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

TÜRKİYE ROMATOLOJİ DERNEĞİ

Ulusal ROMATOLOJİ Dergisi

Journal of Turkish Society for Rheumatology

ISSN: 2651-2653

www.romatolojidergisi.org

Cilt / Volume: **17** • **Sayı** / Issue: **3** • **Kasım** / November **2025**

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

S. Özbek, 2025

galenos yayınevi

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

Editörler Kurulu / Editorial Board

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

Sahibi / Owner

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

Sorumlu Yazı İşleri Müdürü / Managing Editor
R. Haner Direskeneli

Editör / Editor

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

Editör Yardımcıları / Associate Editors

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

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

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

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

galenos yayınevi

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

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

Basım Tarihi/Printing Date: Kasım 2025/November 2025

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

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

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

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

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

Dergi, asitsiz kağıda basılıp ayrıca çevrimiçi olarak yayınlanmaktadır.

Sahip: Türkiye Romatoloji Derneği

Sorumlu Yönetici: R. Haner Direskeneli

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

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

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

Owner: Turkish Society for Rheumatology

Responsible Manager: R. Haner Direskeneli

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

İçindekiler / Contents

Reviews / Derlemeler

Original Articles / Orijinal Araştırmalar

Letter to the Editors / Editöre Mektuplar

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

Case Report / Olgu Sunumu

İndeks / Index

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

Derleme / Review

DOI: 10.4274/raed.galenos.2025.26349
Ulus Romatol Derg 2025;17(3):131-144

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

Turkish Society for Rheumatology guideline for the management of ANCA-associated vasculitides

Ömer Karadağ[1], Emine Sarıyıldız[1], Pınar Akyüz Dağlı[2], Önay Gerçik[3], Rıza Can Kardaş[4], Duygu Şahin[5], Gizem Sevik[6], Elif Durak Ediboğlu[7], Gözde Sevgi Kart Bayram[1], Tahir Saygın Öğüt[8], Mehmet Nedim Taş[9], Gökçe Kenar Artın[10], Hamit Küçük[4], Merve Pamukçuoğlu[11], Serdar Özer[12], Mehmet Engin Tezcan[5], Fatma Alibaz[6], Ahmet Omma[2], Ebru Damadoğlu[13], Ebru Aşıcıoğlu[14], Ayten Yazıcı[15], Deniz Köksal[16], Kenan Aksu[17], Haner Direskeneli[6]

[1]*Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Vaskülit Tanı ve Tedavi Uygulama ve Araştırma Merkezi, Ankara, Türkiye*
[2]*Ankara Bilkent Şehir Hastanesi, Romatoloji Kliniği, Ankara, Türkiye*
[3]*İzmir Demokrasi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir, Türkiye*
[4]*Gazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye*
[5]*Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Romatoloji Kliniği, İstanbul, Türkiye*
[6]*Marmara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul, Türkiye*
[7]*İzmir Katip Çelebi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir, Türkiye*
[8]*Akdeniz Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Antalya, Türkiye*
[9]*Manisa Şehir Hastanesi, Romatoloji Kliniği, Manisa, Türkiye*
[10]*Dokuz Eylül Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara, Türkiye*
[11]*Sağlık Bilimleri Üniversitesi Tıp Fakültesi, Ankara Bilkent Şehir Hastanesi, Hematoloji Kliniği, Ankara, Türkiye*
[12]*Hacettepe Üniversitesi Tıp Fakültesi, Kulak, Burun ve Boğaz Hastalıkları Anabilim Dalı, Ankara, Türkiye*
[13]*Hacettepe Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Alerji ve İmmünoloji Bilim Dalı, Ankara, Türkiye*
[14]*Marmara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Nefroloji Bilim Dalı, İstanbul, Türkiye*
[15]*Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Kocaeli, Türkiye*
[16]*Hacettepe Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları Anabilim Dalı, Ankara, Türkiye*
[17]*Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir, Türkiye*

Özet

Anti-nötrofil sitoplazmik antikor (ANCA) asosiye vaskülitlerde (AAV), üst solunum yolu, deri, nörolojik ve konstitusyonel bulguların yanı sıra kardiyak, renal ve alt solunum yollarını tutan ve organ fonksiyon kaybına yol açan ya da yaşamı tehdit eden klinik tablolar gelişebilir. Bu nedenle erken tanı için hekimler arasında farkındalığın artırılması gerekmektedir. Teknolojik gelişmelerle birlikte tanı, ayırıcı tanı ve hastalık sürecinin izleminde çeşitli laboratuvar, görüntüleme teknikleri ve girişimsel yöntemler kullanılmaktadır. AAV şüphesi bulunan ve kutanöz vaskülit, kronik üst ve/veya alt solunum yolu hastalıkları, hızlı ilerleyen böbrek fonksiyon bozukluğu, periferik nöropati

Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) manifest with involvement of the ear, nose, throat, skin, neurological system, and constitutional symptoms, as well as potentially life-threatening cardiac, renal, and pulmonary organ involvement leading to organ dysfunction. Early diagnosis is critical, necessitating increased awareness among clinicians. Advances in technology have facilitated the use of various laboratory, imaging, and interventional methods for diagnosis, differential diagnosis, and disease monitoring, with composite disease activity indices employed to assess disease activity and organ damage. In patients presenting

İletişim / Correspondence:
Prof. Dr. Ömer Karadağ, Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Vaskülit Tanı ve Tedavi Uygulama ve Araştırma Merkezi, Ankara, Türkiye
E-posta: omerkaradag@ymail.com **ORCID ID:** orcid.org/0000-0002-3443-3117
Geliş Tarihi / Received: 28.07.2025 **Kabul Tarihi / Accepted:** 08.08.2025 **Epub:** 01.09.2025 **Yayın Tarihi / Publication Date:** 28.11.2025

Atıf / Cite this article as: Karadağ Ö, Sarıyıldız E, Akyüz Dağlı P, et al. Turkish Society for Rheumatology guideline for the management of ANCA-associated vasculitides. J Turk Soc Rheumatol. 2025;17(3):131-144

Özet

gibi AAV tanısını düşündüren sistemik bulguları olan hastalarda, birincil tanı yöntemi olarak yüksek kaliteli antijen-spesifik yöntemle proteinaz-3 ANCA ve miyeloperoksidaz ANCA bakılmalıdır. AAV hastalarının, vaskülitler konusunda deneyimli merkezler tarafından multidisipliner bir ekiple değerlendirilmesi akılcı bir yaklaşımdır. Hastalık aktivitesinin ve organ hasarının değerlendirilmesinde çeşitli hastalık kompozit indekslerinden yararlanılmaktadır. AVV 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. Rituksimab ve mepolizumab gibi biyolojik ilaçların kullanımıyla birlikte glukokortikoidler ve diğer immünosupresiflere 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, granulomatöz polianjiitis (GPA), eozinofilik granulomatöz polianjiitis (EGPA), mikroskopik polianjiitis (MPA), immünosupresif tedavi, siklofosfamid, rituksimab, plazma değişimi, glukokortikoid, komorbidite, enfeksiyonlar

Abstract

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 ANCA and myeloperoxidase ANCA should be performed as primary diagnostic tests. Management by multidisciplinary teams experienced in vasculitis is recommended. 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 lower infection risk. The introduction of biologics such as rituximab and mepolizumab has significantly decreased treatment-related damage associated with glucocorticoids and other immunosuppressants. Throughout follow-up, patients should be regularly monitored for treatment-related adverse effects and comorbidities (including hypertension, osteoporosis, and cardiovascular disease) with appropriate lifestyle modifications 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, comorbidity, infections

I. Giriş ve Amaçlar

Anti-nötrofil sitoplazmik antikorları (ANCA) ilişkili (asosiye) vaskülitler (AAV), nadir görülen, heterojen klinik bulgularla seyreden ve potansiyel olarak organları ve/veya yaşamı tehdit edebilen hastalıklardır. Bu nedenle, bu hastalıkların vaskülit konusunda deneyimli veya bu uzmanlığa kolay erişimi olan merkezlerde, multidisipliner ekip tarafından yönetilmesi gerekir. AAV tanılı hastalara, hasta ve hekim arasında paylaşılan karar alma sürecine dayalı olarak, etkinlik, güvenlik ve maliyetler dikkate alınarak, en iyi bakım sunulmalıdır. Hastalık aktivitesi ve organ hasarı, çeşitli kompozit hastalık indeksleri kullanılarak değerlendirilmelidir. Ayrıca, tedaviye bağlı yan etkiler ve komorbiditeler açısından hastalar periyodik olarak taranmalı ve gerekli önlemler alınmalıdır. AAV ile ilgili bu kılavuz, başta romatoloji uzman hekimleri olmak üzere, hastalığın tanı veya takibi sırasında 2. ve 3. basamak hastanelerde bu hastaların başvurabileceği iç hastalıkları, nefroloji, göğüs hastalıkları ve kulak burun boğaz (KBB) hekimlerinin kullanımı için hazırlanmıştır. Hazırlık sürecinde, öncelikle güncel literatür ve uzman görüşleri esas alınmış; Avrupa Romatoloji Derneği (*European League Against Rheumatism* - EULAR), Böbrek Hastalığı Küresel Sonuçları İyileştirme Çalışma Grubu (*Kidney Disease Improving Global Outcomes*), Amerikan Romatoloji Derneği (*American College of Rheumatology* - ACR) gibi uluslararası kuruluşların kılavuzlarından da yararlanılmıştır.

II. Epidemiyoloji

Ülkelere ve etnik kökene göre değişkenlik göstermekle birlikte, yıllık insidans granülomatöz polianjiitis (GPA) için 0,4-11,9/1.000.000, mikroskopik polianjiitis (MPA) için 0,5-24/1.000.000, eozinofilik granülomatöz polianjiitis (EGPA) için ise 0,5-2,3/1.000.000 olarak bildirilmiştir. GPA'nın prevalansı 1 milyon kişide 2,3-146 arasında değişirken, MPA için bu oran 9-94 ve EGPA için 2-22,3 olarak saptanmıştır.[1] Hastalığın ortalama başlangıç yaşı GPA için 45-65, MPA için 55-75, EGPA için ise 38-54 yaş arasında olup, erkek/kadın oranı 1:1'dir. Ülkemizden yapılan Türk Vaskülit Çalışma Grubu (TRVaS) verilerine göre başlangıç yaşının, belirtilen aralıkların alt sınırına daha yakın olduğu saptanmış olup belirgin bir cinsiyet farkı gözlenmemiştir.[2]

III. Semptom ve Bulgular ile AAV'ye Özgü Hastalık Tutulum Özellikleri

AAV'nin semptomları ve tutulan organlara bağlı klinik bulguların heterojen olması nedeni ile hastalar farklı şikayetler ile başvurabilirler. AAV hastalarının tanı anındaki farklı doku ve organlardaki tutulum sıklıkları Eklenti Tablo 1'de yer almaktadır. Bu tabloda hem uluslararası Vaskülitlerde Tanı ve Sınıflandırma Kriterleri (*Diagnostic and Classification Criteria in Vasculitis Study*) çalışması verileri[3] hem de ülkemiz TRVaS Prospektif Veri Tabanı verileri[2] yer almaktadır.

GPA, tipik olarak üst ve alt solunum yollarını tutan nekrotizan granülomatöz enflamasyon ve küçük-orta çaplı damarların vasküliti ile karakterize olup genellikle sinsi bir başlangıç gösterir. MPA ise çoğunlukla pulmoner ve renal tutulumla birlikte vaskülitik bulgular gösterir ve genellikle hızlı başlangıçlı bir klinik seyir izler. EGPA ise astım öyküsü bulunan hastalarda, hastalık süreci içerisinde gelişen eozinofili ve granülom oluşumuyla seyreder.

• Hastalar, hastalığa özgü olmayan ateş, yorgunluk, kilo kaybı gibi konstitüsyonel semptomların yanı sıra tutulan organ/organlara bağlı şikayetler ile başvurabilirler.

• Deri tutulumu olarak palpabl purpura, livedoid lezyonlar, papüller, nodüller, ürtiker benzeri lezyonlar ve nadiren ülserler görülebilir. Bu lezyonlar, sistemik bulgularla birlikte ortaya çıkabileceği gibi, hastalığın ilk belirtisi olarak da karşımıza çıkabilir.

• Oral-mukoza tutulumunda, tedaviye dirençli oral ülserler ve kırmızı renkli eksofitik gingival şişlikler (çilek gingiviti) görülebilir.

• Hastalarda kas iskelet sistemi bulguları olarak artralji, artrit veya miyalji görülebilir.

• Hastalar epistaksis, nazal kabuklanma, nazal polip, nazal septum perforasyonu, semer burun deformitesi, kronik sinüzit, subglottik stenoz (SGS), ses kısıklığı, kulak tıkanıklığı, kulak ağrısı, işitme kaybı ile KBB bölümüne başvurabilirler. Ayrıca işitme kaybı, otore, otalji, tinnitus ve baş dönmesi gibi semptomların yanı sıra, fasiyal sinir paralizisi ve hipertrofik pakimenenjit gibi kafa tabanı etkilenimleri de görülebilir.

• Pulmoner tutulum AAV'de, trakeobronşiyal enflamasyon ve yapısal değişikliklerden, nodül, kitle ve kavitasyon gibi parankimal lezyonlara kadar geniş bir yelpazede görülür. Ayrıca, diffüz alveolar hemoraji (DAH) ve interstisyel akciğer hastalığı (İAH) gibi ciddi komplikasyonlar da gelişebilir.

• Renal tutulumu olan AAV hastalarında genellikle hızlı ilerleyen glomerulonefrite bağlı olarak akut böbrek hasarı gelişir. Ayrıca hematüri, proteinüri, ödem ve/veya hipertansiyon da sık görülür.

• Göz tutulumu, konjonktivit, üveit, proptozis, episklerit/sklerit ve periferal ülseratif keratit gibi çeşitli bulgulara yol açabilir; ayrıca nadiren retinit, optik nörit ve buna bağlı görme kaybı gibi ciddi komplikasyonlar gelişebilir.

• Sinir sistemi tutulumu daha çok periferik sinir sistemini etkileyerek mononöritis mültipleks, duyusal nöropatiler veya polinöropati şeklinde görülebilir. SSS tutulumu daha nadir olup baş ağrısı, bilişsel fonksiyonlarda azalma, nöbet, kraniyal sinir tutulumu, serebrovasküler olaylar görülebilir.

• Gastrointestinal tutuluma bağlı mezenterik iskemi ve bunun sonucunda karın ağrısı, kanlı diyare, perforasyon görülebilir. Bunların dışında kolesistit ve pankreatit de gözlenebilir.

• Kardiyak tutuluma bağlı perikardit, myokardit, kardiyomiyopati, kalp yetmezliği görülebilir.

a. Pulmoner Tutulum

Pulmoner açıdan hastalar asemptomatik olabileceği gibi, tutulum bölgesine göre öksürük, nefes darlığı, ses kısıklığı, stridor, balgam, kanlı balgam ve plöritik göğüs ağrısı gibi belirtilerle başvurabilirler. AAV'deki en sık torasik tutulumlar aşağıda belirtilmiştir:[4]

• Trakeobronşiyal tutulum: Trakeobronşiyal enflamasyon, mukozal değişiklikler, trakeo ve/veya bronkomalazi, SGS

• Pulmoner nodül (soliter/multipl), kitle, konsolidasyon ve kavitasyon

• DAH

• İAH

Yeni tanı alan bir hastada pulmoner belirti olmasa bile immünosupresif tedaviye başlamadan önce, bazal bir toraks bilgisayarlı tomografi (BT) istenmelidir. Akciğer grafisinde saptanamayan nodüller, nodül içindeki kavitasyonlar, subplevral yerleşimli lezyonlar, büyük hava yollarındaki enflamasyon ve stenotik lezyonlar toraks BT'de görülebilir. Yine İAH ve DAH bulguları toraks BT'de daha detaylı değerlendirilebilir. Eğer hastada böbrek tutulumu şüphesi varsa, kontrastsız BT tercih edilmelidir. Çekilen toraks BT'lerde trakeobronşiyal ağacın üç boyutlu rekonstrüksiyonu elde edilebilir.

Trakeobronşiyal tutulum GPA hastalarında sık görülürken, MPA ve EGPA hastalarında daha nadirdir. Mukozal lezyonların önemli bir özelliği segmental ve fokal olmasıdır. Mukozada enflamasyon ve erozyonlarla (mukozal ülser) karakterizedir. Ayrıca, kıkırdak tutulumu varlığında trakeo ve/veya bronkomalaziye veya stenozlara yol açabilirler. SGS, ses tellerinin hemen altındaki hava yolunun daralması olarak tanımlanır ve trakeobronşiyal GPA'nın en yaygın belirtisidir.[5] SGS bulunan hastalarda, stridor, ses kısıklığı ve dispne gibi semptomların varlığı acil değerlendirme gerektirir ve durumun şiddetine bağlı trakeostomi gerekebilir. Endobronşiyal enflamasyon ve stenoz, subglottik hastalıktan daha az sıklıkta görülmekle birlikte, benzer klinik semptomlarla ortaya çıkabilir. Trakeobronşiyal lezyonların biyopsilerinde sıklıkla spesifik olmayan mukozal enflamasyon, ülserasyonlar ve ilerleyen dönemde stenoz ile birlikte fibrozis gözlenir, ancak vaskülit nadiren tespit edilir.[6]

Pulmoner nodüller, AAV'nin tüm alt tiplerinde görülmekle birlikte en sık GPA'da saptanır. Hastaların %40-70'inde başlangıçta tek veya çift taraflı nodüller, pulmoner infiltrat ve konsolidasyon görülür ve bu lezyonların %20 -50'sinde kavitasyon saptanır. Lezyonlar geçici ve gezici nitelikte olabilir.[7,8] Nodüler lezyonlar sıklıkla kan damarları ile ilişkili olup (besleyici damar bulgusu), ağırlıklı olarak subplevral bölgelere yerleşir. Çapları birkaç milimetreden 10 cm'e kadar değişen boyuttadır ve büyüdükçe kaviteleşebilirler. Kaviteler genellikle kalın duvarlıdır, düzensiz iç kenarlara sahiptir ve kalsifikasyon içermez. Nodüllerin çevresinde buzlu cam dansitesi halkasının (halo bulgusu) varlığı sıkça görülür ve bu bulgu, eşlik eden alveolar kanamayı ifade eder. Pulmoner nodüller içinde hava bronkogramının varlığı da tipik bir bulgudur.

AAV asosiye-İAH, özellikle MPO-ANCA pozitif AAV hastalığı seyrinde gelişen bir akciğer tutulumudur. İAH hastalığı AAV tanısı öncesi ya da takibi sırasında saptanabilir. Toraks BT'de buzlu cam, retiküler opasite, interlobüler septal kalınlaşma, konsolidasyon ve bal peteği paternleri görülebilir. Miyeloperoksidaz (MPO)-ANCA pozitif AAV hastalarında sıklıkla görülen İAH radyolojik paterni, olağan interstisiyel pnömoni (*usual interstitial pneumonia*, UIP) paternidir, non-spesifik interstisiyel pnömoni (*non-specific interstital pneumonia*) ve daha az sıklıkla da deskuamatif interstisyel pnömoni paterni de görülebilir. İdiyopatik pulmoner fibrozis tanısı konan hastaların %5-10'unda tanı sırasında ANCA testi pozitif saptanabilir.[9]

DAH, kapiller enflamasyona bağlı damar duvar geçirgenliğinde artış neticesinde kanın alveollere geçmesi ve buna bağlı olarak oksijenizasyonun bozulması olarak tanımlanabilir. Ciddi bir morbidite ve mortalite sebebi olması nedeniyle erken tanı ve tedavisi önemlidir. DAH'den şüphelenilen hastalarda akciğer grafisinin hastaların yarısında normal olabileceği unutulmamalıdır. Toraks BT'de ise bilateral alveolar opasiteler, intra/interlobular kalınlaşma, buzlu cam görünüm ve kaldırım taşı paterni görülebilir. Bronkoalveolar lavajda (BAL) hemosiderin yüklü makrofajların gösterilmesi tanıda altın standarttır, ayrıca BAL ayırıcı tanıda yer alan enfeksiyöz süreçlerin tanısına da katkıda bulunur.[6]

b. Astım

EGPA tanılı hastaların büyük çoğunluğunda (>%90) astım görülür. Astım genellikle yetişkinlik döneminde başlar ve sıklıkla üst solunum yolu bulguları ile beraberdir. Üst hava yollarında eozinofilik nazal poliplerin eşlik ettiği kronik rinosinüzit görülür. Sıklıkla tedaviye dirençli seyreder ve cerrahiye rağmen nazal polipler tekrarlayabilir. EGPA'nın akciğer tutulumunda sıklıkla karşımıza çıkan pulmoner parankimal infiltratların, EGPA olmayan ağır eozinofilik astımda görülmesi beklenmez. Astım tanılı bir hastada, optimal tedaviye rağmen semptomlar kontrol altına alınamıyor ya da astım kontrolü için yüksek doz inhale kortikosteroid (İKS) kullanımı gerekiyorsa ve periferik kanda ≥1500/mm³ eozinofili eşlik ediyorsa, bu hastalar vaskülit semptomları açısından değerlendirilmelidir. Ayrıca, özellikle eozinofilik nazal polipli kronik rinosinüzit, ağır eozinofilik astım ve belirgin eozinofili varlığında da (EGPA) düşünülmeli ve sistemik tutulum yönünden hastalar sorgulanmalıdır.[10]

c. Renal Tutulum

Böbrek tutulumu olan hastalarda böbrek fonksiyonları sıklıkla günler veya haftalar içinde bozularak hızlı ilerleyici glomerulonefrit kliniği ile uyumlu bir şekilde akut böbrek hasarı gelişir. Ayrıca hematüri (özellikle dismorfik eritrositler ve/veya eritrosit silendirlerinin tespiti) ve proteinüri varlığı, renal tutulum açısından dikkate alınması gereken önemli bulgulardır. Tabloya eşlik eden ödem ve hipertansiyon da gözlenebilir. Ancak nadir olarak böbrek fonksiyonlarının daha yavaş bozulduğu olgular da tanımlanmıştır. Tedaviye rağmen olguların %20-25'inde son dönem böbrek yetmezliği gelişir.[11]

d. Nörolojik Tutulum

AAV'ye bağlı periferik nöropati, genellikle alt ekstremitenin distalinde başlayan iğnelenme veya ağrılı parestezi ile kendini gösterir ve sıklıkla mononöritis multipleks paterninde duyusal kayba neden olur. Motor kayıpların eşlik ettiği durumlarda, etkilenen bölgede kas kuvvetinde azalma ve kas atrofisi gözlenebilir; ancak saf motor nöropati AAV'ye bağlı nöropatilerde beklenmez. Elektrofizyolojik çalışmalarda, aksonal tip nöropatiyi işaret eden azalmış bileşik kas ve duyu siniri aksiyon potansiyelleri, korunmuş motor ve duyu ileti hızları ile distal motor latanslar tespit edilir. Sinir biyopsisinde hem miyelinli hem de miyelinsiz sinir liflerinde aksonal dejenerasyon ve epinöral damarlarda enflamasyon görülür. Bununla birlikte, biyopsi sonuçlarını değerlendirirken mononöritis multipleks paternine bağlı olarak biyopsi yapılan sinirin etkilenmemiş olma ihtimalinin yüksek olduğu akılda tutulmalıdır. AAV'de meninks tutulumu, hastalığın erken dönemlerinde ortaya çıkan, nadir ancak klinik açıdan önemli bir durumdur. Bu hastalarda manyetik rezonans görüntüleme tanı için kritik öneme sahiptir.

IV. Laboratuvar ve Histopatolojik Değerlendirme

a. Akut Faz Yanıtı ve Seroloji

ANCA, proteinaz 3 (PR3) ve MPO gibi spesifik antijenlere karşı gelişen otoantikorlardır. ANCA indirekt immünofloresan (IIF) ve ELISA yöntemleri ile bakılabilir. Nötrofillerin etanol ile tespit edildiği slaytlarda, IIF tekniğinde boyanma tipine göre üç tip ANCA tanımlanır:

Sitoplazmik ANCA ⇒ cANCA

Perinükleer ANCA ⇒ pANCA

Atipik ANCA

Antijen-spesifik immünoassayler, dolaylı IIF kıyasla daha yüksek tanısal doğruluğa sahiptir. 2017 uluslararası ANCA test konsensüs bildirgesi, GPA ve MPA tanısı için PR3 ve MPO-ANCA testlerinde yüksek kaliteli immünoassaylerin tercih edilen tarama yöntemi olarak kullanılmasını önermektedir.[12]

AAV tanısını düşündüren belirti ve/veya semptomları olan hastalarda, birincil test yöntemi olarak yüksek kaliteli antijen-spesifik bir analiz kullanılarak hem PR3-ANCA hem de MPO-ANCA testlerinin yapılması önerilmektedir. Eğer immünoassay sonucu negatifse ancak AAV için klinik şüphe yüksekse, ikinci bir testin (başka bir immünoassay ve/veya IIF) uygulanması tavsiye edilir. ANCA negatifliği AAV tanısını dışlamaz, çünkü solunum yolu ile sınırlı hastalık veya izole böbrek tutulumu olan olguların küçük bir kısmında ANCA testleri negatif bulunabilmektedir.[13]

b. Solunum Fonksiyon Testleri

Basit spirometri, SGS'nin tanısında ekstratorasik obstrüksiyonu, trakeobronşiyal tutulumda ise intratorasik obstrüksiyonu göstererek tanıya katkı sağlayabilir. İAH varlığında karbon monoksit difüzyon kapasitesinde (DLCO) azalma tespit edilir. Azalmış akciğer hacimlerinin eşlik ettiği restriktif tipte solunum fonksiyon bozukluğu görülür. İAH olan hastaların takibinde spirometri, DLCO ve beraberinde 6 dakika yürüme testi kullanılabilir.

c. Bronskoskopik Değerlendirme

AAV'lerin tanısında bronkoskopik değerlendirmenin katkısı olduğu durumlar vardır. GPA'da trakeobronşiyal tutulum varlığı değerlendirilebilir. Mukozal tutulumun olduğu alanlardan veya transbronşiyal olarak akciğer parankiminden biyopsi alınabilir. Ancak, alınan biyopsi örneklerinin küçük olması, granülomatöz vaskülitik tutulumun gösterilememesine neden olabilir. Alveoler hemoraji düşünülen ve aktif kanaması olan hastalarda, belirli bir segmente yönelerek yapılan ardışık lavajlarda (20-50 cc) giderek artan hemorajik görünüm, alveolar hemorajiyi düşündürür. Sitolojik incelemede %20 ve üzerinde hemosiderin yüklü makrofajların varlığı tanıda altın standarttır.[14] BAL ayrıca enfeksiyon ayırıcı tanısı için de önemlidir. Mikrobiyolojik analizlerin yapılması gerekir.

d. Histopatoloji

Deri bulguları olan hastalarda erişim kolaylığı nedeni ile histopatolojik inceleme önerilmektedir. Tanısal ipuçları olarak lökositoklastik vaskülit, granülomatöz enflamasyon ve değişen oranlarda eozinofil varlığı saptanabilir. Sinüs biyopsilerinin vaskülit tanısındaki duyarlılığı düşük olmakla birlikte, özellikle mukormikozis gibi invaziv fungal enfeksiyonlar başta olmak üzere granülomatöz enfeksiyonları dışlamak için gerekebilmektedir.

Akciğerde nodül, kitle veya konsolidasyon ile prezente olan GPA hastalarında, perkütan veya torakoskopik biyopsiler tanı amacıyla uygulanabilir. Ancak, perkütan biyopsiler genellikle küçük örnekler sağlamaları nedeniyle tanıda yetersiz kalabilir. Bununla birlikte, görüntüleme (BT, pozitron emisyon tomografi/BT) rehberliğinde nekrotik alanlardan kaçınılarak aktif lezyonlardan alınan biyopsiler, tanı başarısını anlamlı ölçüde artırmaktadır. GPA'da biyopsilerde tipik olarak nekrotizan granülomatöz enflamasyon görülür. Biyopsi yapılması halinde ayırıcı tanı için mutlaka özel boyamalar ve granülomatöz enfeksiyona neden olabilecek enfeksiyonlara (örneğin; tüberküloz) yönelik mikrobiyolojik inceleme ve kültürler rutin olarak yapılmalıdır.

Böbrek biyopsisi hem tanı koymada hem de hastalığın prognozunu belirlemede önemli bir rol oynamaktadır. MPO veya PR3-ANCA pozitifliği bulunan ya da küçük damar vaskülitini düşündüren organ tutulumları olan hastalarda, böbrek fonksiyon bozukluğu geliştiğinde veya hematüri ve/veya proteinüri saptandığında, herhangi bir kontraendikasyon yok ise biyopsi yapılmalıdır. Tedaviye yanıt vermeyen olgularda, kronik hasarın tespiti, diğer akut böbrek yetmezliği nedenlerinin araştırılması veya devam eden hastalık aktivitesinin belirlenmesi amacıyla biyopsi tekrarlanabilir. Biyopsi yapılamayan durumlarda, örneğin kanama riskinin yüksek olduğu anti-koagülan tedavi kullanan hastalar gibi, tedavi geciktirilmemelidir.

Böbrek biyopsisi ile glomerüler, tübülointerstisyel ve vasküler sistemle ilişkili bulgular elde edilebilmektedir. AAV'de görülen tipik böbrek lezyonu pauci-immün (immünoglobulin veya kompleman birikimi çok az olduğu ya da hiç saptanmadığı), nekrotizan kresentik glomerulonefrittir. Böbrek biyopsisi aynı zamanda uzun dönem böbrek yetmezliği gelişme riskini öngörmede kullanılabilir. Biyopsi anındaki histopatolojik bulgulara dayanan çeşitli prognostik skorlama sistemleri geliştirilmiştir.

