or nasal cartilage, stridor, endobronchial involvement, or saddle-nose deformity)	+2		
• Conductive or sensorineural hearing loss	+1		
• Obstructive airway disease			+3
• Nasal polyps			+3
• Mononeuritis multiplex			+1
Laboratory criteria			
• PR3-ANCA (or cANCA) positivity	+5	-1	-3
• MPO-ANCA (or pANCA) positivity	-1	+6	
• Serum eosinophils ≥1000/μL	-4	-4	+5
• Hematuria			-1
Histological criteria			
• Granuloma, granulomatous inflammation, or giant cells	+2		
• Pauci-immune glomerulonephritis	+1	+3	
• Extravascular eosinophilic inflammation			+2
Radiological criteria			
• Pulmonary nodules, masses, or cavitation on chest imaging	+2		
• Fibrosis or interstitial lung disease on chest imaging		+3	
• Nasal/paranasal sinusitis or mastoiditis on imaging	+1		
Score required for classification	≥5	≥5	≥6

ACR: American College of Rheumatology, ANCA: Anti-neutrophil cytoplasmic antibodies, EGPA: Eosinophilic granulomatosis with polyangiitis, EULAR: European Alliance of Associations for Rheumatology, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis, MPO: Myeloperoxidase

polyneuropathy. Central nervous system (CNS) involvement is rare but may present with headache, cognitive decline, seizures, cranial nerve palsy, or cerebrovascular events.

• Mesenteric ischemia may occur, leading to abdominal pain, bloody diarrhea, or intestinal perforation. Other manifestations may include cholecystitis and pancreatitis.

• Cardiac manifestations include pericarditis, myocarditis, cardiomyopathy, and heart failure.

a. Pulmonary Involvement

Pulmonary involvement may range from asymptomatic findings detected incidentally on imaging to severe, symptomatic disease. Depending on the site and extent of involvement, patients may experience cough, dyspnea, hoarseness, stridor, sputum production, hemoptysis, or pleuritic chest pain. The most frequently observed thoracic manifestations of AAV are summarized below.[4]

1. Tracheobronchial involvement: Tracheobronchial inflammation, mucosal alterations, tracheo- and/or bronchomalacia, and subglottic stenosis (SGS)

2. Pulmonary nodules (solitary/multiple), masses, consolidation, and cavitation

3. DAH

4. ILD

A baseline chest computed tomography (CT) scan should be obtained before initiating immunosuppressive therapy, even in the absence of respiratory symptoms in newly diagnosed patients. Thoracic CT may demonstrate cavitating nodules, subpleural lesions, airway inflammation, or stenotic changes of the large airways, as well as small nodules that may not be visible on conventional chest radiography. In addition, thoracic CT provides a more comprehensive evaluation of ILD and DAH. Non-contrast CT is preferred when renal involvement is suspected, to avoid contrast-induced nephropathy. Furthermore, three-dimensional reconstructions of the tracheobronchial tree can be generated using thoracic CT for detailed anatomical assessment. Tracheobronchial involvement is common in GPA but occurs less frequently in MPA and EGPA. The segmental and focal distribution of mucosal lesions represents a key distinguishing feature. These lesions are characterized by erosions (mucosal ulcers) and inflammatory changes within the mucosa. When cartilaginous structures are affected, they may cause tracheomalacia, bronchomalacia, or airway stenosis. SGS is the most common manifestation of tracheobronchial involvement in GPA and is defined as a narrowing of the airway immediately below the vocal cords.[5] Prompt evaluation is warranted in patients presenting with dyspnea, hoarseness, or stridor, as severe cases may require tracheostomy for airway stabilization. Although endobronchial inflammation and stenosis are less common than subglottic involvement, they may present with similar clinical manifestations. Biopsy specimens from tracheobronchial lesions often demonstrate nonspecific mucosal inflammation, ulceration, and fibrosis, leading to secondary stenosis; however, histopathologic evidence of vasculitis is rarely observed.[6] Pulmonary nodules may occur in all forms of AAV, but they are most frequently seen in GPA. Consolidation, pulmonary infiltrates, and unilateral or bilateral nodules are present at disease onset in approximately 40-70% of patients, while cavitation develops in 20-50% of these lesions. The pulmonary lesions may be migratory and transient.[7,8] Nodular lesions are often located in subpleural regions and are commonly associated with adjacent blood vessels, a characteristic described as the “feeding vessel sign.” As these nodules enlarge, they may undergo cavitation, with diameters ranging from a few millimeters to 10 cm.

Cavitating lesions typically exhibit thick walls with irregular inner margins and lack calcification. A ground-glass halo surrounding the nodules—known as the “halo sign”—is frequently observed and suggests concomitant alveolar hemorrhage. In addition, the presence of air bronchograms within pulmonary nodules is a common radiologic finding.

AAV-ILD represents pulmonary involvement that may develop during the course of AAV, particularly in patients with myeloperoxidase (MPO)-ANCA–positive disease. ILD may be detected either during follow-up or prior to the diagnosis of AAV.

Thoracic CT may reveal ground-glass opacities, reticular patterns, consolidation, interlobular septal thickening, and honeycombing. The usual interstitial pneumonia (UIP) pattern is the most common radiologic subtype of ILD in patients with MPO-ANCA-positive AAV. Patterns of non-specific interstitial pneumonia and, less frequently, of desquamative interstitial pneumonia may also be observed. Furthermore, 5-10% of patients with idiopathic pulmonary fibrosis may have positive ANCA serology at diagnosis.[9]

DAH is defined as the extravasation of blood into the alveolar spaces resulting from increased capillary wall permeability secondary to capillaritis, leading to impaired gas exchange and hypoxemia. Early recognition and prompt treatment are crucial because of its significant contribution to morbidity and mortality. Notably, chest radiographs may appear normal in up to 50% of patients with suspected DAH. On thoracic CT, typical findings include bilateral alveolar opacities, interlobular and intralobular septal thickening, a cobblestone appearance, and ground-glass opacities. The gold standard for diagnosis is the identification of hemosiderin-laden macrophages in bronchoalveolar lavage (BAL) fluid. Moreover, BAL is valuable for excluding infectious etiologies that may mimic DAH.[6]

b. Asthma

Asthma occurs in more than 90% of patients with EGPA. It typically develops in adulthood and is frequently accompanied by upper respiratory tract symptoms. Chronic rhinosinusitis with eosinophilic nasal polyposis is common in the upper airways. The disease is often refractory to conventional therapy, and nasal polyps may recur despite surgical intervention.

Pulmonary parenchymal infiltrates, which are frequently observed in EGPA, are not typically present in cases of severe eosinophilic asthma without vasculitic involvement. In patients with asthma whose symptoms remain uncontrolled despite optimal therapy, or in those who require high-dose inhaled corticosteroids (ICS) to maintain control and who exhibit peripheral blood eosinophilia (≥1500/mm^3), an evaluation for vasculitic manifestations should be undertaken. Furthermore, EGPA should be suspected in individuals presenting with chronic rhinosinusitis with eosinophilic nasal polyposis, severe eosinophilic asthma, and marked eosinophilia. Such patients warrant thorough assessment for evidence of systemic involvement.[10]

c. Renal Involvement

In patients with renal involvement, kidney function may deteriorate rapidly over days to weeks, leading to acute kidney injury consistent with RPGN. Hematuria—particularly dysmorphic erythrocytes or erythrocyte casts—and proteinuria are key urinalysis findings that should prompt clinical suspicion for renal vasculitis. Edema and hypertension may also accompany the presentation. Although uncommon, a more gradual decline in renal function has been reported in some cases. Despite appropriate treatment, end-stage renal disease (ESRD) develops in approximately 20-25% of patients.[11]

d. Neurological Involvement

Peripheral neuropathy in AAV typically presents with distal tingling or painful paresthesia in the lower extremities, often progressing to sensory loss in a mononeuritis multiplex pattern. When motor involvement is present, muscle weakness and atrophy may occur in the affected region; however, pure motor neuropathy is uncommon in AAV-related neuropathies. Electrophysiological studies typically reveal findings consistent with axonal neuropathy, characterized by reduced compound muscle and sensory nerve action potentials, while motor and sensory conduction velocities and distal motor latencies are generally preserved. Nerve biopsy demonstrates axonal degeneration affecting both myelinated and unmyelinated fibers, accompanied by inflammation of epineural vessels. However, due to the patchy distribution of mononeuritis multiplex, the biopsied nerve may not consistently demonstrate pathological involvement.

Meningeal involvement in AAV is rare but clinically significant, and it may occur early in the disease course. Magnetic resonance imaging (MRI) plays a critical role in establishing the diagnosis and assessing disease extent.

Laboratory and Histopathological Evaluation

a. Acute Phase Response and Serology

ANCAs are autoantibodies directed against specific antigens such as proteinase 3 (PR3) and MPO. ANCA can be detected by indirect immunofluorescence (IIF) and enzyme-linked immunosorbent assay. Based on the staining pattern observed on ethanol-fixed neutrophil slides, three types of ANCA are identified by the IIF technique:

- Cytoplasmic ANCA (c-ANCA)
- Perinuclear ANCA (p-ANCA)
- Atypical ANCA

Antigen-specific immunoassays demonstrate greater diagnostic accuracy than IIF for the detection of ANCA. The 2017 International Consensus on ANCA Testing recommends high-quality immunoassays targeting PR3 and MPO as the preferred initial screening method for the diagnosis of GPA and MPA.[12]

In patients presenting with clinical features suggestive of AAV, testing for both PR3-ANCA and MPO-ANCA using a high-quality, antigen-specific immunoassay is recommended as the primary diagnostic approach. If immunoassay results are negative but clinical suspicion for AAV remains high, a confirmatory test—using an alternative immunoassay or IIF—should be performed.

A negative ANCA result does not exclude the diagnosis of AAV, as a small subset of patients—particularly those with disease confined to the respiratory tract or isolated renal involvement—may be ANCA-negative.[13]

b. Pulmonary Function Tests

Simple spirometry may aid diagnosis by demonstrating an extrathoracic obstructive pattern in cases of SGS and an intrathoracic obstructive pattern in cases of tracheobronchial involvement. In patients with ILD, a reduction in the diffusing capacity for carbon monoxide (DLCO) is typically observed. A restrictive ventilatory pattern, often accompanied by reduced lung volumes, may also be evident.

For the follow-up of patients with ILD, spirometry, DLCO measurement, and the six-minute walk test can be employed to monitor disease progression and functional decline.

c. Bronchoscopic Evaluation

Bronchoscopic evaluation may be valuable in selected cases for the diagnosis and assessment of AAV. In GPA, bronchoscopy facilitates the direct evaluation of tracheobronchial

involvement. Biopsy specimens can be obtained from areas of mucosal abnormality or transbronchially from the lung parenchyma to support histopathologic confirmation. However, the small size of bronchoscopic biopsy specimens may limit the demonstration of granulomatous or vasculitic involvement. In patients with suspected DAH and active pulmonary bleeding, a progressively more hemorrhagic appearance in sequential BAL aliquots (20-50 mL each) obtained from the same bronchopulmonary segment supports the diagnosis of alveolar hemorrhage. The identification of hemosiderin-laden macrophages comprising ≥20% of total macrophages on cytological examination is considered the gold standard for confirming the diagnosis.[14] BAL is also valuable for the differential diagnosis of infection, and microbiological analyses should be performed accordingly.

d. Histopathology

In patients presenting with cutaneous manifestations, histopathological examination is recommended owing to the ease of tissue accessibility. Diagnostic features may include leukocytoclastic vasculitis, granulomatous inflammation, and variable degrees of eosinophilic infiltration.

Although the sensitivity of biopsy for detecting vasculitic changes is relatively low in cases with sinonasal involvement, tissue sampling may still be warranted to exclude invasive fungal infections, particularly those mimicking mucormycosis.

In patients with GPA who present with pulmonary nodules, masses, or consolidation, percutaneous or thoracoscopic lung biopsies may be performed for diagnostic confirmation. However, percutaneous approaches often yield limited tissue samples, which may be insufficient for definitive histopathologic evaluation. Nonetheless, image-guided biopsies—using CT or positron emission tomography/CT—targeting metabolically active lesions and avoiding necrotic areas can significantly enhance diagnostic yield.

Histopathological examination in GPA typically demonstrates necrotizing granulomatous inflammation. When biopsy is performed, special stains and microbiological investigations, including cultures for infectious agents capable of inducing granulomatous inflammation—such as tuberculosis—should be routinely conducted to facilitate differential diagnosis.

Renal biopsy plays a crucial role in both establishing the diagnosis and assessing the prognosis of AAV. It is recommended for patients with MPO-ANCA or PR3-ANCA positivity, or for those with organ involvement suggestive of small-vessel vasculitis, when renal impairment, hematuria, or proteinuria is present, provided no contraindications exist. In patients unresponsive to therapy, a repeat renal biopsy may be considered to assess chronic renal damage, identify alternative causes of acute kidney injury, or evaluate persistent disease activity. In circumstances where biopsy cannot be performed—such as patients receiving anticoagulant therapy or those at high risk of bleeding—treatment initiation should not be delayed. Renal biopsy provides critical information regarding glomerular, tubulointerstitial, and vascular involvement. The characteristic histopathologic pattern observed in AAV is pauci-immune necrotizing crescentic glomerulonephritis, with minimal or absent immunoglobulin and complement deposition. Furthermore, renal biopsy findings can be used to predict the risk of long-term renal failure and guide prognostic assessment. Several prognostic scoring systems have been developed based on histopathologic features observed at the time of renal biopsy. Among these, the most widely applied are the Berden classification, the Mayo Clinic/Renal Pathology Society (RPS) Chronicity Score, and the ANCA Renal Risk Score (Supplementary Table 2). These prognostic scoring systems differ in their assessment parameters. In the Berden classification, only glomerular lesions identified on renal biopsy are evaluated, and patients are categorized into four classes: focal, crescentic, mixed, and sclerotic. According to this system, the focal class is associated with the most favorable prognosis, whereas the sclerotic class carries the poorest prognosis. The crescentic and mixed classes exhibit intermediate or variable prognoses.[15] The Mayo Clinic/RPS Chronicity Score evaluates the extent of chronic histopathologic changes in the kidney. The degrees of glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis were graded as minimal, mild, moderate, or severe; these grades provide an overall measure of chronic renal damage (Supplementary Table 2). It has been demonstrated that patients with minimal or mild histopathologic changes exhibit greater improvement in renal function and more favorable long-term renal survival.[16] The ANCA Renal Risk Score is a prognostic model designed to predict renal survival in patients with AAV and renal involvement. In this system, the percentage of normal glomeruli, the extent of tubular atrophy and interstitial fibrosis, and the glomerular filtration rate (GFR) at diagnosis—categorized as ≥15 or <15 mL/min/1.73 m²—are incorporated, which distinguishes it from other histopathologic scoring models. Higher values are associated with an increased risk of progression to ESRD.[17]

Differential Diagnosis of AAV and the 2022 ACR/EULAR Classification Criteria

In evaluating a patient with suspected AAV, differential diagnoses that commonly cause symptoms, organ involvement, and laboratory findings associated with AAV are outlined below.[18]

• Infectious diseases (subacute bacterial endocarditis, hepatitis B, hepatitis C, human immunodeficiency virus infection, tuberculosis, fungal infections)

• Malignancies (lymphoma, leukemia, solid organ malignancies)

• Other autoimmune and autoinflammatory diseases (systemic lupus erythematosus, large- and medium-vessel vasculitides, IgG4-related disease, antiphospholipid antibody syndrome, etc.)

• Drug/substance-induced ANCA positivity (propylthiouracil, hydralazine, phenytoin, levamisole, cocaine, etc.)

After excluding secondary causes, the 2022 ACR/EULAR classification criteria for GPA, EGPA, and MPA—which are useful in differentiating patients primarily considered to have small- or medium-vessel vasculitis—can be applied. These are presented in Table 1.[19]

Disease Activity and Damage Assessments

It is recommended that patients with AAV undergo regular evaluations of disease activity and organ damage, with more frequent assessments during induction therapy. In routine clinical practice, follow-up visits may be scheduled at diagnosis and at weeks 2, 4, 8, 12, 18, and 24, depending on the clinical severity and treatment protocol. During these visits, multidisciplinary specialist assessments should be performed based on the affected organ systems (e.g., nephrology, otorhinolaryngology, ophthalmology, pulmonology). For affected organs, functional and radiologic evaluations—including paranasal sinus CT, chest CT, pulmonary function testing with DLCO, electrocardiography, cardiac MRI, and electromyography—may be planned based on the patient's clinical status, disease severity, and treatment-related factors, such as monitoring requirements, tolerability, and potential adverse effects.[20]

Renal function tests are the most critical parameters for assessing and monitoring renal remission in AAV. In addition, hematuria, proteinuria, and ANCA titers may be used as supplementary follow-up markers. The principal criteria for evaluating renal remission are serum creatinine and eGFR, which reflect overall kidney function. Stable or improving serum creatinine levels indicate renal remission. However, hematuria and/or proteinuria may persist in up to 50% of patients during long-term follow-up; therefore, their significance in defining remission, relapse, and renal survival remains controversial. An increase in hematuria, or its recurrence after resolution, may suggest renal relapse once other etiologies are excluded and warrants close monitoring. Persistent proteinuria may reflect either ongoing disease activity or chronic parenchymal injury secondary to previous inflammation. Importantly, proteinuria associated with chronic structural damage constitutes a negative prognostic factor for long-term renal function.[21-24]

In AAV, several standardized indices have been developed to objectively assess disease activity, guide treatment decisions, evaluate therapeutic response, and quantify vasculitis-related damage. In clinical practice, validated scoring systems such as the Birmingham Vasculitis Activity Score (BVAS, version 3) and the BVAS for Wegener's Granulomatosis (BVAS-WG) should be used—alongside structured clinical evaluation and inflammatory markers—to determine the presence of active disease.[20,25] When calculating BVAS and BVAS-WG scores, findings attributable

Table 2. Drugs and dosage regimens used in the treatment of AAV

Treatment	Dosage and administration
Pulse glucocorticoid	Intravenous methylprednisolone 500-1000 mg/day (or equivalent) for 3-5 days.
High-dose oral glucocorticoid	Prednisolone 1 mg/kg/day (up to a maximum of 75 mg/day) or an equivalent dose.
Induction therapy	
Methotrexate	Up to 20 mg weekly (oral or subcutaneous).
Azathioprine	2-3 mg/kg/day (oral).
Mycophenolate mofetil	2000 mg/day (oral, in two divided doses).
Cyclophosphamide	15 mg/kg IV, every 2 weeks for the first 3 doses, then every 3 weeks for the next 3 doses.
Rituximab	375 mg/m² IV weekly for 4 consecutive weeks or 1000 mg IV twice, 14 days apart.
Maintenance therapy	
Methotrexate, azathioprine, mycophenolate mofetil	Initiated at a dose similar to that used for remission induction, with gradual tapering during follow-up based on clinical response.
Rituximab	500 mg or 1000 mg every 4-6 months, depending on the clinical condition of the patient.
Drugs specific to EGPA	
Mepolizumab	100-300 mg subcutaneously every 4 weeks.
Benralizumab	30 mg subcutaneously every 4 weeks.

AAV: ANCA-associated vasculitis, ANCA: Anti-neutrophil cytoplasmic antibody, EGPA: Eosinophilic granulomatosis with polyangiitis, IV: Intravenous

to active vasculitis that have appeared or worsened within the preceding four weeks are classified as new or worsening disease, whereas findings that have persisted since the previous evaluation are recorded as persistent disease. These tools enhance clinical decision-making by allowing for the systematic documentation of treatment response (Supplementary Table 3).[13] The frequency of assessment should be individualized according to the patient's clinical status, disease severity, and the monitoring needs of ongoing therapy.

Refractory disease is defined as the persistence or progression of disease activity despite standard induction therapy. It is characterized by either the absence of clinical improvement or worsening of disease activity within the first four weeks of treatment, or by a reduction in the disease activity score (e.g., BVAS) of less than 50% by week six of therapy. Before confirming disease refractoriness, alternative explanations such as infection, poor treatment adherence, drug intolerance, secondary vasculitic processes, treatment-related toxicity, comorbid conditions, and non-inflammatory causes of organ dysfunction should be carefully excluded.[26] The Five-Factor Score (FFS) is not intended to assess disease activity but rather serves as a prognostic tool that assists in estimating patient outcomes and guiding treatment intensity.[27]

The Vasculitis Damage Index (VDI) is a standardized assessment tool designed to quantify damage resulting from both the disease process and its treatment in systemic vasculitides. Damage is defined as a pathologic change persisting for more than three months after the onset of vasculitis symptoms.[28] The VDI is a validated instrument for documenting irreversible disease- or therapy-related damage in ANCA-AAV and provides standardized definitions that assist in distinguishing permanent damage from active disease.[13]

Table 3. Reduced-dose glucocorticoid regimen in the treatment of AAV

Week	Body weight <50 kg	Body weight 50-75 kg	Body weight >75 kg
1	50	60	75
2	25	30	40
3-4	20	25	30
5-6	15	20	25
7-8	12.5	15	20
9-10	10	12.5	15
11-12	7.5	10	12.5
13-14	6	7.5	10
15-16	5	5	7.5
17-18	5	5	7.5
19-20	5	5	5
21-22	5	5	5
23-52	5	5	5

*The glucocorticoid dose is expressed as the prednisolone equivalent (mg/day) and is based on the reduced-dose regimen used in the PEXIVAS trial, AAV: ANCA-associated vasculitis, ANCA: Anti-neutrophil cytoplasmic antibody

The ANCA-AAV patient-reported outcome measure was published in 2018 and has since been translated and validated for use in Turkish. It comprises 29 items that assess patients' overall experiences during the preceding four weeks, focusing on symptoms and problems attributed to vasculitis or its treatment.[29]

Treatment and Follow-up

a. Induction of Remission

The treatment of AAV consists of two main phases: induction of remission and maintenance therapy. In patients with AAV presenting with life- or organ-threatening involvement (such as glomerulonephritis, DAH, tracheal or subglottic stenosis, meningeal involvement, CNS involvement, retro-orbital disease, cardiac involvement, mesenteric involvement, or mononeuritis multiplex), remission induction therapy is recommended with either rituximab (RTX) or cyclophosphamide (CYC), combined with glucocorticoids.[13,20,25,27,30] The agents and their dosage ranges used in remission induction and maintenance therapy are summarized in Table 2.

Although intravenous (IV) pulse glucocorticoid therapy is often preferred during remission induction due to its rapid clinical efficacy, there is insufficient evidence to support its routine use. Considering the potential increased risk associated with glucocorticoid toxicity, including infections, methylprednisolone pulse therapy should be restricted to the treatment of severe clinical manifestations such as active glomerulonephritis with an eGFR <50 mL/min/1.73 m² or DAH. The cumulative dose should be limited to 1-3 grams, followed by oral glucocorticoid therapy.[13]

The initial dose of oral glucocorticoids is generally equivalent to 50-75 mg per day of prednisolone. Recent studies have demonstrated that reduced-dose glucocorticoid regimens show comparable efficacy to standard-dose therapy in improving overall survival and reducing the risk of ESRD. In addition, patients receiving reduced-dose glucocorticoid therapy demonstrated a lower incidence of serious infections, particularly during the first year of treatment.[31] In this regimen, prednisolone is initiated at 1 mg/kg/day during the first week and subsequently tapered according to the schedule in Table 3.[13,25] However, this tapering regimen may not be suitable for all patients. In cases of renal involvement, the tapering schedule should be individualized to take into account the patient's specific risk factors and clinical condition and may require a slower dose reduction.

In patients with renal involvement, dialysis dependence at diagnosis or severe histopathological findings on renal biopsy do not preclude the initiation of remission induction therapy. On the contrary, even in cases of advanced renal failure requiring dialysis, appropriate remission induction therapy may lead to recovery of renal function. Although RTX or CYC can be used as first-line agents, nephrology societies

recommend CYC as the initial therapy in patients with severe glomerulonephritis (serum creatinine >4.0 mg/dL).[25] In addition to severe renal involvement, CYC may also be preferred in cases presenting with systemic and life- or organ-threatening manifestations, such as DAH; tracheobronchial involvement in patients with AAV and concurrent anti-GBM antibody positivity; and granulomatous disease predominantly involving the orbit or pachymeninges.[20,30] On the other hand, RTX may be considered the first-line option in adult patients with fertility concerns, elderly and/or frail individuals, and those with PR3-ANCA positivity. Mycophenolate mofetil (MMF) may be considered an alternative remission induction option in patients who cannot receive CYC or RTX, particularly in the MPO-ANCA–positive subgroup. The combination of RTX and CYC is rarely used and is generally reserved for refractory and/or life-threatening cases. Studies have shown that the addition of low-dose CYC to RTX therapy may reduce the frequency of relapses. However, these findings are based on limited observational studies. Although avacopan is not yet available in Türkiye, it has been considered a potential alternative to steroid therapy and can be used in combination with other immunosuppressive agents.[25]

Other AAV manifestations that are not life- or organ-threatening (such as pulmonary nodules or localized upper respiratory tract involvement) can be treated with oral glucocorticoids in combination with methotrexate (MTX).[6] In cases where MTX is not tolerated or is deemed inappropriate, MMF, azathioprine (AZA), or RTX may be used as alternative therapies. The response rate of granulomatous pulmonary lesions to treatment varies considerably among patients. Therapy should be continued while the lesions regress under treatment.[32] The treatment of AAV patients with interstitial fibrosis should be managed according to therapeutic recommendations for vasculitis.

b. Renal and Respiratory Supportive Therapies, Plasma Exchange, and Intravenous Immunoglobulin

The management of AAV should, whenever possible, be conducted within a multidisciplinary framework. In patients with renal failure, renal replacement therapies should be coordinated with a nephrologist, while in cases requiring respiratory support (including noninvasive or invasive mechanical ventilation), treatment and follow-up should be planned in collaboration with intensive care specialists.

Plasma exchange enables the rapid and effective removal of pathogenic inflammatory mediators, including ANCA and complement components.[33] In patients with AAV, plasma exchange has not been shown to provide a significant survival benefit. However, it may reduce the risk of developing ESRD in cases of severe renal involvement but is associated with an increased risk of serious infections.[31] Therefore, plasma exchange is not routinely recommended as part of the induction regimen for patients with AAV.[30]

Plasma exchange may be considered in patients with RPGN due to AAV (such as those with serum creatinine levels >3.4 mg/dL, requiring dialysis, or exhibiting a rapid rise in serum creatinine despite immunosuppressive therapy), as well as in patients with DAH accompanied by hypoxemia. In addition, plasma exchange should be considered an effective therapeutic option for patients with AAV who are positive for anti-GBM antibodies.[25] A personalized approach that takes into account individual patient characteristics, as well as clinical and histological parameters, plays a crucial role in determining the potential benefit of plasma exchange.[34]

Although IV immunoglobulin (IVIG) is not a routine component of standard therapy in AAV, it may provide a rapid improvement in disease activity and biomarker levels in certain patients.[35] The parameters to be considered when determining the indication for IVIG are summarized below.[27,30,36]

- Degree of hypogammaglobulinemia
- Presence of severe, persistent, unusual, or recurrent infections
- Demonstration of a poor antibody response to polysaccharide antigens
- Inadequate response to antibiotic prophylaxis
- Individual comorbidities (such as bronchiectasis, neutropenia, and long-term corticosteroid use or concurrent use of additional immunosuppressive agents)

In patients with refractory AAV who do not respond to remission induction therapy, IVIG may be considered at immunomodulatory doses (2 g/kg per course). During remission maintenance with RTX, IVIG replacement therapy (0.4 g/kg monthly) may be administered to patients who develop hypogammaglobulinemia [immunoglobulin G (IgG) <4 g/L] and experience recurrent severe infections.[30]

c. Maintenance Treatment and Approach to Relapses

The duration of maintenance therapy, initiated once disease activity is controlled, should be individualized based on disease severity, ANCA antibody profile, and organ involvement. In patients with GPA and MPA, maintenance therapy is generally recommended for 24-48 months after remission is achieved.[13,25] It should be emphasized that maintenance therapy should be prolonged in patients who experience relapse or are considered at high risk of relapse. The agents currently used for maintenance treatment are summarized in Table 2. Before initiating RTX for maintenance, serum IgG levels should be measured, and in cases of hypogammaglobulinemia (serum IgG <7 g/L), IgG concentrations should be reassessed after 2-4 weeks to re-evaluate the treatment decision.

Relapse is defined as the reappearance of clinical signs or symptoms of active vasculitis in any organ system following the achievement of partial or complete remission. Relapses are classified as major or minor. Major relapse denotes life-threatening or organ-threatening disease activity. Risk factors for relapse include the PR3-ANCA subtype, ENT involvement, elevated serum creatinine at diagnosis, and extensive systemic disease. Persistent ANCA positivity, rising ANCA titers, or seroconversion from negative to positive may serve as partial predictors of future relapse, although their prognostic value remains limited.[25] Renal relapse is defined by the recurrence or worsening of glomerular inflammation, manifesting as increased hematuria, active urinary sediment, and/or new-onset impairment of renal function. Although disease flares most frequently occur in the organ initially affected, involvement of new organs is not uncommon. In cases where the diagnosis of recurrent vasculitis is uncertain, a tissue biopsy may be warranted to confirm disease reactivation and exclude alternative causes of renal dysfunction.[37,38]

Relapses generally respond to immunosuppressive therapy. In cases of severe relapse, treatment should follow a standard induction therapy protocol. In non-severe relapses, the dose of the current immunosuppressive agent may be increased, and CYC should be considered a second-line option.[25] During relapse, treatment choice should be guided by the previous induction and maintenance regimens. CYC may be administered to patients who relapse while receiving RTX, whereas RTX may be used in those who relapse during CYC therapy—both in combination with glucocorticoids. RTX is generally preferred as the first-line treatment option for relapsing disease.[13] Evidence regarding the efficacy of RTX in patients with serum creatinine levels exceeding 4.0 mg/dL remains limited. For patients receiving maintenance RTX therapy, a repeat course may be considered if 4-6 months have elapsed since the previous infusion.[30]

d. Treatment Approaches in Specific Clinical Conditions

In the management of sinonasal involvement in AAV, culture-directed systemic antibiotics and topical antibiotic irrigations, in conjunction with immunosuppressive therapy, are effective in controlling infection and relieving symptoms. High-volume saline irrigations are a valuable adjunct for reducing nasal obstruction and mucopurulent discharge by enhancing mucociliary clearance. In patients with a septal perforation, septal obturators may be used to alleviate crusting and airflow-related symptoms. Rhinoplasty may be considered for patients with saddle-nose deformity or septal perforation once sustained remission has been achieved.

The primary therapeutic objective in tracheal or subglottic stenosis is to prevent progression through early diagnosis and timely initiation of immunosuppressive therapy, thereby reducing the need for surgical intervention. In early or mild SGS, inhaled glucocorticoids and topical anti-inflammatory therapies may be sufficient to control local inflammation. When mechanical airway obstruction results from fibrotic scarring, interventional procedures such as laser ablation, intralesional corticosteroid injection, cryotherapy, balloon dilation, or surgical reconstruction may be required to restore airway patency.[6]

The efficacy of antifibrotic agents, such as nintedanib and pirfenidone, in AAV with interstitial pulmonary fibrosis remains uncertain. Therapeutic management is particularly challenging and controversial in patients with MPO-ANCA positivity and ILD exhibiting a UIP pattern, due to the limited availability of robust evidence.[39] According to the most recent international guideline on the management of progressive pulmonary fibrosis (PPF), antifibrotic therapy is recommended for PPF secondary to autoimmune ILD, including vasculitis-related forms. In this setting, nintedanib is recommended as the first-line antifibrotic agent.[40] Pirfenidone is considered a second-line option due to limited supporting evidence for its use.[41]

Asthma management in patients with EGPA should be maintained at the appropriate step based on disease severity and level of asthma control. At no stage of therapy should bronchodilators be used as monotherapy; ICSs must always be combined with bronchodilators. Patients should undergo monthly monitoring until adequate asthma control is achieved, then attend follow-up visits every 3-6 months.[42,43]

In patients with EGPA whose vasculitic manifestations are in remission, persistent exacerbations or uncontrolled asthma, despite optimized therapy with high-dose ICSs plus long-acting β_2-agonists, should prompt evaluation for biologic therapy targeting interleukin-5 (IL-5) or its receptor (IL-5Rα) for the management of severe eosinophilic asthma. Mepolizumab has been approved by both the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of EGPA at a dose of 300 mg every four weeks. However, observational studies have demonstrated that a 100 mg dose administered every four weeks may also be effective in patients with FFS=0 and without major organ involvement, particularly in those with predominant respiratory manifestations.[44-46] Therefore, in such patients, it is recommended to initiate mepolizumab at a dose of 100 mg every four weeks, with dose escalation to 300 mg if an adequate clinical response is not achieved by week 16. For patients with life-threatening or organ-threatening manifestations, maintenance therapy with mepolizumab at 300 mg every four weeks is recommended. For EGPA patients who are refractory to mepolizumab, benralizumab may be considered an alternative biologic therapy. In Türkiye, the use of benralizumab for EGPA currently requires an application for off-label use.

The management of AAV-associated neuropathy requires a multidisciplinary approach. For residual neuropathic pain, pharmacologic treatments such as gabapentinoids, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and sodium channel blockers may be used in collaboration with neurologists. Given that peripheral neuropathy can substantially impair quality of life, psychosocial support and patient education should be prioritized. During rehabilitation, involvement of physical and occupational therapists may provide functional benefits. In patients with motor deficits, such as foot drop, the use of lower-extremity orthoses may be required to improve mobility and prevent secondary complications.

e. Discontinuation of Therapy During Follow-up

In patients who remain dialysis-dependent for more than three months despite appropriate treatment and have not recovered renal function, reduction or discontinuation of immunosuppressive therapy should be considered, provided there are no indications for continued treatment due to extra-renal disease activity. The risk of relapse in patients on chronic dialysis is significantly lower than during the pre-dialysis period, although relapses may still occur. Conversely, among patients requiring chronic dialysis due to AAV, infections represent the leading cause of death, with a markedly increased incidence of severe infectious complications. Overall, patients who develop ESRD exhibit poorer survival outcomes compared with those who maintain renal function.[11,47-49]

Patients with GPA or MPA who progress to stage 5 chronic kidney disease should be evaluated for kidney transplantation. Candidates are required to be in complete clinical remission for 6-12 months before transplantation. Although persistent ANCA positivity at the time of transplantation is not, in itself, a contraindication, each patient should be individually assessed for residual disease activity. In the post-transplant period, the overall risk of relapse is low, and vasculitis recurrence in the renal allograft is rare. However, patients should continue to be monitored for extra-renal relapses. Following transplantation, both patient and graft survival are comparable to those in recipients transplanted for other causes, whereas overall patient survival is significantly improved compared with those maintained on dialysis.[50,51]

f. Prevention of Morbidity and Complications

In patients with AAV receiving RTX, CYC, and/or high-dose glucocorticoids, prophylaxis with trimethoprim–sulfamethoxazole (400/80 mg daily or 800/160 mg three times per week) is recommended to prevent *Pneumocystis jirovecii* pneumonia and other opportunistic infections.[52] In addition, appropriate vaccinations should be administered in accordance with national and international immunization guidelines to reduce the risk of infection.[53,54]

To minimize corticosteroid-related complications in patients with AAV, steroids should be used at the lowest effective dose and for the shortest possible duration. Regular monitoring of blood glucose, lipid profile, and blood pressure, along with bone mineral density screening to assess osteoporosis risk, is recommended.[55] In addition, supplementation with calcium (1000-1200 mg/day) and vitamin D (800-1500 IU/day) is recommended for patients receiving corticosteroids at any dose for ≥3 months.[56]

Patient Education, Pregnancy Planning, and Management of Surgical Needs

Patients should be thoroughly informed about AAV, including its impact, prognosis, warning symptoms, and the potential effects and complications of therapy. Key points to consider in the education of patients with AAV are as follows:

a. Patients should be informed about the course of the disease, the treatment process, and warning signs or symptoms that may indicate disease activity.

b. Among women of reproductive age, the need for contraception with certain medications used in treatment, the risks of premature menopause or infertility, and potential contraindications related to pregnancy and breastfeeding should be identified, and patients should be counselled appropriately.

c. Vaccination recommendations and plans for infection prevention should be implemented.

d. Patients should be educated about the possible side effects of corticosteroid therapy, the importance of treatment adherence, and necessary dietary and lifestyle modifications.[20]

Pregnancy is considered an independent risk factor for AAV flare, and pregnancies in women with AAV should be regarded as high-risk. If vasculitis develops during pregnancy or pregnancy occurs while a patient is receiving treatment for vasculitis, multidisciplinary collaboration among rheumatologists, perinatologists, and obstetricians is required to improve maternal and fetal outcomes, guide treatment, and ensure appropriate postpartum follow-up.[57] During pregnancy, the use of medications such as MTX, leflunomide, MMF, and CYC is contraindicated. These agents should be discontinued 3-6 months before conception. If disease activity persists during pregnancy, treatment options such as corticosteroids, AZA, and IVIG may be used. In life-threatening situations, plasma exchange, RTX, or CYC may be considered.[58]

In patients with AAV, urgent or elective surgical interventions may be performed, either alone or in combination with

immunosuppressive therapy, depending on disease activity and the patients' clinical condition. In elective cases, surgical intervention is recommended after remission has been sustained for 6-12 months.[59]

In conclusion, interdisciplinary collaboration is of paramount importance in the management of AAV, a multisystem disorder that may involve multiple organs and tissues across diverse medical specialties. This guideline was developed by consensus of experts in rheumatology, nephrology, pulmonology, allergy and clinical immunology, otorhinolaryngology, and hematology appointed by the Executive Board of the Turkish Society for Rheumatology. Additional recommendations have been formulated to address the different stages of disease management, from diagnosis to long-term follow-up. It is our sincere expectation that this guideline will advance clinical practice and enhance patient care for individuals with AAV throughout Türkiye.

Footnotes

Author Contributions

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References

1. Kitching AR, Anders HJ, Basu, N et al. Anca-associated vasculitis. Nat Rev Dis Primers. 2020;6:71.
2. Sariyildiz E, Erpek E, Ozgur D, et al. Demographic and clinical profiling of anca-associated vasculitis in Turkey: a comprehensive analysis from turkish vasculitis study group (trvas) registry. 21st International Vasculitis Workshop. 2024:295.
3. Monti S, Craven A, Klersy C, et al. Association between age at disease onset of anti-neutrophil cytoplasmic antibody-associated vasculitis and clinical presentation and short-term outcomes. Rheumatology (Oxford). 2021;60:617-28.
4. Gómez-Puerta JA, Hernández-Rodríguez J, López-Soto A, Bosch X. Antineutrophil cytoplasmic antibody-associated vasculitides and respiratory disease. Chest. 2009;136:1101-11.
5. Quinn KA, Gelbard A, Sibley C, et al. Subglottic stenosis and endobronchial disease in granulomatosis with polyangiitis. Rheumatology (Oxford, England). 2019;58:2203-11.
6. Sacoto G, Boukhlal S, Specks U, Flores-Suárez LF, Cornec D. Lung involvement in anca-associated vasculitis. Presse Med. 2020;49:104039.
7. Castañer E, Alguersuari A, Gallardo X, et al. When to suspect pulmonary vasculitis: radiologic and clinical clues. Radiographics.
8. Feragalli B, Mantini C, Sperandeo M, et al. The lung in systemic vasculitis: radiological patterns and differential diagnosis. Br J Radiol. 2016;89:20150992.
9. Kagiyama N, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2015;2:e000058.
10. Emmi G, Bettiol A, Gelain E, et al. Evidence-based guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. Nat Rev Rheumatol. 2023;19:378-393.
11. Moiseev S, Novikov P, Jayne D, Mukhin N. End-stage renal disease in anca-associated vasculitis. Nephrol Dial Transplant. 2017;32:248-53.
12. Bossuyt X, Cohen Tervaert JW, Arimura Y, et al. Position paper: revised 2017 international consensus on testing of ancas in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13:683-92.
13. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. Eular recommendations for the management of anca-associated vasculitis: 2022 update. Ann Rheum Dis. 2024;83:30-47.
14. Maldonado F, Parambil JG, Yi ES, Decker PA, Ryu JH. Haemosiderin-laden macrophages in the bronchoalveolar lavage fluid of patients with diffuse alveolar damage. Eur Respir J. 2009;33:1361-6.
15. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of anca-associated glomerulonephritis. J Am Soc Nephrol. 2010;21:1628-36.
16. Berti A, Cornec-Le Gall E, Cornec D, et al. Incidence, prevalence, mortality and chronic renal damage of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in a 20-year population-based cohort. Nephrol Dial Transplant. 2019;34:1508-17.
17. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in anca-associated glomerulonephritis. Kidney Int. 2018;94:1177-88.
18. Armağan B, Karadağ Ö. Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides: differential diagnosis. J Rheumatol-Special Topics. 2018;11:33-8.
19. Pyo JY, Lee LE, Park YB, Lee SW. Comparison of the 2022 acr/eular classification criteria for antineutrophil cytoplasmic antibody-associated vasculitis with previous criteria. Yonsei Med J. 2023;64:11-7.
20. Terrier B, Darbon R, Durel CA, et al. French recommendations for the management of systemic necrotizing vasculitides (polyarteritis nodosa and anca-associated vasculitides). Orphanet J Rare Dis. 2020;15:351.

21. Lv L, Chang DY, Li ZY, Chen M, Hu Z, Zhao MH. Persistent hematuria in patients with antineutrophil cytoplasmic antibody-associated vasculitis during clinical remission: chronic glomerular lesion or low-grade active renal vasculitis? BMC Nephrol. 2017;18:354.

22. Benichou N, Charles P, Terrier B, et al. Proteinuria and hematuria after remission induction are associated with outcome in anca-associated vasculitis. Kidney Int. 2023;103:1144-55.

23. Rhee RL, Davis JC, Ding L, et al. The utility of urinalysis in determining the risk of renal relapse in anca-associated vasculitis. Clin J Am Soc Nephrol. 2018;13:251-7.

24. Odler B, Bruchfeld A, Scott J, et al. Challenges of defining renal response in anca-associated vasculitis: call to action? Clini Kidney J. 2023;16:965-75.

25. Kidney Disease: Improving Global Outcomes (KDIGO) ANCA Vasculitis Work Group. KDIGO 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Kidney Int. 2024;105:S71-116.

26. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of anca-associated vasculitis. Ann Rheum Dis. 2016;75:1583-94.

27. Chung SA, Langford CA, Maz M, et al. 2021 American college of rheumatology/vasculitis foundation guideline for the management of antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheumatol. 2021;73:1366-83.

28. Exley AR, Bacon PA, Luqmani RA, et al. Development and initial validation of the vasculitis damage index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997;40:371-80.

29. Robson JC, Dawson J, Doll H, et al. Validation of the ANCA-associated vasculitis patient-reported outcomes (AAV-PRO) questionnaire. Ann Rheum Dis. 2018;77:1157-64.

30. Terrier B, Charles P, Aumaître O, et al. Anca-associated vasculitides: recommendations of the french vasculitis study group on the use of immunosuppressants and biotherapies for remission induction and maintenance. Presse Med. 2020;49:104031.

31. Walsh M, Merkel PA, Peh CA, et al. Plasma exchange and glucocorticoids in severe anca-associated vasculitis. N Engl J Med. 2020;382:622-31.

32. Seo P, Specks U, Keogh KA. Efficacy of rituximab in limited wegener's granulomatosis with refractory granulomatous manifestations. J Rheumatol. 2008;35:2017-23.

33. Reeves HM, Winters JL. The mechanisms of action of plasma exchange. Br J Haematol. 2014;164:342-51.

34. Nezam D, Porcher R, Grolleau F, et al. Kidney histopathology can predict kidney function in anca-associated vasculitides with acute kidney injury treated with plasma exchanges. J Am Soc Nephrol. 2022;33:628-37.

35. Shimizu T, Morita T, Kumanogoh A. The therapeutic efficacy of intravenous immunoglobulin in anti-neutrophilic cytoplasmic antibody-associated vasculitis: a meta-analysis. Rheumatology (Oxford). 2020;59:959-67.

36. Wijetilleka S, Jayne DR, Mukhtyar C, et al. Recommendations for the management of secondary hypogammaglobulinaemia due to b cell targeted therapies in autoimmune rheumatic diseases. Rheumatology (Oxford). 2019;58:889-96.

37. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Anns Intern Med. 2005;143:621-31.

38. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. J Am Soc Nephrol. 1996;7:33-9.

39. Yamakawa H, Toyoda Y, Baba T, et al. Anti-inflammatory and/or anti-fibrotic treatment of mpo-anca-positive interstitial lung disease: a short review. J Clin Med. 2022;11:3835.

40. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive interstitial lung diseases: data from the whole inbuild trial. Eur Respir J. 2022;59:2004538.

41. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults: an official ats/ers/jrs/alat clinical practice guideline. Am J Respir Crit Care Med. 2022;205:e18-47.

42. Global strategy for asthma management and prevention 2024. Available link: https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf

43. Baççıoğlu A, Bavbek S, Damadoğlu E, et al. Astım tanı ve tedavi rehberi, astımın kronik tedavisi, basamak tedavisi 2022 güncellemesi. Available from: https://www.aid.org.tr/wp-content/uploads/2022/05/Kronik-Tedavide-Basamak-Tedavisi-2021.pdf

44. Bettiol A, Urban ML, Dagna L, et al. Mepolizumab for eosinophilic granulomatosis with polyangiitis: a european multicenter observational study. Arthritis Rheumatol. 2022;74:295-306.

45. Canzian A, Venhoff N, Urban ML, et al. Use of biologics to treat relapsing and/or refractory eosinophilic granulomatosis with polyangiitis: data from a european collaborative study. Arthritis Rheumatol. 2021;73:498-503.

46. Can Bostan O, Duran E, Tuncay G, et al. Sinonasal and respiratory outcomes of eosinophilic granulomatosis with polyangiitis patients receiving 100 mg mepolizumab in real-life clinical practice: 1-year follow up study. J Asthma. 2023;60:931-7.

47. Kauffmann M, Bobot M, Robert T, et al. Disease activity and adverse events in patients with anca-associated vasculitides undergoing long-term dialysis. Clin J Am Soc Nephrol. 2021;16:1665-75.

48. Pope V, Sivashanmugathas V, Moodley D, Gunaratnam L, Barra L. Outcomes in anca-associated vasculitis patients with end-stage kidney disease on renal replacement therapy-a meta-analysis. Semin Arthritis Rheum. 2023;60:152189.

49. Hruskova Z, Stel VS, Jayne D, et al. Characteristics and outcomes of granulomatosis with polyangiitis (wegener) and microscopic polyangiitis requiring renal replacement therapy: results from the european renal association-european dialysis and transplant association registry. Am J Kidney Dis. 2015;66:613-20.

50. Hruskova Z, Tesar V, Geetha D. Renal transplantation in antineutrophil cytoplasmic antibody-associated vasculitis: current perspectives. Kidney Blood Press Res. 2020;45:157-65.

51. Sachez-Alamo B, Moi L, Bajema I, et al. Long-term outcome of kidney function in patients with anca-associated vasculitis. Nephrol Dial Transplant. 2024;39:1483-93.

52. Kronbichler A, Kerschbaum J, Gopaluni S, et al. Trimethoprim-sulfamethoxazole prophylaxis prevents severe/life-threatening infections following rituximab in antineutrophil cytoplasm antibody-associated vasculitis. Ann Rheum Dis. 2018;77:1440-7.

53. Furer V, Rondaan C, Heijstek MW, et al. 2019 update of eular recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79:39-52.

54. Türkiye Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Uzmanlık Derneği (EKMUD). Erişkin Bağışıklama Rehberi 2024 [Internet]. Ankara: EKMUD; 2024 [cited 2026 Feb 10]. Available from: https://www.ekmud.org.tr/files/uploads/files/eriskin-bagisiklama-rehberi-2024.pdf

55. Robson J, Doll H, Suppiah R, et al. Damage in the anca-associated vasculitides: long-term data from the european vasculitis study group (euvas) therapeutic trials. Ann Rheum Dis. 2015;74:177-84.

56. Heffernan MP, Saag KG, Robinson JK, Callen JP. Prevention of osteoporosis associated with chronic glucocorticoid therapy. JAMA. 2006;295:1300-3.

57. Daher A, Sauvetre G, Girszyn N, et al. Granulomatosis with polyangiitis and pregnancy: a case report and review of the literature. Obstet Med. 2020;13:76-82.

58. Pecher AC, Henes M, Henes JC. Optimal management of anca-associated vasculitis before and during pregnancy: current perspectives. Arch Gynecol Obstet. 2023;308:379-85.

59. Kohanski MA, Reh DD. Chapter 11: granulomatous diseases and chronic sinusitis. Am J Rhinol Allergy. 2013;27:39-41.

Management of ANCA-associated vasculitis: Recommendations of the Turkish Society for Rheumatology	
General principles	
A	Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are heterogeneous diseases that may present with variable clinical features and be life- or organ-threatening. Therefore, management should be provided by a multidisciplinary team at centers experienced in vasculitis or at clinics with access to such centers.
B	The broad clinical spectrum of AAV highlights the need for educational meetings to enhance physicians' awareness of the disease. In addition, meetings that promote collaboration among specialities would help optimize disease management.
C	Patients diagnosed with AAV should be informed about the possible course of the disease, the treatment process, and warning signs or symptoms that may indicate disease activity.
D	Patients should be periodically screened for treatment-related adverse effects and comorbidities, including hypertension, osteoporosis, and cardiovascular diseases, and be advised on appropriate lifestyle modifications.
Recommendations	
1	In patients with symptoms and/or findings suggestive of AAV, both PR3-ANCA and myeloperoxidase-ANCA tests are recommended as the primary diagnostic approach, using high-quality antigen-specific assays.
2	Tissue biopsy, particularly from the kidney or lung, is the gold standard for the diagnosis of AAV. However, when biopsy cannot be performed or there is strong clinical suspicion of vasculitis before biopsy results are available, immunosuppressive therapy should not be delayed.
3	In patients with AAV, inflammatory markers and a structured clinical assessment tool [Birmingham Vasculitis Activity Score version 3 (BVAS v3)] are recommended for evaluating disease activity at diagnosis and during follow-up.
4	In life- or organ-threatening manifestations (such as glomerulonephritis, diffuse alveolar hemorrhage, tracheal or subglottic stenosis, meningeal involvement, central nervous system involvement, retro-orbital disease, cardiac involvement, mesenteric involvement, or mononeuritis multiplex), remission induction therapy with glucocorticoids in combination with either cyclophosphamide (CYC) or rituximab (RTX) is recommended.
5	In life- or organ-threatening situations, pulse glucocorticoid therapy may be administered. The initial oral glucocorticoid dose should be adjusted according to the severity of the clinical condition. During long-term corticosteroid use, a reduced-dose regimen is preferred whenever clinically feasible.
6	Other AAV manifestations, such as pulmonary nodules or localized upper respiratory tract involvement, should be treated with oral glucocorticoids in combination with methotrexate (MTX). Alternatively, mycophenolate mofetil (MMF), azathioprine, or rituximab (RTX) may be considered.
7	Plasma exchange is not routinely recommended as part of the induction regimen. It may be considered in patients with rapidly progressive glomerulonephritis (serum creatinine >3.4 mg/dL, requiring dialysis, or with rapidly rising serum creatinine despite immunosuppressive therapy) and/or in those with diffuse alveolar hemorrhage accompanied by hypoxemia.
8	In cases of refractory disease or relapse, referral of patients to centers with expertise in vasculitis may be considered.
9	Pulmonary exacerbations in eosinophilic granulomatosis with polyangiitis (EGPA) should be evaluated in collaboration with pulmonologists or allergy–immunology specialists and managed with a regimen containing an inhaled corticosteroid (ICS) to ensure adequate asthma control.
10	Patients with EGPA who have uncontrolled asthma (persistent exacerbations despite high-dose ICS plus long-acting β-agonist therapy) should be evaluated for treatment with anti–interleukin-5 (IL-5) (mepolizumab) or anti–IL-5Rα (benralizumab).
11	MTX, MMF, azathioprine, or RTX can be used as maintenance therapy in patients with AAV. Fewer relapses have been reported with RTX than with azathioprine. The duration of maintenance therapy may range from 24 to 48 months, depending on the patient's clinical condition.
12	In patients receiving RTX, CYC, and/or high-dose glucocorticoids, prophylaxis with trimethoprim–sulfamethoxazole (400/80 mg daily or 800/160 mg three times per week) is recommended to prevent *Pneumocystis jirovecii* pneumonia. In addition, annual influenza and age-appropriate pneumococcal vaccinations should be administered.
13	Serum immunoglobulin levels should be measured before starting RTX, before each subsequent cycle during treatment, and for at least one year after discontinuation of RTX to monitor for secondary immunodeficiency associated with RTX therapy.
14	Intravenous immunoglobulin (IVIG) is not a routine component of AAV therapy. Its administration should be considered for patients with comorbidities such as bronchiectasis, unusual or recurrent infections, neutropenia, or hypogammaglobulinemia (IgG <4 g/L).

Supplementary Link: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/f798b210-b702-4979-98f8-a7557990577b.pdf

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Clinical and genetic distinctions of pediatric FMF patients with erysipelas-like erythema: Clinical and genetic profile

Pediatrik FMF hastalarında erizipel benzeri eritem: Klinik ve genetik ayrımlar

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Abstract

Objective: Familial Mediterranean fever (FMF) is an autosomal recessive autoinflammatory disease characterized by recurrent fever and serosal inflammation. Erysipelas-like erythema (ELE) is a pathognomonic but under-recognized skin manifestation. This study aimed to compare the clinical and genetic features of FMF patients with and without ELE.

Methods: We retrospectively analyzed 2,325 pediatric FMF patients who were followed from 2016 to 2024 at University of Health Sciences Türkiye, Ümraniye Training and Research Hospital. Patients were grouped based on the presence (Group 1) or absence (Group 2) of ELE. Demographics, clinical data, *MEFV* mutations, and treatment features were compared.

Results: ELE was present in 215 patients (9.25%). Group 1 had higher ages at symptom onset and at diagnosis (p=0.003). Musculoskeletal symptoms—including arthralgia (73.5%), arthritis (54.4%), myalgia (63.7%), leg pain (51.2%), and prolonged febrile myalgia (2.3%)—were significantly more frequent (all p<0.001). Chest pain and splenomegaly were also more common (p<0.05). No differences between groups were observed for fever and abdominal pain. Use of biologics (9.9% vs. 4.7%; p=0.0049) and colchicine doses (p<0.001) were higher in Group 1. Ankle arthritis was markedly more common (38.1% vs. 6.4%, p<0.001). M694V homozygosity was enriched in Group 1 (47.9% vs. 13.7%, p<0.001), whereas M694V/– and E148Q/– mutations were more common in Group 2.

Conclusion: ELE is associated with a more severe FMF phenotype, characterized by predominant musculoskeletal involvement, ankle arthritis, increased treatment requirements, and delayed diagnosis. Its early recognition may aid in timely and personalized FMF management.

Keywords: Familial Mediterranean fever, erysipelas-like erythema, *MEFV* mutation, ankle rash, FMF attacks

Özet

Amaç: Ailesel Akdeniz ateşi (AAA), tekrarlayan ateş ve seröz iltihaplanma ile seyreden otozomal resesif bir otoenflamatuvar hastalıktır. Erizipel-benzeri eritem (EBE), patognomonik ancak yeterince tanınmayan bir deri bulgusudur. Bu çalışmada, EBE varlığına göre AAA'lı hastaların klinik ve genetik özelliklerinin karşılaştırılması amaçlanmıştır.

Yöntem: 2016-2024 yılları arasında Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi'nde izlenen 2.325 pediatrik AAA hastası retrospektif olarak incelendi. Hastalar, EBE varlığına (Grup 1) ve yokluğuna (Grup 2) göre sınıflandırıldı. Demografik veriler, klinik özellikler, *MEFV* mutasyonları ve tedavi profilleri karşılaştırıldı.

Bulgular: EBE, 215 hastada (%9,25) saptandı. Grup 1'de semptom başlangıç yaşı ve tanı yaşı daha yüksekti (p=0,003). Kas-iskelet sistemi bulguları—artralji (%73,5), artrit (%54,4), miyalji (%63,7), bacak ağrısı (%51,2) ve uzamış febril miyalji (%2,3)—belirgin şekilde daha sık görüldü (tümü p<0,001). Göğüs ağrısı ve splenomegali de daha yaygındı (p<0,05). Ateş ve abdominal ağrı bakımından fark saptanmadı. Biyolojik ajan kullanımı (%9,9'a karşı %4,7; p=0,0049) ve kolşisin dozları (p<0,001) Grup 1'de daha yüksekti. Ayak bileği artriti belirgin oranda daha sık görüldü (%38,1'e karşı %6,4; p<0,001). M694V homozigotluğu Grup 1'de daha fazlaydı (%47,9'a karşı %13,7; p<0,001); buna karşın M694V/– ve E148Q/– mutasyonları Grup 2'de daha yaygındı.

Sonuç: EBE, daha şiddetli bir AAA fenotipi ile ilişkili olup kas-iskelet sistemi baskınlığı, ayak bileği artriti, artmış tedavi gereksinimi ve gecikmiş tanı ile karakterizedir. Erken tanınması, zamanında ve kişiselleştirilmiş AAA yönetimine katkı sağlayabilir.

Anahtar Kelimeler: Ailesel Akdeniz ateşi, erizipel-benzeri eritem, *MEFV* mutasyonu, ayak bileği kızarıklığı, AAA atakları

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Introduction

Familial Mediterranean fever (FMF) is the most common monogenic autoinflammatory disease, primarily affecting individuals from the Mediterranean region. It is characterized by recurrent, self-limited episodes of fever and serosal inflammation that typically begin in childhood or adolescence.[1,2]

The disease is caused by mutations in the *MEFV* gene, which encodes the pyrin protein—an essential regulator of innate immunity. While over 300 mutations have been described, a small group of variants—especially *M694V, M680I, V726A,* and *M694I* in exon 10— are most commonly implicated in FMF. The *E148Q* variant in exon 2 is frequently observed but remains controversial in terms of its pathogenicity.[3,4]

Among the cutaneous manifestations of FMF, erysipelas-like erythema (ELE) stands out due to its frequency and diagnostic relevance. ELE typically presents as sharply defined, tender, red plaques on the lower limbs, particularly the feet and ankles. Pathophysiologically, ELE is thought to result from dysregulation of the innate immune response driven by pyrin dysfunction in FMF. Mutations in *MEFV* enhance interleukin-1β–mediated inflammatory signaling and impair apoptosis, resulting in exaggerated neutrophilic activation in the superficial dermis, which clinically manifests as ELE.[5-8] Although observed in 25-47% of FMF patients, its prevalence differs across cohorts. However, when ELE is strictly defined as a pathognomonic finding, its frequency has been reported to be between 7% and 10%.[9-11] Because it can resemble cellulitis or other inflammatory conditions, misdiagnosis is common, especially if ELE is the first or sole manifestation. Physical exertion and trauma often trigger these episodes, which usually resolve spontaneously within a few days.[8,12-15]

Although ELE is only minimally represented in pediatric FMF criteria, several large-scale studies have indicated that it may be associated with a more severe disease profile. ELE has been reported to occur more frequently in colchicine-resistant patients and in individuals homozygous for *M694V*, suggesting a link to both treatment refractoriness and high-risk genetic background.[16,17] Based on this, our central hypothesis was that FMF patients with ELE would differ meaningfully from those without ELE, demonstrating more pronounced musculoskeletal involvement, a higher prevalence of pathogenic *MEFV* variants—particularly *M694V* homozygosity—and greater treatment requirements. To test this hypothesis, we compared the clinical and genetic characteristics of ELE-positive and ELE-negative pediatric FMF patients within our cohort.

This study aims to investigate the clinical and genetic characteristics of FMF patients presenting with ELE compared to those without ELE. We specifically examine whether ELE is associated with distinct demographic features, laboratory findings, and *MEFV* mutations. By clarifying these associations, we seek to improve diagnostic accuracy and facilitate more tailored management strategies in FMF.[9,18]

Materials and Methods

This retrospective study was conducted using the medical records of pediatric patients diagnosed with FMF who were followed at the Pediatric Rheumatology Unit of University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, between 2016 and 2024. A total of 2325 patients who met the diagnostic criteria and had at least 6 months of regular follow-up were included in the study. Patients older than 18 years at diagnosis and lacking genetic *MEFV* analysis reports were excluded. Follow-up duration, treatment protocols, and clinical data were obtained from patient records.

FMF diagnosis was established by pediatric rheumatologists based on clinical evaluation. All included patients fulfilled at least one of the established FMF classification criteria (Eurofever/PRINTO or Turkish pediatric FMF classification criteria).[19,20]

Demographic information, clinical features, attack frequency, colchicine dosage, and treatment were recorded in detail. Patients were divided into two groups based on the presence or absence of ELE, and demographic, clinical and genetic differences between the groups were analyzed.

The study was conducted following approval by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval date: 26.12.2024; number: B.10.1TKH.4.34.H.GP.0.01/460). Informed consent was obtained from all patients or their legal guardians, as required by the institutional ethics committee. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Released 2019. IBM SPSS Statistics for Windows, Version 26.0, Armonk, NY: IBM Corp.). Descriptive measures were calculated: means ± standard deviations for normally distributed quantitative variables and medians with interquartile ranges (IQRs) for non-normally distributed quantitative variables. Absolute frequencies and percentages were presented for qualitative variables. Normality was assessed using the Shapiro-Wilk test. Differences in categorical variables between groups were assessed using the chi-square test, while comparisons of continuous variables were made using the Mann-Whitney U test or the unpaired Student's t-test, depending on the distribution of the data. A p-value of less than 0.05 was considered statistically significant for all analyses.

Results

The study included 2,325 children diagnosed with FMF. The patient population consisted of 1,146 males (49.29%) and 1,179 females (50.71%) (Figure 1). The median age at symptom onset was 4.2 years (IQR, 2-7.8), and the median age at diagnosis was 6 years (IQR, 4-10). The median duration between attack onset and diagnosis was 12 months (IQR 6-24 months). Parental consanguinity was present in 19.6% of patients (n=449). A family history of FMF was documented in 51.2% of patients (n=1171), as was a history of amyloidosis in another 5.3% of patients (n=122) (Table 1).