Bu skorlama sistemleri içerisinde en sık kullanılanları Berden klasifikasyonu, Mayo Klinik/Böbrek Patoloji Cemiyeti Kronisite skoru ile ANCA Renal Risk skorlaması sayılabilir (Eklenti Tablo 2). Skorlama sistemleri arasında bazı farklılıklar mevcuttur. Berden klasifikasyonunda sadece böbrek biyopsisindeki glomerüler yapılar değerlendirilerek 4 kategori tanımlanmıştır. Berden sınıflamasına göre, fokal sınıf en iyi prognozu gösterirken sklerotik sınıf en kötü prognoza sahiptir. Kresentik ve karışık sınıfların prognozu ise değişkenlik göstermektedir.[15] Mayo Klinik/Böbrek Patoloji Cemiyeti Kronisite skoru böbrek histopatolojisindeki kronik değişiklikleri değerlendirir. Glomerüloskleroz, tubuler atrofi, interstisyel fibroz ve arterioskleroz derecelendirilerek minimal, hafif, orta ve ağır şeklinde skorlanır (Eklenti Tablo 2). Minimal ve hafif değişikliklere sahip gruplarda böbrek fonksiyonlarında düzelme ve böbrek sağ kalımının daha iyi olduğu gösterilmiştir.[16] ANCA Renal Risk skorlamasında ise normal glomerül yüzdesi, tubuler atrofi ve interstisyel fibroza ek olarak, diğer skorlamalardan farklı bir biçimde, tanı anındaki glomerüler filtrasyon hızı (GFR) 15 mL/dk/1,73 m^2 altında veya üzerinde olacak şekilde dahil edilmiştir. Renal risk skoru; renal tutulum olan AAV hastalarında renal sağkalımı tahmin etmek amacıyla geliştirilen bir skorlama sistemidir. Yüksek puan yüksek son dönem böbrek hastalığı riski ile ilişkili bulunmuştur.[17]

V. AAV Ayırıcı Tanısı ve 2022 ACR/EULAR AAV Sınıflandırma Kriterleri

AAV şüphesi olan bir hastayı değerlendirirken, AAV ilişkili semptomlar, organ tutulumları ve laboratuvar bulgularına sıklıkla neden olabilecek diğer ayırıcı tanılar aşağıda belirtilmektedir.[18]

- Enfeksiyöz hastalıklar (subakût bakteriyel endokardit, hepatit B, hepatit C ve insan immün yetmezlik virüsü enfeksiyonları, tüberküloz, fungal enfeksiyonlar)
- Maligniteler (lenfoma, lösemi, solid organ maligniteleri)
- Diğer otoimmün ve otoenflamatuvar hastalıklar (sistemik lupus eritematozus, büyük-orta damar vaskülitleri, immünoglobulinG4 ilişkili hastalık, antifosfolipid antikor sendromu vb.)
- İlaç/madde ilişkili ANCA pozitifliği (propiltiyourasil, hidralazin, fenitoin, levamizol, kokain gibi)

Sekonder nedenler dışlandıktan sonra primer olarak küçük/orta çaplı damar vasküliti tanısı düşünülen hastaların birbirinden ayırımında kullanışlı olan 2022 ACR/EULAR GPA, EGPA ve MPA sınıflandırma kriterlerini içeren liste Tablo 1'de sunulmaktadır.[19]

Tablo 1. 2022 ACR/EULAR GPA, MPA ve EGPA sınıflandırma kriterleri

Giriş kriteri: Küçük veya orta çaplı damar vasküliti tanısı konulmuş olmalıdır ve vasküliti taklit eden diğer tıbbi durumlar dışlanmış olmalıdır.			
	GPA	MPA	EGPA
Klinik kriterler			
• Nazal tutulum (kanlı akıntı, ülserler, kabuklanma, konjesyon, blokaj veya septal defekt/perforasyon)	+3	-3	
• Kıkırdak tutulumu (kulak, burun kıkırdağı, stridor, endobronşiyal tutulum veya semer burun)	+2		
• İletim tipi veya sensörinöral işitme kaybı	+1		
• Obstrüktif hava yolu hastalığı			+3
• Nazal polip			+3
• Mononöritis multipleks			+1
Laboratuvar kriterler			
• PR3-ANCA (veya cANCA) pozitifliği	+5	-1	-3
• MPO-ANCA (veya pANCA) pozitifliği	-1	+6	
• Serum eozinofil ≥1000/mikroL	-4	-4	+5
• Hematüri			-1
Histolojik kriterler			
• Granülom, granülomatöz enflamasyon veya dev hücreler	+2		
• Pauci-immün glomerulonefrit	+1	+3	
• Ekstravasküler eozinofilik enflamasyon			+2
Radyolojik kriterler			
• Akciğer görüntülemesinde nodüller, kitle veya kavitasyon	+2		
• Akciğer görüntülemesinde fibrozis veya interstisiyel akciğer hastalığı		+3	
• Görüntülemede nazal/paranazal sinüzit veya mastoidit	+1		
Sınıflandırma için gereken puan	5 ve üzeri	5 ve üzeri	6 ve üzeri

ACR: Amerikan Romatoloji Derneği, ANCA: Anti-nötrofil sitoplazmik antikorları, EGPA: Eozinofilik granülomatöz polianjiitis, EULAR: Avrupa Romatoloji Derneği, GPA: Granülomatöz polianjiitis, MPA: Mikroskopik polianjiitis, MPO: Miyeloperoksidaz

VI. Hastalık Aktivite ve Hasar Değerlendirmeleri

ANCA-AAV hastalarının indüksiyon tedavisi sırasında daha sık olmak üzere belirli periyotlarla hastalık aktivitesi ve hasar açısından değerlendirilmesi önerilmektedir. Genel yaklaşımla tanı anında ve 2, 4, 8, 12, 18 ve 24. haftalarda hastalığın klinik şiddetine ve tedavi rejimine de bağlı olarak kontrol vizitler önerilebilir. Bu vizitlerde organ tutulumuna göre gerekli uzman değerlendirmeleri yapılmalıdır (nefroloji, KBB, göz, göğüs hastalıkları vs.). Etkilenen organlar için hastanın klinik durumu, hastalığın şiddeti ve uygulanan tedavilere (izlem, tolerans, yan etkiler) göre fonksiyonel ve radyolojik değerlendirme (paranazal sinüs BT, toraks BT, SFT-DLCO, elektrokardiyografi, kardiyak manyetik rezonans görüntüleme, elektromiyografi) planlanabilir.[20]

Böbrek remisyonunun değerlendirmesi ve takibinde böbrek fonksiyon testleri en önemli parametre olarak kabul edilmektedir. Ayrıca hematüri, proteinüri ve ANCA titresi de takipte kullanılabilir. Böbrek remisyonunu değerlendirme ve takip etmedeki en önemli kriter böbrek fonksiyonunu gösteren serum kreatinin veya hesaplanmış GFR değerleridir. Azalan veya stabil seyreden serum kreatinin değerleri böbrekte remisyona işaret eder. Uzun dönem takiplerde %50 olguda hematüri ve/veya proteinüri sebat edebileceğinden, remisyon, relaps ve uzun dönem böbrek sağ kalımı üzerindeki rolleri tartışmalıdır. Ancak artan veya kaybolduktan sonra yeniden gelişen hematüri, diğer nedenler dışlandıktan sonra, böbrek relapsı açısından anlamlı olabilir ve yakın takip gerektirir. Sebat eden proteinüri ise böbrek kaynaklı hastalık aktivitesinin göstergesi olabileceği gibi, önceki enflamasyona bağlı gelişen kronik parankimal hasarın göstergesi de olabilir. Kronik hasara bağlı proteinüri uzun dönem böbrek fonksiyonları açısından olumsuz prognoz faktörüdür.[21-24]

AAV'lerde hastalık aktivitesi, tedavi kararı öncesi değerlendirme ve tedavi yanıtları ile vaskülitin hasarını objektif olarak değerlendirebilmek için çeşitli indeksler geliştirilmiştir.

Hastalarda, aktif hastalık bulgularının olup olmadığını değerlendirmek için Birmingham vaskülit aktivite skoru (BVAS) (versiyon 3)/BVAS-WG gibi doğrulanmış bir skor sistemi, takip sürecinde yapılandırılmış bir klinik değerlendirme ve enflamatuvar belirteçler kullanılmalıdır.[20,25] Hem BVAS hem de BVAS-WG skoru hesaplanırken, son 4 hafta içerisinde aktif vaskülite atfedilen ve yeni ortaya çıkan/kötüleşen bulgular yeni/kötüleşen hastalık durumu; bir önceki değerlendirmeden devam eden bulgular ise persistan hastalık durumu olarak işaretlenir. Bu skorlar tedaviye cevabın sistematik bir şekilde belgelenmesinde klinik pratiğe yardımcıdır (Eklenti Tablo 3).[13] Değerlendirme sıklığı hastanın klinik durumu, hastalığın şiddeti ve uygulanan tedavilerin izlemine göre değişebilir.

Refrakter hastalık standart indüksiyon tedavisine rağmen hastalık aktivitesinin devam etmesi veya kötüleşmesi durumunu ifade eder. Tedaviye başlanmasından sonraki 4 hafta içinde hastalık aktivitesinde bir azalma olmaması veya artış gözlenmesi veya tedavinin 6. haftasında hastalık aktivite skorunda (örneğin; BVAS) %50'den az bir azalma olması refrakter hastalık olarak değerlendirilir. Enfeksiyonlar, tedaviye uyumsuzluk, ilaç intoleransı, sekonder vaskülit nedenleri, tedaviye bağlı yan etkiler, eşlik eden diğer hastalıklar ve organ hasarlarının diğer nedenleri dışlanmalıdır.[26]

Beş faktör skoru, temel olarak hastalık aktivitesini değerlendirmeye yönelik değil, prognoz tayini için yardımcı olan bir skorlama sistemidir.[27]

Vaskülit hasar indeksi, sistemik vaskülitlerde hem hastalığa ve hem de tedaviye bağlı gelişen hasarı değerlendirmek üzere geliştirilmiş bir değerlendirme indeksidir. Hasar, özellikle vaskülit semptomlarının başlamasından itibaren üç aydan uzun süredir devam eden patolojik değişiklikler olarak tanımlanmıştır.[28] AAV hastalarında hasarı kaydetmek için doğrulanmış bir araçtır ve aktif hastalıktan hasarı ayırt etmeye yardımcı olan tanımlar sağlamaktadır.[13]

AAV hasta kaynaklı ölçütler (AAV-pro), 2018 yılında yayınlanmıştır ve Türkçeye çevrilerek kullanıma sunulmuştur. Hastaların son 4 hafta içinde, vaskülite veya aldığı tedaviye bağlı olduğunu düşündükleri problemlerle ilgili genel olarak deneyimlerini irdeleyen toplam 29 sorudan oluşmaktadır.[29]

VII. Tedavi ve Takip

a. Remisyon İndüksiyon Tedavisi

AAV'de tedavi, remisyon indüksiyon ve idame rejimlerinden oluşmaktadır. Yaşamı veya organı tehdit eden tutulumları (glomerulonefrit, DAH, trakeal veya SGS, meningeal tutulum, santral sinir sistemi tutulumu, retro-orbital hastalık, kardiyak tutulum, mezenterik tutulum, mononöritis mültipleks) olan AAV hastalarında remisyon indüksiyonu için, rituksimab (RTX) veya siklofosfamid (CYC) ile glukokortikoidlerin kombinasyonu kullanılmaktadır.[13,20,25,27,30] Remisyon indüksiyonu ve idame tedavide kullanılan diğer ilaçlar ve dozları Tablo 2'de özetlenmiştir.

Remisyon indüksiyonunda intravenöz (IV) glukokortikoid tedavisi, hızlı etkinlik sağlaması nedeniyle tercih edilse de rutin kullanımını destekleyici yeterli kanıt bulunmamaktadır. Enfeksiyon riski dahil glukokortikoid toksisitesinde olası risk

Tablo 2. Erişkinlerde AAV tedavisinde kullanılan ilaçlar ve kullanım dozları

Tedavi	Doz
Pulse glukokortikoid	İntravenöz metilprednizolon 500-1000 mg veya eşdeğeri, 3-5 gün süre ile
Yüksek doz oral glukokortikoid	Prednizolon 1 mg/kg/gün (75 mg/gün doza kadar) veya eşdeğeri
İndüksiyon tedavisi	
Metotreksat	20 mg/hafta doza kadar (oral veya subkütan)
Azatiyoprin	2-3 mg/kg/gün
Mikofenolat mofetil	2000 mg/gün
Siklofosfamid	15 mg/kg IV 3 doz 2 haftada bir takiben 15 mg/kg IV 3 doz 3 haftada bir
Rituksimab	375 mg/m² IV, haftada bir kez, toplam 4 hafta boyunca veya 14 gün ara ile toplam 2 kez 1000 mg
İdame tedavi	
Metotreksat, azatiyoprin, mikofenolat mofetil	Remisyon indüksiyon tedavisinde kullanılan doza benzer, takip süresince kademeli olarak doz azaltılır.
Rituksimab	Hastanın kliniğine göre 4-6 ayda bir 500 mg veya 1000 mg
EGPA'ya özgü ilaçlar	
Mepolizumab Benralizumab	100-300 mg/4 haftada bir subkütan 30 mg/4 haftada bir subkütan

AAV: Asosiye vaskülitler, EGPA: Eozinofilik granülomatöz polianjiitis

artışı göz önünde bulundurularak metilprednizolon pulse tedavisi, şiddetli renal hastalık (eGFR <50 mL/dak/1,73/m^2 olan aktif glomerülonefrit) veya diffüz alveoler hemoraji gibi ciddi bulguların tedavisi ile sınırlandırılmalı, kümülatif dozu 1-3 gram ile sınırlı olmalı ve takiben oral dozlarla devam edilmelidir.[13]

Oral glukokortikoid başlangıç dozu 50-75 mg/gün prednizolon eşdeğeridir. Son yıllarda azaltılmış doz glukokortikoid rejiminin standart doz tedaviye göre genel sağkalım ve son dönem böbrek yetmezliği riskini azaltmada benzer etkinliği gösterilmiştir. İlaveten azaltılmış doz glukokortikoid alan hastalarda özellikle ilk yıl boyunca daha az ciddi enfeksiyon gelişmiştir.[31] Bu rejimde prednizolon dozu ilk hafta 1 mg/kg olarak başlanır ve ardından planlı doz azaltımı uygulanır (Tablo 3).[13,25] Ancak bu azaltma şeması her hasta için uygun olmayabilir. Özellikle renal tutulumda kişiye özel olarak, hastanın risk faktörlerine ve klinik durumuna göre daha yavaş azaltma dozları ile planlanma yapılmalıdır.

Böbrek tutulumu olan hastalarda, tanı anında diyaliz ihtiyacının olması veya böbrek biyopsisinde ağır histolojik bulguların varlığı indüksiyon tedavisinin başlanmasını engellemez. Aksine diyaliz gerektiren ileri böbrek yetmezliği olgularında dahi indüksiyon tedavisi ile böbrek fonksiyonlarında düzelme görülebilir. Tedavide RTX veya CYC ilk seçenek olarak kullanılabilse de, ciddi glomerülonefritli hastalarda (kreatinin> 4,0 mg/dL) Nefroloji cemiyetlerince CYC kullanımı ilk aşamada önerilmektedir.[25] Ciddi renal tutulumun yanı sıra diffüz alveolar kanama gibi sistemik ve hayatı ya da organı tehdit

Tablo 3. AAV tedavisinde vücut ağırlığına göre ayarlanmış azaltılmış doz glukokortikoid şeması

Hafta	Vücut ağırlığı		
	<50 kg	50-75 kg	>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

Glukokortikoid dozu prednizolon eşdeğeri mg/gün olarak PEXIVAS çalışmasındaki şemadan oluşturulmuştur

eden tutulumlar mevcutsa, AAV ile birlikte anti-GBM antikor pozitifliği olanlarda ve trakeal, bronşiyal tutulum ile orbital ve pakimenenjit ön planda olan granülomatöz hastalıklarda da CYC tercih edilebilir.[20,30] RTX ise fertilite konusunda endişeleri olan erişkinlerde, yaşlı ve/veya kırılgan hastalarda ve PR3-ANCA pozitifliği olanlarda ilk tercih olabilir. Mikofenolat mofetil (MMF), CYC veya RTX kullanılamayacak hastalarda, özellikle MPO-ANCA pozitif alt grupta, alternatif olarak başlanabilecek seçeneklerden biridir. RTX ile CYC kombinasyonu, dirençli ve/veya hayatı tehdit eden hastalarda nadiren kullanılmaktadır. RTX yanına düşük doz CYC eklenmesiyle relaps sıklığının azaldığını gösteren çalışmalar mevcuttur. Ülkemizde avacopan bulunmamakla birlikte, steroid tedavisine alternatif olarak diğer immünosupresiflerle birlikte kullanılabilecek bir seçenek olarak değerlendirilmiştir.[25]

Yaşamı veya organı tehdit etmeyen diğer AAV tutulumları (örnek pulmoner nodüller, lokalize üst solunum yolları gibi), metotreksat (MTX) ile birlikte oral glukokortikoidlerle tedavi edilebilir.[6] MTX tolere edemeyen veya uygun olmayan durumlarda MMF, azatiopürin veya RTX da kullanılabilir. Granülomatöz akciğer lezyonlarının tedaviye yanıt oranı hastalar arasında oldukça değişkendir ve tedavi, lezyonlar tedavi altında küçülmeye devam ettiği sürece sürdürülmelidir.[32] İnterstisyel fibrozisi olan AAV hastalarının tedavisi, vaskülit tedavi önerilerine uygun şekilde yapılmalıdır.

b. Böbrek ve Solunum Destek Tedavileri, Plazma Değişimi ve İntravenöz İmmünoglobulin (IVIG)

AAV'de hastalık yönetiminde tüm süreçler, mümkünse multidisipliner olarak yürütülmelidir. Böbrek yetmezliği olan hastaların renal replasman tedavileri nefroloji uzmanlarıyla, solunum desteği ihtiyaçları (non-invazif veya invazif mekanik ventilasyon) ve takibi yoğun bakım uzmanlarıyla koordineli olarak planlanmalıdır.

Plazma değişimi, ANCA ve kompleman dahil diğer patojenik enflamasyon aracılarının hızlı ve etkili şekilde ortadan kaldırılabilmesini sağlamaktadır.[33] AAV hastalarında plazma değişiminin genel sağkalıma katkısı gösterilememiştir. Bununla birlikte plazma değişimi şiddetli böbrek tutulumu olan hastalarda son dönem böbrek yetmezliği gelişme riskini azaltmakta, fakat ciddi enfeksiyon riskinde artışa neden olmaktadır.[31] Bu nedenle plazma değişimi AAV hastaları için rutin olarak indüksiyon rejiminin parçası olarak önerilmez.[30]

AAV'ye bağlı hızlı ilerleyen glomerülonefriti olan hastalarda (serum kreatinin >3,4 mg/dL, diyaliz gereken veya immünosupresif tedaviye rağmen serum kreatininin hızla artan hastalar) ve hipoksemisi olan diffüz alveoler hemorajili hastalarda plazma değişimi düşünülmelidir. Ayrıca anti-GBM pozitif olan AAV hastalarında plazma değişiminin uygulanması etkin seçenek olarak değerlendirilmelidir.[25] Bireysel hasta özelliklerini, klinik ve histolojik parametreleri göz önünde bulunduran kişiselleştirilmiş yaklaşım, plazma değişiminin potansiyel faydasını belirlemede önemlidir.[34]

AAV'de IVIG kullanımı rutin tedavinin parçası olmamakla birlikte, hastalarda hastalık aktivitesinde ve biyobelirteçlerde hızlı iyileşme sağlayabilmektedir.[35] IVIG endikasyonunda göz önünde bulundurulması gereken parametreler aşağıda sıralanmıştır.[27,30,36]

- Hipogammaglobulinemi derecesi
- Ciddi, kalıcı, olağan dışı veya tekrarlayan enfeksiyonlar
- Polisakkarit antijenlere karşı zayıf antikor yanıtının gösterilmesi
- Antibiyotik profilaksisine yetersiz yanıt
- Bireysel komorbiditeler (bronşektazi, nötropeni ve steroidlerin veya ek immünosupresiflerin eş zamanlı kullanımı gibi).

Remisyon indüksiyon tedavisine dirençli (refrakter) GPA/MPA hastalarında IVIG kullanımı immünmodülatör dozlarda (2 g/kg/kür) düşünülebilir. RTX ile remisyon idamesi sırasında hipogammaglobulinemi (IgG <4 g/litre) ve tekrarlayan ciddi enfeksiyonları bulunan hastalar için replasman dozunda (aylık 0,4 g/kg) kullanılabilir.[30]

c. İdame Tedavi ve Relapslarda Yaklaşım

Hastalık aktivitesi kontrol altına alındıktan sonra geçilen idame tedavisinin süresi, hastalığın şiddeti, antikor profili ile organ tutulumlarına göre hastaya özgü olarak belirlenmelidir. GPA ve MPA'da remisyonu takiben idame tedavisine en az 24-48 ay süre ile devam edilmelidir.[13,25] Relaps yaşanan ya da relaps riskinin yüksek olduğu hastalarda tedaviye daha uzun süre devam edilmesi gerektiği unutulmamalıdır. Tedavide kullanılmakta olan ilaçlar Tablo 2'de yer almaktadır. İdame RTX öncesi serum IgG düzeyi bakılmalı ve hipogamaglobulinemi (serum IgG düzeyi <7 g/L) durumunda, düzeyin 2-4 hafta sonra tekrar kontrol edilmesi ve tedavi kararının yeniden gözden geçirilmesi önerilir.

Kısmi veya tam remisyon sağlandıktan sonra herhangi bir organ sisteminde aktif vaskülit belirti veya semptomlarının yeniden ortaya çıkması "Relaps" olarak tanımlanmaktadır. Majör ya da minör olarak sınıflandırılır. Majör relaps hayat veya organ tehdit edici özelliktedir. Relaps için risk faktörleri arasında PR3-ANCA alt grubu, kulak-burun-boğaz tutulumu, tanı sırasında yüksek serum kreatinin düzeyi ve hastalığa bağlı yaygın tutulum sayılabilir. ANCA pozitifliğinin devam etmesi, titresindeki artış

veya serokonversiyon (negatiften pozitife dönme) relaps riskinin arttığına işaret edebilir.[25] Renal relaps hematüride artış, aktif idrar sedimenti saptanması ve/veya böbrek fonksiyonlarında yeni gelişen bozulma olarak tanımlanabilir. Hastalık alevlenmesi genellikle başlangıç tutulumu olan organda olsa da yeni bir organda tutulum da nadir değildir. Tekrarlayan vasküliti doğrulamak için doku biyopsisi yapılması gerekebilir.[37,38]

Relapslar genelde immünosupresif tedaviye yanıt vermektedir. Ciddi relapslarda tedaviyi indüksiyon tedavi şeması şeklinde uygulamak gerekmektedir. Ciddi olmayan relapslarda CYC ikinci planda düşünülerek halihazırda kullanılmakta olan immünosupresif dozu yükseltilebilir.[25] Relaps sırasında remisyon indüksiyonda ve idamede kullanılan tedaviye göre CYC kullanan hastada RTX veya RTX altında relaps gelişen hastada CYC tedavisi, glukokortikoid tedavisi ile beraber kullanılabilir. Relapsta RTX tedavisi ön planda tercih edilebilir.[13] Serum kreatinin düzeyi >4,0 mg/dL olan hastalarda RTX etkinliği ile ilgili veri sınırlıdır. RTX ile idame tedavisi alan hastalarda son dozun üzerinden 4-6 aydan uzun bir süre geçmesi durumunda yeni bir kür uygulanabilir.[30]

d. Durumlara Özel Tedavi Yaklaşımları

Sinonazal tutulum tedavisinde immünosupresiflerin yanı sıra, enfeksiyon kontrolünde ve semptomların hafifletilmesinde kültür sonuçlarına göre belirlenen antibiyotikler ve topikal antibiyotik irrigasyonları, etkilidir. Yüksek hacimli serum fizyolojik irrigasyonları, mukosiliyer klirensi artırarak burun tıkanıklığını ve mukopürülan akıntıyı azaltmak için faydalı bir yardımcı yöntemdir. Septal perforasyon varlığında semptomları hafifletmek için septal obtüratörler kullanılabilir. Semer burun deformitesi veya septal perforasyonu olan hastalara, uzun süreli remisyonun sağlanması halinde rinoplasti uygulanabilir.

Trakeal veya SGS'lerde hedeflenen temel yaklaşım, cerrahi girişimlerden kaçınarak erken tanı ve immünosupresif tedavi ile darlığın ilerlemesinin engellenmesidir. Erken dönem veya hafif şiddetli SGS olgularında inhale glukokortikoidler ve topikal tedaviler yeterli olabilir. Fibrozis/skar oluşumuna bağlı mekanik hava yolu tıkanıklıkları lazer ablasyonu, kortikosteroid enjeksiyonu, kriyoterapi, balon dilatasyonu veya cerrahi tedavi ile düzeltilebilir.[6]

İnterstisiyel fibrozisi olan AAV hastalarında anti-fibrotik ilaçların (nintedanib, pirfenidon) etkinliği açısından yeterli veri yoktur. Özellikle MPO-ANCA pozitif, UIP paternine sahip İAH varlığındaki tedavi yönetimi kanıt eksikliği nedeniyle zor ve tartışmalı alanlardan biridir.[39] Son yayınlanan progresif pulmoner fibrozis (PPF) tedavi kılavuzunda vaskülitleri de kapsayan otoimmün interstisyel hastalıklara bağlı PPF'de antifibrotik tedavi önerilmektedir. Öncelikle önerilen ilaç nintedanib'dir.[40] Pirfenidon kanıt yetersizliği nedeniyle ikinci sırada yer almaktadır.[41]

Tüm EGPA hastalarında astım tedavisi uygun tedavi basamağında sürdürülmelidir. Astım tedavisinde hiçbir tedavi basamağında tek başına bronkodilatör ilaçlar önerilmemekte, bronkodilatör ilaçlarla birlikte mutlaka İKS'ler kullanılmaktadır. Hasta takipleri astımda kontrol sağlanana kadar ayda bir, devamında ise 3-6 ay aralıklarla yapılmalıdır.[42,43]

Vaskülit bulguları remisyonda olan EGPA hastalarında, yüksek doz İKS+uzun etkili beta agonist tedavisine ve tedavi optimize edilmiş olmasına rağmen atak ya da kontrolsüz astım varsa ağır eozinofilik astım tanısıyla anti IL-5 (Mepolizumab) ya da anti IL-5Rα (Benralizumab) tedavileri yönünden hastalar değerlendirilmelidir. Mepolizumab, EGPA tedavisinde 300 mg/4 haftada bir olacak şekilde FDA ve EMA tarafından onaylanmıştır. Ancak, FFS=0 olan ve majör organ tutulumu olmayan solunumsal semptomların ön planda olduğu EGPA hastalarında 4 hafta arayla uygulanan 100 mg dozun da etkili olduğu gözlemsel çalışmalarda gösterilmiştir.[44-46] Bu nedenle, bu hastalarda başlangıç dozu olarak 100 mg dozunda başlanması ve 16. haftada yeterli yanıt alınamaması durumunda dozun 300 mg'a çıkılması önerilir. Hayati organ tutulumu olan hastaların idame tedavisi için 300 mg 4 haftada bir olarak kullanılması önerilir. Mepolizumab tedavisine refrakter hastalarda EGPA tedavisinde, mepolizumab tedavisine alternatif bir ajan olarak benralizumab önerilebilir. Ülkemizde EGPA'da kullanımı endikasyon dışı başvuruya tabidir.

AAV'ye bağlı nöropatinin tedavisi, multidisipliner bir yaklaşım gerektirir. Sekel nöropatik ağrının yönetiminde, nöroloji bölümü ile iş birliği yapılarak gabapentinoidler, trisiklik antidepresanlar, serotonin-noradrenalin geri alım inhibitörleri ve sodyum kanal blokörleri gibi farmakolojik tedaviler kullanılabilir. Periferik nöropatinin, hastaların yaşam kalitesini ciddi şekilde etkileyebileceği göz önünde bulundurularak psikososyal destek ve hasta eğitimi önceliklendirilmelidir. Rehabilitasyon sürecinde fiziksel ve mesleki terapistlerin desteği sağlanabilir. Düşük ayak gibi motor disfonksiyonları olan hastalarda alt ekstremite ortezleri kullanımı gerekebilir.

e. Takipte İlaç Kesilmesi

Tedaviye rağmen üç aydan daha uzun süre ile diyaliz ihtiyacı devam eden ve böbrek fonksiyonlarında düzelme olmayan hastalarda, böbrek dışı tutulum açısından tedavi endikasyonları mevcut değil ise, immünosupresif tedavinin azaltılması/kesilmesi gündeme alınmalıdır. Kronik diyaliz tedavisi ile takip edilen hastalarda relaps riski diyaliz öncesi döneme göre belirgin olarak azalmakla birlikte yine de gözlenebilir. Buna karşılık AAV nedeniyle kronik diyaliz ihtiyacı olan hastalarda en önemli ölüm nedeni enfeksiyonlar olup, ciddi enfeksiyon sıklığı artmıştır. Genel olarak son

dönem böbrek yetmezliği gelişen hastalarda sağkalım böbrek fonksiyonu korunmuş hastalardan daha düşüktür.[11,47-49]

Evre 5 kronik böbrek yetmezliği gelişen GPA/MPA hastaları böbrek nakli açısından değerlendirilmelidir. Böbrek nakli için hastanın en az 6-12 ay süreyle tam klinik remisyonda olması gerekmektedir. Nakil esnasında mevcut olan ANCA pozitifliği tek başına nakil için kontrendikasyon oluşturmamakla birlikte, her hasta aktivasyon açısından olgu bazında detaylı değerlendirilmelidir. Nakil sonrası dönemde relaps genel olarak azalır ve nakil böbrekte hastalık tekrarı nadirdir. Ancak hastalar böbrek dışı relapslar açısından takip edilmelidir. Böbrek nakli sonrasında hasta ve böbrek sağ kalımı diğer nedenlere bağlı böbrek nakli hastaları ile benzerlik gösterir. Böbrek nakli olan hastaların sağ kalımı diyaliz ile takip edilen hastalara göre belirgin olarak daha iyidir.[50,51]

f. Morbidite ve Komplikasyonların Önlenmesi

RTX, CYC ve/veya yüksek doz glukokortikoid alan AAV'li hastalarda, pnömosistis karini pnömonisi ve diğer enfeksiyonlara karşı profilaksi olarak trimetoprim sülfametoksazol kullanımı (400/80 mg/gün ya da 800/160 mg/haftada 3 gün) önerilir.[52] AAV hastalarına ulusal ve uluslararası öneriler doğrultusunda enfeksiyonların önlenmesi amacıyla uygun aşılama yapılmalıdır.[53,54]

AAV'de kortikosteroid kullanımına bağlı komplikasyonların gelişmesini engellemek için mümkün olan en kısa dozda ve sürede steroid kullanılmalıdır; kan şekeri, lipid profili, tansiyon takibi ve osteoporoz riski nedeni ile kemik dansitometri ile tarama yapılmalıdır[55] ve kortikosteroid kullanan hastalara (herhangi bir dozda, ≥3 ay), kalsiyum (1000-1200 mg/gün) ve D vitamini (800-1500 IU/gün) desteği önerilir.[56]

VIII. Hastaların Bilgilendirilmesi, Gebelik Planlaması ve Cerrahi Gereksiniminde Yaklaşım

Hastalar AAV'nin etkisi ve prognozu, önemli uyarıcı semptomlar ve tedavi (tedaviye bağlı komplikasyonlar dahil) etkileri konularında yeterli düzeyde bilgilendirilmelidir. AAV hastalarının eğitiminde dikkat edilmesi gereken noktalar şunlardır:

a. Hastalığın seyri, tedavi süreci ve hastalıkla ilişkili gelişebilecek uyarıcı semptom ve bulgular hakkında bilgilendirme yapılmalıdır.

b. Doğurganlık çağındaki kadınlarda tedavide kullanılan belirli ilaçlarla birlikte kontrasepsiyon gerekliliği, erken menopoz veya infertilite riski, gebelik ve emzirmeyle ilgili olası kontrendikasyonlar belirlenmeli ve hasta bilgilendirilmelidir.

c. Enfeksiyonlara karşı koruma amaçlı aşılama önerileri ve planı yapılmalıdır.

d. Kortikosteroid tedavisiyle ilişkili olası yan etkiler, tedavi uyumunun önemi, diyet ve yaşam tarzı değişiklikleri hakkında eğitim verilmelidir.[20]

Gebelik, AAV alevlenmesi için bağımsız bir risk faktörü olarak kabul edilir ve AAV tanılı kadınların gebeliği, yüksek riskli gebelik olarak değerlendirilmelidir. Gebe kadınlarda vaskülit gelişmesi ya da vaskülit tedavisi sırasında gebelik oluşması durumunda, maternal ve fetal sağkalımın artırılması, tedavi yönetimi ve gebelik sonrası takip için romatolog, perinatalog ve kadın doğum hekimlerinin multidisipliner çalışması gerekmektedir.[57] Gebelik sırasında, metotreksat, leflunomid, MMF ve CYC gibi ilaçların kullanımı kontrendikedir. Bu ilaçlar gebelikten en az 3-6 ay önce kesilmelidir. Gebelik sırasında hastalık aktif ise, kortikosteroidler, azatioprin ve IVIG gibi tedavi seçenekleri kullanılabilir. Hayatı tehdit eden durumlarda plazma değişimi, RTX veya CYC düşünülebilir.[58]

AAV'de gerekli durumlarda, hastalık aktivitesine ve hastanın kliniğine bağlı olarak tek başına veya immünosupresif tedavilere ek olarak acil ve/veya elektif cerrahi girişim uygulanabilir. Elektif durumlarda 6-12 ay remisyon sağlandıktan sonra cerrahi girişim uygulanması önerilir.[59]

Son söz, tıbbın çeşitli bölümlerini ilgilendiren doku ve organ sistemlerinin tutulumu görülebilen ANCA AAV'nin yönetiminde disiplinler arası iletişim çok önemlidir. Bu kılavuz, Türkiye Romatoloji Derneği Yönetim Kurulunca görevlendirilen romatoloji, nefroloji, göğüs hastalıkları, allerji ve immünoloji, KBB ve hematoloji gibi çeşitli uzmanların fikir birliği ile oluşturulmuştur. Hastalık yönetimi ile ilgili çeşitli aşamalara yönelik öneriler de belirlenmiştir. Ülkemiz tıbbına ve hastalarımıza faydalı olması temenni olunur.