ELE was detected in 215 patients (9.25%). The patients were divided into two groups based on the presence of ELE. Patients with ELE were assigned to Group 1, and patients without ELE were assigned to Group 2. Group 1 included 215 patients, while Group 2 included 2,110 patients. With respect to gender distribution, both groups exhibited almost equal proportions, with no statistically significant difference (p=0.77). The median age at symptom onset was earlier in Group 2 [4 (IQR 2-7.6)] than in Group 1 [5 (IQR 2.9-9)]; this difference was statistically significant (p=0.003). Similarly, the median age at diagnosis was significantly lower in Group 2 than in Group 1 [6 (IQR 4-9) vs. 7 (IQR 4.25-11); p=0.003].

In Group 1, inflammatory musculoskeletal symptoms were significantly more frequent than in Group 2. Specifically, arthralgia was reported in 158 patients (73.5%) in Group 1 compared with 1,083 patients (51.5%) in Group 2 (p<0.001); arthritis occurred in 117 patients (54.4%) in Group 1 compared with 302 patients (14.4%) in Group 2 (p<0.001). Likewise, myalgia affected 137 patients (63.7%) in Group 1 versus 839 patients (39.9%) in Group 2, and leg pain or stiffness affected 110 patients (51.2%) in Group 1 versus 488 patients (23.2%) in Group 2 (p=0.014). Additionally, myalgia after exercise or walking was significantly more common in Group 1 (41.9%, n=90) than in Group 2 (18.5%, n=389) (p<0.001). Prolonged febrile myalgia, which was reported in 5 patients from Group 1 (2.3%) has been compared with 14 patients from Group 2 (0.7%) (p=0.026). Furthermore, chest pain (23.3% vs. 14.9%) and splenomegaly (5.6% vs. 1.3%) were significantly more common in the ELE-positive group (p<0.001). In contrast, no statistically significant differences were observed between the groups in terms of fever (Group 1: 78.1%, n=168; Group 2: 82.4%, n=1732; p=0.135) or abdominal pain (Group 1: 79.5%, n=171; Group 2: 83.7%, n=1759; p=0.125).

The last colchicine dose was significantly higher among patients with ELE. Group 1 had a median dose of 1 mg/day (IQR 1-1.5; n=175), while Group 2 had a median dose of 1 mg/day (IQR 1-1; n=1664); p<0.001. The use of biologic agents was significantly more frequent in Group 1 than in Group 2: 21 individuals (9.9%) versus 97 individuals (4.7%) (p=0.005) (Table 1).

Joint involvement during arthritis attacks differed between the groups. Ankle arthritis was observed in 82 (38.1%) of ELE-positive patients compared with 135 (6.4%) of ELE-negative patients (p<0.0001). Conversely, the absence of joint involvement was markedly more frequent among ELE-negative individuals (p<0.0001). No significant differences were observed for knee

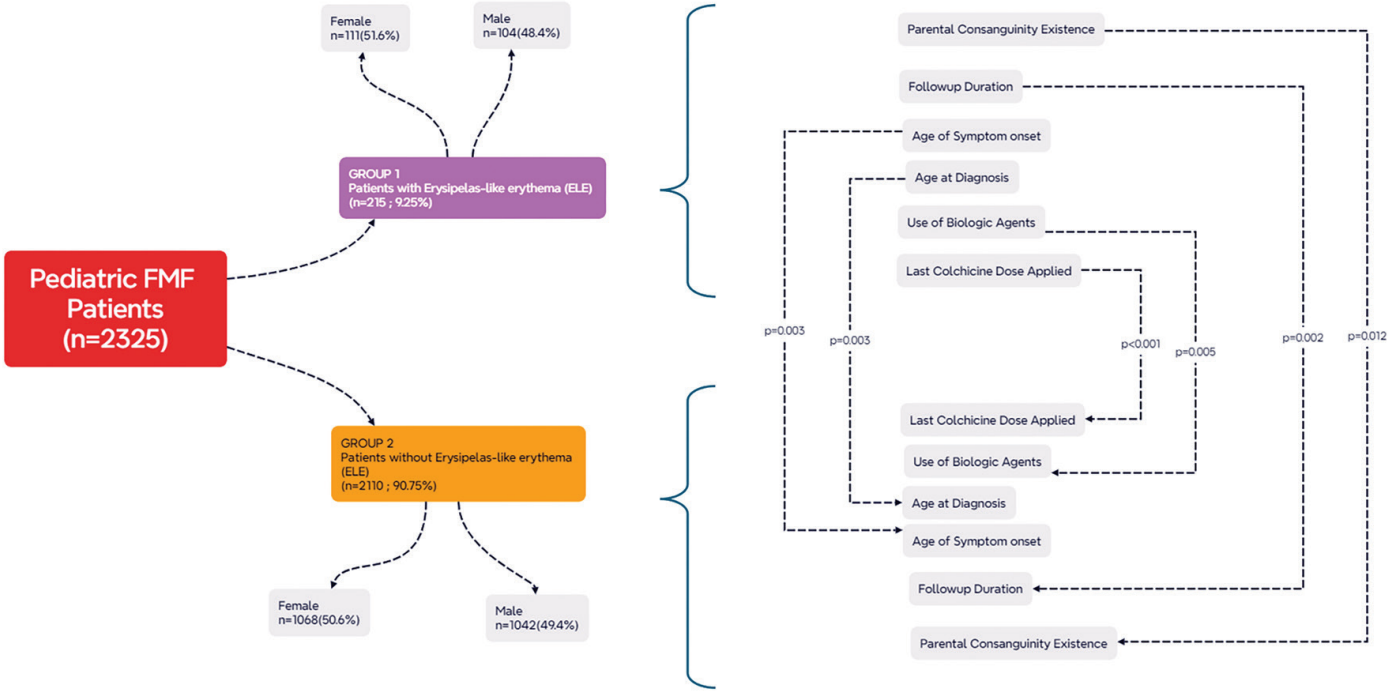

Figure 1. Schematization of the study for Familial Mediterranean fever patients grouped as with or without ELE and major clinical findings with statistical significance across these groups

involvement [43 (20.0%) vs. 366 (17.3%); p=0.772], elbow involvement [2 (0.9%) vs. 5 (0.2%); p=0.534], or hip, wrist, and small-joint involvement (all p>0.05) (Table 1).

A detailed comparison of *MEFV* genotype distributions is presented in Table 2. The *M694V/M694V* genotype was the most common, observed in 47.9% of patients (103/215) in Group 1, compared with 13.7% (290/2110) in Group 2 (p<0.01). Conversely, heterozygous carriers were significantly less frequent in the ELE-positive group; specifically, the *M694V/-* genotype was found in 16.3% of Group 1 versus 25.4% of Group 2 (p<0.01), and the *E148Q/-* genotype was found in 6.0% of Group 1 versus 12.9% of Group 2 (p<0.01). Additionally, the compound heterozygous *M680I/V726A* genotype was absent in Group 1 but was present in 1.8% of Group 2 (p=0.044).

Table 1. Demographic and clinical comparison of patients with and without erysipelas-like erythema

	Patients with ELE (n=215)	Patients without ELE (n=2110)	p-value
Demographic features			
Gender			
Female; [n (%)]	111 (51.63)	1068 (50.62)	0.77
Male; [n (%)]	104 (48.17)	1042 (49.38)	
Age of onset (years); [median (IQR Q1-Q3)]	5 (3-9)	4 (2-7.6)	**0.003**
Age of diagnosis (years); [median (IQR Q1-Q3)]	7 (4.25-11)	6 (4-9)	**0.003**
Duration between attack onset and diagnosis (months); [median (IQR Q1-Q3)]	12 (6-24)	12 (6-24)	0.084
Followup duration (months): [median (IQR Q1-Q3)]	40 (20-62)	34 (15-58)	**0.002**
Parental consanguinity existence; [n (%)]	56 (26.05)	393 (18.93)	**0.012**
Diagnosis of FMF in family; [n (%)]	113 (53.05)	1058 (51.01)	0.613
Diagnosis of amyloidosis in family; [n (%)]	13 (6.07)	109 (5.22)	0.826
Clinical features			
The annual number of attacks; [median (IQR Q1-Q3)]	12 (4-12)	12 (6-12)	0.382
Attack duration (days); [median (IQR Q1-Q3)]	3 (2-3)	3 (2-3)	0.345
Age at colchicine start (months); [median (IQR Q1-Q3)]	85 (55-132)	72 (44-108)	**0.000**
Fever; [n (%)]	168 (78.14)	1732 (82.4)	0.135
Abdominal pain; [n (%)]	171 (79.53)	1759 (83.68)	0.125
Chest pain; [n (%)]	50 (23.26)	314 (14.93)	0.002
Pleural effusion; [n (%)]	1 (0.47)	18 (0.86)	1
Vomiting; [n (%)]	15 (6.98)	266 (12.64)	**0.015**
Diarrhea; [n (%)]	40 (18.6)	275 (13.08)	**0.028**
Constipation; [n (%)]	6 (2.79)	116 (5.52)	0.107
Orchitis; [n (%)]	2 (0.95)	6 (0.29)	0.165
Splenomegaly; [n (%)]	12 (5.61)	27 (1.29)	**0**
Amyloidosis; [n (%)]	0 (0)	4 (0.19)	1.000
Headache; [n (%)]	18 (8.37)	202 (9.62)	0.626
Arthralgia; [n (%)]	158 (73.49)	1083 (51.47)	**0**
Arthritis; [n (%)]	117 (54.42)	302 (14.35)	**0**
Myalgia; [n (%)]	137 (63.72)	839 (39.86)	**0**
Myalgia after exercise/walking; [n (%)]	90 (41.86)	389 (18.48)	**0**
Prolonged febrile myalgia; [n (%)]	5 (2.33)	14 (0.67)	0.026
Non-erysipelas rash; [n (%)]	22 (10.23)	130 (6.18)	**0.021**
Leg pain/stiffness; [n (%)]	110 (51.16)	488 (23.22)	**0.014**
Treatment features			
Colchicine dose at last visit (mg/day); [median (IQR Q1-Q3)]	1.0 (1.0-1.5)	1.0 (1.0-1.0)	**<0.001**
Use of biologic agents; [n (%)]	21 (9.8)	97 (4.6)	0.005

ELE: Erysipelas-like erythema, FMF: Familial Mediterranean fever, IQR: Interquartile range

Table 2. Genotypic manifestations of patients with and without erysipelas-like erythema					
	Group1 (n=215)		Group2 (n=2110)		
Genotype	n	%	n	%	p-value
M694V/M694V	103	47.9	290	13.7	**<0.001**
M694V/-	35	16.3	535	25.4	**<0.001**
M680I/M694V	17	7.9	130	6.2	0.3
E148Q/-	13	6	272	12.9	**<0.001**
E148Q/M694V	10	4.7	67	3.2	0.23
V726A/-	8	3.7	145	6.9	0.08
M694V/V726A	8	3.7	117	5.5	0.34
M680I/-	7	3.3	105	5	0.32
E148Q/E148Q	4	1.9	29	1.4	0.54
R761H/-	1	0.5	44	2.1	0.12
M680I/M680I	1	0.5	36	1.7	0.25
M694V/R761H	1	0.5	36	1.7	0.25
P369S/R408Q	1	0.5	29	1.4	0.52
E148Q/P369S	1	0.5	27	1.3	0.51
K695R/-	1	0.5	17	0,8	1
E148Q/M680I	1	0.5	12	0.6	1
M694V/ M694I	1	0.5	4	0.2	0.38
M694V/G632S	1	0.5	1	0	0.18
E148Q/K695R	1	0.5	0	0	0.09
M680I/V726A	0	0	37	1.8	**0.04**
A744S/-	0	0	22	1	0.26
V726A/V726A	0	0	17	0.8	0.39
E148Q/V726A	0	0	12	0.6	0.62
P369S/-	0	0	11	0,5	0,61
Other genotypes	0	0	115	4	1

Discussion

This study contributes to the understanding of ELE, a distinct but underrecognized cutaneous manifestation in pediatric patients with FMF. ELE was observed in 9.25% of our cohort, consistent with previous reports, ranging from 7% to 10% in similar pediatric populations.[9,11] Although ELE has traditionally been perceived as a minor skin manifestation, our findings affirm that ELE is not merely a dermatological feature but is intricately linked to a more severe inflammatory phenotype characterized by a distinct clinical presentation, delayed diagnosis, pronounced musculoskeletal involvement, and increased treatment needs.

Genetic analysis in our cohort revealed a significantly higher frequency of homozygosity for the *M694V* mutation among patients with ELE (47.9% vs. 13.7%, $p<0.001$), consistent with previous large-scale pediatric FMF studies reporting that ELE occurs more frequently in individuals homozygous for *M694V*. In parallel, ELE has been reported as a clinical feature enriched in colchicine-resistant patients in large registry-based analyses, supporting the view that ELE may be linked to both genetic risk and treatment refractoriness.[9,11,16,17] This striking genotype-phenotype correlation suggests that the observed clinical severity in the ELE group—such as increased frequency of arthritis and higher colchicine requirements—is likely driven by underlying genetic enrichment. Accordingly, ELE may be interpreted not merely as a cutaneous manifestation but as a visible surrogate marker for high-risk genotypes (particularly *M694V* homozygosity), signaling a predisposition to a more severe disease course.

Clinically, ELE-positive patients had a significantly higher prevalence of musculoskeletal symptoms, particularly arthralgia (87.5%), arthritis (52.7%), myalgia (82.4%), and exercise-induced leg pain (74.5%) than their ELE-negative counterparts ($p<0.001$ for all). These findings corroborate one of the prior observations which identified a musculoskeletal-predominant phenotype among ELE-positive patients.[11] Moreover, our data indicate that classical FMF symptoms, such as fever and abdominal pain, did not differ significantly across groups, reinforcing the notion that ELE may delineate an alternative inflammatory axis less reliant on traditional diagnostic criteria.[9,19]

Although splenomegaly is not considered a classical feature of FMF, it may appear as a reactive finding in the context of persistent systemic inflammation. Similar observations have been reported in large pediatric FMF cohorts, where splenomegaly has been described more prominently among individuals carrying high-risk *MEFV* genotypes, particularly *M694V* homozygosity.[16] In the same analysis, splenomegaly was identified as an independent predictor of a more severe genetic profile. Within this framework, the splenomegaly observed in our study likely reflects an increased inflammatory burden and a phenotype aligned with genetically driven disease severity.

Notably, arthritis in ELE-positive patients exhibited a distinct predilection for specific anatomical sites. Ankle arthritis was significantly more common in ELE patients (38.1% vs. 6.4%, $p<0.0001$), whereas other joints, such as the knees and hips, showed no significant differences in prevalence. This aligns with previous findings suggesting that ELE may reflect lower-extremity-dominant inflammation.[11] Furthermore, our dataset revealed that patients with ELE had significantly higher colchicine requirements (median 2 tablets, IQR 2-3; $p<0.001$) and increased use of biologics (9.9% vs. 4.7%; $p=0.005$), suggesting a more treatment-resistant phenotype.

The observation that ELE often emerges as an early and sometimes sole clinical finding further complicates the diagnostic process. Patients with ELE were diagnosed significantly later notwithstanding their clinical symptoms, indicating a diagnostic delay (median age at diagnosis: 7 years vs. 6 years; $p<0.01$), which may be attributed to non-specific or atypical presentations that fail to meet conventional FMF classification criteria.[19] In our cohort, patients with ELE had a slightly older age at disease onset than those without ELE. Although this may appear counterintuitive in the context of a more severe clinical course, the finding is consistent with the inherent heterogeneity of FMF and aligns with previous reports. Recent Turkish studies similarly reported older age at diagnosis among patients with ELE.[10,11,21] Moreover, the literature emphasizes that ELE tends to be a symptom observed more frequently at relatively later ages.[9,21,22] When considered together, these converging data suggest that the somewhat higher age at onset seen in the ELE group reflects the marked clinical heterogeneity of FMF rather than contradicting the more severe phenotype associated with ELE. Given this, the presence of ELE should prompt clinicians to consider FMF even in the absence of hallmark features, particularly when supported by family history or elevated inflammatory markers.

Consistent with one study in the literature, we also noted that ELE is often localized to the lower extremities, unilateral and transient, and not always accompanied by fever-characteristics that distinguish it from infectious cellulitis or erysipelas.[11] ELE may be misdiagnosed as infectious erysipelas due to its sharply demarcated erythematous appearance; however, the absence of high fever, a background of FMF, a spontaneous, short-lived course (usually ≤4 days), a bilateral yet alternating presentation, absence of systemic toxicity, and rapid responsiveness to colchicine help distinguish it from infectious etiologies. Additional differential diagnoses include cellulitis, erysipelas, and acute septic arthritis; the latter is an important contributor to the wide range of reported prevalence (5-30%).[22,23] Differentiation is critical, as misdiagnosis may lead to unnecessary antibiotic use or missed therapeutic opportunities in FMF management.

Finally, the importance of ELE as a predictor of disease severity and treatment escalation warrants inclusion in scoring systems for disease activity or colchicine resistance.[11] While current FMF diagnostic and management algorithms do not universally incorporate ELE, our findings and those of others suggest that its inclusion may enhance phenotypic characterization and therapeutic stratification.

Study Limitations

This study has several limitations. Its retrospective design relies on routinely documented clinical data, which may limit the level of detail available for some variables. Conducting the study in a tertiary referral center may have resulted in a higher proportion of complex cases, potentially reducing generalizability. ELE was identified through expert clinical assessment rather than histopathology, a pragmatic choice to avoid unnecessary invasive procedures for a transient skin manifestation.

Conclusion

This study establishes that ELE is not merely a cutaneous manifestation of FMF but a distinct clinical marker indicating a severe disease phenotype. Our findings demonstrate a strong association between ELE and the *M694V* homozygous genotype, which is characterized by earlier symptom onset, pronounced musculoskeletal involvement—particularly ankle arthritis—and a significantly higher requirement for colchicine and biologic therapies. Consequently, the presence of ELE should be recognized as a "red flag" in pediatric FMF, prompting clinicians to suspect high-risk genotypes and to consider more aggressive management strategies early in the disease course to minimize long-term complications.

Ethics

Ethics Committee Approval: The study was conducted following approval by the University of Health Sciences Türkiye, Ümraniye Training and Research Hospital Ethics Committee (approval date: 26.12.2024; number: B.10.1TKH.4.34.H.GP.0.01/460).

Informed Consent: Informed consent was obtained from all patients or their legal guardians, as required by the institutional ethics committee.

Footnotes

Authorship Contributions

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

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

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References

1. Arpacı A, Doğan S, Erdoğan HF, El Ç, Cura SE. Presentation of a new mutation in FMF and evaluating the frequency of distribution of the *MEFV* gene mutation in our region with clinical findings. Mol Biol Rep. 2021;48:2025-33.
2. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci. 2020;50:1591-610.
3. Batu ED, Basaran O, Bilginer Y, Ozen S. Familial Mediterranean fever: how to interpret genetic results? How to treat? A quarter of a century after the association with the mefv gene. Curr Rheumatol Rep. 2022;24:206-12.
4. Van Gijn ME, Ceccherini I, Shinar Y, et al. New workflow for classification of genetic variants' pathogenicity applied to hereditary recurrent fevers by the International Study Group for Systemic Autoinflammatory Diseases (INSAID). J Med Genet. 2018;55:530-7.
5. Kolivras A, Provost P, Thompson CT. Erysipelas-like erythema of familial Mediterranean fever syndrome: a case report with emphasis on histopathologic diagnostic clues. J Cutan Pathol. 2013;40:585-90.
6. Guz G, Kanbay M, Ozturk MA. Current perspectives on familial Mediterranean fever. Curr Opin Infect Dis. 2009;22:309-15.
7. Rigante D, La Torraca I, Ansuini V, Compagnone A, Sallì A, Stabile A. The multi-face expression of familial Mediterranean fever in the child. Eur Rev Med Pharmacol Sci. 2006;10:163-71.
8. Barzilai A, Langevitz P, Goldberg I, et al. Erysipelas-like erythema of familial Mediterranean fever: clinicopathologic correlation. J Am Acad Dermatol. 2000;42:791-5.
9. Yildirim DG, Seven MB, Gönen S, Söylemezoğlu O. Paediatric rheumatology erysipelas-like erythema in children with familial Mediterranean fever. Clin Exp Rheumatol. 2020;38:S101-4.
10. Çakmak F, Arık SD, Kavrul Kayaalp G, Çağlayan Ş, Ulu K, Coşkuner T. Erysipelas-like erythema: a pathognomonic rash in children with familial Mediterranean fever. Med J Bakirkoy. 2023;19:217-21.
11. Coşkun S, Tanatar A. A unique pathognomic skin manifestation of familial Mediterranean fever: erysipelas-like erythema. Harran Üniversitesi Tıp Fakültesi Dergisi. 2025;22:154-8.
12. Long SS. Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist. Pediatr Clin North Am. 2005;52:811-35.
13. Turkish FMF Study Group. Familial Mediterranean fever (FMF) in Turkey. Medicine 2005;84:1-11.
14. Koné Paut I, Dubuc M, Sportouch J, Minodier P, Garnier JM, Touitou I. Phenotype–genotype correlation in 91 patients with familial Mediterranean fever reveals a high frequency of cutaneomucous features. Rheumatology (Oxford). 2000;39:1275-9.
15. Barut K, Sahin S, Adrovic A, et al. Familial Mediterranean fever in childhood: a single-center experience. Rheumatol Int. 2018;38:67-74.
16. Tunce E, Atamyildiz Uçar SI, Polat MC, et al. Predicting homozygous M694V genotype in paediatric FMF: multicentre analysis and scoring system proposal. Rheumatology (Oxford). 2025;64:4816-24.
17. Batu ED, Şener S, Aydin EA, et al. A score for predicting colchicine resistance at the time of diagnosis in familial Mediterranean fever: data from the TURPAID registry. Rheumatology (Oxford). 2024;63:791-7.
18. Kasapcopur O, Arisoy N. Familial Mediterranean fever and other hereditary auto-inflammatory diseases. Turk Arch Pediatr. 2006;41:9-17.
19. Yalçınkaya F, Özen S, Özçakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford). 2009;48:395-8.
20. Ozen S, Sağ E, Oton T, et al. EULAR/PReS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update. Ann Rheum Dis. 2025;84:899-909.
21. Avar-Aydın PÖ, Özçakar ZB, Aydın F, Karakaş HD, Çakar N, Yalçınkaya F. Erysipelas-like erythema: a manifestation of severe disease phenotype in pediatric patients with familial Mediterranean fever. Turk Arch Pediatr. 2022;57:599-602.
22. Lidar M, Doron A, Barzilai A, et al. Erysipelas-like erythema as the presenting feature of familial Mediterranean fever. J Eur Acad Dermatol Venereol. 2013;27:912-5.
23. Schmit JL. Enquête prospective. Erysipèle et cellulites nécrosantes: quelle prise en charge en milieu hospitalier? [A prospective study on erysipelas and infectious cellulitis: how are they dealt within hospital?]. Ann Dermatol Venereol. 2001;128:334-7. French.

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Ailevi Akdeniz ateşi hastalarının takipten çıkma nedenleri ve hastaların klinik özellikleri

Reasons of lost to follow-up and clinical characteristics of Familial Mediterranean fever patients

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Özet

Amaç: Akdenize komşu ülkelerde yaygın görülen Ailevi Akdeniz ateşi (AAA) diğer kronik enflamatuvar romatolojik hastalıklar gibi düzenli takip gerektirmektedir. Hastalığın tedavi ve takibinde aksamaların olması önemli morbiditelerle sonuçlanabilmektedir. Biz de bu çalışmada, hastanemizde takipli AAA hastalarının takipten çıkma nedenlerini ve bu hastaların demografik, klinik özelliklerini araştırdık.

Yöntem: Çalışmaya 10.09.2016-10.09.2022 aralığında romatoloji polikliniğine başvuran ve bir yıldan uzun süre poliklinik kontrolüne gelmemiş AAA hastaları alındı. Yedi yüz elli sekiz hastadan takipten çıkmış 306 hasta telefon ile arandı. Hastalara kontrole gelmemelerinin muhtemel nedenleri soruldu. Ardından hastalar randevusuz olarak poliklinik kontrollerine davet edildi. Hastaların klinik ve demografik özellikleri kaydedildi. İlaç tedavi uyumu için modifiye Morinsky ölçeği (MMÖ)-motivasyon ve MMÖ-bilgi düzeyi ölçeği kullanıldı. Takipsiz olanlar ile dış merkez takipli hasta gruplarının karşılaştırması yapıldı. Veri analizleri için SPSS Versiyon 22.0 kullanıldı. P<0,05 değeri istatiksel olarak anlamlı kabul edildi.

Bulgular: Ulaşılabilen 176 (%58) hastadan 74'ünün dış merkezlerde takipli, 93 hastanın ise takipsiz olduğu öğrenildi. Tüm hastaların yaş ortalaması 39,44±11,92 yıl olup %55,1'i kadındı. Takipsiz olan hastaların %92,5'i şehir merkezinde, kalanı kırsalda ikamet ediyordu. Hastaların %87'sinde hastalık süresi 5 yıldan daha uzundu. Takipsiz hastaların çoğu üniversite (%48,1) ve lise mezunu (%31,2) idi. Hastaların takibe gelmemelerinin en sık nedeni "ihmal (%28)" ve "randevu bulamama (%25,8)" idi. Hastaların çoğu 1-3 yıl takipsiz kalmıştı. Takipsiz hastalarda atak sırasında en çok karın ağrısı (%84,9) kliniği görülmüştü. MMÖ-motivasyon, MMÖ-bilgi düzeyi ve tanıda hastanın takip gerekliliği hakkında bilgilendirilmesi değişkenlerinin takipsizlik durumuyla istatiksel olarak anlamlı ilişkisi olduğu görüldü (p<0,05).

Sonuç: Çalışmamızda takipsiz AAA hastalarının eğitim durumlarının yüksek olduğu halde takipsizlik nedeninin en sık "ihmal" olması eğitimli hastaların

Abstract

Objective: Familial Mediterranean fever (FMF), which is common in countries neighbouring the Mediterranean, requires regular follow-up like other chronic inflammatory rheumatological diseases. Deficiencies in the treatment and follow-up of the disease may result in significant morbidity. In this study, we investigated the reasons for non-follow-up of FMF patients and the clinical characteristics of these patients.

Methods: FMF patients who had not attended rheumatology control for more than 1 year were included in this study. Patients were telephoned and asked the reasons of lost to follow-up. Clinical and demographic characteristics of the patients were recorded. Modified Morinsky scale (MMS)-motivation and MMS-knowledge level questionnaires were applied for treatment compliance. Comparison was made between the patients with no follow-up and those with follow-up at an external centre. Comparison of the patient groups with follow-up and those without follow-up was made. P<0.05 was considered statistically significant.

Results: It was learnt that of the 176 patients who could be contacted by phone, 74 (42.1%) patients were followed-up in external centres and 93 patients were lost to follow-up. Most of the patients lost to follow-up were university graduates (48.1%) and high school graduates (31.2%). The most common reasons of lost to follow-up were negligence (28%) and failure to find an appointment (25.8%). The variables of MMS-motivation, MMS-knowledge level and informing patients about the need for follow-up at diagnosis had a significant relationship with non-follow-up (p<0.05).

Conclusion: The fact that "negligence" was found to be the most common reason of lost to follow-up despite the high educational status of FMF patients revealed the importance of informing even educated patients about the necessity of follow-up. This was supported by the fact that the MMS-motivation and MMS-knowledge level scores were low in patients lost to follow-up. In addition, setting the green list registrations as indefinite will reduce patients' loss of follow-up.

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Öz

dahi hastalığın tedavi/takibi konusunda yeterli bilgilendirilmesinin önemini ortaya koymuştur. Nitekim dışmerkez takiplilerde MMÖ-motivasyon, MMÖ-bilgi düzeyi skorlarının yüksekliği bunu desteklemekteydi. Ayrıca yeşil liste nedeniyle "randevu alamamak" takipsizliğin ikinci sık sebebi olarak bulundu. Bu bağlamda romatoloji hastalarında yeşil listenin yeniden düzenlemesi faydalı olacaktır.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, hastaların takipsizlik nedenleri, takipsiz hastaların özellikleri

Abstract

Keywords: Familial Mediterranean fever, reasons for patients lost to follow-up, characteristics of patients lost to follow-up

Giriş

Ailevi Akdeniz ateşi (AAA) ülkemizde yaygın görülen romatolojik hastalıklardan olup ateş ve serozit bulguları ile karakterize, ataklar tarzında seyreden, otozomal resesif geçişli bir tablodur. Tedavide kullanılan en önemli ilaç kolşisin olup hastaların ömür boyu tedavi alması ve düzenli takip olması gerekmektedir.[1] Hastalığın tedavi ve takibinde aksamalar olmasının önemli morbiditelere yol açabilmesinin yanında iş gücü kaybıyla topluma ciddi maliyet yükü de getirdiği gösterilmiştir. Hastaların düzenli takiplerine gelmeleri hastalık aktivitelerinin sürekli izlenmesine olanak vermesinin yanı sıra hastalığın başarılı bir şekilde kontrol altına alınmasında ve ilerleyici hasarın önlenmesinde çok önemli bir yere sahiptir. Diğer yandan hastaların takipten çıkması birçok kronik hastalıkta görülebilmekte, hastalığın kötüleşmesinde ve maliyet artışında rol oynamaktadır.[2] Romatolojik hastalıklarda ise takipten çıkma sıklığına ve nedenlerine dair çoğunluğu romatoid artrit (RA), sistemik lupus eritematozus (SLE), sistemik skleroz (SSc) ve ankilozan spondilit (AS) olmak üzere az sayıda çalışma olup AAA hastalarının takipsizlik durumunu belirten çalışma literatürde bulunmamaktadır.[3,4]

AAA, 1/1075 prevalansı ile dünyada en sık ülkemizde görülmekte olup[5] AAA hastalarının takipten çıkmalarının hastalar ve maliyet üzerine etkisi düşünüldüğünde bu problemin sıklığı ve nedenlerinin belirlenmemiş olması önemli bir eksiklikti. Biz de bu çalışmada, merkezimizde takipli AAA tanılı hastaların takipten çıkma nedenleri ve bu hastaların demografik, klinik özelliklerini araştırdık.

Gereç ve Yöntemler

Bu çalışma kesitsel, tanımlayıcı, olgu-kontrol çalışması olup, çalışma için 10.09.2016-10.09.2022 tarihleri aralığında hastanemizin romatoloji polikliniğine başvuran AAA tanılı hastalar belirlendi. Çalışmaya 18 yaş ve üzerinde olan, AAA tanısı olup 1 yıl ve üzerinde hastanemizdeki takibine gelmemiş hastalar dahil edildi. On sekiz yaş altında olan, AAA dışında ek romatolojik hastalığı olan veya verilerinde eksikliği olan hastalar çalışma dışında tutuldu. Hastane veri tabanı tarandığında 2016-2022 yılları arasında hastanemize başvurmuş 758 AAA hastasından bu kriterlere uyan 306 hastanın iletişim bilgileri kayıtlı idi. Bu 306 hastalar telefon ile arandı. Ulaşılabilen 176 hastaya çalışmanın amacı anlatıldı ve hastalardan sözlü onam alındıktan sonra kontrole gelmemelerinin muhtemel nedenleri soruldu. Hastalar sonrasında randevusuz poliklinik kontrollerine davet edildi. Bu hastaların klinik ve demografik özellikleri kaydedildi. Çalışmamızda takipten çıkmış AAA hastalarının tedavi uyumunu değerlendirmek için Türkçe validasyonu daha önceden yapılmış olan[6] modifiye Morisky ölçeği (MMÖ)-motivasyon, MMÖ-bilgi düzeyi anketleri uygulandı. Tamamen takipten çıkmış olan hastalar grup 1, başka merkezlerde takipli olan hastalar grup 2 olarak iki sınıfa ayrıldı. Takipsiz olanlar ile dış merkez takipli hasta gruplarının karşılaştırması yapıldı. Hastaların takipsiz kalma durumlarına etki edebilecek demografik sosyolojik ve klinik faktörler araştırıldı. Çalışmaya Sağlık Bilimleri Üniversitesi, Gülhane Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından (karar no: 2023/262, tarih: 08.11.2023) onay verildikten sonra başlanıldı.

İstatistiksel Analiz

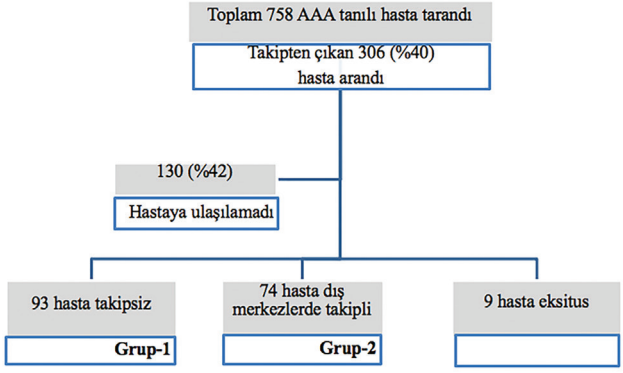
Veri analizleri için SPSS Version 22.0 (IBM Corporation, Armonk, NYC, ABD) kullanıldı. Dağılımların normalliğini belirlemek için Shapiro-Wilk testi, normal dağılmayan sürekli değişkenler için Mann-Whitney U testi, normal dağılan sürekli değişkenler için t-testi, kategorik değişkenler için ki-kare veya Fisher'in kesin testi kullanıldı. $P<0,05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular

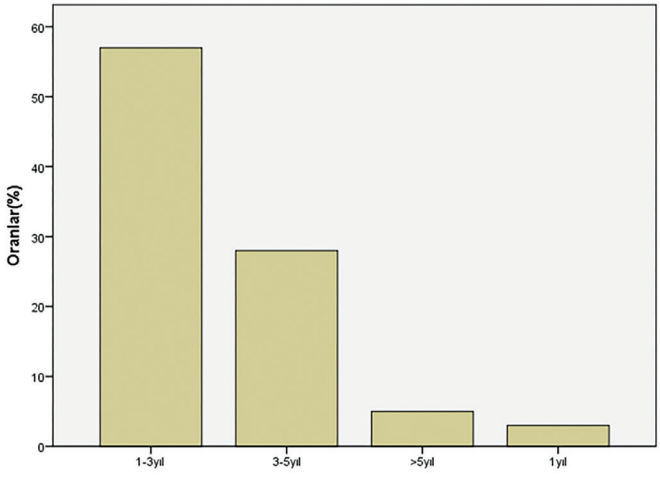
Poliklinik takibine gelmeyen 306 hasta telefon ile arandı. Bunların 130'una (%42) ulaşılamadı. Ulaşılabilen 176 (%58) hastadan, 93'ünün (%52,8) takipsiz olduğu, 74'ünün (%42,1) dış merkezlerde takipli olduğu ve 9'unun (%5,1) eksitus olduğu öğrenildi (Şekil 1).

Tüm hastaların yaş ortalaması 39,44±11,92 yıl olup %55,1'i kadındı. Takipsiz olan hastaların kadın/erkek oranı 49,9/50,1; yaş ortalaması ise 39,58 yıl idi. Hastaların %92,5'i şehir merkezinde, kalanı kırsalda ikamet ediyordu. Hastaların %68,8'i evli olup %66,7'si çalışmakta idi. Grup 2 hastaların %71'i şehir merkezinde, kalanı kırsalda ikamet ediyordu. Tüm hastaların %65,4'ü evli olup %62,2'si çalışmaktaydı. Hastalık sürelerine bakıldığında

grup 1 hastalarının %87'si beş yıl ve üzeri, %13'ü beş yıldan az hastalık süresine sahip iken grup 2'de bu oranlar sırasıyla %86,7 ve %11,1 idi. Takipsiz kalma süreleri bakımından grup 1 hastaları en çok 1 ile 3 yıl arasında takipsiz kalmıştı (Grafik 1). Grup 1 hastaların %59,1'inde ailede AAA öyküsü olup %26,9'unda apendektomi öyküsü vardı. Hastalarının %3,2'si ilaçlarını kesmiş olsa da halen kolşisin kullanmakta olanlar tüm hastaların %95,7 siydi. Geri kalanlar ise sadece interlökin antagonisti tedavisi alıyordu. Grup 2 hastalarında tedavisini kesen yok iken sadece kolşisin kullananların oranı %91,1 idi. Kolşisin ile birlikte interlökin-1 antagonisti tedavisi alanların oranı %8,9 idi. Takipsiz hastaların çoğu üniversite (%48,1) veya lise mezunu (%31,2) idi (Grafik 2). Grup 2 hastalarda üniversite ve lise mezuniyeti oranları sırasıyla %62 ve %22,2 idi. Telefonla ulaşılabilen grup 1 hastalarda takibe gelmemelerinin en sık nedeni "ihmal" daha sonra azalan oranlarla yandal muayenesi için gerekli olan "yeşil liste kayıt süresinin dolması nedeniyle randevu bulamama", "hastalığın düzelmiş olduğunu düşünme", "taşınma", "mesafe", "takip gerekliliğinin farkında olmama", "zaman bulamama" ve "özel nedenler" olarak bulundu (Grafik 3).

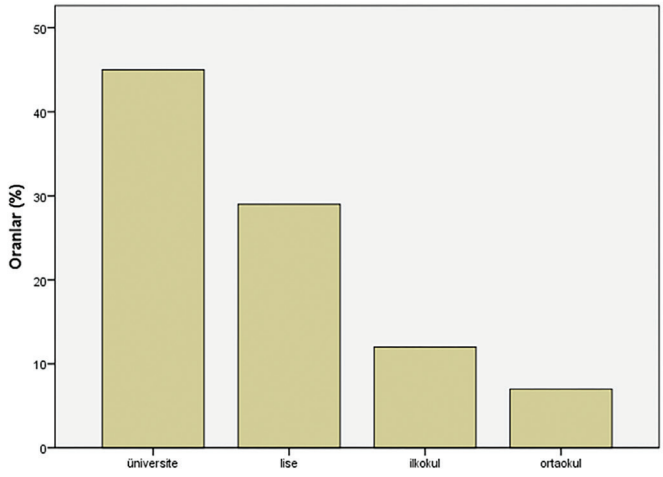


Şekil 1. Taranılan AAA tanılı hastalar
AAA: Ailevi Akdeniz ateşi

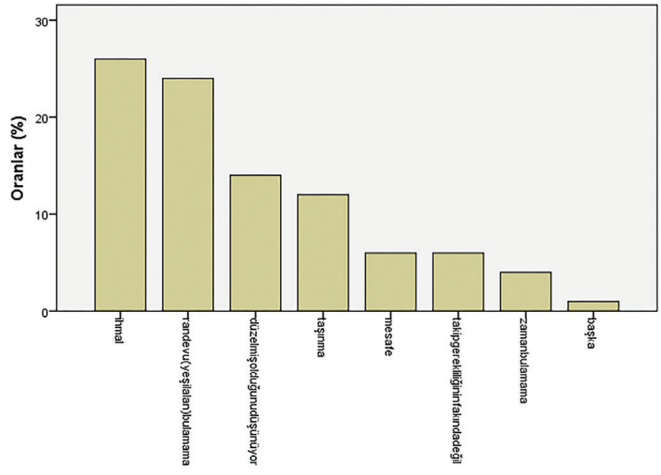


Grafik 1. Hastaların takipsiz kalma süreleri

Grup 2 hastalarının dış merkez takiplerinin en sık nedeni ise "mesafe (%75,6)" daha sonra "taşınma (%20)" idi. Son 3 ayda en az bir ve üzeri atak sayısı takipsiz hastalarda %40,5 iken dış merkez takiplilerde bu oran %37,6 idi. Takipsiz hastalarda atak sırasında en çok karın ağrısı (%84,9) ve ateş (%82,8) kliniği olurken en az erizipel benzeri eritem (%20,4) vardı. Son 3 ayda grup 1 hastalarının %50,5'sinde hiç atak yokken dış merkez takipli grup 2 hastalarında bu oran %55,6 idi. Tüm hasta gruplarının demografik ve klinik özellikleri Tablo 1'de gösterilmiştir. Tanıda "hastanın takip gerekliliği hakkında bilgilendirilmiş olması" sorusuna grup 1 hastalarının %90,3'ü evet cevabı verirken bu oran grup 2 hastalarında %95,6 idi. Hastaların MMÖ ile ölçülen tedaviye uyumlarına bakıldığında MMÖ-motivasyon skoru takipsiz kalan hastaların %54,8'inde düşük, MMÖ-bilgi düzeyi skoru ise %78,5'inde yüksek bulundu. Bu oranlar dış merkez takiplilerde sırasıyla %35,6 ve %88,9 idi. MMÖ-motivasyon skoru bakımından her iki grup arasındaki fark istatistiksel olarak da anlamlıydı ($p<0,05$). Grup 1 ile grup 2 hastalar arasında



Grafik 2. Takipsiz kalan hastaların eğitim durumu



Grafik 3. Hastaların takipsiz kalma nedenleri

regresyon analizi ile bakıldığında cinsiyet, yaş, şehir merkezi-kırsal ikameti, eğitim durumu, medeni durum ve çalışma durumu değişkenlerinin hastaların takipsizlik durumlarına istatiksel olarak anlamlı etkisi olmadığı görüldü. Ancak MMÖ-motivasyon skoru, MMÖ-bilgi düzeyi skoru ve tanıda hastanın takip gerekliliği hakkında bilgilendirilmesi değişkenlerinin takipsizlik durumuyla istatiksel olarak anlamlı ilişkisi olduğu görüldü (sırasıyla p=0,034, p: 0,048, p=0,031) (Tablo 2).

Grup 1 hastalarda korelasyon analizine göre tanıda hastalık hakkında bilgilendirilmiş olmak ve evli olmamak takipsizlik süresi ile negatif korele idi. Ancak istatiksel olarak anlamlılık yoktu. Takipsizlik süresi ile eğitim durumu arasında da pozitif korelasyon olup istatiksel olarak da anlamlı idi (r=-0,075, p=0,01). Takipsiz hastalarda korelasyon analizine göre MMÖ-motivasyon skoru, MMÖ-bilgi düzeyi skoru, eğitim durumu ve hastanın hastalığı hakkında bilgilendirilmiş olması değişkenleri ile son üç aydaki atak sayısı arasında negatif bir korelasyon vardı fakat istatiksel olarak anlamlılık yoktu (Tablo 3).

Tartışma

Düzenli poliklinik kontrolleri romatolojik hastalıklarda hastalığın başarılı bir şekilde kontrol altına alınmasında ve progresif hasarın engellenmesinde çok önemlidir. Takipsiz kalan hastalara dair çoğunluğu RA, SLE, SSc ve AS olmak üzere az sayıda çalışma bulunmaktadır. Bu çalışmalarda araştırmacıların temel hedefleri takipten çıkan hastaların klinik özelliklerini belirlemek olup takipten çıkan hastalara herhangi bir yolla ulaşılmamıştır. Bizim çalışmamızda ise hastalar telefonla aranıp poliklinik kontrolüne davet edilmiş ve takipsizlik nedenleri sorgulanmıştır. Ayrıca AAA hastalarının takipsizlik nedenlerini ve bu hastaların klinik özelliklerini araştırdığımız çalışmamız ilk olması yönüyle önem taşımaktadır. Çünkü AAA'nın en sık ülkemizde görülmesi ve AAA hastalarının takipsizlik verilerinin olmaması büyük bir eksiklikti.

2015 yılında yayınlanmış Tien ve ark.'nın[3] Tayvan'da yapmış olduğu bir çalışmada bizim çalışmamıza benzer olarak takipsiz romatoloji hastalarına ulaşılmıştır. RA (n=406), SLE (n=174), AS (n=136) ve psöriyatik artrit/psöriyazis (n=65) hastalarının dahil edildiği bu çalışmada yaklaşık dört senenin sonunda takipten çıkma sıklığı sırasıyla %24, %24, %35 ve %35 bulundu. Bu çalışmada takipten çıkan hastalara takipsiz kalma nedenleri soruldu. RA ve SLE'de takipsizliğin en sık nedenini hastaların başka bir merkezde takiplerine devam etmeleri iken AS ve psöriyatik artrit/psöriyaziste hastaların şikayetlerinin olmaması

Tablo 1. Hasta gruplarının demografik ve klinik özellikleri

	Grup 1: Takipten çıkmış (%)	Grup 2: Dış merkez takipli (%)	Tüm hastalar (%)
Erkek/kadın	40,9/50,1	53,3/46,7	44,9/55,1
Yaş (yıl) (ortalama + SS)	39,58±10,99	39,16±13,77	39,44±11,92
Hastalık süresi (>5 yıl/<5 yıl)	87,1/12,9	86,7/11,1	87,6/12,4
İkamet (merkez/kırsal)	92,5/7,5	71,1/28,9	93,5/6,5
Eğitim (1/2/3/4/5)*	48,4/31,2/12,9/7,5	62/22,2/6,7/6,7/2,2	52,9/28/10,9/7,2/0,7
Evli/bekar	71/29	65,4/35,6	68,8/29,7
Çalışma (evet/hayır)	68,8/31,2	62,2/37,8	66,7/33,3
Ailede AAA varlığı	59,1	40	52,9/46,4
Apendektomi (evet)	26,9	11,1	31 (%22,5)
Tedavi (1/2/3)**	95,7/1,1/3,2	91,1/8,9/0	94,2/3,6/2,2
Takipsiz süre (1/2/3/4)***	3,2/61,3/30/5,4		
Takipsizlik nedeni (1/2/3/4/5/6/7/8)+	28/25,8/15/13/6,5/6,5/4,3/1,1		
Dış merkez takip nedeni (1/2/3)++		75,6/20/4,4	
Bilgi (evet/hayır)+++	90,3/9,7	95,6/4,4	92/6,5
MMÖ-motivasyon (Y/D)A	45,2/54,8	62,2/35,6	50,7/48,6
MMÖ-bilgi düzeyi (Y/D)B	78,5/21,5	88,9/8,9	81,9/17,4
Son 3 aydaki atak (0/1)C	50,5/7,6	55,6/8,8	

*1: Üniversite, 2: Lise, 3: Ortaokul, 4: İlkokul, 5: Okuryazar değil.
**1: Sadece kolşisin, 2: Kolşisin+anakinra, 3: Tedavisiz,
***1: Bir yıl, 2: Bir-üç yıl, 3: Üç-beş yıl, 4: Beş yıldan fazla,
+1: İhmal, 2: Randevu bulamama, 3: Düzelmiş olduğunu düşünme, 4: Taşınma, 5: Mesafe, 6: Takip gereğinin farkında değil, 7: Zaman bulamama, 8: Başka neden
++1: Mesafe, 2: Taşınma, 3: Randevu bulamama
+++: Hekim tarafından düzenli takip gerektiği bilgisi hastaya ilk tanıda verildi mi (evet/hayır)
MMÖ-motivasyon (Y/D)A: Modifiye morinsky ölçeği motivasyon skoru Y: Yüksek, D: Düşük
MMÖ-bilgi düzeyi (Y/D)B: Modifiye morinsky ölçeği motivasyon skoru Y: Yüksek, D: Düşük
Son 3 aydaki atak (0,1)C 0: Sıfır atak, 1: Üç veya daha fazla sayıda atak, AAA: Ailevi Akdeniz ateşi, MMÖ: Modifiye Morinsky ölçeği, SS: Standart sapma

Tablo 2. Regresyon analizine göre hastaların takip durumlarına etkili faktörler		
	Skor	**p-değeri**
Yaş	0,039	0,844
Cinsiyet	1,907	0,167
Hastalık süresi	0,090	0,764
İkamet	**4,409**	**0,036**
Eğitim durumu	5,142	0,273
Medeni durum	1,247	0,536
Çalışma durumu	0,594	0,441
Takip gerekliliği konusunda bilgilendirilmiş olma	**4,659**	**0,031**
MMÖ-motivasyon skoru	**4,514**	**0,034**
MMÖ-bilgi düzeyi skoru	**3,360**	**0,048**
MMÖ: Modifiye Morinsky ölçeği		

olarak bulundu. Yüz doksan bir AS ve 314 RA hastasının takipsizlik nedenlerinin araştırıldığı daha güncel başka bir çalışmada ise RA hastalarının %65'inin başka bir merkezde takipli olduğu, AS hastalarının ise %54'ünün şikayetleri olmadığı için takipsiz kaldığı bulunmuştur.[7] Bizim çalışmamızda ise hastaların %40'ının merkezimiz takibinden çıkmış olduğu bulundu. Bu hastaların tanıdan kaç yıl sonra takibimizden çıktığı sorulmadı ancak bunların en çok 1-3 yıl süre takipsiz kaldığı öğrenildi. Ulaşılabilen yaklaşık hastaların üçte ikisinin takipsiz ve üçte birinin dış merkezlerde takipli olduğu öğrenildi. Çalışmanın yapıldığı merkezin özellikleri, çalışmaya dahil edilen hastaların demografik ve klinik özellikleri, çalışma dizaynındaki ve takipten çıkma tanımındaki farklılıklar takipsizlik oranlarına etki edebilmektedir.[4] Bizim de ulaşamadığımız hastaların büyük bir kısmı merkezimize sadece bir defa başvurmuşlardı. Bunun muhtemel nedeni kliniğimizin üçüncü basamak bir merkez olması ve birçok hastanın tanı konulduktan sonra tedavilerini kendilerine daha yakın başka bir merkezde devam ettirmek istemeleri olabilir. Ulaşabildiğimiz hastaların önemli bir kısmının (%42) başka bir merkezden takip ediliyor olmaları da bu durumu desteklemekteydi. Çalışmamızdaki diğer çarpıcı bir sonuç da takipsiz hastaların yarısının üniversite, üçte birinin ise lise mezunu olmasına rağmen takipsiz kalmalarının en sık nedeninin "ihmal" olarak cevaplanmış olmasıydı. Hastaların bir kısmının şehir merkezi dışında ve kent kırsalında ikamet ediyor olması da takipsizliği arttıran diğer bir faktör olarak görüldü. Dış merkez takipli olan hastaların da önemli bir kısmı mesafe ve başka bir kente taşındığı için başka bir merkezde takipli idi. Kliniğimizin üçüncü basamak bir sağlık merkezi olması ve kentimizin memur kenti olması da dış merkez takipli hastaların bu gerekçesini makul kılmaktadır. Takipten çıkmış olmanın ikinci en sık nedeni de ülkemizde yandal randevusu alabilmek için gerekli olan ve altı ay geçerlilik süresi olan "yeşil listeden çıkmış olmak" olarak bulundu. Romatolojik hastalıkların kronik enflamatuvar hastalıklar olduğu düşünüldüğünde romatolojik hastalık tanısı konulmuş olan hastaların yeşil liste sürelerinin ne kadar olacağının belirlenmesi hastayı takip eden hekimin insiyatifine bırakılması bu bağlamda sorununun çözümüne katkı sağlayacaktır.

Çalışmanın Kısıtlılıkları

MMÖ-motivasyon ve bilgi düzeyi skorları takipsiz hastalarda dış merkezde takiplerini devam ettiren hastalara göre daha düşük ölçüldü. MMÖ-motivasyon ve bilgi düzeyi skorları bakımından her iki grup arasındaki bu fark istatistiksel olarak da anlamlı bulundu. Korelasyon analizinde de takipsiz hastalarda MMÖ-motivasyon skoru, bilgi düzeyi skorları ve tanıda hastanın takip gerekliliği konusunda bilgilendirilmiş olma durumuyla son üç aydaki atak sayısı arasında negatif korelasyon bulunmuş olması da beklenen bir sonuç idi. Bu veriler de AAA hastalarının takipten çıkması ve hastalığın progrese olması üzerinde hastaların motivasyonun ve hastalık hakkındaki bilgi düzeylerinin etkili olduğunu göstermektedir. Bu çalışmada takipten çıkmış olan hastalar ile halen merkezimizde takipli olan hastaların karşılaştırılması da yapılabilirdi. Ancak biz çalışmayı planlarken merkezimiz takibinden çıkmış olan hastaları çalışma popülasyonu olarak belirlemiştik ve bu hastaların takipsizlik nedenlerini araştırmayı amaçlamıştık. Grup 2 hastalarını, merkezimizde takipli olanlar değil de takibimizden çıkmış olup başka merkezlerde takiplerine devam eden hastaların oluşturuyor olması çalışmanın bir kısıtlılığı olarak değerlendirilebilir. Takipten çıkmış olan ve randevusuz muayeneye davet edilen hastaların bir kısmı poliklinik kontrollerine geldi ve bu hastaların rutin tetkikleri çalışıldı. Ancak istatistiksel değerlendirme yapabilmek için yeterli değildi. Çalışmanın diğer bir kısıtlılığı da takipten çıkmış olan hastaların AAA'nın en sık komplikasyonu olan böbrek fonksiyon

Tablo 3. Grup 1 hastaları için korelasyon analizleri								
		Hastalık süresi	**Eğitim durumu**	**Medeni durum**	**Çalışma durumu**	**Tanıda bilgilendirilme**	**MMÖ motivasyon skoru**	**MMÖ bilgi düzeyi skoru**
Takipsizlik durumu	r	0,073	**0,265**	**-0,075**	0,076	**-0,148**	0,077	0,073
	p	0,488	**0,010**	0,472	0,470	0,157	0,466	0,488
Son üç aydaki atak sayısı	r	0,047	**-0,021**	0,034	0,065	**-0,004**	**-0,152**	**-0,030**
	p	0,653	0,841	0,745	0,538	0,972	0,146	0,778
	n	93	93	93	93	93	93	93
MMÖ: Modifiye Morinsky ölçeği								

bozukluğu açısından değerlendirilmemiş olmasıdır. Çalışmanın odaklandığı nokta AAA hastalarının takipsizlik nedenleri olduğundan takipsiz kalmış hastalar söz konusu komplikasyon yönüyle değerlendirilmedi.

Sonuç

AAA hastalarının takipsizlik nedenlerini ve bu hastalarının klinik özelliklerini araştırdığımız bu çalışmada takipsiz hastaların yarısının üniversite mezunu olması ve en çok takipsizlik nedeninin "ihmal" olarak bulunmuş olması ilginç bir sonuç olup; bu durum eğitimli hastaların dahi hastalığın tedavi ve takibi konusunda yeterli bilgilendirilmesi gerektiğinin önemine işaret etmektedir. Dış merkezlerde takiplerini devam ettiren hastalarda "tanıda hastanın takip gerekliliği konusunda bilgilendirilmiş olması" cevabının istatiksel olarak anlamlı yüksek bulunmuş olması da bu durumu desteklemektedir. Ayrıca hastaların takipsiz kalmalarının ikinci en sık nedeni olan "yeşil listeden çıkma sebebiyle randevu alamamak" problemine romatoloji hastaları için yeşil liste geçerliliğinin sürekli olacak şekilde ayarlanması çözüm sunacaktır.

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Kaynaklar

1. Goldfinger SE. Colchicine for familial Mediterranean fever. N Engl J Med. 1972;287:1302.
2. Van Cutsem G, Ford N, Hildebrand K, et al. Correcting for mortality among patients lost to follow up on antiretroviral therapy in South Africa: a cohort analysis. PLoS One. 2011;6:e14684.
3. Tien YC, Chiu YM, Liu MP. Frequency of lost to follow-up and associated factors for patients with rheumatic diseases. PLoS One. 2016;11:e0150816.
4. Foocharoen C, Yenrom P, Mahakkanukrauh A, Suwannaroj S, Nanagara R. Prevalence and causes of loss to follow-up among patients with systemic sclerosis. J Clin Rheumatol. 2014;20:456.
5. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multicenter study. Medicine (Baltimore). 2005;84:1-11.
6. Vural B, Acar ÖT, Topsever P, Filiz TM. Reliability and validity of Turkish version of modified Morisky scale. J Turk Fam Physician. 2012;3:17-20.
7. Esatoğlu SN, Çelik F, Yeşilsancak M, Doymaz F, Uğurlu S. Frequency of lost to follow-up of rheumatoid arthritis and ankylosing spondylitis patients in a tertiary center. J Turk Soc Rheumatol. 2020;12:7-11.

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Gender- and age-related differences in laboratory, clinical, and functional outcomes in Turkish patients with ankylosing spondylitis: A cross-sectional, single-center study

Ankilozan spondilitli türk hastalarda laboratuvar, klinik ve fonksiyonel sonuçlarda cinsiyet ve yaşa bağlı farklılıklar: Kesitsel, tek merkezli bir çalışma

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Abstract

Objective: Identifying factors influenced by gender- and age-related differences may be critical for predicting disease progression and guiding clinical management in ankylosing spondylitis (AS). Therefore, this study aimed to investigate gender differences in laboratory, demographic, and clinical features. Additionally, it aimed to investigate gender differences in functional outcomes across age groups among Turkish patients with AS.

Methods: Patients with AS were enrolled in the present study. Demographic, laboratory, and clinical features were collected. Functional assessments included pain, disease activity, spinal mobility, lower-limb performance, static and dynamic balance, kinesiophobia, and fall-related concerns. Demographic and laboratory features and tumor necrosis factor alpha (TNF-α) from history were compared between genders. Functional features were compared between genders in two age groups (36-45 and 46-60 years).

Results: A total of 103 patients with AS participated in the present study. Erythrocyte sedimentation rates were significantly higher in women ($p=0.01$). In contrast, radiological stage levels, history of anti-TNF-α treatment, and the proportion of patients who were current or former smokers were significantly higher in men ($p<0.05$). In the 36-45 age group, dynamic balance scores and fall-related concerns were significantly higher in women than in men ($p<0.05$). In the 46-60-year age group, spinal mobility was significantly worse in men ($p<0.05$).

Conclusion: The findings of this study indicate that women aged 36-45 years may particularly benefit from targeted interventions to improve dynamic balance and reduce fall-related concerns. Among men aged 46-60 years, approaches that enhance spinal mobility and flexibility may be especially useful. Overall, these results highlight the importance of implementing gender- and age-specific monitoring and preventive strategies in clinical practice for patients with AS.

Keywords: Ankylosing spondylitis, gender, age group, spinal mobility, balance

Özet

Amaç: Cinsiyet ve yaşa bağlı farklılıklardan etkilenen faktörlerin belirlenmesi, ankilozan spondilitli (AS) hastalığın ilerlemesini tahmin etmek ve klinik tedaviye yön vermek açısından kritik öneme sahip olabilir. Bu nedenle, bu çalışma laboratuvar, demografik ve klinik özelliklerdeki cinsiyet farklılıklarını araştırmayı amaçlamıştır. Ayrıca, AS'li Türk hastalarda yaş gruplarına göre fonksiyonel sonuçlardaki cinsiyet farklılıklarını araştırmayı hedeflemiştir.

Yöntem: Çalışmaya AS hastaları dahil edildi. Hastaların demografik, laboratuvar ve klinik özellikleri toplandı. Fonksiyonel değerlendirmeler arasında ağrı, hastalık aktivitesi, omurga mobilitesi, alt ekstremite performansı, statik denge, dinamik denge, kinezyofobi ve düşmeyle ilgili endişeler yer aldı. Demografik, laboratuvar ve klinik özellikler cinsiyetler arasında karşılaştırıldı. Fonksiyonel özellikler iki yaş grubunda (36-45 ve 46-60 yaş grupları) cinsiyetler arasında analiz edildi.

Bulgular: Bu çalışmaya toplam 103 AS hastası katıldı. Eritrosit sedimantasyon hızı düzeyleri kadınlarda anlamlı olarak daha yüksekti ($p=0,01$). Buna karşın radyolojik evre düzeyleri, anti-tümör nekroz faktörü alfa (TNF-α) tedavi öyküsü ve hastaların halen veya daha önce sigara içenlerin oranı erkeklerde anlamlı derecede daha yüksekti ($p<0,05$). Otuz altı-45 yaş grubunda dinamik denge ve düşmeyle ilgili endişe puanları, kadınlarda erkeklere göre anlamlı derecede daha yüksekti ($p<0,05$). Kırk altı-60 yaş grubunda ise omurga hareketliliği erkeklerde istatistiksel olarak daha kötüydü ($p<0,05$).

Sonuç: Bu çalışmanın bulguları, 36-45 yaş aralığındaki kadınların dinamik dengeyi iyileştirmek ve düşmeyle ilgili endişeleri azaltmak için hedefli müdahalelerden özellikle faydalanabileceğini göstermektedir. Kırk altı-60 yaş arası erkeklerde, omurga hareketliliğini ve esnekliğini artıran yaklaşımlar özellikle faydalı olabilir. Elde edilen veriler klinik pratikte cinsiyet ve yaşa dayalı izleme ve önleme stratejilerinin önemini ortaya koymaktadır.

Anahtar Kelimeler: Ankilozan spondilit, cinsiyet, yaş grubu, omurga hareketliliği, denge

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Intoduction

Ankylosing spondylitis (AS) is a systemic, progressive rheumatic condition characterized by chronic inflammation of the spine and sacroiliac joints.[1] It has been estimated that the number of cases ranges from 1.30 to 1.56 million in Europe and from 4.63 to 4.98 million in Asia.[2]

The progression of AS is characterized by increasing spinal stiffness, reduced lumbar lordosis, and increased thoracic kyphosis. Spinal mobility is an important outcome in both observational and treatment studies on AS and serves as a predictor of poor prognosis.[3] Changes in spinal mobility can make it difficult for the body to maintain an optimal position and may be associated with an increased risk of falling.[4] Studies have shown that patients with AS have poorer balance compared with healthy individuals.[5] In addition, 66.6% of patients with AS have been reported to experience kinesiophobia, defined as fear of physical movement and activity.[6]

In AS, with respect to sex and age, the disease predominantly affects men, and age is linearly associated with the progression of spinal radiographic changes.[7-11] A study examining the progression of radiographic changes over time, with age groups in 10-year increments, suggested that spinal structural damage in AS progresses most rapidly in patients aged 30-39 years. [12] Given the availability of effective treatments for AS, it is essential for physicians to be aware of the distinctive features and management options of this disorder in the population. While studies have examined gender differences in populations such as those from Iran, Morocco, and Japan, data on the Turkish population are lacking.

The present study aimed to investigate gender differences in laboratory and clinical outcomes and functional variations across age groups among Turkish patients with AS.

Materials and Methods

Study Design and Patient Selection

This cross-sectional study was conducted at the Hatay Mustafa Kemal University of Medicine, Division of Rheumatology, Department of Internal Medicine from October 2022 to January 2023. The study protocol was conducted in accordance with the Declaration of Helsinki. Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Hatay Mustafa Kemal University Faculty of Medicine (date: 02.02.2021, decision no: 03, protocol code: 2021/170). All participants provided written informed consent before enrollment.