AAV Yönetimi Türkiye Romatoloji Derneği Önerileri

Genel Prensipler	
A	Anti-nötrofil sitoplazmik antikor asosiye vaskülitler (AAV), heterojen klinik bulguları olabilen ve potansiyel olarak organları ve/veya yaşamı tehdit eden hastalıklardır. Bu nedenle vaskülitler konusunda deneyimli merkezler veya bu merkezlere kolay erişimi olan klinikler tarafından multidisipliner bir ekiple yönetim gerektirir.
B	AAV klinik spektrumunun geniş olması nedeniyle, hekimlerin farkındalık artışını sağlayıcı toplantılara ihtiyaç duyulmaktadır. Ayrıca hastalık yönetimini optimum hale getirmek için disiplinler arasında iş birliklerini amaçlayan görüşmelerin yapılması faydalı olacaktır.
C	AAV tanılı hastalar, hastalıklarının olası seyri, tedavi süreci ve hastalıkla ilişkili gelişebilecek uyarıcı semptom ve bulgular hakkında bilgilendirilmelidir.
D	Hastalar, tedavi ilişkili yan etkiler ve komorbiditeler (hipertansiyon, osteoporoz, kardiyovasküler hastalıklar) açısından periyodik olarak taranmalı ve hastalara gerekli yaşam tarzı değişiklikleri önerilmelidir.
Öneriler	
1	AAV tanısını düşündüren semptomları ve/veya bulguları olan hastalarda, birincil test yöntemi olarak yüksek kaliteli antijen-spesifik bir analiz kullanılarak hem PR3-anti-nötrofil sitoplazmik antikor (ANCA) hem de miyeloperoksidaz-ANCA testlerinin yapılması önerilir.
2	AAV tanısında altın standart yöntem, biyopsidir (özellikle böbrek, akciğer biyopsileri). Ancak, biyopsi yapılamadığı durumlar ile biyopsi sonuçlanmadan önce kuvvetli vaskülit şüphesi varlığında immünosupresif tedavi geciktirilmemelidir.
3	AAV hastalarında ilk tanı sırasında ve takip süresince, aktif hastalık bulgularının varlığını değerlendirmek için enflamatuvar belirteçler ve yapılandırılmış klinik değerlendirme sistemi (Birmingham vaskülit aktivite skoru-versiyon 3) kullanılması tavsiye edilir.
4	Hayati/organ tehdit edici durumlarda (glomerulonefrit, diffüz alveolar hemoraji, trakeal veya subglottik stenoz, meningeal tutulum, santral sinir sistemi tutulumu, retro-orbital hastalık, kardiyak tutulum, mezenterik tutulum, mononöritis múltipleks), remisyon indüksiyon tedavisi olarak glukokortikoid tedavisi ile birlikte siklofosfamid (CYC) veya rituksimab (RTX) başlanması önerilir.
5	Hayati/organ tehdit edici durumlarda pulse glukokortikoid tedavisi uygulanabilir. Başlangıç oral glukokortikoid dozu, klinik durumun ciddiyetine göre düzenlenir. Uzun süreli steroid kullanımında, klinik durum elverdiği sürece azaltılmış doz steroid rejimi tercih edilir.
6	Pulmoner nodüller veya lokalize üst solunum yolları gibi diğer AAV tutulumları, oral glukokortikoid tedavisi ile birlikte metotreksatla (MTX) tedavi edilir. Alternatif olarak mikofenolat mofetil (MMF), azatiopürin veya RTX düşünülebilir.
7	Plazma değişimi indüksiyon rejiminin rutin bir parçası olarak önerilmez. Hızlı ilerleyen glomerülonefriti olan hastalarda (serum kreatinin düzeyi >3,4 mg/dL, diyaliz gereken veya immünosupresif tedaviye rağmen serum kreatininin hızla artan hastalar) ve/veya hipoksemisi olan diffüz alveoler hemorajili hastalarda düşünülmelidir.
8	Refrakter hastalık veya relaps durumunda, hastaların deneyimli merkezlere refere/sevk edilmesi düşünülebilir.
9	Eozinofilik granülomatöz polianjiitis (EGPA) pulmoner alevlenme bulguları, göğüs hastalıkları veya allerji-immünoloji uzmanı iş birliğinde değerlendirilmeli ve hastada astım kontrolünü sağlayacak inhale kortikosteroid (İKS) içeren tedavi rejimi şeklinde uygulanmalıdır.
10	EGPA hastaları, kontrolsüz astım (yüksek doz İKS+ uzun etkili beta-agonist tedavisine rağmen atak) varlığında anti interlökin (IL)-5 (mepolizumab) ya da anti IL-5Rα (benralizumab) tedavileri yönünden değerlendirilmelidir.
11	AAV hastalarında idame tedavi olarak MTX, MMF, azatiopurin veya RTX kullanılabilir. RTX kullanımında azatiopürine göre daha az relaps bildirilmiştir. İdame tedavisi, hastanın klinik durumuna bağlı olarak 24 ile 48 ay arasında sürdürülebilir.
12	RTX, CYC ve/veya yüksek doz glukokortikoid alan hastaların, Pneumocystis jirovecii pnömonisine profilaksisi olarak trimetoprim/sülfametoksazol (400/80 mg/gün ya da 800/160 mg/haftada 3 gün) kullanması önerilir. Ayrıca hastalara yıllık influenza aşısı ve yaş grubuna göre pnömokok aşıları önerilmelidir.
13	RTX sonrası gelişebilen sekonder immün yetmezliği tespit etmek amacıyla RTX tedavisine başlamadan önce, tedavi süresince her RTX döngüsünden önce ve tedavi kesildikten sonra ise en az bir yıl boyunca serum immünoglobulin konsantrasyonlarının ölçülmesini önerilir.
14	İntravenöz immünoglobulin, rutin AAV tedavisinin bileşeni değildir. Bireysel komorbiditelerin varlığında kullanılabileceği akılda tutulmalıdır (bronşektazi, olağan dışı veya tekrarlayan enfeksiyonlar, nötropeni ve hipogamaglobulinemi (IgG <4 g/litre).

Eklenti Tablolar. https://d2v96fxpocvxx.cloudfront.net/ecbfe058-16b4-48ee-945f-aeecbad1b86a/content-images/891801d4-d953-45c8-a12f-b849bbaf1b3c.pdf

Dipnotlar

Yazarlık Katkıları

Konsept: Ö.K., E.S., P.A.D., Ö.G., R.C.K., D.Ş., G.S., E.D.E., G.S.K.B., T.S.Ö., M.N.T., G.K.A., Dizayn: Ö.K., E.S., P.A.D., Ö.G., R.C.K., D.Ş., G.S., E.D.E., G.S.K.B., T.S.Ö., M.N.T., G.K.A., Veri Toplama veya İşleme: Ö.K., E.S., P.A.D., Ö.G., R.C.K., D.Ş., G.S., E.D.E., G.S.K.B., T.S.Ö., M.N.T., G.K.A., Analiz veya Yorumlama: Ö.K., E.S., P.A.D., Ö.G., R.C.K., D.Ş., G.S., E.D.E., G.S.K.B., T.S.Ö., M.N.T., G.K.A., Literatür Arama: Ö.K., E.S., P.A.D., Ö.G., R.C.K., D.Ş., G.S., E.D.E., G.S.K.B., T.S.Ö., M.N.T., G.K.A., Yazan: Ö.K., E.S., P.A.D., Ö.G., R.C.K., D.Ş., G.S., E.D.E., G.S.K.B., T.S.Ö., M.N.T., G.K.A.

Çıkar Çatışması: Dr. Haner Direskeneli, Ulusal Romatoloji Dergisi'nin baş editörü, Dr. Ömer Karadağ yardımcı editörüdür. Bu makalenin hakem değerlendirmesinde herhangi bir rolleri olmamıştır ve hakem değerlendirmesiyle ilgili bilgilere erişimleri yoktur.

Finansal Destek: Yazarlar tarafından finansal destek almadıkları bildirilmiştir.

Kaynaklar

1. Kitching AR, Anders HJ, Basu, N et al. Anca-associated vasculitis. Nat Rev Ris 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). 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. 2010;30:33-53.
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;19:378-93.
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 Risper 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. Antinötrofil sitoplazmik antikor ilişkili vaskülitler: ayırıcı tanısı. Turkiye Klinikleri 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? Clin Kidney J. 2023;16:965-75.
25. Kdigo 2024 clinical practice guideline for the management of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Kidney Int. 2024;105:S71-S116.
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 Rheumatol. 1997;40:371-80.
29. Robson JC, Dawson J, Doll H, et al. alidation 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, Cai J, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann 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. The European respiratory journal. 2022;59.

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, ve ark. Astım tanı ve tedavi rehberi, astımın kronik tedavisi, basamak tedavisi 2022 güncellemesi. Erişim Linki: 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. Erratum in: Nephrol Dial Transplant. 2025;40:1258.

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 erişkin bağışıklama rehberi 2024. 2024. Erişim Linki: https://www.ekmud.org.tr/haber/1151-eriskin-bagisiklama-rehberi-2024

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. Obstetric 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(Suppl 1):39-41.

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

Review / Derleme

DOI: 10.4274/raed.galenos.2025.38257
Ulus Romatol Derg 2025;17(3):145-154

Inflammatory arthritis and malignancy: A consensus report on risk assessment and clinical management based on a systematic review from the Turkish Society of Rheumatology Malignancy Study Group

Türkiye Romatoloji Derneği - Romatoloji ve Malignite Çalışma Grubu enflamatuvar artrit ve malignite: Sistematik derlemeye dayalı risk değerlendirmesi ve klinik yönetim üzerine fikir birliği raporu

Hakan Babaoğlu[1], Emre Tekgöz[2], Pınar Akyüz Dağlı[3], İbrahim Vasi[4], Bahar Özdemir Ulusoy[5], Dilara Bulut Gökten[6], Reşit Yıldırım[7], Gülşah Soytürk[1], Buğu Bulat[8], Özlem Doğan Ağbuğa[9], Gül Güzelant Özköse[10], Seda Çolak[3], Emine Duygu Ersözlü[11], Nazife Şule Yaşar Bilge[7], Cemal Bes[10], Timuçin Kaşifoğlu[7], İhsan Ertenli[8]

[1]*Ankara Bilkent City Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[2]*University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[3]*University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[4]*Gazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[5]*Ankara Gaziler Physical Medicine and Rehabilitation Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[6]*Tekirdağ Namık Kemal University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Tekirdağ, Türkiye*
[7]*Eskişehir Osmangazi University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Eskişehir, Türkiye*
[8]*Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye*
[9]*Van Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Van, Türkiye*
[10]*University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye*
[11]*University of Health Sciences Türkiye, Adana City Training and Research Hospital, Clinic of Internal Medicine, Division of Rheumatology, Adana, Türkiye*

Abstract

Inflammatory arthritis (IA) is associated with an increased risk for certain malignancies, particularly lymphoma, due to underlying chronic inflammation. Conventional and targeted therapies used in IA modulate the immune system, raising concerns about the development of *de novo* malignancies or the progression of pre-existing ones. Managing IA patients with a history of cancer remains one of the most challenging areas for clinicians, and while international guidelines exist, they generally focus on a narrower scope. This report is the first comprehensive consensus report from Türkiye to address the relationship between IA and malignancy across a wide spectrum, including baseline risk, treatment-related risk, management of patients with a history of cancer, treatment during active malignancy, premalignant lesions, and family history. Based on a systematic literature review, this report provides evidence-based, practical

Özet

Enflamatuvar artrit (İA), altta yatan kronik enflamasyona bağlı özellikle lenfoma başta olmak üzere bazı malignite türleri için bir risk artışı ile ilişkilidir. İA tedavisinde kullanılan konvansiyonel ve hedefe yönelik tedaviler, immün sistemi modüle etmeleri nedeniyle *de novo* malignite gelişimi veya var olan malignitenin seyri konusunda endişeler barındırmaktadır. Kanser öyküsü olan İA hastalarının yönetimi, hekimler için en zorlayıcı alanlardan biridir ve bu konudaki uluslararası rehberler mevcut olsa da genellikle daha dar bir kapsama odaklanmıştır. İA ve malignite ilişkisini; temel risk, tedaviye bağlı risk, kanser öyküsü olan hasta yönetimi, aktif kanser sırasında tedavi, premalign lezyonlar ve aile öyküsü gibi geniş bir yelpazede ele alan ilk kapsamlı Türkiye fikir birliği raporudur. Sistematik literatür taramasına dayalı olarak, mevcut uluslararası rehberlerin daha dar kapsamda ele aldığı; aktif tedavi altında kanser gelişimi, premalign lezyonlar ve aile öyküsü gibi

Correspondence / İletişim:
Hakan Babaoğlu MD, Ankara Bilkent City Hospital, Clinic of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
E-mail: drhakanbabaoglu@gmail.com **ORCID ID:** orcid.org//0000-0002-3728-0259
Received / Geliş Tarihi: 30.08.2025 **Accepted / Kabul Tarihi:** 03.09.2025 **Epub:** 20.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Tekgöz E, Akyüz Dağlı P, et al. Inflammatory arthritis and malignancy: a consensus report on risk assessment and clinical management based on a systematic review from the Turkish Society of Rheumatology Malignancy Study Group. J Turk Soc Rheumatol. 2025;17(3):145-154

recommendations for specific scenarios frequently encountered in daily practice—such as cancer development during active treatment, premalignant lesions, and family history—which are often narrowly addressed in existing international guidelines. This report will help rheumatologists standardize decision-making processes regarding the coexistence of IA and malignancy, enabling them to take safer clinical steps. By promoting risk individualization and shared decision-making between patients and clinicians, it will strengthen personalized treatment approaches that ensure both effective control of rheumatic disease and oncologic safety.

Keywords: Inflammatory arthritis, rheumatoid arthritis, spondyloarthritis, malignancy, cancer, biological therapies, disease modifying anti-rheumatic drugs (DMARDs)

günlük pratikte sık karşılaşılan spesifik senaryolar için kanıta dayalı pratik öneriler sunar. Sistematik literatür taramasına dayalı olarak, mevcut uluslararası rehberlerin daha dar kapsamda ele aldığı; aktif tedavi altında kanser gelişimi, premalign lezyonlar ve aile öyküsü gibi günlük pratikte sık karşılaşılan spesifik senaryolar için kanıta dayalı pratik öneriler sunar. Bu rapor, romatologların İA ve malignite birlikteliğindeki karar verme süreçlerini standartlaştırmasına ve daha güvenli adımlar atmasına yardımcı olacaktır. Risklerin bireyselleştirilmesi ve hasta ile hekim arasında paylaşılan karar verme süreçlerinin teşvik edilmesi yoluyla, hem romatizmal hastalığın etkin kontrolünü hem de onkolojik güvenliği gözeten kişiselleştirilmiş tedavi yaklaşımlarını güçlendirecektir.

Anahtar Kelimeler: Enflamatuvar artrit, romatoid artrit, spondiloartrit, malignite, kanser, biyolojik tedaviler, hastalık modifiye edici antiromatizmal ilaçlar (DMARD)

Introduction

The management of inflammatory arthritis (IA), including rheumatoid arthritis (RA) and spondyloarthritis (SpA), has been revolutionized over the past two decades with the widespread adoption of disease-modifying anti-rheumatic drugs (DMARDs), especially biologic and targeted synthetic DMARDs (b/tsDMARDs). While these therapies significantly improve patients' quality of life by controlling disease activity, their complex relationship with malignancy is a major concern for both clinicians and patients due to their immunomodulatory effects.

This relationship has two key dimensions. The first is the underlying disease itself. It is well-established that chronic inflammation and autoimmune processes are risk factors for certain types of cancer, particularly malignant lymphomas. The second dimension involves the potential risks of the therapies used to suppress this inflammation. Specifically, b/tsDMARDs have raised theoretical concerns regarding the risk of *de novo* malignancy, as they target critical pathways involved in cancer surveillance, such as tumor necrosis factor (TNF), interleukin (IL)-6, and Janus kinase/signal transducer and activator of transcription (JAK/STAT). Elucidating this complex risk profile requires a systematic evaluation of the evidence.

This overall picture raises a series of complex clinical questions in practice. With advancements in cancer treatment and an aging population, the number of IA patients with a history of cancer is steadily increasing. In these patients, balancing the need to treat active rheumatic disease against the concern of cancer recurrence is a primary challenge. Furthermore, there is a significant need for clear, unified guidance on the optimal management of patients who develop malignancy while on active anti-rheumatic therapy, and personalizing treatment choices for individuals with premalignant lesions or a strong family history of cancer.

To address these comprehensive clinical questions and fill existing evidence gaps, a systematic literature review (SLR) was conducted based on pre-defined Population, Intervention, Comparison, Outcome (PICO) questions. The primary aim of this study is to integrate the evidence obtained from the SLR with the clinical experience of expert rheumatologists, presenting an evidence-based consensus report and practical clinical management recommendations on the broad relationship between IA and malignancy. This report systematically addresses risks stemming from the disease itself, the risk profiles of different treatment options, and the management of patients with a history of cancer and other special circumstances.

Methodology

The objective of this study was to assess the malignancy risk associated with the underlying disease and its treatments in patients with RA and SpA, and also to create an evidence-based consensus report and a set of clinical practice recommendations, particularly for the management of patients with a history of cancer.

1. Formation of the Study Group

A task force was established among rheumatologist members of the Turkish Society of Rheumatology (TSR) to achieve the project's objectives. All participants submitted potential conflict of interest declarations before commencing the process.

2. Definition of PICO Questions and Systematic Literature Review

In its initial meeting, the task force finalized the research questions in the PICO format, which formed the foundation of the project. The study group was divided into subgroups for each PICO question, and these groups shared the findings of their work with the entire task force in regular meetings.

These questions determined the scope and strategy of the SLR. The core research questions examined were:

• **PICO 1:** In individuals with RA (P), is the overall incidence of malignancy (O) higher compared to the general population (C)?

• **PICO 2:** In individuals with SpA [including ankylosing spondylitis and psoriatic arthritis (PsA) subtypes] (P), is the overall incidence of malignancy (O) higher compared to the general population (C)?

• **PICO 3:** In RA patients (P), how does the use of a specific class of DMARD (I) affect the risk of developing *de novo* malignancy (O) compared to another DMARD class or no treatment (C)?

3a. Conventional synthetic DMARDs (csDMARDs)

3b. TNF inhibitors

3c. Non-TNF biologic DMARDs (bDMARDs)

3d. Targeted synthetic DMARDs (tsDMARDs)

• **PICO 4:** In RA patients with a history of malignancy (P), what is the effect of initiating a specific DMARD class (csDMARD, bDMARD, tsDMARD) (I) on malignancy recurrence or the development of a new primary malignancy (O) compared to patients not receiving active treatment or receiving a different DMARD class (C)?

4a. In those with a history of solid organ tumors

4b. In those with a history of melanoma

4c. In those with a history of non-melanoma skin cancer

4d. In those with a history of lymphoproliferative disease

• **PICO 5:** In RA patients diagnosed with malignancy during active DMARD (cs/b/tsDMARD) therapy (P), what is the effect of different management strategies for the current anti-rheumatic treatment (I) on the patient's rheumatologic and oncologic survival outcomes (O)?

• **PICO 6:** In RA patients with a known premalignant lesion (P), what is the effect of initiating or continuing a specific DMARD therapy (I) on the risk of the lesion's progression to malignancy (O)?

• **PICO 7:** In RA patients with a strong family history of cancer (e.g., in first-degree relatives) (P), is there an evidence-based approach to optimizing treatment selection among different DMARD classes (I), considering the patient's future malignancy risk (O)?

Data Sources and Search Strategy: A comprehensive literature search was conducted in major medical databases, including PubMed/MEDLINE, Embase, and the Cochrane Library. A detailed search strategy was developed using keywords and Medical Subject Headings (MeSH) terms specific to each PICO question.

Study Selection Criteria:

• **Inclusion Criteria:** Randomized controlled trials, observational cohort studies, case-control studies, meta-analyses, and systematic reviews that answered the defined PICO questions were included. To broaden the scope of evidence, studies on other inflammatory diseases where similar treatment mechanisms are used, such as inflammatory bowel disease (IBD), were also considered.

• **Exclusion Criteria:** Case reports, editorials, expert opinion articles, animal studies, and studies not relevant to the PICO questions were excluded.

The SLR was conducted by the designated subgroups for each PICO question. Data extraction and quality assessment were performed according to a predefined standard protocol. Extracted data included study design, patient population, treatment type, follow-up duration, and outcomes such as cancer incidence, cancer recurrence, hazard ratios, and relative risk.

3. Development of Recommendations and Voting

The SLR results were discussed within the respective PICO subgroups and reported in evidence summary tables. Subsequently, the Task Force convened in online meetings to discuss these data holistically. At the end of this process, draft statements were prepared by each PICO group under the headings "General Principles" and "Specific Recommendations" addressing the PICO questions.

Voting and Consensus: The drafted recommendations were subjected to an anonymous voting process involving all task force members. Each recommendation was rated on a 6-point Likert scale from 0 (completely disagree) to 5 (completely agree). Recommendations with a mean agreement score of 4.0 or higher were accepted with strong consensus. Items that did not reach sufficient consensus were rediscussed and revoted.

Final Text Approval

The final recommendation text was first reviewed and approved by all members of the task force and subsequently by the members and executive board of the TSR.

Recommendations

This section presents the consensus recommendations reached following the SLR and expert opinion, guided by the PICO questions outlined in the methodology.

Note: The number in parentheses at the end of each recommendation indicates the mean level of agreement on a 0 (completely disagree) to 5 (completely agree) Likert scale.

Section 1. Inflammatory Arthritis and Baseline Malignancy Risk (PICO 1&2)

This section assesses the impact of the underlying inflammatory rheumatic disease itself on the development of malignancy.

1.1. Rheumatoid Arthritis

• 1.1.1. Overall and Hematologic Risk

An increased risk of cancer development has been identified in RA patients compared to the general population. High and cumulative disease activity is considered the primary driver of the increased risk of lymphoma (4.87).[1-6]

An overall increased risk of hematologic malignancies has been found in RA patients (4.68).[2-5,7-16]

Lymphoma is the hematologic malignancy with the most significantly increased risk in this group (4.75).[2-4,7,9-16]

While there are data suggesting an increased risk of leukemia and multiple myeloma in RA, this evidence is insufficient (4.43).[3,5,7,8]

• 1.1.2. Solid Organ Risk

It is difficult to establish increased cumulative risk of solid organ malignancy in RA patients, as an increased risk has been observed for some solid organ cancers, while a decreased risk has been seen for others (4.5).

- Lung Cancer: This is the solid organ malignancy with the highest observed risk increase in RA patients (4.68).[2-5,7,17-20] The evidence is insufficient to conclude that RA is an independent risk factor for lung cancer, separate from known factors like interstitial lung disease and smoking (4.5).[17,18]

- Colorectal Cancer: The risk of colorectal cancer in RA is lower than in the general population, and this has been suggested to be associated with the frequent use of non-steroidal anti-inflammatory drugs (4.62).[1,5-7,11,16]

- Other Solid Organs: RA is not considered a risk factor for gastric, hepatic, biliary tract, pancreatic, or thyroid cancers (4.56).[2,5,7,16,19] It has also not been associated with the development of breast cancer (4.66).[2,5,7,21,22] The risk status for urinary tract malignancies remains uncertain (4.56).[2,5,7,19] Likewise, current data do not provide clear evidence of an increased risk for gynecological malignancies (4.5).[2,4,5,7] Moreover, there are insufficient data to suggest an increased risk of prostate cancer (4.75).[2,5,23]

• 1.1.3. Skin Cancer Risk: The risk of malignant melanoma in RA is uncertain (4.5).[2,4,5] The current evidence is insufficient to state that RA is a risk factor for other skin cancers (4.62).[3]

1.2. Spondyloarthritis

• 1.2.1. While the overall risk of malignancy in SpA patients does not significantly differ from the general population, some studies have reported an increased risk for certain hematologic malignancies, such as lymphoma and multiple myeloma (4.62).[24-35]

• 1.2.2. In PsA patients, the overall risk of solid and hematologic malignancies is not increased (4.56).[24,27,36-38] However, some studies have reported an increased risk of non-melanoma skin cancer (NMSC) (4.56).[27,37,39-42]

• 1.2.3. Patients with enteropathic arthritis are at an increased risk for gastrointestinal cancers due to the concomitant IBD (4.81).[43-47]

Section 2. Anti-Rheumatic Therapies and *de novo* Malignancy Risk (PICO 3)

This section examines the effect of anti-rheumatic treatments on malignancy development.

• 2.1. Conventional Synthetic DMARDs (csDMARDs): The use of csDMARDs does not cause increase in malignancy risk in patients with RA (4.81).[48,49] Data on its association with lymphoma risk are conflicting (4.18).[50,51] However, csDMARDs may increase the risk of NMSC (4.43).[52,53]

• 2.2. Biologic and Targeted Synthetic DMARDs (b/tsDMARDs):

- Overall Malignancy Risk: The relationship between TNF inhibitors and malignancy development is controversial, and recent meta-analyses have not confirmed this link. Data for non-TNF biologics are more limited, but no significant risk increase has been reported (4.5).[2,54-58]

- JAK Inhibitors: The ORAL surveillance trial found that tofacitinib use in high-risk RA patients increased the risk of malignancy, particularly lung cancer (4.68).[59] The FDA considers this risk increase as a class effect for other JAK inhibitors. However, other studies comparing bDMARDs with JAK inhibitors have not observed an overall increase in solid organ malignancy risk (4.31).[60,61]

- Lymphoma Risk: There is some evidence suggesting that bDMARD use may be associated with a slight increase in lymphoma risk, possibly due to the underlying high disease activity (4.31).[62-65]

Section 3. Treatment Management in Patients with a History of Malignancy (PICO 4)

This section addresses the safety of anti-rheumatic treatment options in patients previously diagnosed with cancer.

• 3.1. History of Solid Organ Tumor: Current evidence indicates that methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, TNFi, and non-TNFi bDMARDs such as tocilizumab and rituximab do not increase the risk of recurrence (4.75, 4.5, 4.5).[56,66-77] Therefore, patients with a

history of malignancy may be treated in a manner similar to those without such a history, provided that an individualized assessment is conducted and, when necessary, collaboration with oncology is ensured (4.18).[78] For JAK inhibitors, there are insufficient data in this population (4.5).[66,69,74] Although data are limited, given its mechanism of action, abatacept should be used cautiously in situations where no alternative therapeutic options are available.[79]

• **3.2. History of Non-Melanoma Skin Cancer:** Although historic data reports an association of increased *de novo* NMSC risk, current evidence suggests that TNF inhibitors and non-TNF bDMARDs do not increase recurrence risk (4.43, 4.5).[56,71-77,80] JAK inhibitors and abatacept may be used with caution if therapeutic alternatives are unavailable. Data regarding methotrexate and leflunomide are insufficient, whereas sulfasalazine and hydroxychloroquine are considered safe (4.75).[66,78,81] These patients should undergo regular skin examinations every 6-12 months (4.81).[66]

• **3.3. History of Melanoma:** Given melanoma's strong dependence on immune surveillance and the lack of sufficient data, a more cautious approach is warranted in patients with a history of melanoma, who should be considered separately from the general recommendations for TNF inhibitors in patients with a history of solid cancers.[79]

• **3.4. History of Lymphoproliferative Disease:** Rituximab may be the preferred first-line option in this patient group, as it does not increase the risk of recurrence (4.81).[66,68-70,73,76,82] Tocilizumab and abatacept also do not increase recurrence risk and may be preferred over TNF inhibitors (4.4).[66,82-84] There is no evidence that TNF inhibitor use increases the risk (4.43).[72-77] Although data for methotrexate and leflunomide are limited, they do not suggest an increased risk of recurrence (4.68).[66,82,78]

Section 4. Management of Patients Who Develop Malignancy During Active Treatment (PICO 5)

This section addresses the management of patients diagnosed with malignancy while on active anti-rheumatic therapy.

• **4.1. General Approach:**

- **Malignancy Development on csDMARDs:** Treatment is personalized. Generally, agents with lower immunosuppressive potential, such as hydroxychloroquine and sulfasalazine, are preferred (4.5).[85-90] In cases of lymphoproliferative disease, discontinuation of methotrexate and leflunomide should be considered (4.5).[91,92]

- **Malignancy Development on b/tsDMARDs:** Although the level of evidence is insufficient, the standard approach in routine practice is to discontinue these agents due to the risk of potential drug interactions and toxicity (4.68).[93,94]

• **4.2. RA Management During Active Cancer Treatment:** If RA activity persists, glucocorticoids and/or csDMARDs are the preferred initial choice (4.81, 4.43).[85-90] If these treatments are inadequate, a bDMARD (TNF inhibitor or rituximab) may be initiated on a case-by-case basis in collaboration with an oncologist (4.43).[57,93,95-97]

• **4.3. Special Situation: Immune Checkpoint Inhibitors (ICIs):** ICI therapy can exacerbate RA.[98] If steroids and csDMARDs are insufficient for flares, TNF inhibitors or IL-6 inhibitors may be used.[96,97] Abatacept should be avoided due to concerns that it may negatively affect the anti-tumor response of ICIs.[93]

• **4.4. Palliative Patients:** In palliative patients, quality of life is paramount, and treatment is personalized in collaboration with an oncologist. Methotrexate is not recommended due to its potential hematologic toxicity (4.62).[86]

Section 5. Treatment Management in Special Situations (PICO 6&7)

This section examines the management of patients with premalignant lesions or a family history of cancer.

• **5.1. Approach in the Presence of Premalignant Lesions (PICO 6):** A strategy of proactive monitoring and early intervention should be adopted for these patients (4.81). Evidence is insufficient to suggest that medications increase the development or progression of lesions (4.56, 4.5, 4.62),[98,99] although it has been reported that TNF inhibitors may increase the risk of *in situ* squamous cell carcinoma (4.25).[100] It is recommended to eliminate the lesion before starting therapy. If this is not possible, options other than JAK inhibitors and abatacept may be prioritized (4.5).[101]

• **5.2. Approach in the Presence of a Family History of Malignancy (PICO 7):** More rigorous surveillance programs are recommended for these patients instead of standard screening programs (4.75). There is no evidence that immunosuppressive therapies further increase this risk (4.56). However, the decision to use bDMARDs and tsDMARDs requires a careful risk-benefit analysis (4.56).

Discussion

In this study, the task force examined the complex relationship between IA and malignancy through seven main PICO questions, culminating in an evidence-based consensus report. This report offers a comprehensive framework, starting from the baseline malignancy risk in inflammatory arthritis, to the impact of anti-rheumatic

therapies on *de novo* cancer risk, the management of patients with a history of cancer or an active cancer, and special situations such as premalignant lesions and family history.

The core themes of this work include: (a) the necessity of individualizing risk for each patient, (b) the importance of striking a balance between the risks of undertreated rheumatic disease and the potential risks of anti-rheumatic therapy, and (c) the principle that treatment decisions should be made through a process of shared decision-making between the patient and clinician. Furthermore, the recognition that chronic inflammation itself is a risk factor and that effective disease control can mitigate this risk is another crucial element underpinning all recommendations.

The findings from this systematic review have confirmed several key points. Patients with RA have an increased risk of lymphoma, particularly associated with high disease activity. Regarding treatments, csDMARDs and bDMARDs may slightly increase the risk of NMSC. Among the tsDMARDs, the ORAL Surveillance trial highlighted a specific risk increase (lung cancer) with JAK inhibitors in high-risk patients (advanced age, smoking history), emphasizing the need for careful patient selection when using these agents.

These recommendations, although based on the best available evidence, should be interpreted with consideration for several important limitations in the literature. First, the vast majority of available data is derived from RA patients. The data for the SpA and other IA subtypes are more limited. Second, long-term safety data for b/tsDMARDs other than TNF inhibitors remain insufficient. A third and major limitation is that the median follow-up times in studies are often short (e.g., <5 years), which may not be long enough to detect late recurrences of some solid organ cancers. Finally, most studies do not differentiate between a new primary cancer and a recurrence of an existing cancer, and they often do not report oncologic outcomes such as survival. These factors underscore the need for clinician caution, especially concerning newer agents and rare cancer types, and highlight the necessity for more observational studies in this field.

This study provides several important messages for clinical practice. The approach to treatment in patients, with a history of cancer, has shifted away from the previously held, more rigid stance of avoiding all targeted therapies. There is growing evidence that many DMARDs, particularly TNF inhibitors—supported by the largest available dataset—do not increase the risk of cancer recurrence, especially in patients with a history of a solid organ tumor. For patients with a history of lymphoma, the consensus has solidified, indicating that rituximab, which causes B-cell depletion, is a rational choice for both its rheumatologic efficacy and oncologic safety profile. For JAK inhibitors and abatacept, due to a lack of direct evidence and reliance on indirect data, the prevailing cautious approach is to limit their use to situations where other therapeutic alternatives are not available, especially in patients with a history of cancer or premalignant lesions.

The scenario where malignancy develops during active treatment represents one of the areas with the weakest evidence base. In this situation, our recommendation to discontinue b/tsDMARDs is not based on definitive evidence but rather represents a pragmatic, safety-first approach aimed at avoiding potential drug interactions and unforeseen risks. The management of such complex cases requires close collaboration between the rheumatologist and the oncologist.

Conclusion

In conclusion, this consensus report provides a comprehensive, practical, and evidence-based framework to guide rheumatologists in Türkiye through the complex intersection of IA and malignancy. Its goal is to standardize clinical decision-making, enhance clinical safety, and ultimately achieve the optimal treatment balance for patients.

Footnotes

Authorship Contributions

Concept: H.B., G.S., E.T., P.A.D., S.Ç., İ.V., B.Ö.U., D.B.G., R.Y., N.Ş.Y.B., T.K., B.B., İ.E., Ö.D.A., G.G.Ö., C.B., E.D.E., Design: H.B., G.S., E.T., P.A.D., S.Ç., İ.V., B.Ö.U., D.B.G., R.Y., N.Ş.Y.B., T.K., B.B., İ.E., Ö.D.A., G.G.Ö., C.B., E.D.E., Data Collection and Processing: H.B., G.S., E.T., P.A.D., S.Ç., İ.V., B.Ö.U., D.B.G., R.Y., N.Ş.Y.B., T.K., B.B., İ.E., Ö.D.A., G.G.Ö., C.B., E.D.E., Analysis or Interpretation: H.B., G.S., E.T., P.A.D., S.Ç., İ.V., B.Ö.U., D.B.G., R.Y., N.Ş.Y.B., T.K., B.B., İ.E., Ö.D.A., G.G.Ö., C.B., E.D.E., Literature Search: H.B., G.S., E.T., P.A.D., S.Ç., İ.V., B.Ö.U., D.B.G., R.Y., N.Ş.Y.B., T.K., B.B., İ.E., Ö.D.A., G.G.Ö., C.B., E.D.E., Writing: H.B., G.S., E.T., P.A.D., S.Ç., İ.V., B.Ö.U., D.B.G., R.Y., N.Ş.Y.B., T.K., B.B., İ.E., Ö.D.A., G.G.Ö., C.B., E.D.E.

Conflict of Interest: Hakan Babaoğlu MD, İhsan Ertenli MD, Timuçin Kaşifoğlu MD, is section editors in Journal of Turkish Society for Rheumatology. They had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

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

References

1. Li Q, Zhou L, Xia D, Wang J. Rheumatoid arthritis reduces the risk of colorectal cancer through immune inflammation mediation. J Cell Mol Med. 2024;28:e18515.
2. Beydon M, Pinto S, De Rycke Y, et al. Risk of cancer for patients with rheumatoid arthritis versus general population: a national claims database cohort study. Lancet Reg Health Eur. 2023;35:100768.
3. Wang F, Palmer N, Fox K, Liao KP, Yu KH, Kou SC. Large-scale real-world data analyses of cancer risks among patients with rheumatoid arthritis. Int J Cancer. 2023;153:1139-50.
4. Mercer LK, Davies R, Galloway JB, et al. Risk of cancer in patients receiving non-biologic disease-modifying therapy for rheumatoid arthritis compared with the UK general population. Rheumatology (Oxford). 2013;52:91-8.
5. Hemminki K, Li X, Sundquist K, Sundquist J. Cancer risk in hospitalized rheumatoid arthritis patients. Rheumatology (Oxford). 2008;47:698-701.
6. Kauppi M, Pukkala E, Isomäki H. Low incidence of colorectal cancer in patients with rheumatoid arthritis. Clin Exp Rheumatol. 1996;14:551-3.
7. Yang TO, Floud S, Reeves GK. Rheumatoid arthritis and cancer risk in the million women study. Int J Epidemiol. 2024;53:dyae006.
8. Luo X, He Y, Xu W, et al. The risk of leukemia in patients with rheumatoid arthritis: a systematic review and meta-analysis. Clin Rheumatol. 2021;40:1283-9.
9. Hellgren K, Baecklund E, Backlin C, Sundstrom C, Smedby KE, Askling J. Rheumatoid arthritis and risk of malignant lymphoma: is the risk still increased? Arthritis Rheumatol. 2017;69:700-8.
10. Hashimoto A, Chiba N, Tsuno H, et al. Incidence of malignancy and the risk of lymphoma in Japanese patients with rheumatoid arthritis compared to the general population. J Rheumatol. 2015;42:564-71.
11. Huang WK, Chiou MJ, Kuo CF, Lin YC, Yu KH, See LC. No overall increased risk of cancer in patients with rheumatoid arthritis: a nationwide dynamic cohort study in Taiwan. Rheumatol Int. 2014;34:1379-86.
12. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004;50:1740-51.
13. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007;56:1433-9.
14. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54:692-701.
15. Kauppi M, Pukkala E, Isomäki H. Elevated incidence of hematologic malignancies in patients with Sjögren's syndrome compared with patients with rheumatoid arthritis (Finland). Cancer Causes Control. 1997;8:201-4.
16. Gridley G, McLaughlin JK, Ekbom A, et al. Incidence of cancer among patients with rheumatoid arthritis. J Natl Cancer Inst. 1993;85:307-11.
17. Cho MH, Cho JH, Eun Y, et al. Rheumatoid arthritis and risk of lung cancer: a nationwide cohort study. J Thorac Oncol. 2024;19:216-26.
18. Chatzidionysiou K, di Giuseppe D, Soderling J, Catrina A, Askling J. Risk of lung cancer in rheumatoid arthritis and in relation to autoantibody positivity and smoking. RMD Open. 2022;8:e002465.
19. Choi HG, Kang HS, Lim H, et al. Potential cancer risk in patients with rheumatoid arthritis: a longitudinal Korean population-based analysis. J Pers Med. 2022;12:965.
20. Wu X, Peng H, Wen Y, et al. Rheumatoid arthritis and risk of lung cancer: meta-analysis and Mendelian randomization study. Semin Arthritis Rheum. 2021;51:565-75.
21. Wadström H, Pettersson A, Smedby KE, Askling J. Risk of breast cancer before and after rheumatoid arthritis, and the impact of hormonal factors. Ann Rheum Dis. 2020;79:581-6.
22. Tian G, Liang JN, Wang ZY, Zhou D. Breast cancer risk in rheumatoid arthritis: an update meta-analysis. Biomed Res Int. 2014;2014:453012.
23. Wheeler AM, Roul P, Yang Y, et al. Risk of prostate cancer in US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2023;75:785-92.
24. Fanto M, Peragallo MS, Pietrosanti M, et al. Risk of malignancy in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis under immunosuppressive therapy: a single-center experience. Intern Emerg Med. 2016;11:31-40.
25. Bautista-Molano W, Landewe R, Burgos-Vargas R, et al. Prevalence of comorbidities and risk factors for comorbidities in patients with spondyloarthritis in Latin America: a comparative study with the general population and data from the ASAS-COMOSPA study. J Rheumatol. 2018;45:206-12.
26. Kelty E, Raymond W, Inderjeeth C, Keen H, Nossent J, Preen DB. Cancer diagnosis and mortality in patients with ankylosing spondylitis: a Western Australian retrospective cohort study. Int J Rheum Dis. 2021;24:216-22.
27. Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis. Jan 2017;76:105-11.
28. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. Blood. 2008;111:3388-94.
29. Lindqvist EK, Goldin LR, Landgren O, et al. Personal and family history of immune-related conditions increase the risk of plasma cell disorders: a population-based study. Blood. 2011;118:6284-91.
30. Deng C, Li W, Fei Y, Li Y, Zhang F. Risk of malignancy in ankylosing spondylitis: a systematic review and meta-analysis. Sci Rep. 2016;6:32063.
31. Feltelius N, Ekbom A, Blomqvist P. Cancer incidence among patients with ankylosing spondylitis in Sweden 1965-95: a population based cohort study. Ann Rheum Dis. 2003;62:1185-8.
32. Hemminki K, Liu X, Forsti A, Ji J, Sundquist J, Sundquist K. Effect of autoimmune diseases on incidence and survival in subsequent multiple myeloma. J Hematol Oncol. 2012;5:59.
33. Chang CC, Chang CW, Nguyen PA, et al. Ankylosing spondylitis and the risk of cancer. Oncol Lett. 2017;14:1315-22.
34. Alehashemi S, Ward MM. Risk of hematologic malignancies in elderly patients with ankylosing spondylitis: a cohort study and systematic review. Mayo Clin Proc. 2023;98:100-10.

35. Chan TM, Luo SF, Yu KH, See LC, Huang LH, Kuo CF. Risk of cancer in patients with ankylosing spondylitis: a nationwide cohort study in Taiwan. Scand J Rheumatol. 2021;50:132-8.

36. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol. 2011;64:1035-50.

37. Kaine J, Song X, Kim G, Hur P, Palmer JB. Higher incidence rates of comorbidities in patients with psoriatic arthritis compared with the general population using U.S. Administrative claims data. J Manag Care Spec Pharm. 2019;25:122-32.

38. Rohekar S, Tom BD, Hassa A, Schentag CT, Farewell VT, Gladman DD. Prevalence of malignancy in psoriatic arthritis. Arthritis Rheum. 2008;58:82-7.

39. Egeberg A, Thyssen JP, Gislason GH, Skov L. Skin cancer in patients with psoriasis. J Eur Acad Dermatol Venereol. 2016;30:1349-53.

40. Luo X, Deng C, Fei Y, et al. Malignancy development risk in psoriatic arthritis patients undergoing treatment: a systematic review and meta-analysis. Semin Arthritis Rheum. 2019;48:626-31.

41. Fagerli KM, Kearsley-Fleet L, Mercer LK, et al. Malignancy and mortality rates in patients with severe psoriatic arthritis requiring tumour-necrosis factor alpha inhibition: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2019;58:80-5.

42. Krzysztofik M, Brzewski P, Cuber P, et al. Risk of melanoma and non-melanoma skin cancer in patients with psoriasis and psoriatic arthritis treated with targeted therapies: a systematic review and meta-analysis. Pharmaceuticals (Basel). 2023;17:14.

43. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. Clin Gastroenterol Hepatol. 2012;10:639-45.

44. Jess T, Gamborg M, Matzen P, Munkholm P, Sorensen TI. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol. 2005;100:2724-9.

45. Laukoetter MG, Mennigen R, Hannig CM, et al. Intestinal cancer risk in Crohn's disease: a meta-analysis. J Gastrointest Surg. 2011;15:576-83.

46. Axelrad JE, Olen O, Sachs MC, et al. Inflammatory bowel disease and risk of small bowel cancer: a binational population-based cohort study from Denmark and Sweden. Gut. 2021;70:297-308.

47. Trivedi PJ, Crothers H, Mytton J, et al. Effects of primary sclerosing cholangitis on risks of cancer and death in people with ınflammatory bowel disease, based on sex, race, and age. Gastroenterology. 2020;159:915-28.

48. Dore RK, Antonova JN, Burudpakdee C, Chang L, Gorritz M, Genovese MC. The incidence, prevalence, and associated costs of anemia, malignancy, venous thromboembolism, major adverse cardiovascular events, and infections in rheumatoid arthritis patients by treatment history in the United States. ACR Open Rheumatol. 2022;4:473-82.

49. Harigai M, Tanaka E, Inoue E, et al. Incidence of malignancies and the association with biological disease-modifying antirheumatic drugs in japanese patients with rheumatoid arthritis: a time-dependent analysis from the IORRA patient registry. Rheumatol Ther. 2024;11:1181-95.

50. Hellgren K, Di Giuseppe D, Smedby KE, et al. Lymphoma risks in patients with rheumatoid arthritis treated with biological drugs-a Swedish cohort study of risks by time, drug and lymphoma subtype. Rheumatology (Oxford). 2021;60:809-19.

51. Askling J, Baecklund E, Granath F, et al. Anti-tumour necrosis factor therapy in rheumatoid arthritis and risk of malignant lymphomas: relative risks and time trends in the Swedish Biologics Register. Ann Rheum Dis. 2009;68:648-53.

52. Mercer LK, Green AC, Galloway JB, et al. The influence of anti-TNF therapy upon incidence of keratinocyte skin cancer in patients with rheumatoid arthritis: longitudinal results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2012;71:869-74.

53. Amari W, Zeringue AL, McDonald JR, Caplan L, Eisen SA, Ranganathan P. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. Rheumatology (Oxford). 2011;50:1431-9.

54. Carmona L, Abasolo L, Descalzo MA, et al. Cancer in patients with rheumatic diseases exposed to TNF antagonists. Semin Arthritis Rheum. 2011;41:71-80.

55. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009;60:3180-9.

56. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010;12:R5.

57. Holroyd CR, Seth R, Bukhari M, et al. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. Rheumatology (Oxford). 2019;58:e3-42. Erratum in: Rheumatology (Oxford). 2019;58:372.

58. Staples MP, March L, Hill C, Lassere M, Buchbinder R. Malignancy risk in Australian rheumatoid arthritis patients treated with anti-tumour necrosis factor therapy: an update from the Australian Rheumatology Association Database (ARAD) prospective cohort study. BMC Rheumatol. 2019;3:1.

59. Curtis JR, Yamaoka K, Chen YH, et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial. Ann Rheum Dis. 2023;82:331-43.

60. Song YJ, Cho SK, You SH, et al. Association between malignancy risk and Janus kinase inhibitors versus tumour necrosis factor inhibitors in Korean patients with rheumatoid arthritis: a nationwide population-based study. RMD Open. 2022;8:e002614.

61. Westermann R, Cordtz RL, Duch K, et al. Cancer risk with tocilizumab/sarilumab, abatacept, and rituximab treatment in patients with rheumatoid arthritis: a Danish cohort study. Rheumatology (Oxford). 2025;64:1019-28.

62. Huss V, Bower H, Wadström H, Frisell T, Askling J; ARTIS group. Short- and longer-term cancer risks with biologic and targeted synthetic disease-modifying antirheumatic drugs as used against rheumatoid arthritis in clinical practice. Rheumatology (Oxford). 2022;61:1810-8.

63. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev. 2010;9:175-80.

64. Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Ann Rheum Dis. 2010;69:400-8.

65. Huss V, Bower H, Hellgren K, et al. Cancer risks with JAKi and biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis or psoriatic arthritis: a national real-world cohort study. Ann Rheum Dis. 2023;82:911-9.

66. Wong PKK, Bagga H, Barrett C, et al. A Practical approach to the use of conventional synthetic, biologic and targeted synthetic disease modifying anti-rheumatic drugs for the treatment of inflammatory arthritis in patients with a history of malignancy. Curr Rheumatol Rep. 2018;20:64.

67. Conti F, Atzeni F, Massaro L, et al. The influence of comorbidities on the efficacy of tumour necrosis factor inhibitors, and the effect of tumour necrosis factor inhibitors on comorbidities in rheumatoid arthritis: report from a National Consensus Conference. Rheumatology (Oxford). 2018;57(57 Suppl 7):vii11-22.

68. Slimani S, Lukas C, Combe B, Morel J. Rituximab in rheumatoid arthritis and the risk of malignancies: report from a French cohort. Joint Bone Spine. 2011;78:484-7.

69. Regierer AC, Strangfeld A. Rheumatoid arthritis treatment in patients with a history of cancer. Curr Opin Rheumatol. 2018;30:288-94.

70. Tekgoz E, Colak S, Yardimci KG, et al. Physicians' biological drug preference in patients with rheumatoid arthritis and spondyloarthritis with a history of malignancy: perspectives from the treasure database. J Clin Rheumatol. 2022;28:e318-23.

71. Wetzman A, Lukas C, Gaujoux-Viala C, et al. Risk of cancer after ınitiation of targeted therapies in patients with rheumatoid arthritis and a prior cancer: systematic review with meta-analysis. Arthritis Care Res (Hoboken). 2023;75:260-71.

72. Chen Y, Friedman M, Liu G, Deodhar A, Chu CQ. Do tumor necrosis factor inhibitors increase cancer risk in patients with chronic immune-mediated inflammatory disorders? Cytokine. 2018;101:78-88.

73. Dreyer L, Cordtz RL, Hansen IMJ, Kristensen LE, Hetland ML, Mellemkjaer L. Risk of second malignant neoplasm and mortality in patients with rheumatoid arthritis treated with biological DMARDs: a Danish population-based cohort study. Ann Rheum Dis. 2018;77:510-4.

74. Gupta A, Peyrin-Biroulet L, Ananthakrishnan AN. Risk of cancer recurrence in patients with immune-mediated diseases with use of immunosuppressive therapies: an updated systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2024;22:499-512.e6.

75. Xie W, Xiao S, Huang Y, et al. A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy. Rheumatology (Oxford). 2020;59:930-9.

76. Silva-Fernández L, Lunt M, Kearsley-Fleet L, et al. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology (Oxford). 2016;55:2033-9.

77. Dixon WG, Watson KD, Lunt M, et al. Influence of anti-tumor necrosis factor therapy on cancer incidence in patients with rheumatoid arthritis who have had a prior malignancy: results from the British Society for Rheumatology Biologics Register. Arthritis Care Res (Hoboken). 2010;62:755-63..

78. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2016;68:1-25.

79. Sebbag E, Lauper K, Molina-Collada J, et al. 2024 EULAR points to consider on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer. Ann Rheum Dis. 2024:ard-2024-225982.

80. Raaschou P, Simard JF, Asker Hagelberg C, Askling J; ARTIS Study Group. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden. BMJ. 2016;352:i262.

81. Scott FI, Mamtani R, Brensinger CM, et al. Risk of nonmelanoma skin cancer associated with the use of immunosuppressant and biologic agents in patients with a history of autoimmune disease and nonmelanoma skin cancer. JAMA Dermatol. 2016;152:164-72.

82. Lopez-Olivo MA, Colmegna I, Karpes Matusevich AR, et al. Systematic review of recommendations on the use of disease-modifying antirheumatic drugs in patients with rheumatoid arthritis and cancer. Arthritis Care Res (Hoboken). 2020;72:309-18.

83. Kunishita Y, Ichikawa K, Uzawa Y, et al. Efficacy and safety of abatacept in patients with rheumatoid arthritis with previous malignancy. Ther Adv Musculoskelet Dis. 2023;15:1759720X231186874.

84. Nakano K, Tanaka Y, Saito K, et al. Treatment of rheumatoid arthritis after regression of lymphoproliferative disorders in patients treated with methotrexate: a retrospective, multi-center descriptive study. Mod Rheumatol. 2022;32:41-9.

85. Sonomoto K, Tanaka Y. Malignancies and rheumatoid arthritis, csDMARDs, biological DMARDs, and JAK inhibitors: challenge and outlook. Expert Rev Clin Immunol. 2023;19:1325-42.

86. Kleinert S, Waldner M, Wendler J, Kunzmann V. Basistherapie bei Patienten mit rheumatoider arthritis und kolorektaler tumoranamnese [Disease-modifying antirheumatic drugs in rheumatoid arthritis patients with a history of colorectal cancer]. Z Rheumatol. 2016;75:41-6. German.

87. Singh JA, Cameron DR. Summary of AHRQ's comparative effectiveness review of drug therapy for rheumatoid arthritis (RA) in adults--an update. J Manag Care Pharm. 2012;18(4 Supp C):S1-S18.

88. Wilton KM, Matteson EL. Malignancy ıncidence, management, and prevention in patients with rheumatoid arthritis. Rheumatol Ther. 2017;4:333-47.

89. Lange E, Blizzard L, Venn A, Francis H, Jones G. Disease-modifying anti-rheumatic drugs and non-melanoma skin cancer in inflammatory arthritis patients: a retrospective cohort study. Rheumatology (Oxford). 2016;55:1594-600.

90. Ramiro S, Sepriano A, Chatzidionysiou K, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis. 2017;76:1101-36.

91. De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: epidemiology, risk factors and management. Best Pract Res Clin Rheumatol. 2018;32:869-86.

92. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020;79:760-70.

93. Kostine M, Finckh A, Bingham CO, et al. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. Ann Rheum Dis. 2021;80:36-48.

94. Sebbag E, Molina-Collada J, Ndoye R, et al. Systematic literature review and meta-analysis informing the EULAR points to consider on the initiation of targeted therapies in patients with inflammatory arthritis and a history of cancer. Ann Rheum Dis. 2025;84:643-52.

95. McCarter KR, Arabelovic S, Wang X, et al. Immunomodulator use, risk factors and management of flares, and mortality for patients with pre-existing rheumatoid arthritis after immune checkpoint inhibitors for cancer. Semin Arthritis Rheum. 2024;64:152335.

96. Bass AR, Abdel-Wahab N, Reid PD, et al. Comparative safety and effectiveness of TNF inhibitors, IL6 inhibitors and methotrexate for the treatment of immune checkpoint inhibitor-associated arthritis. Ann Rheum Dis. 2023;82:920-6.

97. Petit PF, Daoudlarian D, Latifyan S, et al. Tocilizumab provides dual benefits in treating immune checkpoint inhibitor-associated arthritis and preventing relapse during ICI rechallenge: the TAPIR study. Ann Oncol. 2025;36:43-53.

98. Garritsen FM, Verheijen RHM, Gerestein CG, et al. Is there an increased risk of cervical neoplasia in atopic dermatitis patients treated with oral immunosuppressive drugs?. J Eur Acad Dermatol Venereol. 2018;32:271-5.

99. Cordtz R, Mellemkjær L, Glintborg B, Hetland ML, Dreyer L. Malignant progression of precancerous lesions of the uterine cervix following biological DMARD therapy in patients with arthritis. Ann Rheum Dis. 2015;74:1479-80.

100. Adalsteinsson JA, Muzumdar S, Waldman R, et al. Anti-tumor necrosis factor therapy is associated with increased in situ squamous cell carcinoma of the skin: a population-based case-control study. J Am Acad Dermatol. 2021;84:1760-2.

101. Faganello D, Bertrand A, Meunier P, et al. Evolution of monoclonal gammopathy of undetermined significance in patients treated with JAK inhibitors for rheumatic diseases: data from the MAJIK-SFR registry. Rheumatology (Oxford). 2024;63:787-90.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.33043
Ulus Romatol Derg 2025;17(3):155-161

Retroperitoneal fibrosis: Features of patients followed-up by a single tertiary rheumatology center

Retroperitoneal fibrozis: Bir tersiyer romatoloji merkezi tarafından izlenen hastaların özellikleri

Fatih Taştekin, Duygu Kerim, Semiha Köroğlu, Gökhan Keser, Yasemin Kabasakal, Kenan Aksu

Ege University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İzmir, Türkiye

Abstract

Objective: Retroperitoneal fibrosis (RPF) is a rare autoimmune and fibro-inflammatory disorder affecting the retroperitoneum, often leading to ureteral obstruction. In this study, we analyzed the differences in demographic characteristics, clinical, laboratory, and imaging findings of patients with RPF, a rare disease followed in our clinic.

Methods: This retrospective study analyzed demographic, clinical, laboratory, imaging findings, and treatment outcomes of RPF patients aged over 18 years at Ege University Rheumatology Division. Diagnosis was based on clinical, imaging, and histopathological findings.

Results: The study included 26 patients (male/female: 17/9, mean age: 60.77 years). The most common symptom was abdominal pain, predominantly localized to the left lower quadrant. The most common cause was chronic periaortitis (CP). The majority of cases (24/26; 92.3%) had infrarenal aortic involvement. All other patients without infrarenal involvement were female. Infrarenal aneurysms were observed in 7.7%. Acute renal failure (ARF) at diagnosis occurred in 69.2% of patients, with no significant differences based on sex, age, or smoking. Immunoglobulin G4 (IgG4) related disease was identified in 19.2%, with non-IgG4 patients exhibiting higher C-reactive protein levels (p=0.082) and more frequent ARF (p=0.150). Cyclophosphamide (80.8%) and corticosteroids were the primary treatments, followed by azathioprine (61.5%), mycophenolate mofetil (34.6%), and rituximab (15.4%). None of the IgG4-related patients received rituximab.

Conclusion: In this retrospective analysis, most cases had idiopathic RPF, mainly as a complication of infrarenal CP. IgG4-related disease was the possible cause in only 19.2% of cases. The higher ARF incidence and inflammation markers in non-IgG4 along with the more frequent use of rituximab in this group suggest a more severe and treatment-resistant disease course in the non-IgG4 group. Further studies with larger cohorts are necessary.

Keywords: Retroperitoneal fibrosis, aortitis, aneurysm, periaortitis, immunoglobulin G4, IgG4

Özet

Amaç: Retroperitoneal fibrozis (RPF), nadir görülen otoimmün ve fibro-enflamatuvar bir hastalıktır. En önemli komplikasyonu üreter tıkanıklığıdır. Biz bu çalışmada kliniğimizde takipli nadir bir hastalık olan RPF'li hastaların demografik özelliklerini ve klinik, laboratuvar ve görüntüleme bulgularındaki farklılıkları analiz etmeyi amaçladık.

Yöntem: Bu retrospektif çalışmada, Ege Üniversitesi Romatoloji Anabilim Dalı'nda izlenen 18 yaş ve üzeri RPF hastalarının demografik, klinik ve laboratuvar özellikleri incelenmiştir. Tanı, klinik bulgular ve görüntüleme yöntemleriyle konmuş, bazı olgularda histopatolojik değerlendirme yapılmıştır.

Bulgular: Çalışmaya 26 hasta dahil edilmiştir (erkek/kadın: 17/9, ortalama yaş: 60,77 yıl). En sık görülen semptom karın ağrısı olup, çoğunlukla sol alt kadranda lokalizeydi. En sık neden kronik periaortit (KP) idi. Olguların 24'ünde (%92,3) infrarenal aortik tutulum vardı. Sadece infrarenal tutulumu olmayan diğer tüm hastalar kadındı. İnfrarenal anevrizmalar %7,7 oranında gözlendi. Tanı anında akut böbrek yetmezliği (ABY) %69,2 oranında görülmüş olup cinsiyet, yaş veya sigara kullanımına göre anlamlı bir fark bulunmamıştır. İmmünoglobulin G4 (IgG4) ile ilişkili hastalık %19,2 oranında tespit edilmiş olup IgG4 ilişkili hastalık olmayan hastalarda daha yüksek C-reaktif protein seviyeleri (p=0,082) ve daha sık ABY (p=0,150) görülmüştür. Siklofosfamid (%80,8) ve kortikosteroidler birincil tedaviler olup,, bunları azatioprin (%61,5), mikofenolat mofetil (%34,9) ve rituksimab (%15,4) izlemiştir. IgG4 ile ilişkili hastaların hiçbiri rituksimab almamıştır.

Sonuç: Bu retrospektif analizde, olgularımızın çoğunun idiyopatik RPF'ye sahip olduğunu ve bunun çoğunlukla infrarenal KP'nin komplikasyonu olduğunu tespit ettik. Hem KP hem de RPF'nin olası altta yatan nedeni olarak IgG4 ile ilişkili hastalık sıklığı yalnızca %19,2 idi. IgG4 olmayan grupta daha yüksek ABY insidansı ve enflamasyon belirteçleri ile bu grupta daha sık rituximab kullanımı, IgG4 olmayan grupta daha şiddetli ve tedaviye dirençli bir hastalık seyrine işaret etmektedir. Daha geniş kohortlarla yapılacak ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Retroperitoneal fibrozis, aortit, anevrizma, periaortit, immünoglobulin G4, İgG4

Correspondence / İletişim:
Fatih Taştekin MD, Ege University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, İzmir, Türkiye
E-mail: fatihtastekin@gmail.com **ORCID ID:** orcid.org/0000-0003-4979-5484
Received / Geliş Tarihi: 25.02.2025 **Accepted / Kabul Tarihi:** 24.09.2025 **Epub:** 27.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Taştekin F, Kerim D, Köroğlu S, Keser G, Kabasakal Y, Aksu K. Retroperitoneal fibrosis: Features of patients followed-up by a single tertiary rheumatology center. J Turk Soc Rheumatol. 2025;17(3):155-161

Introduction

Chronic periaortitis (CP) refers to a spectrum of idiopathic diseases whose common denominator is a fibro-inflammatory tissue developing in the periaortic retroperitoneum and frequently encasing neighboring structures such as the ureters and the inferior vena cava. CP includes idiopathic retroperitoneal fibrosis (RPF), inflammatory abdominal aortic aneurysms, and a combination of the two diseases, called perianeurysmal RPF.[1-3] RPF often occurs as a secondary complication of CP. While RPF with CP can be idiopathic, some cases previously classified as idiopathic may now be linked to immunoglobulin G4 (IgG4)-related disease, an autoimmune disorder first described in 2003.[3] Additionally, one-third of RPF cases are secondary to malignancies, medications (such as methysergide, hydralazine, and beta-blockers), previous radiotherapy, or certain infections. Recent studies, however, suggest that smoking and occupational asbestos exposure are also risk factors for the development of idiopathic RPF.[3-7]

The exact etiopathogenesis of the disease remains unclear; however, it is believed to result from an abnormal immune reaction to antigens present in atherosclerotic lesions of the abdominal aorta. The predominance of inflammation in the adventitia and the observation of vasa vasorum vasculitis sometimes suggests that RPF may initially occur as primary aortitis and may later cause secondary periaortic fibrosis.[3,6-10]

The clinical symptoms of RPF generally result from compression and obstruction of retroperitoneal structures. Patients may present with flank, dorsal, low back, or abdominal pain. The pain is usually constant, but colicky, if the ureter is affected. The most significant and widely recognized complication of RPF is hydronephrosis, leading to secondary renal failure due to ureteral obstruction. In addition to obstructive nephropathy, compression of retroperitoneal lymphatics and veins can result in lower extremity edema, deep vein thrombosis, scrotal swelling, varicocele, or hydrocele. Hypertension (HT) and constipation may also occur. Furthermore, RPF can be associated with systemic constitutional symptoms, including low-grade fever, fatigue, nausea, weight loss, and myalgias.[7,10,11] RPF may be associated with aortic aneurysms, however RPF does not directly cause aneurysm formation, rather CP causing RPF may also cause aneurysm formation.[1-4]

Acute phase reactants, including serum C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR), may be elevated in 80-100% of cases. Mild to moderate anemia is commonly observed, while leukocytosis, eosinophilia, proteinuria, and microscopic hematuria occur less frequently. Antinuclear antibodies (ANA) can be found in nearly 60% of patients with idiopathic RPF. Additionally, anti-neutrophilic cytoplasmic antibodies (ANCA) and rheumatoid factor (RF) may be elevated in some cases. Although these antibody titers are generally low and nonspecific, their presence could suggest an underlying vasculitis or connective tissue disorder in some cases. Imaging techniques such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) can be utilized for diagnostic evaluation.[3,7,10,11]

Different findings may change the approach to the disease and affect follow-up and treatment strategies. Therefore, we aimed to analyze the demographic features, along with the variations in clinical, laboratory, and imaging findings among patients with RPF.