A total of 136 patients with AS who attended the outpatient rheumatology clinic of Hatay Training and Reseach Hospital were screened for eligibility. Patients were included if they met the diagnostic criteria for AS[13] and were between 36 and 60 years of age. Exclusion criteria included the presence of other concomitant rheumatic diseases, orthopedic joint prostheses, spinal surgery, neuromuscular disorders, cognitive or psychiatric conditions.

Data Collection

The following demographic characteristics, laboratory features, and medical treatments were recorded: age, gender, body mass index (BMI), disease duration, radiographic level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), diagnostic delay, history of anti-tumor necrosis factor alpha (TNF-α), and smoking status (current or former). Clinical outcomes assessed in all patients were pain, disease activity, spinal mobility, lower-limb performance, static balance, dynamic balance, kinesiophobia, and fall-related concerns.

Pain scores at rest and during movement were measured using the visual analogue scale (0-10 mm; 0 = no pain, 10 = severe pain).[14] Disease activity was evaluated using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), which consists of six questions assessing five major AS symptoms: fatigue, spinal pain, joint pain and swelling, localized tenderness, and morning stiffness (duration and severity). Each item is scored on a 1-10 scale, with final scores ranging from 0 (best) to 10 (worst).[15]

The spinal mobility was assessed using the finger-to-floor distance (FFD) and the Bath AS Metrology Index (BASMI). The BASMI is a composite index consisting of four spinal measurements (tragus-to-wall distance, lateral lumbar flexion, lumbar flexion, and cervical rotation) and one hip mobility measure (intermalleolar distance). Each measurement is scored 0, 1, or 2, and the five scores are summed, with higher scores indicating greater mobility impairment. For FFD, patients performed maximal lumbar flexion with the knees extended, and the distance from the tip of the middle finger to the floor was measured using a measuring tape.[16]

Lower extremity strength was assessed using the 30-second chair stand test.[17] Patients were seated in an armless chair with their backs straight, arms crossed over the chest, and feet approximately shoulder-width apart. and placed on the floor. They were instructed to stand up and sit down as quickly as possible for 30 seconds. The mean of the two trials was recorded as the patient's score.[17]

Dynamic balance was evaluated using the timed up and go (TUG) test, and static balance was assessed using the tandem stance test (TST). The TUG test measures the time (in seconds) required for a participant to stand from an armchair, walk 3 meters, turn, return, and sit down.[18] In the TST, participants stood with one foot in front of the other and arms crossed; the researcher recorded the time, up to a maximum of 30 seconds, or until participants moved or required support. The

test was repeated three times, and the average time was used for analysis.[19]

Kinesiophobia was assessed using the Tampa scale for kinesiophobia, which contains 17 items rated on a 4-point Likert scale (1 = strongly disagree, 4 = strongly agree).[20] Total scores range from 11 to 44 points, with scores ≥37 indicating high kinesiophobia.[21]. The Turkish version of the scale was used.[21]

Concern about falling was assessed using the falls efficacy scale-international (FES-I). which includes 16 questions regarding confidence in performing activities without falling. Each item is scored on a 1-4 scale (1 = not at all concerned; 4 = very concerned), with higher scores indicating greater fear of falling.[22] The Turkish version of the scale was used.[23]

Gender differences in demographic characteristics, laboratory features, and medical treatments were analyzed. For clinical outcomes, gender differences were examined in two age groups: 36-45 years and 46-60 years.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 21.0 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant for all analyses.

The normality of the data distribution was assessed using the Shapiro-Wilk test. Parametric tests were applied to normally distributed data, whereas nonparametric tests were applied to non-normally distributed data. The chi-square test was used to compare categorical variables.

Results

A total of 103 patients with AS met the inclusion criteria and were enrolled in the study. Fifty-two patients were in the 36-45-year age group (mean age = 40.38 years; 26 female patients) and 51 patients were in the 46-60-year age group (mean age = 52.37 years; 26 female patients).

As demonstrated in Table 1, ESR values were significantly higher in women (p=0.01); however, this difference is expected due to known sex-related physiological variations in ESR and is not considered clinically significant. In contrast, men had a significantly worse radiological stage, a higher proportion had a history of anti-TNF-α therapy, and a greater proportion were current or former smokers (p<0.001, p=0.033, and p=0.008, respectively). No statistically significant differences in BMI, CRP levels, age at diagnosis, diagnostic delay, or age at disease onset were observed between genders.

As shown in Table 2, clinical outcomes were analyzed by gender within two age groups (36-45 and 46-60 years). Among participants aged 36-45 years, dynamic balance (TUG test) and fall-related concerns (FES-I scores) were significantly higher in women than in men (p=0.005 and p=0.01, respectively). No significant gender differences were found for pain, disease activity, spinal mobility, lower limb performance, static balance, or kinesiophobia in this age group. In the 46-60 age group, spinal mobility measures (BASMI and FFD scores) were significantly worse in men (p=0.005 and p=0.003, respectively). However, no significant gender differences were found for pain, disease activity, lower-limb performance, static balance, dynamic balance, kinesiophobia, or fall-related concerns in this age group.

Table 1. Comparison of demographic features between genders

Variables Mean ± SD		Female (52)	Male (51)	P*
		Mean ± SD		
Age		45.81±6.37	46.84±7.88	0.46
BMI		28.47±4.58	27.90±4.10	0.50
Age at onset		35.62±9.02	32.36±9.68	0.08
Diagnose age		41.06±7.17	37.97±9.51	0.06
Diagnostic delay time		5.46±6.89	5.60±6.02	0.91
ESR		15.38±10.84	10.60±9.08	**0.01**
CRP		6.56±7.11	9.10±12.76	0.21
		n (%)	**n (%)**	**P****
Radiological stage	1	32 (61.5)	11 (21.6)	**<0.001**
	2	16 (30.8)	21 (41.2)	
	3	4 (7.7)	19 (37.3)	
History of having anti-TNF-alfa therapy	Yes	26 (50)	36 (70.6)	**0.033**
	No	26 (50)	15 (29.4)	
Smoking/ex-smoking	Yes	19 (36.5)	32 (62.7)	**0.008**
	No	33 (63.5)	19 (37.3)	

BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, SD: Standard deviation, TNF: Tumour necrosis factor

Table 2. **Comparison of age groups' clinical features data between gender**						
Variables	**36-45 age group (n=52)**		**p**	**46-60 age group (n=51)**		**p**
	Female (26)	**Male (26)**		**Female (26)**	**Male (25)**	
	Mean ± SD	**Mean ± SD**		**Mean ± SD**	**Mean ± SD**	
Age	40.54±2.48	40.23±3.70		51.08±4.35	53.72±4.29	
BMI	27.85±5.01	26.84±3.73	0.41	29.09±4.10	29.00±4.26	0.93
BASDAI	5.57±2.41	4.49±2.56	0.12	5.35±2.39	4.68±2.02	0.28
BASMI	6.80±2.11	7.42±1.57	0.24	7.38±2.43	9.36±2.30	**0.005**
Timed up and go (sec)	9.06±2.44	7.57±0.92	**0.005**	9.34±1.49	8.91±2.42	0.44
Tandem (sec.)	23.57±10.15	27.19±5.83	0.12	24.95±8.09	25.69±8.56	0.75
VAS-activity	4.84±3.67	4.57±3.18	0.77	5.65±3.42	4.96±3.00	0.44
VAS-rest	4.80±3.47	3.96±3.28	0.37	4.57±3.50	3.80±3.06	0.40
Sit-up-test	11.33±3.85	13.00±2.77	0.07	11.21±3.21	11.39±2.94	0.83
Falls efficacy scale-international	29.81±12.33	22.30±7.15	**0.01**	26.62±8.50	24.76±8.45	0.72
Tampa kinesiophobia	43.00±7.02	40.15±9.22	0.21	45.08±9.04	42.52±6.91	0.26
Finger to floor distance	-13.12±14.41	-12.20±12.88	0.80	-7.75±13.40	-19.99±14.58	**0.003**

BASDAI: Bath ankylosing spondylitis disease activity index, BASMI: The Bath AS metrology index, BMI: Body mass index, SD: Standard deviation, VAS: Visual analogue scale

Discussion

Gender-based comparisons revealed that women had higher ESR levels, while men exhibited more advanced radiological stages, greater use of anti-TNF-α therapy, and higher rates of smoking among Turkish patients with AS. No significant differences were observed between genders in BMI, CRP, age at diagnosis, or diagnostic delay. When analyzed by age group, women aged 36-45 had poorer balance and greater fear of falling, whereas men aged 46-60 showed more severe spinal mobility limitations. Notably, this is the first study to examine gender differences among Turkish patients with AS and provides valuable insights into the potential impact of gender on the clinical presentation and severity of the disease.

Understanding gender-specific differences in disease patterns is essential for improving diagnostic and treatment decisions for AS patients. Ibn et al.[24] reported that elevated CRP levels were significantly more prevalent among men in the Chinese population. In other studies, whereas Yacoub et al. found no differences in CRP among Moroccan patients with AS, Shahlaee et al.[25] reported that women had lower CRP levels.[24] In contrast, our study found no significant difference in CRP levels between genders in the Turkish population. Nevertheless, Turkish men had more severe radiographic damage, consistent with earlier studies.[24,26] This may relate to findings from previous research showing that women report greater peripheral joint pain and arthritis, which could be associated with fewer radiographic changes in the spine.[10,24,27] In our study, men had a higher prevalence of anti-TNF-α therapy use. Interestingly, a study in Japanese patients with AS[10] found that anti-TNF agents were more frequently prescribed to women, suggesting that differences in healthcare access, treatment-seeking behavior, or disease presentation may vary across populations.

Regarding age at diagnosis and diagnostic delay, Garrido-Cumbrera et al.[28] reported that female patients with axial spondyloarthritis (axSpA) experienced longer diagnostic delays than male patients (8.2 years vs. 6.1 years). However, studies in Moroccan and Iranian patients with AS found no gender differences in age at onset, diagnostic delay, or disease duration.[24,25] Among patients with axSpA across Europe, females reported a considerably longer diagnostic delay than males (6.1±7.4 vs. 8.2±8.9 years; $p<0.001$).[28] In In our study of Turkish patients with AS, no significant gender differences were observed in diagnostic delay, age at diagnosis, or age at disease onset.

In studies comparing disease activity between genders, including the European Map of axSpA and studies on Moroccan cohorts, females reported higher BASDAI scores.[24,28] Conversely, a study in China found no gender difference in BASDAI.[29] No prior studies have analyzed gender differences across age groups. In our cohort, no significant differences in BASDAI scores were observed between genders in either age group.

In Moroccan and Iranian patients with AS, men have been reported to exhibit higher BASMI scores and greater FFD scores.[24,25] Similarly, our study found that men in the 46-60 age group had higher BASMI and FFD scores than women, whereas no significant gender differences were observed in the 36-45 age group. These findings suggest that age may modulate the impact of gender on physical function in AS, highlighting the importance of stratifying patients not only by gender but also by age when assessing disease severity and planning management strategies.

Loss of balance and an increased risk of falls have been observed more frequently among patients with AS than among healthy individuals.[30] However, to date, the literature lacks studies specifically comparing balance performance and fall-related concerns between genders across age groups within

this population. Our study addressed this gap by showing that women aged 36-45 exhibited significantly poorer dynamic balance and greater concern about falling than men of the same age. No significant gender differences were observed in the 46-60 age group. These findings suggest that younger female patients (aged 36-45) with AS may be at higher risk for impaired dynamic balance and fear of falling, underscoring the value of age- and gender-specific assessments to guide targeted interventions and reduce fall-related complications

Kinesiophobia has been reported in 53.3% of patient with AS,[31] and AS patients exhibit a significant 12% reduction in lean mass in the arms and legs.[32] To date, no studies have specifically compared kinesiophobia and lower limb endurance between genders across age groups in patients with AS. In our study, no significant gender differences were observed in either age group, suggesting that gender does not appear to be a determining factor for kinesiophobia or lower limb endurance in this population.

Study Limitations

This study has several limitations. First, the study population was restricted to patients aged 36-60 years, limiting generalizability to other age groups. Second, the sample size was relatively small, which may have reduced the statistical power of the analyses. Third, the single-center design may have introduced selection bias. Future research would benefit from a multicenter study with a larger and more diverse observational cohort to strengthen the validity and applicability of the findings. Larger national studies using community-based cohorts or nationwide patient registries are needed to more accurately assess gender differences in AS and its prevalence in Türkiye.

Conclusion

The findings suggest that younger women (36-45 years) experience poorer balance and greater fear of falling, whereas older men (46-60 years) demonstrate more pronounced spinal mobility limitations. Among Turkish patients, women exhibited less radiological damage, while men showed more severe spinal involvement and a higher rate of advanced therapy use, possibly reflecting a more aggressive disease course. These observations highlight the need for targeted clinical assessment and management strategies tailored to both gender and age to optimize outcomes in patients with AS.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Hatay Mustafa Kemal University Faculty of Medicine (date: 02.02.2021, decision no: 03, protocol code: 2021/170).

Informed Consent: All participants provided written informed consent before enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.K., M.P., Concept: G.Ku., M.P., Design: G.Ku., Data Collection and Processing: G.Ku., M.P., Analysis or Interpretation: G.Ku., M.P., Literature Search: G.Ku., M.P., Writing: G.Ku., M.P., G.K.

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References

1. Zhu W, He X, Cheng K, et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res. 2019;7:1-16.
2. Dean LE, Jones GT, MacDonald AG, Downham C, Sturrock RD, Macfarlane GJ. Global prevalence of ankylosing spondylitis. Rheumatology. 2014;53:650-7.
3. Ramiro S, Landewé RBM, van der Heijde D, et al. Hierarchy of impairment of spinal mobility measures in ankylosing spondylitis: twelve-year data. Arthritis Care Res (Hoboken). 2015;67:1571-7.
4. Dursun N, Sarkaya S, Ozdolap S, et al. Risk of falls in patients with ankylosing spondylitis. J Clin Rheumatol. 2015;21:76-80.
5. Acar Y, Ilçin N, Gürpinar B, Can G. Core stability and balance in patients with ankylosing spondylitis. Rheumatol Int. 2019;39:1389-96.
6. 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.
7. Gran JT, Ostensen M, Husby G. A clinical comparison between males and females with ankylosing spondylitis. J Rheumatol. 1985;12:126-9.
8. Kennedy LG, Will R, Calin A. Sex ratio in the spondyloarthropathies and its relationship to phenotypic expression, mode of inheritance and age at onset. J Rheumatol. 1993;20:1900-4.
9. Rusman T, Van Vollenhoven RF, Van Der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep. 2018;20:1-12.
10. Lee W, Reveille JD, Davis Jr JC, Learch TJ, Ward MM, Weisman MH. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. Ann Rheum Dis. 2007;66:633-8.
11. Brophy S, Mackay K, Al-Saidi A, Taylor G, Calin A. The natural history of ankylosing spondylitis as defined by radiological progression. J Rheumatol. 2002;29:1236-43.
12. Lee T-H, Koo BS, Nam B, et al. Age-stratified trends in the progression of spinal radiographic damage in patients with ankylosing spondylitis: a longitudinal study. Ther Adv Musculoskelet Dis. 2022;14:1759720X221100301.
13. 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.
14. Ogon M, Krismer M, Söllner W, Kantner-Rumplmair W, Lampe A. Chronic low back pain measurement with visual analogue scales in different settings. Pain. 1996;64:425-8.
15. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the bath ankylosing spondylitis disease activity index. J Rheumatol. 1994;21:2286-91.

16. Johnson M, Mulcahey MJ. Interrater reliability of spine range of motion measurement using a tape measure and goniometer. J Chiropr Med. 2021;20:138-47.

17. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999;70:113-9.

18. Nightingale CJ, Mitchell SN, Butterfield SA. Validation of the timed up and go test for assessing balance variables in adults aged 65 and older. J Aging Phys Act. 2019;27:230-3.

19. Joo B, Marquez JL, Osmotherly PG. Ten-second tandem stance test: a potential tool to assist walking aid prescription and falls risk in balance impaired individuals. Arch Rehabil Res Clin Transl. 2022;4:100173.

20. Dupuis F, Cherif A, Batcho C, Massé-Alarie H, Roy J-S. The tampa scale of kinesiophobia: a systematic review of its psychometric properties in people with musculoskeletal pain. Clin J Pain. 2023;39:236-47.

21. Yilmaz O, Yakut Y, Uygur F, Ulug N. Turkish version of the tampa scale for kinesiophobia and its test-retest reliability. Turk J Physiother Rehabil. 2011;22:44-9.

22. Marques-Vieira CMA, Sousa LMM, Severino S, Sousa L, Caldeira S. Cross-cultural validation of the falls efficacy scale international in elderly: systematic literature review. Journal of Clinical Gerontology and Geriatrics. 2016;7:72-6.

23. Ulus Y, Durmus D, Akyol Y, Terzi Y, Bilgici A, Kuru O. Reliability and validity of the Turkish version of the falls efficacy scale international (FES-I) in community-dwelling older persons. Arch Gerontol Geriatr. 2012;54:429-33.

24. Ibn Yacoub Y, Amine B, Laatiris A, Hajjaj-Hassouni N. Gender and disease features in Moroccan patients with ankylosing spondylitis. Clin Rheumatol. 2012;31:293-7.

25. Shahlaee A, Mahmoudi M, Nicknam MH, Farhadi E, Fallahi S, Jamshidi AR. Gender differences in Iranian patients with ankylosing spondylitis. Clin Rheumatol. 2015;34:285-93.

26. van der Slik B, Spoorenberg A, Wink F, et al. Although female patients with ankylosing spondylitis score worse on disease activity than male patients and improvement in disease activity is comparable, male patients show more radiographic progression during treatment with TNF-α inhibitors. In: Seminars in Arthritis and Rheumatism. Elsevier; 2019. p. 828-33.

27. Jimenez-Balderas FJ, Mintz G. Ankylosing spondylitis: clinical course in women and men. J Rheumatol. 1993;20:2069-72.

28. Garrido-Cumbrera M, Poddubnyy D, Gossec L, et al. Gender differences in patient journey to diagnosis and disease outcomes: results from the European Map of Axial Spondyloarthritis (EMAS). Clin Rheumatol. 2021;40:2753-61.

29. Wen YQ, Jiang YT, Liu ZY, et al. Gender difference in clinical manifestations and comorbidities in the patients with spondyloarthritis. Zhonghua Yi Xue Za Zhi. 2019;99:812-7.

30. Bingöl M, Karadağ A. Loss of balance and fall risk, and their relationship with disease activity, functional status, spinal mobility, quality of life and enthesitis score in patients with ankylosing spondylitis: a cross-sectional study. CMJ. 2020;42:441-8.

31. 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;17:107-19.

32. Marcora S, Casanova F, Williams E, Jones J, Elamanchi R, Lemmey A. Preliminary evidence for cachexia in patients with well-established ankylosing spondylitis. Rheumatology (Oxford). 2006;45:1385-8.

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Polimiyaljiya romatika hastalarında subklinik ateroskleroz ve ilişkili sitokinler

Subclinical atherosclerosis and related cytokines in polymyalgia rheumatica patients

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Özet

Amaç: Bu çalışmada, polimiyaljiya romatika (PMR) hastalarında subklinik aterosklerozun karotis intima-media kalınlığı (KİMK) ve plak varlığı ile değerlendirilmesi; ayrıca proenflamatuvar [interlökin (IL)-6, IL-8, IL-32, interferon (IFN)-γ, Pentraxin-3 (PTX-3)] ve antienflamatuvar (IL-5, IL-33, adiponektin) sitokinlerin hastalık ile olası ilişkilerinin ortaya konulması amaçlanmıştır.

Yöntem: Çalışmaya, Nisan 2011-Haziran 2012 arasında PMR tanılı 33 hasta ve 28 sağlıklı kontrol dahil edildi. Klinik veriler, aterosklerotik risk faktörleri ve biyokimyasal parametreler kaydedildi. IL-5, IL-6, IL-8, IL-32, IL-33, IFN-γ, adiponektin ve PTX-3 düzeyleri enzim bağlı immünosorbent testi yöntemiyle ölçüldü. KİMK ve plak varlığı yüksek çözünürlüklü ultrasonografi ile değerlendirildi.

Bulgular: Çalışmaya alınan PMR hastalarının yaş ortalaması 66,3±9,6 yıl, kontrol grubunun ise 62,5±5,1 yıldı (p=0,103). Aterosklerotik risk faktörleri açısından iki grup arasında anlamlı fark saptanmadı. IL-5 düzeyleri PMR grubunda kontrol grubuna göre anlamlı olarak yüksek bulundu (167,7±16,6 vs. 155±18,3 pg/mL; p=0,009). PTX-3 düzeyi de PMR olgularında anlamlı yüksek bulundu [433 (227,5-1059,5) vs. 347,3 (251-697,5) pg/mL; p=0,008]. IL-6, IL-8, IL-32, IL-33, IFN-γ ve adiponektin düzeylerinde gruplar arasında anlamlı fark saptanmadı. Ortalama KİMK ölçümü sırasıyla hastalık ve kontrol grubunda 0,749±0,101 vs. 0,715±0,055 mm (p=0,270) ve karotis plak varlığı %20,7 vs. %4,2 (p=0,108) idi.

Sonuç: Bu çalışma, PMR hastalarında IL-5 düzeyinin anlamlı yüksek bulunduğunu gösteren ilk çalışmadır. Ayrıca PTX-3 düzeylerinin yüksekliği, PMR'de subklinik vasküler enflamasyon varlığını destekleyebilir. Buna karşın KİMK ve plak varlığında anlamlı fark saptanmaması, kortikosteroid tedavisinin vasküler parametreler üzerindeki olası etkisini düşündürmektedir. Bulgular, PMR patogenezinde IL-5'in potansiyel rolüne dikkat çekmekte olup, daha geniş kapsamlı çalışmalarla desteklenmelidir.

Anahtar Kelimeler: Polimiyaljiya romatika, sitokinler, karotis intima media, ateroskleroz

Abstract

Objective: This study aimed to evaluate subclinical atherosclerosis in patients with polymyalgia rheumatica (PMR) using carotid intima-media thickness (CIMT) and plaque assessment, and to investigate the potential association between PMR and inflammatory [interleukin (IL)-6, IL-8, IL-32, interferon (IFN)-γ, pentraxin-3 (PTX-3)] and anti-inflammatory (IL-5, IL-33, adiponectin) levels.

Methods: Between April 2011 and June 2012, thirty-three patients with PMR and twenty-eight healthy controls were enrolled. Clinical data, atherosclerotic risk factors, and biochemical parameters were recorded. Serum levels of IL-5, IL-6, IL-8, IL-32, IL-33, IFN-γ, adiponectin, and PTX-3 were measured using enzyme-linked immunosorbent assay. CIMT and plaque presence were evaluated by high-resolution ultrasonography.

Results: The mean age of the PMR group was 66.3±9.6 years and of the controls 62.5±5.1 years (p=0.103). No significant differences were observed regarding atherosclerotic risk factors. IL-5 levels were significantly higher in PMR patients compared to controls (167.7±16.6 vs. 155±18.3 pg/mL; p=0.009). PTX-3 levels were also significantly higher in the PMR group [433 (227.5-1059.5) vs. 347.3 (251-697.5) pg/mL; p=0.008]. No significant differences were detected for IL-6, IL-8, IL-32, IL-33, IFN-γ, or adiponectin levels between PMR and control groups. Mean CIMT (0.749±0.101 vs. 0.715±0.055 mm; p=0.270) and carotid plaque presence (20.7% vs. 4.2%; p=0.108) were not significantly different between groups.

Conclusion: This is the first study which has been demonstrated significantly elevated IL-5 levels in patients with PMR. Increased PTX-3 levels may indicate the presence of subclinical vascular inflammation. However, the absence of significant differences in CIMT and plaque presence suggests a possible influence of corticosteroid therapy on vascular parameters. These findings highlight a potential role of IL-5 in PMR pathogenesis, warranting further large-scale investigations.

Keywords: Polimyalgia romatica, cytokines, carotis intima media, atherosclerosis

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***Bu çalışma Dr. Öğr. Üyesi Ahmet Aydın'ın 2012 iç hastalıkları uzmanlık bitirme tezinden üretilmiştir.**

Giriş

Polimiyaljiya romatika (PMR), 50 yaş üzeri bireyleri etkileyen, omuz ve pelvik kuşağın proksimal kaslarında ağrı ve tutukluk ile giden enflamatuvar romatizmal bir hastalıktır.[1] Kadınlarda görülme sıklığı 2-3 kat fazladır.[2] PMR'nin insidansı İngiltere'de yılda 100.000 kişide 84[3] Danimarka'da 68,3[4] İsveç'te 50[5] olarak bildirilirken güney Avrupa'da 50 yaş ve üzeri kişilerde yıllık insidans 12/100.000'in altındadır.[6] Pamuk ve ark.[7] Türkiye'nin kuzeybatısında hastalık prevalansını 3,15/100.000 olarak bildirmiştir.

PMR'nin etiyolojisi tam bilinmemekle birlikte, bir veya daha fazla çevresel etkenin veya genetik faktörün etkili olduğu, özellikle mevsimsel, viral maruziyetlerin katkıda bulunduğunu düşündürmektedir.[8]

PMR hastalarının glenohumeral eklemlerinden alınan artroskopik biyopsiler, lökosit infiltrasyonu ve vasküler proliferasyonla birlikte sinovit göstermiştir.[9] PMR'de sistemik ve lokal interlökin-6 (IL-6) düzeyleri yüksek saptanmıştır.[10]

PMR'li hastalarda, proksimal sinovitin varlığı sintigrafi, manyetik rezonans ve konvansiyonel ultrasonografi (USG) gibi değişik teknikler kullanılarak kanıtlanmıştır.[11,12] Laboratuvarda eritrosit sedimentasyon hızı veya C-reaktif protein (CRP) gibi enflamasyon parametreleri yüksek bulunur. Epidemiyolojik çalışmalar, PMR'li olguların %16-21'inde temporal arterit (TA), TA olgularının %40-60'ında PMR olduğunu göstermektedir.[13]

Tanı için altın standart yoktur. Ayırıcı tanıda romatoid artrit dışlanmalıdır. Healey[14] kriterleri tanı için yardımcı olurken, 2012'de Avrupa Romatoloji Dernekleri Birliği/Amerikan Romatoloji Koleji (*European League Against Rheumatism/ American College of Rheumatology* - EULAR/ACR) tarafından skorlama dayalı sınıflandırma kriterleri[15] ise epidemiyolojik çalışmalarda kullanılmak üzere geliştirilmiş olup bireysel hastalarda tanı koyma amacı taşımamaktadır (Tablo 1).

PMR tedavisinin temeli glukokortikoid tedavisidir. Tüm PMR semptomları genellikle glukokortikoidlere hızlı yanıt verir. En son ACR/EULAR önerisine göre PMR'de önerilen günlük başlangıç prednizolon dozu 12,5-25 mg'dır.[16]

Ateroskleroz çocukluk çağında başlayan, uzun yıllar içinde yavaşça ilerleyen, büyük ve orta boy arterlerin duvarlarında asimetrik ve fokal olarak ortaya çıkan, temel olarak intima tabakasında oluşan, damar lümeninde daralmaya yol açan kalınlaşmadır. Artmış karotis intima-media kalınlığı (KİMK) bağımsız kardiyovasküler risk faktörü olup subklinik aterosklerozun göstergesidir. Yaş, cinsiyet, aile öyküsü, etnik grup aterosklerozun değiştirilemeyen risk faktörleriyken, sigara kullanımı, hipertansiyon (HT), hiperkolesterolemi, diabetes mellitus (DM), obezite, sedanter yaşam değiştirilebilir risk faktörleridir. Aterosklerozun oluşmasında enflamasyon önemli rol oynar.[17] Ateroskleroz gelişiminde tümör nekroz faktör alfa (TNF-α), IL-1β, IL-6, IL-8, IL-12, IL-15, interferon gama (IFN-γ), IL-18, pentraxin-3 (PTX-3), IL-32 proenflamatuvar sitokinlerken, IL-4, IL-5, IL-10, IL-13, IL-33, tümör growth faktör-β (TGF-β), adiponektin antienflamatuvar sitokinlerdir.[18-24]

Bu çalışmanın amacı, PMR hastalarında subklinik ateroskleroz varlığını KİMK ölçümleri ile değerlendirmek ve bu bulguların aterosklerotik risk faktörleri ile ilişkisini araştırmanın yanı sıra, enflamatuvar ve antienflamatuvar belirteçler olan IL-5, IL-6, IL-8, IL-32, IL-33, adiponektin, IFN-γ ve PTX-3 düzeyleri ile PMR ile subklinik ateroskleroz arasındaki olası ilişkiyi ortaya koymaktır.

Tablo 1. Polimiyaljia romatika tanı kriterleri

Healey[14] kriterleri	**EULAR/ACR[15]**	
1. İzleyen bölgelerden en az ikisinde en az 1 ay veya daha uzun süredir olan ağrı: boyun, omuzlar ve pelvik kuşak 2. Sabah tutukluğu >1 saat 3. Prednizona (20 miligram veya daha az) hızlı cevap 4. Kas-iskelet sistemi semptomlarına neden olabilecek diğer hastalıkların olmaması 5. Elli yaş veya daha üstü 6. Eritrosit sedimentasyon hızı 40 milimetre/saatten yüksek olması ***Yukardaki kriterlerin hepsi varsa, polimiyaljiya romatika tanısı konulur.**	**50 yaş ve üzeri, bilateral omuz ağrısı anormal CRP ve/veya ESR**	
	Kriter	**Puan**
	Sabah tutukluğu >45 dk	2
	Kalça ağrısı veya hareket açıklığının sınırlı olması	1
	Romatoid faktör ve/veya anti sitrulin protein antikoru negatifliği	2
	Diğer eklem tutulumunun olmaması	1
	En az bir omuzda subdeltoit bursit ve/veya biceps tenosinoviti ve/veya glunohumeral sinovit ve En az bir kalçada sinovit ve/veya trokanterik bursit (ultrason ile)	1
	Her iki omuzda subdeltoit bursit, biceps tenosinoviti veya glunohumeral bursit (ultrason ile)	1
	***USG olmadan 4 veya üzeri/USG varlığında 5 veya üzeri puan**	

ACR: Amerikan Romatoloji Koleji, CRP: C-reaktif protein, ESR: Eritrosit sedimentasyon hızı, EULAR: Avrupa Romatoloji Dernekleri Birliği, USG: Ultrasonografi

Gereç ve Yöntemler

Bu çalışma kesitsel (cross-sectional), gözlemsel, olgu-kontrol tasarımlı bir çalışmadır. Çalışmaya Trakya Üniversitesi Tıp Fakültesi Romatoloji Bilim Dalı'nda, Nisan 2011 ve Haziran 2012 tarihleri arasında arasında Healey[14] kriterlerine göre PMR tanısıyla takipli 33 hasta ve kontrol grubu olarak romatolojik hastalığı olmayan 28 gönüllü dahil edildi.

PMR'li hastaların yaş, cinsiyet, hastalık başlangıç zamanı, şikayetleri, ek hastalıkları, ilaç kullanımları ile ilgili bilgiler dosyalarından ve kontrol grubunun yaş, cinsiyet, hastalık bilgileri ise kan alımı sırasında kayıt edildi. PMR ve kontrol grubunun aterosklerotik risk faktörleri; sigara kullanımı, HT, DM, ailede aterosklerotik hastalık öyküleri, serebrovasküler olay (SVO) ve miyokard infarktüsü (MI) öyküsü sorgulanarak, boy ve kilo ölçümleri ile vücut kitle indeksi (VKİ) kg/m² cinsinden hesaplanarak sonuçlar takip formuna kaydedildi. Her iki grubun açlık kan şekeri (AKŞ), total kolesterol, düşük yoğunluklu lipoprotein (LDL)-kolesterol, yüksek yoğunluklu lipoprotein (HDL)-kolesterol, trigliserit değerleri kaydedildi.

Çalışma protokolünün amacı, gereç ve yöntemleri, gönüllü bilgilendirme metninin gözden geçirilmesi sonucunda, Helsinki Deklarasyonu kararlarına, hasta hakları yönetmeliğine ve etik kurallarına uygun olarak tasarlandığına ilişkin Trakya Üniversitesi Tıp Fakültesi Etik Kurulu tarafından 23.03.2011 tarihinde 07/07 karar numarası ile etik kurul onay belgesi alındı. Çalışma, Trakya Üniversitesi Bilimsel Araştırma Projeleri Fonu tarafından desteklenmiştir (proje no: TÜBAP-2011/74).

Kan Analizi

Çalışmaya katılan tüm olgulardan antekubital brakial venden 10 mL periferik kan örneği alındı. 4,000 devirde 10 dakika santrifüj edilerek elde edilen plazmalar, -80 ºC'de saklandı. Çalışılacak sitokinler; IL-5, IL-6, IL-8, IL-32, IL-33, adiponektin, IFN-γ ve PTX-3 düzeyi için enzim bağlantılı immünosorbent ölçüm yöntemi kullanıldı.

Karotis İntima Media Kalınlığının Değerlendirilmesi

Tüm hastaların KİMK; Esaote, MyLab70 Xvision ile 7,5 MHz transduser kullanılarak elde edilen yüksek çözünürlüklü USG görüntülerinden ölçülmüştür. Ölçümlerin tamamı tek gözlemci tarafından verilerden habersiz olarak yapılmıştır. Böylece ölçümler arası değişkenlik en aza indirgenmiştir.

KİMK ölçümü için USG, birey sırtüstü yatırılıp boyun ekstansiyonda ve çene incelenen tarafın karşısına çevrilerek yapıldı. Tarama sırasında karotis arterler longitudinal düzlemlerde incelendi. KİMK, karotis bulbus dilatasyonunun sagital olarak 1 cm altındaki proksimal segmentinde ölçülmüştür. Ortalama KİMK değerlendirilirken plak kalınlığı hesaplamaya katılmamıştır. Sağ ve sol KİMK ölçülerek ortalaması kaydedilmiştir. Damar duvarında damar lümenine komşu ilk ekojenik alan intima olup, sonraki zayıf ekojenik alan ise mediadır. Hastalarda plak varlığı; kalsifiye olsun ya da olmasın, tüm karotis segmenti değerlendirilirken, damar lümeni içerisine doğru, lokal olarak artmış, düzensiz KİMK olarak tanımlanmıştır.

İstatistiksel Analiz

Tüm istatistiksel analizler SPSS 12.0 (SPSS Inc., Chicago, IL, ABD) programı kullanılarak gerçekleştirildi.

Temel özellikler; normal dağılım gösteren değişkenler için ortalama ± standart sapma, normal dağılım göstermeyen değişkenler için medyan (çeyrekler arası aralık) ve kategorik veriler için frekans ve yüzde olarak sunuldu. Sürekli değişkenlerin normal dağılıma uygunluğu Kolmogorov-Smirnov ve Shapiro-Wilk testleri ile değerlendirildi. Kategorik değişkenler ki-kare testi ile karşılaştırılırken, sürekli ve kategorik değişkenler arasındaki ilişkiler Mann-Whitney U testi ve Kruskal-Wallis testi ile analiz edildi. Tüm p-değerleri çift yönlü olarak hesaplandı ve $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular

PMR tanısı ile izlenen 29 kadın, 4 erkek toplam 33 hasta ile kontrol grubu olan 24 kadın ve 4 erkek toplam 28 gönüllü çalışmaya dahil edildi. Çalışmaya TA tanılı hasta dahil edilmedi.

PMR grubunun yaş ortalaması 66,3±9,6 yıl, kontrol grubunun yaş ortalaması ise 62,5±5,1 yıldı (p=0,103).

PMR hastalarının başvuru şikayetleri; tüm hastalarda sabah tutukluğu ve halsizlik, 32'sinde omuz ve üst kolda ağrı, 30'unda kalça ve uylukta ağrı, 9'unda ateş ve 9'unda kilo kaybı şeklindeydi. Ortalama hastalık süresi 35,2±32 ay idi. Otuz bir hasta aktif olarak steroid tedavisi almakta olup, ortalama kümülatif steroid dozu 5,76±6,82 gramdı.

Eşlik eden hastalıklar değerlendirildiğinde; DM PMR'li 9 ve kontrol 3 olguda (p=0,083), HT PMR'li 23 ve kontrol 12 olguda (p=0,062), geçirilmiş SVO veya MI PMR'li 2 ve kontrol 1 olguda (p=0,542) mevcuttu. Ailede aterosklerotik hastalık öyküsü PMR'li 1 ve kontrol 3 olguda (p=0,286), sigara kullanımı ise PMR'li 3 ve kontrol 4 olguda (p=0,647) vardı.

VKİ PMR grubunda ortalama 32,5±6,2 kg/m², kontrol grubunda 31,4±6,2 kg/m² olarak hesaplandı (p=0,740).

Total kolesterol düzeyi PMR'lilerde ortalama 194,1±30,2 mg/dL, kontrol grubunda 200,8±4 mg/dL (p=0,42), LDL kolesterol düzeyi PMR'lilerde ortalama 133,9±29,9 mg/dL, kontrol grubunda 136±28,6 mg/dL (p=0,71), HDL kolesterol düzeyi PMR'lilerde ortalama 55,2±11 mg/dL, kontrol grubunda 58,3±16,6 mg/dL (p=0,38) trigliserid düzeyi PMR'lilerde ortalama 121,2±50,1 mg/dL, kontrol grubunda 120,2±67,8 mg/dL (p=0,95), AKŞ düzeyi PMR'lilerde 102,4±20,8 mg/dL, kontrol grubunda ise 99±25,4 mg/dL olarak bulundu (p=0,63) (Tablo 2).

IL-5 düzeyi PMR'lilerde 167,7±16,6 pg/mL, kontrol grubunda ise 155±18,3 pg/mL olarak saptanmış olup, PMR grubunda anlamlı derecede yüksek bulundu (p=0,009).

IL-6 düzeyi PMR'lilerde 128,8±15,4 pg/mL, kontrol grubunda 130,6±13,6 pg/mL (p=0,58). IL-8 düzeyi PMR'lilerde 158,6±17,6 pg/mL, kontrol grubunda 155±19 pg/mL (p=0,46). IL-32 düzeyi PMR'lilerde 200,2±37,4 ng/mL, kontrol grubunda 199,1±37,8 ng/mL (p=0,89). IL-33 düzeyi PMR'lilerde 168±12,4 pg/mL, kontrol grubunda ise 161±15,1 pg/mL (p=0,29). IFN-γ düzeyi PMR'lilerde 152,9±13,1 pg/mL, kontrol grubunda 148,9±17,8 pg/mL (p=0,42), adiponektin düzeyi PMR'lilerde 156,8±16,8 ng/mL, kontrol grubunda 155,5±17,1 ng/mL olarak bulundu (p=0,77).

PTX-3 düzeyleri normal dağılım göstermediğinden, medyan ve dağılım aralığı ile değerlendirildi. PMR grubunda medyan PTX-3 düzeyi 433 pg/mL (227,5-1059,5 pg/mL), kontrol grubunda ise 347,3 pg/mL (251-697,5 pg/mL) olarak saptandı. PTX-3 düzeyi PMR olgularında kontrol grubuna göre anlamlı derecede yüksek bulundu (p=0,008) (Tablo 3).

Ultrason eşliğinde ölçülen KİMK PMR'li olgularda 0,749±0,101 mm ve kontrol grubunda KİMK ölçümü 0,715±0,055 mm olup PMR olgularından düşük ancak anlamlı fark saptanmadı (p=0,270).

USG ile değerlendirilen hastalarda karotis intima-media plak varlığı PMR grubunda 6 olguda (%20,7), kontrol grubunda ise 1 olguda (%4,2) saptandı. Gruplar arasında bu açıdan fark istatistiksel olarak anlamlı bulunmadı (p=0,108).

Tartışma

Bu çalışmada PMR hastalarında subklinik ateroskleroz KİMK ve plak varlığı ile değerlendirilmiş, ayrıca çeşitli proenflamatuvar ve antienflamatuvar sitokin düzeyleri incelenmiştir. Bulgularımıza göre, IL-5 ve PTX-3 düzeyleri PMR grubunda kontrol grubuna kıyasla anlamlı düzeyde yüksek bulunurken; IL-6, IL-8, IL-32, IL-33, IFN-γ ve adiponektin düzeyleri açısından iki grup arasında anlamlı fark saptanmamıştır. KİMK ve karotis plak varlığı açısından da anlamlı farklılık gözlenmemiştir.

Tablo 2. PMR ve kontrol grubunun aterosklerotik risk faktörleri

	Polimiyaljiya romatika	Kontrol	p
Cinsiyet (K/E)	29/4	24/4	
Yaş ortalaması (yıl)	66,3±9,6	62,5±5,1	0,103
Diabetes mellitus (n)	9	3	0,083
Hipertansiyon (n)	23	12	0,062
Geçirilmiş miyokard enfarktüsü/ serebrovasküler olay (n)	2	1	0,542
Ailede aterosklerotik hastalık öyküsü (n)	3	3	0,286
Sigara kullanımı (n)	3	4	0,647
Vücut kitle indeksi (kg/m²)	32,5±6,2	31,4±6,2	0,740
Total kolesterol (mg/dL)	194,1±30,2	200,8±40	0,42
LDL kolesterol (mg/dL)	133,9±29,9	136±28,6	0,71
HDL kolesterol (mg/dL)	55,2±11	58,3±16,6	0,38
Trigliserit (mg/dL)	121,2±50,1	120,2±67,8	0,95
Açlık kan şekeri (mg/dL)	102,4±20,8	99±25,4	0,63

HDL: Yüksek yoğunluklu lipoprotein, K/E: Kız/erkek, LDL: Düşük yoğunluklu lipoprotein, PMR: Polimiyalji romatika

Tablo 3. PMR ve kontrol grubunun sitokin seviyeleri

	Polimiyaljiya romatika (pg/mL)	Kontrol (pg/mL)	p
IL-5	167,7±16,6	155±18,3	0,009
IL-6	128,8±15,4	130,6±13,6	0,58
IL-8	158,6±17,6	155±19	0,46
IL-32	200,2±37,4	199,1±37,8	0,89
IL-33	168±12,4	161±15,1	0,29
IFN-γ	152,9±13,1	148,9±17,8	0,42
Adiponektin	156,8±16,8	155,5±17,1	0,77
PTX-3*	433 (227,5-1059,5)	347,3 (251-697,5)	0,008

*Pentraxin 3 normal dağılıma uymadığından medyan (minimum-maksimum) şeklinde verildi. IFN: İnterferon, IL: İnterlökin, PMR: Polimiyalji romatika, PTX-3: Pentraxin 3

PMR patogenezinde IL-6'nın merkezi rol oynadığı çok sayıda çalışmada gösterilmiştir. Weyand ve ark.[25], aktif PMR hastalarında IL-6'nın hem serumda hem de sinovyal dokuda anlamlı olarak arttığını bildirmiştir. Ancak bizim çalışmamızda IL-6 düzeyleri kontrol grubuyla karşılaştırıldığında anlamlı farklılık göstermemiştir (p=0,58). Cutolo ve ark.'nın[26] yapmış olduğu kortikosteroid tedavisi sonrası adrenal aks ve IL-6 düzeyini incelediği çalışmada 12 aylık glukokortikoid tedavisi sırasında IL-6 düzeylerinin birinci ayda anlamlı şekilde düştüğü, daha sonra stabil kaldığı ve glukokortikoid dozunun azaltılmasına rağmen tekrar artmadığı saptamıştır. Roche ve ark.'nın[27] yaptığı çalışmada, PMR tanılı ve kortikosteroid tedavisi almayan hastalar ile 14 ay tedavi almış hastaların IL-6 konsantrasyonları karşılaştırılmış; kortikosteroid uygulanmasının dolaşımdaki IL-6 düzeylerini hızla düşürdüğü saptanmış ve klinik semptomlarla yakın korelasyonu, bu sitokinin hastalık belirtilerine doğrudan katkıda bulunduğunu göstermiştir. Bizim çalışmamızda hastalarımızın büyük çoğunluğunun (%94) aktif olarak kortikosteroid tedavisi almakta olması, yeni tanı hastanın olmaması IL-6 düzeylerini baskılamış olabileceğini desteklemektedir.

PTX-3 düzeyinin PMR grubunda anlamlı düzeyde yüksek bulunması (p=0,008), enflamatuvar aktivitenin devam ettiğini düşündürmektedir. PTX-3, özellikle endotel hücreleri ve makrofajlar tarafından sentezlenen ve vasküler enflamasyonla ilişkili bir proteindir. Ramirez ve ark.[28] temporal arteritte PTX-3'ün yüksek olduğunu göstermiş; ancak Pulsatelli ve ark.'nın[29] yapmış olduğu 93 PMR'li hastayı içeren çalışmada artmadığı gözlenmiştir. Bu nedenle çalışmamız PTX-3 düzeyinin yalnızca TA değil, belki de PMR'nin subklinik vasküler bileşenlerine dair ipuçları verebileceği düşündürmektedir.

IL-5 düzeyinin PMR hastalarında anlamlı yüksek bulunması ise dikkat çekicidir. Literatürde PMR'de IL-5 düzeyine ilişkin herhangi bir çalışmaya rastlanmamıştır. IL-5, mast hücreleri, B lenfositler ve T helper 2 (Th2) hücreleri tarafından salgılanan, eozinofil aktivasyonu ve immünoglobülin üretimi üzerinde etkili bir sitokindir. Ayrıca bazofil çoğalması, histamin ve lökotrien salınımını da tetikleyerek enflamatuvar süreçlere katkıda bulunur.[30,31] PMR'de gözlenen IL-5 artışı, hastalıkta Th2 yanıtının rolü olabileceğini düşündürmektedir. Bu bulgu, IL-5'in PMR patogenezinde olası rolünü ortaya koyan ilk veri olup, ileri çalışmalarla desteklenmelidir.

IL-8 PMR ilişkisini inceleyen klinik çalışmalar sınırlıdır. Álvarez-Rodríguez ve ark.'nın[32] yaptığı bir çalışmada IL-8 düzeyleri yüksek bulunmuştur. Galbo ve Kall[33] yapmış olduğu PMR de prednizolon öncesi ve tedavi sırasında IL-6, IL-8, TNF-α'yı değerlendiren çalışmada ise IL-6 ve IL-8 düzeylerinin prednizolon tedavisi sonrası normal seviyede olduğunu bildirmiştir. Çalışmamızda IL-8 düzeylerinde farklılık saptanmaması, hastaların tedavi altında olması ile ilişkilendirilebilir.

IL-32 aktive T lenfositleri ve natural killer (NK) hücreleri tarafından sentezlenen yeni bulunan sitokinlerdendir. Timus, kolon, ince barsakta orta düzeyde bulunurken dalak ve periferik lökositlerde yüksek düzeylerde bulunur. TNF-α, IL-8 gibi proenflamatuvar sitokinlerin salınımını indükler.[34] IL-33, IL-1 ailesine ait yeni tanımlanmış sitokinlerdendir. Endotel ve epitel gibi stromal hücrelerden eksprese edilir. Hedef hücreleri bazofil, mast hücreleri, eozinofil, NK, Th2 hücreler ve dendritik hücrelerdir. *İn vitro* Th2 polarize hücrelerden kuvvetli IL-5 ve IL-13 salgılatır. Mast hücrelerinde IL-1b, IL-6, IL-13 ve TNF-α sentezi, bazofil ve eozinofillerde ise integrin ekspresyonunda artış sağlar.[35,36] PMR'de periferik kanda IL-32 ve IL-33 düzeyine yönelik bir çalışma yoktur. Ciccia ve ark.'nın[37] temporal arteritli hastalardaki arter biyopsisi örneklerinde IL-32 ve IL-33[38] düzeylerinin yüksek olduğu saptanmıştır. Bizim çalışmamızda iki grup arasında anlamlı farklığın saptanmaması; sitokin ekspresyonunun dokuda sınırlı kalabileceğini, sistemik dolaşıma yansımayabileceğini veya hastalık aktivitesinin düşük olduğu bir evrede örnekleme yapılmış olabileceğini düşündürmektedir. Ayrıca kortikosteroid kullanımı da IL-32 ve IL-33 düzeylerini düşürmüş olabilir.

Adiponektin, esas olarak adipositler tarafından üretilen ve salgılanan bir antienflamatuvar adipokin olarak tanımlanmıştır.[39] Scrivo ve ark.'nın[40], KİMK, abdominal aorta ve karotis arter stenozu ile adipositokinler arasındaki ilişkiyi değerlendirdikleri çalışmada KİMK artışı yanında adiponektin düzeyinde de artış saptadılar. Çalışmamızda adiponektin düzeylerinin kontrol grubuna göre artmadığını saptadık. Kaser ve ark.'nın[41] yapmış olduğu çalışma obezitenin adiponektin düzeyini azalttığını göstermiştir. PMR grubundaki hastaların ortalama kiloları 32,5±6,2 kg/m², kontrol grubunda 31,4±6,2 kg/m² olması ve bu değerlerin aşırı kilolu ve obez kategorilerinde olması adiponektin düzeylerinde artış saptanmamasını desteklemektedir.

IFN-γ, başlıca Th1 hücreleri, NK hücreleri ve sitotoksik T lenfositler tarafından üretilen proenflamatuvar bir sitokindir. Makrofajları aktive ederek fagositoz ve mikrobisidal aktivitelerini artırır, böylece hücre içi patojenlere karşı savunmada kritik rol oynar. Ayrıca MHC sınıf I ve II ekspresyonunu ile antijen sunumunu güçlendirir ve adaptif bağışıklık yanıtını düzenler.[42] Weyand ve ark.[25], TA hastalarının arter biyopsi örneklerinde IFN-γ düzeylerinin yükseldiğini gözlemlerken, izole PMR'li hastaların arter biyopsilerinde bu artışın saptanmadığını bildirmiştir. Her ne kadar IFN-γ düzeylerinin biyopsi örneklerinde yükselebileceği öne sürülmüş olsa da, dolaşımdaki tip I IFN-γ seviyelerinde artışın olmadığı düşünülmektedir.[43]

KİMK ve karotis plak varlığı açısından PMR ve kontrol grubu arasında anlamlı fark saptanmamıştır. Buna karşın, bazı çalışmalarda PMR hastalarında KİMK'nin kontrol gruplarına göre anlamlı olarak yüksek bulunduğu bildirilmektedir. Dasgupta ve ark.'nın[15] yaptığı çalışmada PMR hastalarında kontrollere

göre KİMK artışının yanı sıra adiponektin düzeylerinde de artış saptanmıştır; ancak bu çalışmada tüm hastalar PMR'nin yeni tanı döneminde değerlendirilmiştir. Schillaci ve ark.[44] tarafından yapılan çalışmada PMR hastalarında aort nabız dalga hızı (PWV), prednizon tedavisinden sonra azaldı. Bu çalışmada aort PWV'deki değişiklik, plazma CRP'deki yüzdelik değişiklikle doğrudan ilişkiliydi. Hastaların tedavisi aort büyütme indeksinde önemli bir azalma ile de ilişkilendirildi. Çalışmamızda karotis plak prevalansı gruplar arasında istatistiksel olarak anlamlı farklılık göstermemekle birlikte (p=0,108), PMR grubunda daha yüksek plak oranı (%20,7'ye karşı %4,2) klinik açıdan dikkat çekicidir ve bu sınırlı örneklem büyüklüğüne bağlı güç yetersizliğini de düşündürmektedir. Kesitsel tasarım ve kortikosteroid kullanımı gibi olası karıştırıcılar nedeniyle bu bulgu temkinli yorumlanmalı ve daha geniş örneklemli çalışmalarda doğrulanmalıdır.

Çalışmanın Kısıtlılıkları

Çalışmamızın bazı kısıtlamaları bulunmaktadır. Öncelikle çalışmamızda sınırlı sayıda hasta ve hastaların sitokin düzeyleri yeni tanı aldığında değerlendirilmediğinden, hastalığın başlangıçtaki immünolojik profili tam olarak yansıtılamamıştır. Ayrıca bu durum özellikle KİMK ve plak gibi sonlanımlar için istatistiksel gücü azaltmış ve bazı farkların anlamlılık eşiğine ulaşmasını engellemiş olabilir. Hastaların büyük çoğunluğunun (%94) kortikosteroid tedavisi altında olması sitokin seviyelerini baskılamış olabilir ve bu durum özellikle IL-6, IL-8, IL-32 ve IL-33 gibi parametrelerde anlamlı farklılık saptanamamasını açıklayabilir. Çalışmada hastalık aktivitesi ile sitokinlerin korelasyonu ile ve steroid dozu ile sitokin seviyesi arasında ilişkinin değerlendirilmemiş olması çalışmanın bir diğer önemli limitasyonlarından biridir.

Bu çalışmanın en güçlü yönü ise, PMR'de hem subklinik ateroskleroz göstergelerinin (KİMK ve karotis plak) hem de geniş bir sitokin panelinin aynı kohortta ve aynı zaman diliminde birlikte değerlendirilmiş olmasıdır. Karotis USG ölçümlerinin verilerden habersiz tek gözlemci tarafından yapılması, ölçüm yanlılığını ve gözlemciler arası değişkenliği azaltarak internal geçerliliği güçlendirmiştir. Ayrıca PMR ve kontrol grubunun klasik aterosklerotik risk faktörleri açısından benzer bulunması, gözlenen biyobelirteç farklılıklarının (özellikle IL-5 ve PTX-3) PMR ile ilişkili biyolojik süreçleri yansıtma olasılığını artırmaktadır.

Sonuç

Sonuç olarak IL-5 düzeyinin PMR'de ilk kez anlamlı yüksek bulunması, literatüre yeni bir katkıdır. PTX-3 düzeyinin PMR'de yüksek olduğunun gösterilmesi, hastalıkta subklinik vasküler enflamasyon olabileceğine dair ek bir kanıt sunar. Ayrıca PMR'de KİMK ve plak varlığında anlamlı farklılık olmaması, kortikosteroid tedavisinin vasküler parametreler üzerindeki etkisine dair bir ipucu sağlar. Ancak konuyla ilgili daha geniş çalışmalara ihtiyaç vardır.

Etik

Etik Kurul Onayı: Çalışma protokolünün amacı, gereç ve yöntemleri, gönüllü bilgilendirme metninin gözden geçirilmesi sonucunda, Helsinki Deklarasyonu Kararlarına, Hasta Hakları Yönetmeliği'ne ve etik kurallarına uygun olarak tasarlandığına ilişkin Trakya Üniversitesi Tıp Fakültesi Etik Kurulu tarafından 23.03.2011 tarihinde 07/07 karar numarası ile etik kurul onay belgesi alındı.

Hasta Onayı: Tüm katılımcılar yazılı muvafakatname verdi.

Dipnotlar

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Kaynaklar

1. Raheel S, Shbeeb I, Crowson CS, Matteson EL. Epidemiology of polymyalgia rheumatica 2000-2014 and examination of incidence and survival trends over 45 years: a population-based study. Arthritis Care Res (Hoboken). 2017;69:1282-5.
2. Noltorp S, Svensson B. High incidence of polymyalgia rheumatica and giant cell arteritis in a Swedish community. Clin Exp Rheumatol. 1991;9:351-5.
3. Smeeth L, Cook C, Hall AJ. Incidence of diagnosed polymyalgia rheumatica and temporal arteritis in the United Kingdom, 1990-2001. Ann Rheum Dis. 2006;65:1093-8.
4. Boesen P, Sørensen SF. Giant cell arteritis, temporal arteritis, and polymyalgia rheumatica in a Danish county. A prospective investigation, 1982-1985. Arthritis Rheum. 1987;30:294-9.
5. Schaufelberger C, Bengtsson BA, Andersson R. Epidemiology and mortality in 220 patients with polymyalgia rheumatica. Br J Rheumatol. 1995;34:261-4.
6. González-Gay MA, García-Porrúa C. Systemic vasculitis in adults in northwestern Spain, 1988-1997. Clinical and epidemiologic aspects. Medicine (Baltimore). 1999;78:292-308.
7. Pamuk ON, Dönmez S, Karahan B, Pamuk GE, Cakir N. Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: clinical features and epidemiological data. Clin Exp Rheumatol. 2009;27:830-3.
8. Sobrero A, Paolino S, Hysa E, et al. Seasonal onset of polymyalgia rheumatica: correlations with the pattern of clinical presentation, disease severity and outcome in 383 patients from a single centre. Clin Exp Rheumatol. 2021;39:564-9.
9. Meliconi R, Pulsatelli L, Uguccioni M, et al. Leukocyte infiltration in synovial tissue from the shoulder of patients with polymyalgia rheumatica. Quantitative analysis and influence of corticosteroid treatment. Arthritis Rheum. 1996;39:1199-207.
10. Pulsatelli L, Boiardi L, Pignotti E, et al. Serum interleukin-6 receptor in polymyalgia rheumatica: a potential marker of relapse/recurrence risk. Arthritis Rheum. 2008;59:1147-54.

11. Cantini F, Salvarani C, Olivieri I, et al. Shoulder ultrasonography in the diagnosis of polymyalgia rheumatica: a case-control study. J Rheumatol. 2001;28:1049-55.

12. McGonagle D, Pease C, Marzo-Ortega H, O'Connor P, Gibbon W, Emery P. Comparison of extracapsular changes by magnetic resonance imaging in patients with rheumatoid arthritis and polymyalgia rheumatica. J Rheumatol. 2001;28:1837-41.

13. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970-1991. Arthritis Rheum. 1995;38:369-73.

14. Healey LA. Long-term follow-up of polymyalgia rheumatica: evidence for synovitis. Semin Arthritis Rheum. 1984;13:322-8.

15. Dasgupta B, Cimmino MA, Maradit-Kremers H, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2012;71:484-92.

16. Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Ann Rheum Dis. 2015;74:1799-807.

17. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105:1135-43.

18. Matsuura E, Kobayashi K, Lopez LR. Atherosclerosis in autoimmune diseases. Curr Rheumatol Rep. 2009;11:61-9.

19. Tokgözoğlu L. Ateroskleroz ve enflamasyonun rolü [Atherosclerosis and the role of inflammation]. Turk Kardiyol Dern Ars. 2009;37(Suppl 4):1-6.

20. Shindo A, Tanemura H, Yata K, et al. Inflammatory biomarkers in atherosclerosis: pentraxin 3 can become a novel marker of plaque vulnerability. PLoS One. 2014;9:e100045.

21. Feijóo-Bandín S, Aragón-Herrera A, Moraña-Fernández S, et al. Adipokines and inflammation: focus on cardiovascular diseases. Int J Mol Sci. 2020;21:7711.

22. Heinhuis B, Popa CD, van Tits BL, et al. Towards a role of interleukin-32 in atherosclerosis. Cytokine. 2013;64:433-40.

23. Miller AM, Xu D, Asquith DL, et al. IL-33 reduces the development of atherosclerosis. J Exp Med. 2008;205:339-46.

24. Binder CJ, Hartvigsen K, Chang MK, et al. IL-5 links adaptive and natural immunity specific for epitopes of oxidized LDL and protects from atherosclerosis. J Clin Invest. 2004;114:427-37.

25. Weyand CM, Hicok KC, Hunder GG, Goronzy JJ. Tissue cytokine patterns in patients with polymyalgia rheumatica and giant cell arteritis. Ann Intern Med. 1994;121:484-91.

26. Cutolo M, Straub RH, Foppiani L, et al. Adrenal gland hypofunction in active polymyalgia rheumatica. Effect of glucocorticoid treatment on adrenal hormones and interleukin 6. J Rheumatol. 2002;29:748-56.

27. Roche NE, Fulbright JW, Wagner AD, Hunder GG, Goronzy JJ, Weyand CM. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. Arthritis Rheum. 1993;36:1286-94.

28. Ramirez GA, Rovere-Querini P, Blasi M, et al. PTX3 intercepts vascular inflammation in systemic immune-mediated diseases. Front Immunol. 2019;10:1135.

29. Pulsatelli L, Peri G, Macchioni P, et al. Serum levels of long pentraxin PTX3 in patients with polymyalgia rheumatica. Clin Exp Rheumatol. 2010;28:756-8.

30. Mahanty S, Nutman TB. The biology of interleukin-5 and its receptor. Cancer Invest. 1993;11:624-34.

31. Bischoff SC, Brunner T, De Weck AL, Dahinden CA. Interleukin 5 modifies histamine release and leukotriene generation by human basophils in response to diverse agonists. J Exp Med. 1990;172:1577-82.

32. Álvarez-Rodríguez L, López-Hoyos M, Calvo-Alén J, Aurrecoechea E, Villa I, Martínez-Taboada VM. Phagocyte dysfunction in polymyalgia rheumatica and other age-related, chronic, inflammatory conditions. J Leukoc Biol. 2013;94:1071-8.

33. Galbo H, Kall L. Circadian variations in clinical symptoms and concentrations of inflammatory cytokines, melatonin, and cortisol in polymyalgia rheumatica before and during prednisolone treatment: a controlled, observational, clinical experimental study. Arthritis Res Ther. 2016;18:174.

34. Heinhuis B, Koenders MI, van de Loo FA, Netea MG, van den Berg WB, Joosten LA. Inflammation-dependent secretion and splicing of IL-32{gamma} in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2011;108:4962-7.

35. Miller AM. Role of IL-33 in inflammation and disease. J Inflamm (Lond). 2011;8:22.

36. Palmer G, Talabot-Ayer D, Lamacchia C, et al. Inhibition of interleukin-33 signaling attenuates the severity of experimental arthritis. Arthritis Rheum. 2009;60:738-49.

37. Ciccia F, Alessandro R, Rizzo A, et al. Expression of interleukin-32 in the inflamed arteries of patients with giant cell arteritis. Arthritis Rheum. 2011;63:2097-104.

38. Ciccia F, Alessandro R, Rizzo A, et al. IL-33 is overexpressed in the inflamed arteries of patients with giant cell arteritis. Ann Rheum Dis. 2013;72:258-64.

39. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem. 1995;270:26746-9.

40. Scrivo R, Silvestri V, Ciciarello F, et al. An exploratory cross-sectional study of subclinical vascular damage in patients with polymyalgia rheumatica. Sci Rep. 2020;10:11407.

41. Kaser S, Tatarczyk T, Stadlmayr A, et al. Effect of obesity and insulin sensitivity on adiponectin isoform distribution. Eur J Clin Invest. 2008;38:827-34.

42. Tau G, Rothman P. Biologic functions of the IFN-gamma receptors. Allergy. 1999;54:1233-51.

43. Floris A, Piga M, Cauli A, Salvarani C, Mathieu A. Polymyalgia rheumatica: an autoinflammatory disorder? RMD Open. 2018;4:e000694.

44. Schillaci G, Bartoloni E, Pucci G, et al. Aortic stiffness is increased in polymyalgia rheumatica and improves after steroid treatment. Ann Rheum Dis. 2012;71:1151-6.