Materials and Methods

This study was conducted on patients with RPF over the age of 18 who were being followed up at the Ege University Rheumatology Clinic between January 2000 and June 2024. RPF was diagnosed based on clinical findings, imaging findings such as typical irregular fibro-sclerosing lesions around the aorta, and histopathological evaluation. Demographic characteristics, clinical, laboratory, and imaging features of patients with RPF were retrospectively examined. In this study, RPF cases with and without IgG4 were included. None of the cases had any other defined systemic autoimmune disease, infection, malignancy, drug use that causes RPF. Our study included five patients with IgG4-related disease and 21 patients with non-IgG4-related disease, all with RPF. In the present study, IgG4-RD was diagnosed according to the 2020 revised comprehensive IgG4-RD diagnostic criteria.[12] The location of aortic involvement, smoking, diabetes mellitus, HT, and hyperlipidemia was evaluated in these patients. Acute renal failure (ARF) is a condition characterized by an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or an increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or a decrease in urine volume to less than 0.5 mL/kg/hour within 6 hours.[13] The presence and location of pain and the presence of constitutional symptoms were obtained from the data records. Laboratory parameters such as ESR, CRP, hemoglobin, serum creatinine, ANA, ANCA, were obtained from the Ege University patient registration program. Ege University Ethics Committee approved this study (approval number: 24-9.1T/40, date: 19.09.2024).

Statistical Analysis

The SPSS 21 software package was used to perform the statistical analysis. Patient characteristics were summarized using means, standard deviation (SD), ranges, and percentages as appropriate. Continuous variables were analyzed using the Mann-Whitney U test (Wilcoxon rank sum test) or t-test, and categorical data were analyzed using the χ^2 test or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

Results

The study consisted of 26 patients, 65.4% of whom were male and 34.6% female. The mean age of the patients was 60.77 (SD: 9.2) years. The great majority of the cases, 24 (92.3%), only had infrarenal aortic involvement. One patient had infra and suprarenal fibrosis, while another patient had mediastinal, infra, and suprarenal fibrosis. All patients with more than just infrarenal involvement were female. The most common symptom was abdominal pain, mostly localized to the left lower quadrant. ARF was detected in 18 (69.2%) patients at the time of diagnosis. Double J stents had to be implanted in 15 of these patients. No statistically significant difference was found in gender, age, acute phase response, or smoking status between patients with and without ARF. However, although not significant, ESR was higher in patients without ARF than in patients with ARF (p=0.238). The most common cause was CP. IgG4-related disease was diagnosed in only five patients (19.2%) (male/female: 3/2); the mean age was 63.6 (SD: 7.0) years. The male ratio was higher in the non-IgG4 related group (p=0.580) and the mean age was higher in the IgG4-related group (p=0.461), although both were not statistically significant. While only one out of five patients diagnosed with IgG4 describes pain, 76.2% of non-IgG4 related patients initially described abdominal pain (p=0.034). Although statistically not significant, the CRP elevation was higher in the non-IgG4-related group (p=0.082). Additionally, the ESR at the time of diagnosis was higher in the non-IgG4-related group (p=0.500). ARF at the time of diagnosis was higher in the non-IgG4-related group (p=0.150). No significant differences were observed in other clinical and laboratory features between IgG4-related and non-IgG4-related diseases. Aneurysms were detected in only two (7.7%) of the patients, with diameters of 3.7 and 4.5 cm. The location of both aneurysms was infrarenal. Serum IgG4 levels were normal, and autoantibodies were negative in these patients with aneurysms.

Among the patients with IgG4 related RPF, one patient had ocular, pancreatic and lympadenopathy (LAP) involvement. One patient had bone marrow and LAP involvement Table 1.

ANCA was negative in all patients with RPF. Four (14.8%) patients had ANA positivity above 1/160 dilution. Among them, ENA profiles were negative in two patients, only AMA was positive in one patient, and PM-Scl, Mi-2, and DFS-70 were positive in one patient. Two (7.4%) patients were positive for lupus anticoagulants. Three of the ANA positive cases were in the IgG4-related group. Neither the patients with idiopathic RPF nor the patients with IgG4-related diseases had additional symptoms and clinical signs of connective tissue disease, and none of these patients met the classification criteria for connective tissue diseases.

RPF was demonstrated in 8 patients with MRI, in 17 patients with CT, and in 1 patient with PET CT. Fibrosis was seen in 3 patients, who underwent retroperitoneal biopsy. Among the patients in the study, one patient underwent eye biopsy and two patients underwent minor salivary gland biopsy. Except for the two biopsies that were performed retroperitoneally and one minor salivary gland biopsy, other biopsies showed IgG4- related disease findings.

Most of the patients received cyclophosphamide (80.8%) as initial treatment together with corticosteroids. The mean initial daily dose of methylprednisolone was 49.0 mg. Maintenance therapy consisted mostly of azathioprine (61.5%). Mycophenolate mofetil (34.6%) and rituximab (15.4%) were other agents used as alternative therapies. None of the patients with IgG4-related disease required rituximab treatment.

Clinical and laboratory parameters of these six patients with IgG4 related disease were given in Table 1. Comparison of laboratory, clinical and treatment features of patients with IgG4-related and non-IgG4-related RPF was given in Table 2.

Discussion

The incidence of RPF reported in the literature is 0.1-1.3/100,000, being more common in men and most frequently seen in the 40-60 age group.[3,5,7,10,14-17] In this study, the mean age of RPF patients was higher than reported in the literature. The mean age was higher in the IgG4-related group than in the non-IgG4-related group, in accordance with the literature.[14-20] The male ratio was higher in the non-IgG4 related group (p=0.580). Although some publications in the literature state the opposite,[14-17] studies by Kim et al.[18], Khosroshahi et al.[19], and Poddar et al.[20] similarly mentioned an increase in male dominance in the non-IgG4 related group.

CP can affect multiple vascular regions. In the study conducted by Kim et al.[18], the abdominal aorta was the most frequently affected site (84%), with the thoracic aorta

Table 1. Clinical and laboratory characteristics of patients diagnosed with IgG4-related disease

Patient	Gender	Age	Involvement	Acute renal failure	Cigarette	Pain location	ESR (mm/h)	CRP (mg/L)	IgG4 (g/L)	Involvement side	Biopsy
1	Male	52	Infrarenal	-	Quit smoking	No pain	5	1.4	6.2	Eye, LAP, pancrease	Eye
2	Male	65	Infrarenal	-	Quit smoking	Abdomen	22	2	2.41	-	
3	Male	64	Infrarenal	+	Smoking	No pain	4	5	4.69	-	
4	Female	71	Mediastinal and abdomen	-	No smoking	No pain	119	3	5	Lung, bone marrow	MSG
5	Female	66	Infrarenal	+	No smoking	No pain	18	7	1.03	-	Retroperitoneal

CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, Hb: Hemoglobin, LAP: Lympadenopathy, MSG: Minor salivary gland biopsy

Table 2. Comparison of laboratory, clinical and treatment features of patients with IgG4-related and non-IgG4-related retroperitoneal fibrosis

		CP (n=26)	IgG4-CP (n=5)	Non-IgG4-CP (n=21)	p-value
Male, n (%)		17 (65.4)	3 (60)	14 (66.7)	0.580
Mean age n (SD)		60.7 (9.3)	63.6 (7.0)	60.1 (9.8)	0.461
Pain n (%)		17 (65.4)	1 (20)	16 (76.2)	**0.034**
Pain location	Abdominal n (%)	8 (30.8)	1 (20)	7 (33.3)	NA
	Back n (%)	4 (15.4)	0 (0)	4 (19.0)	
	Left flank n (%)	8 (30.8)	0 (0)	8 (38.1)	
	Right flank n (%)	1 (3.8)	0 (0)	1 (4.8)	
Renal failure n (%)		18 (69.2)	2 (40.0)	16 (76.2)	0.150
Doble J stent n (%)		15 (57.7)	2 (40.0)	13 (61.9)	0.346
Constitutional symptoms n (%)		6 (23.1)	2 (40.0)	4 (19.0)	
Hypertension n (%)		9 (34.6)	2 (40.0)	7 (33.3)	0.580
Diabetes mellitus n (%)		7 (26.9)	2 (40.0)	5 (23.8)	0.411
Hyperlipidaemia n (%)		4 (15.4)	1 (20.0)	3 (14.3)	0.600
Smoking history n (%)		11 (42.3)	3 (60)	8 (38.1)	0.346
ESR n (25-75)		20.5 (8.5-43.2)	18 (4.5-70.5)	26.0 (18.7)	0.749
High ESR n (%)		13 (50.0)	2 (40)	11 (52.4)	0.500
CRP n (25-75)		5.5 (1.8-14.7)	2.0 (0.9-5.0)	13.5 (17.3)	0.185
High CRP n (%)		15 (57.7)	1 (20)	14 (66.7)	0.082
Localization	Infrarenal n (%)	26 (100)	5 (100)	21 (100)	NA
	Mediastinal n (%)	1 (3.8)	1 (20)	0 (0)	
	Suprarenal n (%)	2 (7.7)	1 (20)	1 (4.8)	
Aneurysm n (%)		2 (7.7)	0 (0)	2 (9.5)	0.646
Treatments	CYC n (%)	21 (80.8)	3 (60)	18 (85.7)	0.236
	AZA n (%)	16 (61.5)	3 (60)	13 (61.9)	0.657
	MMF n (%)	9 (34.6)	1 (20)	8 (38.1)	0.420
	Rtx n (%)	4 (15.4)	0 (0)	4 (19.0)	0.400

AZA: Azathioprine, CP: Chronic periaortitis, Constitutional symptoms (malaise, fatigue, weight loss), CRP: C-reactive protein, CYC: Cyclophosphamide, ESR: Erythrocyte sedimentation rate, MMF: Mycophenolate mofetil, NA: Non-available, Rtx: Rituximab

(46%) being the next most commonly involved, while 38% of patients had an accompanying aortic aneurysm. Another study reported thoracic vascular involvement in about 35% of 77 CP patients.[7] In comparison to patients with isolated abdominal CP, those with diffuse CP were more likely to be female, older, and show systemic symptoms, along with back or abdominal pain.[7] In a cohort of 51 patients studied by Yardimci et al.[5], 43 patients (84.3%) had infrarenal abdominal aortitis, while nine (17.6% re-evaluate percentage based on accurate patient data) had suprarenal involvement-eight of whom also had infrarenal periaortitis. Additionally, three patients (12%) had inflammatory abdominal aortic aneurysms.[5] Patients with diffuse CP had a higher prevalence of aneurysmal disease.[5] Similarly, a study from the Netherlands found that 25% of 53 consecutive patients with idiopathic RPF had aneurysmal

dilatation.[21] In this study, 24 (92.3%) of the patients with RPF had only infrarenal involvement, while one patient had infra and suprarenal fibrosis, and one patient had mediastinal, infra, and suprarenal fibrosis. Aneurysms were detected in two patients (7.4%), both of whom had infrarenal aneurysms. Interestingly, all other patients without exclusive infrarenal involvement were female, suggesting a potential difference in disease distribution based on sex. Given this, female patients may benefit from a full abdominal and thoracic scan. However, it is important to scan the infrarenal area for aneurysm involvement.

In the study, the median age of patients involving more than just infrarenal involvement was higher, but there was no significant difference (p=0.812). Similarly, patients with aneurysms and those diagnosed with IgG4-related disease tended to be older, but again, the differences were not significant (p=0.554, p=0.447). There were no significant differences in disease-related symptoms between patients with or without aneurysms or across different locations of involvement. To make more accurate analyses about this subject, research should be conducted with a larger number of patients.

In the literature, chronic CP has been frequently associated with IgG4-related disease. Yardimci et al.[5] diagnosed IgG4-related CP in 31 of 51 CP patients, while Kim et al.[18] identified 10 cases of IgG4-related CP in their cohort of 61 CP patients. Li et al.[22] reported that 77 of 105 CP cases belonged to the IgG4-related group, with no significant differences in age or disease course between IgG4-related and non-IgG4-related groups. However, the male-to-female ratio was significantly higher in the IgG4-related group. Similarly, Ozawa et al.[23] found periaortitis in 65 of 179 patients with IgG4-RD, with periaortitis predominantly affecting the abdominal aorta below the renal artery. In a study from China involving 587 IgG4- related disease patients, large vessel involvement was observed in 15.2%, and renal failure occurred in 48.3%.[24] Serum IgG4 levels may be high in both aneurysmal and non-aneurysmal types of CP.[7] In the study by Poddar et al.[20] 6 of 33 RPF patients were diagnosed with IgG4-related disease, while in the study by Hu et al.[17] 47 of 117 RPF patients were diagnosed with IgG4-related disease. In the study by Wang et al.[14] the rate of IgG4-related disease was 35.6%. In this study, IgG4-related disease was diagnosed in only five patients (19.2%). The most common cause was CP. Among these five patients, four had only infrarenal involvement, and one had both thoracic and abdominal involvement. No accompanying aneurysms were observed in these patients. The male ratio was higher in the non-IgG4-related group (p=0.580). CRP elevation was significantly higher in the non-IgG4-related group (p=0.082); in addition, ARF at diagnosis was also more common in this group (p=0.150). No significant differences were found in other clinical and laboratory features between the two groups. As a result, the higher CRP levels in the non-IgG4-related group suggest a more pronounced inflammatory response. In contrast, Li et al.[22] reported that ARF due to ureteral obstruction was more common in the IgG4-related group, which also exhibited higher ESR and CRP levels and recurrence rates.[22] Choi et al.[15] reported more ARF in the IgG4-related group; however, acute phase responses were similar, although slightly higher in the non-IgG4 group. Hu et al.[17] found higher CRP levels and higher ARF in IgG4-related disease patients. Conversely, Kim et al.[18] found no differences in laboratory findings, treatment, or outcomes between IgG4-related and non-IgG4-related CP cases and Wang et al.[14] found that the proportion of high CRP patients in the non-IgG4-related group was higher than that in the IgG4-related RPF group but there was no difference in ARF rates. In this study, the rate of IgG4-related disease was lower; CP was found to be the most common cause of RPF. In addition, the higher rates of ARF and high CRP levels in patients with non-IgG4-related RPF, and the need to use rituximab in this group, while it was not used in the IgG4-related group, suggest that more severe, aggressive, and treatment-resistant disease was observed in the group with non-IgG4-related RPF.

In the literature, low back pain was found to be the most frequent symptom in RPF patients.[6,8] In the present study, 65.4% of patients had pain at the beginning of the disease. The majority of these patients described abdominal pain (reported by 29.6% of patients) and left flank pain (reported by 29.6% of patients). In patients with IgG4-related disease, four out of five reported no pain, while only one experienced abdominal pain. In contrast, 76.2% of non-IgG4-related patients initially presented with abdominal pain. In the study by Kasashima et al.[25] abdominal or back pain was more prevalent in non-IgG4-related CP patients. In the study by Wang et al.[14], 48.4% of patients had lower back pain, which was more common in non-IgG4 related patients. In this study, the rate of abdominal pain was low in patients with IgG4-related disease. This may lead to delayed recognition and diagnosis of these patients. More attention should be paid to this respect.

ANA may be positive in 25-60% of patients with RPF. In addition, anti-thyroid antibodies have been reported to be positive in 31% of patients, RF in 14% of patient and ANCA in 10% of patients with RPF. Their presence is often associated with the accompanying autoimmune disease, although not always.[10,12] In this study, ANCA was found to be negative in all patients. Four patients

had ANA profiles with positivity above a 1/160 titer, and two patients had negative ANA profiles. One patient had AMA-M2 positivity; one patient had DFS-70, PM-SCL, and Mi-2 positivity. Two patients were positive for lupus anticoagulant. None of the patients had thromboembolic events. None of the patients with idiopathic RPF and patients with IgG4-related diseases had additional symptoms and clinical signs of connective tissue disease, and none of these patients met the classification criteria for connective tissue disease. Antibody positivity was considered a tendency to systemic autoimmunity in patients with RPF. One patient with RPF. who was not included in the study, was diagnosed with Erdheim-Chester disease. In the study conducted by Hu et al.[17] on 117 RFP patients, ANA positivity was observed in 32 patients, RF positivity in 17 patients, and anticardiolipin antibody positivity in 23 patients.[18] For differential diagnosis, it is important to screen for different autoimmune events and other diseases that may develop in patients with RPF.

Glucocorticoids, mycophenolate mofetil, cyclophosphamide, azathioprine, methotrexate, cyclosporine, rituximab, and tocilizumab can be used in the treatment of RPF.[6] In the present study, most patients (80.8%) were given cyclophosphamide as initial treatment, and azathioprine was the most commonly used maintenance treatment (61.5%). Rituximab (15.4%) and mycophenolate mofetil (34.6%) were used as alternative treatments. Rituximab is generally the treatment regimen of choice in resistant patients and patients with severe conditions. The preference for rituximab in non-IgG4-associated patients, but not in IgG4-associated patients, suggests that IgG4-associated cases may respond better to induction therapies, whereas non-IgG4-associated patients may be more resistant to treatment. Furthermore, the fact that high serum CRP levels and ARF were more frequent in the non-IgG4-related group may suggest more severe inflammation, and an aggressive disease course in this group. While Kim et al.[18] reported similar treatment responses between the IgG4-related and non-IgG4-related groups, Li et al.[22] found a higher probability of relapse in the IgG4-related group compared to the non-IgG4-related group.

Surgery is considered for CP patients with aneurysms. In a single-center study analyzing 1,555 aortic surgeries, periaortic RPF was identified in 1.09% of cases. Among these 17 RPF patients, 11 received only optimal medical treatment, while six underwent endovascular abdominal aneurysm repair after medical treatment failure, achieving a 100% technical success rate.[24] Additionally, one study reported that RPF patients with aortic aneurysms smaller than 5 cm did not require endovascular intervention, as regression occurred with corticosteroid treatment.[7] In this study, surgery was not performed for two patients with aneurysms, and the mean maximum aneurysm diameter was 4.1 cm.

Study Limitations

In this article, we present single-center data on patients with RPF. Given that RPR is a rare disease, a small number of cases seem acceptable. Another main limitation of the study is the retrospective design. Additionally, a potential limitation is that IgG4 levels were assessed in some patients after they had received immunosuppressive treatment and entered remission. This might have led to an underestimation of IgG4-related RPF cases, as prior treatment could have influenced IgG4 levels and involvements.

Conclusion

This study analyzed demographic, clinical, and laboratory data, imaging findings, and treatment outcomes of RPF patients, which is a rare disease. Patients with non-IgG4-related RPF showed more severe disease, with higher rates of ARF and elevated CRP levels, suggesting a more aggressive and treatment-resistant form of the disease. On the other hand, there was no difference between patients with and without ARF that could distinguish these patients or predict ARF. Additionally, all non-infrarenal RPF cases were female, indicating possible sex-based differences in disease distribution. The study calls for further research with larger patient populations to clarify these findings and improve management strategies.

Ethics

Ethics Committee Approval: Ege University Ethics Committee approved this study (approval number: 24-9.1T/40, date: 19.09.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: G.K., K.A., Design: G.K., K.A., Data Collection and Processing: F.T., D.K., S.K., G.K., Y.K., K.A., Analysis or Interpretation: F.T., G.K., Y.K., K.A., Literature Search: F.T., D.K., S.K., Writing: F.T., D.K., S.K., G.K.

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

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

References

1. Jois RN, Gaffney K, Marshall T, Scott DG. Chronic periaortitis. Rheumatology (Oxford). 2004;43:1441-6.
2. Koster MJ, Ghaffar U, Duong SQ, et al. Incidence, prevalence and mortality of chronic periaortitis: a population-based study. Clin Exp Rheumatol. 2022;4:751-7.
3. Engelsgjerd JS, Leslie SW, LaGrange CA. Retroperitoneal fibrosis. 2024 Aug 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
4. Becker M. Chronische periaortitis [chronic periaortitis]. Ther Umsch. 2022;79:254-9. German.
5. Yardimci GK, Ardali Düzgün S, et al. Comprehensive assessment and outcomes of patients with chronic periaortitis. Clin Exp Rheumatol. 2022;40:801-10.
6. Łoń I, Lewandowski J, Wieliczko M, Małyszko J. Retroperitoneal fibrosis, a rare entity with urorenal and vascular subtypes - preliminary data. Ren Fail. 2022;44:688-92.
7. Palmisano A, Maritati F, Vaglio A. Chronic periaortitis: an update. Curr Rheumatol Rep. 2018;20:80.
8. Gianfreda D, Superchi E, Peyronel F, Mazzariol M, Vaglio A. Chronic periaortitis: a clinical approach. Rev Med Interne. 2023;44:79-84.
9. Yuan Z, Lu Y, Wei J, Wu J, Yang J, Cai Z. Abdominal aortic aneurysm: roles of inflammatory cells. Front Immunol. 2021;11:609161.
10. Gómez Rivas J, Quintana LM, Álvarez-Maestro M, Aguilera A, Martinez Piñeiro L, Sarikaya S. Retroperitoneal fibrosis: a literature review. Arch Esp Urol. 2020;73:60-7. English, Spanish.
11. Vaglio A, Maritati F. Idiopathic retroperitoneal fibrosis. J Am Soc Nephrol. 2016;27:1880-9.
12. Umehara H, Okazaki K, Kawa S, et al; Research Program for Intractable Disease by the Ministry of Health, Labor and Welfare (MHLW) Japan. The 2020 revised comprehensive diagnostic (RCD) criteria for IgG4-RD. Mod Rheumatol. 2021;31:529-33.
13. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-84.
14. Wang K, Wang Z, Zeng Q, et al. Clinical characteristics of IgG4-related retroperitoneal fibrosis versus idiopathic retroperitoneal fibrosis. PLoS One. 2021;16:e0245601.
15. Choi YK, Yang JH, Ahn SY, et al. Retroperitoneal fibrosis in the era of immunoglobulin G4-related disease. Kidney Res Clin Pract. 2019;38:42-8.
16. Zen Y, Onodera M, Inoue D, et al. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. Am J Surg Pathol. 2009;33:1833-9.
17. Hu JQ, Jin ZY, Yu YY, Min DM, Cai Q, Gao J. Clinical characteristics of IgG4-related retroperitoneal fibrosis in a cohort of 117 patients with idiopathic retroperitoneal fibrosis: a retrospective study. Clin Rheumatol. 2025;44:757-66.
18. Kim IY, Eun YH, Jeong H, et al. Clinical characteristics and outcomes of 61 patients with chronic periaortitis including IgG4-related and non-IgG4-related cases. Int J Rheum Dis. 2017;20:1751-62.
19. Khosroshahi A, Carruthers MN, Stone JH, et al. Rethinking Ormond's disease: "idiopathic" retroperitoneal fibrosis in the era of IgG4-related disease. Medicine (Baltimore). 2013;92:82-91.
20. Poddar P, Billings S, Calabrese LH, Gota CE. Comparison of IgG4-related and non-IgG4-related retroperitoneal fibrosis; a 12 year retrospective study [abstract]. Arthritis Rheumatol. 2015;67(Suppl 10).
21. van Bommel EFH, Jansen I, Hendriksz TR, Aarnoudse ALHJ. Idiopathic retroperitoneal fibrosis: prospective evaluation of incidence and clinicoradiologic presentation. Medicine (Baltimore). 2009;88:193-201.
22. Li J, Wang H, Wang M, Xu F, Guo F, Ye F. Differences of clinicopathological features between IgG4-related and non-IgG4-related idiopathic retroperitoneal fibrosis. Int J Rheum Dis. 2022;25:440-6.
23. Ozawa M, Fujinaga Y, Asano J, et al. Clinical features of IgG4-related periaortitis/periarteritis based on the analysis of 179 patients with IgG4-related disease: a case-control study. Arthritis Res Ther. 2017;19:223.
24. Peng L, Zhang P, Li J, et al. IgG4-related aortitis/periaortitis and periarteritis: a distinct spectrum of IgG4-related disease. Arthritis Res Ther. 2020;22:103.
25. Kasashima S, Zen Y, Kawashima A, Endo M, Matsumoto Y, Kasashima F. A new clinicopathological entity of IgG4-related inflammatory abdominal aortic aneurysm. J Vasc Surg. 2009;49:1264-71; discussion 1271.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.96268
Ulus Romatol Derg 2025;17(3):162-173

Effect of MEFV gene variants and treatment modalities on attack-free period acute phase reactants of patients with familial Mediterranean fever

Ailevi Akdeniz ateşi hastalarında MEFV gen varyantları ve tedavi yöntemlerinin ataksız dönemdeki akut faz reaktanları üzerindeki etkisi

Ege Sinan Torun[1], Duygu Birinci[2], Ezgi Fındık[2], Elif Ertaş[3]

[1]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Internal Medicine, İstanbul, Türkiye
[3]Selçuk University Faculty of Medicine, Department of Biostatistics, Konya, Türkiye

Abstract

Objective: Attack-free period C-reactive protein (CRP) and serum amyloid A (SAA) are reliable indicators of subclinical inflammation in familial Mediterranean fever (FMF). We aimed to compare the acute phase reactants during the attack-free period, and the presence of subclinical inflammation in FMF patients with different gene variants and different treatment modalities.

Methods: CRP and SAA levels during a symptom-free period of at least 2 weeks were obtained, and the median CRP and SAA levels were calculated during the attack-free period. "Subclinical inflammation" was defined as "median attack-free CRP >10 mg/L or median attack-free SAA >10 mg/L." Patients were classified according to MEFV variants (two, one, or zero exon 10 variants) and treatments (colchicine-only or colchicine+interleukin 1 inhibitors).

Results: Seventy-six patients had two exon 10 variants, 79 had one exon 10 variant, and 17 had non-exon 10 variants. Most patients used colchicine (n=155), and 17 patients used colchicine + interleukin-1 inhibitors. Attack-free CRP, SAA, and rate of subclinical inflammation were significantly different among variant groups, higher among patients with 2 exon 10 variants. Patients receiving combination treatment had higher levels of attack-free CRP and SAA compared to the colchicine-only group. CRP and SAA were strongly correlated.

Conclusion: Patients with two exon 10 variants had higher attack-free acute phase reactants and more frequent subclinical inflammation, which reflects the pathogenicity of exon 10 variants. Patients receiving interleukin 1+colchicine continue to have higher attack-free acute phase reactants, which reflects their higher inflammatory burden and severe clinical features.

Keywords: C-reactive protein, familial Mediterranean fever, serum amyloid A, subclinical inflammation

Özet

Amaç: Ataksız dönemdeki C-reaktif protein (CRP) ve serum amiloid A (SAA), ailevi Akdeniz ateşi (AAA) hastalarında subklinik enflamasyonun güvenilir belirteçleri arasındadır. Bu çalışmada farklı genetik varyantlar taşıyan ve farklı yöntemlerle tedavi edilen AAA hastalarında ataksız dönemdeki akut faz reaktanlarını ve subklinik enflamasyonu karşılaştırmayı amaçladık.

Yöntem: Hastaların en az 2 haftadır semptomsuz olduğu dönemlerde bakılan CRP ve SAA düzeyleri kaydedilerek ataksız dönemdeki medyan CRP ve SAA değerleri hesaplanmıştır. "Subklinik enflamasyon," "ataksız dönemde medyan CRP'nin >10 mg/L olması veya medyan SAA'nın >10 mg/L olması şeklinde tanımlanmıştır. Hastalar MEFV varyantlarına göre (iki, bir ya da sıfır 10. ekzon varyantı olan hastalar) ve tedavilerine göre (yalnızca kolşisin alanlar veya kolşisin+interlökin 1 inhibitörü alanlar) şeklinde sınıflandırılmıştır.

Bulgular: Yetmiş altı hastada iki 10. ekzon varyantı, 79 hastada bir 10. ekzon varyantı, 17 hastadaysa 10. ekzon dışı varyantlar mevcuttu. Hastaların çoğu yalnızca kolşisin (n=155), 17 hasta ise kolşisin+interlökin 1 inhibitörü kullanmaktaydı. Ataksız dönem CRP, SAA ve subklinik enflamasyon oranı iki 10. ekzon varyantı taşıyan hastalarda anlamlı olarak daha yüksekti. Kombinasyon tedavisi alan hastalarda ataksız dönem CRP ve SAA, yalnızca kolşisin kullananlara göre daha yüksekti. CRP ve SAA arasında güçlü korelasyon mevcuttu.

Sonuç: İki 10. ekzon varyantlı hastalardaki daha yüksek ataksız dönem akut faz reaktanı düzeyleri ve subklinik inflamasyon oranı, 10. ekzon varyantlarının patojenitesini yansıtmaktadır. Kolşisin+interlökin 1 inhibitörü alan hastalarda ataksız dönem akut faz reaktanlarının daha yüksek olması bu hastaların daha yoğun enflamasyon yükünü ve daha ağır klinik özelliklerini ortaya koymaktadır.

Anahtar Kelimeler: C-reaktif protein, ailevi Akdeniz ateşi, serum amiloid A, subklinik inflamasyon

Correspondence / İletişim: Ege Sinan Torun MD,
University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital, Department of Internal Medicine, Division of Rheumatology, İstanbul, Türkiye
E-mail: egesinantorun@hotmail.com **ORCID ID:** orcid.org/0000-0002-4842-0683
Received / Geliş Tarihi: 21.04.2025 **Accepted / Kabul Tarihi:** 06.10.2025 **Epub:** 18.11.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Torun ES, Birinci D, Fındık E, Ertaş E. Effect of MEFV gene variants and treatment modalities on attack-free period acute phase reactants of patients with familial Mediterranean fever. Ulus Romatol Derg. 2025;17(3):162-173

Introduction

Familial Mediterranean fever (FMF) is recognized as the most prevalent monogenic autoinflammatory disorder, with Türkiye exhibiting the highest rates of incidence and prevalence globally.[1,2] The condition arises from variants in the *MEFV* gene, which is responsible for encoding the protein pyrin. Among these variants, those found in exon 10, particularly the widely studied M694V variant, have been identified as the most pathogenic and thoroughly characterized.[2,3]

FMF is marked by recurring episodes of fever and serositis, accompanied by a significantly elevated acute phase response.[4] Between these episodes, acute phase reactants typically return to normal levels. However, some patients may experience persistently elevated levels of these reactants even during periods without acute symptoms.[5] Various studies have utilized markers to indicate subclinical inflammation, one of which is serum amyloid A (SAA). The activation pattern of SAA closely resembles that of C-reactive protein (CRP), and studies have indicated that the sensitivity of SAA is comparable to or even exceeds that of CRP.[4] If not addressed, subclinical inflammation heightens the risk of complications, including AA amyloidosis.[6] AA amyloidosis initially manifests as proteinuria, which can escalate to nephrotic levels and ultimately lead to end-stage renal disease.[7]

The objectives of treatment for FMF involve preventing the recurrence of attacks, normalizing acute phase reactants, and effectively managing subclinical inflammation during periods without attacks to avert complications.[8] Colchicine is the primary medication used for FMF management. In cases that respond inadequately to colchicine or in patients who cannot tolerate colchicine, interleukin-1 inhibitors such as anakinra and canakinumab are employed.[9] Colchicine therapy may help reduce levels of markers that are indicative of subclinical inflammation.[6] For patients who do not achieve sufficient control of inflammation, interleukin-1 inhibitors are introduced. A recent study conducted by Atalar et al.[10] revealed that even interleukin-1 inhibitors might not sufficiently suppress subclinical inflammation in FMF patients suffering from AA amyloidosis. A Phase III trial of canakinumab in FMF also demonstrated that, in patients treated with this agent, even though median CRP concentrations were always normal, median SAA concentrations remained over the limit of normal (10 mg/L).[11]

Persistent subclinical inflammation is a significant factor in FMF management and should be taken into account in the long-term care of FMF patients because of the increased risk of AA amyloidosis, which can negatively impact long-term prognosis. We hypothesize that FMF patients with two exon 10 variants will have higher attack-free CRP and SAA levels, and therefore, a higher rate of subclinical inflammation compared to patients with one or zero exon 10 variants, because the literature clearly demonstrates that the most pathogenic variants of the *MEFV* gene are found in exon 10 and these variants are associated with a more severe phenotype characterized by earlier disease onset and more frequent attacks.[12] We also hypothesize that, in accordance with the preexisting studies, patients who require interleukin-1 inhibitors in addition to colchicine will have higher attack-free CRP and SAA levels and more frequent subclinical inflammation compared to patients who only receive colchicine. Therefore, this study aims to compare the levels of acute phase reactants and the presence of subclinical inflammation among FMF patients with different MEFV gene variants (categorized by the number of exon 10 variants) who are receiving different treatment modalities.

Materials and Methods

Patient Selection and Data Collection

This research was granted approval by the Non-Interventional Clinical Research Ethics Committee of Prof. Dr. Cemil Taşcıoğu City Hospital, University of Health Sciences, Türkiye, with the decision number 230, dated 22.10.2024. Informed consent was acquired from the patients involved.

In this cohort study, we conducted a retrospective analysis of the medical records of patients diagnosed with FMF based on the Tel-Hashomer criteria, who visited our Rheumatology Outpatient Clinic at Prof. Dr. Cemil Taşcıoğlu City Hospital from March 2022 to August 2023, without accompanying vasculitis (including Behçet's disease) or spondylarthritis. FMF patients with concomitant spondylarthritis or vasculitis would have additional reasons for elevated attack-free acute phase reactants and were therefore excluded. The study included patients for whom MEFV gene variants were identifiable. Those without any detectable MEFV gene variants were excluded from the analysis. Patients with MEFV gene variants that were classified as "pathogenic," "likely pathogenic", or "variants of uncertain significance" according to the Infevers database were included. Conversely, patients with variants deemed "likely benign" or "benign", such as R202Q, were excluded. Additionally, patients who did not have at least one measurement of CRP or SAA that indicated an "attack-free" status were also excluded.

Patients were classified into three groups according to their MEFV gene variants. Group 1 consisted of patients with two variants in exon 10 of the *MEFV* gene, while Group 2 included those with a single variant in the same exon. Group 3 was made up of patients who did not have any variants in exon 10. Additionally, patients were categorized into two treatment groups: Group A included those who were treated solely with colchicine, whereas Group B contained patients who received both colchicine and interleukin-1 inhibitors during the specified 18-month period.

The medical records of the patients included in the study were analyzed for various biomarkers, including serum CRP, SAA, serum creatinine, estimated glomerular filtration rate (eGFR), serum albumin, proteinuria, the presence of end-stage renal disease, and the occurrence of AA amyloidosis, which was confirmed through kidney biopsy samples. Kidney biopsies were performed on FMF patients who exhibited proteinuria exceeding 1 gram per day and/or a progressive rise in creatinine levels, provided that no other causes of renal failure were identified. The attack-free period for acute phase reactants was defined by CRP and/or SAA levels measured during a symptom-free interval of at least two weeks. Blood samples collected during FMF attacks, within two weeks following an attack, or during infections (with both FMF attacks and infections ruled out based on the patient's history and clinical assessment) were excluded, as they would not accurately represent the "attack-free" period. Subsequently, the median values for CRP, SAA, serum creatinine, eGFR, serum albumin, and proteinuria were calculated. Human leukocyte antigen (HLA)-B27 results were also recorded, if present.

To establish a definition for "subclinical inflammation" in patients, we examined existing literature on the topic. Our definition draws from the review by Ben-Zvi and Livneh[6], which indicated that an increase in colchicine dosage was necessary to effectively manage subclinical inflammation when SAA levels surpassed 10 mg/L. Based on this literature, subclinical inflammation is identified when the median attack-free CRP exceeds 10 mg/L or the median attack-free SAA is greater than 10 mg/L. Additionally, we recorded the patients who were classified as having "subclinical inflammation".

Statistical Analysis

For continuous variables, the mean ± standard deviation and median (Q1-Q3) were employed. For categorical variables, frequency and percentage were calculated.

In assessing the variations in attack-free median CRP, attack-free mean SAA, median serum creatinine, median eGFR, median serum albumin, and median proteinuria across various MEFV gene variant groups and treatment groups, non-parametric tests were employed.

In assessing the differences in attack-free median CRP, attack-free median SAA, median serum creatinine, median eGFR, median serum albumin, and median proteinuria, across various MEFV gene variant groups, the Kruskal-Wallis H test was employed. If a statistical difference was identified among the groups, a post-hoc analysis using the Tukey test was conducted. For comparisons of the median attack-free CRP and SAA among genetic subgroups in Group 2, the Mann-Whitney U test was applied. Similarly, when examining the median attack-free CRP and SAA of genetic subgroups in Group 3, the Kruskal-Wallis H test was utilized, followed by a post-hoc Tukey test if significant differences were found.

The Mann-Whitney U test was employed to assess the differences in attack-free median CRP, attack-free median SAA, median serum creatinine, median eGFR, median serum albumin, and median proteinuria across various treatment groups.

The chi-square test was employed to evaluate the association between genotype—encompassing various variant groups and subgroups, the count of "pathogenic" alleles, "likely pathogenic" alleles, "variants of uncertain significance", and the quantity of each specific allele—and the occurrence of subclinical inflammation, end-stage renal disease, and AA amyloidosis. Additionally, the chi-square test was utilized to examine the relationship between treatment groups and the presence of subclinical inflammation, end-stage renal disease, and AA amyloidosis.

Patients with subclinical inflammation and the risk factors identified for subclinical inflammation (age, sex, number of exon 10 variants, number of non-exon 10 variants, mean colchicine dose, and HLA-B27 positivity) were reported with odds ratios and 95% confidence intervals. Univariate binary logistic regression analysis was utilized to assess the effect of these risk factors on the presence of subclinical inflammation.

The Spearman's correlation test was employed to examine the relationship between the median attack-free values of CRP and SAA.

A statistical significance level of $p<0.05$ was applied during the evaluation. The analysis was conducted using IBM SPSS version 25.

Results

Between March 1, 2022, and August 31, 2023, a total of 253 patients with FMF (without accompanying spondylarthritis or vasculitis, including Behçet's disease)

attended the Rheumatology Outpatient Clinic. The medical records of 56 patients were found to be missing information on the MEFV gene variants, leading to their exclusion from the study. Upon reviewing the MEFV variants of the remaining patients, we identified that 18 individuals were either homozygous or heterozygous for the R202Q variant. While some research suggests that R202Q variants may have clinical significance, we opted to exclude these patients from our analysis, as the "Infevers" database classifies this variant as benign. The MEFV gene variants of the remaining 179 patients were classified as "pathogenic", "likely pathogenic", or "variants of uncertain significance" based on the Infevers database. Among these, 7 patients did not have acute phase reactants measured during the attack-free period and were therefore excluded. Consequently, a total of 172 patients were included in the study. A flowchart illustrating the patient selection process is presented in Figure 1.

Demographic Characteristics

A total of fifty patients (30.2%) were male, while 122 patients (69.8%) were female. The average age of the patients was 38.1±12.3 years, with a median age of 39 years (ranging from a minimum of 17 to a maximum of 66 years). The mean duration of follow-up for the patients was 8.8±5.7 months, with a minimum of 1 month and a maximum of 18 months.

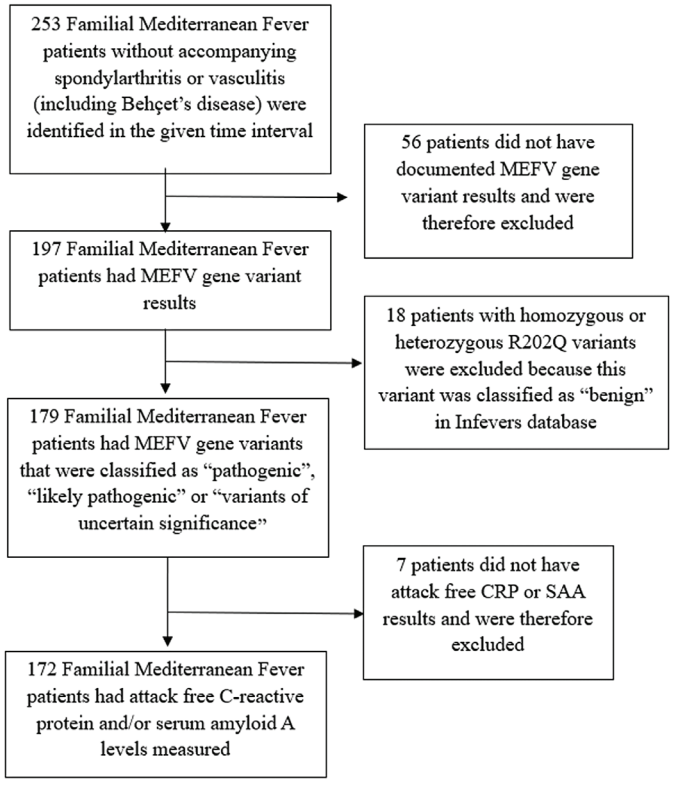

Figure 1. Flowchart of patient selection for the study
CRP: C-reactive protein, SAA: Serum amyloid A

MEFV Gene Variants of the Patients and Different Treatment Groups

Table 1 presents the variants of the *MEFV* gene observed in the patients. Among the participants, 76 patients (44.2%) exhibited two variants in exon 10 (Group 1), 79 patients (45.9%) had one variant in exon 10 (Group 2), and 17 patients (9.9%) showed no variants in exon 10 (Group 3). The predominant variant in Group 1 was the homozygous M694V variant, found in 38 patients, while the most frequent variant in Group 2 was the heterozygous M694V variant, identified in 34 patients. In Group 3, the most common variant was the heterozygous E148Q variant, which was present in 9 patients.

Table 1. MEFV gene variant analysis of the patients

Variants	Number (percent)
Patients with 2 exon 10 variants	**76 (44.2%)**
M694V homozygote	38 (22.1%)
M694V/V726A compound heterozygote	9 (5.2%)
M694V/M680I compound heterozygote	7 (4.1%)
M694V/R761H compound heterozygote	2 (1.2%)
M694V/A744S compound heterozygote	2 (1.2%)
M694I homozygote	2 (1.2%)
M694I/V726A compound heterozygote	1 (0.6%)
M680I homozygote	3 (1.7%)
M680I/V726A compound heterozygote	6 (3.5%)
M680I/R761H compound heterozygote	1 (0.6%)
V726A homozygote	3 (1.7%)
V726A/R761H compound heterozygote	1 (0.6%)
R761H homozygote	1 (0.6%)
Patients with 1 exon 10 variant	**79 (45.9%)**
M694V heterozygote	34 (19.8%)
M694V heterozygote, E148Q heterozygote	7 (4.1%)
M694I heterozygote, E148Q heterozygote	2 (1.2%)
M680I heterozygote	7 (4.1%)
M680I heterozygote, E148Q heterozygote	3 (1.7%)
V726A heterozygote	15 (8.7%)
V726A heterozygote, E148Q heterozygote	1 (0.6%)
R761H heterozygote	5 (2.9%)
R761H heterozygote, F479L heterozygote	1 (0.6%)
A744S heterozygote	2 (1.2%)
K695R heterozygote	2 (1.2%)
Patients with no exon 10 variants	**17 (9.9%)**
E148Q homozygote	1 (0.6%)
E148Q heterozygote	9 (5.2%)
E148Q heterozygote, T309M heterozygote	2 (1.2%)
E148Q heterozygote, P369S heterozygote	1 (0.6%)
E148Q heterozygote, P369S heterozygote, R408 heterozygote	2 (1.2%)
T267I heterozygote	1 (0.6%)
P369S heterozygote, R408 heterozygote	1 (0.6%)

The majority of patients (n=155, 90.1%) were treated only with colchicine (Group A), while 17 patients (9.9%) received a combination of colchicine and interleukin-1 inhibitors (anakinra or canakinumab) (Group B). Mean dose of colchicine was 1.27±0.34 mg/day, median colchicine dose was 1.15 (1-1.5) mg/day; where the minimum dose was 0.5 mg/day and the maximum dose was 2 mg/day. The addition of interleukin-1 inhibitors was necessitated by an insufficient response to colchicine in all 17 patients. Among them, ten patients were administered anakinra, with a mean duration of use of 4.55±4.8 months, (ranging from a minimum of 1 month to a maximum of 14 months). The average dosage of anakinra was 100±40.8 mg/day, with a minimum of 50 mg/day and a maximum of 200 mg/day. Three patients transitioned from anakinra to canakinumab, with one patient citing skin reactions following anakinra injections and two patients reporting inadequate responses to anakinra. Additionally, ten patients were treated with canakinumab, all receiving a consistent dose of 150 mg per month. The mean duration of canakinumab treatment was 5.7±3.4 months, and none of the patients discontinued canakinumab during the 18-month observation period.

Comparison of Attack-free Period C-reactive Protein and Serum Amyloid A in Patients in Different Groups

CRP values were recorded for 171 patients. The median CRP level during attack-free periods was 5.2±7.8 mg/L, with values ranging from a minimum of 0.10 mg/L to a maximum of 53 mg/L. SAA values were available for 156 patients, with a median attack-free SAA value of 20±43 mg/L, ranging from a minimum of 1.1 mg/L to a maximum of 332 mg/L.

Table 2 presents the mean and median values of attack-free CRP and SAA for patients categorized into Group 1 (two exon 10 variants), Group 2 (one exon 10 variant), and Group 3 (no exon 10 variants). The findings indicate a statistically significant difference in the median attack-free mean CRP across the groups (p<0.001). Specifically, Group 1 exhibited a significantly higher median attack-free CRP than Group 2 (p=0.01) and Group 3 (p=0.006). Additionally, the analysis revealed a significant difference in attack-free SAA levels among the groups (p=0.02), with Group 1 showing a notably higher median attack-free SAA than Group 2 (p=0.009).

In Group 2, 65 patients exhibited a single exon 10 variant, while 14 patients presented with one exon 10 variant and one non-exon 10 variant. The subgroup analysis revealed that the levels of attack-free CRP and SAA were not significantly different between patients with only one exon 10 variant and those with one exon 10/one non-exon 10 variant (p=0.44 for CRP, p=0.24 for SAA).

In Group 3, there were 10 patients with a single non-exon 10 variant, 5 patients with two non-exon 10 variants, and 2 patients with three non-exon 10 variants. The analysis revealed no statistically significant differences among the three groups concerning attack-free median CRP or attack-free median SAA levels (p=0.82 for CRP, p=0.91 for SAA).

Table 3 illustrates the mean and median values of attack-free CRP and SAA for patients in Group A (colchicine) and Group B (colchicine combined with interleukin 1 inhibitors). The median attack-free CRP in Group B was notably greater than that in Group A [p=0.004], and the median attack-free SAA in Group B also exceeded that of Group A significantly [p=0.03].

Presence of Subclinical Inflammation According to Different Groups

As detailed in the Methods section, we documented patients exhibiting subclinical inflammation. Based on our criteria, 37 out of 76 patients in Group 1, 21 out of 79 patients in Group 2, and 4 out of 17 patients in Group 3 were identified as having subclinical inflammation. The chi-square test indicated a statistically significant difference among the three groups (p=0.009) regarding the occurrence of subclinical inflammation.

In the comparison of the two subgroups within Group 2 regarding the presence of subclinical inflammation, no statistically significant difference was observed between patients with one exon 10 variant/one non-exon 10 variant

Table 2. Evaluation of the attack free CRP and SAA according to *MEFV* gene variant groups of the patients

	Group 1-two exon 10 variants n=76	Group 2-one exon 10 variant n=79	Group 3-no exon 10 variants n=17	p-value*	p-value**
	Mean ± SD Median (Q1-Q3)	Mean ± SD Median (Q1-Q3)	Mean ± SD Median (Q1-Q3)		1 vs. 2 1 vs. 3 2 vs. 3
Mean and median attack free CRP (mg/L)	8.08±10.11 3.31 (1.69-11)	3.27±4.88 1.94 (0.72-4.19)	1.74±1.97 0.85 (0.5-3.16)	**<0.001**	**0.001 0.006** 0.73
Mean and median attack free SAA (mg/L)	31.2±60.3 9.2 (4.1-27.7)	9.9±13.1 5 (2-12.1)	10.9±11 8.1 (2.9-15.9)	**0.02**	**0.009** 0.19 0.99

*CRP: C-reactive protein, SAA: Serum amyloid A, SD: Standard deviation, Q1-Q3: First and third quartile, *Kruskal-Wallis H test, **Pos-hoc Tukey test, 1: Two exon 10 variants, 2: One exon 10 variant, 3: No exon 10 variants*

and those who had only one exon 10 variant (p=0.18). Similarly, when the three subgroups of Group 3 were analyzed, the chi-square test did not reveal any statistical significance in relation to the presence of subclinical inflammation among patients with one, two, or three non-exon 10 variants (p=0.64).

The investigation into the correlation between subclinical inflammation and the quantity of specific alleles revealed that only the V726A alleles showed statistical significance (p=0.03). Furthermore, when examining the relationship between subclinical inflammation and the numbers of "pathogenic" variants, "likely pathogenic", and "variants of uncertain significance," it was found that only the number of "pathogenic" alleles reached statistical significance (Supplementary Table 1).

When patients were classified based on their treatment modalities, 53 individuals in Group A and 9 individuals in Group B exhibited subclinical inflammation. The chi-square test indicated that there was no significant difference between the two groups regarding the presence of subclinical inflammation (p=0.18).

Comparison of Renal Parameters, AA Amyloidosis, and End Stage Renal Disease in Different Groups

No notable differences were observed among the three variant groups regarding median serum creatinine, median eGFR, median serum albumin, and median proteinuria. In Group 1, seven patients were diagnosed with AA amyloidosis, while neither Group 2 nor Group 3 had any cases of this condition. The chi-square test indicated that this disparity among the three variant groups was statistically significant (p=0.02). Additionally, two patients in Group 1 had end-stage renal disease, whereas there were no cases of end-stage renal disease in either Group 2 or Group 3. The chi-square test revealed that the difference in this regard among the three variant groups was not statistically significant (Supplementary Table 2).

There was no notable difference in the median values of serum creatinine and eGFR between the two treatment groups. However, the median serum albumin level in Group A was significantly greater than that in Group B (p=0.04). Additionally, median proteinuria was significantly higher in Group B compared to Group A (p<0.001). In Group A, two patients were diagnosed with AA amyloidosis, while in Group B, five patients had the same condition. The chi-square test revealed a significantly higher prevalence of AA amyloidosis in Group B (p<0.001). Additionally, none of the patients in Group A experienced end-stage renal disease, whereas two patients in Group B did. This difference was statistically significant, as indicated by the chi-square test (p=0.009) (Supplementary Table 3).

Risk Factors for Subclinical Inflammation

According to our definition of subclinical inflammation, 62 patients (36%) had subclinical inflammation. Supplementary Table 4 demonstrates the risk factors for the presence of subclinical inflammation and the results of the univariate logistic regression analysis. In this analysis, presence of subclinical inflammation was not associated with age, sex, number of exon 10 variants, number of non-exon 10 variants, mean colchicine dose, and HLA-B27 positivity.

Correlation of C-reactive Protein and Serum Amyloid A

The Spearman's correlation test revealed a strong positive correlation (correlation coefficient: 0.70) between the median levels of CRP and SAA levels without attacks, with a significance level of p<0.001.

Discussion

Our research categorized patients based on the presence and quantity of variants in exon 10. The identified exon 10 variants among our patients included M694V, M694I, M680I, V726A, R761H, A744S, and K695R. The variants M680I, M694V, M694I, K695R, V726A, and A744S, which are situated within the B30.2 domain of the pyrin protein, are associated with the most prevalent and severe manifestations of FMF.[13] In the investigation conducted by Van Gorp et al.[14], a functional assay was established, revealing that the

Table 3. Evaluation of the attack free CRP and SAA according to treatment groups of the patients

	Group A- Only colchicine n=155	Group B- Colchicine+anti interleukin-1 n=17	p-value
	Mean ± SD Median (Q1-Q3)	Mean ± SD Median (Q1-Q3)	
Mean and median attack free CRP (mg/L)	4.65±7.33 2.1 (0.76-4.98)	10.09±10.14 7.15 (2.44-13.5)	**0.004**
Mean and median attack free SAA (mg/L)	16.4±34.1 6.4 (3.3-15.9)	55.4±89.7 16.8 (6.1-79.5)	**0.03**

CRP: C-reactive protein, SAA: Serum amyloid A, SD: Standard deviation, first and third quartile, Mann-Whitney U test

R761H variant in exon 10 also contributes to pyrin activation independently of microtubule dynamics, akin to the disease-associated FMF variants M680I, M694V, and M694I. Nevertheless, this study indicated that the mechanism of pyrin inflammasome activation in patients carrying K695R alleles may differ from that observed in FMF patients with the classical exon 10 variants.

Research comparing phenotype-genotype correlations in children with FMF has shown that those with homozygous or compound heterozygous variants in the *MEFV* gene experienced an earlier onset of the disease, more frequent attack episodes, and a higher incidence of fever, serositis, arthritis, and erysipelas-like erythema.[15,16] Our study provided a unique classification of FMF patients based on the number of variants in exon 10 and examined the state of subclinical inflammation by assessing CRP and SAA levels during attack-free periods. Patients with two variants in exon 10 exhibited significantly elevated median levels of CRP and SAA compared to other variant categories. Consistent with our findings, Kelesoglu et al.[17] reported that CRP levels during attack-free periods were higher in homozygous M694V patients than in other groups, despite these patients generally having normal CRP levels. Additionally, a study indicated that individuals with homozygous or compound heterozygous exon 10 MEFV variants had increased SAA levels during attack-free periods.[5]

Effectively managing subclinical inflammation is a key goal in the treatment of FMF to avert complications such as AA amyloidosis. Nonetheless, a universally accepted definition of "subclinical inflammation" in FMF patients is lacking. In this study, we examined the levels of CRP and SAA in FMF patients during periods free from attacks, and based on existing literature,[6] we proposed a definition for subclinical inflammation. Our findings indicated a significant difference in the prevalence of subclinical inflammation among the three variant groups. Specifically, as per our proposed definition, patients with two variants in exon 10 exhibited notably higher rates of subclinical inflammation compared to those with a single variant.

This study primarily examines variants in exon 10; however, subgroup analyses were conducted to assess the potential impact of non-exon 10 variants on baseline inflammation in FMF patients. The findings indicated no statistically significant difference in the levels of attack-free acute phase reactants and the presence of subclinical inflammation between patients with one exon 10 variant and a non-exon 10 variant, compared to those with only one exon 10 variant. Additionally, subgroup analysis of Group 3 did not reveal significant differences in attack-free CRP, attack-free SAA levels, or subclinical inflammation among patients with one, two, or three non-exon 10 variants. Consequently, non-exon 10 variants do not appear to significantly influence baseline inflammatory markers in FMF patients. This aligns with existing literature, suggesting that individuals with non-exon 10 variants exhibit a "milder" phenotype, characterized by reduced disease severity, fewer joint symptoms, a lower requirement for biologic treatments, and greater responsiveness to colchicine, in contrast to patients with the homozygous M694V variant.[18,19]

The analysis of the correlation between subclinical inflammation and the quantity of specific alleles, as well as the counts of "pathogenic variants", "likely pathogenic variants", and "variants of uncertain significance", revealed a statistically significant association between subclinical inflammation and both the number of "pathogenic variants" and the count of V726A alleles. While the link between pathogenic variants and subclinical inflammation is expected, the notable association between V726A alleles and subclinical inflammation is particularly intriguing. The research conducted by Lofty et al.[20] indicated that children with FMF who possessed the V726A allele experienced a higher frequency of attack-free SAA, which corroborates our findings.

AA amyloidosis, recognized as the most serious complication of FMF, was found to be more prevalent in patients carrying two variants in exon 10. This increase was associated with heightened levels of subclinical inflammation within this patient cohort. Additional research has shown that individuals with homozygous M694V variants also exhibited elevated rates of subclinical inflammation and AA amyloidosis, corroborating the findings of our study.[21,22]

Our research also categorized FMF patients based on their treatment approaches. Those who were treated with both interleukin-1 inhibitors and colchicine (Group B) exhibited significantly higher median values of attack-free CRP and SAA, compared to those who received only colchicine (Group A). This observation may be attributed to the more severe phenotype of FMF in these patients, as they were prescribed interleukin-1 inhibitors due to an insufficient response to colchicine. Nevertheless, no significant difference was observed between the two treatment groups regarding the presence of subclinical inflammation. The relatively small sample size in Group B (only 17 patients) may have hindered the ability to achieve statistical significance. Consequently, future research involving a larger cohort may enhance our understanding of subclinical inflammation among patients receiving different treatment regimens.

Patients treated with interleukin-1 inhibitors alongside colchicine also exhibited lower median albumin levels,

increased median proteinuria, and a higher incidence of AA amyloidosis and end-stage renal disease. Although they are receiving a more potent treatment, subclinical inflammation remains inadequately managed in this group, potentially leading to the development of AA amyloidosis. This situation indicates a greater inflammatory burden among these patients. While some studies have indicated that both anakinra and canakinumab can effectively manage subclinical inflammation,[23] our findings did not support this outcome. A Phase III trial of canakinumab in FMF also demonstrated that even though the CRP of patients remained below 10 mg/L under canakinumab treatment, SAA levels remained above 10 mg/L.[11] Despite significant clinical improvements and partial management of subclinical inflammation in these severe FMF patients receiving a combination of interleukin-1 inhibitors and colchicine, there remains a critical need for more effective strategies to control subclinical inflammation and further mitigate the risk of AA amyloidosis.

In order to better comprehend the factors associated with the presence of subclinical inflammation, we performed univariate binary logistic regression analysis for certain demographic, laboratory, and treatment parameters. In our analysis, none of the parameters (age, sex, number of exon 10 variants, number of non-exon 10 variants, mean colchicine dose, and HLA B27 positivity) were associated with the presence of subclinical inflammation. Due to the incompleteness of our retrospective data, we were unable to incorporate different clinical features (such as presence and frequency of pleuritis, peritonitis, arthritis, erysipelas-like erythema, smoking status, body mass index) into our analysis. Our cohort had a relatively high percentage of patients with subclinical inflammation (36%). In a similar study, Babaoglu et al.[24] detected a lower percentage of subclinical inflammation (15%) among their 917 FMF patients. Their analysis demonstrated that male sex, history of exertional leg pain, inflammatory comorbidities, M694V homozygosity, colchicine resistance, lower education levels, and musculoskeletal attack dominance were the independent predictors of persistent inflammation.

Evidence for the superiority of monitoring FMF with one acute phase reactant over another is scarce.[25] Nonetheless, several earlier studies have indicated that SAA levels might be a more sensitive indicator of subclinical inflammation compared to CRP levels.[26,27] Our findings revealed a significant correlation between CRP and SAA. Consequently, we propose that in healthcare environments where SAA is not accessible, CRP can be utilized independently to identify subclinical inflammation, as long as taking thorough histories and performing detailed physical examinations exclude the possibility of an FMF attack or infection.

Study Limitations

The retrospective design of the study, along with the absence of data regarding the frequency of FMF attacks within a specified timeframe, the lack of information about the number of patients with and the frequency of serositis, musculoskeletal symptoms, or presence of family history of FMF are notable limitations of the study.

During the study's design phase, we chose not to include the number of attacks, as we believed that this information was not consistently documented in the patients' medical records. Additionally, the patients themselves reported the attacks, which raises the possibility of incorrectly identifying symptoms related to other conditions as FMF attacks. Furthermore, patients did not always seek medical attention during these episodes, which would have allowed trained medical professionals to utilize patient history, physical examinations, and laboratory results to objectively confirm the attacks. Consequently, our findings should be approached with caution, as the variations observed in inflammatory markers may be influenced by the frequency of attacks rather than indicating genuine subclinical inflammation. Data concerning the number of patients with serositis and frequency of serositis and musculoskeletal symptoms, and number of patients with a positive family history were unfortunately incomplete for most of our patients. Therefore, these parameters were not reported. Long-term prospective studies, performed in a larger number of patients, which report more optimally on the clinical features relevant to this topic, are necessary to address the limitations identified in this study.

Conclusion

In summary, this research highlights the elevated levels of attack-free CRP and SAA, increased instances of subclinical inflammation, and a greater prevalence of amyloidosis among patients who are either homozygous or compound heterozygous for variants in exon 10. Furthermore, it reveals that in individuals with a significant inflammatory burden necessitating the use of interleukin-1 inhibitors, subclinical inflammation may remain insufficiently controlled. There is a strong correlation between attack-free CRP and SAA levels and in situations where SAA testing is not available, CRP can be effectively utilized to evaluate subclinical inflammation.

Ethics

Ethics Committee Approval: This research was granted approval by the Non-Interventional Clinical Research Ethics Committee of Prof.Dr. Cemil Taşcıoğu City Hospital, University of Health Sciences, Türkiye, with the decision number 230, dated 22.10.2024.

Informed Consent: Informed consent was acquired from the patients involved.