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Evaluation of physiotherapy and rehabilitation awareness of physicians working with rheumatological patients: The example of Türkiye

Romatolojik hastalarla çalışan hekimlerin fizyoterapi ve rehabilitasyon farkındalığının değerlendirilmesi: Türkiye örneği

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Abstract

Objective: Physiotherapy, rehabilitation and exercise have an important place in the treatment of rheumatoid arthritis. The aim of our study is to examine physicians' awareness of physiotherapy and rehabilitation for patients with rheumatological conditions.

Methods: This is a descriptive cross-sectional study. Data were obtained using the Demographic and Data Collection Form and the Questionnaire, and were analyzed using descriptive statistics (mean, standard deviation, frequency, and percentage).

Results: A total of 60 rheumatologists participated in the study (response rate, 23.07%). Of the participants, 61.7% were female and 38.3% were male; 91.7% completed subspecialty training in internal medicine and 8.3% completed subspecialty training in physical medicine and rehabilitation. The majority (93.3%) reported recommending physiotherapy and rehabilitation to their patients, and 86.7% considered it necessary for treatment. Most physicians believed physiotherapy and rehabilitation improved joint mobility (91.7%), and fatigue (70%), and enhanced muscle strength (98.3%), activities of daily living (95%), and functional independence (90%). While 65% agreed that exercise therapy is a significant component of rehabilitation for rheumatoid arthritis, 75% reported recommending exercise to their patients. Additionally, 91.7% expressed a willingness to receive further information about physiotherapy and rehabilitation.

Conclusion: These results suggest that while rheumatology physicians demonstrate considerable interest in physiotherapy, there remains a need to further enhance awareness through structured educational content and multidisciplinary strategies.

Keywords: Rheumatology, awareness, rehabilitation

Özet

Amaç: Fizyoterapi, rehabilitasyon ve egzersiz, romatoid artrit tedavisinde önemli bir yere sahiptir. Çalışmamızın amacı, romatolojik hastalarla çalışan hekimlerin fizyoterapi ve rehabilitasyon farkındalıklarını incelemektir.

Yöntem: Bu çalışma tanımlayıcı kesitsel bir çalışmadır. Çalışmaya toplam 60 hekim katılmıştır. Veriler Demografik Bilgi Formu ve Anket Formu aracılığıyla toplanmış; ortalama, standart sapma, frekans ve yüzde gibi tanımlayıcı istatistiklerle analiz edilmiştir.

Bulgular: Çalışmaya toplam 60 romatoloji hekimi katılmıştır (yanıt oranı: %23,07). Katılımcıların %61,7'si kadın, %38,3'ü erkektir; %91,7'si iç hastalıkları, %8,3'ü fiziksel tıp ve rehabilitasyon alanında yandal uzmanlık eğitimini tamamlamıştır. Katılımcıların büyük çoğunluğu (%93,3) hastalarına fizyoterapi ve rehabilitasyon önermekte, %86,7'si bunu tedavide gerekli görmektedir. Hekimlerin çoğu, fizyoterapi ve rehabilitasyonun eklem hareketliliğini artırdığını (%91,7), ağrıyı (%81,7) ve yorgunluğu (%70) azalttığını, kas gücünü (%98,3), günlük yaşam aktivitelerini (%95) ve fonksiyonel bağımsızlığı (%90) artırdığını belirtmiştir. Katılımcıların %65'i egzersiz tedavisinin romatoid artritte rehabilitasyonun önemli bir bileşeni olduğunu kabul ederken, %75'i hastalarına egzersiz önerdiğini bildirmiştir. Ayrıca %91,7'si fizyoterapi ve rehabilitasyon konusunda daha fazla bilgi edinmek istediğini ifade etmiştir.

Sonuç: Bu sonuçlar, romatoloji hekimlerinin fizyoterapiye büyük ilgi gösterdiğini, ancak farkındalığın yapılandırılmış eğitim içerikleri ve multidisipliner stratejilerle daha da artırılmasına ihtiyaç duyulduğunu göstermektedir.

Anahtar Kelimeler: Romatoloji, farkındalık, rehabilitasyon

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterized primarily by symmetrical involvement of multiple joints. The basic clinical picture of RA is joint damage, manifested by deformities and cartilage and bone erosions, resulting from displacement of tendons and ligaments and loss of structural support due to inflammatory processes.[1] When disease management in RA is inadequate or appropriate responses to applied treatments are not achieved, inflammation, joint damage, and deformities can lead to loss of physical function and limitations in activities of daily living.[2]

Low physical activity is a characteristic but modifiable feature of rheumatoid arthritis. Research suggests that individuals with RA engage in less physical activity than healthy individuals. While some countries report that over 80% of RA patients are physically inactive, this figure is approximately 68% in the United Kingdom.[3] Physical inactivity negatively impacts both overall health and disease progression in RA patients, creating a vicious cycle. Therefore, encouraging regular physical activity and exercise is considered an integral and primary component of RA treatment.[4]

Physiotherapy, rehabilitation, and exercise play an important role in the treatment of RA.[2] However, no studies in the literature have examined the awareness of physiotherapy and rehabilitation among physicians who treat patients with rheumatic diseases. It is not known to what extent physicians working with rheumatological patients refer their patients to physiotherapy and rehabilitation, and to what extent they are aware of these services.

The aim of our study is to examine the physiotherapy and rehabilitation awareness of physicians working with rheumatological patients.

Materials and Methods

Study Design

This study is a descriptive cross-sectional study. This study was approved by the Ethics Committee at Sakarya University of Applied Sciences (approval date: 12.05.2025, approval number: 56/23) and was conducted in accordance with the principles of the Declaration of Helsinki. Eligible participants received written information and provided informed consent before participation.

Study Population

The study included 60 physicians who worked with rheumatological patients in both private and public hospitals in Türkiye. The study was conducted between May 2025 and August 2025. Inclusion criteria for the study were: being a physician in any medical specialty; having at least three years of theoretical and practical experience in the treatment, surgery, or rehabilitation of rheumatological diseases; and being a native Turkish speaker.

A demographic and data-collection form was used to assess demographic information and general knowledge about the profession, and a questionnaire was used to assess physicians' awareness of physiotherapy and rehabilitation.

Demographic and data collection form: Demographic information, such as gender, date of birth, weight, height, and body mass index, and descriptive information, such as major specialization, years working with rheumatology patients, and whether the team included a physiotherapist, were recorded.

Questionnaire form: The authors developed the questionnaire based on a review of the relevant literature. To ensure face validity and content relevance, the items were reviewed by two rheumatologists and two physiotherapists with clinical experience in the field. However, no formal psychometric validation procedures were conducted prior to data collection. It consisted of questions designed to evaluate physicians' awareness of physiotherapy and rehabilitation when working with rheumatology patients. Survey questions were answered using a 5-point Likert scale: 1. Not sufficient at all; 2. Partially sufficient; 3. Sufficient; 4. Completely sufficient; 5. Question not appropriate. It aimed to evaluate the awareness of exercise one of the basic components of physiotherapy and rehabilitation, the practices applied in patient management, and the joint-protection techniques taught to patients.

Statistical Analysis

Evaluations of the obtained data were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe the demographic characteristics of the participants and their awareness of physiotherapy and rehabilitation. Mean, standard deviation, minimum, and maximum values were calculated for continuous variables, and frequency (n) and percentages (%) were calculated for categorical variables.

Results

This study was conducted with the participation of 60 rheumatology physicians. The response rate for the survey distributed to the Rheumatology Physicians' WhatsApp group, which had 260 members, was 23.07%. Among the rheumatology physicians, 6 (10%) had 3-5 years, 18 (30%) had 6-10 years, 24 (40%) had 11-15 years, and 12 (20%) had 16-20 years of professional experience. Among the rheumatologists, 91.7% completed their rheumatology subspecialty training through the Department of Internal Medicine, while 8.3% completed it through the Department of Physical Medicine

and Rehabilitation. Among the rheumatology physicians who participated in the study, 61.7% were female and 38.3% were male. The demographic characteristics of the rheumatology physicians are presented in Table 1. 93.3% of rheumatology physicians reported recommending physiotherapy and rehabilitation to their patients (Figure 1). 86.7% of rheumatology physicians consider physiotherapy and rehabilitation necessary in treating their patients. While 1.7% did not consider it necessary, 11.7% responded with "I don't know" (Table 2). Of the rhumatology physicians, 65% reported they believe that exercize therapy constituted a significant component of physiotherapy and rehabilitation in rheumatoid arthritis; 15% do not share this view, and 20% responded "I don't know" (Table 3). Of the rheumatology physicians, 91.7% believe that physiotherapy and rehabilitation improve joint range of motion in rheumatoid arthritis; 1.7% do not share this view, and 6.7% responded "I don't know". Among rheumatology physicians, 81.7% reported that they believe that physiotherapy and rehabilitation reduce pain in rheumatoid arthritis, 8.3% did not believe they are effective, and 10% responded "I don't know". Seventy percent of rheumatology physicians reported that physiotherapy and rehabilitation are effective in reducing fatigue in rheumatoid arthritis; 3.3% did not hold this view, and 26.7% responded "I don't know". Of the rheumatology physicians, 98.3% believe that physiotherapy and rehabilitation effectively improve muscle strength and power in patients with rheumatoid arthritis; 1.7% responded "I don't know". Ninety-five percent of rheumatology physicians reported that physiotherapy and rehabilitation are effective in facilitating activities of daily living in patients with rheumatoid arthritis, while 5% responded "I don't know". Of the rhumatology physicians, 65% reported they believe that excersize therapy constituted a significant component of physiotherapy and rehabilitation in rheumatoid arthritis; 15% do not share this view, and 20% responded "I don't know" (Table 3). Seventy-five percent of the rheumatology physicians recommended exercise for patients with rheumatoid arthritis, 13.3% did not recommend it, and 11.7% were not familiar with the exercises (Figure 2). The types of exercises

Table 1. Demographic characteristics of the rheumatology physicians

Descriptives	Minimum	Maximum	Mean ± standard deviation
Age (yrs)	30	45	36.21±3.68
Years of professional experience (yrs)	3	20	10.78±4.59
Height (cm)	150	186	168.91±8.01
Weight (kg)	45	99	70.48±14.08

cm: Centimeter, kg: Kilogram, yrs: Years

Table 2. The percentage of physicians who consider physiotherapy and rehabilitation necessary in the treatment of their patients

Consideration status	Percentage (%)	n
Considering	86.7	52
Not considering	1.7	1
Undecided	11.7	7

Table 3. Exercise therapy constitutes a significant component of physiotherapy and rehabilitation in the management of rheumatoid arthritis

Response	Percentage (%)	n
Yes	65	39
No	15	9
Undecided	20	12

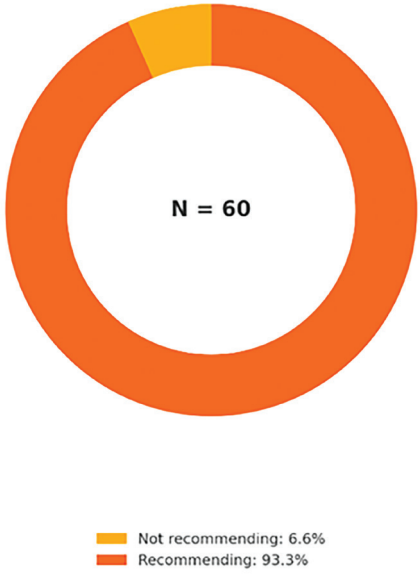

Figure 1. Referral to physiotherapy and rehabilitation

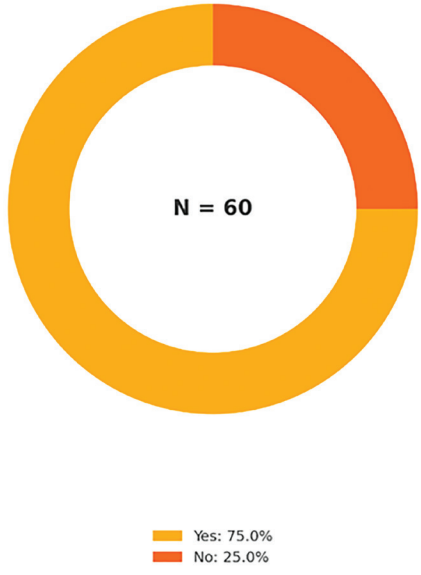

Figure 2. The percentage of rheumatology physicians who recommend exercise for patients with rheumatoid arthritis

recommended by the rheumatologists to their patients are presented in Table 4. Among the rheumatology physicians, 46.7% reported that they believe that physiotherapy and rehabilitation is as effective as pharmacological treatment in rheumatoid arthritis, 43.3% did not consider it equally effective, and 10% responded "I don't know" (Figure 3). The percentage of rheumatology physicians who reported addressing the importance of energy conservation techniques in physiotherapy and rehabilitation of patients with RA was 26.7%, while 73.3% stated that they did not address this topic. Among rheumatology physicians, 91.7% expressed a desire to receive more information about physiotherapy and rehabilitation; 6.7% stated that they did not wish to receive further information, and 1.7% responded with "I don't know". The percentage of rheumatology physicians who believe that regular participation in physiotherapy and rehabilitation has a positive effect on walking in patients with RA is 83.3%, while 16.7% responded with "I don't know". Ninety percent of rheumatology physicians believe that regular participation in physiotherapy and rehabilitation facilitates stair climbing in patients with rheumatoid arthritis; 10% responded "I don't know". 86.7% of the rheumatology physicians reported that they believe that regular participation in physiotherapy and rehabilitation improves fine motor skills in patients with rheumatoid arthritis; 1.7% did not share this view, and 11.7% responded "I don't know". Among rheumatology physicians, 91.7% reported that they believe that regular participation in physiotherapy and rehabilitation enables patients with RA to perform household tasks more easily, while 8.3% responded "I don't know". Ninety percent of rheumatology physicians reported that they believe that regular participation in physiotherapy and rehabilitation enables patients with RA to perform activities of daily living more comfortably, while 10% responded, "I don't know".

Table 4. The types of exercises recommended by rheumatology physicians to their patients (multiple responses allowed)

Category	Percentage (%)	n
No activity recommends	8.33	5
Aerobic exercises	6.67	4
Range of motion exercises	13.33	8
Walking	10	6
Stretching exercises	13.33	8
Isometric exercises	5	3
Swimming	11.67	7
Calisthenic exercises	1.67	1
Yoga	3.33	2
Pilates	6.67	4
Hydrotherapy	1.67	1
Expert recommendation	1.67	1
Strengthening exercises	10	6
Cycling	1.67	1
Does not know any exercise	1.67	1
Brochure based exercises	1.67	1
YouTube rheumatism TV	1.67	1

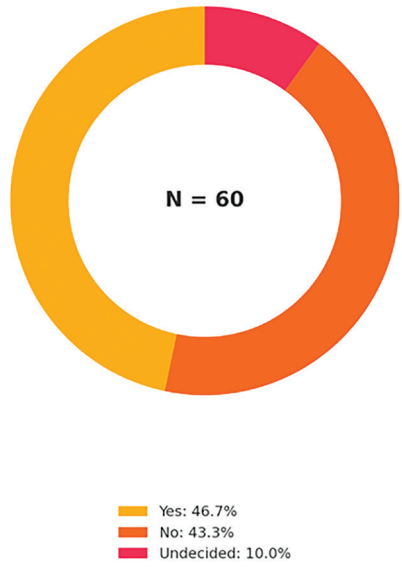

Figure 3. The percentage of rheumatology physicians who believe that physiotherapy and rehabilitation are as effective as pharmacological treatment in rheumatoid arthritis

Discussion

This study aimed to assess physicians' awareness of and attitudes toward physiotherapy and rehabilitation for patients with rheumatological conditions. The findings indicate that physicians generally have a positive view of physiotherapy, but their levels of knowledge and practice remain limited in some areas.

Physiotherapy plays an indispensable role in managing pain in rheumatology. Mohapatra et al.[5] reported that various methods, such as aerobic exercise, hydrotherapy, and manual therapy, are essential in alleviating pain, restoring functionality, and improving quality of life. England et al.[6] also emphasized the positive effects of physiotherapy on pain, fatigue, and functional capacity in individuals with rheumatoid arthritis. In our study, 93.3% of physicians stated that they recommend physiotherapy and rehabilitation to their patients. This rate indicates a high level of awareness of the clinical value of physiotherapy. This finding is consistent with the literature.

During comprehensive patient assessments, rheumatology physiotherapists determine the physical effects of the patient's condition and the extent to which these effects impair their function, including posture and mobility.[7] Hurkmans et al.[8] stated that providing clear and personalized physical activity recommendations for individuals with inflammatory arthritis increases treatment adherence. In our study, 86.7% of physicians stated that physiotherapy is a necessary part of the treatment,

while 75% recommended exercise to their patients. However, 11.7% of the participants reported that they were not familiar with exercise, highlighting the need for educational support in clinical practice.

Physiotherapy and occupational therapy are non-pharmacological approaches that aim to restore and optimize patient function. While physiotherapy primarily focuses on improving joint mobility, flexibility, and muscle strength, occupational therapy emphasizes activity modification and improvement of daily functioning.[9] Akıncı et al.[10] reported that exercise increased joint range of motion and functional capacity in individuals with rheumatoid arthritis. Similarly, Sieczkowska et al.[11] reported that home-based physiotherapy provided significant improvements in patient function. In our study, 98.3% of physicians agreed that physiotherapy improved muscle strength, and 95% agreed that it contributed to activities of daily living. These findings are consistent with the literature.

On the other hand, Musumeci[12] reported that physical activity can reduce tender points and fatigue, increase energy, and serve as an excellent stress reliever. Similarly, Li and Wang[13] noted that physiotherapy are effective in reducing symptoms such as fatigue and functional disability. In our study, 70% of physicians considered physiotherapy effective for fatigue management, whereas 26.7% emphasized the importance of energy conservation techniques. These rates suggest that the multidisciplinary and holistic approaches emphasized in the literature are not fully reflected in physicians' practice and suggest that awareness of this issue is low.

Current evidence indicates that exercise and physical therapy, especially in the chronic phase, when combined with medications, have a positive impact on the course of the disease.[14,15] Only 46.7% of physicians in our study believed that physiotherapy was as effective as pharmacological treatment. This finding suggests that treatment approaches for RA remain predominantly medical, and some clinicians consider physiotherapy a complementary option.

An important finding is that 91.7% of the participated physicians expressed a desire for more information about physiotherapy and rehabilitation. This result suggests that clinicians are highly interested in the topic, and their knowledge can be further enhanced through training. Integrating physiotherapy approaches into educational content can improve both physician-physiotherapist collaboration and patient outcomes.

A key strength of our study is that it collected data directly from physicians who care for rheumatology patients in clinical practice, unlike previous studies. Therefore, it is an original study in its field.

Study Limitations

Several limitations of this study should be acknowledged. The relatively limited sample size and the online distribution of the survey through a single WhatsApp group may have introduced sampling bias and restricted the generalizability of the findings. In addition, the low response rate (23%) raises the possibility of non-response bias, as individuals with greater interest in or awareness of the topic may have been more likely to participate, potentially leading to an overestimation of awareness levels.

Data were collected using a self-reported questionnaire, which may be subject to social desirability bias. Moreover, the cross-sectional design of the study precludes the establishment of causal relationships, and the findings should therefore be interpreted with caution.

The questionnaire used in this study was not subjected to formal psychometric validation. Quantitative measures such as the content validity index, internal consistency, and test–retest reliability were not assessed, which may affect the precision of the measurements. Future studies are encouraged to perform comprehensive validation.

Finally, the inclusion of physicians with formal training in physical medicine and rehabilitation may have influenced the reported awareness levels. Consequently, awareness among physicians with such training may be overestimated compared with that of physicians without such training. Future research may benefit from stratifying participants according to prior training or focusing on physicians with limited exposure to rehabilitation medicine.

Conclusion

These results suggest that rheumatology physicians are highly interested in physiotherapy, and current awareness levels can be further improved through educational content and multidisciplinary approaches. Increasing physiotherapy awareness in medical education and continuing professional development programs could facilitate strengthening physician-physiotherapist collaboration and providing patients with a more holistic approach to care.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee at Sakarya University of Applied Sciences (approval date: 12.05.2025, approval number: 56/23) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Eligible participants received written information and provided informed consent before participation.

Footnotes

Authorship Contributions

Concept: S.G.A., B.D.G., E.B., Design: S.G.A., B.D.G., E.B., Data Collection and Processing: S.G.A., B.D.G., E.B., Analysis or Interpretation: S.G.A., B.D.G., E.B., Literature Search: S.G.A., B.D.G., E.B., Writing: S.G.A., B.D.G., E.B.

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

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References

1. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.
2. Peter WF, Swart NM, Meerhoff GA, Vliet Vlieland TPM. Clinical practice guideline for physical therapist management of people with rheumatoid arthritis. Phys Ther. 2021;101:pzab127.
3. Sokka T, Häkkinen A. Poor physical fitness and performance as predictors of mortality in normal populations and patients with rheumatic and other diseases. Clin Exp Rheumatol. 2008;26(Suppl 51):S14-20.
4. Cooney JK, Law RJ, Matschke V, et al. Benefits of exercise in rheumatoid arthritis. J Aging Res. 2011;2011:681640.
5. Mohapatra A, Patwari S, Pansari M, Padhan S. Navigating pain in rheumatology: a physiotherapy-centric review on non-pharmacological pain management strategies. Cureus. 2023;15:e51416.
6. England BR, Smith BJ, Baker NA, et al. 2022 American College of Rheumatology Guideline for exercise, rehabilitation, diet, and additional integrative interventions for rheumatoid arthritis. Arthritis Care Res (Hoboken). 2023;75:1603-15.
7. Dziedzic, Krysia, and Alison Hammond, eds. Rheumatology E-Book: Rheumatology E-Book. Elsevier Health Sciences, 2010.
8. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev. 2009;2009:CD006853.
9. Allameen NA, Lai YW, Lian G, et al. Physiotherapy and occupational therapy in rheumatoid arthritis: bridging functional and comorbidity gaps. Best Pract Res Clin Rheumatol. 2025;39:102032.
10. Akıncı M, Akinci M, Çınar Fİ. Romatoid artrit ve egzersiz. Gazi Sağlık Bilimleri Dergisi. Ağustos 2025;10(Özel Sayı):13-14.
11. Sieczkowska SM, Smaira FI, Mazzolani BC, Gualano B, Roschel H, Peçanha T. Efficacy of home-based physical activity interventions in patients with autoimmune rheumatic diseases: a systematic review and meta-analysis. Semin Arthritis Rheum. 2021;51:576-87.
12. Musumeci G. Effects of exercise on physical limitations and fatigue in rheumatic diseases. World J Orthop. 2015;6:762-9.
13. Li Z, Wang XQ. Clinical effect and biological mechanism of exercise for rheumatoid arthritis: a mini review. Front Immunol. 2023;13:1089621.
14. Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil. 2013;27:1059-71.
15. Gwinnutt JM, Wieczorek M, Cavalli G, et al. Effects of physical exercise and body weight on disease-specific outcomes of people with rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs. RMD Open. 2022;8:e002168.

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Biological treatment predictors and gender-based clinical features in Takayasu arteritis: A single-center cohort from Western Türkiye

Takayasu arteritinde biyolojik tedavi belirleyicileri ve cinsiyete dayalı klinik özellikler: Batı Türkiye'den tek merkezli bir kohort çalışması

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Abstract

Objective: Takayasu arteritis (TAK) is a rare large-vessel vasculitis with female predominance, affecting the aorta and its branches. Although many cohorts have been described, predictors of biologic therapy use and gender-related differences in clinical features remain insufficiently characterized. This study aimed to investigate clinical characteristics, imaging findings, and treatment approaches of patients with TAK from Western Türkiye, focusing on factors associated with initiation of biologic therapy and gender-based comparisons of clinical features.

Methods: A retrospective observational study was conducted among patients diagnosed with TAK between 2017 and 2025. Demographic, clinical, laboratory, and angiographic data, as well as disease activity indices, were collected. Treatment regimens and interventional procedures were documented. Comparative analyses were performed by gender, and predictors of biologic therapy use were assessed.

Results: The cohort consisted of 34 women (85%) and 6 men (15%), with a mean age of 43.5 years. Disease onset occurred later in males (42.8 vs. 32.1 years, p=0.048). The most frequent angiographic type was type 1 (42.5%). Fatigue (45%) and claudication (37.5%) were common, whereas a decreased radial pulse was more frequent among women. All patients received glucocorticoids; methotrexate was the most common immunosuppressant. Biologic therapy was administered to 45% of patients. Higher baseline C-reactive protein, erythrocyte sedimentation rate, disease severity score, and positron emission tomography-computed tomography (PET-CT) vascular activity score were associated with biologic use.

Conclusion: This single-center cohort highlights comparable clinical features across genders in TAK. Elevated inflammatory markers and PET-CT vascular activity correlated with biologic therapy initiation, yet robust predictive factors were not identified.

Keywords: Takayasu arteritis, antirheumatic agents, sex differences

Özet

Amaç: Takayasu arteriti (TAK), kadınlarda daha sık görülen, aort ve dallarını etkileyen nadir bir büyük damar vaskülitidir. Birçok kohort tanımlanmış olmasına rağmen, cinsiyete bağlı farklılıklar ve biyolojik tedavi kullanımının belirleyicileri henüz yeterince tanımlanmamıştır. Bu çalışma, Türkiye'de tek bir merkezdeki TAK hastalarının klinik özelliklerini, görüntüleme bulgularını ve tedavi yaklaşımlarını, cinsiyete dayalı karşılaştırmalara ve biyolojik tedavi başlangıcıyla ilişkili faktörlere odaklanarak incelemeyi amaçlamaktadır.

Yöntem: Üçüncü basamak bir romatoloji kliniğinde 2017-2025 yılları arasında TAK tanısı almış hastalarda retrospektif bir gözlemsel analiz gerçekleştirildi. Demografik, klinik, laboratuvar ve anjiyografik veriler ile hastalık aktivite indeksleri toplandı. Tedavi rejimleri ve girişimsel işlemler belgelendi. Cinsiyete göre karşılaştırmalı analizler yapıldı ve biyolojik tedavi kullanımının öngörücüleri lojistik regresyon ile değerlendirildi.

Bulgular: Kohort 34 kadın (%85) ve 6 erkekten (%15) oluşuyordu ve yaş ortalaması 43,5 idi. Hastalığın başlangıcı erkeklerde daha geç idi (42,8'e karşı 32,1 yıl, p=0,048). En sık görülen anjiyografik tip tip 1'di (%42,5). Yorgunluk (%45) ve kladikasyo (%37,5) yaygınken, radial nabız azalması kadınlarda daha sıktı. Tüm hastalar glukokortikoid aldı ve metotreksat en sık kullanılan immünosüpresandı. Hastaların %45'ine biyolojik tedavi uygulandı. Biyolojik ajan kulllananlarda daha yüksek bazal C-reaktif protein, eritrosit sedimentasyon hızı, hastalık şiddet skoru ve pozitron emisyon tomografisi-bilgisayarlı tomografi (PET-BT) vasküler aktivite skoru saptandı; ancak hiçbiri çok değişkenli analizde bağımsız öngörücüler olarak görülmedi.

Sonuç: Bu tek merkezli kohort kadınlarda daha sık görülen radial nabız kaybı dışında, cinsiyetler arasında genel olarak benzer klinik özellikler olduğunu ortaya koymaktadır. Yükselmiş enflamatuvar belirteçler ve PET-BT vasküler aktivitesi biyolojik tedavi başlangıcıyla ilişkili bulunmuş, ancak güçlü öngörücü faktörler tanımlanamamıştır.

Anahtar Kelimeler: Takayasu arteriti, antiromatizmal ilaçlar, cinsiyet farklılıkları

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Introduction

Takayasu arteritis (TAK) is a chronic large-vessel vasculitis that predominantly affects individuals under the age of 50, primarily involving the aorta and its major branches.[1] Granulomatous inflammation of large vessels leads to diffuse wall thickening, resulting in stenotic and occlusive lesions.[2] The overall incidence has been reported to range between 0.3 and 3.4 per million, while prevalence varies from 0.9 to 40 per million.[3] The disease predominantly affects young women of reproductive age.[4]

The exact etiology of TAK remains uncertain; however, genetic predisposition, environmental triggers, and autoimmune mechanisms are thought to contribute.[5] The disease progresses through distinct phases, beginning with inflammation of the arterial wall and followed by stenotic lesions. In the later stages, clinical manifestations such as ischemia may emerge, along with hypertension and diminished pulses.[6] In the early stages of TAK, non-specific symptoms such as fever, weight loss, and fatigue are often predominant.[7] Cardiovascular involvement may occur, including renovascular hypertension and heart failure. Patients may also experience claudication of the extremities, as well as neurological and gastrointestinal symptoms.[2]

Glucocorticoids constitute the first-line treatment. In addition to glucocorticoids, conventional non-biologic immunosuppressive agents are commonly used, while tumor necrosis factor (TNF) inhibitors and tocilizumab have shown efficacy in refractory cases.[8] Contrast-enhanced magnetic resonance angiography (MRA), positron emission tomography (PET), and computed tomography angiography (CTA) are key modalities for the diagnosis and monitoring of the disease. These imaging techniques are effective in evaluating vascular lumen, wall thickness, and assessing disease activity.[9,10] Vascular surgery and endovascular interventions are frequently required during the disease course.[11]

Although numerous studies have addressed the epidemiology of TAK, relatively few have specifically examined predictors of biologic therapy use and gender-based differences in clinical features.[12,13] Although data on gender related differences in TAK symptoms remain limited, contemporary cohorts suggest that women more frequently present with upper extremity claudication and pulse deficits, whereas men more commonly exhibit renovascular and lower extremity ischemic manifestations, including hypertension.[14,15] In a large Indian cohort, approximately five percent of patients received biologic agents.[16,17] Similarly, data from a Brazilian cohort showed that biologics were used in 11 percent of patients. Although the association between gender and clinical involvement in TAK has been previously reported, emerging evidence suggests that patterns of vascular involvement may differ across ethnic and geographic populations. The aim of the current study is to evaluate the clinical characteristics, imaging findings, and treatment approaches of patients with TAK who are followed in a specific region of Türkiye. Additionally, gender-based differences in clinical features within the cohort were analyzed, and potential predictors of biologic therapy use were investigated.

Materials and Methods

Study Design and Population

This retrospective observational study included 40 patients with TAK who were followed between 2017 and 2025 in the rheumatology outpatient clinic of the tertiary care institution. All participants were assessed according to the 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology classification criteria, with each scoring ≥5 points, confirming a diagnosis consistent with TAK.[18] Patients under the age of 18 were excluded. Additional exclusion criteria included other systemic vasculitides at the time of diagnosis, such as Behçet's disease and polyarteritis nodosa, or meeting the ACR criteria for giant cell arteritis, as well as other inflammatory or immune-mediated conditions, including IgG4-related disease, relapsing polychondritis, and sarcoidosis. Patients with infectious conditions, including human immunodeficiency virus infection, syphilis, tuberculosis, and infectious aortitis, were also excluded. Furthermore, individuals with a history of malignancy or hematologic disorders, prior radiotherapy, cocaine use and those with insufficient clinical or imaging data were not included in the study.[19] Furthermore, age at disease onset in all included patients was consistent with TAK.

Data Collection

Demographic, clinical, laboratory, and treatment characteristics of the patients were analyzed using the hospital's electronic medical records system. Demographic data included age, gender, age at disease onset, and diagnostic delay. Recorded comorbidities comprised diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease (CAD). Diagnoses of diabetes, hypertension, CAD and dyslipidemia were based on either a prior medical diagnosis or the use of related medications. Individuals who were current or former smokers were grouped together as having a history of smoking.

Clinical manifestations, physical examination findings, and laboratory data at the time of diagnosis were reviewed. Systemic and ischemic symptoms evaluated included exertional claudication in the upper and lower extremities, headache, chest pain, dyspnea, generalized fatigue, dizziness, amaurosis fugax, fever, night sweats, arthritis, and Raynaud's phenomenon. Physical examination findings included the presence of cardiac murmurs, a marked reduction in radial pulse, a systolic blood pressure difference of ≥10 mmHg between arms, and vascular bruits. Laboratory parameters assessed at initial presentation

included C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

To assess vascular involvement, conventional imaging modalities such as contrast-enhanced MRA, CTA, and digital subtraction angiography were used. Additionally, PET-CT was employed in selected cases. Angiographic assessments focused on identifying vascular wall abnormalities such as stenosis, occlusion, segmental narrowing, aneurysmal dilatation, and signs of vasculitis. Based on these findings, patients were classified into angiographic types I-V according to the system proposed by Hata et al.[20] Imaging data were reviewed by an experienced rheumatologist.

Interventional procedures performed during the disease course, such as bypass surgery and angioplasty, were evaluated. Complications developing during follow-up, including hypertension, heart failure, renal dysfunction, aneurysm formation, and recurrent vascular stenosis after interventional procedures, were documented. In addition, the presence of active arteritis was recorded and defined as vascular wall inflammation detected on PET-CT imaging.

The treatment approach included glucocorticoids, statins, and antiplatelet agents, alongside immunosuppressive therapies. Immunosuppressive regimens included both conventional agents, such as methotrexate (MTX), leflunomide, mycophenolate mofetil, and azathioprine, and biologic agents, including TNF inhibitors and tocilizumab. The decision to initiate biologic therapy was based on refractory disease activity, defined as persistent clinical symptoms, elevated inflammatory markers, and/or radiological progression despite adequate treatment with glucocorticoids and conventional immunosuppressive agents. Biologic agents were considered for patients who experienced disease relapse or an insufficient response to at least one glucocorticoid-sparing immunosuppressive therapy.

Disease Activity Assessment

To quantitatively assess disease activity at presentation, criteria established by the Japanese Research Committee for Intractable Vasculitis were applied,[21] along with the Indian Takayasu Arteritis Activity Score (ITAS-2010).[22] The ITAS score and disease activity score were calculated at the time of diagnosis. To assess the correlation between imaging findings and disease activity, the PET-CT vascular activity score (VAS) was evaluated.[23] Mortality and intensive care unit admissions were recorded.

Subgroup analyses by gender compared age, diagnostic delay, inflammatory markers, disease activity scores, vascular involvement patterns, and treatment approaches. Regarding treatment, patients receiving biologic agents (TNF inhibitors and tocilizumab) were compared with those not receiving biologic agents. Factors associated with the initiation of biologic therapy were analyzed in relation to age, age at disease onset, CRP and ESR levels, disease severity, and PET-CT VAS.

Statistical Analysis

All statistical procedures were carried out using IBM SPSS Statistics version 26.0. Continuous variables were described as either mean ± standard deviation or median with interquartile range, depending on the distribution pattern assessed by the Kolmogorov-Smirnov test. Categorical data were presented as counts and percentages. Comparisons between two independent groups were made using the independent samples t-test for normally distributed variables or the Mann-Whitney U test for non-normally distributed data. For categorical variables, Pearson's chi-square test or Fisher's exact test were applied where appropriate. To identify factors associated with the use of biologic therapy, logistic regression analysis was performed. Variables with a p-value below 0.1 in univariate comparisons were entered into the multivariate model. Results were expressed as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A p-value less than 0.05 was considered statistically significant.

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Tekirdağ Namık Kemal University Ethics Committee (date: 25.03.2025; approval number: 2025.60.03.18). Due to the retrospective design of the study, the requirement for informed consent was waived.

Results

Study Cohort

Among the 40 patients included in the study, 6 (15.0%) were male and 34 (85.0%) were female. The mean age of the cohort was 43.5±13.0. Age at disease onset was significantly higher in males (42.8±10.1) (40-55) compared to females (p=0.048). 27.5% of patients had disease onset after the age of 40. This was significantly more common in males than in females (p=0.038). Mean length of follow-up was 36±12 months. During the follow-up period, two patients (both female) died (Table 1). Comorbidities included hypertension (17.5%), diabetes mellitus (12.5%), CAD and hyperlipidemia (10.0% each), hypothyroidism and Crohn's disease (5.0% each), and, less commonly, breast cancer, psoriasis, ankylosing spondylitis, and hepatitis B virus carrier status (2.5% each).

Clinical Features and Treatment Modalities

Among clinical features, the most frequently reported symptoms were fatigue (45.0%), malaise (40.0%), myalgia (40.0%), and claudication (37.5%). Weight loss and upper

Table 1. Demographic characteristics of Takayasu arteritis patients by gender				
	Male (mean ± SD)	Female (mean ± SD)	Total (mean ± SD)	p-value
Age (years)	47.0±7.9	42.8±13.7	43.5±13.0	0.326
Age at onset (years)	42.8±10.1	32.1±9.7	33.7±10.4	0.048
Age at onset >40 years n (%)	4 (66.7)	7 (20.5)	11 (27.5)	0.038
Diagnostic delay (years)	3.2±1.0	3.6±2.7	3.4±2.0	0.668
Smokers (ever) n (%)	4 (66.7)	12 (35.3)	16 (40)	0.195
P-values <0.05 were considered statistically significant, SD: Standard deviation				

extremity claudication were also relatively common. On physical examination, a decreased radial pulse was the most prominent finding: it was observed in 52.5% of patients and was not detected in any male patient. Blood pressure discrepancy and vascular bruits were present in 52.5% and 40.0% of patients, respectively.

Regarding treatment modalities, all patients received glucocorticoids. The most commonly used immunosuppressive agents were MTX, azathioprine, and leflunomide. Among biologic therapies, infliximab and tocilizumab were the most frequently administered. Antiaggregant therapy was used in 75% of patients. Except for a decreased radial pulse, no significant gender-based differences were observed in the use of treatment modalities or in the frequency of presenting clinical symptoms (Table 2).

Laboratory Findings

In the overall cohort, the mean CRP level was 32.9±23.5 mg/L, and the mean ESR was 44.5±20.8 mm/h. The average disease severity score was 3.1±0.78, while the mean ITAS was 8.45±4.85. In gender based subgroup analysis, female patients had a mean CRP of 32.4±23.0 mg/L and ESR of 46.0±20.9 mm/h, whereas in male patients, these values were 35.5±28.9 mg/L and 36.0±19.7 mm/h. The mean disease severity score was 3.18±0.80 in females and 2.67±0.52 in males, while the mean ITAS was 8.85±5.00 and 6.17±3.31, respectively. No statistically significant differences were observed between genders for CRP (p=0.955), ESR (p=0.256), disease severity (p=0.131), or ITAS scores (p=0.246).

Imaging Findings, Interventions and Complications

Among males, the most common angiographic type was type 1 (33.3%), followed by types 2A, 2B, 4, and 5. No males had type 3. In females, type 1 was also the most frequent (44.1%). In the total cohort, type 1 was the most common (42.5%), followed by types 2B and 5.

At least one vascular stenosis was identified in 85% of patients. Multivessel involvement was relatively common, occurring in 11 patients (27.5%). Based on angiographic findings, the most commonly affected vessels were the bilateral common carotid arteries, the left and right subclavian arteries, the abdominal aorta, and the renal arteries. Aneurysms were detected in 22% of patients. Aneurysms were most frequently located in the aortic arch (n=5), followed by the thoracic descending aorta (n=2) and the abdominal aorta (n=2).

Interventional procedures were performed in a subset of patients, including stenting in 9 patients (22.5%), graft placement in 3 patients (7.5%), and bypass surgery in 2 patients, one undergoing aortofemoral bypass and the other undergoing coronary bypass. All interventions were performed on female patients; no male patients required intervention during follow-up. Complications were mainly observed among female patients. 1 patient underwent embolectomy. Among those who received stents, 2 were placed in the left carotid artery, 2 in the left subclavian artery, 5 in the renal arteries, and 1 in the superior mesenteric artery and abdominal aorta. No histopathological samples were obtained from any of the patients.

PET-CT scan was performed in nearly half of the cohort and arteritis was identified in 47.5% of patients and defined by the presence of vascular wall inflammation on PET-CT imaging. Hypertension was the most common complication. There were no statistically significant gender-based differences in the distribution of vascular involvement (Table 3).

Factors Associated with the Use of Biologic Therapies in the Cohort

Patients who received biologics had significantly higher baseline CRP and ESR values. Disease severity scores were also higher in this group. Moreover, PET-CT VAS were markedly elevated among those receiving biologics. No statistically significant differences were found in age, age at disease onset, or baseline ITAS scores between patients who did and those who did not receive biologic therapy. Multivariable logistic regression analysis showed that none of the variables were statistically significant predictors of biologic therapy use. However, the initial CRP level remained marginally associated with biologic treatment (adjusted OR: 1.05, 95% CI: 0.99-1.10, p=0.087) (Table 4).

Table 2. Gender based comparison of clinical manifestations, physical examination findings and treatment modalities in patients with Takayasu arteritis

	Male, n (%)	Female, n (%)	Total, n (%)	p-value
Clinical features at initial presentation				
Fatigue	1 (16.7)	17 (50.0)	18 (45.0)	0.196
Malaise	1 (16.7)	15 (44.1)	16 (40.0)	0.372
Myalgia	1 (16.7)	15 (44.1)	16 (40)	0.372
Claudication	3 (50.0)	12 (35.3)	15 (37.5)	0.654
Weight loss	0 (0)	15 (44.1)	15 (37.5)	0.067
Upper extremity claudication	1 (16.6)	20 (58.8)	21 (52.5)	0.085
Light headedness	1 (16.7)	11 (32.4)	12 (30)	0.647
Headache	2 (33.3)	9 (26.5)	11 (27.5)	1.000
Chest pain	2 (33.3)	9 (26.5)	11 (27.5)	1.000
Fever	1 (16.7)	9 (26.5)	10 (25)	1.000
Carotidynia	1 (16.7)	8 (23.5)	9 (22.5)	1.000
Abdominal pain	1 (16.7)	8 (23.5)	9 (22.5)	1.000
Raynaud	0 (0)	4 (11.8)	4 (10)	1.000
Lower extremity claudication	0 (0)	3 (8.8)	3 (7.5)	1.000
Night sweats	0 (0)	3 (8.8)	3 (7.5)	1.000
TIA-stroke	0 (0)	3 (8.8)	3 (7.5)	1.000
Amaurosis fugax	0 (0.0%)	2 (5.9)	2 (5.0)	1.000
Dyspnea	1 (16.7)	0 (0)	1 (2.5)	0.150
Physical examination findings				
Decreased radial pulse	0 (0)	21 (61.8)	21 (52.5)	NA
Blood pressure discrepancy	1 (16.7)	20 (58.8)	21 (52.5)	0.085
Bruit	1 (16.7)	15 (44.1)	16 (40.0)	0.372
Cardiac murmur	2 (33.3)	9 (26.5)	11 (27.5)	1.000
Arthritis	0 (0)	3 (8.8)	3 (7.5)	1.000
Treatment modalities				
Glucocorticoids	6 (100)	34 (100)	40 (100)	NA
Statins	3 (50)	10 (29.4)	13 (32.5)	0.603
Antiaggregants	6 (100)	24 (70.6)	30 (75)	0.306
Methotrexate	3 (50)	24 (70.6)	27 (67.5)	0.603
Leflunomid	3 (50)	5 (14.7)	8 (20)	0.150
Tocilizumab	0 (0)	6 (17.6)	6 (15)	1.000
Azathioprine	1 (16.7)	14 (41.2)	15 (37.5)	0.493
Adalimumab	0 (0)	4 (11.7)	4 (10)	1.000
Infliximab	1 (16.7)	11 (32.3)	12 (30)	0.648
Certolizumab	0 (0)	2 (5.8)	2 (5)	1.000
Mycophenolate mofetil	0 (0)	3 (8.8)	3 (7.5)	1.000

P-values <0.05 were considered statistically significant, NA: Not applicable, TIA: Transient ischemic attack

Discussion

This study demonstrates that, in a regional Turkish cohort, patients with TAK exhibit diverse patterns of vascular involvement, while gender does not significantly influence clinical features, treatment strategies, or use of biologic therapy. By integrating an assessment of potential treatment predictors and gender-based comparative analyses of clinical features, it seeks to address a gap in the national literature on TAK.

Regarding demographic characteristics, TAK shows a marked female predominance in the literature, with reported female to male ratios ranging between 5:1 and 14:1[24] and most studies indicating an average ratio of approximately 8-9:1,[25] which is consistent with the 5:1 ratio observed in the present cohort. In this study, the age at disease onset was higher among male patients, a trend also reported in previous studies. For instance, Watanabe et al.[21] observed a median onset age of 43.5 years in

Table 3. Gender based comparison of angiographic findings, interventions and complications in patients with Takayasu arteritis				
	Male n, (%)	**Female n, (%)**	**Total n, (%)**	**p-value**
Angiographic stenosis areas				
Left subclavian artery	3 (50)	10 (29.4)	13 (32)	0.369
Bilateral common carotid arteries	3 (50)	6 (17.6)	9 (22.5)	0.114
Abdominal aorta	0 (0)	5 (14.7)	5 (12.5)	1.000
Renal arteries	0 (0)	6 (17.6)	6 (15)	0.565
Right subclavian artery	0 (0)	4 (11.8)	4 (10)	1.000
Superior mesenteric artery	0 (0)	2 (5.9)	2 (5)	1.000
Bilateral iliac arteries	0 (0)	2 (5.9)	2 (5)	1.000
Descending aorta	1 (16.7)	1 (2.9)	2 (5)	0.280
Left internal carotid artery	1 (16.7)	1 (2.9)	2 (5)	0.280
Aortic arch	1 (16.7)	1 (2.9)	2 (5)	0.280
Bilateral subclavian arteries	0 (0)	2 (5.9)	2 (5)	1.000
Right common carotid artery	0 (0)	1 (2.9)	1 (2.5)	1.000
Brachial artery	0 (0)	1 (2.9)	1 (2.5)	1.000
Ascending aorta	0 (0)	1 (2.9)	1 (2.5)	1.000
Coronary arteries	0 (0)	1 (2.9)	1 (2.5)	1.000
Aneurysm in angiography	2 (33.3)	7 (20.6)	9 (22)	0.601
Patients undergoing PET-CT	5 (83.3)	12 (35.3)	17 (42.5)	0.066
Arteritis	5 (83.3)	14 (41.2)	19 (47.5)	0.080
Interventions				
Patients undergoing intervention	0 (0)	12 (35.3)	12 (30)	NA
Stent placement	0 (0)	9 (26.5)	9 (22.5)	NA
Vascular graft	0 (0)	3 (8.8)	3 (7)	NA
Bypass surgery	0 (0)	2 (5.9)	2 (5)	NA
Complications				
Hypertension	3 (50.0)	10 (29.4)	13 (32.5)	0.369
Aortic insufficiency	0 (0)	4 (11.8)	4 (10)	NA
Heart failure	0 (0)	3 (8.8)	3 (7.5)	NA
Abdominal aortic thrombosis	0 (0)	1 (2.9)	1 (2.5)	NA
Mesenteric ischemia	0 (0)	1 (2.9)	1 (2.5)	NA
Gastrointestinal hemorrhage	0 (0)	1 (2.9)	1 (2.5)	NA
Pulmonary hypertension	0 (0)	1 (2.9)	1 (2.5)	NA
Angina pectoris	0 (0)	2 (5.9)	2 (5)	NA
Renal failure	0 (0)	1 (2.9)	1 (2.5)	NA
Myocardial infraction	0 (0)	1 (2.9)	1 (2.5)	NA
Pericardial effusion	0 (0)	1 (2.9)	1 (2.5)	NA
Lymphadenopathy	0 (0)	1 (2.9)	1 (2.5)	NA
Mortality	0 (0)	2 (5.9)	2 (5)	NA
Intensive care unit admissions	0 (0)	4 (11.8)	4 (10)	NA

P-values <0.05 were considered statistically significant, PET-CT: Positron emission tomography-computed tomography, NA: Not applicable; arteritis was defined as active vascular wall inflammation detected on PET-CT imaging

men compared with 34 years in women, and similar findings were noted by Wan and Wang.[26] The relatively later onset observed in male patients may be influenced by gender-related biological factors, environmental exposures, or differences in healthcare-seeking behavior, although the underlying reasons remain unclear. This finding should be interpreted cautiously due to the insidious and often delayed diagnosis of TAK, which may influence the accuracy of reported symptom onset. Regarding comorbidities, the prevalence of hypertension, dyslipidemia, and diabetes mellitus was broadly comparable to that reported in previous series, such as the Italian cohort, although hypertension was slightly less frequent.[27]

Table 4. Predictive factors for biologic therapy use in patients with Takayasu arteritis				
	Patients receiving biologic therapy	Patients not receiving biologic therapy	p-value	OR and CI
Age (years)	41.7±12.3	44.7±13.6	0.600	0.98 and 0.93-1.03
Initial ITAS score, mean ± SD	10.0±5.34	7.3±4.22	0.113	1.07 and 0.85-1.35
Age at onset (years), mean ± SD	31.5±10.8	35.4±10.0	0.150	0.96 and 0.90-1.03
Initial CRP value, mean ± SD	**48.1±26.8**	21.7±14.3	**<0.001**	1.07 and 1.02-1.12
Initial ESR, mean ± SD	**58.2±22.3**	34.4±17.6	**<0.001**	1.08 and 1.03-1.14
Disease severity score, mean ± SD	**3.41±0.70**	2.87±0.73	**0.019**	2.85 and 1.03-7.89
PET-CT VAS, mean ± SD	3.86±1.40	1.76±1.04	**<0.001**	4.04 and 1.66-9.83

P-values <0.05 were considered statistically significant, CI: Confidence interval, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, ITAS: Indian Takayasu arteritis activity score, PET-CT VAS: Positron emission tomography-computed tomography vascular activity score, SD: Standard deviation, OR: Odds ratio

The clinical presentation of the disease ranges from asymptomatic cases to very severe manifestations. In a cohort from Türkiye, the most common clinical characteristics were constitutional symptoms (84%) and limb claudication (31%), consistent with the most frequently reported clinical features and physical examination findings in the current study. On physical examination, asymmetric blood pressure was observed in 52% of patients, and loss of peripheral pulses was noted in 47%.[28] In a United States study, the most frequently reported symptoms were fatigue and upper-extremity claudication, and the most common physical examination finding was reduced radial pulse; no gender-based differences were reported. In the current study, however, radial pulse loss was detected only among female patients.

Regarding treatment modalities, consistent with current findings, glucocorticoids were the most commonly used treatment (96.5%), followed by immunosuppressive agents, primarily MTX (56%) and azathioprine. Among biologic treatments, infliximab was the most frequently administered, used in 22% of cases.[6] In a large cohort from China, the majority of patients received glucocorticoid therapy (85.9%), and only a small number required immunosuppressive agents due to resistance.[29] These findings suggest that regional differences and access to treatment may influence therapeutic strategies.

In this cohort, the only gender-based difference was a higher frequency of decreased radial pulse in females; there were no differences between genders in presenting symptoms, inflammatory markers, disease severity indices, or vascular involvement. This relatively limited gender-based difference contrasts with larger datasets reporting more pronounced divergence between sexes. The Japanese national registry found that women had a younger age at onset and longer disease duration, whereas men accumulated more complications overall, notably ischemic heart disease, ocular complications, aortic aneurysm, aortic dissection, and renal dysfunction, while women more often had aortic regurgitation.[30] Similarly, the large single center Chinese series showed that men more frequently had iliac and renal artery disease and higher prevalences of systemic hypertension, renal dysfunction, and aortic aneurysm, whereas women had greater involvement of aortic-arch branches, a pattern consistent with upper-extremity ischemia and compatible with current observation of more frequent decreased radial pulse in females.[14,15]

Taken together, these external data, including findings from the Italian cohort, suggest a recurring phenotype of supradiaphragmatic vessel predominance in women and abdominal/lower-extremity vessel predominance with more hemodynamic complications in men.[31] In the current cohort, the most frequent angiographic subtype was type 1. This distribution was consistent across both genders. By contrast, the Korean cohort demonstrated that female patients more commonly exhibited thoracic aorta and branch involvement, corresponding to types I, whereas male patients more frequently had abdominal aorta and branch involvement, reflected by a higher proportion of type IV disease.[13] The absence of parallel, gender-stratified differences in this study may reflect limited power in a single-center sample, shorter or heterogeneous follow-up, and regional or referral-pattern effects. Differences in imaging modalities, timing, and disease-duration structure at enrollment may further attenuate detectable gender-related contrasts in smaller cohorts.

In the present study, higher baseline inflammatory markers, disease severity scores, and PET-CT vascular activity were associated with subsequent biologic therapy use; however, none of these parameters remained independent predictors in multivariable analysis; only baseline CRP showed a borderline association. These findings emphasize the clinical and laboratory disease burden in patients requiring biologics. In contrast, a recent Turkish cohort employing the Combined Arteritis Damage Score (CARDS) demonstrated that imaging-based parameters at diagnosis, particularly the modified CARDS, were independent predictors of biologic treatment requirement.[32] More broadly, the identification of factors predicting the use of biologics in TAK remains largely unexplored. In adult cohorts, available studies have primarily described clinical features, angiographic patterns or treatment responses, but few have systematically analyzed

predictors of biologic therapy, with most reports noting biologics only as rescue treatment for refractory or relapsing disease.[33] Pediatric studies have provided some additional insight; however, data remain limited. Studies from Türkiye have largely emphasized treatment outcomes and safety of biologic agents, with limited investigation into predictors of biologic initiation.[34] Conversely, international data, including the study by Aeschlimann et al.[35], have demonstrated an association between biologic use and baseline disease activity. A recent systematic review emphasized that, even in children, no robust predictors for biologic initiation have been identified, with treatment decisions still largely driven by persistent activity, relapses, or steroid dependence.[36] Thus, both adult and pediatric literature highlight a knowledge gap, underlining the importance of further studies to correlate laboratory and imaging parameters with subsequent biologic requirements.

Study Limitations

This study is subject to several limitations. First, its retrospective single-center design may limit the external validity of the results, particularly given possible geographic and ethnic differences in disease presentation and treatment practices. Second, the small sample size, especially in subgroup analyses by gender and exposure to biologic therapy, may have reduced statistical power. Third, although a broad range of laboratory and imaging data were evaluated, potentially influential variables such as treatment compliance, socioeconomic background, and access to biologic medications were not systematically captured. In addition, variability in follow-up duration among patients may have affected the identification of long-term outcomes and predictors for biologic therapy. Lastly, the multivariable regression did not reveal independent predictors; this may be explained by the limited cohort size and potential collinearity among clinical and imaging parameters. Larger, multicenter, prospective studies with standardized imaging protocols will be essential to confirm and extend these observations.

Conclusion

In this single-center cohort from Western Türkiye, TAK showed a marked female predominance, with women presenting at a younger age but otherwise demonstrating similar clinical, laboratory, and angiographic characteristics and treatment approaches compared with men. The only significant gender-based difference was that female patients had a higher frequency of decreased radial pulse. Higher inflammatory markers, disease severity scores, and PET-CT vascular activity were associated with subsequent use of biologic therapy, although no independent predictors were identified. Overall, the results underscore the need for larger, multicenter, prospective studies integrating standardized imaging and clinical assessments to better define reliable prognostic markers of the requirement for biologic therapy and of gender-related differences in clinical features in TAK.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Tekirdağ Namık Kemal University Ethics Committee (date: 25.03.2025; approval number: 2025.60.03.18).

Informed Consent: Due to the retrospective design of the study, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.B.G., R.M., Concept: D.B.G., R.M., Design: D.B.G., R.M., Data Collection and Processing: D.B.G., Ö.A.S., Analysis or Interpretation: D.B.G., Ö.A.S., Literature Search: D.B.G., Ö.A.S., R.M., Writing: D.B.G.

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References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1-11.
2. Trinidad B, Surmachevska N, Lala V. Takayasu arteritis. StatPearls [Internet]: StatPearls Publishing; 2023.
3. Sanchez-Alvarez C, Crowson CS, Koster MJ, Warrington KJ. Prevalence of Takayasu arteritis: a population-based study. J Rheumatol. 2021;48:952.
4. Rutter M, Bowley J, Lanyon PC, et al. A systematic review and meta-analysis of the incidence rate of Takayasu arteritis. Rheumatology (Oxford). 2021;60:4982-90.
5. Russo RA, Katsicas MM. Takayasu arteritis. Front Pediatr. 2018;6:265.
6. Sanchez-Alvarez C, Mertz LE, Thomas CS, Cochuyt JJ, Abril A. Demographic, clinical, and radiologic characteristics of a cohort of patients with Takayasu arteritis. Am J Med. 2019;132:647-51.
7. Alibaz-Oner F, Direskeneli H. Update on Takayasu's arteritis. Presse Med. 2015;44:e259-e65.
8. Misra DP, Singh K, Rathore U, et al. The effectiveness of tocilizumab and its comparison with tumor necrosis factor alpha inhibitors for Takayasu arteritis: a systematic review and meta-analysis. Autoimmun Rev. 2023;22:103275.
9. Dejaco C, Ramiro S, Bond M, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. Ann Rheum Dis. 2024;83:741-51.
10. de Leeuw K, Bijl M, Jager PL. Additional value of positron emission tomography in diagnosis and follow-up of patients with large vessel vasculitides. Clin Exp Rheumatol. 2004;22:S21-6.

11. de Aguiar MF, Soares AM, de Souza AWS. Vascular interventions in Takayasu arteritis. Current Treatment Options in Rheumatology. 2024;10:25-33.

12. Mont'Alverne AR, Paula LE, Shinjo SK. Features of the onset of Takayasu's arteritis according to gender. Arq Bras Cardiol. 2013;101:359-63.

13. Lim AY, Lee GY, Jang SY, et al. Gender differences in clinical and angiographic findings of patients with Takayasu arteritis. Clin Exp Rheumatol. 2015;33:S-132-7.

14. Zhang Z, Wang W, Zhou M, Lu PYJ, Li Y, Chen Y. An observational study of sex differences in Takayasu arteritis in China: implications for worldwide regional differences. Ann Vasc Surg. 2020;66:309-17.

15. Zhou J, Li J, Wang Y, et al. Age, sex and angiographic type-related phenotypic differences in inpatients with Takayasu arteritis: a 13-year retrospective study at a national referral center in China. Front Cardiovasc Med. 2023;10:1099144.

16. Danda D, Goel R, Joseph G, et al. Clinical course of 602 patients with Takayasu's arteritis: comparison between childhood-onset versus adult onset disease. Rheumatology (Oxford).2021;60:2246-55.

17. de Araujo PC, Donato ANA, Franco AS, Echauri CEI, Shinjo SK. A retrospective cohort study of 203 patients with Takayasu arteritis: experience from a Brazilian tertiary center. Adv Rheumatology. 2025;65:37.

18. Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for eosinophilic granulomatosis with polyangiitis. Ann Rheum Dis. 2022;81:309-14.

19. Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. Ann Rheum Dis. 2022;81:1647-53.

20. Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of Takayasu arteritis: new classification. Int J Cardiol. 1996;54:155-63.

21. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: age and sex specificity. Circulation. 2015;132:1701-9.

22. Misra R, Danda D, Rajappa SM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). Rheumatology (Oxford). 2013;52:1795-801.

23. Galli E, Muratore F, Mancuso P, et al. The role of PET/CT in disease activity assessment in patients with large vessel vasculitis. Rheumatology (Oxford). 2022;61:4809-16.

24. Ureten K, Öztürk MA, Onat AM, et al. Takayasu's arteritis: results of a university hospital of 45 patients in Turkey. Int J Cardiol. 2004;96:259-64.

25. Gudbrandsson B, Molberg Ø, Garen T, Palm Ø. Prevalence, incidence, and disease characteristics of Takayasu arteritis by ethnic background: data from a large, population-based cohort resident in Southern Norway. Arthritis Care Res (Hoboken). 2017;69:278-85.

26. Wan J, Wang T. FRI0376 Comparison of Clinical Characteristics of Patients with Takayasu's Arteritis by Age and Gender. Ann Rheum Dis. 2016;75:570-1.

27. Dammacco F, Cirulli A, Simeone A, et al. Takayasu arteritis: a cohort of Italian patients and recent pathogenetic and therapeutic advances. Clin Exp Med. 2021;21:49-62.

28. Akay T, Harman A, Yücel E, et al. Diagnosis and treatment of takayasu arteritis in turkey: a single center results. Turk J Thorac Cardiovasc Surg. 2015;23.

29. Yang L, Zhang H, Jiang X, et al. Clinical manifestations and longterm outcome for patients with Takayasu arteritis in China. J Rheumatol. 2014;41:2439-46.

30. Shimizu Y, Murohara T. Takayasu arteritis in terms of disease duration and sex differences. Circ J. 2024;88:295-6.

31. Tomelleri A, Campochiaro C, Sartorelli S, et al. Gender differences in clinical presentation and vascular pattern in patients with Takayasu arteritis. Scand J Rheumatol. 2019;48:482-90.

32. Deniz R, Güzelbey T, Tanrikulu M, Bes C. AB1303 does combined arteritis damage score (CARDS) at the diagnosis of Takayasu' arteritis predict the need for biologic therapy? Ann Rheum Dis. 2024;83(Suppl 1):1998-9.

33. Mekinian A, Comarmond C, Resche-Rigon M, et al. Efficacy of biological-targeted treatments in Takayasu arteritis: multicenter, retrospective study of 49 patients. Circulation. 2015;132:1693-700.

34. Sener S, Basaran O, Kaya Akca U, et al. Treatment of childhood-onset Takayasu arteritis: switching between anti-TNF and anti-IL-6 agents. Rheumatology (Oxford). 2022;61:4885-91.

35. Aeschlimann FA, Eng SWM, Sheikh S, et al. Childhood Takayasu arteritis: disease course and response to therapy. Arthritis Res Ther. 2017;19:255.

36. Batu ED, Sener S. A systematic review of anti-TNF and anti-IL-6 treatments for pediatric Takayasu arteritis: addressing a therapeutic dilemma. Pediatric Drugs. 2025;27:563-74.

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Clinical characteristics of treatment-resistant spondyloarthritis patients treated with multiple biologic pathways

Çoklu biyolojik yolakların kullanıldığı tedavi dirençli spondiloartrit hastalarının klinik özellikleri

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Abstract

Objective: With increasing use of biologics targeting multiple pathways in treatment-resistant spondyloarthritis (SpA), understanding patient characteristics has become crucial. This study aims to assess the clinical and demographic characteristics of patients with SpA treated with anti-tumour necrosis factor (TNF) and interleukin (IL)-17/23 inhibitors.

Methods: We retrospectively reviewed 90 SpA patients treated at Gazi University Faculty of Medicine, Rheumatology Clinic between 2018 and 2022 who had received both anti-TNF and IL-17/23 inhibitors. Clinical data, treatment lines, and responses were evaluated using ankylosing spondylitis disease activity scores.