Footnotes

Authorship Contributions

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

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

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

References

1. Yaşar Bilge Ş, Sarı İ, Solmaz D, et al. The distribution of MEFV mutations in Turkish FMF patients: multicenter study representing results of Anatolia. Turk J Med Sci 2019;49:472-7.
2. Chirita D, Bronnec P, Magnotti F, et al. Mutations in the B30.2 and the central helical scaffold domains of pyrin differentially affect inflammasome activation. Cell Death Dis. 2023;14:213.
3. Jamilloux Y, Lefeuvre L, Magnotti F, et al. Familial Mediterranean fever mutations are hypermorphic mutations that specifically decrease the activation threshold of the Pyrin inflammasome. Rheumatology (Oxford). 2018;57:100-11.
4. Yalçinkaya F, Cakar N, Acar B, et al. The value of the levels of acute phase reactants for the prediction of familial Mediterranean fever associated amyloidosis: a case control study. Rheumatol Int. 2007;27:517-22.
5. Duzova A, Bakkaloglu A, Besbas N, et al. Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. Clin Exp Rheumatol. 2003;21:509-14.
6. Ben-Zvi I, Livneh A. Chronic inflammation in FMF: markers, risk factors, outcomes and therapy. Nat Rev Rheumatol. 2011;7:105-12.
7. Kukuy OL, Beckerman P, Dinour D, Ben-Zvi I, Livneh A. Amyloid storm: acute kidney injury and massive proteinuria, rapidly progressing to end-stage kidney disease in AA amyloidosis of familial Mediterranean fever. Rheumatology (Oxford). 2021;60:3235-42.
8. Maggio MC, Corsello G. FMF is not always "fever": from clinical presentation to "treat to target". Ital J Pediatr. 2020;46:7.
9. Tufan A, Lachmann HJ. Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review. Turk J Med Sci. 2020;50:1591-610.
10. Atalar E, Doğan İ, Gök K, et al. The effectiveness of anti-interleukin-1 therapy on subclinical inflammation parameters during the attack-free period in familial Mediterranean fever patients: a case-control study. Turk J Med Sci. 2022;52:522-3.
11. Ozen S, Ben-Cherit E, Foeldvari I, et al Long-term efficacy and safety of canakinumab in patients with colchicine-resistant familial Mediterranean fever: results from the randomised phase III CLUSTER trial. Ann Rheum Dis. 2020;79:1362-9.
12. Kisaoglu H, Baba O, Kalyoncu M. Genotype-Phenotype associations of children with familial Mediterranean fever in a cohort consisting of M694V mutation and implications for colchicine-resistant disease. J Clin Rheumatol. 2023;29:207-13.
13. Arakelov G, Arakelov V, Nazaryan K. Complex formation dynamics of native and mutated pyrin's B30.2 domain with caspase-1. Proteins. 2018;86:676-83.
14. Van Gorp H, Huang L, Saavedra P, et al. Blood-based test for diagnosis and functional subtyping of familial Mediterranean fever. Ann Rheum Dis. 2020;79:960-8.
15. Öztürk K, Coşkuner T, Baglan E, et al. Real-life data from the largest pediatric familial Mediterranean fever cohort. Front Pediatr. 2022;9:805919.
16. Inal A, Yilmaz M, Kendirli SG, Altintas DU, Karakoc GB. The clinical and genetical features of 124 children with familial Mediterranean fever: experience of a single tertiary center. Rheumatol Int. 2009;29:1279-85.
17. Kelesoglu FM, Aygun E, Okumus NK, et al. Evaluation of subclinical inflammation in familial Mediterranean fever patients: relations with mutation types and attack status: a retrospective study. Clin Rheumatol. 2016;35:2757-63.
18. Adıgüzel Dundar H, Türkuçar S, Açarı C, Altuğ Gücenmez Ö, Makay B, Ünsal E. Is there any difference between M694V heterozygote and non-exon 10 mutations on symptoms onset and response to colchicine treatment? Pam Med J 2024;17:550-9.
19. Touitou I. The spectrum of familial Mediterranean fever (FMF) mutations. Eur J Hum Genet. 2001;9:473-83.
20. Lofty HM, Marzouk H, Farag Y, et al. Serum amyloid A level in Egyptian children with familial Mediterranean fever. Int J Rheumatol. 2016;2016:7354018.
21. Duşunsel R, Dursun I, Gündüz Z, Poyrazoğlu MH, Gürgöze MK, Dundar M. Genotype-phenotype correlation in children with familial Mediterranean fever in a Turkish population. Pediatr Int. 2008;50:208-12.
22. Kisla Ekinci RM, Balci S, Dogruel D, Altintas DU, Yilmaz M. Twenty-year experience of a single referral center on pediatric familial Mediterranean fever: what has changed over the last decade? J Clin Rheumatol. 2021;27:18-24.
23. Ugurlu S, Ergezen B, Egeli BH, Selvi O, Ozdogan H. Anakinra treatment in patients with familial Mediterranean fever: a single-centre experience. Rheumatology (Oxford). 2021;60(5):2327-32.
24. Babaoglu H, Armagan B, Bodakci E, et al. Predictors of persistent inflammation in familial Mediterranean fever and association with damage. Rheumatology (Oxford). 2021;60:333-9.
25. Kavrul Kayaalp G, Sozeri B, Sönmez HE, et al; PeRA-Research Group. Adherence to best practice consensus guidelines for familial Mediterranean fever: a modified Delphi study among paediatric rheumatologists in Turkey. Rheumatol Int. 2022;42:87-94.
26. Siligato R, Gembillo G, Calabrese V, Conti G, Santoro D. Amyloidosis and glomerular diseases in familial Mediterranean fever. Medicina (Kaunas). 2021;57:1049.
27. Çakan M, Karadağ ŞG, Tanatar A, Sönmez HE, Ayaz NA. The value of serum amyloid A levels in familial Mediterranean fever to identify occult inflammation during asymptomatic periods. J Clin Rheumatol. 2021;27:1-4.

Supplementary Table 1. Relationship of presence of subclinical inflammation and the number of specific alleles and the number of "pathogenic variants", "likely pathogenic variants" and "variants of uncertain significance"

	Subclinical inflammation		
	Present n=62	Absent n=110	
Number of M694V alleles	**n (%)**	**n (%)**	**p-value**
0	20 (32.3)	50 (45.5)	0.11
1	23 (37.1)	40 (36.4)	
2	19 (30.6)	20 (18.2)	
Number of V726A alleles			
0	51 (82.3)	88 (80)	**0.03**
1	8 (12.9)	22 (20)	
2	3 (4.8)	0 (0)	
Number of M694I alleles			
0	61 (98.4)	106 (96.4)	0.12
1	0 (0)	4 (3.6)	
2	1 (1.6)	0 (0)	
Number of M680I alleles			
0	54 (87.1)	92 (83.6)	0.49
1	8 (12.9)	15 (13.6)	
2	0 (0)	3 (2.7)	
Number of R761H alleles			
0	58 (93.5)	103 (93.6)	0.38
1	3 (4.8)	7 (6.4)	
2	1 (1.6)	0 (0)	
Number of A744S alleles			
0	60 (96.8)	109 (99.1)	0.30
1	2 (3.2)	1 (0.9)	
Number of K695R Alleles			
0	61 (98.4)	109 (99.1)	0.99
1	1 (1.6)	1 (0.9)	
Number of E148Q alleles			
0	53 (85.5)	91 (82.7)	0.71
1	9 (14.5)	17 (15.5)	
2	0 (0)	2 (1.8)	
Number of F479L alleles			
0	61 (98.4)	110 (100)	0.36
1	1 (1.6)	0 (0)	
Number of T309M alleles			
0	62 (100)	108 (98.2)	0.41
1	0 (0)	2 (1.8)	
Number of P369S alleles			
0	60 (96.8)	108 (98.2)	0.46
1	2 (3.2)	2 (1.8)	
Number of R408Q alleles			
0	61 (98.4)	108 (98.2)	0.99
1	1 (1.6)	2 (1.8)	
Number of T267I alleles			
0	62 (100)	109 (99.1)	0.99
1	0 (0)	1 (0.9)	
Number of pathogenic variants			
0	9 (14.5)	19 (17.3)	**0.03**
1	20 (32.2)	55 (50)	

2	33 (53.2)	36 (32.7)	
Number of likely pathogenic variants			
0	57 (91.9)	102 (92.7)	0.14
1	3 (4.8)	8 (7.3)	
2	2 (3.2)	0 (0)	
Number of variants of uncertain significance			
0	50 (80.6)	88 (80)	0.85
1	10 (16.1)	16 (14.5)	
2	1 (1.6)	5 (4.5)	
3	1 (1.6)	1 (0.9)	

Supplementary Table 2. Evaluation of the renal parameters, AA amyloidosis and end stage renal disease according to ***MEFV*** gene variant groups of the patients

	Group 1-two exon 10 variants n=76	Group 2-one exon 10 variant n=79	Group 3-no exon 10 variants n=17	p-value*	p-value**
	Mean ± SD Median (Q1-Q3)	Mean ± SD Median (Q1-Q3)	Mean ± SD Median (Q1-Q3)		1 vs. 2 1 vs. 3 2 vs. 3
Mean and median serum creatinine (mg/dL)	0.88±0.82 0.7 (0.62-0.84)	0.70±0.14 0.67 (0.61-0.78)	0.68±1.13 0.68 (0.61-0.75)	0.57	-
Mean and median estimated glomerular filtration rate (mL/min)	86.4±13.5 90 (90-90)	88.9±2.9 90 (90-90)	89.7±1.4 90 (90-90)	0.38	-
Mean and median serum albumin (g/dL)	4.51±0.42 4.5 (4.4-4.7)	4.53±0.34 4.5 (4.3-4.78)	4.49±0.29 4.5 (4.25-4.65)	0.87	-
Mean and median proteinuria (mg/day)	309.39±480.01 104 (70.25-181.5)	142.82±223.38 94 (70-125)	112.26±64.25 100 (65-139)	0.59	-
AA amyloidosis absent	69 (90.8)	79 (100)	17 (100)	**0.02**	
AA amyloidosis present	7 (9.2)	0 (0)	0 (0)		
End stage renal disease absent	74 (97.4)	79 (100)	17 (100)	0.38	
End stage renal disease present	2 (2.6)	0 (0)	0 (0)		

*AA: Amyloid A, SD: Standard deviation, Q1-Q3: First and third quartile *Kruskal-Wallis H test, **Post-hoc Tukey test, 1: Two exon 10 variants, 2: One exon 10 variant, 3: No exon 10 variants*

Supplementary Table 3. Evaluation of the renal parameters, AA amyloidosis and end stage renal disease according to treatment groups of the patients

	Group A-only colchicine n=155	Group B-colchicine+anti interleukin-1 n=17	p-value
	Mean ± SD Median (Q1-Q3)	Mean ± SD Median (Q1-Q3)	
Mean and median serum creatinine (mg/dL)	0.71±0.14 0.69 (0.62-0.77)	0.94±0.71 0.65 (0.59-0.85)	0.87
Mean and median estimated glomerular filtration rate (mL/min)	89±2.48 90 (90-90)	74.43±23.75 90 (85.7-90)	0.10
Mean and median serum albumin (g/dL)	4.54±0.35 4.5 (4.35-4.70)	4.29±0.49 4.4 (4.08-4.62)	**0.04**
Mean and median proteinuria (mg/day)	155.83±341.77 93 (67-129)	822.64±1665.81 184 (147.5-533.75)	**<0.001**
AA amylodosis absent	153 (98.7)	12 (70.6)	**<0.001**
AA amyloidosis present	2 (1.3)	5 (29.4)	
End stage renal disease absent	155 (100)	15 (88.2)	**0.009**
End stage renal disease present	0 (0)	2 (11.8)	

AA: Amyloid A, SD: Standard deviation, Q1-Q3: First and third quartile, Mann-Whitney U test

Supplementary Table 4. Assessment of presence of subclinical inflammation according to different risk factors

	Odds ratio	%95 CI	p-value
Age	0.99	0.97-1.02	0.61
Sex	1.31	0.67-2.5	0.44
Number of exon 10 variants	0.77	0.40-1.47	0.43
Number of non-exon 10 variants	0.41	0.04-4.01	0.44
Mean colchicine dose	1.04	0.39-2.81	0.94
HLA-B27	0.62	0.12-3.12	0.56

CI: Confidence interval, HLA: Human leukocyte antigen, univariate binary logistic regression

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.59672
Ulus Romatol Derg 2025;17(3):174-180

Validity and reliability of the Turkish version of the early psoriatic arthritis screening questionnaire in patients with psoriasis

Psoriazisli hastalarda erken psoriatik artrit tarama anketinin Türkçe geçerlik ve güvenirlik çalışması

Fikret Yaman[1], İrem Şahinoğlu[2], Özgül Soysal Gündüz[3], Aylin Turel Ermertcan[4], Beyhan Cengiz Özyurt[5]

[1]Celal Bayar University Faculty of Medicine, Department of Internal Medicine, Manisa, Türkiye
[2]Toros State Hospital, Clinic of Rheumatology, Mersin, Türkiye
[3]Celal Bayar University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Manisa, Türkiye
[4]Celal Bayar University Faculty of Medicine, Department of Dermatology, Manisa, Türkiye
[5]Celal Bayar University Faculty of Medicine, Department of Public Health, Manisa, Türkiye

Abstract

Objective: Early psoriatic arthritis screening (EARP) questionnaire is a simple, fast and useful tool to screen psoriatic arthritis among psoriasis patients. We aimed to evaluate the validity and reliability of the EARP questionnaire in Turkish patients with psoriasis.

Methods: One hundred nineteen psoriasis patients who had not previously been diagnosed with psoriatic arthritis and visited our dermatology clinic between February 2023 and November 2023 were completed the Turkish EARP questionnaire. Patients were evaluated for psoriatic arthritis by a rheumatologist who was blinded to the questionnaire results.

Results: Psoriatic arthritis was detected in 28 (23%) out of the 119 psoriasis patients participating in the study. The Cronbach's alpha value of the questions in the Turkish version of the EARP questionnaire was determined as 0.760, and the reliability and validity of all questions in the study were found to be appropriate for the Turkish population. In the receiver operating characteristic analysis, the area under the curve cut-off value was found to be 3.5. When the cut-off value was taken as ≥3.5, sensitivity and specificity were both 89%.

Conclusion: The Turkish version of EARP is a reliable and valid tool for screening psoriatic arthritis in Turkish patients with psoriasis in dermatology clinics.

Keywords: Early psoriatic arthritis screening questionnaire, psoriasis, psoriatic arthritis

Özet

Amaç: Erken psoriatik artrit tarama (EARP) anketi, psoriazis hastalarında psoriatik artriti taramak için geliştirilmiş basit, hızlı ve kullanışlı bir araçtır. Bu çalışmada EARP anketinin Türk psoriazis hastalarında geçerliğini ve güvenirliğini değerlendirmeyi amaçladık.

Yöntem: Daha önce psoriatik artrit tanısı almamış ve Şubat 2023 ile Kasım 2023 arasında dermatoloji kliniğimize başvuran 119 psoriazis hastasına Türkçe EARP anketi uygulandı. Anket sonuçlarını bilmeyen ve alanında uzman olan bir romatolog tarafından hastalar psoriatik artrit açısından değerlendirdi.

Bulgular: Çalışmaya katılan 119 psoriazis hastasının 28'inde (%23) psoriatik artrit tespit edildi. EARP anketinin Türkçe versiyonundaki soruların Cronbach's alpha değeri 0,760 olarak belirlendi ve çalışmadaki tüm soruların güvenirliği ve geçerliği Türk popülasyonu için uygun bulundu. Alıcı işletim karakteristiği analizinde eğri altında kalan alan kesme değeri 3,5 olarak bulundu. Kesme değeri ≥3,5 olarak alındığında duyarlılık %89, özgüllük ise %89 olarak bulundu.

Sonuç: EARP Türkçe versiyonu, dermatoloji kliniğiklerinde psoriazisli Türk hastalarda psoriatik artrit taranması için güvenilir ve geçerli bir araçtır.

Anahtar Kelimeler: Erken psoriatik artrit tarama anketi, psoriazis, psoriatik artrit

Correspondence / İletişim:
Fikret Yaman MD, Celal Bayar University Faculty of Medicine, Department of Internal Medicine, Manisa, Türkiye
E-mail: fikretyamann@gmail.com **ORCID ID:** orcid.org/0009-0006-2051-8861
Received / Geliş Tarihi: 25.04.2025 **Accepted / Kabul Tarihi:** 03.09.2025 **Epub:** 27.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Yaman F, Şahinoğlu İ, Soysal Gündüz Ö, Turel Ermertcan A, Cengiz Özyurt B. Validity and reliability of the Turkish version of the early psoriatic arthritis screening questionnaire in patients with psoriasis. Ulus Romatol Derg. 2025;17(3):174-180

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis that is mostly seronegative and associated with psoriasis.[1] Asymmetric joint involvement, dactylitis, enthesopathy, spinal involvement, and human leukocyte antigen-B27 positivity in some patients, are helpful in diagnosing PsA. Among patients with psoriasis 6-42% were diagnosed as PsA.[1,2] During follow-up, it has been observed that in most patients, skin involvement begins years before joint involvement. In some patients, joint and skin involvement may occur simultaneously. In approximately 15-20% of patients, joint involvement may develop before skin symptoms appear.[3]

PsA diagnosis should be considered if joint symptoms occur in patients with psoriasis. If PsA diagnosis is delayed, the disease may progress more rapidly, leading to serious irreversible joint erosions and joint deformities. Early diagnosis and therapy are therefore crucial in the clinical approach.[4]

Studies indicate that undiagnosed PsA may affect as many as 15.5% of psoriasis patients.[5] Dermatologists play an important role in detecting psoriasis early, since they generally see patients with the skin disease before arthritis develops. For the purpose of early diagnosis and follow-up, a number of screening strategies have been created and validated in several independent populations in psoriasis patients. Some of these are simple PsA screening questionnaire,[6] the psoriasis epidemiology screening tool (PEST),[7] the Toronto PsA screen (ToPAS),[8] the ToPAS version 2,[9] the PsA screening and evaluation (PASE),[10] and the center of excellence for psoriasis and PsA.[11]

These methods were not developed to identify PsA in its early phases, and they have not proved effective for patient self-reporting. Tinazzi et al.[12] developed the early PsA screening (EARP) questionnaire, which was easy and quick to use, and had high sensitivity (85.2%) and specificity (91.6%).

The purpose of this research was to determine whether the Turkish version of the EARP questionnaire can reliably identify early-stage PsA in psoriasis patients being followed in dermatology clinics.

Materials and Methods

Study Population

This prospective study included psoriasis patients over the age of 18 who were able to read and understand Turkish, and who applied to Celal Bayar University Faculty of Medicine Dermatology Clinic between February 2023 and November 2023. The study cohort comprised 119 patients with a dermatologist-confirmed diagnosis of psoriasis, none of whom had a prior diagnosis of PsA. Patients who received immunosuppressive treatment within the last 6 months or were receiving systemic treatment for psoriasis, had another inflammatory rheumatic disease, or who were unable to read or comprehend Turkish were not included. Psoriasis patients who presented to the dermatology clinic and met the eligibility criteria for the study were administered the EARP-Turkish questionnaire. The patients completed the EARP questionnaire consisting of 10 items by reading and answering it independently of the physician, and then, their dermatological examinations were performed by the dermatologist. The patients' the psoriasis activity index (PASI) was calculated. Age, sex, educational status, duration of psoriasis, nail involvement, PASI score, treatment, smoking, inflammatory low back pain, peripheral arthritis, enthesitis, dactylitis, family history, and body mass index (BMI) were among the clinical and demographic information that was documented. Following completion of the questionnaire, the patients were referred to the Rheumatology Clinic at Celal Bayar University Faculty of Medicine for a PsA evaluation. The patients were then assesed by a rheumatologist who was blind to EARP results, performing a detailed history and musculoskeletal examination. Patients were evaluated for PsA using CASPAR classification criteria. This classification, improved in 2006, has a sensitivity of 95% and a specificity of 98%, and is the most widely used classification for diagnosing PsA worldwide.[13] Patients diagnosed with PsA were recorded. This prospective study was approved by Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (dated: 08/03/2023, numbered: 20.478.486/1730). The sample size in the study was found to be 90 using the G*Power 3.1 program, taking type I error as 0.05, effect size as 0.3, and power as 80%.

Questionnaire

Permission to use the scale and to conduct a reliability and validity study of the Turkish version was obtained from Dr. Tinazzi, who developed the original scale. The translation was subsequently performed. The translation process was carried out in accordance with the principles of the phases of intercultural adaptation.[14]

The English version of the EARP was translated into Turkish by two independent professional bilingual translators, both fluent in English and native speakers of Turkish. After completion, these translations were compared. Following a discussion on the differences between the independent translations, the final translation was decided. Two independent native English speakers, blind to the

original scale, translated this final Turkish version back into English to highlight the differences between the original and translated versions. Subsequently, a comparison between the backward translation and the original scale was conducted. There were no noticeable differences. The Turkish version of the questionnaire was created through the forward and backward translation stages performed by EARP. A pilot sample of ten patients over the age of eighteen, who could read and understand Turkish and who had a dermatologist's confirmed diagnosis of psoriasis, was given the final Turkish version of EARP to see whether they had any concerns about its meaning.

The EARP questionnaire comprises 10 items and was developed by combining typical symptoms and findings observed in patients with PsA. Its evaluation has been performed by calculating the total score based on patients' yes/no responses to each item.

Statystical Analysis

Statistical evaluation of all results was done using SPSS (Statistical Package for the Social Sciences) 21. Descriptive statistics for continuous data were created, which included average, standard deviation, median, minimum, and maximum values. For percentage values were provided discrete data. The chi-square test, Mann-Whitney U test, Kruskal-Wallis test, and Fisher's exact test were used in univariate analyses. Cronbach's alpha value was calculated for the internal reliability of the test questions. To find the cut-off value, a receiver operating characteristic (ROC) analysis was performed. In all analyses, the accepted type 1 error value was as $p<0.05$.

Results

The study population consisted of 119 patients. The study population included 73 females (61.3%) and 46 males (38.7%). The ages of the patients ranged between 18 and 84 years, with mean ages of 40.38±14.73 years for women and 43.82±15.97 years for men. PsA was detected in 28 (23%) of the 119 psoriasis patients participating in the study.

When the relationship between family history, age, education status, non-steroidal anti-inflammatory drug use, smoking status, PASI score and PsA was examined, no statistically significant result was obtained. When the relationship between female gender, topical steroid use, BMI, duration of psoriasis, low back pain, hip pain, peripheral arthritis, enthesitis, dactylitis, nail involvement, and PsA was examined, a statistically significant result was detected (Table 1).

The rates of yes responses to the EARP questions of patients with and without PsA were recorded. A statistically higher frequency of "yes" responses to all questions was observed in the PsA patient group ($p<0.05$) (Table 2). The EARP total score was significantly higher in patients with PsA compared to those without PsA ($p<0.05$). While the median score was 5 (minimum 3 - maximum 10) in patients with PsA, the median score was 1 (minimum 0 - maximum 6) in patients without PsA. The sensitivity, specificity, positive predictive value, negative predictive value, and test validity of the EARP questions are given in the table (Table 3). The Cronbach's alpha value of the questions in the Turkish validation study of the EARP questionnaire was determined to be 0.760, and the reliability and validity of all questions

Table 1. Clinical characteristics and demographics of psoriasis patients

		PsA	Non- PsA	p-value
Number		28	91	
Sex, n (%)	Female	24 (32.9%)	49 (67.1%)	**0.002**
	Male	4 (8.7%)	42 (91.3%)	
Age, years (mean ± SDS)		39.8±10.8	42.3±16.4	0.368
Family history of psoriasis, n (%)	Has	12 (36.3%)	21 (63.7%)	0.11
	Does not have	14 (17.7%)	65 (82.3%)	
NSAID, n (%)		4 (57.1%)	3 (42.9%)	**0.05**
Topical steroid, n (%)		6 (13%)	40 (87%)	**0.042**
Smoker, n (%)	Smokers	8 (19.5%)	33 (80.5%)	0.328
	Non-smokers	20 (27.8%)	52 (72.2%)	
BMI, n (median; min-max)		25.9 (16-34)	24.2 (15.6-46.3)	**0.05**
Duration of psoriasis, months (median; min-max)		14.5 (3-240)	9 (1-360)	**0.004**
Low back pain	Has	18 (69.2)	8 (30.8)	**<0.001**
	Does not have	10 (10.9)	82 (89.1)	
Hip pain	Has	9 (81.8)	2 (18.2)	**<0.001**
	Does not have	19 (17.6)	89 (82.4)	
Periferic arthritis, n (%)	Has	22 (84.6%)	4 (15.4%)	**<0.001**
	Does not have	6 (6.5%)	87 (93.5%)	
Nail involvement, n (%)	Has	13 (52%)	12 (48%)	**<0.001**
	Does not have	14 (15.2%)	78 (84.4%)	
Enthesitis	Has	8 (100)	0 (0)	**<0.001**
	Does not have	20 (18.0)	91 (82)	
Dactylitis	Has	7 (100)	0 (0)	**<0.001**
	Does not have	21 (18.8)	91 (81.3)	
PASI score, n (median; min-max)		5.3 (0.3-17)	8 (0-37.4)	0.436

BMI: Body mass index, max: Maximum, min: Minimum, NSAID: Non-steroidal antiinflammatory drug, PASI: Psoriasis activity index, PsA: Psoriatic arthritis, SDS: Standard deviation score

in the study were found to be appropriate for the Turkish population (Supplementary Table 1). The total value of the questions was calculated, and result was obtained. The ROC analysis showed a cut-off value of 3.5 for the detection of PsA by using EARP questionnaire. The area under the curve value was determined as 0.963, p<0.001. Sensitivity was found to be 0.89, and specificity was found to be 0.89 (Figure 1).

Among patients with a cut-off value below 3.5, 3 (10.7%) were diagnosed with PsA, while 81 (89.3%) were without PsA. Among patients with a cut-off value ≥3.5, 25 (89.3%) were diagnosed with PsA, while 10 (11%) were not diagnosed as PsA (Table 4).

Table 2. Percentage of patients with and without PsA responding yes to EARP questions

EARP "YES"	PsA (n=28) n (%)	No PsA (n=91) n (%)	p-value
EARP 1	28 (100)	50 (54.9)	<0.01
EARP 2	22 (78.6)	7 (7.8)	<0.01
EARP 3	8 (28.6)	5 (5.5)	0.02
EARP 4	13 (46.4)	2 (2.2)	<0.01
EARP 5	21 (75)	29 (31.9)	<0.01
EARP 6	13 (46.4)	5 (5.5)	<0.01
EARP 7	5 (17.9)	0 (0)	<0.01
EARP 8	5 (17.9)	1 (1.1)	0.03
EARP 9	21 (75)	25 (27.5)	<0.01
EARP 10	13 (46.4)	11 (12.1)	<0.01

EARP: Early psoriatic arthritis screening questionnaire, PsA: Psoriatic arthritis

Table 3. Sensitivity, specificity, negative predictive value, positive predictive value, and test validity of the EARP questionnaire

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Test validity (%)
EARP 1	100	45.1	35.9	100	58
EARP 2	78.6	92.2	75.9	93.3	88.2
EARP 3	28.6	94.5	61.5	81.1	79
EARP 4	46.4	97.8	86.7	85.6	85.7
EARP 5	75	68.1	42	89.9	69.7
EARP 6	46.4	94.5	72.2	85.1	81.5
EARP 7	17.9	100	100	79.8	80.7
EARP 8	17.9	98.9	83.3	79.6	79.8
EARP 9	75	72.5	45.7	90.4	69.7
EARP 10	46.4	87.9	54.2	84.2	78.2

EARP: Early psoriatic arthritis screening questionnaire

Table 4. EARP questionnaire cut-off value

EARP cut-off	PsA n (%)	No PsA n (%)
<3.5	3 (10.7%)	81 (89%)
≥3.5	25 (89.3%)	10 (11%)
Total	28 (100%)	91 (100%)

EARP: Early psoriatic arthritis screening questionnaire, PsA: Psoriatic arthritis

Discussion

Early PsA detection may lead to early treatment, which is possible with the current medical treatments, to prevent or slow the progression of damage.[15] Consequently, early PsA detection is crucial.

In this study, we evaluated the validity and reliability of the EARP questionnaire in Turkish patients with psoriasis. The findings of this study demonstrate that the Turkish version of the EARP is capable of distinguishing patients with PsA from those without arthritis with high sensitivity and specificity.

In this study, the prevalence of PsA was 23%, compared to 26.7% in the original study.[12] Previous studies have reported that the prevalence of PsA among patients with psoriasis ranges from 6% to 42%.[16] In this respect, our results are consistent with the literature.

In our study, when the cut-off value was taken as ≥3.5, sensitivity was 89% and specificity was 89%. The sensitivity of the Turkish version of the EARP is slightly less (89% vs. 91.6%, respectively) than the original questionnaire,[12] but its specificity is greater (89% vs. 85.2%, respectively).

The total Cronbach's alpha value, calculated for all questions, was found to be 0.760. These results show that the EARP questionnaire is applicable and reliable within Turkish society in the early diagnosis of PsA.

In patients with a cut-off value of ≥3.5, 11% were found to be false positive and with a cut-off value of <3.5, 10.7% (n=3) were found to be false negative. The false positive rate

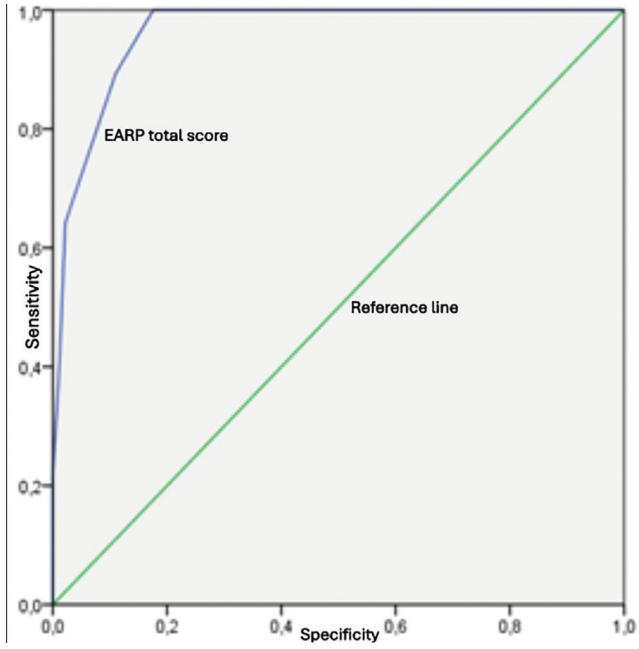

Figure 1. Receiver operating characteristic of the early psoriatic arthritis screening (EARP) items. The area under the curve of EARP is 0.963
EARP: Early psoriatic arthritis screening questionnaire

was lower than in the original study (11% vs. 22.3%) and the false negative rate was higher than in the original study (10.7% vs. 3.5%), respectively.[12]

In previous studies, the cut-off value was found to be 3 in EARP questionnaire ROC analyses.[12,17-19] In our study, this cut-off value was determined as 3.5. When looking at the EARP questionnaire, which is answered in a yes/no format, yes should receive one point, while no should receive 0 points. Since the result will be evaluated on a patient basis, we recommend that patients scoring 3 points or more be referred to a rheumatologist. The rate of positive responses to all ten items was higher in patients with PsA. This difference was found to be statistically significant ($p<0.05$).

The total EARP score was found to be significantly higher in patients with PsA than in patients without PsA. All patients answered all items of the EARP questionnaire, and no multiple responses were given to any item, indicating that the items were well-understood by the patients.

According to a study comparing four questionnaires (ToPAS II, PASE, PEST, and EARP) for the early identification of PsA, EARP had the best sensitivity (91%) and the strongest specificity (88%).[20] Additionally, the EARP questionnaire demonstrated robust features after being translated and tested in other languages and populations.[18,19,21,22]

In their 2016 Japanese EARP validation study, Maejimaet al.[19] conducted a total of 90 psoriasis patients, 19 PsA patients and 71 psoriasis patients with no joint involvement, who performed the Japanese EARP questionnaire. ROC analysis was used to assess the diagnostic performance of the Japanese EARP questionnaire for the determination of PsA and early-stage PsA. The cut-off threshold value was determined as 3. The sensitivity and specificity of the Japanese EARP version were greater than those of the Turkish version created for this study, at 97.2% and 97.2%, respectively. Their study indicated that the Japanese version of the EARP is effective in detecting PsA at its early stages. Furthermore, it was shown to be applicable for diagnosing both early and advanced stages of PsA.[21]

In 2016, Chiowchamwisawakit et al.[18] developed a Thai version of the questionnaire and administered it to 159 patients. The reported sensitivity and specificity were 83% and 79.3%, respectively, which were lower than those obtained with the Turkish version of the EARP questionnaire in the present study.

The observed differences in questionnaire performance may be attributable to variations in participant characteristics and ethnic factors. The study population's various PsA patterns may have an impact on the tools' performance. It seems that some tools work better in polyarticular patterns than in non-polyarticular ones.[23]

In 2023, Shirzadian Kebria et al.[17] evaluated 100 patients with psoriasis to assess the reliability of the Persian version of the questionnaire, reporting a Cronbach's alpha of 0.85. ROC analysis revealed a sensitivity of 90.48% and a specificity of 96.55%. Consistent with the original EARP questionnaire, a cut-off threshold of 3 was applied. The authors concluded that the Persian version of the EARP questionnaire is a reliable and appropriate screening tool for detecting PsA in dermatology clinics.