Results: 51% of patients were female, with a mean disease duration of 10.9 years. Of the patients, 76% had axial SpA and 24% had peripheral SpA. Remission rate with IL-17 inhibitors was 79% when used as second-line therapy, but decreased to 35% when used as fourth-line therapy (p=0.044). Patients with comorbid fibromyalgia showed a significantly lower response to treatment.

Conclusion: Our findings indicate that IL-17 inhibitors are more effective when used earlier in the treatment course. Fibromyalgia negatively impacts treatment outcomes, highlighting the importance of differentiating centralized pain from inflammatory disease. Early initiation of IL-17 and careful evaluation for fibromyalgia are recommended.

Keywords: Spondyloarthritis, IL-17 inhibitors, TNF inhibitors, fibromyalgia, biologic DMARDs, treatment resistance

Özet

Amaç: Tedaviye dirençli spondiloartrit (SpA) hastalarında, çoklu biyolojik yolakları hedefleyen tedavi seçeneklerinin artmasıyla birlikte, bu hastaların klinik özelliklerini değerlendirmek önem kazanmıştır. Bu çalışmanın amacı, hem anti-tümör nekrozis faktör (TNF) hem de interlökin (İL)-17/23 inhibitörleriyle tedavi edilen SpA hastalarının demografik, klinik ve tedavi yanıtlarını değerlendirmektir.

Yöntem: Gazi Üniversitesi Tıp Fakültesi, Romatoloji Kliniği'nde, 2018-2022 yılları arasında hem anti-TNF hem de İL-17/23 inhibitörleri kullanmış 90 SpA hastasının verileri retrospektif olarak incelendi. Hastaların klinik verileri, biyolojik tedavi sıraları ve tedavi yanıtları ankilozan spondilit hastalık aktivite skorlarıyla değerlendirildi.

Bulgular: Hastaların %51'i kadın, ortalama hastalık süresi 10.9 yıldı. Hastaların %76'sı aksiyel SpA, %24'ü periferik SpA tanısı aldı. İL-17 inhibitörleri ikinci basamakta kullanıldığında %79 remisyon oranı gözlendi, bu oran dördüncü basamakta %35'e düştü (p=0,044). Fibromiyalji eşlik eden hastalarda biyolojik tedavilere yanıt oranı belirgin olarak düşüktü.

Sonuç: Çalışmamız, İL-17 inhibitörlerinin özellikle erken basamakta daha etkili olduğunu ve fibromiyaljinin tedavi yanıtını olumsuz etkileyebileceğini göstermektedir. Tedavi planlamasında fibromiyalji ayırıcı tanısının dikkatle yapılması ve İL-17 tedavisinin geciktirilmemesi önerilmektedir.

Anahtar Kelimeler: Spondiloartrit, İL-17 inhibitörleri, TNF inhibitörleri, fibromiyalji, biyolojik DMARD'lar, tedavi direnci

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Introduction

Spondyloarthritis (SpA) comprises a group of related but phenotypically distinct inflammatory diseases.[1] SpA is classified into two main categories: axial SpA (AxSpA) and peripheral SpA (pSpA).[1] In patients with AxSpA who do not respond to first-line treatment with non-steroidal anti-inflammatory drugs (NSAIDs), or in those with pSpA who fail conventional disease-modifying antirheumatic drug (DMARD) therapy, a transition to biologic DMARDs is recommended, with tumour necrosis factor inhibitors (TNFi) as the preferred initial option.[2] However, approximately 40% of AxSpA patients have inadequate responses to TNFi treatments.[1]

Treatment failure with biologic DMARDs can be identified through persistent symptoms or physical examination findings, elevated C-reactive protein (CRP) levels, or the presence of inflammatory lesions on magnetic resonance imaging (MRI).[3] Additionally, indices such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS) are commonly used to assess disease activity and clinical response in AxSpA.[4]

Numerous studies have demonstrated the roles of interleukin-23 (IL-23) and IL-17 in SpA pathogenesis, suggesting that targeting the IL-17/IL-23 cytokine pathway could be an effective therapeutic strategy.[1] Secukinumab and ixekizumab, developed as anti-IL-17A monoclonal antibodies, have demonstrated efficacy in the treatment of ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis in clinical trials.[1,5] Ustekinumab, which targets the IL-23 pathway by blocking the p40 subunit shared by IL-12 and IL-23, has proven efficacy in psoriasis and psoriatic arthritis (PsA) and is approved for their treatment.[2,6]

While tumor necrosis factor inhibitors were previously the only approved biologic DMARDs for AxSpA, the development of the first two IL-17 inhibitors, secukinumab and ixekizumab, has expanded therapeutic options, especially for patients unresponsive to TNFi therapy.[7]

In light of these points, the present study aims to comprehensively evaluate the demographic characteristics, clinical findings, treatment histories, comorbidities, acute-phase reactant levels, imaging features, and disease activity scores of patients with SpA treated with biologic therapies targeting different pathways. Furthermore, this study seeks to compare patients who responded to, and those who did not respond to, treatments targeting two distinct pathways-TNFi and IL-17/23 inhibitors.

Materials and Methods

Patient Selection

This single-centre retrospective study reviewed the data of 539 patients aged 18 years or older who were diagnosed with SpA and received biologic DMARD therapy at the Rheumatology Clinic of Gazi University Faculty of Medicine, Department of Internal Medicine, between January 2018 and October 2022.

The inclusion criteria were patients aged 18 years or older who were followed up at the Gazi University Rheumatology Clinic for SpA, had been treated with both anti-TNF agents and IL-17 and/or IL-23 inhibitors, and had received biologic DMARD therapy for at least 12 weeks. Patients with incomplete medical records and those under 18 years of age were excluded from the study. A total of 90 patients who met these inclusion criteria were enrolled in the study.

Data Collection

The following parameters were retrospectively collected: age, sex, diagnosis, date of diagnosis, disease duration, comorbidities, height, weight, body mass index (BMI), exercise history, family history, orthopedic surgery history, presence of concomitant fibromyalgia, history of prior rheumatologic treatments before biologic DMARDs, erythrocyte sedimentation rate (ESR), and CRP values prior to each biologic DMARD initiation, as well as BASDAI, ASDAS-ESR, and ASDAS-CRP scores. Reasons for switching biologic agents (primary or secondary non-response, adverse events, patient or physician preference, or change in administration route) were also recorded.

BMI was calculated as weight divided by height squared (kg/m^2). Patients who had received biologic DMARDs for at least 12 weeks and whose ASDAS-CRP and/or ASDAS-ESR scores were ≥ 2.1 during follow-up were considered to have active disease. Remission was defined as ASDAS <1.3, while scores between 1.3 and 2.1 were classified as low disease activity. These cases were classified as treatment failures, and subsequent changes in therapy were recorded. For each biologic DMARD initiated, ESR, CRP, BASDAI, ASDAS-ESR, and ASDAS-CRP scores were documented.

Statistical Analysis and Ethical Considerations

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22. Categorical variables (qualitative) were expressed as frequencies, and numerical variables (quantitative) were expressed as means ± standard deviations for normally distributed data or medians (interquartile range) for non-normally distributed data. The normality of the distribution was assessed using the Kolmogorov-Smirnov test. Parametric or nonparametric tests were applied as appropriate. For subgroup analyses, the chi-square test was used for categorical variables, and the Bonferroni-adjusted Mann-Whitney U test was employed for numerical variables. A p-value of <0.05 was considered statistically significant.

This study, titled "Clinical characteristics of treatment-resistant SpA patients treated with multiple biologic pathways",

was approved by the Clinical Research Ethics Committee of Gazi University on December 5, 2022, with decision number 883.

Results

Axial SpA, Peripheral SpA, and Sequential Biologic Outcomes

A total of 90 patients with SpA who had received both anti-TNF agents and IL-17 or IL-23 pathway inhibitors were included in the study. Of these patients, 46 (51%) were female. The mean age at diagnosis was 35.0±12.0 years, while the mean age at the last follow-up visit was 46.2±12.3 years. The mean disease duration was 10.9±7.4 years. Among the included patients, 54 (60%) had AS, 19 (21.1%) had PsA, 14 (15.6%) had non-radiographic axSpA, and 3 (3.3%) had enteropathic arthritis. Comorbidities included psoriasis (38 patients, 42.2%), hypertension (19 patients, 21.1%), diabetes mellitus (12 patients, 13.3%), and familial Mediterranean fever (9 patients, 10%). Among patients with psoriasis, only 19 met the CASPAR criteria for psoriatic arthritis, while the remaining patients had psoriasis without articular involvement or paradoxical psoriasis that developed during TNF inhibitor therapy.

Of the 90 patients, 68 (76%) had axSpA, while 22 (24%) had peripheral SpA. Table 1 presents the demographic, clinical, and radiological features and pre-biologic DMARD treatments of patients with axial and peripheral SpA. The median time from diagnosis to the initiation of biologic DMARD therapy was 34 months (12-95 months) for axSpA patients and 42 months (17-96 months) for peripheral SpA patients (p=0.906). The biologic agents used at each treatment step for patients with axSpA and pSpA are summarised in Table 2.

Among the 90 patients who received two lines of biologic DMARDs, 23 (25.6%) achieved remission after second-line therapy. The median disease duration was shorter in patients who achieved remission (median 6 years; range 4-9) than in those who did not (median 12 years; range 6-15) (p=0.009). The median time from diagnosis to initiation of biologic DMARD therapy was similar between patients who achieved remission (31.0 months, range 14.5-81.0 months) and those who did not (40.0 months, range 12.0-115.0 months; p=0.610).

For third-line biologic DMARDs, the median duration of use was 10.1 months (range, 4.0-21.5 months). Of the 67 patients who received a third-line therapy, 21 (31.3%) achieved remission. Among these patients, the median time from diagnosis to biologic DMARD initiation was 28.5 months (12.0-121.5) for those in remission, compared to 48.0 months (11.5-115.0) for those not in remission (p=0.857).

Among the 46 patients who did not achieve remission and who proceeded to fourth-line biologic DMARD therapy, 18 (39.1%) were treated with IL-17 inhibitors (13 with secukinumab and 5 with ixekizumab), 5 (10.9%) with IL-12/23 inhibitors, and 23 (50.0%) with TNFi. The median duration of fourth-line therapy was 6.3 months (3.9-10.5 months). Remission was achieved in 16 patients (34.8%) following fourth-line treatment.

In the fifth line, 30 patients who did not achieve remission received biologic DMARDs, including IL-17 inhibitors (10 patients, 33.3%), IL-12/23 inhibitors (5 patients, 16.7%), and TNFi (15 patients, 50%). Among these, remission was achieved in 15 patients (50%). In the sixth line, 15 patients received biologic DMARDs: IL-17 inhibitors (n=6; 40%), IL-12/23 inhibitors (n=1; 6.7%), and TNFi (n=8; 53.3%). Remission was achieved in eight patients (53.3%) after sixth-line therapy.

Among the 81 patients treated with IL-17 inhibitors, 49 (60.5%) achieved remission. Of these, five patients (6.1%) initiated secukinumab as first-line therapy. As second-line therapy, 24 patients (29.6%) received IL-17 inhibitors, and 19 patients (79%) achieved remission. In the third line, 20 patients (24.7%) received IL-17 inhibitors, of whom 13 (65%) achieved remission. Comparison of remission rates between second- and fourth-line IL-17 inhibitor use showed a higher rate in the second-line group (p=0.044). Detailed comparisons between patients who achieved remission and those who did not while receiving IL-17 inhibitors are shown in Table 3.

Among the 25 patients treated with IL-23 inhibitors, 7 (28%) achieved remission. Of these, one patient received IL-23 inhibitors as second-line therapy, two as third-line therapy, and four in later lines.

Overall, 27 patients (30%) achieved remission on TNFi. Of these, 18 patients achieved remission in later lines (fourth line and beyond), 6 in the third line, and 3 in the second line. Transitions between biologic classes were also recorded to describe treatment sequencing. As shown in Table 4, the most frequent transition occurred from TNF inhibitors to IL-17 inhibitors, followed by transitions from TNF inhibitors to IL-12/23 inhibitors. Reverse transitions and movements between other classes were observed less frequently.

Discussion

The concept of treatment-resistant SpA was acknowledged as an emerging clinical entity, emphasizing its relevance to our study design and future research directions.

Table 1. Demographic and clinical parameters of patients				
	All patients (n=90)	**Axial SpA (n=68)**	**Peripheral SpA (n=22)**	**p***
Age at diagnosis, mean ± SD	35.0±12.0	33.1±11.5	40.8±11.7	0.056
Age at last visit, mean ± SD	46.2±12.3	45.0±12.6	49.7±10.8	0.178
Sex, female, n (%)	46 (51.1)	29 (42.6)	17 (77.3)	0.005
Disease duration, year, mean ± SD	10.9±7.4	11.6±7.8	8.9±5.7	0.356
BMI (kg/m^2), mean ± SD	27.5±6.2	26.9±5.6	29.2±6.7	0.496
Diagnosis, n (%)				
Ankylosing spondilitis	54 (60.0)	54 (79.4)	-	-
Nr-axSpA	14 (15.6)	14 (20.6)	-	-
Psoriatic arthritis	19 (21.1)	-	19 (86.4)	-
Enteropathic SpA	3 (3.3)	-	3 (13.6)	-
History of orthopedic surgery, n (%)	8 (8.9)	7 (10.3)	1 (4.5)	0.405
Fibromyalgia, n (%)	23 (25.6)	19 (27.9)	4 (18.2)	0.362
Exercise, n (%)	24 (26.7)	16 (23.5)	8 (36.4)	0.237
Family history of SpA	23 (25.6)	19 (27.9)	4 (18.2)	0.362
X-ray finding of sacroiliitis (right) n (%)				
Normal-grade 2	49 (54.4)	27 (39.7)	22 (100)	**<0.001**
Grade 3-4	41 (45.6)	41 (60.3)	0 (0)	**<0.001**
X-ray finding of sacroiliitis (left) n (%)				
Normal-grade 2	51 (56.7)	29 (42.6)	22 (100)	**<0.001**
Grade 3-4	39 (43.3)	39 (57.3)	0 (0)	**<0.001**
MRI before biologic treatment, n (%)	n=40			
Ankylosis n (%)	3 (7.5)	3 (8.3)	0 (0)	-
Sclerosis n (%)	11 (27.5)	11 (27.5)	0 (0)	-
Bone marrow edema n (%)	29 (72.5)	29 (72.5)	0 (0)	-
Sacroiliitis n (%)	31 (77.5)	31 (77.5)	0 (0)	-
MRI after biologic treatment, n (%)	n=21			
Ankylosis	2 (9.5)	2 (9.5)	0 (0)	-
Sklerosis	13 (61.9)	13 (61.9)	0 (0)	-
Bone marrow edema	12 (57.1)	12 (57.1)	0 (0))	-
Sacroileitis	12 (57.1)	12 (57.1)	0 (0)	-
Kyphosis, n (%)	29 (32.2)	23 (33.8)	6 (27.3)	0.568
Scoliosis, n (%)	18 (20.0)	14 (20.6)	4 (18.2)	0.806
Syndesmophyte, n (%)	15 (16.7)	14 (20.6)	1 (4.5)	0.079
HLA-B27, n (%)	58 (64.4)	50 (73.5)	8 (36.4)	**0.036**
Enthesitis, n (%)	56 (62.2)	42 (61.8)	14 (63.6)	0.875
Dactylitis, n (%)	18 (20.0)	8 (11.8)	10 (45.5)	**0.001**
Anterior uveitis, n (%)	18 (20.0)	18 (26.5)	0 (0)	**0.007**
Peripheral arthritis, n (%)	60 (66.7)	38 (55.9)	22 (100)	**<0.001**
Kidney findings, n (%)	6 (6.7)	5 (7.4)	1 (4.5)	0.646
Aortic regurgitation, n (%)	6 (6.7)	5 (7.4)	1 (4.5)	0.646
Corticosteroid, n (%)	63 (70.0)	43 (63.2)	20 (90.9)	**0.014**
NSAID, n (%)	82 (91.1)	65 (95.6)	17 (77.3)	**0.029**
Conventional DMARD, n (%)	84 (93.3)	62 (91.2)	22 (100)	0.146
Sulfasalazin, n (%)	70 (77.8)	56 (82.4)	14 (63.6)	0.066
Methotrexate, n (%)	58 (64.4)	39 (57.4)	19 (86.4)	**0.013**
Leflunomide, n (%)	36 (40.0)	19 (27.9)	17 (77.3)	**<0.001**

Comparison results of axial and peripheral spondyloarthritis are provided. BMI: Body mass index, DMARDs: Disease-modifying anti-rheumatic drugs, HLA-B27: Human leukocyte antigen-B27, MRI: Magnetic resonance imaging, nr-axSpA: Non-radiographic axial spondyloarthritis, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation

Table 2. The biologic agents used at each treatment step for axial and peripheral SpA patients					
	Axial SPA	**Peripheral SPA**		**Axial SPA**	**Peripheral SPA**
First line biological DMARD	n=68	n=22	**Fourth line biological DMARD**	n=36	n=10
Adalimumab	29 (42.7)	14 (63.7)	Secukinumab	13 (36.1)	-
Infliximab	12 (17.7)	2 (9.1)	Sertolizumab	9 (25.0)	3 (30.0)
Etanercept	11 (16.2)	2 (9.1)	Golimumab	4 (11.1)	-
Certolizumab	8 (11.8)	2 (9.1)	Infliximab	3 (8.3)	-
Golimumab	4 (5.9)	1 (4.5)	Adalimumab	2 (5.6)	-
Secukinumab	4 (5.9)	1 (4.5)	Etanercept	2 (5.6)	-
Second line biological DMARD	n=68	n=22	Ixekizumab	2 (5.6)	3 (30.0)
Adalimumab	12 (17.6)	2 (9.1)	Ustekinumab	1 (2.7)	4 (40.0)
Etanercept	21 (30.9)	5 (22.8)	**Fifth line biological DMARD**	n=26	n=4
Secukinumab	16 (23.5)	6 (27.3)	Secukinumab	10 (38.5)	-
Certolizumab	7 (10.3)	1 (4.5)	Infliximab	4 (15.4)	-
Golimumab	5 (7.4)	-	Ustekinumab	3 (11.5)	2 (50.0)
Infliximab	5 (7.4)	4 (18.2)	Adalimumab	3 (11.5)	-
Ustekinumab	2 (2.9)	1 (4.5)	Etanercept	3 (11.5)	1 (25.0)
Ixekizumab	-	2 (9.1)	Certolizumab	2 (7.7)	-
Vedolizumab	-	1 (4.5)	Golimumab	1 (3.9)	1 (25.0)
Third line biological DMARD	n=51	n=16	**Sixth line biological DMARD**	n=13	n=2
Secukinumab	17 (33.3)	3 (18.7)	Secukinumab	4 (30.7)	1 (50.0)
Adalimumab	9 (17.6)	3 (18.7)	Adalimumab	2 (15.4)	
Ustekinumab	8 (15.7)	4 (25.0)	Golimumab	2 (15.4)	
Etanercept	6 (11.8)	1 (6.3)	Etanercept	1 (7.7)	
Certolizumab	5 (9.8)	3 (18.7)	Infliximab	1 (7.7)	1 (50.0)
Golimumab	2 (3.9)	-	Ixekizumab	1 (7.7)	
Infliximab	4 (7.9)	1 (6.3)	Certolizumab	1 (7.7)	
Ixekizumab	-	1 (6.3)	Ustekinumab	1 (7.7)	
DMARD: Disease modifying anti-rheumatic drug, SpA: Spondyloarthritis					

Among the 81 patients treated with IL-17 inhibitors, 49 (60.5%) achieved remission, demonstrating the efficacy of IL-17 pathway inhibition in the management of SpA. However, response rates declined with each successive treatment line; remission was significantly higher in the second-line group (79%) than in the fourth-line group (34.8%; p=0.044), underscoring the advantage of earlier IL-17 use. In contrast, patients with coexisting fibromyalgia showed persistently poor treatment responses, regardless of biologic choice, reinforcing the challenge of distinguishing true inflammatory disease activity from centralised pain sensitisation. This highlights the critical need for precision in treatment decisions, as delayed IL-17 initiation and fibromyalgia both emerged as key factors associated with poor remission outcomes.

The introduction of biologic DMARDs in the treatment of SpA has transformed disease management. For patients unresponsive to NSAIDs and conventional DMARDs, treatment guidelines now include options such as anti-TNF agents, IL-17 inhibitors, IL-23 inhibitors, and Janus kinase (JAK) inhibitors. Despite expanding therapeutic options, treatment-resistant patients continue to present a significant management challenge in our clinical practice. With the development of new treatment options for SpA, there has been growing interest in exploring the causes of treatment resistance and optimising treatment strategies. In this study, we examined the characteristics of SpA patients who received biologic therapies targeting multiple pathways and evaluated changes in their treatment regimens.[8]

In our study, patients who achieved remission with a second-line biologic DMARD had a median disease duration of 6 years, compared to 12 years in those who did not achieve remission. Previous studies have shown that patients with shorter disease durations respond more effectively to anti-TNF therapy. For instance, a study involving 1,281 patients divided into groups receiving etanercept, sulfasalazine, or placebo demonstrated that patients with a disease duration of less than 2 years experienced greater improvement in BASFI scores than those with longer disease durations.[9] These findings emphasise the importance of initiating biologic DMARD therapy promptly, particularly in patients with longer disease durations.

Table 3. Comparison results of patients absence and presence of remission with IL-17 inhibitor therapy			
	Absence of remission (n=32)	**Presence of remission (n=49)**	**p**
Age at last visit, mean ± SD	47.7±12.1	45.9±12.6	0.526
Sex, female, n (%)	14 (43.8)	26 (53.1)	0.413
Disease duration, year, median (IQR)	12.0 (7.0-16.0)	8.5 (4.3-14.8)	0.380
Duration between diagnosis and biologic DMARD, month, median (IQR)	35.0 (9.8-106.5)	38.5 (12.8-83.3)	0.807
BMI (kg/m^2), mean ± SD	28.2±5.7	27.8±6.8	0.825
Diagnosis, n (%)			
Ankylosing spondilitis	22 (68.8)	28 (57.1)	0.293
Nr-axSpA	4 (12.5)	10 (20.4)	0.357
Psoriatic arthritis	6 (18.8)	11 (22.4)	0.689
History of orthopedic surgery, n (%)	4 (12.5)	3 (6.1)	0.318
Fibromyalgia, n (%)	13 (40.6)	9 (18.4)	**0.028**
Exercise, n (%)		13 (26,5)	0.878
Family history of SpA	10 (31.3)	12 (24.5)	0.504
X-ray finding of sacroiliitis (right), n (%)			
Normal-grade 2	15 (46.9)	28 (57.1)	0.365
Grade 3-4	17 (53.1)	21 (42.9)	0.365
X-ray finding of sacroiliac joint (left), n (%)			
Normal-grade 2	14 (43.8)	30 (61.2)	0.123
Grade 3-4	18 (56.2)	19 (38.8)	0.123
MRI before biologic treatment, n (%)			
Ankylosis, n (%)	2 (6.3)	1 (2.0)	0.485
Sclerosis, n (%)	7 (21.9)	4 (8.2)	0.200
Bone marrow edema, n (%)	13 (40.6)	14 (28.6)	0.880
Sacroiliitis, n (%)	13 (40.6)	16 (32.7)	0.573
Kyphosis, n (%)	13 (40.6)	11 (22.4)	0.080
Scoliosis, n (%)	5 (15.6)	11 (22.4)	0.451
Syndesmophyte, n (%)	8 (25.0)	5 (10.2)	0.076
HLA-B27, n (%)	23 (71.9)	30 (65.2)	0.535
Enthesitis, n (%)	19 (59.4)	32 (65.3)	0.589
Dactylitis, n (%)	3 (9.4)	12 (24.5)	0.087
Anterior uveitis, n (%)	7 (21.9)	9 (18.4)	0.698
Peripheral arthritis, n (%)	21 (65.6)	31 (63.3)	0.829
Kidney findings, n (%)	3 (9.4)	2 (4.1)	0.333
Aortic regurgitation, n (%)	3 (9.4)	3 (6.1)	0.585
Corticosteroid, n (%)	20 (62.5)	34 (69.4)	0.520
NSAID, n (%)	30 (93.8)	47 (95.9)	0.660
Conventional DMARD, n (%)	28 (87.5)	47 (95.9)	0.157
Sulfasalazin, n (%)	23 (71.9)	40 (81.6)	0.302
Methotrexate, n (%)	22 (68.8)	31 (63.3)	0.612
Leflunomide, n (%)	11 (34.4)	20 (40.8)	0.546
Before first line biologic treatment, median (IQR)	n=32	n=49	
ASDAS-CRP	3.7 (3.1-4.4)	3.8 (3.4-4.3)	1.000
ASDAS-ESR	3.6 (3.1-4.9)	3.9 (3.3-4.3)	0.450
BASDAI	7.9 (5.3-8.3)	6.4 (5.7-6.8)	0.522
Erythrocyte sedimentation rate	27.0 (14.0-41.0)	31.5 (18.0-43.5)	0.766
C-reactive protein	11.0 (7.1-18.7)	15.3 (4.5-27.0)	0.371

Table 3. Continued			
	Absence of remission (n=32)	**Presence of remission (n=49)**	**p**
Before second line biologic treatment, median (IQR)	n=32	n=49	
ASDAS-CRP	3.9 (3.5-4.5)	3.8 (3.2-4.3)	0.929
ASDAS-ESR	3.6 (3.2-4.6)	3.7 (3.1-4.3)	0.737
BASDAI	7.0 (6.6-8.2)	6.0 (5.5-6.4)	**<0.001**
Erythrocyte sedimentation rate	22.0 (10.0-37.0)	29.0 (12.0-52.0)	0.306
C-reactive protein	8.1 (3.0-18.2)	10.1 (3.5-20.8)	0.424
Before third line biologic treatment, median (IQR)	n=32	n=30	
ASDAS-CRP	3.8 (3.2-4.9)	3.9 (3.4-4.2)	1.000
ASDAS-ESR	3.7 (2.9-4.8)	3.9 (3.5-4.1)	0.722
BASDAI	6.2 (5.4-7.0)	6.2 (5.9-7.0)	0.874
Erythrocyte sedimentation rate	24.0 (12.8-33.5)	30.0 (14.0-40.0)	0.480
C-reactive protein	12.0 (3.0-27.0)	9.1 (2.7-20.8)	0.478

ASDAS-CRP: Ankylosing spondylitis disease activity score-C-reactive protein, ASDAS-ESR: Ankylosing spondylitis disease activity score-erythrocyte sedimentation rate, BASDAI: Bath ankylosing spondylitis disease activity index, BMI: Body mass index, CRP: C-reactive protein, DMARDs: Disease-modifying anti-rheumatic drugs, HLA-B27: Human leukocyte antigen-B27, IQR: Interquartile range, MRI: Magnetic resonance imaging, nr-axSpA: Non-radiographic axial spondyloarthritis, NSAIDs: Non-steroidal anti-inflammatory drugs, SD: Standard deviation

Table 4. Distribution of biologic DMARDs in patients with absence and presence of remission with IL-17 inhibitor therapy			
	Absence of remission (n=32)	**Presence of remission (n=49)**	**p**
1st DMARD			
Adalimumab	11 (34.4)	27 (55.1)	0.068
Infliximab	5 (15.6)	8 (16.3)	0.933
Etanercept	7 (21.9)	4 (8.2)	0.078
Certolizumab	3 (9.4)	6 (12.2)	0.688
Golimumab	1 (3.1)	4 (8.2)	0.357
Secukinumab	5 (15.6)	0 (0)	**0.004**
2nd DMARD			
Adalimumab	8 (25.0)	4 (8.2)	**0.037**
Etanercept	8 (25.0)	16 (32.7)	0.461
Secukinumab	5 (15.6)	17 (34.1)	0.059
Certolizumab	5 (15.6)	3 (6.1)	0.161
Golimumab	2 (6.3)	3 (6.1)	0.981
Infliximab	3 (9.4)	3 (6.1)	0.585
Ustekinumab	1(3.1)	1 (2.0)	0.759
Ixekizumab	0 (0)	2 (4.1)	0.247
3rd DMARD	n=32	n=30	
Secukinumab	7 (24.1)	13 (43.3)	0.119
Adalimumab	7 (24.1)	5 (16.7)	0.476
Ustekinumab	10 (21.7)	2 (9.5)	0.226
Etanercept	5 (17.2)	2 (6.7)	0.209
Certolizumab	3 (10.3)	2 (6.7)	0.612
Golimumab	1 (3.4)	0 (0)	-
Infliximab	1 (3.4)	3 (10.0)	0.317
Ustekinumab	4 (13.8)	5 (16.7)	0.759
Ixekizumab	1 (3.4)	0 (0)	-

DMARD: Disease modifying anti-rheumatic drug, IL: Interleukin

In a study evaluating patients with axSpA, secukinumab was used as a first-line therapy in 8% of cases, as a second-line therapy in 15% of cases, and as a third-line or later therapy in 77% of cases.[10] Similarly, in a study involving patients with psoriatic arthritis, secukinumab was used as first-, second-, third-, and fourth-line or beyond treatments in 15%, 17%, 21%, and 47% of patients, respectively.[11] Our findings align with these data, showing that among 81 patients treated with IL-17 inhibitors, 6% used them as first-line therapy, 30% as second-line, 25% as third-line, and 39% as fourth-line or beyond. This dataset shows similar treatment patterns and physician preferences in the management of SpA patients globally.

In addition to individual treatment responses, class-to-class transitions provided further insight into therapeutic sequencing (Table 5). Most patients underwent at least one switch between biologic classes during follow-up, reflecting the complexity of managing treatment-resistant disease. The predominance of transitions from TNFi to IL-17 inhibitors highlights a common pathway of escalation in patients with inadequate TNFi response, whereas reverse transitions and transitions to IL-12/23 inhibitors were less frequent. These patterns underscore the clinical relevance of sequencing decisions and emphasise the need to define optimal transition strategies for refractory SpA more precisely.

When comparing patients who achieved remission with IL-17 inhibitors to patients who did not, we found that fibromyalgia was present in 18.4% of patients in remission, compared with 40.6% of patients not in remission. A meta-analysis revealed that approximately one in six patients with axSpA has fibromyalgia.[12] Similarly, another study reported that 11-34% of SpA patients had coexisting fibromyalgia.[8] In our study, fibromyalgia was present in 25.6% of the included patients. Fibromyalgia is frequently observed in patients with SpA and can complicate the assessment of disease activity and treatment response. Symptoms of fibromyalgia may overlap with those of inflammation, potentially leading to the misclassification of patients as treatment-resistant and to premature, unnecessary changes in therapy.[8,12]

A study of 196 patients demonstrated that fibromyalgia in patients with SpA could impact disease activity and anti-TNF treatment retention rates.[13] In this study, patients with fibromyalgia had higher BASDAI scores than patients without fibromyalgia. Additionally, the average duration of the first anti-TNF therapy was 1.7±2.4 years in patients with fibromyalgia, compared with 3.5±4.0 years in those without the condition. Patients with fibromyalgia were also significantly affected. The study concluded that fibromyalgia is associated with higher disease activity scores, poorer functional indices, shorter treatment retention, and more frequent therapy changes.[13] These findings emphasise the challenge of distinguishing true inflammatory burden from fibromyalgia-driven symptom amplification potentially leading to misguided treatment decisions. Because patients with fibromyalgia tend to have lower response rates to biologic therapies, clinicians must carefully assess whether persistent symptoms stem from active SpA or from centralised pain sensitisation, to avoid unnecessary escalation of therapy.

Our findings and existing literature underscore the importance of assessing fibromyalgia in SpA patients who are candidates for biologic DMARDs, particularly before initiating therapy changes. Addressing fibromyalgia in these patients may improve overall outcomes; however, attributing all symptoms to fibromyalgia and focusing solely on its treatment may delay appropriate care and allow the underlying inflammatory disease to progress. Larger studies are needed to better understand how to manage treatment plans in SpA patients with coexisting fibromyalgia.

A study evaluating treatment retention rates for secukinumab and anti-TNF therapies in SpA patients found that secukinumab retention rates at one year were comparable to those of adalimumab when used as a first- or second-line biologic DMARD, but were significantly lower for secukinumab when used as a third-line or later therapy.[14] Another study showed that biologic therapies used as third-line or later treatments were associated with a higher risk of discontinuation compared to those used as second-line therapies.[15]

In our study, 79% of patients using IL-17 inhibitors in the second line achieved remission, compared to 65% in the third line and 53% in the fourth line or beyond (Supplementary Graph 1). Response rates to IL-17 inhibitors were significantly

Table 5. Class-to-class transitions between biologic treatment pathways in spondyloarthritis patients

From → to*	TNFi	IL-17i	IL-12-23i	Other
TNFi	-	65	24	1
IL-17i	28	-	1	0
IL-12/23i	8	11	-	0
Other	1	0	0	-

*: Transitions represent the number of patients who switched from one biologic class to another at any point during follow-up. IL: Interleukin, TNFi: Tumour necrosis factor inhibitor

higher in the second-line group than in the fourth-line and later groups. However, even in later lines of therapy, more than 50% of patients achieved remission with IL-17 inhibitors, suggesting they remain a viable option in advanced treatment stages. These findings highlight the importance of early use of IL-17 inhibitors; however, even in late stages, IL-17 inhibitors show promising results, according to these data.

Study Limitations

Our study has several limitations. The small sample size, single-centre design, absence of a control group, limited number of JAK inhibitor-treated patients, and retrospective data collection are significant constraints. Additionally, the lack of data on initial dosages and subsequent dose adjustments for biologic DMARDs is another limitation.

The concept of patients resistant to multiple biological pathways, which has emerged with the growing number of biological treatment options for SpA, is relatively new. Future studies are needed to define this concept and investigate clinical and pathogenetic predispositions.

Conclusion

As disease duration increases, treatment response declines, reinforcing the importance of starting biologic DMARD therapy as early as possible. However, significant uncertainties persist regarding treatment-resistant patients. The exact mechanisms underlying their lack of response to biologic DMARDs are not yet fully understood, with potential contributors including genetic factors, immune system dysregulation, and central sensitisation. A deeper understanding of these mechanisms is crucial for developing more targeted and effective treatment strategies for patients with refractory conditions.

Prospective studies with larger patient cohorts and control groups of SpA patients who achieve remission with a single biologic pathway are needed to optimise treatment changes and to better understand the reasons for treatment resistance in these patients.

Ethics

Ethics Committee Approval: This study, titled "Clinical characteristics of treatment-resistant SpA patients treated with multiple biologic pathways", was approved by the Clinical Research Ethics Committee of Gazi University on December 5, 2022, with decision number 883.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.Y., B.Ö., İ.V., R.D., B.G., M.A.Ö., H.K., Concept: G.D.İ., A.E., H.K., Design: İ.Y.Ç., A.E., H.K., Data Collection and Processing: G.D.İ., R.C.K., Analysis or Interpretation: R.C.K., M.A.Ö., H.K., Literature Search: G.D.İ., R.C.K., H.K., Writing: G.D.İ., İ.Y.Ç., A.E.

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References

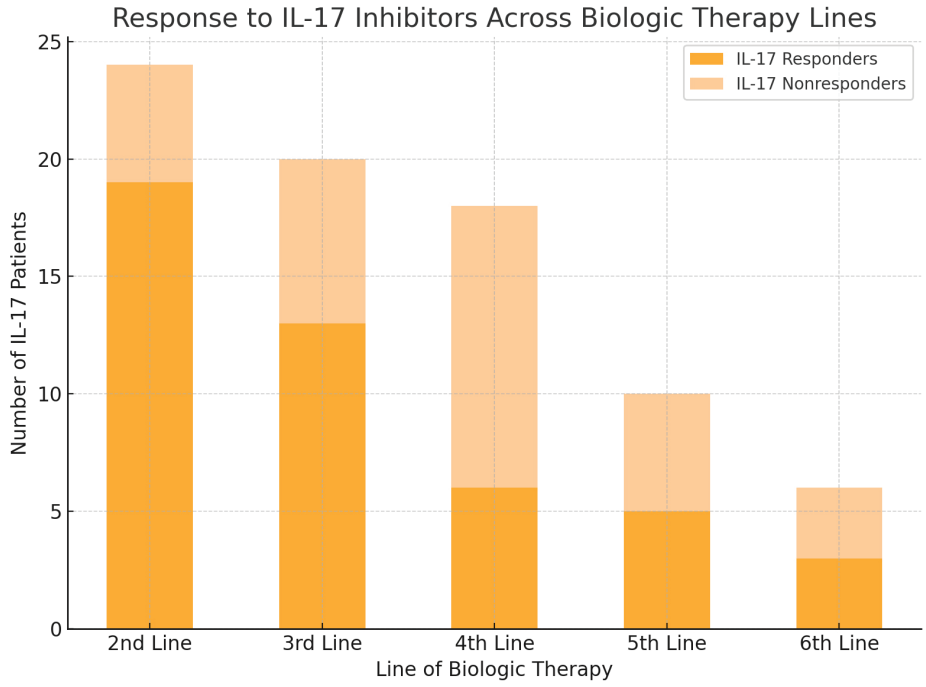
1. Groen SS, Sinkeviciute D, Bay-Jensen AC, et al. Exploring IL-17 in spondyloarthritis for the development of novel treatments and biomarkers. Autoimmun Rev. 2021;20:102760.
2. Cantini F, Niccoli L, Nannini C, et al. Second-line biologic therapy optimisation in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Semin Arthritis Rheum. 2017;47:183-92.
3. Juanola X, Ramos MJM, Belzunegui JM, Fernández-Carballido C, Gratacós J. Treatment failure in axial spondyloarthritis: insights for a standardised definition. Adv Ther. 2022;39:1490-501.
4. Kilic E, Kilic G, Akgul O, Ozgocmen S. Discriminant validity of the ankylosing spondylitis disease activity score (ASDAS) in patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis: a cohort study. Rheumatol Int. 2015;35:981-9.
5. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/ Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Care Res (Hoboken). 2019;71:1285-99.
6. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology (Oxford). 2020;59(Suppl 1):i37-46.
7. Atzeni F, Carriero A, Boccassini L, D'Angelo S. Anti-IL-17 agents in the treatment of axial spondyloarthritis. Immunotargets Ther. 2021;10:141-53.
8. Danve A, Deodhar A. Treatment of axial spondyloarthritis: an update. Nat Rev Rheumatol. 2022;18:205-16.
9. Baraliakos X, Koenig AS, Jones H, Szumski A, Collier D, Bananis E. Predictors of clinical remission under anti-tumor necrosis factor treatment in patients with ankylosing spondylitis: pooled analysis from large randomized clinical trials. J Rheumatol. 2015;42:1418-26.
10. Dougados M, Lucas J, Desfleurs E, et al. Factors associated with the retention of secukinumab in patients with axial spondyloarthritis in real-world practice: results from a retrospective study (FORSYA). RMD Open. 2023;9:e002802.
11. Eviatar T, Zisman D, Gendelman O, et al. Secukinumab real world drug retention compared to TNF-alpha inhibitors in psoriatic arthritis. Clin Exp Rheumatol. 2022;40:15-23.

12. Jones GT, Mallawaarachchi B, Shim J, Lock J, Macfarlane GJ. The prevalence of fibromyalgia in axial spondyloarthritis. Rheumatol Int. 2020;40:1581-91.

13. Bello N, Etcheto A, Béal C, Dougados M, Moltó A. Evaluation of the impact of fibromyalgia in disease activity and treatment effect in spondyloarthritis. Arthritis Res Ther. 2016;18:42.

14. Glintborg B, Lindström U, Giuseppe DD, et al. One-year treatment outcomes of secukinumab versus tumor necrosis factor inhibitors in spondyloarthritis: results from five nordic biologic registries including more than 10,000 treatment courses. Arthritis Care Res (Hoboken). 2022;74:748-58.

15. Min HK, Kim HR, Lee SH, et al. Retention rate and effectiveness of secukinumab vs TNF inhibitor in ankylosing spondylitis patients with prior TNF inhibitor exposure. Rheumatology (Oxford). 2021;60:5743-52.



Supplementary Graph 1. Response to IL-17 inhibitors across biologic therapy lines
IL: Interleukin

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Clinical heterogeneity in childhood-onset systemic lupus erythematosus: Single tertiary center experience

Çocukluk çağı başlangıçlı sistemik lupus eritematozusta klinik heterojenite: Tek üçüncü basamak merkez deneyimi

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Abstract

Objective: To characterize the clinical spectrum, pattern of organ involvement, treatment strategies, and disease severity in patients with childhood-onset systemic lupus erythematosus (cSLE) at a tertiary pediatric rheumatology center.

Methods: This retrospective study included patients <18 years with cSLE diagnosed by Systemic Lupus International Collaborative Clinics criteria and followed between August 2019 and September 2025. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and lupus nephritis was classified according to International Society of Nephrology/Renal Pathology Society criteria.

Results: The age at diagnosis was 13 years [interquartile range (IQR): 11-15]. Mucocutaneous manifestations predominated, with a cutaneous rash present in 29 patients (54.7%). Other common features included non-erosive arthritis (43.4%, n=23), oral ulcers (13.2%, n=7), and alopecia (11.3%, n=6). Renal involvement occurred in 31 patients (58.5%). Renal biopsies were conducted in 25 patients (47.1% of the study population), all of whom had histopathological confirmation of lupus nephritis. The distribution among biopsied patients was as follows: Class II: 11 (20.7%); Class IV: 11 (20.7%); Class I: 2 (3.7%); and Class V: 1 (1.8%). All patients received hydroxychloroquine. Systemic corticosteroids were administered to 50 patients (94.3%). Mycophenolate mofetil was the primary immunosuppressive treatment in 43.4% (n=23) of patients, whereas cyclophosphamide was the primary immunosuppressive treatment in 41.5% (n=22) of patients. Disease activity was high at baseline (median SLEDAI-2K score: 16, IQR: 8-20), but showed a significant improvement by the final assessment (median SLEDAI-2K score: 1.5, IQR: 0-4; p<0.001).

Özet

Amaç: Üçüncü basamak bir pediatrik romatoloji merkezinde çocukluk çağı başlangıçlı sistemik lupus eritematozus (çSLE) hastalarının klinik spektrumunu, organ tutulum paternini, tedavi stratejilerini ve hastalık şiddetini karakterize etmektir.

Yöntem: Bu retrospektif çalışmaya, Sistemik Lupus Uluslararası İşbirliği Klinikleri kriterlerine göre çSLE tanısı almış ve Ağustos 2019 ile Eylül 2025 arasında takip edilen 18 yaş altı hastalar dahil edildi. Hastalık aktivitesi Sistemik Lupus Eritematozus Hastalık Aktivite İndeksi 2000 (SLEDAI-2K) ile değerlendirildi ve lupus nefriti Uluslararası Nefroloji Derneği/Böbrek Patolojisi Derneği kriterlerine göre sınıflandırıldı.

Bulgular: Tanı anındaki ortanca yaş 13 yıldı [çeyreklik aralık (IQR): 11-15]. Mukokutanöz bulgular baskındı ve 29 hastada (%54,7) akut veya subakut kutanöz lupus döküntüsü mevcuttu. Diğer yaygın özellikler arasında eroziv olmayan artrit (%43,4, n=23), oral ülserler (%13,2, n=7) ve alopesi (%11,3, n=6) yer aldı. Takip sırasında 31 hastada (%58,5) böbrek tutulumu meydana geldi. Yirmi beş hastaya (kohortun %47,1'i) böbrek biyopsisi yapıldı ve tüm olgularda histopatolojik olarak lupus nefriti doğrulandı. Biyopsi yapılan hastalar arasındaki dağılım şu şekildeydi: 11'inde Sınıf II (%20,7), 11'inde Sınıf IV (%20,7), 2'sinde Sınıf I (%3,7) ve 1'inde Sınıf V (%1,8). Tüm hastalara (%100) hidroksiklorokin verildi. Elli hastaya (%91,3) sistemik kortikosteroidler uygulandı. Mikofenolat mofetil en sık kullanılan immünosüpresif ajandı (%43,4, n=23), bunu siklofosfamid (%41,5, n=22) izledi. Hastalık aktivitesi başlangıçta yüksekti (ortanca SLEDAI-2K skoru: 16, IQR: 8-20), ancak son değerlendirmede önemli bir iyileşme gösterdi (ortanca SLEDAI-2K: 1,5, IQR: 0-4; p<0,001).

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Abstract

Conclusion: This study emphasizes the heterogeneous presentation of cSLE, with frequent mucocutaneous and musculoskeletal involvement and notable renal and neurological manifestations. Early diagnosis and appropriate therapy are essential for favorable outcomes.

Keywords: Childhood, disease severity, lupus erythematosus, organ involvement

Özet

Sonuç: Bu çalışma, sık görülen mukokutanöz ve kas-iskelet sistemi tutulumu ve belirgin renal ve nörolojik bulgularla birlikte çSLE'nin heterojen bir tablo sergilediğini vurgulamaktadır. Olumlu sonuçlar için erken tanı ve uygun tedavi esastır.

Anahtar Kelimeler: Çocukluk çağı, hastalık şiddeti, lupus eritematozus, organ tutulumu

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by heterogeneous clinical presentations and broad organ involvement. Its pathogenesis involves the deposition of immune complexes and autoantibody-mediated tissue damage. Although it most commonly affects the skin and musculoskeletal system, SLE may involve any organ, including the kidneys, the central nervous system, the heart, and the lungs.[1] Approximately 15% to 20% of all SLE cases are diagnosed in pediatric patients (under 18 years of age), a subgroup formally termed childhood-onset SLE (cSLE). Although the disease usually appears after the first decade of life, it can rarely begin before age 5; findings in this early period require consideration of monogenic forms of SLE.[2,3]

Comparative analyses of adult-onset SLE and cSLE have revealed that different clinical profiles may exist. cSLE is characterized by a significantly higher prevalence of constitutional and mucocutaneous manifestations—including fever, lymphadenopathy, and malar rash—as well as hematological abnormalities, such as cytopenias.[4-6] Furthermore, renal involvement, particularly lupus nephritis, is reported more frequently in cSLE; however, the distribution of histopathological subtypes appears similar to that observed in adults.[7,8] Neuropsychiatric manifestations of SLE (NPSLE) have been reported more commonly in cSLE, although their exact prevalence remains uncertain.[6,9]

The diagnosis of cSLE is established using validated classification systems, including those from the American College of Rheumatology (ACR), the Systemic Lupus International Collaborating Clinics (SLICC), and the European Alliance of Associations for Rheumatology/ACR 2019 criteria.[10-12] Symptoms and age at diagnosis can influence the disease phenotype, organ involvement, and serological characteristics.[13] Advances in diagnostic techniques and increased disease awareness have contributed to improved outcomes compared with earlier reports.[14] Nevertheless, cSLE tends to present with higher disease activity and severity, primarily due to the increased frequency of major organ involvement, such as lupus nephritis.[15] The management of cSLE requires a multidisciplinary approach aimed at controlling disease activity, preventing flares and irreversible organ damage, achieving remission, and minimizing treatment-related adverse effects.[16]

The aim of this study is to present the clinical features, disease activity and severity, and disease management of cSLE patients followed at a tertiary pediatric rheumatology center.

Materials and Methods

This retrospective longitudinal study was conducted at our institution between August 2019 and September 2025 in patients aged <18 years who met SLICC criteria and were followed with a diagnosis of cSLE. Patients with missing data or a follow-up period shorter than 6 months were excluded from the study.

Data were systematically collected on demographic characteristics, clinical findings, and organ system involvement. Recorded laboratory data included hematological parameters (hemoglobin levels, leukocyte counts, and platelet counts) and inflammatory indicators, specifically C-reactive protein and erythrocyte sedimentation rate. The immunological assessment focused on the presence of antinuclear antibodies (ANA), anti–double-stranded DNA (anti-dsDNA), and extractable nuclear antigens (ENA). Additionally, pathological data, particularly renal biopsy results for patients with lupus nephritis, were documented. Disease activity was quantified at diagnosis and at the most recent clinical evaluation using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).[17,18] The histopathological classification of lupus nephritis was conducted in accordance with the International Society of Nephrology/Renal Pathology Society (ISN/RPS) recommendations.[19]

Antiphospholipid antibody (aPL) positivity was defined as the persistent presence of lupus anticoagulant, anticardiolipin [immunoglobulin G (IgG)/immunoglobulin M (IgM)], and/or anti-β2 glycoprotein I (IgG/IgM) antibodies on at least two occasions, measured ≥12 weeks apart. Pediatric antiphospholipid syndrome (APS) was defined according to the revised 2006 Sapporo criteria, which require at least one clinical event (documented arterial, venous, or small-vessel thrombosis) and at least one persistently positive aPL test on two occasions at least 12 weeks apart.[20]

For the assessment of SLE disease activity, remission was categorized as off-treatment or on-treatment. Off-treatment

remission was defined as an SLEDAI-2K score of 0 in the absence of systemic corticosteroids and immunosuppressive therapy, whereas on-treatment remission was defined as an SLEDAI-2K score of 0 with prednisolone ≤5 mg/day and maintenance-dose immunosuppressive therapy. Low disease activity state was defined as an SLEDAI-2K score <4 with prednisolone <7.5 mg/day and maintenance-dose immunosuppressive therapy, whereas high disease activity state was defined as an SLEDAI-2K score >4 with prednisolone >7.5 mg/day and induction-dose immunosuppressive therapy.[21]

At our center, renal biopsy is performed in pediatric SLE patients in the presence of significant proteinuria (including nephrotic-range proteinuria) persistent hematuria, reduced renal function, or rapidly progressive glomerulonephritis. Biopsy is also considered in cases of persistent active lupus nephritis despite therapy or when clinical findings suggest subclinical renal involvement.

The study was approved by University of Health Sciences Türkiye, Ankara Bilkent City Hospital's Ethical Committee (approval number: TABED1-25-1785, date: 22.10.2025) and conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were conducted using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as counts (n) for categorical data and as means, medians, and standard deviations for continuous variables. The Shapiro-Wilk test was employed to assess the normality of data distribution. For group comparisons, independent Student's t-tests were used for normally distributed variables, and Mann-Whitney U tests were used for non-normally distributed variables. Statistical significance was defined as $p<0.05$.

Results

A total of 53 patients diagnosed with cSLE according to the SLICC classification criteria were enrolled in this study. The cohort was predominantly female (n=48, 90.6%), corresponding to a female-to-male ratio of approximately 9:1. The median age at cSLE diagnosis was 13 years (range: 11-15 years), and the median follow-up duration was 26 months (range: 12-48 months) (Table 1).

Mucocutaneous involvement was a common feature, with an acute or subacute cutaneous lupus rash observed in 29 patients (54.7%). Other frequent manifestations included non-erosive arthritis (n=23, 43.4%), oral ulcers (n=7, 13.2%), and alopecia (n=6, 11.3%). All clinical findings and their frequencies are given in Table 1.

Serological profiling revealed a high prevalence of autoantibodies. ANA was detected in 51 (96.2%) of patients, and anti-dsDNA was positive in 43 (81.1%) of patients. Hypocomplementemia, defined by low C3 and/or C4 levels, was observed in 39 (73.6%) of the study population. Antiphospholipid antibodies were present in 11 patients (21.6%), and 8 patients (15.1%) met the criteria for aPL syndrome. Raynaud's phenomenon was noted in two patients (3.7%). A summary of immunological characteristics is presented in Table 1.

Hematological abnormalities were common, with anemia detected in 18 patients (33.9%), lymphopenia in 16 (30.1%), and thrombocytopenia in 5 (9.4%). Pancytopenia was documented in four patients (7.5%).

Renal involvement developed in 31 patients (58.5%) during the follow-up period. A renal biopsy was performed in 25 patients (47.1% of the total cohort); all biopsies confirmed lupus nephritis. Histopathological classification, according to the ISN/RPS 2003 criteria, revealed the following distribution among biopsied cases: Class II in 11 cases (20.7%), Class IV in 11 cases (20.7%), Class I in 2 cases (3.7%), and Class V in 1 case (1.8%).

Neurological involvement was observed in 19 patients (33.9%), with mood changes being the most common manifestation (n=10, 18.2%), followed by seizures (n=3, 5.6%), psychosis (n=2, 3.7%), neuropathy (n=2, 3.7%), mononeuritis multiplex (n=1, 1.8%), and myelitis (n=1, 1.8%).

The cohort exhibited high disease activity at baseline, with a median SLEDAI-2K score of 16 (IQR: 8-20). At the final assessment, a significant reduction was observed, with the median SLEDAI-2K score decreasing to 1.5 (IQR 0-4; $p<0.001$), as detailed in Table 1.

Hydroxychloroquine was universally administered (n=53, 100%). Systemic corticosteroids were used in 50 patients (94.3%). Regarding immunosuppressive agents, mycophenolate mofetil (MMF) was the most frequently prescribed (n=23, 43.4%), followed by cyclophosphamide (n=22, 41.5%). In a subset of eight patients with renal involvement, rituximab was administered following cyclophosphamide treatment. Plasmapheresis was performed in the management of 4 patients (7.5%) (Table 1).

Comorbid conditions, distinct from manifestations attributable to cSLE, were present in 30 patients (56.6%) at the time of diagnosis. The spectrum of documented comorbidities included epilepsy (n=4), delayed puberty or amenorrhea (n=4), hepatitis or cholestasis (n=3), Hashimoto's thyroiditis (n=2), type 1 diabetes mellitus (n=1), and Klippel-Feil syndrome (n=1) (Table 2).

Discussion

This study delineates the clinical, serological, and histopathological profiles of cSLE within a single tertiary pediatric rheumatology referral center. While mucocutaneous and musculoskeletal symptoms were the most prevalent clinical manifestations, renal and neurological complications

were the primary organ systems involved. Within the lupus nephritis subgroup, class II and IV emerged as the predominant histopathological patterns. Furthermore, the substantial decline in initially high SLEDAI-2K scores throughout the follow-up period reflects the efficacy of the administered immunosuppressive regimens in achieving disease stabilization.

cSLE is a multisystem inflammatory disorder marked by pronounced heterogeneity in its clinical presentation. The disease spans a broad clinical spectrum, ranging from relatively mild manifestations to severe, life-threatening organ involvement. Many initial symptoms, including oral ulcers, fever, arthralgia, headache, and weight loss, are non-specific and commonly overlap with other childhood illnesses, complicating early diagnosis. Notably, the incidence of major organ involvement—such as arthritis, nephritis, and neuropsychiatric manifestations—is inversely related to age at disease onset.[22,23] A Turkish cohort study demonstrated that patients with cSLE exhibit an increased prevalence of involvement of the renal, mucocutaneous, hematologic, and neuropsychiatric organ systems, coupled with elevated seropositivity rates for anti-dsDNA and anticardiolipin antibodies.[24] These observations are supported by parallel findings from a Canadian cohort, which reported significantly elevated frequencies of neuropsychiatric and anticardiolipin antibody positivity in patients with cSLE.[25] Furthermore, cross-national epidemiological studies conducted in France and China consistently report that pediatric-onset disease is associated with higher rates of renal and hematologic involvement, as well as overall greater disease severity compared with adult-onset SLE. Collectively, these distinctions not only highlight the critical need for early recognition and intervention in cSLE, but also point to fundamental challenges in applying classification criteria developed primarily for adult populations to pediatric cases.[26,27]

Renal involvement is the most prevalent and serious organ manifestation in cSLE, occurring more frequently than in adult-onset disease. Epidemiological studies report prevalence estimates for lupus nephritis in cSLE ranging from 30% to 75%.[28] A definitive diagnosis requires histopathological confirmation via renal biopsy, a procedure recommended when renal disease is clinically suspected in SLE patients.[29] While immune complex-mediated glomerulonephritis is the most common lesion, the

Table 1. Demographic, clinical, laboratory and disease severity characteristics of patients with childhood lupus erythematosus (n=53)

Variables	
Gender, female (n, %)	48 (90.6%)
Age at diagnosis, (years, min-max)	13 (11-15)
Follow-up period, (months, min-max)	26 (12-48)
Clinical findings (n, %)	
Constitutional symptoms	37 (69.8%)
Cutaneous involvement	29 (54.7%)
Arthritis	23 (43.4%)
Oral ulcer	7 (13.2%)
Alopecia	6 (11.3%)
Serositis	19 (35.8%)
Renal involvement	31 (58.5%)
Neurological involvement	19 (33.9%)
Gastrointestinal involvement	6 (11.3%)
Cardiac involvement	8 (15.1%)
Lung involvement	10 (18.8%)
Antiphospholipid antibody syndrome	8 (15.1%)
Raynaud phenomenon	2 (3.7%)
Laboratory findings (n, %)	
Hypocomplementemia	39 (73.6%)
Direct Coombs positivity	33 (68.8%)
ANA positivity	51 (96.2%)
Anti-dsDNA positivity	43 (81.1%)
Antiphospholipid antibody positivity	11 (21.6%)
Remission status (n, %)	38 (71.7%)
Treatment (n, %)	
Hydroxychloroquine	53 (100%)
Corticosteroids	50 (94.3%)
Mycophenolate mofetil	23 (43.4%)
Cyclophosphamide	22 (41.5%)
Intravenous immunoglobulin	14 (26.4%)
Rituximab	8 (15.1%)
Plasmapheresis	4 (7.5%)
SLEDAI-2K score at diagnosis (median, min-max)	16 (8-20)
Last visit SLEDAI-2K score (median, min-max)	1.5 (0-4)

ANA: Antinuclear antibodies, min-max: Minimum-maximum, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000

Table 2. Comorbidities in childhood lupus erythematosus patients in our cohort

Comorbid diseases	n (%)
Epilepsy	4 (7.5%)
Delayed puberty, amenorrhea	4 (7.5%)
Hepatitis, cholestasis	3 (5.4%)
Hashimoto's thyroiditis	2 (3.7%)
Short stature	2 (3.7%)
Insulin resistance	2 (3.7%)
Obesity	2 (3.7%)
Glial tumor	2 (3.7%)
Precocious puberty	1 (1.8%)
Type 1 diabetes mellitus	1 (1.8%)
Secondary Cushing's syndrome	1 (1.8%)
Psoriasis	1 (1.8%)
Migraine	1 (1.8%)
Asthma	1 (1.8%)
Klippel Feil syndrome	1 (1.8%)

histopathological spectrum also includes tubulointerstitial nephritis, lupus podocytopathy, and various forms of renal vascular injury.[30] Akgun et al.[31] found the incidence of lupus nephritis to be 43.2%. Class IV lupus nephritis, the most common subtype, was the most frequently observed class in our study. In one study, renal involvement was observed in 115 (53.2%) of 216 patients in a cSLE cohort. Lupus nephritis developed in 85 of these patients. Among those who developed nephritis, class IV was the most common.[24] Renal involvement was detected in 31 patients (58.5%) of our cohort. Of these patients, eleven had class II and the remainder had class IV lupus nephritis.

Neuropsychiatric involvement is more frequent and is associated with substantial morbidity in cSLE. The clinical spectrum is highly diverse, encompassing manifestations ranging from headaches and cognitive dysfunction to psychosis and cerebrovascular events. These neuropsychiatric features can serve as the initial presentation of the disease and are often correlated with poorer long-term outcomes. The diagnosis and management of NPSLE remain particularly challenging in the pediatric population.[22] Artim-Esen et al.[24] reported a higher prevalence of neuropsychiatric involvement in the cSLE group (12.1%) and less associated damage than in the adult-onset SLE group. Neuropsychiatric involvement was observed in 19 (35.8%) of the 53 patients in the cohort. The most common diagnosis in this group was mood swings, observed in 10 patients.

Hematologic abnormalities are a common feature of cSLE, with autoimmune cytopenias representing a frequent finding. The spectrum of involvement includes leukopenia, lymphopenia, neutropenia, thrombocytopenia, and anemia. In clinical practice, during the diagnostic evaluation, it is essential to exclude other potential causes of cytopenias, such as nutritional deficiencies, concurrent infections, or medication effects.[22] In two studies published in Türkiye, Artim-Esen et al.[24] reported that the most common hematological abnormality in their cohort was lymphopenia (59.7%), followed by anemia (33.3%), and thrombocytopenia (29.6%). In contrast, Akgun et al.[31], similar to our study, reported that the most common abnormalities were anemia (51.6%), lymphopenia (37.8%), and thrombocytopenia (21.6%), respectively. All patients in the cohort had hematologic involvement. Anemia was the most common (n=18, 33.9%), followed by lymphopenia (n=16, 30.1%) and thrombocytopenia (n=15, 28.3%). Pancytopenia was observed in 4 patients (14.3%).

The presence of antiphospholipid antibodies is associated with hypercoagulability, predisposing patients to thrombosis and thromboembolism. Additionally, systemic manifestations, such as lymphadenopathy and hepatosplenomegaly, may be observed; in severe cases, macrophage activation syndrome, a life-threatening complication can develop.[32] In a previous study of patients tested for antiphospholipid antibodies, positivity for aCL (IgM and/or IgG) was observed in 12% of patients. However, only three of these seropositive patients (3.3% of the total cohort) met the diagnostic criteria for aPL syndrome.[5] While aPL positivity was observed in 11 patients in the cohort, APS was detected in 8 of these patients.

Mucocutaneous involvement is a common clinical feature of cSLE. Cardinal manifestations include photosensitive malar rash, discoid lesions, non-scarring alopecia, and painless oral or nasal ulcers. The recognition of these cutaneous signs is diagnostically crucial, as identifying lupus-specific rashes can facilitate earlier diagnosis and help prevent delays in disease management.[22] In a cohort of 512 patients with cSLE, Zhang et al.[33] identified cutaneous lupus as the most common mucocutaneous manifestation (29.3%), followed by oral ulcers (23.1%) and non-scarring alopecia (19.5%). Cutaneous involvement was observed in 29 patients (54.7%). Oral ulcers were observed in 7 (13.2%) patients, and regional alopecia in 6 (11.3%).

The management of cSLE poses considerable challenges, largely attributable to the marked clinical heterogeneity among patients. Although treatment guidelines from various rheumatology societies are primarily derived from adult studies, they are routinely applied to pediatric cases, including guidelines for lupus nephritis.[34-36] A cornerstone of these recommendations is the universal administration of hydroxychloroquine, unless contraindications exist.[37] Treatment intensity is typically escalated based on organ involvement through the use of corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs), and other immunosuppressive agents. This finding aligns with a UK cohort study that identified MMF as the predominant immunosuppressive agent.[38] A recent study reported that all but one patient used hydroxychloroquine, and the most commonly used DMARD was MMF, accounting for 51.3% of cases.[31] In our study, MMF was the most frequently used DMARD, accounting for 43.3% of cases. For lupus nephritis, specific induction therapy for proliferative disease involves cyclophosphamide or MMF in combination with corticosteroids. Recent guideline updates indicate that belimumab or calcineurin inhibitors added to standard of care may also be considered first-line options, though patient selection criteria remain undefined.[36] Consequently, in the absence of definitive treatment algorithms, institutional experience and center-specific protocols play a decisive role in therapeutic decision-making.

Adherence to established treatment guidelines and the implementation of early, aggressive therapeutic strategies are associated with significant improvements in disease activity metrics. This is evidenced by longitudinal studies; for instance, one Turkish cohort reported a decline in SLEDAI-2K scores from a mean of 22.5±8.1 at diagnosis to a final median of 0. Similarly, a 2021 multinational study of 670 cSLE patients documented a reduction in the mean SLEDAI-2K score from 16.5±8.9 at baseline to 4.6±5.8

at the final assessment.[39,40] The SLEDAI-2K score for patients in the cohort was 16 (8-20) at diagnosis and 1.5 (0-4) at last follow-up.

Study Limitations

Certain limitations of the current study warrant consideration. Primarily, its retrospective nature and the relatively modest sample size may limit the generalizability of the conclusions. As this was a single-center investigation focused on a rare pediatric condition, the distribution of lupus nephritis classes may not fully align with the broader literature, which could affect the generalizability of our results. Conversely, a major strength of this research is the comprehensive documentation of disease activity trajectories and long-term patient outcomes, which are critical for managing a high-morbidity disease such as cSLE.

Conclusion

This study highlights the heterogeneous clinical spectrum of cSLE, characterized by frequent mucocutaneous and musculoskeletal involvement and by significant renal and neurological involvement. Despite high initial disease activity, favorable outcomes were achieved through timely diagnosis and appropriate immunosuppressive therapy. These findings underscore the importance of early diagnosis, close follow-up, and multidisciplinary management in optimizing long-term outcomes in cSLE.

Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Türkiye, Ankara Bilkent City Hospital's Ethical Committee (approval number: TABED1-25-1785, date: 22.10.2025) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.E., U.S.B., B.Ç.A., Concept: Ş.E., U.S.B., B.Ç.A., Design: Ş.E., U.S.B., B.Ç.A., Data Collection and Processing: Ş.E., E.Ö., Ş.E.T., D.Ö., M.I.E., Y.U.E., S.N.Y., N.Ç.P., E.E., Analysis or Interpretation: Ş.E., Z.E.T., Literature Search: Ş.E., N.Ç.P., U.S.B., B.Ç.A., Writing: Ş.E.

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References

1. Tucker LB, Menon S, Schaller JG, Isenberg DA. Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. Br J Rheumatol. 1995;34:866-72.
2. Rodrigues Fonseca A, Felix Rodrigues MC, Sztajnbok FR, Gerardin Poirot Land M, Knupp Feitosa de Oliveira S. Comparison among ACR1997, SLICC and the new EULAR/ACR classification criteria in childhood-onset systemic lupus erythematosus. Adv Rheumatol. 2019;59:20.
3. Batu ED. Monogenic systemic lupus erythematosus: insights in pathophysiology. Rheumatol Int. 2018;38:1763-75.
4. Tirosh I, Spielman S, Barel O, et al. Whole exome sequencing in childhood-onset lupus frequently detects single gene etiologies. Pediatr Rheumatol Online J. 2019;17:52.
5. Sahin S, Adrovic A, Barut K, et al. Juvenile systemic lupus erythematosus in Turkey: demographic, clinical and laboratory features with disease activity and outcome. Lupus. 2018;27:514-9.
6. Livingston B, Bonner A, Pope J. Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. Lupus. 2011;20:1345-55.
7. Tarr T, Dérfalvi B, Győri N, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus. 2015;24:796-803.
8. Tucker LB, Uribe AG, Fernández M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). Lupus. 2008;17:314-22.
9. Mina R, Brunner HI. Pediatric lupus--are there differences in presentation, genetics, response to therapy, and damage accrual compared with adult lupus? Rheum Dis Clin North Am. 2010;36:53-80, vii-viii.
10. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40:1725.
11. 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.
12. Mosca M, Costenbader KH, Johnson SR, et al. Brief report: how do patients with newly diagnosed systemic lupus erythematosus present? A multicenter cohort of early systemic lupus erythematosus to inform the development of new classification criteria. Arthritis Rheumatol. 2019;71:91-8.
13. Ruiz-Irastorza G, Khamashta MA, Castellino G, Hughes GR. Systemic lupus erythematosus. Lancet. 2001;357:1027-32.
14. Lehman TJ, McCurdy DK, Bernstein BH, King KK, Hanson V. Systemic lupus erythematosus in the first decade of life. Pediatrics. 1989;83:235-9.
15. Descloux E, Durieu I, Cochat P, et al. Influence of age at disease onset in the outcome of paediatric systemic lupus erythematosus. Rheumatology (Oxford). 2009;48:779-84.
16. Hollander MC, Sage JM, Greenler AJ, et al. International consensus for provisions of quality-driven care in childhood-onset systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2013;65:1416-23.
17. Silva CA, Aikawa NE, Bonfa E. Updates in the care and management of children and adolescents with systemic lupus erythematosus. Curr Opin Rheumatol. 2024;36(5):315-21.
18. Lai NS, Lu MC, Chang HH, et al. A comparison of the correlation of systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) and systemic lupus erythematosus disease activity score (SLE-DAS) with health-related quality of life. J Clin Med. 2021;10:2137.
19. Groot N, de Graeff N, Marks SD, et al. European evidence-based recommendations for the diagnosis and treatment of childhood-onset lupus nephritis: the SHARE initiative. Ann Rheum Dis. 2017;76:1965-73.

20. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4:295-306.

21. Ugarte-Gil MF, Gamboa-Cárdenas RV, Reátegui-Sokolova C, et al. Better health-related quality of life in systemic lupus erythematosus predicted by low disease activity state/remission: data from the peruvian almenara lupus cohort. Arthritis Care Res (Hoboken). 2020;72:1159-62.

22. Smith EMD, Lythgoe H, Midgley A, Beresford MW, Hedrich CM. Juvenile-onset systemic lupus erythematosus: update on clinical presentation, pathophysiology and treatment options. Clin Immunol. 2019;209:108274.

23. Benseler SM, Silverman ED. Neuropsychiatric involvement in pediatric systemic lupus erythematosus. Lupus. 2007;16:564-71.

24. 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.

25. Kim H, Levy DM, Silverman ED, et al. A comparison between childhood and adult onset systemic lupus erythematosus adjusted for ethnicity from the 1000 Canadian faces of lupus cohort. Rheumatology (Oxford). 2019:kez006.

26. Kachaner A, Mageau A, Timsit JF, Rio J, Papo T, Sacré K. SLE patients with childhood-onset: a nation-wide population-based study. Autoimmun Rev. 2025;24:103802.

27. Gao S, Yu Z, Ma X, et al. Childhood-onset systemic lupus erythematosus in China, 2016-21: a nationwide study. Lancet Child Adolesc Health. 2024;8:762-72.

28. Sousa S, Gonçalves MJ, Inês LS, et al. Clinical features and long-term outcomes of systemic lupus erythematosus: comparative data of childhood, adult and late-onset disease in a national register. Rheumatol Int. 2016;36:955-60.

29. Hahn BH, McMahon MA, Wilkinson A, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64:797-808.

30. Avar-Aydın PÖ, Brunner HI. Revisiting childhood-onset systemic lupus erythematosus. Turk Arch Pediatr. 2024;59:336-44.

31. Akgun O KKG, Demirkan FG, Arik SD, Aktay Ayaz N. Childhood-onset systemic lupus erythematosus: a tertiary pediatric rheumatology center experience. Compreh Med. 2024;16:267-74.

32. Akca UK, Ayaz NA. Comorbidities of antiphospholipid syndrome and systemic lupus erythematosus in children. Curr Rheumatol Rep. 2020;22:21.

33. Zhang Y, Shen T, Gao S, et al. Validation and optimization of classification criteria for childhood-onset systemic lupus erythematosus in a multi-center Chinese cohort. Front Immunol. 2025;16:1611349.

34. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79:713-23.

35. Groot N, de Graeff N, Avcin T, et al. European evidence-based recommendations for diagnosis and treatment of childhood-onset systemic lupus erythematosus: the SHARE initiative. Ann Rheum Dis. 2017;76:1788-96.

36. Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the management of LUPUS NEPHRITIS. Kidney Int. 2024;105:S1-S69.

37. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019;78:736-45.

38. Smith EMD, Egbivwie N, Jorgensen AL, et al. Real world treatment of juvenile-onset systemic lupus erythematosus: data from the UK JSLE cohort study. Clin Immunol. 2022;239:109028.

39. Balci S, Ekinci RMK, Bayazit AK, et al. Juvenile systemic lupus erythematosus: a single-center experience from southern Turkey. Clin Rheumatol. 2019;38:1459-68.

40. Pitta AC, Silva CA, Insfrán CE, et al; Brazilian Childhood-onset Systemic Lupus Erythematosus Group. The new 2019-EULAR/ACR classification criteria specific domains at diagnosis can predict damage accrual in 670 childhood-onset systemic lupus erythematosus patients. Lupus. 2021;30:2286-91.

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Cardiac MRI patterns in cardiac amyloidosis vs. non-amyloid inflammatory and fibrotic cardiac involvement: A single-center pilot study

Kardiyak amiloidoz ile non-amiloid enflamatuvar ve fibrotik kardiyak tutulumda kardiyak MRG paternleri: Tek merkezli pilot çalışma

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Abstract

Objective: Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy that various non-amyloid inflammatory and fibrotic cardiac diseases with overlapping clinical features can mimic. This study aims to compare cardiac magnetic resonance imaging (CMR) patterns between these conditions to identify imaging features that facilitate accurate differential diagnosis.

Methods: This single-center, retrospective, pilot comparative study included 27 patients who underwent CMR between December 2021 and November 2025. Fourteen patients had confirmed CA and 13 patients had non-amyloid inflammatory or fibrotic cardiac involvement, including cardiac sarcoidosis, connective tissue disease-related cardiac involvement, inflammatory myocarditis, systemic sclerosis, and endocardial fibroelastosis. All CMR examinations were performed on a 1.5-T magnetic resonance imaging system using a standardized protocol. Imaging parameters included left ventricular wall thickness, atrial size, presence of pericardial or pleural effusion, late gadolinium enhancement (LGE) patterns, and myocardial edema on T2-weighted imaging. Groups were compared using appropriate parametric or non-parametric statistical tests, as applicable.

Results: Patients with CA were older than the non-amyloid group (51.7±13.8 vs. 36.6±13.4 years, p=0.008). Biatrial dilatation was more frequent in CA (71.4% vs. 15.4%, p=0.006), whereas pericardial and pleural effusions were more common in the non-amyloid group (61.5% vs. 14.3%, p=0.018; and 53.8% vs. 14.3%, p=0.046, respectively). Diffuse subendocardial LGE was strongly associated with CA (64.3% vs. 0%, p<0.001). In contrast, the non-amyloid group more frequently demonstrated transmural (84.6% vs. 21.4%, p=0.002), patchy (61.5% vs. 7.1%, p=0.004), mid-myocardial (76.9% vs. 14.3%, p=0.002), and subepicardial LGE patterns (84.6% vs. 0%, p<0.001). Myocardial edema on T2 mapping was observed only in the non-amyloid group (30.8% vs. 0%, p=0.041).

Conclusion: CMR reveals distinct and reproducible imaging patterns that enable differentiation of CA from non-amyloid inflammatory and fibrotic cardiac diseases. A pattern-based CMR approach may improve diagnostic confidence and support disease-specific clinical management, even in small, real-world cohorts.

Keywords: Cardiac amyloidosis, cardiac magnetic resonance, differential diagnosis, inflammatory cardiomyopathy, late gadolinium enhancement

Özet

Amaç: Kardiyak amiloidoz (KA), çeşitli non-amiloid enflamatuvar ve fibrotik kardiyak hastalıkların benzer klinik özelliklerle taklit edebildiği infiltratif bir kardiyomiyopatidir. Bu çalışmada, bu durumlar arasında ayırıcı tanıyı kolaylaştırabilecek görüntüleme bulgularını belirlemek amacıyla kardiyak manyetik rezonans görüntüleme (KMR) paternlerinin karşılaştırılması amaçlandı.

Yöntem: Bu tek merkezli, retrospektif, pilot karşılaştırmalı çalışmaya Aralık 2021-Kasım 2025 tarihleri arasında KMR yapılan 27 hasta dahil edildi. On dört hastada KA tanısı doğrulanmıştı; 13 hastada ise kardiyak sarkoidoz, bağ dokusu hastalığı ilişkili kardiyak tutulum, enflamatuvar miyokardit, sistemik skleroz ve endokardiyal fibroelastozisi içeren non-amiloid enflamatuvar/fibrotik kardiyak tutulum mevcuttu. Tüm KMR incelemeleri 1,5-T cihazda standart protokol ile gerçekleştirildi. Sol ventrikül duvar kalınlığı, atriyal boyutlar, perikardiyal/plevral efüzyon varlığı, geç gadolinyum tutulumu (LGE) paternleri ve T2 ağırlıklı görüntülerde miyokardiyal ödem değerlendirildi. Gruplar uygun parametrik veya non-parametrik testlerle karşılaştırıldı.

Bulgular: KA grubundaki hastalar non-amiloid gruba göre daha yaşlıydı (51,7±13,8 vs. 36,6±13,4 yıl; p=0,008). Biatriyal dilatasyon KA grubunda daha sıktı (%71,4 vs. %15,4; p=0,006). Buna karşılık perikardiyal ve plevral efüzyon non-amiloid grupta daha sık izlendi (%61,5 vs. %14,3; p=0,018 ve %53,8 vs. %14,3; p=0,046). Diffüz subendokardiyal LGE, KA ile güçlü ilişki gösterdi (%64,3 vs. %0; p<0,001). Non-amiloid grupta ise transmural (%84,6 vs. %21,4; p=0,002), yamalı/patchy (%61,5 vs. %7,1; p=0,004), mid-miyokardiyal (%76,9 vs. %14,3; p=0,002) ve subepikardiyal LGE paternleri (%84,6 vs. %0; p<0,001) daha sık görüldü. T2 mapping ile miyokardiyal ödem yalnızca non-amiloid grupta saptandı (%30,8 vs. %0; p=0,041).

Sonuç: KMR, KA'yı non-amiloid enflamatuvar ve fibrotik kardiyak hastalıklardan ayırt etmeye yardımcı olan belirgin ve tekrarlanabilir görüntüleme paternleri ortaya koymaktadır. Patern temelli KMR değerlendirmesi, küçük ve gerçek yaşam kohortlarında dahi tanısal güveni artırabilir ve hastalığa özgü klinik yönetimi destekleyebilir.

Anahtar Kelimeler: Kardiyak amiloidoz, kardiyak manyetik rezonans, ayırıcı tanı, enflamatuvar kardiyomiyopati, geç gadolinyum tutulumu

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Introduction

Cardiac amyloidosis (CA) is an infiltrative cardiomyopathy characterized by extracellular deposition of misfolded amyloid fibrils within the myocardial interstitium, leading to progressive myocardial stiffening, restrictive physiology, heart failure, and a poor prognosis.[1-3] Because clinical presentation is often nonspecific and overlaps with other causes of myocardial thickening, CA may remain underrecognized, particularly in early disease. Timely identification has become increasingly important with the availability of disease-modifying therapies, especially for transthyretin-related amyloid cardiomyopathy.[4,5]

In rheumatology practice, systemic inflammatory diseases may involve the myocardium through inflammation and/or fibrosis and can mimic infiltrative phenotypes on imaging. CA, inflammatory myocarditis in systemic lupus erythematosus (SLE), rheumatoid arthritis-related myocardial involvement, systemic sclerosis, and rare fibrotic entities may present with heart failure symptoms and arrhythmias and may show myocardial enhancement on cardiac magnetic resonance (CMR).[6-9] Although these conditions can share overlapping clinical and imaging findings, their pathophysiology differs fundamentally from amyloid deposition, and this difference is expected to translate into distinct tissue characterization profiles on CMR.

CMR enables comprehensive non-invasive evaluation of myocardial morphology and tissue characterization. In particular, the distribution of late gadolinium enhancement (LGE), assessment of myocardial edema (including T2 mapping), and associated morphological features may provide practical clues for differential diagnosis in real-world clinical settings.[8,10-12] However, direct comparative data contrasting CA with a spectrum of non-amyloid inflammatory and fibrotic myocardial involvement remain limited.

The objective of this single-center pilot study was to compare CMR patterns in patients with CA and those with non-amyloid inflammatory or fibrotic cardiac involvement, and to identify imaging features, particularly LGE distribution, myocardial edema on T2 mapping, and relevant morphological findings, that facilitate accurate differential diagnosis.

Materials and Methods

Study Design and Setting

This was a single-center, retrospective, pilot comparative study conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (approved number: 07-2025/377, date: 18.12.2025). Informed consent was waived due to the retrospective design and use of anonymized data.

Study Population and Group Definitions

Consecutive patients who underwent CMR for suspected infiltrative or inflammatory cardiac disease between December 2021 and November 2025 were identified from the institutional imaging archive and electronic medical record system. Patients were included if they had diagnostic-quality CMR and a confirmed diagnosis of either CA or non-amyloid inflammatory/fibrotic cardiac involvement based on clinical evaluation and supporting diagnostic investigations.

Cardiac Amyloidosis Group

The CA group included patients with a confirmed diagnosis of CA (n=14) established by cardiology/hematology assessment using disease-specific criteria supported by clinical, laboratory, and imaging findings (and histopathology when available).

Non-amyloid Inflammatory/Fibrotic Group

The comparison group included patients with inflammatory or fibrotic myocardial involvement unrelated to amyloid deposition (n=13), comprising cardiac sarcoidosis (n=5), rheumatoid arthritis-related cardiac involvement (n=3), SLE-associated myocarditis (n=3), systemic sclerosis (n=1), and endocardial fibroelastosis (n=1). Given the limited number of patients within each diagnosis, subgroup analyses were reported descriptively.

Exclusion Criteria

Patients were excluded if CMR image quality was non-diagnostic (e.g., severe motion artifacts), key clinical/imaging data were unavailable, or the examination was incomplete for tissue characterization.

CMR Acquisition

All CMR examinations were performed on a 1.5-T system (Achieva; Philips Healthcare, Best, the Netherlands) using a standardized institutional protocol. The protocol included:

(i) cine steady-state free precession (SSFP) sequences acquired in standard long-axis and contiguous short-axis planes for assessment of cardiac morphology and ventricular function;

(ii) T1-weighted imaging;

(iii) T2 mapping for evaluation of myocardial edema, when clinically indicated; and

(iv) LGE imaging.

A gadolinium-based contrast agent was administered intravenously at a dose of 0.1 mmol/kg. LGE images were acquired 10-15 minutes after contrast administration using phase-sensitive inversion recovery sequences.

Image Analysis

All CMR images were independently reviewed by two radiologists experienced in cardiac imaging, who were blinded to clinical diagnoses and laboratory data. Final interpretations were reached by consensus.

The following parameters were systematically assessed:

- Maximum left ventricular wall thickness,
- Left and right atrial size (presence of biatrial dilatation),
- Presence of pericardial and/or pleural effusion,
- Presence and distribution of LGE,
- Evidence of myocardial edema on T2-weighted imaging (present/absent).

LGE Pattern Classification

LGE distribution was classified by visual assessment according to the predominant location within the myocardial wall and the extent of involvement. Enhancement was categorized as subendocardial, mid-myocardial, subepicardial, or transmural when it predominantly involved the corresponding myocardial layer. A pattern was considered diffuse when enhancement involved multiple segments in a circumferential or widespread manner, whereas patchy enhancement referred to focal or multifocal non-contiguous areas of LGE. LGE patterns were not mutually exclusive, and more than one pattern could be present in the same patient.

Outcome Measures

The primary imaging discriminator was the presence of diffuse subendocardial LGE, considered characteristic of CA. Secondary imaging features included biatrial dilatation, pericardial/pleural effusion, alternative LGE patterns (transmural, mid-myocardial, subepicardial, patchy), and myocardial edema on T2 mapping.

Statistical Analysis

Distributional assumptions for continuous variables were assessed using the Shapiro-Wilk test. Continuous variables are reported as mean ± standard deviation when approximately normally distributed and compared using the Welch t-test; otherwise, they are presented as median (interquartile range) and compared using the Mann-Whitney U test. Categorical variables are summarized as n (%) and compared using Fisher's exact test. A two-sided $p<0.05$ was considered statistically significant. Given the pilot design, analyses were exploratory and no adjustment for multiple comparisons was applied.

Sample Size and Power Analysis

This study was retrospective, and the sample size was determined by the number of eligible patients undergoing CMR during the study period (December 2021-November 2025). A post-hoc power analysis was performed for the primary imaging discriminator, diffuse subendocardial LGE, using the observed proportions in the CA and non-amyloid groups (9/14 vs. 0/13). Assuming a two-sided $\alpha=0.05$, the achieved power to detect this difference was 0.998. In a conservative sensitivity analysis assuming a 10% prevalence of diffuse subendocardial LGE in the non-amyloid group, the achieved power was 0.885. Given the pilot design, other comparisons were considered exploratory.

Results

Study Population

A total of 27 patients were included in the final analysis: 14 with CA and 13 with non-amyloid inflammatory/fibrotic cardiac involvement. Within the non-amyloid group, diagnoses included cardiac sarcoidosis [5/13 (38.5%)], rheumatoid arthritis-related cardiac involvement [3/13 (23.1%)], SLE-associated myocarditis [3/13 (3.1%)], systemic sclerosis [1/13 (7.7%)], and endocardial fibroelastosis [1/13 (7.7%)].

Baseline Demographic and Clinical Characteristics

Baseline characteristics are summarized in Table 1. Patients with CA were older than those in the non-amyloid group (51.7±13.8 vs. 36.6±13.4 years, p=0.008). Sex distribution and the prevalence of hypertension and diabetes mellitus were similar between groups (all $p>0.05$). Pericardial and pleural effusions were more frequent in the non-amyloid group [pericardial effusion: 2/14 (14.3%) vs. 8/13 (61.5%), p=0.018; pleural effusion: 2/14 (14.3%) vs. 7/13 (53.8%), p=0.046].

CMR Morphological and Functional Findings

CMR morphological and functional parameters are presented in Table 2. Maximum left ventricle wall thickness, LV end-diastolic

Table 1. Baseline demographic and clinical characteristics of patients with cardiac amyloidosis and non-amyloid inflammatory/fibrotic cardiac involvement

Variable	Cardiac amyloidosis (n=14)	Non-amyloid inflammatory/fibrotic group (n=13)	p-value
Age, years (mean ± standard deviation)	51.7±13.8	36.6±13.4	**0.019**
Sex (male), n (%)	4 (28.6)	5 (38.5)	0.695
Hypertension, n (%)	7 (50.0)	5 (38.5)	0.704
Diabetes mellitus, n (%)	4 (28.6)	4 (30.8)	1.000
Pericardial effusion, n (%)	2 (14.3)	8 (61.5)	**0.018**
Pleural effusion, n (%)	2 (14.3)	7 (53.8)	**0.046**

Values are presented as mean ± standard deviation or number (percentage), as appropriate. Continuous variables were compared using the Welch t-test. Categorical variables were compared using Fisher's exact test (two-sided). A two-sided $p<0.05$ was considered statistically significant

volume (LVEDV), and LVEF did not differ significantly between groups (all p>0.05). Biatrial dilatation was more common in the CA group [10/14 (71.4%) vs. 2/13 (15.4%), p=0.006]. Right ventricle involvement was numerically more frequent in CA, but this difference did not reach statistical significance [5/14 (35.7%) vs. 1/13 (7.7%), p=0.165].

LGE Tissue Characterization Patterns

LGE distribution patterns differed significantly between groups (Table 2). CA was strongly associated with diffuse subendocardial LGE [9/14 (64.3%) vs. 0/13 (0%), p<0.001]. In contrast, the non-amyloid group more frequently demonstrated transmural [11/13 (84.6%) vs. 3/14 (21.4%), p=0.002], patchy [8/13 (61.5%) vs. 1/14 (7.1%), p=0.004], mid-myocardial [10/13 (76.9%) vs. 2/14 (14.3%), p=0.002], and subepicardial LGE [11/13 (84.6%) vs. 0/14 (0%), p<0.001]. Representative examples are shown in Figures 1, 2.

Myocardial Edema

Myocardial edema on T2 mapping was observed only in the non-amyloid group [0/14 (0%) vs. 4/13 (30.8%), p=0.041] (Table 2).

Descriptive Subgroup Findings

Given the limited number of patients within individual non-amyloid subgroups, analyses for specific diagnoses were descriptive. Cardiac sarcoidosis cases typically demonstrated patchy mid-myocardial and/or subepicardial LGE with associated myocardial edema. Rheumatoid arthritis-related and SLE-associated cases showed inflammatory enhancement patterns without the diffuse subendocardial LGE pattern characteristic of CA. Endocardial fibroelastosis was characterized by predominant endocardial involvement. In the non-amyloid cohort, transmural-appearing LGE was observed in 6/13 (46.2%) patients, contributed

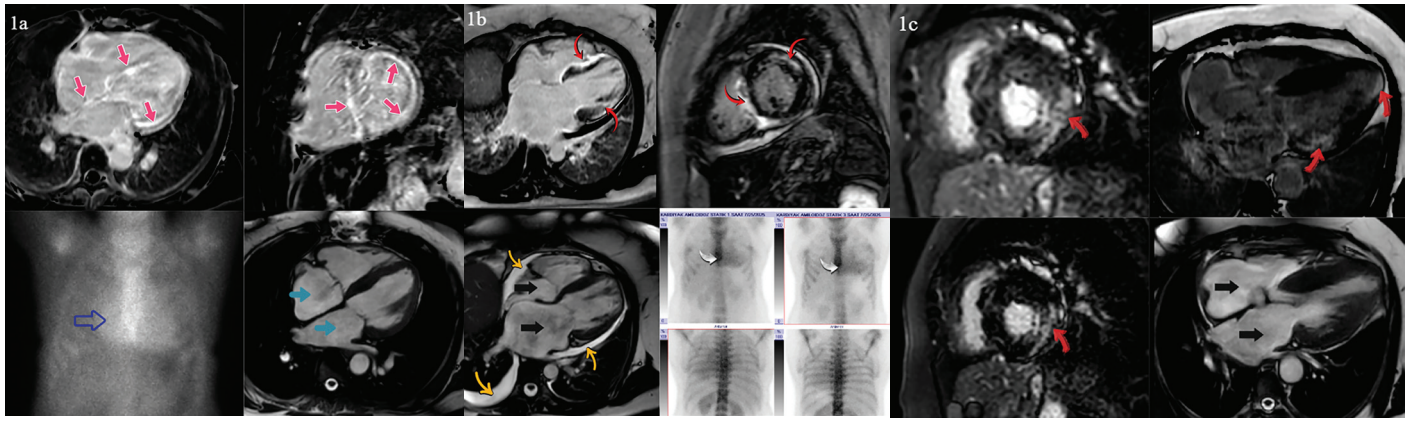

Figure 1. Representative CMR imaging LGE and bone scintigraphy findings in two patients with cardiac amyloidosis showing diffuse subendocardial enhancement and increased myocardial radiotracer uptake, (1a) In a 58-year-old woman, LGE images show diffuse subendocardial enhancement (pink arrows). Biatrial enlargement is also present (green arrows), and bone scintigraphy demonstrates increased myocardial radiotracer uptake (blue arrow), (1b) In a 62-year-old man patient, LGE demonstrates an atypical distribution with subendocardial, mid-myocardial, and subepicardial involvement (red arrows). Biatrial enlargement (black arrows) and pleural/pericardial effusions (yellow arrows) are noted. Bone scintigraphy again shows increased cardiac radiotracer uptake (white arrows), supporting the diagnosis of cardiac amyloidosis, (1c) In a 58-year-old woman with cardiac amyloidosis, LGE images demonstrate a predominantly subendocardial enhancement pattern (red arrows). Marked biatrial enlargement is also present (black arrows)

CMR: Cardic magnetic resonance, LGE: Late gadolinium enhancement

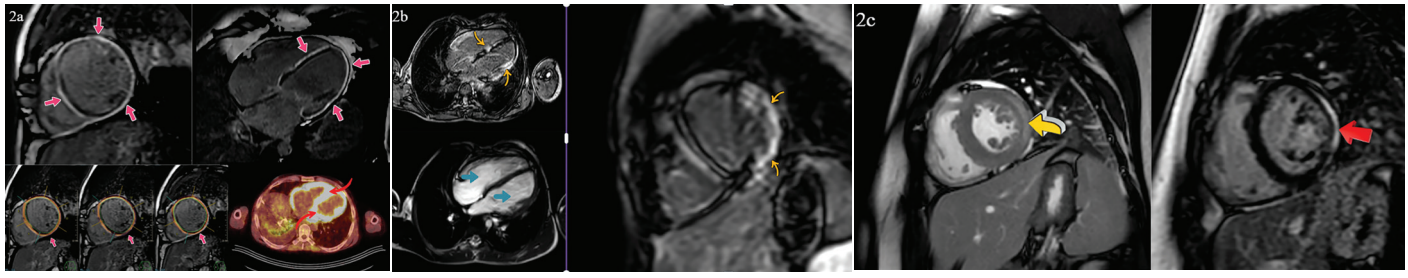

Figure 2. Representative CMR imaging patterns across non-amyloid inflammatory/fibrotic diagnoses (sarcoidosis, endocardial fibroelastosis, and systemic lupus erythematosus-associated myocarditis), highlighting subepicardial/mid-myocardial enhancement and edema on T2 mapping, (2a) In a 44-year-old man with cardiac sarcoidosis, late gadolinium enhancement images demonstrate diffuse subepicardial enhancement (pink arrows). Corresponding positron emission tomography/computed tomography shows increased myocardial fluorodeoxyglucose uptake (red arrow), consistent with active inflammatory involvement, (2b) In a 15-year-old boy with endocardial fibroelastosis, late gadolinium enhancement images show diffuse transmural and subepicardial enhancement (yellow arrows). Cine imaging demonstrates cardiomegaly (green arrow), (2c) In a 34-year-old woman with systemic lupus erythematosus, T2-weighted imaging demonstrates mid-myocardial edema in the lateral wall (yellow arrow), with corresponding LGE images (red arrow), consistent with myocarditis

CMR: Cardic magnetic resonance, LGE: Late gadolinium enhancement

mainly by cardiac sarcoidosis [2/5 (40.0%)], rheumatoid arthritis-related involvement [1/3 (33.3%)], SLE-associated myocarditis [1/3 (33.3%)], systemic sclerosis [1/1 (100%)], and endocardial fibroelastosis [1/1 (100%)]. Figure 2 provides representative CMR examples of characteristic patterns across disease categories.

Overall, CA and non-amyloid inflammatory/fibrotic cardiac diseases demonstrated distinct CMR patterns, particularly with respect to LGE distribution, atrial involvement, and the presence of myocardial edema, supporting the utility of CMR as a non-invasive tool for differentiating amyloid-related myocardial infiltration from inflammatory and fibrotic cardiac processes.

Discussion

In this single-center pilot study, we demonstrated that CMR reveals distinct and reproducible myocardial involvement patterns that enable differentiation between CA and non-amyloid inflammatory or fibrotic cardiac diseases. Despite overlapping clinical presentations and the shared classification of these entities as infiltrative cardiac conditions, their underlying pathophysiological mechanisms translated into markedly different CMR phenotypes.

The most important finding of our study was the strong association between CA and diffuse subendocardial LGE. This pattern is widely recognized as a hallmark of amyloid infiltration and reflects expansion of the extracellular space due to amyloid deposition.[1-3] Previous studies have reported that diffuse subendocardial LGE is highly suggestive of CA and correlates with disease burden and prognosis.[13] In our cohort, diffuse subendocardial LGE was observed exclusively in the CA group, whereas transmural LGE was more frequently encountered in the non-amyloid inflammatory/fibrotic group, underscoring the importance of interpreting LGE distribution together with edema and the overall clinical context.

Although transmural enhancement is often discussed in the context of advanced infiltrative disease, extensive inflammatory injury and fibrotic remodeling may also yield transmural-appearing LGE, particularly in severe or widespread myocarditis-like involvement and in fibrotic endocardial disorders. In our non-amyloid cohort, transmural LGE frequently co-occurred with subepicardial or patchy enhancement and with edema on T2 mapping, supporting an inflammatory/fibrotic mechanism rather than amyloid deposition. Therefore, we emphasize that differentiation should be based on a pattern-based interpretation, integrating LGE distribution, edema assessment, and associated morphological findings, rather than relying on a single LGE descriptor.[6-8]

In contrast, the non-amyloid group—including cardiac sarcoidosis, connective tissue disease-related myocardial involvement, inflammatory myocarditis, systemic sclerosis, and endocardial fibroelastosis—more commonly demonstrates patchy, mid-myocardial, and/or subepicardial LGE distributions, frequently accompanied by myocardial edema on T2-based imaging. This pattern aligns with prior CMR studies of inflammatory cardiomyopathies, in which immune-mediated myocardial injury typically results in focal or regional fibrosis and edema rather than diffuse extracellular infiltration.[7,8,14] Notably, cardiac sarcoidosis often shows heterogeneous enhancement patterns consistent with granulomatous inflammation and scarring, with common involvement of the basal septum and lateral wall.[10,15]

Table 2. CMR morphological and tissue characterization findings in cardiac amyloidosis versus non-amyloid inflammatory/fibrotic cardiac involvement, including LGE pattern distribution and T2 mapping-based edema

Variable	Cardiac amyloidosis (n=14)	Non-amyloid inflammatory/fibrotic group (n=13)	p-value
Morphological/functional findings			
Max LV wall thickness, mm	18.9	17.4	**0.410**
LV hypertrophy pattern (concentric), n (%)	10 (71.4)	7 (53.8)	**0.440**
LV end-diastolic volume (LVEDV), mL	105	88	**0.215**
LVEF, %	44	38	0.240
Biatrial dilatation (yes), n (%)	10 (71.4)	2 (15.4)	**0.006**
RV involvement (RV wall thickening and/or RV LGE), n (%)	5 (35.7)	1 (7.7)	0.165
Diffuse subendocardial LGE, n (%)	9 (64.3)	0 (0.0)	**<0.001**
Transmural LGE, n (%)	3 (21.4)	11 (84.6)	**0.002**
Patchy LGE, n (%)	1 (7.1)	8 (61.5)	**0.004**
Mid-myocardial LGE, n (%)	2 (14.3)	10 (76.9)	**0.002**
Subepicardial LGE, n (%)	0 (0.0)	11 (84.6)	**<0.001**
Myocardial edema on T2 (present), n (%)	0 (0.0)	4 (30.8)	**0.041**

Values are presented as n (%) or mean, as appropriate. Categorical variables were compared using Fisher's exact test (two-sided). Continuous variables were compared using [t-test/Mann-Whitney U] depending on distribution. LGE patterns were not mutually exclusive; more than one LGE pattern could be present in the same patient, LGE: Late gadolinium enhancement, RV: Right ventricle, CMR: Cardiac magnetic resonance imaging, LVEF: Left ventricular ejection fraction

The presence of myocardial edema emerged as another important discriminating feature. In our cohort, edema was largely absent in CA but commonly detected in inflammatory myocardial diseases, especially sarcoidosis and lupus-associated myocarditis. This observation aligns with existing literature emphasizing the value of T2-based imaging for identifying active myocardial inflammation.[12,16] The absence of edema in amyloidosis reflects the chronic, non-inflammatory nature of amyloid deposition and further supports the role of multiparametric CMR in differential diagnosis.

Morphological differences also contributed to diagnostic separation. Biatrial dilatation was significantly more common in CA, consistent with restrictive physiology and elevated filling pressures.[17,18] In our cohort, pericardial and pleural effusions were more frequently observed in the non-amyloid inflammatory/fibrotic group, which may reflect active inflammation and serosal involvement in systemic inflammatory diseases. Although effusions are non-specific, they can provide a supportive context when interpreted alongside LGE distribution and edema assessment.[11]

Our results support the concept that CMR pattern recognition, rather than reliance on a single imaging feature, offers the greatest diagnostic value in complex infiltrative and inflammatory cardiac diseases. While advanced techniques such as T1 mapping and extracellular volume (ECV) quantification have further improved tissue characterization in recent years,[19-21] our study demonstrates that even conventional CMR parameters, particularly LGE distribution and edema assessment, can provide meaningful diagnostic discrimination in routine clinical practice.

Study Limitations

Several limitations should be acknowledged. First, the retrospective single-center design is inherently subject to selection bias and limits causal inference. Second, the small sample size reduces statistical power; therefore, our analyses should be interpreted as exploratory and hypothesis-generating. Third, the non-amyloid comparator cohort was heterogeneous, intentionally reflecting real-world inflammatory and fibrotic myocardial involvement; however, this heterogeneity precluded robust subgroup-level statistical comparisons, which were reported descriptively. Fourth, there was an age imbalance between groups, which may have acted as a potential confounder and could influence myocardial remodeling and comorbidity profiles. Finally, although T2 mapping was available for edema assessment, advanced parametric mapping for diffuse myocardial characterization (e.g., native T1 mapping and ECV quantification) was not routinely performed, and LGE was evaluated visually without quantitative scar burden measurement. Larger prospective studies incorporating comprehensive multiparametric mapping and quantitative LGE assessment are warranted to validate and refine these findings.

Despite these limitations, our findings have important clinical implications. Early and accurate differentiation between CA and inflammatory or fibrotic myocardial disease is essential because management strategies diverge substantially. From a rheumatology perspective, systemic inflammatory disorders including autoinflammatory conditions may involve the myocardium and present with overlapping clinical features, underscoring the need for careful cardiac evaluation in inflammatory disease contexts.[22] In this setting, a pattern-based CMR approach can help identify inflammatory involvement while prompting targeted evaluation for CA when appropriate. This distinction is clinically critical, as disease-modifying therapies are now available for transthyretin amyloidosis, whereas inflammatory conditions often require immunosuppression and targeted arrhythmia management.[4,6,23] Misclassification may delay appropriate treatment and adversely affect outcomes.

Conclusion

This pilot study demonstrates that CMR provides distinct and complementary imaging patterns that facilitate differentiation of CA from non-amyloid inflammatory and fibrotic cardiac involvement. Recognition of characteristic LGE distribution, assessment of myocardial edema (including T2 mapping), and evaluation of associated morphological features can enhance diagnostic confidence and support disease-specific management. Larger prospective studies incorporating comprehensive multiparametric tissue characterization and quantitative assessment are warranted to further validate and refine these findings.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (approved number: 07-2025/377, date: 18.12.2025).

Informed Consent: Informed consent was waived due to the retrospective design and use of anonymized data.

Footnotes

Authorship Contributions

Concept: G.T., Design: G.T., A.A., Data Collection and Processing: G.T., A.A., Analysis and Interpretation: G.T., A.A., Literature Search: A.A., Writing: G.T.

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References

1. Falk RH, Alexander KM, Liao R, Dorbala S. AL (light-chain) amyloidosis: cardiac involvement and treatment. J Am Coll Cardiol. 2016;68:1323-41.
2. Banypersad SM, Moon JC, Whelan C, Hawkins PN, Wechalekar AD. Updates in cardiac amyloidosis: a review. J Am Heart Assoc. 2012;1:e000364.
3. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2005;111:186-93.
4. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med. 2018;379:1007-16.
5. Fontana M, Pica S, Reant P, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2015;132:1570-9.
6. Birnie DH, Nery PB, Ha AC, Beanlands RS. Cardiac sarcoidosis. J Am Coll Cardiol. 2016;68:411-21.
7. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol. 2009;53:1475-87.
8. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 2018;72:3158-76.
9. Tzelepis GE, Kelekis NL, Plastiras SC, Mitseas P, Economopoulos N, Moyssakis I. Pattern and distribution of myocardial fibrosis in systemic sclerosis: a delayed enhanced MRI study. Arthritis Rheum. 2007;56:3827-36.
10. Patel MR, Cawley PJ, Heitner JF, et al. Detection of myocardial damage in patients with sarcoidosis. Circulation. 2009;120:1969-77.
11. Syed IS, Glockner JF, Feng D, et al. Role of cardiac magnetic resonance imaging in the detection of cardiac amyloidosis. J Am Coll Cardiol Img. 2010;3:155-64.
12. Abdel-Aty H, Zagrosek A, Schulz-Menger J, et al. Delayed enhancement and T2-weighted cardiovascular magnetic resonance imaging differentiate acute from chronic myocardial infarction. Circulation. 2004;109:2411-6.
13. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis. J Am Coll Cardiol. 2008;51:1022-30.
14. Lurz P, Eitel I, Adam J, et al. Diagnostic performance of CMR imaging compared with EMB in patients with suspected myocarditis. J Am Coll Cardiol. 2012;59:755-63.
15. Greulich S, Deluigi CC, Gloekler S, et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. J Am Coll Cardiol Img. 2013;6:501-11.
16. Ferreira VM, Piechnik SK, Dall'Armellina E, et al. Native T1 mapping detects the location, extent and patterns of acute myocarditis. J Cardiovasc Magn Reson. 2014;16:36.
17. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. Clin Med (Lond). 2018;18(Suppl 2):s30-5.
18. Banypersad SM, Sado DM, Flett AS, et al. Quantification of myocardial extracellular volume fraction in systemic amyloidosis. J Am Coll Cardiol Img. 2013;6:34-9.
19. Karamitsos TD, Piechnik SK, Banypersad SM, et al. Noncontrast T1 mapping for the diagnosis of cardiac amyloidosis. J Am Coll Cardiol Img. 2013;6:488-97.
20. Fontana M, Banypersad SM, Treibel TA, et al. Native T1 mapping in transthyretin amyloidosis. J Am Coll Cardiol Img. 2014;7:157-65.
21. Moon JC, Messroghli DR, Kellman P, et al. Myocardial T1 mapping and extracellular volume quantification. J Cardiovasc Magn Reson. 2013;15:92.
22. Gunay Y, Karagozlu F, Gemici S, et al. Examination of cardiac functions during acute attack and remission period in children with familial Mediterranean fever. Eur J Pediatr. 2024;183:3137-45.
23. Gilstrap LG, Dominici F, Wang Y, et al. Epidemiology of cardiac amyloidosis-associated heart failure hospitalizations. Circulation. 2019;140(2):170-80.

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Clinical and radiological outcomes of sacroiliac joint ankylosis in radiographic axial spondyloarthritis

Radyografik aksiyel spondiloartritte sakroiliak eklem ankilozunun klinik ve radyolojik sonuçları

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Abstract

Objective: To compare the clinical, functional, and radiological features of patients with radiographic axial spondyloarthritis (r-AxSpA) according to the presence of sacroiliac joint (SIJ) ankylosis.

Methods: This retrospective study included 290 patients fulfilling the modified New York criteria for ankylosing spondylitis. SIJ ankylosis was defined on pelvic radiographs as unilateral or bilateral grade 4 sacroiliitis. Patients with unilateral and bilateral ankylosis were initially analysed together as the overall ankylosis group and compared with patients without ankylosis; subsequently, a separate subgroup analysis was performed focusing exclusively on patients with bilateral ankylosis. Clinical, functional, radiographic, and treatment-related characteristics were compared between groups.

Results: Among 290 patients, 30 (10.3%) had unilateral and 101 (34.8%) had bilateral sacroiliac ankylosis. Compared with patients without ankylosis, patients with sacroiliac ankylosis showed a male predominance, longer symptom and disease duration, and higher rates of smoking, alcohol consumption, hip involvement, sacral enthesitis, and syndesmophytes. Human leukocyte antigen B27 positivity was increased in patients with sacroiliac ankylosis overall but was not significantly associated in the bilateral ankylosis group. Symptom and disease duration were positively correlated with Bath Ankylosing Spondylitis Metrology Index and modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), whereas spinal mobility measures were negatively correlated, with stronger associations observed in the bilateral ankylosis group. In multivariable models, total mSASSS and hip involvement were independently associated with bilateral sacroiliac ankylosis.

Conclusion: SIJ ankylosis, particularly when bilateral, is associated with more extensive structural damage and impaired spinal mobility in r-AxSpA.

Keywords: Radiographic axial spondyloarthritis, sacroiliac joint ankylosis, structural damage, spinal mobility, BASMI, mSASSS

Özet

Amaç: Radyografik aksiyel spondiloartrit (r-AxSpA) hastalarında sakroiliak eklem (SİE) ankilozu varlığına göre klinik, fonksiyonel ve radyolojik özellikleri karşılaştırmaktır.

Yöntem: Bu retrospektif çalışmaya, modifiye New York kriterlerine göre ankilozan spondilit tanısı almış 290 hasta dahil edildi. SİE ankilozu, pelvis grafilerinde unilateral veya bilateral evre 4 sakroiliit olarak tanımlandı. Unilateral ve bilateral ankilozu olan hastalar başlangıçta birlikte değerlendirilerek ankilozu olmayan hastalarla karşılaştırıldı; ardından yalnızca bilateral ankilozu olan hastalara yönelik alt grup analizi yapıldı. Klinik, fonksiyonel, radyografik ve tedaviye ilişkin özellikler gruplar arasında karşılaştırıldı. Spinal Mobilite Bath Ankilozan Spondilit Metrologi İndeksi (BASMI) ile, yapısal hasar ise modifiye Stoke Ankilozan Spondilit Omurga Skoru (mSASSS) kullanılarak değerlendirildi.

Bulgular: Hastaların 30'unda (%10,3) unilateral, 101'inde (%34,8) bilateral sakroiliak ankiloz saptandı. Sakroiliak ankilozu olan hastalarda (unilateral veya bilateral, n=131) erkek cinsiyet predominansı, daha uzun semptom ve hastalık süresi ile sigara ve alkol kullanımı, kalça tutulumu, sakral entezit ve sindesmofit sıklığı daha yüksekti. İnsan lökosit antijeni B27 pozitifliği genel olarak ankiloz grubunda daha yüksek olmakla birlikte, bilateral ankiloz ile anlamlı bir ilişki göstermedi. Semptom ve hastalık süresi BASMI ve mSASSS ile pozitif korelasyon gösterirken, spinal mobilite ölçümleri negatif korelasyon gösterdi; bu ilişkiler bilateral ankiloz grubunda daha belirgindi. Çok değişkenli analizlerde toplam mSASSS ve kalça tutulumu, sakroiliak ankiloz ile bağımsız olarak ilişkili bulundu.

Sonuç: SİE ankilozu, özellikle bilateral olduğunda, r-AxSpA'da daha yaygın yapısal hasar ve belirgin spinal mobilite kısıtlılığı ile ilişkilidir.

Anahtar Kelimeler: Radyografik aksiyel spondiloartrit, sakroiliak eklem ankilozu, yapısal hasar, spinal mobilite, BASMI, mSASSS

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Introduction

Radiographic axial spondyloarthritis (r-AxSpA) is a chronic inflammatory rheumatic disease characterized by inflammation of the sacroiliac joints (SIJs) and spine, leading to new bone formation, ankylosis, and progressive loss of mobility.[1] The SIJs are the earliest and most characteristic sites of involvement, and radiographic sacroiliitis remains central to the diagnosis of ankylosing spondylitis (AS), as established in the modified New York (mNY) criteria.[2]

Structural damage in r-AxSpA has been widely evaluated using scoring methods such as the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), which quantifies vertebral changes in the cervical and lumbar spine.[3] Radiographic progression, especially syndesmophyte formation, is one of the strongest determinants of functional decline and reduced spinal mobility in axSpA, as demonstrated in large prospective cohorts.[4,5] However, while spinal damage has been extensively studied, the implications of SIJ ankylosis itself remain less well explored.

SIJ ankylosis, defined as complete fusion of the joint, represents a late and irreversible stage of sacroiliitis. Although some studies suggest that SIJ damage is associated with disease severity and functional impairment, its independent contribution compared with spinal changes is not fully understood.[5]

In addition, a recent multicentre study from the TReasure cohort reported that advanced structural phenotypes such as bamboo spine were independently associated with male sex, higher body mass index (BMI), hip arthritis, and entheseal involvement.[6] These findings highlight the complex interplay between pelvic structural damage and spinal new bone formation, further supporting the need to understand the specific clinical implications of SIJ ankylosis. Furthermore, little is known about how unilateral versus bilateral SIJ ankylosis differentially impacts structural damage, clinical features, and treatment patterns in AS.

Given the central role of the SIJs in disease initiation and progression, clarifying the clinical, functional, and radiological implications of SIJ ankylosis may provide important insights for disease monitoring and risk stratification. Therefore, this study aimed to compare the demographic, clinical, functional, and radiological characteristics of r-AxSpA patients with and without sacroiliac ankylosis, with particular attention to bilateral involvement.

Materials and Methods

This retrospective cross-sectional study included patients diagnosed with AS according to the mNY criteria.[2] Medical records from three tertiary rheumatology centers were systematically reviewed between January 2025 and April 2025. Pelvic and spinal radiographs were generally obtained during the same clinical visit as part of routine care. Only patients with both pelvic and spinal radiographs acquired within the preceding 12 months were included; when obtained at different visits, the interval did not exceed 12 months. Patients with incomplete radiographic or clinical data were excluded. A total of 290 patients with complete datasets were included in the final analysis.

Radiographic Assessment

SIJ ankylosis was defined radiographically as unilateral or bilateral grade 4 sacroiliitis on conventional pelvic radiographs, in accordance with the mNY criteria.[2] Any ankylosis was defined as grade 4 involvement in at least one SIJ (unilateral or bilateral total ankylosis), and bilateral total ankylosis required grade 4 sacroiliitis in both joints. According to the mNY criteria, grade 3 sacroiliitis was characterized by erosions, sclerosis, joint space widening or narrowing, or partial ankylosis, and grade 4 indicated total ankylosis. Sacroiliitis was assessed separately for the right and left SIJs; patients with a maximum sacroiliitis grade of 3 across both joints were classified in the without ankylosis group and were not included in any ankylosis group. Two primary comparisons were performed: (1) patients with any ankylosis (unilateral or bilateral) versus those without ankylosis, and (2) patients with bilateral ankylosis versus those without ankylosis, excluding unilateral cases.

Spinal structural damage was evaluated using the mSASSS, which assesses vertebral squaring, erosions, syndesmophytes, and ankylosis in the cervical and lumbar regions (3). Hip involvement was graded according to the Bath Ankylosing Spondylitis Radiology Index for the hip (BASRI-hip), providing a standardized measure of radiographic damage.[7] A BASRI-hip score ≥2 was considered indicative of hip involvement. Total hip replacement was also recorded and classified as hip involvement. Additional radiographic features, including pubic symphysis involvement and sacral enthesitis, were also documented based on expert radiological review. Pubic symphysis involvement (symphysitis) was defined as the presence of subchondral sclerosis, erosions, joint-space irregularity or partial/complete ankylosis of the symphysis pubis on anteroposterior pelvic radiographs. Sacral enthesitis was defined as cortical irregularity, erosions, subchondral sclerosis or bony proliferation at the sacral entheseal sites visible on pelvic radiographs.

All radiographs were independently evaluated by two rheumatologists (GA and HC) with expertise in axSpA imaging, who worked in a tertiary referral spondyloarthritis clinic with regular exposure to the assessment of SIJ and spinal radiographs. Intra-rater reliability was excellent [intraclass correlation coefficient (ICC)=0.83 and 0.88], and inter-rater reliability was similarly high (ICC=0.85), demonstrating robust consistency in both SIJ grading and mSASSS scoring.

Clinical and Functional Assessments

Collected data included age, sex, BMI, symptom duration, disease duration, human leukocyte antigen B27 (HLA-B27) status, smoking and alcohol use, and the presence of comorbidities. Extra-articular manifestations, including uveitis, inflammatory bowel disease (IBD), and psoriasis, were recorded, along with peripheral features such as enthesitis, peripheral arthritis, and dactylitis.

Treatment history was assessed, including prior and current use of non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (DMARDs); methotrexate (MTX), sulfasalazine, and biological or targeted synthetic DMARDs (b/tsDMARDs), in accordance with international recommendations.[8]

Functional status was evaluated using the Bath Ankylosing Spondylitis Radiology Index (BASMI), which comprises measurements of cervical rotation, tragus-to-wall distance, lateral lumbar flexion, intermalleolar distance, and the modified Schober test.[9] All clinical and functional assessments were performed at the patients' most recent clinical visit.

Ethics Approval

The study protocol was approved by the Clinical Research Ethics Committee of Uşak University Faculty of Medicine (approval no: 630-630-28; date: 10.04.2025). Informed consent was waived due to the retrospective design and anonymized data.

Statistical Analysis

All analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were reported as mean ± standard deviation or median and interquartile range for continuous variables and as frequencies and percentages for categorical variables. Comparisons between groups were conducted using the chi-square test for categorical variables, the independent samples t-test for normally distributed continuous variables, and the Mann-Whitney U test for skewed data. Correlation analyses were performed using Spearman's rank correlation coefficients. A p-value of <0.05 was considered statistically significant. Variables associated with sacroiliac ankylosis were analysed using multivariable logistic regression.

Results

Demographic and Clinical Characteristics (Any Ankylosis vs. Non-ankylosis)

Among the 290 patients with AS, 131 had SIJ ankylosis (unilateral or bilateral), while 159 had no ankylosis. Patients with ankylosis were significantly more often male (80.2% vs. 56.0%, $p<0.001$) and older (45.9±10.2 vs. 40.5±10.3 years, $p<0.001$). They also had longer symptom duration (median 20 vs. 12 years, $p<0.001$) and disease duration (median 14 vs. 8 years, $p<0.001$). Smoking, alcohol consumption, and HLA-B27 positivity were more frequent in the ankylosis group. No significant differences were observed in BMI, enthesitis, uveitis, peripheral arthritis, psoriasis, IBD, or NSAID use. Use of MTX and biologic therapy were higher among patients with ankylosis (Table 1).

Functional and Radiographic Findings (Any Ankylosis vs. Non-ankylosis)

Among the 290 patients included in the study, the distribution of sacroiliitis grades differed between the right and left SIJs. For the right SIJ, grade 1 was observed in 1 patient (0.3%), grade 2 in 55 patients (19.0%), grade 3 in 115 patients (39.7%), and grade 4 in 119 patients (41.0%). For the left SIJ, grade 1 was present in 12 patients (4.1%), grade 2 in 61 patients (21.0%), grade 3 in 106 patients (36.6%), and grade 4 in 111 patients (38.3%).

Patients with ankylosis demonstrated significantly worse functional outcomes, with higher BASMI scores (4.38±2.28 vs. 2.42±1.51, $p=0.002$) and reduced spinal mobility in all domains, including cervical rotation, lumbar flexion, intermalleolar distance, tragus-to-wall distance, and modified Schöber test (all $p<0.01$). Radiographically, they had higher rates of syndesmophytes (cervical: 55.8% vs. 19.0%; lumbar: 55.0% vs. 21.7%), hip involvement (62.6% vs. 25.2%, $p<0.001$), sacral enthesitis (34.4% vs. 13.8%), and symphysitis (21.4% vs. 6.3%). The median total mSASSS score was significantly higher in the ankylosis group (5 vs. 1, $p<0.001$) (Table 2). Total hip replacement was observed in 11 patients in the ankylosis group.

Multivariable Analysis for Any SIJ Ankylosis

In the multivariable logistic regression model, higher structural damage and hip involvement were independently associated with SIJ ankylosis. Total mSASSS remained a robust predictor, with each unit increase conferring higher odds of SIJ ankylosis. Hip involvement was also independently associated with the presence of ankylosis. HLA-B27 positivity showed a borderline association but did not reach statistical significance in the adjusted model. Age, sex, smoking status, disease duration, and biologic therapy were not independently associated with any SIJ ankylosis (Table 3).

Demographic and Clinical Characteristics (Bilateral Ankylosis vs. Non-Ankylosis)

In the subgroup analysis restricted to bilateral SIJ ankylosis ($n=101$), differences were even more pronounced. Male predominance (83.2% vs. 58.2%, $p<0.001$), older age (46.4±9.6 vs. 41.1±10.6 years, $p<0.001$), smoking (79.2% vs. 64.6%, $p=0.008$), and alcohol consumption (25% vs. 13.8%, $p=0.018$). HLA-B27 positivity was also higher (73.4% vs. 59.7%), although the

difference was not statistically significant (p=0.058). Symptom duration and disease duration were longer. Methotrexate and biologic therapy use were higher in the bilateral ankylosis group. Other variables, including BMI, enthesitis, uveitis, peripheral arthritis, psoriasis, and IBD showed no significant differences (Table 4).

Functional and Radiographic Findings (Bilateral Ankylosis vs. Non-ankylosis)

Bilateral ankylosis was associated with markedly impaired spinal mobility, reflected in higher BASMI scores (4.8±2.26 vs. 2.45±1.48, p<0.001) and worse performance in all mobility measures. Radiographic damage was greater in the bilateral ankylosis group, with higher frequencies of cervical

Table 1. Comparison of demographic, clinical, and treatment characteristics between patients with and without any SIJ ankylosis (unilateral or bilateral)

Variables	With ankylosis (n=131)	Without ankylosis (n=159)	p-value
Sex, male, n (%)	105 (80)	89 (56)	**<0.001**
Age, years, mean (SD)	46 (10)	41 (10)	**<0.001**
Ever smoker, n (%)	105 (80)	97 (61)	**<0.001**
Alcohol consumption, n (%)	32 (25)	19 (12)	**0.005**
Symptom duration, years, median (IQR)	20 (9)	12 (8)	**<0.001**
Disease duration, years, median (IQR)	14 (9)	8 (6)	**<0.001**
HLA-B27 positive, n/N (%)	61/84 (73)	66/114 (58)	**0.03**
BMI, kg/m², mean (SD)	27 (4.7)	26 (4.3)	0.88
History of enthesitis, n (%)	54 (41)	75 (47)	0.31
History of uveitis, n (%)	26 (20)	23 (15)	0.22
History of psoriasis, n (%)	7 (5.4)	17 (10)	0.13
History of IBD, n (%)	10 (7.6)	8 (5.0)	0.47
History of peripheral arthritis, n (%)	46 (35)	50 (31)	0.51
Current NSAID use, n (%)	77 (59)	93 (59)	0.96
SSZ use, ever, n (%)	77 (59)	77 (48)	0.08
MTX use, ever, n (%)	36 (28)	26 (16)	**0.02**
Biologic therapy, n (%)	114 (87)	111 (70)	**<0.001**

Percentages were calculated based on available data. N reflects the number of patients with available data for each variable. BMI: Body mass index, HLA: Human leukocyte antigen, IQR: Interquartile range, MTX: Methotrexate, NSAID: Non-steroidal anti-inflammatory drug, SD: Standard deviation, SIJ: Sacroiliac joint, SSZ: Sulfasalazine

Table 2. Comparison of functional parameters and radiographic findings between patients with and without any SIJ ankylosis (unilateral or bilateral)

Variables	With ankylosis (n=131)	Without ankylosis (n=159)	p-value
BASMI total score, mean (SD)	4.4 (2.3)	2.4 (1.5)	**0.002**
Cervical rotation, mean (SD)	52 (22)	67 (18)	**<0.001**
Tragus-to-wall distance, cm, mean (SD)	19 (6.4)	15 (3.4)	**0.004**
Lateral lumbar flexion, cm, mean (SD)	12 (12)	20 (19)	**<0.001**
Intermalleolar distance, cm, mean (SD)	89 (24)	100 (18)	**<0.001**
Modified Schober test, cm, mean (SD)	3.3 (2.0)	5.0 (2.1)	**<0.001**
Cervical syndesmophyte, n (%)	72 (56)	30 (19)	**<0.001**
Lumbar syndesmophyte, n (%)	71 (55)	34 (22)	**<0.001**
Sacral enthesitis, n (%)	45 (34)	21 (13)	**<0.001**
Symphysitis, n (%)	28 (21)	10 (6)	**<0.001**
Hip involvement, n (%)	82 (63)	39 (25)	**<0.001**
Cervical mSASSS, median (IQR)	4 (10)	0 (1)	**0.001**
Lumbar mSASSS, median (IQR)	1 (2)	0 (1)	**0.02**
Total mSASSS, median (IQR)	5 (11)	1 (2)	**<0.001**

BASMI: Bath ankylosing spondylitis metrology index, IQR: Interquartile range, mSASSS: Modified stoke ankylosing spondylitis spinal score, SD: Standard deviation, SIJ: Sacroiliac joint

syndesmophytes (58.6% vs. 23.4%), lumbar syndesmophytes (67.6% vs. 32.0%), sacral enthesitis (32.7% vs. 17.5%), symphysitis (21.8% vs. 8.5%), and hip involvement (66.3% vs. 28.6%) (all p≤0.003). Median total mSASSS was also higher (5 vs. 1, p<0.001) (Table 5). Total hip replacement was observed in 10 patients in the bilateral ankylosis group.

Multivariable Analysis for Bilateral SIJ Ankylosis

In the model evaluating bilateral SIJ ankylosis, disease duration and total mSASSS emerged as independent predictors. Longer disease duration modestly increased the likelihood of bilateral ankylosis, while higher total mSASSS [odds ratio (OR): 1.075, 95% confidence interval (CI): 1.023-1.130; p=0.004] remained strongly associated with its presence. Hip involvement was the strongest independent factor, conferring approximately three-fold increase in odds (OR: 2.904, 95% CI: 1.100-7.666; p=0.031). Other demographic and clinical variables, including age, sex, smoking history, and HLA-B27, were not independently associated with bilateral ankylosis in the adjusted model (Table 6).

To account for the potential confounding effect of disease duration, additional stratified analyses were performed based on the median disease duration of the cohort (10 years). Within both duration strata (<10 and ≥10 years), patients with bilateral SIJ ankylosis consistently demonstrated worse functional outcomes, reduced spinal mobility, and higher structural damage compared to those without ankylosis. These findings remained consistent across both clinical and radiographic parameters (Supplementary Tables 1 and 2).

Correlation Analyses

Correlation analysis demonstrated that longer symptom and disease duration were positively correlated with functional limitation (BASMI) and radiographic damage (mSASSS).

Table 3. Multivariable logistic regression analysis for any SIJ ankylosis (unilateral or bilateral)

Variable	OR	CI lower	CI upper	p-value
Age	0.985	0.929	1.045	0.62
Male sex	2.597	0.760	8.876	0.13
Disease duration	1.084	0.992	1.185	0.07
Ever smoker	1.789	0.604	5.297	0.29
HLA-B27	2.991	0.971	9.209	0.06
Total mSASSS	1.075	1.023	1.130	**0.004**
Hip involvement	2.904	1.100	7.666	**0.03**

CI: Confidence interval, HLA-B27: Human leukocyte antigen B27, mSASSS: Modified Stoke Ankylosing Spondylitis Spine Score, OR: Odds ratio, SIJ: Sacroiliac joint

Table 4. Comparison of demographic, clinical, and treatment characteristics between patients with and without bilateral SIJ ankylosis

Variables	With ankylosis (n=101)	Without ankylosis (n=189)	p-value
Sex, male, n (%)	84 (83)	110 (58)	**<0.001**
Age, years, mean (SD)	46 (9.6)	41 (11)	**<0.001**
Ever smoker, n (%)	80 (79)	122 (65)	**0.01**
Alcohol consumption, n (%)	25 (25)	26 (14)	**0.02**
Symptom duration, years, median (IQR)	21 (9)	13 (9)	**<0.001**
Disease duration, years, median (IQR)	15 (9)	9 (7)	**<0.001**
HLA-B27 positive, n/N (%)	47/64 (73)	80/134 (60)	0.06
BMI, kg/m², mean (SD)	27 (4.6)	26 (4.3)	0.86
History of enthesitis, n (%)	43 (43)	86 (46)	0.63
History of uveitis, n (%)	19 (19)	30 (16)	0.53
History of psoriasis, n (%)	6 (6.0)	18 (9.5)	0.37
History of IBD, n (%)	7 (6.9)	11 (5.8)	0.80
History of peripheral arthritis, n (%)	31 (31)	65 (34)	0.52
Current NSAID use, n (%)	60 (59)	110 (58)	0.84
SSZ use, ever, n (%)	56 (55)	98 (52)	0.56
MTX use, ever, n (%)	26 (26)	36 (19)	0.19
Biologic therapy, n (%)	85 (84)	140 (74)	**0.05**

Percentages were calculated based on available data. N reflects the number of patients with available data for each variable. BMI: Body mass index, HLA: Human leukocyte antigen, IQR: Interquartile range, MTX: Methotrexate, NSAID: Non-steroidal anti-inflammatory drug, SD: Standard deviation, SSZ: Sulfasalazine

Table 5. Comparison of functional parameters and radiographic findings between patients with and without bilateral SIJ ankylosis			
Variables	**With ankylosis (n=101)**	**Without ankylosis (n=189)**	**p-value**
BASMI total score, mean (SD)	4.8 (2.3)	2.5 (1.5)	**<0.001**
Cervical rotation, mean (SD)	48 (22)	67 (18)	**<0.001**
Tragus-to-wall distance, cm, mean (SD)	19 (6.9)	15 (3.7)	**<0.001**
Lateral lumbar flexion, cm, mean (SD)	11 (12)	19 (17)	**0.004**
Intermalleolar distance, cm, mean (SD)	89 (23)	99 (19)	**0.002**
Modified Schober test, cm, mean (SD)	3.3 (2.0)	5.0 (2.1)	**<0.001**
Cervical syndesmophyte, n (%)	58 (59)	44 (23)	**<0.001**
Lumbar syndesmophyte, n (%)	71 (68)	58 (32)	**<0.001**
Sacral enthesitis, n (%)	33 (33)	33 (18)	**0.003**
Symphysitis, n (%)	22 (22)	16 (9)	**0.001**
Hip involvement, n (%)	67 (66)	54 (29)	**<0.001**
Cervical mSASSS, median (IQR)	4 (10)	0 (1)	**<0.001**
Lumbar mSASSS, median (IQR)	1 (2)	0 (1)	**<0.001**
Total mSASSS, median (IQR)	5 (11)	1 (2)	**<0.001**
BASMI: Bath ankylosing spondylitis metrology index, IQR: Interquartile range, mSASSS: Modified stoke ankylosing spondylitis spine score, SD: Standard deviation, SIJ: Sacroiliac joint			

Table 6. Multivariable logistic regression analysis for bilateral SIJ ankylosis				
Variable	**OR**	**CI lower**	**CI upper**	**p-value**
Age	0.995	0.935	1.058	0.86
Male sex	2.056	0.577	7.328	0.27
Disease duration	1.088	1.002	1.181	**0.04**
Ever smoker	1.331	0.433	4.088	0.62
HLA-B27	2.444	0.734	8.144	0.15
Total mSASSS	1.044	1.006	1.084	**0.02**
Hip involvement	3.208	1.189	8.653	**0.02**
CI: Confidence interval, HLA-B27: Human leukocyte antigen B27, mSASSS: Modified stoke ankylosing spondylitis spine score, OR: Odds ratio, SIJ: Sacroiliac joint				

Conversely, spinal mobility measures such as cervical rotation, lumbar flexion, intermalleolar distance, tragus-to-wall distance, and the Schober test showed significant negative correlations with both BASMI and mSASSS. These associations were more pronounced in the bilateral ankylosis subgroup, where the correlation between BASMI and mSASSS reached moderate strength ($\rho=0.50$, $p<0.001$) (Figure 1).

Discussion

In this retrospective study of 290 patients with r-axSpA, we found that SIJ ankylosis is closely associated with more advanced structural damage, worse spinal mobility, and greater functional impairment. Patients with ankylosis particularly those with bilateral fusion were more often male, had longer symptom and disease durations, and more frequently exhibited smoking, HLA-B27 positivity, hip involvement, sacral enthesitis, and syndesmophytes. These findings suggest that SIJ ankylosis reflects a more severe, structurally progressive phenotype within r-AxSpA.

Although SIJ involvement is recognized as a hallmark of axSpA, only a limited number of studies have evaluated the specific consequences of SIJ disease itself. Earlier research has largely focused on radiographic sacroiliitis grading rather than complete fusion, and the prognostic relevance of ankylosis has remained insufficiently characterised.

Our findings are supported in part by previous work showing that structural damage in the SIJ contributes to functional impairment in axSpA. Protopopov et al.[10] demonstrated in a longitudinal cohort of 210 patients that radiographic sacroiliitis severity (SIJ sum-score) was independently associated with small but statistically significant worsening in BASFI and BASMI, even after adjustment for disease activity and spinal structural damage. These results indicate that SIJ damage plays a role in functional limitation beyond spinal involvement. However, their analysis focused on the full spectrum of radiographic sacroiliitis grades and did not specifically address complete ankylosis or distinguish between unilateral and bilateral fusion. In contrast, our study extends this evidence by showing that SIJ ankylosis

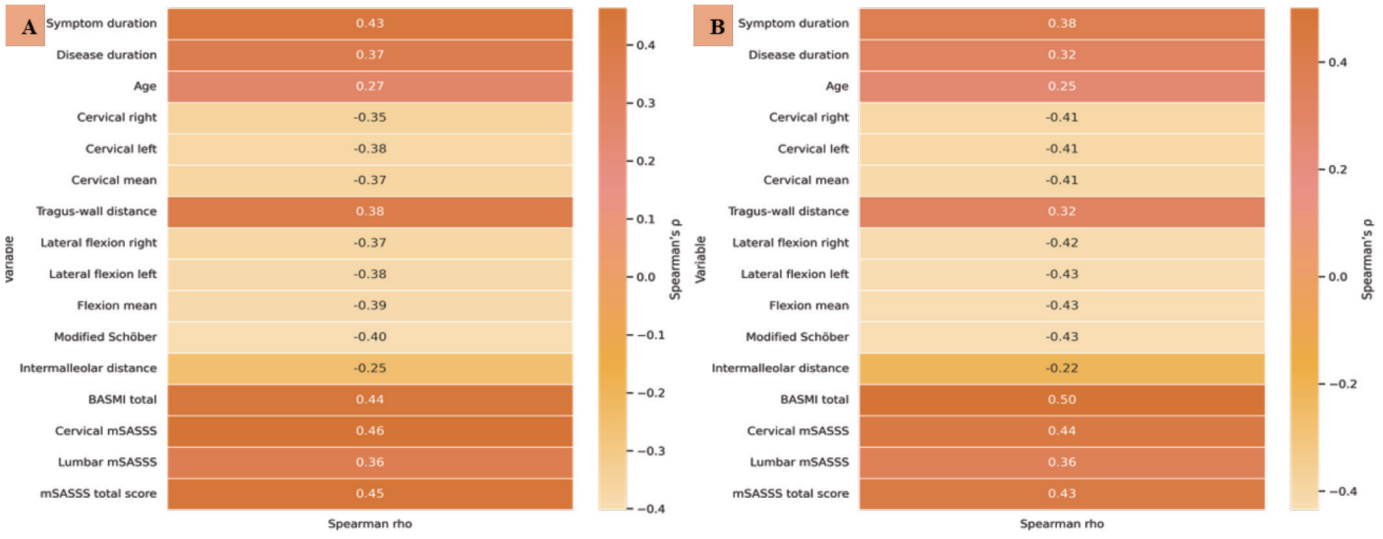

Figure 1. Spearman correlation heatmaps of demographic, functional, and radiographic variables in ankylosing spondylitis

Panel A: Overall ankylosis group. Panel B: Bilateral ankylosis subgroup.
Positive correlations (orange) indicate that longer disease duration is associated with higher BASMI and mSASSS scores, whereas negative correlations (lighter shades) reflect reduced spinal mobility with increasing structural damage.
BASMI: Bath ankylosing spondylitis metrology index, mSASSS: Modified stoke ankylosing spondylitis spinal score

particularly bilateral ankylosis represents the most advanced structural phenotype and is associated with the greatest mobility limitation and radiographic burden.

However, prior studies did not differentiate unilateral versus bilateral ankylosis or comprehensively evaluate their associations with syndesmophytes, hip involvement, and detailed mobility indices. Our findings extend this literature by showing that bilateral ankylosis is associated with the most profound mobility limitations, higher mSASSS scores, and widespread pelvic and spinal structural changes, highlighting the clinical relevance of distinguishing the degree of SIJ fusion.

In our cohort, sacroiliac ankylosis was markedly more frequent in male patients. Similarly, a computed tomography-based population study reported male sex as an independent risk factor for spontaneous SIJ ankylosis even in non-inflammatory settings.[11] This parallel finding suggests that sex-related predisposition may influence both inflammatory and degenerative pathways leading to SIJ ankylosis.

The relationship between SIJ ankylosis and spinal structural damage is particularly notable. Patients with ankylosis had significantly higher rates of cervical and lumbar syndesmophytes and bridging lesions, suggesting parallel progression of pelvic and spinal new bone formation. These associations were strongest in the bilateral subgroup, supporting the concept that complete SIJ fusion represents a late and advanced stage of axial structural progression. The strong correlations between disease duration, BASMI, and mSASSS further reinforce the cumulative nature of radiographic damage in axSpA. To further explore whether these findings were solely driven by disease duration, we performed additional stratified analyses based on the median disease duration of the cohort (10 years). Notably, the differences in functional impairment, spinal mobility, and structural damage between patients with and without bilateral SIJ ankylosis persisted within both duration strata. These findings suggest that SIJ ankylosis is not merely a reflection of longer disease duration, but rather represents a distinct structural phenotype associated with more severe clinical and radiographic involvement. A recent multicentre Turkish cohort similarly reported that advanced spinal ankylosis (bamboo spine) clustered with hip involvement, higher BMI, and entheseal disease, further supporting the parallel progression of pelvic and spinal structural damage.[6]

Long-term prospective data from the OASIS cohort demonstrated that radiographic progression in axSpA continues over several decades and follows an approximately linear trajectory, with new syndesmophytes developing in more than half of patients over 12 years.[5] These findings emphasize that structural damage in axSpA is a cumulative and ongoing process. In this context, SIJ ankylosis in our cohort likely represents the extreme end of this structural continuum, supported by the markedly higher mSASSS values, widespread syndesmophytes, hip involvement, and impaired mobility observed in patients with bilateral fusion.

Our findings regarding the strong association between SIJ ankylosis and hip involvement are consistent with recent evidence from orthopaedic cohorts. In a study of patients with AS, Ido et al.[12] demonstrated that SIJ fusion was an independent risk factor for radiographic hip involvement. Their analysis suggested that reduced spinopelvic mobility and increased mechanical

stress on adjacent joints may contribute to hip pathology. These results align with our observation that patients with sacroiliac ankylosis particularly those with bilateral fusion had markedly higher rates of hip involvement, supporting the concept that SIJ fusion reflects a more severe structural phenotype affecting both the pelvis and the spine. Similarly, sacral enthesitis and pubic symphysis involvement clustered in the ankylosis group, reflecting more diffuse pelvic structural pathology.

Inflammation is generally regarded as a contributing factor in the development of structural damage in axSpA; however, the relationship between inflammatory activity and ankylosis remains complex. Ankylosis reflects cumulative structural change over time and may not correspond directly to inflammatory activity measured at a single time point. As this study was cross-sectional and did not include baseline or longitudinal inflammatory assessments, we were unable to examine this association in detail. Further longitudinal investigations would be needed to better clarify this relationship.

Study Limitations

This study benefits from a relatively large sample size, standardized radiographic evaluation using validated scoring systems, and detailed assessment of spinal mobility. A key strength is the distinction between unilateral and bilateral sacroiliac ankylosis, which has been minimally addressed in previous research but appears clinically important. However, several limitations should be acknowledged. The retrospective and cross-sectional design precludes causal inference and does not permit direct evaluation of structural progression over time. Moreover, the lack of longitudinal baseline data limits assessment of the temporal relationship between disease duration, cumulative structural damage, and the development of SIJ ankylosis. Similarly, the absence of baseline and longitudinal inflammatory assessments restricts evaluation of the potential contribution of cumulative inflammatory burden to structural damage. In addition, patient-reported outcomes were not included, limiting a comprehensive understanding of the broader functional and patient-perceived impact of the disease. Nevertheless, the objective measures used BASMI and mSASSS offer a robust evaluation of functional and structural burden.

Conclusion

SIJ ankylosis is a clinically meaningful marker of advanced disease in r-AxSpA. Patients with ankylosis especially those with bilateral fusion demonstrated more extensive structural damage, greater pelvic and spinal involvement, and significantly impaired spinal mobility. Recognising SIJ ankylosis in routine clinical practice may help identify patients with a more progressive disease phenotype.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Uşak University Faculty of Medicine (approval no: 630-630-28; date: 10.04.2025).

Informed Consent: Informed consent was waived due to the retrospective design and anonymized data.

Footnotes

Authorship Contributions

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

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References

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369:1379-90.
2. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-8.
3. Creemers MCW, Franssen MJAM, van't Hof MA, Gribnau FWJ, van de Putte LBA, van Riel PLCM. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005;64:127-9.
4. Haroon N, Inman RD, Learch TJ, et al. The impact of tumor necrosis factor-α inhibitors on radiographic progression in ankylosing spondylitis. Arthritis Rheum. 2013;65:2645-54.
5. Ramiro S, Stolwijk C, van Tubergen A, et al. Evolution of radiographic damage in ankylosing spondylitis: 12-year follow-up of the OASIS study. Ann Rheum Dis. 2015;74:52-9.
6. Atagündüz P, Kiraz S, Akar S, et al. Clinical and laboratory factors associated with bamboo spine in patients with axial spondyloarthritis. Clin Exp Rheumatol. 2023;41:620-7.
7. MacKay K, Brophy S, Mack C, Doran M, Calin A. The development and validation of a radiographic grading system for the hip in ankylosing spondylitis: the bath ankylosing spondylitis radiology hip index. J Rheumatol. 2000;27:2866-72.
8. Ramiro S, Nikiphorou E, Sepriano A, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2023;82:19-34.
9. Zochling J. Measures of symptoms and disease status in ankylosing spondylitis. Arthritis Care Res (Hoboken). 2011;63(Suppl 11):S47-58.
10. Protopopov M, Sieper J, Haibel H, Listing J, Rudwaleit M, Poddubnyy D. Relevance of structural damage in the sacroiliac joints for the functional status and spinal mobility in patients with axial spondyloarthritis:

results from the German Spondyloarthritis Inception Cohort. Arthritis Res Ther. 2017;19:240.

11. Gahleitner A, Pamnani S, Huschbeck A, Petersein J, Dengler J, Lenga P. Spontaneous ankylosis of the sacroiliac joint: prevalence and risk factors. Eur J Orthop Surg Traumatol. 2023;33:1821-5.

12. Ido H, Osawa Y, Takegami Y, et al. Sacroiliac joint fusion in patients with ankylosing spondylitis is associated with hip involvement. J Orthop Sci. 2024;29:939-44.

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Twenty-year retrospective analysis of mortality risk factors in patients with systemic lupus erythematosus: A single-center cohort with variable individual follow-up

Sistemik lupus eritematozus hastalarında mortalite risk faktörlerinin 20 yıllık retrospektif analizi: Tek merkezli kohort ve hastalar arasında değişken bireysel izlem süreleri

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Abstract

Objective: Mortality in systemic lupus erythematosus (SLE) reflects a complex interplay between disease activity, organ involvement, and treatment-related complications. This study aimed to evaluate the impact of demographic, clinical, and laboratory parameters on survival and identify independent predictors of mortality in a tertiary hospital-based SLE cohort over a 20-year accrual period with variable individual follow-up durations.

Methods: We retrospectively analyzed 184 patients with SLE who fulfilled the American College of Rheumatology/The European Alliance of Associations for Rheumatology classification criteria and were followed at a tertiary university hospital between 2005 and 2025. Clinical manifestations, baseline laboratory parameters, and survival outcomes were recorded. Follow-up duration was expressed as median (interquartile range) due to a skewed distribution. Independent predictors of mortality were assessed using univariable and multivariable Cox proportional hazards regression analyses.

Results: The mean age of the cohort was 36.0±12.8 years, and 92.9% of patients were female. Over the 20-year accrual period, 20 patients (10.9%) died. The median follow-up duration was significantly shorter among deceased patients than among survivors [3.0 (1.0-7.0) vs. 32.0 (12.0-64.0) months; p<0.001], indicating predominantly early mortality. The leading cause of death was infection/sepsis (50.0%), with a substantial proportion related to thrombotic/antiphospholipid syndrome manifestations; however, antiphospholipid antibody profiles were not systematically available. In multivariable analysis, intensive care unit admission [hazard ratio (HR): 11.4, p<0.001], elevated baseline C-reactive protein (CRP) levels (HR: 1.02 per 1 mg/L increase, p=0.04), and lower serum albumin levels (HR: 0.31 per 1 g/dL increase, p=0.008) were independently associated with increased mortality risk. Pulse steroid therapy was associated with improved survival

Özet

Amaç: Sistemik lupus eritematozus (SLE) mortalitesi, hastalık aktivitesi, organ tutulumu ve tedaviye bağlı komplikasyonlar arasındaki karmaşık etkileşimi yansıtır. Bu çalışma, 20 yıllık hasta dahil edilme dönemi boyunca değişken bireysel takip süreleri olan bir üçüncü basamak SLE kohortunda, demografik, klinik ve laboratuvar parametrelerinin sağkalım üzerine etkilerini değerlendirmeyi ve mortalitenin bağımsız prediktörlerini belirlemeyi amaçladı.

Yöntem: 2005-2025 yılları arasında üçüncü basamak bir üniversite hastanesinde izlenen ve Amerikan Romatoloji Derneği/Avrupa Romatoloji Dernekleri Birliği sınıflama kriterlerini karşılayan 184 SLE hastası retrospektif olarak analiz edildi. Klinik bulgular, başlangıç laboratuvar parametreleri ve sağkalım sonuçları kaydedildi. Takip süreleri, simetrik olmayan dağılımları nedeniyle medyan (çeyrekler arası aralık) ile raporlandı. Mortalitenin bağımsız prediktörleri, tek değişkenli ve çok değişkenli Cox orantılı risk regresyon analizleri ile değerlendirildi.

Bulgular: Kohortun ortalama yaşı 36,0±12,8 yıl ve hastaların %92,9'u kadındı. Yirmi yıllık hasta dahil edilme döneminde 20 hasta (%10,9) hayatını kaybetti. Medyan takip süresi, ölen hastalarda sağ kalanlara göre anlamlı olarak daha kısaydı [3,0 (1,0-7,0) vs. 32,0 (12,0-64,0) ay, p<0,001] ve ağırlıklı olarak erken mortaliteyi gösteriyordu. Ölümün başlıca nedeni enfeksiyon/sepsis (%50,0) idi; trombotik/antifosfolipid sendromu ilişkili olaylar da önemli oranda yer almakta olup, antifosfolipid antikoru profilleri sistematik olarak mevcut değildi. Çok değişkenli analizde, yoğun bakım ünitesine kabul [tehlike oranı (HR): 11,4, p<0,001], yüksek başlangıç C-reaktif protein düzeyleri (HR: 1,02, 1 mg/L artış başına, p=0,04) ve düşük serum albümin düzeyleri (HR: 0,31, 1 g/dL artış başına, p=0,008) mortalite riskini bağımsız olarak artıran faktörler olarak saptandı. Pulse steroid tedavisi sağkalım

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Abstract

(HR: 0.38, p=0.033). Causality cannot be inferred. Notably, the presence of lupus nephritis was associated with reduced mortality (HR: 0.09, p=0.035), which likely reflects more intensive monitoring and treatment in this subgroup.

Conclusion: Mortality in this cohort was primarily driven by acute inflammatory burden and the need for critical care, rather than by chronic organ damage. The "nephritis paradox" likely reflects an association with proactive management rather than a direct protective effect. These findings underscore the need for vigilant early risk stratification to mitigate acute, non-renal complications such as sepsis.

Keywords: Systemic lupus erythematosus, mortality, nephritis, C-reactive protein, albumin, APS, risk factors, survival analysis

Öz

ile ilişkili bulundu (HR: 0,38, p=0,033); nedensellik çıkarılamaz. İlginç bir şekilde, lupus nefriti varlığı mortalitenin azalmasıyla ilişkiliydi (HR: 0,09, p=0,035); bu durum muhtemelen bu alt grupta daha yoğun izlem ve tedavi uygulanmasıyla ilgilidir.

Sonuç: Bu kohortta mortalite, kronik organ hasarından ziyade akut enflamatuvar yük ve kritik bakım gereksinimi tarafından yönlendirilmektedir. "Nefrit paradoksu", doğrudan koruyucu bir etki yerine proaktif yönetimle ilişkili gibi görünmektedir. Bulgular, sepsis gibi akut, renal dışı komplikasyonları azaltmak için erken risk stratifikasyonunun önemini vurgulamaktadır.

Anahtar Kelimeler: Sistemik lupus eritematozus, mortalite, nefrit, C-reaktif protein, albümin, APS, risk faktörleri, sağkalım analizi

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with an incompletely understood etiology that predominantly affects young adults, particularly women of reproductive age.[1] It is characterized by widespread autoantibody production and immune complex deposition resulting from a loss of immune tolerance, leading to multi-organ involvement, including the skin, joints, kidneys, hematologic system, cardiopulmonary system, and nervous system.[2] The clinical course of SLE is highly heterogeneous, ranging from mild mucocutaneous manifestations to life-threatening multi-organ failure. This variable presentation, coupled with the relapsing nature of disease flares, necessitates a meticulous, multidisciplinary approach to diagnosis, treatment, and longitudinal follow-up.[3] Epidemiological studies in Türkiye indicate that while the overall clinical characteristics of Turkish SLE patients are broadly comparable to European cohorts, significant regional variations exist in organ involvement and mortality patterns.[4,5] Mortality in SLE may result not only from chronic organ damage but also from acute complications such as infections, sepsis, or thrombotic events, including those related to antiphospholipid syndrome (APS). Understanding these local disease patterns and the variable duration of patient follow-up in hospital-based cohorts is essential for improving patient survival and managing the high burden of disease activity often observed in tertiary care settings.

SLE is associated with high mortality due to its multisystem involvement and the risk of severe complications.[6] Key determinants of SLE-related mortality reported in the literature include disease activity indices, specific organ involvement, and concomitant complications.[7] In particular, renal involvement [lupus nephritis (LN)], cardiovascular events, pulmonary complications, recurrent flares, thrombotic events including those related to APS, and the need for intensive care unit (ICU) admission have been identified as the strongest predictors of poor prognosis.[8] Recent data from large Turkish cohorts indicate that infections, sepsis, and renal flares remain the leading causes of early mortality, consistent with global patterns.[9] Beyond clinical manifestations, laboratory parameters are crucial for mortality risk stratification. Systemic inflammation, reflected by elevated C-reactive protein (CRP) levels, and hypoalbuminemia—which serves as a surrogate marker for both nutritional status and severe organ dysfunction—are recognized as important biomarkers associated with increased mortality risk.[8] It is important to note that associations between treatment interventions (e.g., immunosuppressive therapy) and survival outcomes may reflect confounding factors such as closer monitoring of high-risk patients, rather than a direct protective effect. Notably, the effect of specific organ involvement on mortality remains a topic of ongoing debate. In some tertiary care centers, classical risk factors such as nephritis may show unexpected associations with survival, a phenomenon often attributed to "treatment-effect bias", whereby high-risk patients receive closer monitoring and more aggressive therapy compared with those with non-renal SLE manifestations.[10]

Despite significant advances in management, data on SLE-related mortality remain limited, particularly regarding outcomes from specialized tertiary centers in Türkiye with extended accrual periods, rather than data from individual long-term follow-up. While previous studies have identified general risk patterns, comprehensive evaluations of the interplay between baseline laboratory biomarkers, specific organ involvement, thrombotic events [including (APS)], and contemporary treatment strategies are scarce.[11] Much of the existing literature is constrained by smaller cohorts and variable follow-up durations, which hinder the systematic assessment of early- and late-stage complications, acute inflammatory events, and chronic organ damage.[12]

To address this gap, the present study evaluated a hospital-based SLE cohort accrued over a 20-year period (2005-2025), rather than through individual long-term follow-up. Our primary objective was to identify independent predictors of mortality by integrating demographic characteristics, baseline clinical manifestations—including thrombotic events and APS when documented—and laboratory biomarkers of systemic

inflammation. By analyzing outcomes over the study period, we aimed to refine risk stratification and provide insights into how contemporary management strategies influence survival patterns in a high-acuity SLE population, while acknowledging the limitations of incomplete antiphospholipid antibody (aPL) profiling and variable follow-up durations.

Materials and Methods

Study Design and Ethical Approval

This retrospective, single-center, observational cohort study was conducted at a tertiary referral center. Medical records of 184 patients diagnosed with SLE who fulfilled the 2019 the European Alliance of Associations for Rheumatology (EULAR)/ American College of Rheumatology (ACR) classification criteria and who were followed at the Department of Rheumatology, Dicle University Hospital between January 2005 and January 2025 were reviewed. This represents a 20-year cohort accrual period rather than an individual long-term follow-up. The study protocol was approved by the Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (approval no: 4, date: 24.12.2025). Given the retrospective design and use of anonymized archival data, the requirement for written informed consent was waived. All procedures adhered to the ethical principles of the Declaration of Helsinki and complied with national regulations on patient data confidentiality.

Study Population and Selection Criteria

The study cohort included adult patients (aged ≥18 years) who fulfilled the 2019 EULAR/ACR and/or 1997 updated ACR classification criteria for SLE.[13,14] To ensure data integrity and clinical relevance, patients were required to have:

1. A confirmed SLE diagnosis based on the above criteria, including documentation of at least one clinical and one immunologic domain contributing to classification (for patients without major organ involvement).

2. Regular follow-up at the rheumatology department for a minimum of three months, unless death occurred earlier.

3. Complete baseline laboratory and clinical data at study inclusion.

Patients with overlapping autoimmune syndromes (e.g., mixed connective tissue disease) or incomplete medical records regarding primary outcomes (mortality and major SLE-related events) were excluded. The patient selection process and exclusion criteria are summarized in the study flow chart (Figure 1).

Some patients classified as "non-organ-involving SLE" met the criteria based on combinations of hematologic, mucocutaneous, and serologic domains and had no major organ involvement. The presence of aPL-related events was recorded descriptively when available; however, systematic aPL profiling was not consistently performed, precluding formal assessment of APS-related mortality.

Data Collection and Definitions

Patient data were systematically extracted from physical hospital archives and the electronic medical record system. To ensure consistency across the 20-year study period, a standardized data abstraction form was used. Baseline demographic and clinical characteristics included age at diagnosis, sex, and follow-up duration (calculated from diagnosis to last visit or death).

Disease flares were originally defined by SLE disease activity index 2000 (SLEDAI-2K) as an increase of >4 points. However, because SLEDAI-2K data were missing in a substantial proportion of visits, flares were operationally defined based on clinical deterioration requiring therapy escalation, as determined from chart review. This approach was applied consistently across the cohort, and flare-related findings should be interpreted cautiously.

Clinical severity was further evaluated by total hospitalizations and ICU admissions. Organ involvement was adjudicated according to ACR classification guidelines and corroborated by biopsy, imaging, and clinical reports. Specific definitions included:

• LN: biopsy-confirmed ISN/RPS class or persistent proteinuria >0.5 g/day or presence of cellular casts.

• Neuropsychiatric SLE: seizures, psychosis, or organic brain syndrome after exclusion of metabolic or infectious causes.

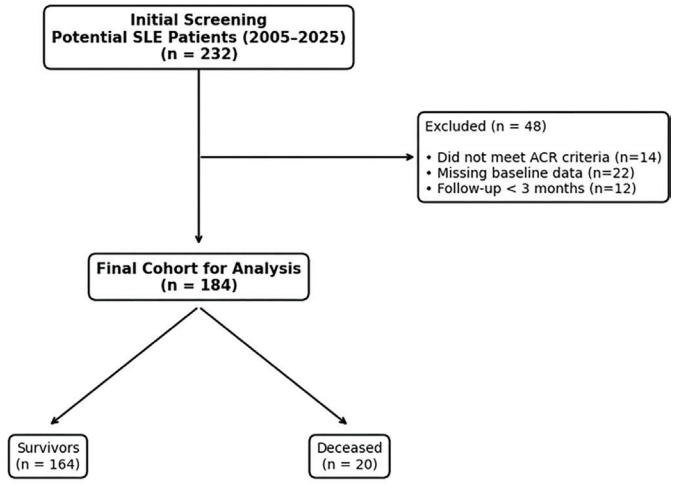

Figure 1. Flowchart of patient selection and study design. The flowchart illustrates the inclusion and exclusion process of the study cohort. Between 2005 and 2025, a total of 232 patients with suspected SLE were screened. Of these, 48 patients were excluded based on predefined criteria, including failure to meet the ACR/EULAR classification criteria, missing baseline data, or short-term follow-up unrelated to mortality outcomes. The final analysis included 184 patients, who were stratified into survivors (n=164) and deceased (n=20) groups for the evaluation of mortality risk factors

ACR: American College of Rheumatology, EULAR: The European Alliance of Associations for Rheumatolog, SLE: Systemic lupus erythematosus

• Serositis: clinically or radiologically confirmed pleuritis or pericarditis (ultrasonography/computed tomography).

Laboratory parameters included inflammatory markers (CRP and erythrocyte sedimentation rate) and complement levels. Hypocomplementemia was defined as C3 <80 mg/dL and C4 <15 mg/dL; complement levels were analyzed as categorical variables (normal vs. low). Serologic assessments included antinuclear antibody (immunofluorescence), anti-dsDNA (ELISA), and anti-Smith antibodies, recorded as present or absent.

Immunosuppressive treatment history included major modalities such as pulse steroid therapy (intravenous methylprednisolone ≥250 mg/day for 3 consecutive days) and cyclophosphamide (cumulative or induction), to evaluate associations with survival. Observed associations should be interpreted as associative rather than causal, and potential confounding by indication or immortal time bias should be acknowledged. Importantly, immunosuppressive therapies are well-known to increase the risk of infection and sepsis; therefore, any observed survival association should not be interpreted as a biological protective effect.

Statistical Analysis

All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk and Kolmogorov-Smirnov tests, complemented by visual inspection of histograms and Q-Q plots.

Descriptive statistics are presented as mean ± standard deviation for normally distributed variables. Due to the skewed distributions of follow-up periods and inflammatory markers, non-normally distributed data are reported as medians [interquartile range (IQR)]. Categorical variables are expressed as counts (n) and percentages (%).

Comparisons between survivors and deceased patients were performed using independent-samples t-tests or Mann-Whitney U tests for continuous variables, and chi-square or Fisher's exact tests for categorical variables, as appropriate. Cumulative survival probabilities were estimated using the Kaplan-Meier method, and subgroup differences were assessed with the log-rank test.

To identify independent predictors of mortality, Cox proportional hazards regression models were constructed. Variables with $p<0.10$ in univariable analyses, along with clinically relevant parameters such as organ involvement, complement levels, hypoalbuminemia, and treatment modalities, were included in the multivariable model using backward stepwise selection.

• Albumin hazard ratio (HR) directionality: albumin was modeled per 1 g/dL increase; an HR <1 indicates a protective effect of higher albumin, consistent with descriptive findings.

• Complement variables: both low C3 and low C4 were evaluated using univariable Cox models. They were excluded from the final multivariable model due to collinearity with CRP and clinical severity markers.

• Treatment effects (pulse steroids, immunosuppressives): observed associations with mortality should be interpreted as associational rather than causal, acknowledging the potential for confounding by indication, immortal time bias, or enhanced clinical monitoring in high-risk patients.

• APS/aPL limitation: due to incomplete aPL profiling, the impact of antiphospholipid syndrome-related events on mortality is described qualitatively, and no causal inference is made.

Results are presented as HRs with 95% confidence intervals (CIs); two-sided p-values <0.05 are considered statistically significant.

Results

A total of 184 patients diagnosed with SLE were included in this longitudinal, hospital-based cohort. The population demonstrated a marked female predominance (n=171, 92.9%), with a mean age at diagnosis of 36.0±12.8 years. The median follow-up duration for the cohort was 14.0 months (IQR: 5.0-42.0), reflecting a skewed distribution due to predominantly early mortality among a subset of patients. Although the mean follow-up was 29.1±38.7 months, the wide variance underscores the heterogeneous nature of patient trajectories across the 20-year study period.

Regarding organ involvement, LN was the most frequent manifestation, observed in 58 patients (31.5%). APS or aPL positivity, documented in 35 patients (19.0%), contributed substantially to thrombotic events and mortality in this cohort. Hematologic involvement was present in 27 patients (14.7%) and neuropsychiatric SLE was present in 8 patients (4.3%). Baseline immunological evaluation revealed positivity for anti-double-stranded DNA (anti-dsDNA) in 83.2% (n=153). Hypocomplementemia was common: low C3 and C4 levels were detected in 52.1% and 44.0% of patients, respectively (Table 1).

During the 20-year study period, 20 patients (10.9%) died. There were no significant differences between survivors and deceased patients with respect to age ($p=0.781$) or sex ($p=0.665$). However, the median follow-up duration was markedly shorter for deceased patients [3.0 months (IQR: 1.0-7.0)] than survivors [32.0 months (IQR: 12.0-64.0); $p<0.001$], reflecting predominantly early mortality after diagnosis.

Markers of clinical severity were significantly more pronounced in the deceased group. These patients experienced a higher mean number of hospitalizations (2.5±2.2 vs. 0.8±1.4, $p<0.001$) and a greater frequency of disease flares (1.9±1.8 vs. 1.1±1.4, $p=0.024$). Due to incomplete SLEDAI-2K data, flares

were primarily defined based on clinical deterioration requiring treatment escalation, as documented in medical charts. ICU admission was markedly more frequent among deceased patients (80.0% vs. 19.5%, p<0.001).

Baseline laboratory analyses demonstrated that deceased patients had higher median CRP levels (21.5 mg/L vs. 3.5 mg/L, p<0.001) and lower median serum albumin levels (3.3 g/dL vs. 3.8 g/dL, p<0.001). While anti-dsDNA positivity was similar between groups, deceased patients had a higher prevalence of low C4 levels (65.0% vs. 41.4%, p=0.041) and a non-significant trend toward lower C3 levels (70.0% vs. 50.0%, p=0.084).

Notably, LN was less frequent among deceased patients (5.0% vs. 34.8%, p=0.012), consistent with the so-called "nephritis paradox", which likely reflects closer monitoring and more intensive treatment in nephritis patients. Conversely, APS or aPL positivity was more common among deceased patients, highlighting the contribution of thrombotic complications to mortality (Table 1).

Significant differences in treatment strategies were observed between survivors and non-survivors. Antimalarial therapy with hydroxychloroquine was administered to nearly all survivors (96.3%) but to fewer deceased patients (65.0%, p<0.001). Pulse methylprednisolone therapy was administered more frequently to survivors than to deceased patients (39.6% vs. 15.0%, p=0.033). However, this observation reflects an association and should not be interpreted as causal, since higher-risk patients may have received different treatment intensities or closer monitoring.

The distribution of daily prednisolone doses differed significantly between groups (p<0.001). Approximately half of the survivors were maintained on moderate-dose prednisolone (7.5-30 mg/day), whereas the majority of deceased patients (60.0%) received high-dose glucocorticoids (>30 mg/day). Among the immunosuppressive agents, use of mycophenolate mofetil was more common in survivors (30.5% vs. 10.0%, p=0.048), whereas use of cyclophosphamide and azathioprine did not differ significantly between groups (Table 2).

An in-depth analysis of the 20 patients who died during follow-up revealed that mortality was predominantly driven by acute complications. The leading causes of death were infection and sepsis, accounting for 50.0% (n=10) of all fatalities. This was followed by SLE-related acute organ failure (including refractory alveolar hemorrhage and multi-organ dysfunction) in 25.0% (n=5) of cases. Cardiovascular events, such as myocardial infarction or stroke, were responsible for 15.0% (n=3) of deaths, while the remaining 10.0% (n=2) were attributed to other or unspecified complications. Kaplan-Meier survival analysis demonstrated that the risk of mortality was highest during the early months following diagnosis, with survival curves stabilizing thereafter (Figure 2).

Table 1. Baseline clinical, laboratory, and immunological characteristics of the study cohort according to survival status

Variable	Total cohort (n=184)	Survivors (n=164)	Deceased (n=20)	p-value
Demographics				
Age, years	36.0±12.8	35.9±12.8	36.9±13.0	0.781
Female, n (%)	171 (92.9)	152 (92.7)	19 (95.0)	0.665
Disease follow-up & activity				
Follow-up duration, months, median (IQR)	14.0 (5.0-42.0)	32.0 (12.0-64.0)	3.0 (1.0-7.0)	<0.001
Total hospitalizations	1.0±1.6	0.8±1.4	2.5±2.2	<0.001
Number of disease flares*	1.2±1.5	1.1±1.4	1.9±1.8	0.024
Clinical involvement, n (%)				
Lupus nephritis	58 (31.5)	57 (34.8)	1 (5.0)	0.012
Antiphospholipid syndrome	35 (19.0)	31 (18.9)	4 (20.0)	0.892
Hematologic involvement	27 (14.7)	27 (16.5)	0 (0.0)	0.114
Laboratory findings (baseline), median (IQR)				
C-reactive protein (mg/L)	4.5 (1.6-13.9)	3.5 (1.4-10.3)	21.5 (7.7-35.8)	<0.001
Serum albumin (g/dL)	3.7 (3.3-4.1)	3.8 (3.4-4.1)	3.3 (2.9-3.7)	<0.001
Immunological findings, n (%)				
Low C3	96 (52.1)	82 (50.0)	14 (70.0)	0.084
Low C4	81 (44.0)	68 (41.4)	13 (65.0)	0.041
Anti-dsDNA positivity	153 (83.2)	138 (84.1)	15 (75.0)	0.322

Data are presented as mean ± SD, median (IQR), or number (n) and percentage (%). Follow-up duration represents time from diagnosis to last visit or death and is reported as median (IQR) due to skewed distribution. Disease flare was defined as an increase of >4 points in the SLEDAI-2K score or clinical worsening requiring therapeutic escalation. Baseline laboratory and immunological parameters were obtained at study inclusion, prior to treatment escalation. Hypocomplementemia was defined according to local laboratory reference ranges (C3 <80 mg/dL, C4 <15 mg/dL). ANA: Antinuclear antibody, anti-dsDNA: Anti-double-stranded DNA antibody, Anti-Sm: Anti-Smith antibody, APS: Antiphospholipid syndrome, C3: Complement component 3, C4: Complement component 4, CRP: C-reactive protein, ICU: Intensive care unit, IQR: Interquartile range, SLE: Systemic lupus erythematosus, SD: Standard deviation, SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000

In multivariable Cox proportional hazards analysis, ICU admission emerged as the strongest independent predictor of mortality (HR: 11.4; 95% CI: 4.2-31.5; p<0.001). Among laboratory parameters, each 1 mg/L increase in CRP was associated with a 2% increase in mortality risk (HR: 1.02; p=0.04). Serum albumin was modeled per 1 g/dL increase; higher levels were associated with reduced mortality risk (HR: 0.31; p=0.008), which is consistent with lower albumin being linked to worse outcomes.

Pulse steroid therapy was observed more frequently among survivors (HR: 0.38; p=0.033), which reflects an association rather than causation and may partly indicate intensified monitoring or treatment in higher-risk patients. Similarly, the presence of LN was associated with improved observed survival (HR: 0.09; p=0.035), likely reflecting closer clinical surveillance and proactive management of patients with renal involvement (Table 3).

Table 2. Comparison of treatment characteristics between survivors and deceased patients with SLE

Treatment modality, n (%)	All cohort (n=184)	Survivors (n=164)	Deceased (n=20)	p-value
Glucocorticoids (ever)	175 (95.1)	156 (95.1)	19 (95.0)	0.999
Pulse methylprednisolone	68 (37.0)	65 (39.6)	3 (15.0)	0.033
Daily prednisolone dose				<0.001
Low dose (<7.5 mg/day)	42 (22.8)	40 (24.4)	2 (10.0)	
Moderate dose (7.5-30 mg/day)	88 (47.8)	82 (50.0)	6 (30.0)	
High dose (>30 mg/day)	54 (29.4)	42 (25.6)	12 (60.0)	
Antimalarials (hydroxychloroquine)	171 (92.9)	158 (96.3)	13 (65.0)	<0.001
Immunosuppressants (any)	124 (67.4)	115 (70.1)	9 (45.0)	0.024
Cyclophosphamide	42 (22.8)	38 (23.2)	4 (20.0)	0.751
Azathioprine	78 (42.4)	72 (43.9)	6 (30.0)	0.235
Mycophenolate mofetil	52 (28.3)	50 (30.5)	2 (10.0)	0.048
Rituximab	12 (6.5)	11 (6.7)	1 (5.0)	0.999

Data are presented as number (n) and percentage (%). Pulse methylprednisolone was defined as intravenous methylprednisolone ≥250 mg/day administered for three or more consecutive days. Daily prednisolone dose categories (<7.5 mg/day, 7.5-30 mg/day, >30 mg/day) were compared using a chi-square test for trend. Other immunosuppressive agents include cyclophosphamide, azathioprine, mycophenolate mofetil, and rituximab. HCQ: Hydroxychloroquine, SLE: Systemic lupus erythematosus

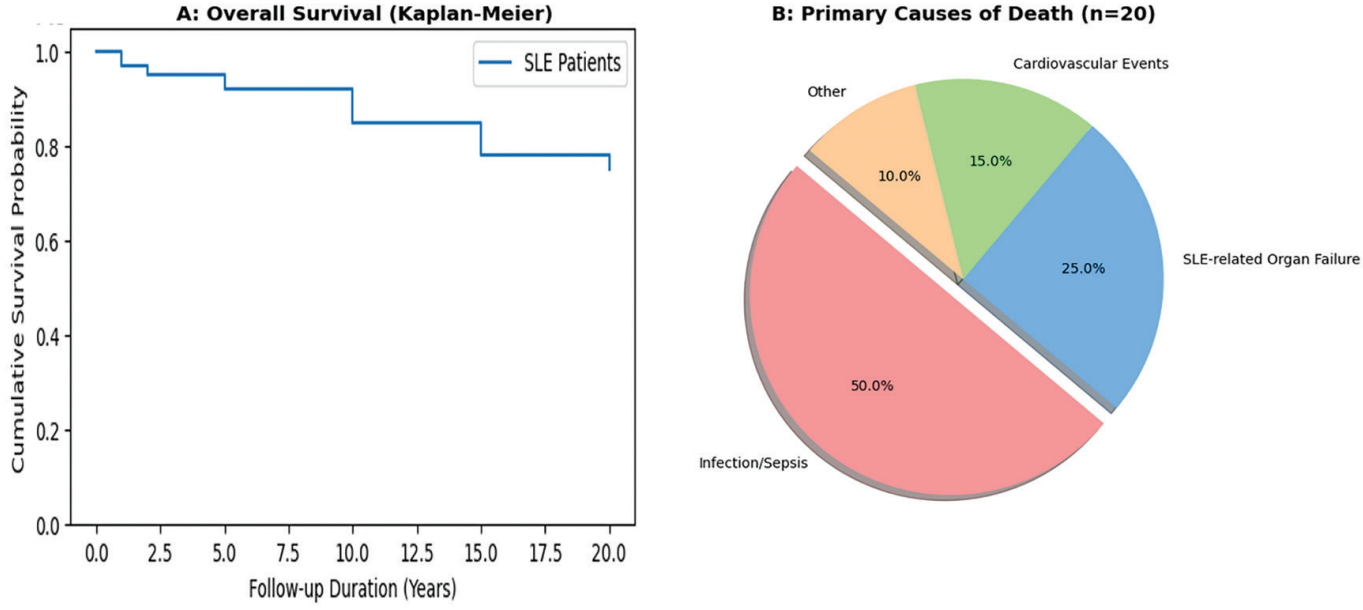

Figure 2. Survival characteristics of the study cohort. (A) Kaplan-Meier survival curve showing the probability of survival over time using longitudinal follow-up data (n=184). The X-axis represents the duration of follow-up (years), while the Y-axis indicates the cumulative survival probability. (B) Distribution of the primary causes of death among the deceased patients (n=20), with infection and sepsis accounting for 50% of the total mortality
SLE: Systemic lupus erythematosus

Table 3. Univariate and multivariate cox proportional hazards analysis of mortality risk factors in SLE patients				
Feature	**Univariate analysis HR (95% CI)**	**p-value**	**Multivariate analysis HR (95% CI)**	**p-value**
Clinical severity				
ICU admission (yes)	15.5 (6.2-38.9)	<0.001	11.4 (4.2-31.5)	<0.001
Organ involvement				
Presence of nephritis	0.13 (0.02-0.99)	0.048	0.09 (0.01-0.78)	0.035
Laboratory parameters				
CRP (per 1 mg/L increase)	1.03 (1.02-1.05)	<0.001	1.02 (1.00-1.04)	0.04
Albumin (per 1 g/dL increase)	0.20 (0.07-0.58)	0.003	0.31 (0.11-0.88)	0.008
Treatment factors				
Pulse steroid therapy	0.42 (0.21-0.85)	0.015	0.38 (0.15-0.92)	0.033
Cyclophosphamide use	1.03 (0.33-3.20)	0.96	—	—

Multivariate model was constructed using Cox proportional hazards regression, including variables with p<0.10 in univariate analysis and adjusted for age and sex. CI: Confidence interval, CRP: C-reactive protein, HR: Hazard ratio, ICU: Intensive care unit. "—" indicates that the variable was not included in the multivariate analysis

Discussion

This study, which represents two decades of clinical experience (2005-2025) at a tertiary referral center, identifies key clinical and laboratory determinants of mortality in a cohort of 184 patients with SLE. The overall mortality rate was 10.9% (n=20), with a notable concentration of deaths occurring early in the disease course. Mortality in this cohort was predominantly driven by acute complications, particularly infection and sepsis, rather than late-stage chronic organ damage.

In multivariable analyses, ICU admission (HR: 11.4), elevated baseline CRP levels, and hypoalbuminemia were the strongest independent predictors of mortality. Pulse steroid therapy and the presence of LN were associated with better observed survival (HR: 0.38 and 0.09, respectively), likely reflecting closer monitoring and more aggressive management in these higher-risk subgroups, rather than a direct protective effect. These associations should be interpreted cautiously because confounding by indication and immortal time bias may contribute to the observed outcomes.

Collectively, these results delineate a high-risk "inflammatory phenotype" predisposed to acute complications, emphasizing the importance of early risk stratification, vigilant clinical monitoring, and prompt intervention to improve survival. Limitations due to incomplete aPL profiling should be acknowledged, as APS-related events contributed substantially to mortality in a subset of patients and systematic assessment was not uniformly available.

The mortality risk factors identified in our study largely align with prognostic profiles reported in both global and Turkish cohorts. The observed overall mortality rate of 10.9% is comparable to previous Turkish studies: Pamuk et al.[4] reported a mortality rate of approximately 9.1%, and Artim-Esen et al.[5] similarly described early mortality as predominantly associated with high disease activity. In our cohort, elevated CRP and low serum albumin levels were associated not only with the acute-phase response but also with profound systemic inflammation and poor prognosis. These findings are consistent with previous observations that high baseline disease activity and inflammatory markers are linked to early mortality in Turkish patients with SLE. Notably, our results reinforce the concept that in severe SLE, often complicated by secondary infections, these biomarkers—reflecting a high-risk "acute inflammatory phenotype"—are associated with short-term mortality. Limitations related to incomplete aPL profiling should be acknowledged because APS-related events likely contributed to mortality in some patients, and a systematic assessment of these events was not available.

This finding is supported by our data, which show that 50.0% of deaths were due to infection or sepsis. The short median follow-up of 3.0 months among the deceased group (Table 1) further highlights the potential role of a high systemic inflammatory burden—objectively reflected by elevated CRP and hypoalbuminemia—in predisposing patients to rapid clinical deterioration and the need for intensive care.[8,11] As shown by our cumulative mortality analysis (Figure 2A), the risk of death is highest shortly after diagnosis. Accordingly, CRP and albumin levels are associated with this high-risk "acute inflammatory phenotype" and may help identify patients at increased risk of sepsis-related mortality. Importantly, associations observed between pulse steroid therapy or other immunosuppressive interventions and survival should be interpreted cautiously, as these findings reflect correlations rather than causal effects and may be influenced by confounding factors such as treatment intensity, closer monitoring, or survivor bias. Early recognition of this high-risk profile may facilitate closer clinical surveillance and informed decision-making regarding supportive care and therapeutic intensity.

On the other hand, the impact of LN on mortality remains a topic of ongoing debate.[15] Although LN has traditionally been considered a marker of severe organ involvement and a potential risk factor for death, our observation of an inverse

association (HR: 0.09; Table 3) aligns with several contemporary cohorts reporting heterogeneous survival outcomes.[16] This apparent paradox likely reflects a combination of factors, including intensified monitoring, closer clinical follow-up, and more aggressive immunosuppressive therapy in patients with renal involvement, rather than a direct protective effect of LN itself. Consequently, these findings should be interpreted as associations, and causal inferences cannot be drawn from this observational study.

At our tertiary center, patients with renal involvement are generally monitored more closely and often receive more intensive therapy. Treatment data (Table 2) show that survivors—many of whom had LN—were significantly more likely to receive antimalarials (hydroxychloroquine, 96.3% vs. 65.0%, $p<0.001$) and mycophenolate mofetil (mycophenolate mofetil, 30.5% vs. 10.0%, $p=0.048$) than deceased patients. Additionally, the higher frequency of pulse methylprednisolone use among survivors (39.6% vs. 15.0%, $p=0.033$) suggests that patients with major organ involvement, such as LN, were managed with more intensive anti-inflammatory regimens. These observations likely reflect an association between proactive therapeutic strategies and improved short-term survival, rather than a direct protective effect of renal involvement itself. Such intensive management may mitigate the risk of acute, potentially fatal complications—including sepsis and severe disease flares—that were the predominant causes of death in our cohort (Figure 2B).[17]

Consistent with our findings, multivariable analysis identified pulse steroid therapy as an independent factor associated with improved short-term survival (HR: 0.38). This treatment modality was more commonly used in survivors, particularly among patients with LN. Importantly, most deaths in our cohort occurred early after diagnosis and were primarily related to acute sepsis rather than chronic organ damage.[18] These observations suggest that intensive monitoring and early immunosuppressive therapy are associated with lower early mortality, rather than a direct protective effect of LN. Conversely, patients without major organ-specific involvement—sometimes classified as "non–organ-involving SLE"—may still experience severe systemic inflammation, which can lead to rapid clinical deterioration if not addressed with comparable vigilance.[8,19,20] Furthermore, a substantial proportion of early deaths were related to thrombotic complications potentially associated with APS or aPL positivity. Because aPL profiling in our cohort was incomplete, this relationship should be interpreted with caution, and we emphasize that APS-related events may significantly contribute to early mortality in patients without classic organ involvement. Overall, these findings highlight that in SLE, early mortality risk is influenced less by the specific organ affected and more by the timely recognition and management of acute systemic inflammation and thrombotic complications.

The strong association between ICU admission and mortality (HR: 11.4; Table 3) indicates that patients requiring critical care often present with a high-risk "inflammatory phenotype", characterized by elevated CRP and hypoalbuminemia. These laboratory abnormalities serve as markers of systemic inflammation and metabolic depletion, identifying a critical window of vulnerability during which patients are at increased risk for refractory sepsis and multi-organ failure. A subset of patients who died had thrombotic events compatible with APS. However, a formal APS classification could not be established in many cases due to incomplete aPL profiling during the long accrual period. Consequently, while APS-compatible manifestations were observed among non-survivors, a statistically robust association between APS and mortality could not be demonstrated. These findings should therefore be interpreted descriptively, and no causal inference regarding APS-related mortality can be made.

Importantly, classification as non–organ-involving SLE does not preclude the occurrence of severe systemic complications. In our cohort, several patients without classical major organ involvement (such as LN or neuropsychiatric SLE) nonetheless fulfilled classification criteria in the hematologic, mucocutaneous, and serologic domains and later developed thrombotic or hemorrhagic complications. This highlights the heterogeneity of SLE phenotypes and underscores that the absence of traditional organ involvement does not necessarily imply a benign disease course.

Conversely, the observed survival advantage in patients with LN (HR: 0.09) highlights that early mortality is not inevitable. The "clinical vigilance" inherent in the management of renal involvement—as reflected by the more frequent use of pulse steroids (HR: 0.38) and intensive immunosuppressive regimens (Table 2)—was associated with improved survival, likely because of closer monitoring and timely intervention during acute flares. However, these therapies carry inherent risks, including an increased susceptibility to infection, underscoring the need to balance immunosuppressive intensity with vigilant infection prophylaxis. Our findings indicate that in contemporary SLE cohorts, survival is determined not only by the organ involved but also by the effectiveness of clinical strategies that mitigate both inflammatory and thrombotic complications. Early recognition and management of high-risk profiles, including the potential contribution of APS-related events, are essential for reducing preventable early deaths through the combined control of disease activity and maintenance of physiological reserve.

Similarly, ICU admission and the absence of LN among non-survivors likely reflect extreme acute disease severity rather than protective or harmful effects of specific organ involvement. Together, these findings suggest that early mortality in SLE is driven predominantly by acute systemic inflammatory burden and critical illness, rather than by cumulative organ damage alone.

A primary strength of this study is its 20-year accrual period, enabling the identification of early mortality patterns and risk profiles. Integration of comprehensive laboratory panels with detailed clinical data, including ICU admissions and treatment modalities, provides a practical framework for risk stratification in high-acuity SLE patients. Multivariable Cox regression models were used to evaluate associations between inflammatory biomarkers and clinical indicators; residual confounding, including potential APS contributions, was acknowledged. The single-center design enhances internal validity by reducing inter-center variability.

Study Limitations

Despite the valuable insights provided by our study, several limitations should be acknowledged. First, the retrospective design may have posed challenges in consistently capturing longitudinal clinical parameters and standardized disease activity scores (e.g., SLEDAI-2K), which were frequently missing. As a result, disease flares were sometimes inferred from chart review and from escalation of therapy rather than by objective scoring, which may have reduced the precision of flare-related analyses. Second, the single-center design of this study, conducted at a tertiary referral hospital, may limit the generalizability of our findings to SLE populations in primary-care settings or other geographic regions. Third, although our cohort size (n=184) was sufficient to identify major independent risk factors, the relatively small number of deaths (n=20) may have limited the statistical power to detect associations with less common manifestations, such as specific neuropsychiatric or cardiac involvement, in multivariable analyses. Fourth, systematic assessment of aPL profiles was not available for all patients; therefore, APS-related mortality and thrombotic risk could not be fully evaluated. This limitation should be considered when interpreting the contribution of APS to deaths in this cohort. In addition, because data were derived from hospital records, complications or minor flares occurring outside our center may not have been fully captured. Finally, the 20-year accrual period (2005-2025) encompassed substantial advances in SLE management, including evolving immunosuppressive protocols and the introduction of biologic therapies. Although major interventions, such as pulse steroids, were incorporated into our models, these temporal changes, together with potential confounding by indication, may have influenced the observed associations between treatment and outcomes, particularly regarding sepsis and infection-related mortality.

Conclusion

This study underscores the prognostic value of early risk stratification in patients with SLE, drawing on a 20-year accrual period at a tertiary referral center. Elevated CRP, hypoalbuminemia, frequent hospitalizations, and ICU admission were identified as practical, low-cost, and reliable predictors of increased mortality risk, with ICU admission showing the strongest association with poor outcomes. Importantly, our findings highlight a high-risk "inflammatory phenotype", which—if recognized early—may allow clinicians to intensify monitoring and implement proactive interventions to prevent acute, life-threatening complications, particularly sepsis. Additionally, the observed survival advantage in patients with LN reflects the potential benefits of intensive monitoring and aggressive management, rather than a direct protective effect. Limitations include incomplete aPL profiling, which may have influenced assessment of APS-related mortality. Overall, our 20-year experience demonstrates that vigilant attention to inflammatory and metabolic markers, coupled with tailored therapeutic strategies, is critical for improving early and long-term survival outcomes in SLE.

Ethics

Ethics Committee Approval: Non-Interventional Clinical Research Ethics Committee of Dicle University Faculty of Medicine (approval no: 4, date: 24.12.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A.A., D.Y., Concept: Z.A.A., D.Y., Design: Z.A.A., D.Y., Data Collection and Processing: Z.A.A., D.Y., Analysis or Interpretation: Z.A.A., D.Y., Literature Search: Z.A.A., D.Y., Writing: Z.A.A., D.Y.

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References

1. Su X, Yu H, Lei Q, et al. Systemic lupus erythematosus: pathogenesis and targeted therapy. Mol Biomed. 2024;5:54.
2. Tsokos GC. The immunology of systemic lupus erythematosus. Nat Immunol. 2024;25:1332-43.
3. Ameer MA, Chaudhry H, Mushtaq J, et al. An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus. 2022;14:e30330.
4. Pamuk ON, Akbay FG, Dönmez S, Yilmaz N, Calayir GB, Yavuz S. The clinical manifestations and survival of systemic lupus erythematosus patients in Turkey: report from two centers. Lupus. 2013;22:1416-24.
5. 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.
6. Lee YH, Song GG. Mortality in patients with systemic lupus erythematosus: a meta-analysis of overall and cause-specific effects. Lupus. 2024;33:929-37.

7. Lai CC, Sun YS, Chen WS, et al. Risk factors for mortality in systemic lupus erythematosus patients: Analysis of adult and pediatric cohorts in Taiwan. J Chin Med Assoc. 2022;85:1044-50.

8. He S, Tang C, Yu J, et al. Combining C reactive protein and serum albumin to predict 90-day mortality in systemic lupus erythematosus with serious community-acquired infections. Lupus Sci Med. 2021;8:e000505.

9. Kanık HK, Erden A, Yıldırım D, et al. Evolution of clinical characteristics and treatment strategies in Turkish SLE patients over two decades: a retrospective cohort study. Bratisl Med J. 2025;126:2329-36.

10. Artim-Esen B, Çene E, Şahinkaya Y, et al. Cluster analysis of autoantibodies in 852 patients with systemic lupus erythematosus from a single center. J Rheumatol. 2014;41:1304-10.

11. Üsküdar Cansu D, Üsküdar Teke H, Korkmaz C. Survival analysis of Turkish patients with systemic lupus erythematosus: older age at diagnosis affects mortality. Arch Rheumatol. 2017;32:141-8.

12. 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.

13. Eilertsen GØ, Becker-Merok A, Nossent JC. The influence of the 1997 updated classification criteria for systemic lupus erythematosus: epidemiology, disease presentation, and patient management. J Rheumatol. 2009;36:552-9.

14. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1400-12.

15. Reppe Moe SE, Molberg Ø, Strøm EH, Lerang K. Assessing the relative impact of lupus nephritis on mortality in a population-based systemic lupus erythematosus cohort. Lupus. 2019;28:818-25.

16. Luo W, Farinha F, Isenberg DA, Rahman A. Survival analysis of mortality and development of lupus nephritis in patients with systemic lupus erythematosus up to 40 years of follow-up. Rheumatology (Oxford). 2022;62:200-8.

17. Reppe Moe S, Haukeland H, Molberg Ø, Lerang K. Long-term outcome in systemic lupus erythematosus; knowledge from population-based cohorts. J Clin Med. 2021;10:4306.

18. Howe HS, Boey ML, Feng PH. Methylprednisolone in systemic lupus erythematosus. Singapore Med J. 1990;31:18-21.

19. Ponticelli C, Zucchelli P, Moroni G, Cagnoli L, Banfi G, Pasquali S. Long-term prognosis of diffuse lupus nephritis. Clin Nephrol. 1987;28:263-71.

20. Figueroa-Parra G, Cuéllar-Gutiérrez MC, González-Treviño M, et al. Impact of glucocorticoid dose on complete response, serious infections, and mortality during the initial therapy of lupus nephritis: a systematic review and meta-analysis of the control arms of randomized controlled trials. Arthritis Rheumatol. 2024;76:1408-18.

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Efficacy, retention, and safety of baricitinib in real-life: HUR-BIO monocentric experience

Baricitinibin gerçek hayattaki etkinliği, kalıcılığı ve güvenliği: HÜR-BİO tek merkezli deneyimi

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Abstract

Objective: This study evaluates the effectiveness, retention rate and safety of baricitinib, including a comparison between baricitinib and a tumour necrosis factor inhibitor (adalimumab) in a real-life cohort of patients with rheumatoid arthritis (RA).

Methods: RA patients from the Hacettepe University Biological Prospective Database who received at least one dose of baricitinib or adalimumab between June 2020 and January 2023 were analyzed. Drug survival analysis included patients with at least one dose, while efficacy and safety analyses required at least one follow-up visit. Adverse events, major adverse cardiovascular events (MACE), malignancies, and medication adherence were assessed. The European Alliance of Associations for Rheumatology (EULAR) response classified patients as either good responders or non-responders.

Results: A total of 280 patients (86 baricitinib, 194 adalimumab) were included, with a mean age of 52.4 (±13.6) years; 77.5% were female. Baricitinib significantly improved disease activity parameters. High patient global assessment [odds ratio (OR): 1.05 (95% confidence interval (CI): 1.02-1.09)] predicted a good response, while RF positivity [OR: 7.66 (95% CI: 1.46-40.07)] indicated a poor response. MACE occurred in 2 patients (2.5%) on baricitinib and in 4 patients (2.5%) on adalimumab, with rates of 15.3 and 9.1 per 1000 patient-years, respectively (p=0.20).

Conclusion: Baricitinib improved disease activity parameters and a high patient global assessment predicted a good EULAR response. MACE incidence was comparable to that with adalimumab.

Keywords: Rheumatoid arthritis, baricitinib, real life, major adverse cardiovascular events, adverse events

Özet

Amaç: Bu çalışma, romatoid artrit (RA) hastalarının gerçek yaşam koşullarında tedavisinde barisitinibin güvenliliğini, etkililiğini ve tedavide kalıcılığını değerlendirmek; barisitinib içinde ve bir tümör nekroz faktörü inhibitörü (adalimumab) ile karşılaştırmayı amaçlamaktadır.

Yöntem: Haziran 2020 ile Ocak 2023 arasında en az bir doz barisitinib veya adalimumab alan Hacettepe Üniversitesi Biyolojik Prospektif Veritabanı'ndan RA hastaları analiz edildi. İlaç sağkalımı analizi en az bir doz baricitinib ve adalimumab alan hastaları içerirken, etkililik ve güvenlilik analizleri için en az bir takip viziti bulunması gerekiyordu. Advers olaylar, majör olumsuz kardiyovasküler olaylar (MACE), maligniteler ve ilaca uyum değerlendirildi. Avrupa Romatoloji Dernekleri Birliği (EULAR) yanıtı, iyi yanıt verenler veya yanıt vermeyenler olarak sınıflandırdı.

Bulgular: Toplam 280 hasta (86 barisitinib, 194 adalimumab) çalışmaya dahil edildi; ortalama yaş 52,4 (±13,6) yıl olup hastaların %77,5'i kadındı. Barisitinib, hastalık aktivitesi parametrelerini anlamlı düzeyde iyileştirdi. Yüksek hasta global değerlendirmesi iyi yanıtı öngördü [risk oranı (OR): 0,95 (%95 güven aralığı (GA): 0,92-0,98)], RF pozitifliği ise kötü yanıtı işaret etti [OR: 7,66 (%95 GA: 1,46-40,07)]. MACE, barisitinib kullanan 2 hastada (%2,5) ve adalimumab kullanan 4 hastada (%2,5) görüldü; oranlar sırasıyla 1000 hasta-yıl başına 15,3 ve 9,1 idi (p=0,20).

Sonuç: Barisitinib tedavisi hastalık aktivitesi göstergelerinde düzelme sağladı ve yüksek hasta global değerlendirmesi iyi EULAR yanıtının öngördürücüsüydü. MACE sıklığı adalimumab ile benzerdi.

Anahtar Kelimeler: Romatoid artrit, baricitinib, gerçek yaşam, majör kardiyak olaylar, advers olaylar

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent joint deterioration and additional symptoms, often leading to long-term disability and increased mortality.[1] The primary goal in treating RA is to achieve and maintain either remission or low disease activity (LDA) in all patients.[2]

Targeted therapies, such as biologic disease modifying anti-rheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), have led to significant advances in the treatment of RA. These agents have significantly improved treatment effectiveness and increased the likelihood of achieving treatment goals that are often not achievable with traditional synthetic DMARDs (csDMARDs).[3]

Baricitinib, an oral selective inhibitor of Janus kinase inhibitors 1 (JAK1) and JAK2 with lower affinity for JAK3 and tyrosine kinase 2, received approval from the European Medicines Agency (EMA) in February 2017 and from the Food and Drug Administration (FDA) in May 2018 for the treatment of RA. The effectiveness and safety of baricitinib have been assessed in clinical trials, both as monotherapy and in combination with methotrexate, for patients with active RA. The importance of real-life evidence in complementing clinical study data is well recognized, as it provides valuable information. In numerous real-world studies, treatment with baricitinib has been shown to significantly improve disease activity, leading to remission or LDA in many patients. Additionally, it has displayed high persistence rates and comparable or better survival rates compared to tumour necrosis factor (TNF) inhibitors and other bDMARDs.[4] The incidence of opportunistic infections, herpes zoster (HZ), and nonmelanoma skin cancer was higher with JAK inhibitors than with TNF inhibitors. In the last randomized controlled trial (RCT), the odds of major adverse cardiovascular events (MACE) and cancer were higher in the tofacitinib group than in the TNF-inhibitor group, and this effect was interpreted as class-specific.[5] On the other hand, in the most extensive real-life cohort study comparing patients initiating JAK inhibitors versus adalimumab, the risks of MACEs and venous thromboembolisms did not differ significantly between groups.[6]

Given geographic and racial differences, no real-world data on baricitinib in the Turkish population are yet available, and differences in MACE outcomes exist between RCTs and real-world studies. This study aims to evaluate the effectiveness, retention rate and safety of baricitinib, including intra-baricitinib comparisons and comparisons to a TNF inhibitor in real-life settings in patients with RA.

Materials and Methods

Study Population

In this retrospective longitudinal analysis, we examined RA patients who had received at least one dose of baricitinib between June 2020 and the end of January 2023. These patients were part of the Hacettepe University Biological Prospective Database, established in 2005.[7] All patients met the classification criteria set forth by the American College of Rheumatology (ACR) in 1987 and/or by the European League Against Rheumatism (EULAR/ACR) in 2010.[8,9]

According to Turkish social security and prescription rules, the treating physician should see patients receiving biologic/targeted-synthetic DMARDs every three months. Patients who had taken at least one dose were included in the drug survival analysis, while patients who had at least one follow-up visit were included in the efficacy and safety analysis. Furthermore, all patients were contacted by telephone, regardless of whether they attended follow-up visits, to inquire about any potential drug-related adverse effects, major adverse cardiovascular events (after 60 days of drug exposure), malignancies, and adherence to their prescribed medication regimen. Furthermore, relevant variables for consenting patients were obtained from the National Electronic Health Records.

During this period, baricitinib and adalimumab were prescribed to 86 and 194 patients, respectively; 62 (72.1%) and 142 (73.2%) of these patients had at least one follow-up visit. All patients used the medication as recommended. To assess potential differences in major adverse cardiovascular events and side effects relative to anti-TNFs, a control group comprising 194 RA patients who started adalimumab during the same period (June 2020-January 2023) was used. Adalimumab was selected because it is the most common first-line biologic for RA treatment in our country and because it was used in the RCT evaluating the cardiovascular and cancer risks of tofacitinib. The study, based on real-world data, included patients with a minimum follow-up of 3 months and at least one control visit for effectiveness and drug-retention analyses. The maximum observation time was defined by the duration of the study period, with follow-up visits for both treatments scheduled at approximately 3-month intervals. Informed consent was obtained from all patients. This study was approved by Hacettepe University Ethics Commission (approval number: 2023-02-02, date: 24.01.2023).

Data Collection and Assessments

Demographic Data and Population Characteristics

Sex, age, smoking history, body mass index (BMI), and presence of hypertension, hyperlipidemia, chronic kidney disease, and diabetes mellitus (DM) were recorded. Regarding RA, the following data were collected: disease duration, positivity for rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP), duration of baricitinib treatment, concomitant use of DMARDs (methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), and glucocorticoids at the last visit; the baseline and final-visit data on disease activity and functional status parameters. These parameters included erythrocyte

sedimentation rate, C-reactive protein (CRP) concentration, number of tender and swollen joints (28 joints), patient global assessment using a visual analogue scale (PGA-VAS), disease activity score [DAS28- estimated sedimentation rate (ESR)], and health assessment questionnaire-disability index (HAQ-DI).

In the main analyses, patients were categorized according to the following criteria: biologicnaïve versus biologic experienced; baricitinib monotherapy versus baricitinib with concomitant csDMARDs; EULAR good response versus EULAR not-good response (moderate or no response); and baricitinib versus adalimumab.

Assessment of Efficacy

The efficacy analysis included patients who had at least one follow-up visit while receiving baricitinib and who had complete baseline disease activity data. Patients were classified into responders and non-responders at baseline and the last follow-up visit based on DAS28 scores: DAS28 ≤3.2 for responders and DAS28 >3.2 for non-responders.[10] We used the EULAR response criteria to evaluate the efficacy of baricitinib. The patients were divided into three groups: good response (DAS28 improvement from baseline >1.2 and DAS28 at the last visit ≤ 3.2), moderate response (DAS28 improvement from baseline >1.2 and DAS28 at the last visit visit >3.2 or DAS28 improvement from baseline >0.6 to ≤1.2 and DAS28 at last visit ≤5.1) and no response (DAS28 improvement from baseline ≤0.6, regardless of DAS28 at last visit, or DAS28 improvement from baseline >0.6 to ≤1.2 and DAS28 at last visit >5.1).[11] In addition to assessing disease activity, HAQ-DI scores were compared between the first and last visits to analyze the impact of baricitinib on patients' functional status. A minimal clinically significant difference in HAQ-DI scores has been suggested to be 0.22 (calculated for patients with a baseline HAQ-DI >0.5), and previous studies have defined functional remission as HAQ-DI ≤0.5.[12,13]

Assessment of Retention Rate

Patients who received at least one dose of baricitinib were included in the drug retention analysis. For a more accurate calculation of drug retention, patients prescribed baricitinib or adalimumab who neither had a follow-up visit within six months nor were identified in the national database as being prescribed any other biologic therapy were categorized as continuing their respective treatment. Patients who had no follow-up visit for more than six months and who were not prescribed baricitinib by another healthcare provider were categorized as having discontinued baricitinib and adalimumab.

Baricitinib Discontinuation and Adverse Events

Analyses of baricitinib discontinuation and adverse events were performed in patients with complete baseline data who had at least one follow-up visit or a final telephone assessment during baricitinib treatment. Adverse events attributable to baricitinib were analyzed for safety, including neutropenia (<1,500/mm^3), leukopenia (<4,000/mm^3), transaminase elevation (alanine aminotransferase >3x upper limit of normal=40 IU/L), changes in lipid profile (assessed in patients with baseline and follow-up values), HZ, infections other than HZ, hepatitis reactivation, tuberculosis, cancer, and major adverse cardiovascular events. Although there are various definitions for MACE, the most commonly used definition in the field of rheumatology includes cardiovascular death (excluding pulmonary embolism), nonfatal myocardial infarction, and nonfatal stroke.[5,14] The incidence rates for MACE and cancer were calculated per 1,000 patient-years.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS statistics version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were expressed as mean (standard deviation) for normally distributed numerical variables, and as median (minimum-maximum) and number and percentage for non-normally distributed numerical variables. The chi-square and Fisher's exact tests were used to compare percentages. Student's t-test and the Mann-Whitney U test were used to analyze the differences between variables according to their distributional patterns.

In the univariate analysis, disease duration, BMI ≥30, positive RF, duration of baricitinib, steroid use at last visit, CRP at first visit, HAQ, patient's VAS, DAS28 CRP, biological naive and baricitinib monotherapy were included in the logistic regression analysis to identify independent predictors of EULAR Responder Index response at the last visit. Hosmer-Lemeshow goodness-of-fit statistics were used to assess model fit.

Factors affecting medication adherence and differences in duration were assessed using Kaplan-Meier analysis. Potential factors identified by univariate analyses ($p<0.20$) were subsequently entered into a Cox regression analysis with backward selection to determine independent predictors of baricitinib retention. MACE was estimated per 1,000 patient-years. To compare the rates of major adverse cardiovascular events between patients treated with baricitinib and adalimumab, a Poisson regression model with a log link function was applied. The natural logarithm of follow-up time in person-years was included as an offset variable to account for varying observation periods among participants. The primary predictor was the treatment group, categorized as receiving baricitinib or adalimumab, while additional covariates included smoking status, treatment duration, family history of cardiovascular disease, and treatment-naive status. Goodness-of-fit measures, including the deviance-to-degrees-of-freedom ratio and Pearson

chi-square, were used to assess model adequacy, and rate ratios with 95% confidence intervals were reported for each predictor. Statistical significance was set at $p<0.05$.

Results

Study Population and Patient Characteristics

The study included 280 patients: 86 in the baricitinib group and 194 in the adalimumab group. The mean age was 52.4 (±13.6) years, and 77.5% of patients were female. The mean disease duration was 9.5 (±8.2) years overall, 10.7 (±8.5) years for the baricitinib group, and 8.9 (±8.0) years for the adalimumab group (p=0.09) while the mean disease duration at the time of the first biologic was 5.9 (±7.2) years overall, 6.0 (±7.2) years for baricitinib, and 5.9 (±7.2) years for adalimumab (p=0.91). The proportion of biologic-naive patients was significantly lower in the baricitinib group (30.2%) than in the adalimumab group (55.2%) (p<0.001), suggesting a prevalent inclination towards anti-TNFs as the primary biologic treatment. Interestingly, the baricitinib-treated population had a higher prevalence of smokers than the adalimumab group (51.9% vs. 24.0%). Comorbidities did not differ significantly between groups, but prior percutaneous coronary intervention, hypertension, and chronic kidney disease were more common in the baricitinib group (Table 1). Additionally, treatment-naïve patients in both medication groups were compared, and no significant differences were observed between the groups (Supplementary Table 1).

Baricitinib is utilized more frequently as monotherapy (±GC) than adalimumab (27.9% vs. 20.6%, respectively, p=0.18), although this difference did not achieve statistical significance (Table 2). Supplementary Tables 2 and 3 compare the biologic-naive and biologic-experienced groups, and the baricitinib monotherapy and baricitinib+cs DMARD combined-treatment groups.

Baricitinib Efficacy and Retention Rate

Efficacy

Of the 86 patients prescribed baricitinib, 24 (27.9%) had no control visit data, and 10 (11.6%) were missing first visit data. Therefore, 52 patients (60.5%) with complete baseline and follow-up visit data were included in further analyses to evaluate the drug's effectiveness (Table 3).

Table 1. Comparison of demographic and baseline characteristics between patients receiving baricitinib and adalimumab

	All patients (n=280)	Baricitinib (n=86)	Adalimumab (n=194)	p
Female n (%)	217 (77.5)	68 (79.1)	149 (76.8)	0.67
Age (SD)	52.4 (13.6)	52.5 (13.8)	52.4 (13.5)	0.95
Disease duration, years (SD)	9.5 (8.2)	10.7 (8.5)	8.9 (8.0)	0.09
Disease duration at the time of the first biologic drug: years (SD)	5.9 (7.2)	6.0 (7.2)	5.9 (7.2)	0.91
Biological naive n (%)	133 (47.5)	26 (30.2)	107 (55.2)	**<0.001**
Smoking (%)				
-Never	137/210 (65.2)	39/81 (48.1)	98/129 (76.0)	**<0.001**
-Ex-smoker or active smoker	73/210 (34.8)	42/81 (51.9)	31/129 (24.0)	
BMI (SD)	27.8 (5.4)	27.5 (5.4)	28.0 (5.3)	0.44
BMI ≥30 (%)	68/221 (30.8)	23/81 (28.4)	45/140 (32.1)	0.56
Coronary artery disease (%)	26/242 (10.7)	10/80 (12.5)	16/162 (9.9)	0.53
Early family history of CAD (%)	36/237 (13.4)	7/80 (8.8)	29/157 (18.5)	**0.04**
Percutaneous coronary intervention (%)	24/242 (9.9)	10/80 (12.5)	14/162 (8.6)	0.34
Bypass (%)	6/241 (2.5)	3/80 (3.8)	3/161 (1.9)	0.40
Hypertension (%)	89/241 (36.9)	32/80 (40)	57/161 (35.4)	0.48
Diabetes n (%)	48/241 (19.9)	17/80 (21.3)	31/161 (19.3)	0.71
Hyperlipidemia n (%)	109/225 (48.4)	37/80 (46.3)	72/145 (49.7)	0.62
CKD n (%)	12/240 (5.0)	6/80 (7.5)	6/160 (3.8)	0.22
Infection requiring hospitalization (%)	31/231 (13.4)	11/80 (13.8)	20/151 (13.2)	0.91
History of cancer in first- and second-degree relatives	61/240 (25.4)	13/80 (16.3)	48/160 (30.0)	**0.02**
MACE (%)	6/242 (2.5)	2/80 (2.5)	4/162 (2.5)	1
DVT (%)	4/241 (1.7)	0	4/161 (2.5)	0.30
PTE (%)	5/241 (2.1)	1/80 (1.3)	4/107 (2.5)	0.63

BMI: Body mass index, CAD: Coronary artery disease, CKD: Chronic kidney disease, MACE: Major adverse cardiovascular event, DVT: Deep vein thrombosis, PTE: Pulmonary thromboembolism, SD: Standard deviation

Table 2. Comparison of medication use between patients receiving baricitinib and adalimumab				
	All patients (n=280)	**Baricitinib (n=86)**	**Adalimumab (n=194)**	**p**
Duration of biological drug use, months (SD)	**8.0 (8.9)**	**5.8 (5.0)**	**9.1 (9.9)**	**<0.001**
Monotherapy (±GC) (%)	64 (22.9)	24 (27.9)	40 (20.6)	0.18
Last visit (%)				
- Methotrexate	46 (16.4)	17 (19.8)	29 (14.9)	0.31
- Sulfasalazine	4 (1.4)	1 (1.2)	3 (1.5)	1
- Hydroxychloroquine	120 (42.9)	27 (31.4)	93 (47.9)	**0.01**
- Leflunomide	139 (49.6)	38 (44.2)	101 (52.1)	0.22
- Glucocorticoid	219 (78.2)	59 (68.6)	160 (82.5)	**0.009**
Glucocorticoid (%)				
-<5 mg	35 (23.5)	15 (25.4)	39 (24.4)	0.87
-≥5 mg	114 (76.5)	44 (74.6)	121 (75.6)	
GC: Glucocorticoid, SD: Standard deviation				

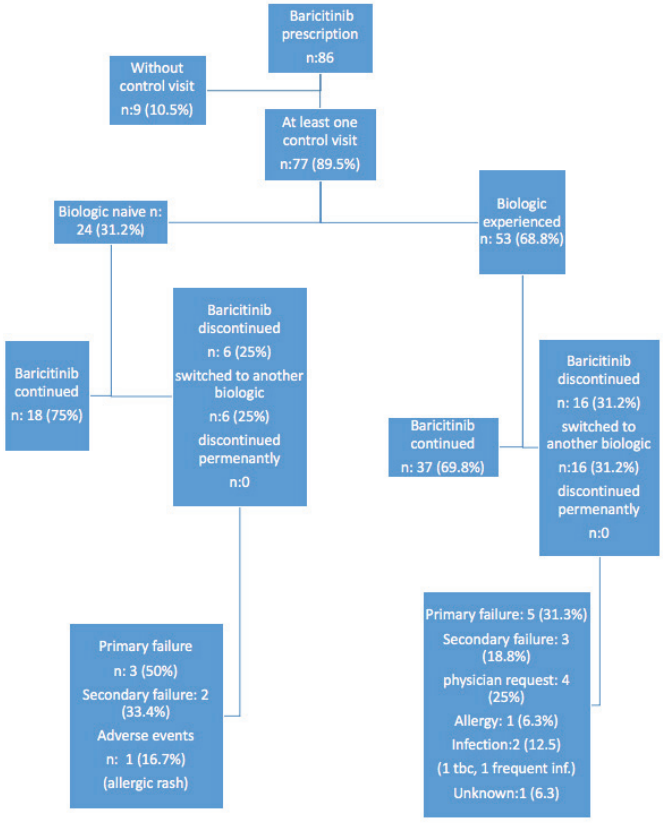

Figure 1. Patient enrollment and discontinuation flowchart

The mean follow-up time for patients who received baricitinib was 5.8 (±5.0) months. Disease activity parameters at baseline and final evaluation were as follows: ESR 30.1 (20) vs. 11.5 (30.0) (p<0.001); CRP 0.9 (1.1) vs. 0.40 (0.6) (p<0.001); DAS28 CRP 4.2 (1.5) vs. 2.7 (2.3) (p<0.001); HAQ 0.91 (0.6) vs. 0.52 (1.3) (p<0.001); SJ 1 (2.0) vs. 0 (0) (p<0.001); TJ 3 (6.0) vs. 0 (3.0) (p<0.001); and P-VAS 60 (30.0) vs. 50 (40.0) (p<0.001). According to the EULAR response index, there was no difference in comorbidities and cs DMARDs between those who responded well and those who did not. Biologic-naive status and use of baricitinib as monotherapy were significantly more common in the good-responder group than in the non-responder group (Table 4).

Predictors of EULAR good response were determined by logistic regression analysis. A high patient global assessment before baricitinib treatment [odds ratio (OR): 1.05 (95% CI: 1.02-1.09)] was associated with a good response, whereas RF positivity [OR: 7.66 (95% CI: 1.46-40.07)] was associated with a poor response (Table 4). Model fit was assessed using the Hosmer-Lemeshow test (p=0.71).

While a significant improvement in DAS 28 CRP was noted in both the baricitinib and adalimumab arms, the EULAR responder index showed that the proportion of good and moderate responses was significantly higher in the adalimumab arm compared to the baricitinib arm (Table 4). At the last visit, no significant differences were observed between baricitinib and adalimumab on disease activity assessment indices, except for the EULAR good response index.

Retention

Baricitinib retention rate was calculated for the entire study population (n=86; 100%) (Figure 1). The one-year drug survival rate for adalimumab was 61.1%, while that for baricitinib was 54.4% (log-rank test p=0.47). Median retention was 15.1 months for baricitinib and 22.9 months for adalimumab (Figure 2). The median duration of baricitinib treatment was 4.4 (6.3) months [median, interquartile range (IQR)] for biologic-naive patients and 7.5 (6.5) months [med, (IQR)] for biologic experienced patients (p=0.09) (Supplementary Table 1). Survival on baricitinib was significantly higher in biologic-naïve patients compared to biologic-experienced patients [18 (75%) & 37 (69.8%) log rank p=0.02] (Supplementary Figure 1).

Table 3. Clinical and demographic characteristics of patients treated with baricitinib: good vs. non-good responders								
	All patients (n=52)	Good response (n=24)	Non good response (n=28)	p	Multivariate analysis		Final multivariate analysis	
					Adjusted odds ratio (95% CI)	p	Adjusted odds ratio (95% CI)	p
Female n (%)	39 (75.0)	19 (79.2)	20 (71.4)	0.52				
Age (SD)	51.6 (14.0)	51.8 (13.2)	51.2 (15.2)	0.89				
Disease duration, years (SD)	10.4 (6.9)	8.7 (6.3)	11.4 (7.1)	0.15	0.99 (0.88-1.11)	0.90		
Disease duration at the time of the first biologic drug: years (SD)	5.7 (6.0)	5.9 (5.4)	5.1 (6.2)	0.64				
Smoking (%)								
-Never	25/47 (53.2)	12/23 (52.2)	13/24 (54.2)	0.89				
-Ex-smoker or active smoker	22/47 (46.8)	11/23 (47.8)	11/24 (45.8)					
BMI (SD)	26.7 (5.0)	26.7 (4.9)	26.8 (5.1)	0.94				
BMI ≥30 (%)	10/47 (21.3)	4/23 (17.4)	6 (25.0)	0.72				
Hypertension (%)	16/46 (34.8)	9/23 (39.1)	7/23 (30.4)	0.53				
Diabetes n (%)	8/46 (17.4)	2/23(8.7)	6/23 (26.1)	0.24				
Hyperlipidemia n (%)	21/46 (45.7)	11/23 (47.8)	10/23 (43.5)	0.76				
CKD n (%)	4/46 (6.6)	2/23 (8.7)	2/23 (8.7)	1				
Positive RF n (%)	37/50 (74.0)	14/23 (61.0)	23/27 (85.2)	0.05	6.12 (0.89-41.95)	0.06	**7.66 (1.46-40.07)**	**0.01**
Positive CCP n (%)	32/42 (76.2)	14/19 (73.7)	18/23 (78.3)	1				
Duration of baricitinib, months (med, IQR)	5.8 (5.0)	6.8 (4.5)	8.0 (4.3)	0.32				
Last visit (%)								
- Methotrexate	9 (17.3)	4 (16.7)	5 (17.9)	1				
- Salazopyrine	1 (1.9)	0	1 (3.6)	1				
- Hydroxychloroquine	16 (30.8)	5 (20.8)	11 (39.3)	0.15				
- Leflunomide	23 (44.2)	9 (37.5)	14 (50.0)	0.36				
- Glucocorticoid	34 (65.4)	14 (58.3)	20 (71.4)	0.32				
First-visit disease activity								
- ESR (mm/h) (SD)	30.1 (20.0)	29.0 (20.1)	31.0 (19.4)	0.73	1.03 (0.76-1.40)	0.80		
- CRP (mg/dL) (IQR)	0.9 (1.1)	1.27 (0.91)	0.69 (0.98)	**0.05**	0.85 (0.45-1.60)	0.62		
- DAS28 CRP (SD)	4.2 (1.5)	4.7 (1.2)	3.8 (1.7)	**0.04**	0.96 (0.92-1.00)	0.10	**1.05 (1.02-1.09)**	**0.02**
- HAQ (SD)	0.91 (0.6)	0.88 (0.6)	0.94 (0.7)	0.73				
- Swollen joint (IQR)	1 (2.0)	1 (3.0)	0 (2.0)	0.26				
- Tender joint (IQR)	3 (6.0)	3 (5.0)	3 (7.0)	0.15				
- Patient global assessment (VAS) (IQR)	60.0 (30.0)	72.5 (40.0)	50.0 (20.0)	**0.02**				
Last-visit disease activity								
- ESR (IQR)	11.5 (30.0)	7.5 (10.5)	21.0 (40.3)	**<001**				
- CRP (IQR)	0.40 (0.6)	0.34 (0.5)	0.65 (1.2)	**0.07**				
- DAS28 CRP (IQR)	2.7 (2.3)	1.9 (1.4)	3.8 (1.9)	**<001**				
- HAQ (IQR)	0.52 (1.3)	0.05 (0.44)	1.1 (1.01)	**<001**				
- Swollen joint (IQR)	0 (0)	0 (0)	0 (0.8)	**0.03**				
- Tender joint (IQR)	0 (3.0)	0 (0)	2.5 (5.8)	**<001**				
- Patient global assessment (VAS) (IQR)	50 (40.0)	25 (30.0)	50 (30.0)	**0.001**				
DAS28 CRP, last visit (%)								
≤3.2	33 (63.5)	24 (100)	9 (32.1)	**<0.001**				
>3.2	19 (36.5)	0	19 (67.9)					
Biological naive n (%)	18 (34.6)	12 (50.0)	6 (21.4)	**0.03**	2.04 (0.40-10.40)	0.38		
Baricitinib monotherapy (%)	14 (26.9)	10 (41.7)	4 (14.3)	**0.02**	0.42 (0.07-2.32)	0.32		
MACE (%)	2/46 (4.3)	1/23 (4.3)	1/23 (4.3)	1				

BMI: Body mass index, CAD: Coronary artery disease, CKD: Chronic kidney disease, GC: Glucocorticoid, CRP: C-reactive protein, HAQ: The health assessment questionnaire, VAS: Visual analogue scale, TG: Triglyceride, HDL: High density lipoprotein, LDL: Low density lipoprotein, MACE: Major adverse cardiovascular event, DVT: Deep vein thrombosis, PTE: Pulmonary thromboembolism

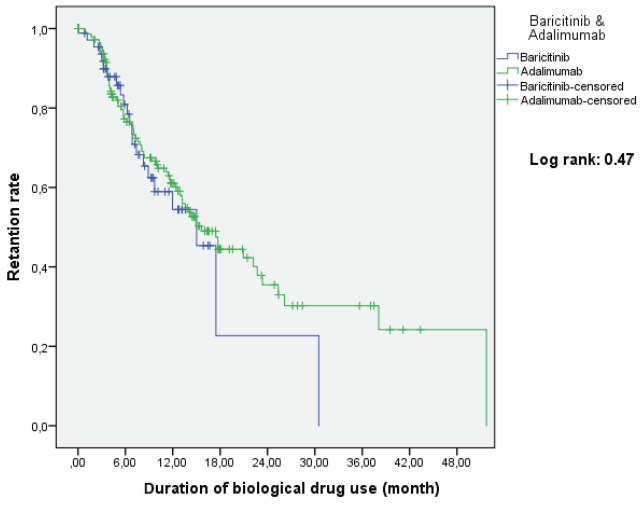

Figure 2. Drug survival rate for adalimumab and baricitinib

Cox regression analysis was performed to evaluate factors associated with survival in patients treated with baricitinib and adalimumab, including disease duration, smoking status, history of cancer in first- and second-degree relatives, HAQ and DAS28 CRP at the first visit, RF positivity, and anti-CCP positivity. We did not identify any significant predictors of improved retention of baricitinib. However, in the adalimumab arm, a higher DAS28 CRP at the first visit [OR: 0.63 (95% CI: 0.41-0.97)] was associated with reduced drug retention.

Adverse Event

Baricitinib was discontinued in 22/77 (28.5%) patients. The primary reason for drug discontinuation in both the biologic-naïve and biologic-experienced groups was treatment failure (Figure 1). In the biologic-naïve group, baricitinib was discontinued in one patient due to an allergic rash. In the biologic-experienced group, one patient experienced an allergic reaction, two patients had infections (tuberculosis and recurrent respiratory and urinary tract infections), four patients discontinued treatment at

Table 4. Comparison of disease activity and response indices between patients receiving baricitinib and adalimumab

	All patients (n=280)	Baricitinib (n=86)	Adalimumab (n=194)	p
First-visit disease activity				
- ESR (mm/h) (SD)	28.7 (21.5)	28.1 (20.2)	29.2 (22.1)	0.72
- CRP (mg/dL) (IQR)	0.9 (1.75)	0.8 (1.3)	1.0 (2.2)	0.23
- DAS28 CRP (SD)	4.4 (1.5)	4.2 (1.5)	4.4 (1.5)	0.37
- HAQ (SD)	1.3 (0.6)	1 (0.6)	1.2 (0.6)	0.07
- Swollen joint (IQR)	0 (2.0)	1 (3.0)	0 (2.0)	0.14
- Tender joint (IQR)	3.0 (7.0)	3.0 (6.0)	3.0 (9.0)	0.62
- Patient global assessment (VAS) (IQR)	70 (30)	60.0 (30.0)	75 (30.0)	0.10
Last-visit disease activity				
- ESR (IQR)	17.5 (31.0)	12.0 (34.0)	19.0 (29.5)	0.06
- CRP (IQR)	0.6 (1.1)	0.5 (0.9)	0.6 (1.2)	0.08
- DAS28 CRP (IQR)	3.6 (2.3)	3.2 (2.7)	3.7 (2.1)	0.21
- HAQ (IQR)	1.1 (1.2)	1.0 (1.4)	1.2 (1.3)	0.27
- Swollen joint (IQR)	0 (1.0)	0 (1.0)	0 (1.0)	0.34
- Tender joint (IQR)	1.0 (5.0)	1.0 (5.0)	1.0 (5.0)	0.94
- Patient global assessment (VAS) (IQR)	57.5 (40.0)	50.0 (50.0)	60.0 (30.0)	0.10
DAS28 CRP, first visit (%)				
≤3.2	50/237 (21.1)	20/76 (26.3)	30/161 (18.6)	0.17
>3.2	187/237 (78.9)	56/76 (73.7)	131/161 (81.4)	
DAS28 CRP, last visit (%)				
≤3.2	74/180 (41.1)	42/83 (50.6)	64/177 (36.2)	**0.02**
>3.2	106/180 (58.9)	41/83 (49.4)	113/177 (73.4)	
EULAR good response index (%)				
Good response	60/159 (37.7)	24 (46.2)	36 (33.6)	**0.03**
Moderate response	30/159 (18.9)	4 (7.7)	26 (24.3)	
Poor response	69/159 (43.4)	24 (46.2)	45 (42.1)	

CRP: C-reactive protein, DAS28: Disease activity score, ESR: Estimated sedimentation rate, EULAR: The European Alliance of Associations for Rheumatology, HAQ: The health assessment questionnaire, IQR: Interquartile range, VAS: Visual analogue scale

Table 5. Comparison of MACE rates between baricitinib and adalimumab in different patient subgroups			
Patient group	**Baricitinib**	**Adalimumab**	**p**
Treatment-naïve patients (events per 1000 patient-years)	25	16.5	0.21
Patients with prior exposure to at least one biologic agent (events per 1000 patients-year)	11	3.8	0.08
Patients without a family history of cardiovascular disease (events per 1000 patients-year)	11.8	7.5	0.41
Non-smokers (events per 1000 patients-year)	17.6	14.1	0.67
MACE: Major adverse cardiovascular event			

the physician's request, and one patient discontinued treatment for unclear reasons. Pulmonary thromboembolism occurred in 1 patient (1.3%) in the baricitinib group and in 3 patients (2.8%) in the adalimumab group. No hepatitis activation was observed in either group; however, HZ was reported in one patient in the adalimumab group but not in the baricitinib group.

Major cardiovascular events occurred in 2 patients (2.5%) [1 myocardial infarction, 1 cerebrovascular event in the baricitinib group and 4 patients (2.5%)]. [One patient had both a myocardial infarction and a cerebrovascular event, and three had a cerebrovascular event] in the adalimumab group (Table 1). The median age of these six patients was 60 years (range: 51-78 years). Among the patients with major adverse cardiovascular events, 1 patient presented with hyperlipidemia (HL); 2 patients presented with HL, DM, and hypertension (HT); 1 patient presented with HL, DM, HT, and dysrhythmia; 1 patient presented with DM and HT; and 1 patient presented with HT and deep vein thrombosis. MACE events were recorded at rates of 15.3 and 9.1 per 1,000 patient-years among individuals taking baricitinib and adalimumab, respectively (p=0.2). We separately evaluated MACE rates between the two groups (baricitinib and adalimumab) within the following subgroups: treatment-naive patients; patients with prior exposure to at least one biologic agent; patients without a family history of cardiovascular disease; and non-smokers, and found no statistically significant differences between the groups (Table 5). None of the baseline population characteristics, including treatment group, treatment-naïve status, treatment duration, smoking status, and family history of cardiovascular disease, were significantly associated with the risk of MACE in the multivariate analysis (overall model p=0.93). One patient in the adalimumab group developed renal cell carcinoma within the first year of treatment, while no cancer was detected in the baricitinib group.

Discussion

The study compares the effectiveness, retention rate and safety of baricitinib with adalimumab in treating RA patients in a real-life clinical setting. In addition, this study includes comparisons between biologically naïve and experienced groups, and between baricitinib monotherapy and baricitinib combined with csDMARD treatment groups.

After 6 months of follow-up, significant improvements were observed in disease activity parameters, such as ESR, CRP, DAS, HAQ, patient VAS scores, and swollen and tender joint counts. A high patient global assessment was associated with a good EULAR response. Although both baricitinib and adalimumab showed significant improvement in DAS28 CRP, the EULAR responder index showed a higher proportion of good and moderate responses in the adalimumab arm than in the baricitinib arm. At the last visit, no significant difference was observed between baricitinib and adalimumab in disease activity assessment indices, except for the EULAR good response index. Most studies reported follow-up durations of 24 weeks (6 months), like ours.[4] All JAK inhibitors, including baricitinib, demonstrated non-inferiority or superiority to adalimumab or abatacept.[3,15] In our study, the higher EULAR good-response index in the adalimumab arm may be explained by the adalimumab group being biologic-naïve. Similar discrepancies in the responses of various effectiveness measures have been noted in the relevant literature, including the post-marketing study by Wu et al.[16] on baricitinib in RA (DAS28-CRP and SDAI/CDAI), the Chinese CREDIT study (DAS28-CRP and CDAI), and the RA-BEAM study (DAS28-CRP and SDAI/CDAI). These results highlight the variability in assessing treatment response across scales and the need for careful consideration when interpreting clinical results in RA management.[15-17] In a multicenter study by Guidelli et al.[18], 446 RA patients who were treated with baricitinib were evaluated at baseline and at 3, 6, and 12 months. The cohort consisted of 34% bDMARD-naïve responders and 66% bDMARD-insufficient responders. At 3 and 6 months, 36% and 51.6% of patients achieved remission, while 20% and 15.9% had LDA at those time points, respectively. In the ELECTRA-i study by Benucci et al.[19], baricitinib significantly improved DAS 28, VAS, and HAQ scores, as well as measures of swollen and tender joints, consistent with our study.

RF positivity was an independent predictor of poor treatment response in our cohort (OR: 7.66). This differs from reports showing better responses to rituximab and abatacept in seropositive RA patients. For JAK inhibitors, the evidence is less

consistent: several real-world studies found no clear relationship between RF/anti-CCP positivity and either effectiveness or treatment discontinuation due to lack of effect, and a large claims-based analysis reported similar 1-year effectiveness in seropositive and seronegative patients initiating bDMARDs/JAK inhibitors.[20-22] In contrast, a pooled post hoc analysis of Phase III tofacitinib trials suggested higher ACR responses in anti-CCP+/RF+ patients than in double-seronegative patients.[23] Overall, our findings may reflect differences in patient characteristics, prior treatments, and outcome definitions, and should be confirmed in prospective cohorts.

Adalimumab had a higher one-year drug survival rate (61.1%) than baricitinib (54.4%), with median retention times of 22.9 months and 15.1 months, respectively. Nonetheless, this finding has not reached statistical significance. In contrast, the Australia-wide study by Lieke Scheepers reported a 12-month persistence rate of 61% for baricitinib and 58% for subcutaneous TNF-alpha inhibitors. This discrepancy highlights regional differences in drug persistence and suggests that factors such as patient populations, health practices, and treatment protocols may influence the long-term adherence and effectiveness of these therapies.[24] In our study, biologics-naïve patients had significantly higher baricitinib survival rates than biologics-experienced patients. In the RA-BE-REAL study (baricitinib, n=509), b/tsDMARD-naïve patients had a lower discontinuation rate of baricitinib at 12 months than patients who had received more than two prior b/tsDMARDs.[25]

Baricitinib was discontinued in 28.5% of patients, primarily due to treatment failure across all groups. In the biologic-naïve and biologic-experienced groups, discontinuations of baricitinib were due to allergic reactions, infections, and other reasons; pulmonary thromboembolism was less frequent with baricitinib whereas HZ occurred only with adalimumab. In RCTs, the most common side effects of baricitinib, in addition to HZ, were upper respiratory tract infections, urinary tract infections, nasopharyngitis, influenza, and gastroenteritis. In contrast to these studies, which reported no cases of tuberculosis in baricitinib-treated patients, our series documented one case.[15,26] However, consistent with the literature, our series does not show a significant increase in risk of severe infection.[3] Although solid cancers associated with baricitinib have been reported in RCTs, no such cases were observed in our series. This can be attributed to the relatively small number of patients and the short follow-up period. In real-world data, similar to those from RCTs and our study, the most commonly observed adverse reactions were HZ, upper respiratory tract infections, and gastroenteritis.[27-31]

MACE events occurred at higher rates in the baricitinib group (15.3 per 1000 patient-years) than in the adalimumab group (9.1 per 1000 patient-years); however, this difference was not statistically significant. Although we reported MACE, malignancy, and thromboembolic events for both treatment groups, the absolute number of events was low. Therefore, these safety results are descriptive, and between-group comparisons should be interpreted with caution due to limited statistical power. The ORALSURV study focused on patients with R who were over 50 years old and had cardiovascular risk factors. They received either tofacitinib or anti-TNF therapy (etanercept or adalimumab, depending on the region). During a median follow-up of 4.0 years, the incidence of MACE was higher with combined doses of tofacitinib (3.4%) than with a TNF inhibitor (2.5); the hazard ratio was 1.33 (95% CI: 0.91-1.94). Although the study only evaluated tofacitinib, the FDA applied the study's results to all JAK inhibitors used to treat immune-mediated inflammatory diseases. As a result, they limited the use of this class of drugs to patients with RA only after TNF inhibitor treatment had failed [5]. On the other hand, in a study by Smolen et al.[32] using the "All-Bari-RA" method, which included 3492 patients over 6637 patient years (PY) and data from six studies comparing 4 mg baricitinib and placebo through week 24, the MACE rate was 0.5/100 PY and did not increase with prolonged exposure to baricitinib compared to placebo. In real-world data from the German RABBIT registry, the incidence of MACE in 1,416 RA patients using baricitinib was 0.49 (0.25 to 0.85). This rate did not increase compared with other JAK inhibitors, anti-TNF therapies, and biologics.[33] In a 24-week study of RA patients in Japan, the MACE rate was found to be 0.38/100 PY.[34] The long-term extension study by Taylor et al.[35] assessing the safety of baricitinib found that the safety data reported in previous studies remained unchanged. Given these data, it seems reasonable to re-evaluate the FDA's generalization of a molecular-based class effect for MACE. MACE incidence appeared slightly higher in our study than reported in the literature, possibly because the patients were >50 years old and had multiple comorbidities.

Study Limitations

Our study has limitations, including a short follow-up period and a small sample size. Given the non-randomized, real-world nature of this cohort, baseline characteristics differed between groups; most notably, the baricitinib arm had a lower proportion of biologic-naïve patients. Such imbalances may have influenced comparative effectiveness and retention; thus, between-group differences should be interpreted with caution, as they may partially reflect confounding by indication, rather than isolated treatment effects. Missing baseline and/or follow-up data led to the exclusion of a subset of baricitinib-treated patients from efficacy analyses. Because missingness cannot be assumed to be completely random in a real-life registry, these results may be affected by selection bias and have limited generalizability. Our database did not contain routine assessments of pain scores, and therefore we were unable to assess the effect of baricitinib on

pain. The single-center study design presented another notable drawback. On the other hand, because of the short duration of the study, the impact on radiological progression was not assessed.

The study's strengths lie in its prospective design and the rigorous, three-monthly patient monitoring mandated by the Turkish healthcare system for prescribing targeted and biological DMARDs. Thus, patient-reported outcomes and laboratory checks are completed without exception.

Conclusion

In conclusion, this study highlights that baricitinib has a similar effectiveness and safety profile to adalimumab in patients with RA. Both drugs effectively reduced disease activity, and no significant difference was observed in the incidence of MACE (Major Adverse Cardiovascular Events) between the two groups. Baricitinib was more frequently used as monotherapy and showed favorable responses, particularly in biologic-naïve patients. These findings suggest that baricitinib is a safe and effective alternative to adalimumab for the management of RA.

Ethics

Ethics Committee Approval: This study was approved by Hacettepe University Ethics Commission (approval number: 2023-02-02, date: 24.01.2023).

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.E., Z.Ö., G.A., G.S.U., E.Ü., B.F.Y., G.S.K.B., B.B., L.K., A.A., Ş.A.B., S.K., İ.E., Concept: M.E., E.B., L.K., İ.E., Design: M.E., E.B., L.K., İ.E., Data Collection and Processing: M.E., İ.Y.İ., E.E.D., Z.Ö., G.A., G.S.U., E.Ü., B.F.Y., G.S.K.B., B.B., A.A., Ş.A.B., S.K., İ.E., Analysis or Interpretation: M.E., L.K., İ.E., Literature Search: M.E., E.Ü., L.K., İ.E., Writing: M.E., E.B., L.K., İ.E.

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Supplementary Tables Link: https://d2v96fxpocvxx.cloudfront.net/7a593d95-86ec-4d2b-8dd3-26b0d0b79ea4/content-images/2190214e-bfdc-41e1-b5e1-7e23b97036ab.pdf

Supplementary Figure 1 Link: https://d2v96fxpocvxx.cloudfront.net/7a593d95-86ec-4d2b-8dd3-26b0d0b79ea4/content-images/1c15ec3a-a9a2-47d1-ba99-74338e97cfb9.pdf

References

1. Finckh A, Gilbert B, Hodkinson B, et al. Global epidemiology of rheumatoid arthritis. Nat Rev Rheumatol. 2022;18:591-602.
2. Smolen JS, Landewé RB, Bijlsma JW, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79:685-99.
3. Szekanecz Z, Buch MH, Charles-Schoeman C, et al. Efficacy and safety of JAK inhibitors in rheumatoid arthritis: update for the practising clinician. Nat Rev Rheumatol. 2024:1-15.
4. Hernández-Cruz B, Kiltz U, Avouac J, et al. Systematic literature review of real-world evidence on baricitinib for the treatment of rheumatoid arthritis. Rheumatol Ther. 2023;10:1417-57.
5. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386:316-26.
6. Hoisnard L, Vegas LP, Dray-Spira R, et al. Risk of major adverse cardiovascular and venous thromboembolism events in patients with rheumatoid arthritis exposed to JAK inhibitors versus adalimumab: a nationwide cohort study. Ann Rheum Dis. 2023;82:182-8.
7. Nikiphorou E, Buch MH, Hyrich KL. Biologics registers in RA: methodological aspects, current role and future applications. Nat Rev Rheumatol. 2017;13:503-10.
8. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.
9. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.
10. Prevoo M, van 't Hof MA, Kuper H, et al. Modified disease activity scores that include twenty-eight-joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44-8.
11. Van Gestel A, Prevoo M, van 't Hof M, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis: comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. Arthritis Rheum. 1996;39:34-40.
12. Wells G, Tugwell P, Kraag G, et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol. 1993;20:557-560.
13. Fries JF, Spitz P, Kraines RG, et al. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137-45.
14. Bosco E, Hsueh L, McConeghy KW, et al. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol. 2021;21:241.
15. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376:652-62.
16. Wu C-Y, Wang Q, Shi J, et al. Safety and effectiveness of baricitinib in Chinese patients with moderate-to-severe rheumatoid arthritis: 24-week results from a post-marketing safety study. Rheumatol Ther. 2023;10:1609-22.
17. Song X, Wang Y-H, Li M-T, et al. Chinese registry of rheumatoid arthritis: IV. Correlation and consistency of rheumatoid arthritis disease activity indices in China. Chin Med J (Engl). 2021;134:1465-70.

18. Guidelli GM, Viapiana O, Luciano N, et al. Efficacy and safety of baricitinib in 446 patients with rheumatoid arthritis: a real-life multicentre study. Clin Exp Rheumatol. 2020;39:868-73.

19. Benucci M, Li Gobbi F, Damiani A, et al. Real-Life Comparison of Four JAK Inhibitors in Rheumatoid Arthritis(ELECTRA-i Study). J Clin Med. 2024;13:1821.

20. Martinez-Molina C, Gich I, Diaz-Torne C, et al. Patient-related factors influencing the effectiveness and safety of Janus Kinase inhibitors in rheumatoid arthritis: a real-world study. Sci Rep. 2024;14:172.

21. Martinez-Molina C, Vidal S, Diaz-Torne C, et al. Interindividual variability and its impact on the effectiveness of Janus kinase inhibitors in rheumatoid arthritis treatment. Front Med (Lausanne). 2025;12:1512501.

22. Jin Y, Liu J, Desai RJ, Kim SC. Real-World Treatment Effectiveness of Disease-Modifying Antirheumatic Drugs by Serostatus Among Patients With Rheumatoid Arthritis. ACR Open Rheumatol. 2023;5:571-80.

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

24. Scheepers L, Yang Y, Chen YL, Jones G. Persistence of Janus-kinase (JAK) inhibitors in rheumatoid arthritis: Australia wide study. Semin Arthritis Rheum. 2024;64:152314.

25. Alten R, Burmester GR, Matucci-Cerinic M, et al. P131 Time to Discontinuation and Effectiveness with Baricitinib in Rheumatoid Arthritis: 12-Month European Data from a Multinational, Prospective, Observational Study. Arthritis Rheumatol. 2023;62(Supplement_2):kead104.172.

26. Genovese MC, Kremer J, Zamani O, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med. 2016;374:1243-52.

27. Deprez V, Le Monnier L, Sobhy-Danial J-M, et al. Therapeutic maintenance of baricitinib and tofacitinib in real life. J Clin Med. 2020;9:3319.

28. Choi W, Ahn SM, Kim Y-G, et al. Safety of JAK inhibitor use in patients with rheumatoid arthritis who developed herpes zoster after receiving JAK inhibitors. Clin Rheumatol. 2022;41:1659-63.

29. Fitton J, Melville AR, Emery P, et al. Real-world single centre use of JAK inhibitors across the rheumatoid arthritis pathway. Rheumatology (Oxford). 2021;60:4048-54.

30. Takahashi N, Asai S, Kobayakawa T, et al. Predictors for clinical effectiveness of baricitinib in rheumatoid arthritis patients in routine clinical practice: data from a Japanese multicenter registry. Sci Rep. 2020;10:21907.

31. Mazarío RG, Gil JJF, Cortés JI, et al. Real-world effectiveness and safety of JAK inhibitors in rheumatoid arthritis: a single-centre study. Reumatol Clin (Engl Ed). 2022;18:523-30.

32. Smolen JS, Genovese MC, Takeuchi T, et al. Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. J Rheumatol. 2019;46:7-18.

33. Meissner Y, Schäfer M, Albrecht K, et al. Risk of major adverse cardiovascular events in patients with rheumatoid arthritis treated with conventional synthetic, biologic and targeted synthetic disease-modifying antirheumatic drugs: observational data from the German RABBIT register. RMD Open. 2023;9:e003489.

34. Takagi M, Atsumi T, Matsuno H, et al. Safety and effectiveness of baricitinib for rheumatoid arthritis in Japanese clinical practice: 24-week results of all-case post-marketing surveillance. Mod Rheumatol. 2023;33:647-56.

35. Taylor PC, Takeuchi T, Burmester GR, et al. Safety of baricitinib for the treatment of rheumatoid arthritis over a median of 4.6 and up to 9.3 years of treatment: final results from long-term extension study and integrated database. Ann Rheum Dis. 2022;81:335-43.

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Letter to the Editor / Editöre Mektup

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Acute gout arthritis after COVID-19: Secondary to infection or secondary to treatment?

COVID-19 sonrası gelişen akut gut artriti: Enfeksiyona mı sekonder, tedaviye mi sekonder?

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Anahtar Kelimeler: COVID-19, hiperürisemi, gut, favipiravir

Dear Editor,

Gout is an inflammatory arthritis caused by the deposition of monosodium urate crystals in the setting of hyperuricemia.[1,2] Hyperuricemia generally results from either increased urate production or decreased renal excretion and may occur due to primary or secondary factors. Among secondary causes, acute illness and medications are particularly relevant, as both infection-related metabolic stress and certain drugs can precipitate rapid increases in serum urate levels and trigger gout flares.[3] Favipiravir, an antiviral agent used during the coronavirus disease 2019 (COVID-19) pandemic, is known to induce hyperuricemia through inhibition of renal urate excretion.[4]

In this letter, we describe the clinical presentation of acute gouty arthritis that developed during a COVID-19 infection in a patient with pre-existing hyperuricemia.

A 39-year-old male patient presented with severe pain, tenderness, swelling, and redness in both big toes. His history revealed that exactly 10 days prior to the onset of joint symptoms, he had presented to a pandemic outpatient clinic with fever, cough, and fatigue and had been diagnosed with COVID-19 infection by a polymerase chain reaction (PCR) test. Since he did not have significant respiratory distress, he was not hospitalized and was treated as an outpatient. According to the Turkish Ministry of Health's Adult COVID-19 Treatment Guideline,[5] he received favipiravir 200 mg (loading dose of 2x1600 mg on the first day, followed by 2x3 tablets for a total of 5 days).[4] His COVID-19 symptoms resolved. The patient, who had no history of similar joint complaints, had no other joint symptoms. He reported no back pain, morning stiffness, oral/genital ulcers, skin disease, genital discharge, or gastrointestinal symptoms. His past medical history was unremarkable, with no chronic disease or regular medication use. He had no history of kidney stones. Previous laboratory tests showed hyperuricemia. On physical examination, both first metatarsophalangeal joints showed redness, swelling, warmth, and severe tenderness, more prominent on the right (Figure 1). Examination of the other joints was normal. Laboratory evaluation revealed serum uric acid of 8.9 mg/dL (3.4-7.2), an erythrocyte sedimentation rate of 42 mm/h (0-15), and C-reactive protein of 7.2 mg/dL (0.1-4). Other routine laboratory tests, including complete blood

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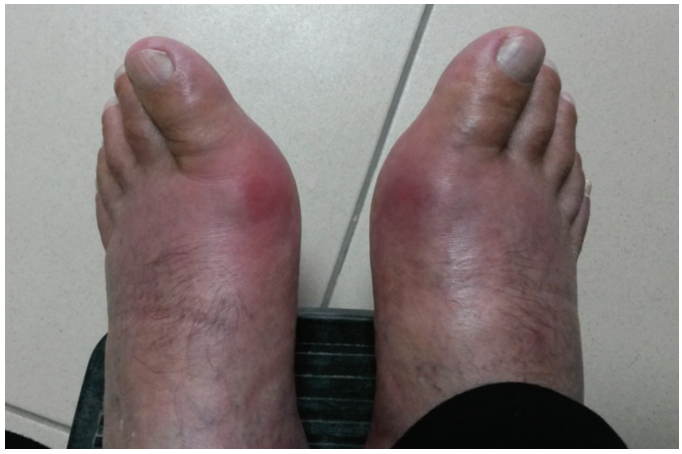

Figure 1. Clinical photograph showing bilateral foot involvement during an acute gout attack, characterized by soft-tissue swelling, erythema, and tenderness consistent with active inflammation

count, renal and liver function tests, electrolytes, coagulation tests, and lipid profile, were normal. X-ray showed soft tissue swelling, and ultrasonography revealed a hyperechoic irregular band on the dorsal surface of the first metatarsophalangeal joints consistent with the "double contour sign". The patient was diagnosed with gout arthritis according to the 2015 American College of Rheumatology (ACR)/European League Against Rheumatism Classification Criteria for Gout.[6] Considering the international pandemic context, national rheumatology society recommendations were taken into account for treatment.[7] The treatment plan was developed based on the recommendations of the 2020 ACR gout management guideline.[8] Based on these findings, treatment with colchicine and prednisolone was initiated. The next day, his symptoms had improved. Continuation of colchicine, tapering and discontinuation of prednisolone, and a follow-up in one month were recommended. At follow-up, uric acid remained elevated (8.8 mg/dL), but no other abnormalities were detected. Allopurinol was added in combination with colchicine prophylaxis to prevent further attacks.

A review of the literature revealed a retrospective study of hospitalized COVID-19 patients that included 8,697 individuals, of whom 146 had gout; 26 of these (18%) developed gout flares. Patients who experienced flares had higher baseline urate levels, were less likely to receive urate-lowering or prophylactic therapy, and had hospital stays that were three days longer. The authors concluded that inadequate use of urate-lowering therapy was the main risk factor.[9] However, acute illnesses including infections are known risk factors for gout and pseudogout flares, and gout flares in hospitalized patients may complicate hospitalizations for conditions such as heart failure, pneumonia, and acute kidney injury.[10] In a case series by López-González et al.,[11] among 306 patients hospitalized for COVID-19, 4 developed acute arthritis, 3 of whom had pre-existing gout. None were receiving colchicine prophylaxis, and urate-lowering therapy (allopurinol) was used at varying doses. None had received favipiravir. In a large Korean retrospective study using the National Health Insurance database (~50 million individuals), the frequency of gout flares increased during the COVID-19 pandemic compared with the pre-pandemic period. Both men and women showed increases, but the difference was statistically significant only among men, who were approximately twice as numerous as women. Age-stratified analysis showed a significant increase only in the 20-59 age group.[12]

Kihara et al.[13] conducted a multicenter observational study in Japan of 222 rheumatology patients with COVID-19. The most frequent diseases were rheumatoid arthritis (48.2%), gout (14.4%), and systemic lupus erythematosus (8.1%). The authors noted that gout prevalence was significantly higher in Japan compared with global data from the COVID-19 Global Rheumatology Alliance,[14] which reported only 2.6%. They suggested that this discrepancy may be related to the widespread use of favipiravir in Japan, which is known to cause hyperuricemia, prompting physicians to inquire more actively about gout history. Favipiravir is also widely used in Türkiye during the pandemic and hyperuricemia is a well-known side effect.[4] Our presented patient received favipiravir at the guideline-recommended dose.[5]

Kihara et al.[13] reported no statistically significant difference in COVID-19 outcomes in patients with gout compared to other rheumatologic diseases. In multivariate analysis, "disease category" (including gout in the "other diseases" group) was not significantly associated with severe COVID-19.

When interpreting this case, the central question raised by the title—whether the acute gout flare was secondary to infection or to treatment—requires a structured evaluation of potential triggers. Acute systemic illnesses, including infections, are well-recognized precipitants of gout flares, and COVID-19 infection itself may induce a pro-inflammatory state and metabolic stress that promote monosodium urate crystal-driven inflammation. Previous studies have demonstrated that gout flares occur in a substantial proportion of patients hospitalized with COVID-19, particularly among those with elevated baseline serum urate levels and insufficient prophylactic therapy, supporting the possibility that COVID-19 infection may act as a biological trigger in susceptible individuals.[9] In addition to infection-related mechanisms, antiviral therapy may also contribute to gout flares. Favipiravir is known to increase serum urate levels through its effects on renal urate transport, and prior case reports have described acute gouty arthritis developing during favipiravir treatment for COVID-19. Notably, Hase et al.[15] reported a patient who developed acute gouty arthritis following favipiravir-associated elevation in serum urate, suggesting that favipiravir may trigger not only biochemical hyperuricemia but also clinically overt gout flares. Beyond isolated triggers, patient susceptibility plays a critical role. Studies evaluating

gout flare during COVID-19 hospitalization have identified elevated baseline serum urate levels, absence of urate-lowering therapy, and lack of flare prophylaxis as major risk factors.[16] In this context, the present patient's pre-existing hyperuricemia likely created a vulnerable biological background. Rather than representing mutually exclusive mechanisms, infection-related inflammation and drug-induced hyperuricemia may have acted synergistically, and this "multiple-hit" model may provide a more comprehensive explanation than attributing the flare solely to either infection or treatment. Taken together, this case highlights that COVID-19 infection and favipiravir exposure may jointly increase the likelihood of acute gouty arthritis in patients with underlying hyperuricemia, underscoring the importance of careful monitoring of serum urate levels and musculoskeletal symptoms in patients receiving favipiravir, particularly those with known hyperuricemia or previous gout risk factors.

Although the pandemic has subsided, seasonal increases in COVID-19 cases are expected. Therefore, patients with gout or asymptomatic hyperuricemia should be monitored closely for gout arthritis during COVID-19 infection.

Ethics

Authorship Contributions

Surgical and Medical Practices: F.A.K., İ.D., Concept: F.A.K., İ.D., Design: F.A.K., İ.D., G.Ü., Data Collection and Processing: F.A.K., İ.D., Analysis and Interpretation: G.Ü., Literature Search: G.Ü., Writing: F.A.K., G.Ü.

Footnotes

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References

1. Dalbeth N, Merriman TR, Stamp LK. Gout. Lancet 2016;388:2039-52.
2. Kozanoğlu E. Gut hastalığı. In: Bodur H, Ataman Ş, editors. Romatoloji e-Kitap. İstanbul: Türkiye Romatoloji Derneği; 2019. p. 2-26. Available from: https://www.trasdromatolojiekitap.org/icindekiler.php?id=114
3. McLean L, Dalbeth N. Etiology and pathogenesis of gout. In: Hochberg MC, Silman AJ, Smolen JS et al., editors. Rheumatology. 6th ed. Philadelphia: Mosby Elsevier; 2015. P. 1555-68.
4. Ministry of Health of the Republic of Türkiye. Favipiravir 200 mg Tablet – Information for Drugs Used in the Treatment of COVID-19 (SARS-CoV-2 Infection). Ankara: Ministry of Health; 2021. Available from: khgmstokyonetimidb.saglik.gov.tr (Accessed Feb 2026).
5. Ministry of Health of the Republic of Türkiye, General Directorate of Public Health. COVID-19 (SARS-CoV-2 Infection) Adult Patient Treatment Guideline. Ankara: Ministry of Health; 2020. Available from: https://www.ekmud.org.tr/files/uploads/files/Saglik-Bakanligi-COVID-19-rehberi-23032020.pdf (Accessed Feb 2026).
6. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74:1789-98.
7. Babaoğlu H. Türkiye Romatoloji Derneği Romatoloji Uzmanları için Koronavirüs (Covid-19) salgını sırasında hastalık yönetimi önerileri. J Turk Soc Rheumatol 2020;12:1-2.
8. FitzGerald JD, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken). 2020;72:744-60.
9. Jatuworapruk K, Satpanich P, Robinson PC, Grainger R. Prevalence, risk factors, and outcomes of gout flare in patients hospitalized for PCR-confirmed COVID-19: a multicenter retrospective cohort study. J Rheumatol. 2023;50:556-63.
10. Robinson PC, Kempe S, Tebbutt I, et al. Epidemiology of inpatient gout in Australia and New Zealand: temporal trends, comorbidities and gout flare site. Int J Rheum Dis. 2017;20:779-84.
11. López-González MD, Peral-Garrido ML, Calabuig I, et al. Case series of acute arthritis during COVID-19 admission. Ann Rheum Dis. 2021;80:e58.
12. Kim JH, Kwon MJ, Choi HG, et al. Changes in the mean incidence and variance of orthopedic diseases before and during the COVID-19 pandemic in Korea: a retrospective study. BMC Musculoskelet Disord. 2023;24:540.
13. Kihara M, Sugihara T, Asano J, et al. Clinical characteristics of COVID-19 patients with underlying rheumatic diseases in Japan: data from a multicenter observational study using the COVID-19 Global Rheumatology Alliance physician-reported registry. Clin Rheumatol. 2022;41:3661-73.
14. COVID-19 Global Rheumatology Alliance. The COVID-19 Global Rheumatology Alliance (GRA). Available from: https://rheum-covid.org/ (Accessed Feb 2026).
15. Hase R, Kurata R, Ishida K, et al. Acute gouty arthritis during favipiravir treatment for coronavirus disease 2019. Intern Med. 2020;59:2327-9.
16. Mongkolporn A, Satpanich P, Grainger R, Jatuworapruk K. GOUT-36 prediction rule is sensitive in predicting gout flare during COVID-19 hospitalization. Int J Rheum Dis. 2024;27:e15010.