Lajevardi et al.[22] compared the PEST questionnaire and EARP questionnaire in their study of 75 psoriasis patients in 2020. The cut-off threshold value for both questionnaires was determined as 3. In Iranian psoriatic patients without a prior PSA diagnosis, both the EARP and PEST questionnaires performed well (specificity 78.6% and 96.4%, sensitivity 94.7% and 58%, respectively). Because EARP has a significantly greater sensitivity and acceptable specificity compared to PEST, they recommend it as a PsA screening tool in dermatological clinics.

In their study, Rodrigues et al.[24] linguistically and culturally adapted the EARP questionnaire for psoriatic patients to European Portuguese. They demonstrated that the items on the Portuguese-language EARP questionnaire are easy to understand and do not present comprehension issues. Although a validation study with Portuguese patients is required, the results address the use of this measure in clinical practice and future research.

Study Limitations

The present study has certain limitations, as it was conducted in a single-center setting. Since our hospital is the only tertiary care hospital in the city, we thought that the presence of more severe psoriasis cases and the long-term follow-up of these patients may have affected the EARP questionnaire results. However, the prevalence of patients diagnosed with PSA among psoriasis patients in our study was consistent with the literature. We also believe that with longer patient follow-up, new cases of PsA may emerge among those not initially diagnosed. A key strength of this study is that it included only patients without a prior PsA diagnosis. In contrast, previous studies that enrolled both diagnosed and undiagnosed PsA patients may have overestimated sensitivity due to recall bias in individuals with established PsA.[18,19] Additionally, each participant underwent PSA evaluations by a rheumatologist who was unaware of the questionnaire data.

Conclusion

This study demonstrates that the Turkish version of the EARP questionnaire is a suitable instrument for detecting early PsA in dermatology clinics, although multicenter studies are warranted to further validate its utility. To summarize, the Turkish version of the EARP questionnaire is a valid and reliable tool for identifying PsA, and its high sensitivity makes it a valuable aid for dermatologists in the diagnostic process.

Ethics

Ethics Committee Approval: This prospective study was approved by Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (dated: 08/03/2023, numbered: 20.478.486/1730).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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

References

1. Moll JMH, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3:55-78.
2. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73.
3. Gladman DD, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005;64(Suppl 2):ii14-7.
4. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74:1045-50.
5. Villani AP, Rouzaud M, Sevrain M, et al. Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: systematic review and meta-analysis. J Am Acad Dermatol. 2015;73:242-8.
6. Salaffi F, Di Carlo M, Bugatti L, Lato V, Nicolini M, Carotti M. Development and pilot-testing of a new tool to screen psoriasis patients for the presence of psoriatic arthritis: the simple psoriatic arthritis screening (SiPAS) questionnaire. J Eur Acad Dermatol Venereol. 2017;31:e167-9.
7. Ibrahım GH, Buch MH, Lawson C, Waxman R, Hellıwell PS: Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the psoriasis epidemiology screening tool (PEST) questionnaire. Clin Exp Rheum. 2009;27:469-74.
8. Gladman DD, Schentag CT, Tom BD, et al. Development and initial validation of a screening questionnaire for psoriatic arthritis: the Toronto psoriatic arthritis screen (ToPAS). Ann Rheum Dis. 2009;68:497-501.
9. Tom BD, Chandran V, Farewell VT, Rosen CF, Gladman DD: validation of the Toronto psoriatic arthritis screen version 2 (ToPAS 2). J Rheumatol. 2015;42:841-6.
10. Husni ME, Meyer KH, Cohen DS, Mody E, Qureshi AA. The PASE questionnaire: pilot-testing a psoriatic arthritis screening and evaluation tool. J Am Acad Dermatol. 2007;57:581-7.
11. Garg N, Truong B, Ku JH, et al. A novel, short, and simple screening questionnaire can suggest presence of psoriatic arthritis in psoriasis patients in a dermatology clinic. Clin Rheumatol. 2015;34:1745-51.
12. Tinazzi I, Adami S, Zanolin EM, et al. The early psoriatic arthritis screening questionnaire: a simple and fast method for the identification of arthritis in patients with psoriasis. Rheumatology (Oxford). 2012;51:2058-63.
13. Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis. 2005;64 (Suppl 2):ii3-8.
14. Wild D, Grove A, Martin M, et al; ISPOR Task Force for Translation and Cultural Adaptation. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation. Value Health. 2005;8:94-104.
15. Addimanda O, Possemato N, Caruso A, Pipitone N, Salvarani C. The role of tumor necrosis factor-α blockers in psoriatic disease. Therapeutic options in psoriatic arthritis. J Rheumatol Suppl. 2015;93:73-8.
16. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med. 2017;376:957-70.
17. Shirzadian Kebria A, Eftekhari A, Ezoji K, et al. Reliability and validity of the Persian version of psoriatic arthritis screening questionnaire. Caspian J Intern Med. 2023;14:213-7.
18. Chiowchanwisawakit P, Wattanamongkolsil L, Srinonprasert V, Petcharat C, Siriwanarangsun P, Katchamart W. Developing the thai siriraj psoriatic arthritis screening tool and validating the thai psoriasis epidemiology screening tool and the early arthritis for psoriatic patients questionnaire. Rheumatol Int. 2016;36:1459-68.
19. Maejima H, Katayama C, Taniguchi T, et al. Japanese version of the early psoriatic arthritis screening questionnaire (EARP). J Dermatol. 2016;43:385-8.
20. Mishra S, Kancharla H, Dogra S, Sharma A. Comparison of four validated psoriatic arthritis screening tools in diagnosing psoriatic arthritis in patients with psoriasis (COMPAQ Study). Br J Dermatol. 2017;176:765-70.
21. García-Gavín J, Pérez-Pérez L, Tinazzi I, Vidal D, McGonagle D. Spanish cultural adaptation of the questionnaire early arthritis for psoriatic patients. Actas Dermosifiliogr. 2017;108:924-30. English, Spanish.
22. Lajevardi V, Ghodsi SZ, Shafiei M, Teimourpour A, Etesami I. Evaluating the Persian versions of two psoriatic arthritis screening questionnaires early arthritis for psoriatic patients questionnaire

(EARP) and psoriasis epidemiology screening tool (PEST) in Iranian psoriatic patients. Turk J Med Sci. 2021;51:159-66.

23. Haroon M, Kirby B, FitzGerald O. High prevalence of psoriatic arthritis in patients with severe psoriasis with suboptimal performance of screening questionnaires. Ann Rheum Dis. 2013;72:736-40.

24. Rodrigues AM, Jacinto S, Henriques AR, et al. Linguistic and cultural adaptation of the EARP Questionnaire to European Portuguese. ARP Rheumatol. 2022;1:271-7. English.

Supplementary Table 1. Cronbach's alpha values of EARP questions

Question	Cronbach's alpha
1. Do your joints hurt?	0.740
2. Have you taken anti-inflammatory more than twice a week for joint pain in the last 3 months?	0.721
3. Do you wake up at night because of low back pain?	0.760
4. Do you feel stiffness in your hands for more than 30 min in the morning?	0.730
5. Do your wrists and fingers hurt?	0.732
6. Do your wrists and fingers swell?	0.723
7. Does one finger hurt and swell for more than 3 days?	0.747
8. Does your achilles tendon swell?	0.753
9. Do your feet or ankles hurt?	0.746
10. Do your elbow or hips hurt?	0.744

EARP: Early psoriatic arthritis screening questionnaire

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.70894
Ulus Romatol Derg 2025;17(3):181-187

Sleep quality and blood pressure variability after anti-TNF-α treatment in axial spondyloarthritis patients: A prospective preliminary study

Aksiyel spondiloartropati hastalarında anti-TNF-α tedavisi sonrası uyku kalitesi ve kan basıncı değişkenliği: Prospektif bir ön çalışma

Kenan Moral[1], Emre Bilgin[2], Ömer Karadağ[2], Ali Akdoğan[2], Şule Apraş Bilgen[2], Sedat Kiraz[2], İhsan Ertenli[2], Tolga Yıldırım[3], Levent Kılıç[2]

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

Abstract

Objective: Anti-tumor necrosis factor-α (TNF-α) agents are known to improve inflammation and may reduce cardiovascular risk in axial spondyloarthritis (axSpA). This study prospectively evaluated their effect on sleep quality and ambulatory blood pressure parameters.

Methods: Twenty-eight anti-TNF-α–naïve patients with axSpA (57% female) were enrolled. Clinical activity, sleep quality, and ambulatory blood pressure monitoring—including blood pressure average real variability (ARV) and dipping patterns—were recorded at baseline and after three months of therapy.

Results: Participants had a mean age of 40.0±10 years and a median disease duration of 6.5 years. Following treatment, both disease activity indices and sleep quality scores improved significantly. ARV did not change significantly. The proportion of patients with a dipper pattern rose from 46% to 61%, though this change was not statistically significant (p=0.388). Nighttime systolic blood pressure, however, decreased significantly (p=0.020).

Conclusion: Despite improvements in sleep quality, no impact was noted on ARV and dipper patterns. While anti-TNF-α therapy may enhance sleep quality, its long-term effects on cardiovascular morbidity require further validation through larger, long-term studies.

Keywords: Axial spondylitis, anti-TNF-α, ambulatory blood pressure, sleep quality

Özet

Amaç: Anti-tümör nekroz faktörü-α (TNF-α) tedavisi, aksiyel spondilitli (axSpA) hastalarda hastalık aktivitesini, uyku kalitesini ve kan basıncı parametrelerini iyileştirerek kardiyovasküler morbiditeyi azaltabilir. Bu prospektif çalışmada, axSpA hastalarında anti-TNF-α tedavisinin uyku kalitesi ve ambulatuvar kan basıncı izleme parametreleri üzerindeki etkisi araştırılmıştır.

Yöntem: Bu çalışmaya 28 (%57 kadın) anti-TNF-α naif axSpA hastası dahil edildi. Hastalık aktivitesi, uyku kalitesi, kan basıncı değişkenliği (ARV) ve dipper paternleri dahil olmak üzere ambulatuvar kan basıncı izleme parametreleri başlangıçta ve üç aylık anti-TNF-α tedavisinden sonra değerlendirildi.

Bulgular: Hastaların ortalama yaşı 40,0±10 yıl ve tanıdan sonraki ortanca hastalık süresi 6,5 (4-11) yıldı. Hastaların anti-TNF-α tedavi sonrası, hastalık aktivite skorları ve uyku kaliteler anlamlı olarak iyileşti. Ancak ARV'de anlamlı bir değişiklik görülmedi. Dipper paterni sergileyen hastaların yüzdesi %46'dan %61'e yükselmesine rağmen, bu değişiklik istatistiksel olarak anlamlı değildi (p=0,388). Bununla birlikte, gece sistolik kan basıncında da anlamlı bir düşüş gözlendi (p=0,020).

Sonuç: Anti-TNF-α tedavisi, axSpA hastalarında uyku kalitesini anlamlı düzeyde iyileştirmiştir. Ancak, kan basıncı değişkenliği ve dipper paternleri üzerinde anlamlı bir etkisi gözlenmemiştir. Anti-TNF-α tedavisinin kardiyovasküler morbidite üzerindeki etkilerini daha iyi değerlendirecek uzun süreli ve daha geniş kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Aksiyel spondilit, anti-TNF-α, ambulatuar kan basıncı, uyku kalitesi

Correspondence / İletişim:
Levent Kılıç Assoc. Prof., Hacettepe University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
E-mail: drleventkilic@yahoo.com **ORCID ID:** orcid.org/0000-0003-1064-9690
Received / Geliş Tarihi: 28.04.2025 **Accepted / Kabul Tarihi:** 15.08.2025 **Epub:** 03.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Moral K, Bilgin E, Karadağ Ö, et al. Sleep quality and blood pressure variability after anti-TNF-α treatment in axial spondyloarthritis patients: a prospective preliminary study. Ulus Romatol Derg. 2025;17(3):181-187

Introduction

Spondyloarthritis refers to a group of inflammatory rheumatic disorders that share common genetic predispositions, clinical characteristics, and radiological features.[1] It has been reported that aortitis, cardiac conduction defects, valve failure, ischemic heart disease, metabolic syndrome, obesity, hypertension, and dyslipidemia occur with greater frequency in individuals with ankylosing spondylitis (AS) than in the normal population.[2,3]

Sleep disorders are also a significant comorbidity, and poor sleep quality, insomnia, morning sleep inertia, and obstructive sleep apnea have been reported in 50-65% of individuals with AS.[4-6] Chronic inflammation and sleep disorders may contribute to an elevated likelihood of cardiovascular complications among individuals with AS. Beneficial impacts of anti-tumor necrosis factor-α (TNF-α) treatment on chronic inflammation and sleep quality have been documented in individuals with AS.[7] Blood pressure measurement variables such as blood pressure average real variability (ARV) and dipper patterns are directly related to adverse cardiovascular outcomes.[8,9] These parameters can be positively affected by decreasing inflammation, reducing pain, and improving sleep quality. The current literature does not contain any studies that have examined the influence of anti-TNF-α therapy on ambulatory ARV, dipper patterns, and sleep quality in patients with AS. This study aimed to evaluate how anti-TNF-α treatment influences sleep quality and ambulatory blood pressure parameters.

Materials and Methods

Study Population

Patients with axial spondyloarthritis (axSpA) who meet the ASAS 2009 criteria and applied to our rheumatology outpatient clinic between March 1, 2021, and December 1, 2021, were included in this study. They were planned to receive anti-TNF-α treatment for the first time. During this period, 127 TNF-naïve patients with axSpA were scheduled to receive anti-TNF therapy. Of these patients, 74 declined to participate in the study because of an application outside Ankara, unsuitable working hours, or time constraints. In addition, 23 patients with hypertension and/or cardiovascular disease were excluded from the study. The study population consisted of 30 individuals diagnosed with axSpA. One patient was excluded from the analysis because the first ambulatory blood pressure measurement (ABPM) was insufficient, and another patient refused a controlled blood pressure measurement at the 3rd month (Figure 1). Age, sex, age at diagnosis, disease duration, use of drugs, erythrocyte sedimentation rate (ESR), C-reactive

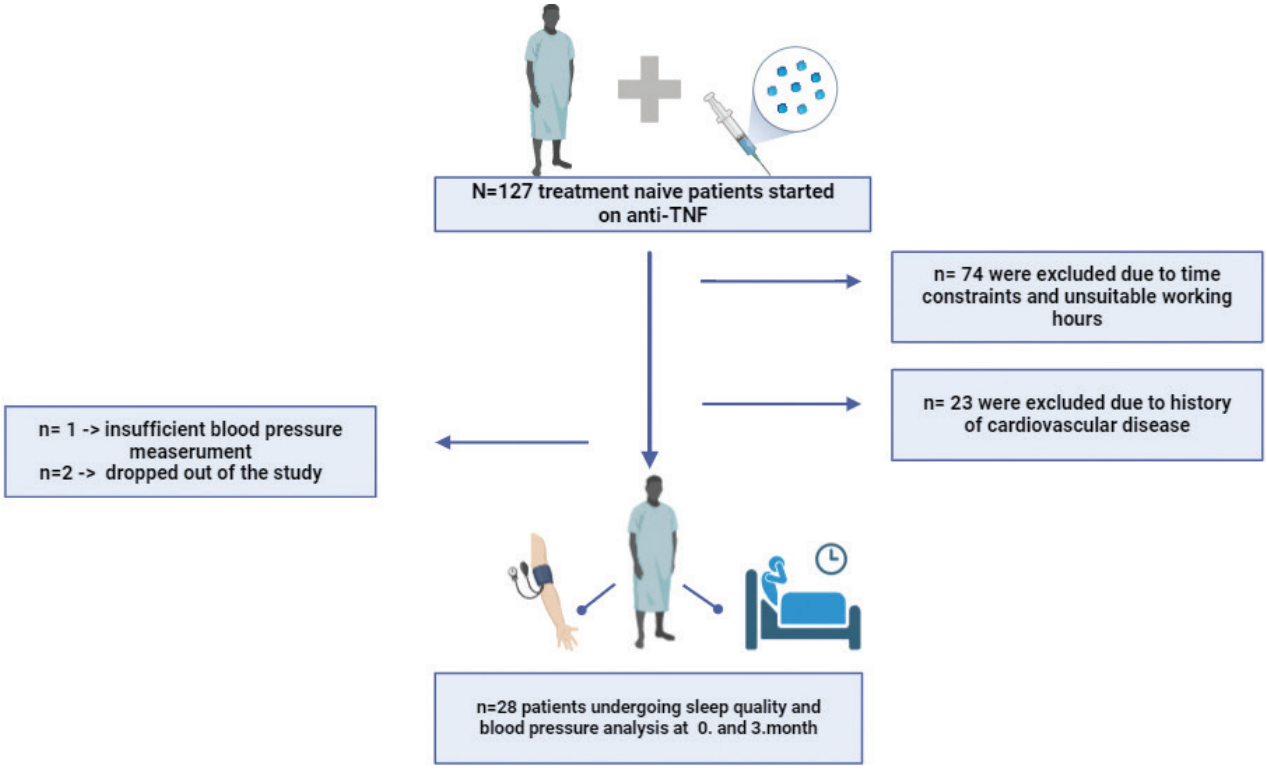

Figure 1. Flow chart of the study
TNF: Tumor necrosis factor

protein (CRP), and disease activity parameters such as the Bath ankylosing spondylitis disease activity index (BASDAI) and Bath ankylosing spondylitis functional index (BASFI) were analyzed at 0 and 3rd month. Sleep quality was assessed using the Pittsburgh sleep quality questionnaire (PSQI), and ambulatory blood pressure monitoring was performed at months 0 and 3. Furthermore, body mass index, concomitant non-steroidal anti-inflammatory drugs (NSAID), conventional disease-modifying antirheumatic drugs (DMARD), and steroid usage was also recorded. This was a single-center, prospective, non-randomized, descriptive study.

Approval was granted by the Hacettepe University Ethics Board (approval number: 2021/02-04-KA-20092, date: 02.04.2021), with all patients giving informed consent. The study adhered to the ethical standards of the Declaration of Helsinki.

Ambulatory Blood Pressure Measurement

ABPM was performed with a Mobil-O-Graph NG (Industrielle Entwicklung Medizintechnik, Germany) portable blood pressure monitor using the oscillometric method, which has met the validation protocols. Measurements were taken every 15 minutes between 07:00 and 23:00 during the day and every 20 minutes between 23:00 and 07:00 at night. Patients were told to continue with their normal daily activities and remain immobile during the measurement, if possible. If the measurements were ≥70% valid, the 24-hour blood pressure measurement was considered to be sufficiently valid. Three parameters were calculated for ambulatory ARV: systolic BP, diastolic BP, and mean blood pressure. The dipper patterns were also examined.

Dipper, Non-dipper and Reverse Dipper

In healthy individuals, nighttime blood pressure values were lower than daytime blood pressure values. A decrease of 10-20% or more in nighttime blood pressure compared to daytime mean blood pressure is considered a "dipper" pattern. A non-dipper was defined as a reduction in nighttime blood pressure of <10%, and a reverse dipper was defined as experiencing no decrease or even an increase in nighttime blood pressure. The non-dipper and reverse dipper patterns are linked to higher cardiovascular mortality.[10]

Blood Pressure Variability

Variations in blood pressure throughout the day are influenced by respiratory dynamics, regulation by the nervous system, and humoral as well as vasomotor control within the vascular bed.

Increased ARV is linked to end-organ damage and cardiovascular mortality. ARV is a sensitive and specific tool for determining blood pressure variability.[11] ARV was determined by averaging the absolute differences between successive blood pressure readings (Figure 2).

Assessment of Sleep Quality

There are several questions regarding the determination of sleep quality in patients. We used the PSQI to determine sleep quality, which was validated in Turkish.[12] The PSQI includes items evaluating perceived sleep quality, time taken to fall asleep, total sleep period, efficiency of sleep, use of insomnia drugs, and impairment in daily activities due to sleep deprivation. A total score ≥5 indicated poor sleep quality. As the total score increased, the sleep quality deteriorated further.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 26.0. Normality of the variables was assessed with the Shapiro-Wilk test. Categorical data were expressed as frequencies and percentages, while normally distributed continuous variables were summarized as mean ± standard deviation, and non-normally distributed data as median, range, and interquartile range. Within-group comparisons between baseline and the third month were carried out using the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate. Between-group comparisons were performed with the independent samples t-test or the Mann-Whitney U test. Associations between continuous variables were explored using Pearson or Spearman correlation analyses. A two-sided p value <0.05 was considered statistically significant.

Results

Twenty-eight patients with axSpA were recruited for the study. Sixteen (57%) patients were female and 12 (43%) were male. The mean patient age was 40.0±10.4 years, and the median disease duration after diagnosis was 6.5 (4-11) years. Thirteen (46%) patients were current smokers, and

$$ARV = \frac{1}{\sum w} \sum_{k=1}^{n-1} w \times |BP_{k+1} - BP_k|$$

Figure 2. Formula for ambulatory blood pressure variability

nine (32%) were considered obese. Before the anti-TNF-α therapy, all patients were using intermittent or continuous NSAIDs, while 17 (60%) patients were taking DMARDs and 4 (14%) were taking prednisolone at doses below 7.5 mg/day. The baseline demographic and clinical profiles of the participants at the initiation of anti-TNF-α therapy are presented in Table 1.

Initially, 29% of the patients experienced good sleep quality, while 71% reported poor sleep quality. Following anti-TNF therapy, the proportion of patients with good sleep quality increased to 57%, and those with poor sleep quality decreased to 43%, which was statistically significant ($p<0.05$). Prior to anti-TNF therapy, the sleep quality score was 8.5, indicating poor sleep quality. Following anti-TNF treatment, this score decreased to 4, demonstrating a significant improvement in sleep quality ($p<0.001$) (Table 2).

The patients had normal 24-hour systolic blood pressure (112.8±8.2), 24-hour diastolic blood pressure (70.3±8.1) and 24-hour mean blood pressure (89.8±7.1) at month 0. In correlation with these results, the day and night systolic/diastolic/mean values were found to be in the normotensive range. By the third month, 24-hour systolic blood pressure, 24-hour diastolic blood pressure, and 24-hour mean blood pressure values were also within normotensive limits. A statistically significant decrease was found in the comparison between 0 and 3 months in systolic night and mean night values [respectively: 109.1±9.5 vs. 105.6±10.7 p (0.042) vs 86.6±8.1 vs. 83.3±9.2 p (0.028)]. ARV did not differ significantly between the initial and 3rd months (Table 3).

At the baseline before anti-TNF-α treatment, 46% of the patients were dippers (n=13), and 57% (n=15) were non-dipper/reverse dippers. The dipper ratio was 61% (n=17) and the non-dipper/reverse dipper ratio was 39% (n=11) at the 3rd month after anti-TNF-α treatment; however, the change did not reach statistical significance (p=0.388). When comparing 0th and 3rd month, the decrease in night time systolic blood pressure reached statistical significance [4.8% (-7to -9.2) vs. 9.2% (4.7 to 11.1); p=0.020].

Table 1. Baseline characteristics of patients with axSpA

Men/women n (%)		12 (43%)/16 (57%)
Age* year		40.0±10
Disease duration** year		6.5 (4-11)
HLA-B27 positivity n (%)		13 (59%)
Peripheric arthritis n (%)		11 (39%)
VAS pain**		7.5 (5.3-9.0)
BASDAI** (0-10)		5.8 (3.5-7.1)
BASFI** (0-10)		6.4 (3.6-7.3)
ESR** (mm/st)		14.0 (6.3-30.0)
CRP** (mg/dL)		0.8 (0.3-2.3)
BMI* (kg/m^2)		27±6
LDL (mg/dL)*		123±38
HDL (mg/dL)*		50±10
Triglycerides (mg/dL)*		118±72
Smoking n (%)		13 (46%)
Obes n (%)		9 (32%)
Drugs*	NSAID n (%)	28 (100%)
	kDMARD n (%)	17 (61%)
	Steroid# n (%)	4 (14%)

**: (Mean ± standard deviation), **: (Median 25-75%), #: <7.5 mg prednisone or equivalent, axSpA: Axial spondyloarthritis, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HDL: High-density lipoprotein, HLA: Human leukocyte antigen, LDL: Low-density lipoprotein, NSAID: Non-steroidal anti-inflammatory drug, kDMARD: Conventional DMARD, VAS: Visual analog scale, Steroid (users under <7.5 mg), Obesity is considered as having a BMI >30*

Table 2. Comparison of baseline and 3rd month sleep quality (n=28)

Variable		0th month	3rd month	p
Sleep quality* n (%)	**Good**	8 (29%)	16 (57%)	**0.008****
	Bad	20 (71%)	12 (43%)	
Sleep quality point [median (25-75%)]		8.5 (4.0-12.8)	4.0 (1.0-5.8)	**<0.001&**

**: Assessed using the Pittsburgh questionnaire, **: Mc Nemar test, &: Wilcoxon test were used*

The decrease in nocturnal diastolic blood pressure, however, failed to attain statistical significance [6.4% (1.5-14.7%) vs. 9.6% (5.0-15.8%); p=0.112] (Table 4). When the clinical features of patients with dipper and non-dipper, before anti-TNF-α treatment were compared, the BASFI scores (4.32±2.49 vs. 6.33±1.84, p=0.021) and PSQI scores [5 (2.5-11) vs. 10 (8-13) p=0.049] were considerably lower in the dipper group (Table 5). Three months after initiating anti-TNF-α therapy, clinical features did not differ between dipper and non-dipper patients (p>0.05 for all).

Discussion

In the present study, sleep quality was significantly better at the 3-month follow-up following anti-TNF-α therapy, while no significant alterations in ARV were noted relative to pretreatment. In addition, 46% of the patients were dippers before anti-TNF-α treatment. However, after the anti-TNF-α treatment, the dipper rate increased to 61%. Although the difference was not statistically significant, this suggests that anti-TNF-α treatment could have had an effect on patients' dipper status.

Table 3. Comparison of ambulatory blood pressure parameters (0th and 3. month)

Variable (mean ± standard deviation)	0th month	3rd month	p
Systolic 24 hour (mmHg)	112.8±8.2	111.4±9.3	0.354&
Diastolic 24 hour (mmHg)	70.3±7.2	69.9±8.6	0.701&
Mean 24 hour (mmHg)	89.8±7.1	89.04±8.3	0.547&
Systolic day (mmHg)	114.2±9.0	113.9±9.3	0.865&
Diastolic day (mmHg)	71.8±8.1	72.3±9.1	0.749&
Mean day (mmHg)	91.4±8.1	91.4±8.6	0.980&
Systolic night (mmHg)	109.1±9.5	105.6±10.7	**0.042**&
Diastolic night (mmHg)	67.1±8.3	64.7±9.2	0.108&
Mean night (mmHg)	86.6±8.1	83.3±9.2	**0.028**&
ARV systolic	9.8±2.3	10.7±2.6	0.092*
ARV diastolic	8.4±2.1	8.4±1.8	0.912&
ARV mean	7.0±1.8	7.4±2.0	0.088*

*&: T-test was used in dependent groups, *: Wilcoxon test was used, ARV: Average real variability*

Table 4. Comparison of dipper/non-dipper ratios of axSpA patients (0th and 3. month) (n=28)

Variable	0th month	3rd month	p
Dipper n (%)	13 (46%)	17 (61%)	0.388*
Non-dipper/reverse dipper n (%)	15 (54%)	11 (39%)	
Reduction in systolic blood pressure (%) Median (25-75%)	4.8 [(-7) -9.2]	9.2 (4.7-11.1)	**0.020****
Reduction in diastolic blood pressure (%) Median (25-75%)	6.4 (1.5-14.7)	9.6 (5.0-15.8)	0.112**

**: Mc Nemar, **: T-test in dependent groups, axSpA: Axial spondyloarthritis*

Table 5. Comparison of laboratory and parameter values of dipper and non-dipper patients

Variable 0. month	0th month Dipper n=13	3rd month non-Dipper n=15	p
	Mean ± standard deviation and median (25-75%)		
Disease duration (year)	7 (4-15)	6 (4-8)	0.816&
Age (year)	36.4 (26.6-42.6)	43.6 (34.6-51.1)	0.152*
VAS pain (0-10)	6.08±3.09	7.80±1.42	0.083*
BASDAI (0-10)	4.99±2.28	5.96±1.87	0.226*
BASFI (0-10)	4.32±2.49	6.33±1.84	**0.021***
ESR (mm/st)	9 (4-18)	21 (12-41)	0.088&
C-reaktif protein (mg/dL)	0.71 (0.25-1.11)	1.41 (0.39-3.34)	0.134&
Sleep quality (PSQI)	5 (2.5-11)	10 (8-13)	**0.049**&

**: t-test, &: Mann-Whitney U test, BASDAI: Bath ankylosing spondylitis disease activity index, BASFI: Bath ankylosing spondylitis functional index, ESR: Erythrocyte-sedimentation rate, PSQI: Pittsburgh sleep quality questionnaire, VAS: Visual analog scale*

At baseline, poor sleep quality was identified in 71% of patients as assessed by the PSQI; however, this rate decreased to 43% at the 3rd month ($p<0.05$). Following treatment with anti-TNF-α, a statistically significant decrease in the Pittsburgh Sleep Scale scores was observed at the third month ($p<0.001$). Sleep disturbances, in addition to pain and fatigue, are serious comorbidities in patients with AS, with 50-65% of patients reporting sleep disturbances.[13,14] Multiple studies indicate that elevated disease activity correlates with impaired sleep quality and that sleep disturbances increase cardiovascular mortality. In a prospective study involving 60,586 people followed for cardiovascular events, Lao et al.[15] reported that poor sleep quality was linked to a higher risk of coronary artery disease. Anti-TNF-α therapy has the potential to improve sleep quality in individuals with AS by decreasing disease activity

In this study, 46% of the patients were categorized as dippers before anti-TNF-α treatment. By the third month after treatment, this percentage had increased to 61% ($p=0.388$), although the increase was not statistically significant. On the other hand, a significant reduction in systolic nocturnal blood pressure was observed, consistent with the dipper pattern ($p<0.05$). Lo et al.[16] investigated the connection between sleep quality and hypertension through a meta-analysis of 29 articles and 45,041 patients.

Poor sleep quality was strongly related to hypertension, with patients showing greater systolic and diastolic values than individuals with normal sleep quality.[17] Evidence from another study indicated that enhanced sleep quality corresponded to decreased nighttime blood pressure (dipper pattern).[18] Several investigations have suggested that the link between hypertension and sleep quality may be bidirectional. These findings imply that anti-TNF-α therapy could exert beneficial effects on pain and sleep quality, in addition to lowering nocturnal blood pressure and reducing cardiovascular risk.[6]

In our study, anti-TNF-α treatment did not have a statistically significant impact on ARV. Our results align with previous research. In a prospective study, Capkin et al.[19] examined 28 AS patients both at the start of therapy and after a six-month course of TNF treatment. Although there was a significant reduction in the BASDAI, ESR, and CRP levels, no change was observed in pulse wave velocity (PWV) before and after treatment. Although the authors did not demonstrate a significant improvement in PWV in this study, they suggested that anti-TNF-α therapy could modulate these parameters over the long-term emphasizing the need for long-term studies to assess this hypothesis.

Study Limitations

The limited number of patients, short follow-up periods, and absence of cardiovascular comorbidities in our study group could explain the lack of change in ABPM parameters. It is also possible that blocking the TNF-pathway is not sufficient to modulate cardiovascular risk in these patients.

Conclusion

While anti-TNF-α therapy may modulate cardiovascular risk factors in patients with AS by improving sleep quality, its effect on blood pressure parameters needs to be clarified. Further research is required to evaluate the immediate and long-range impacts of anti-TNF therapy on cardiovascular risk in patients with AS.

Ethics

Ethics Committee Approval: Approval was granted by the Hacettepe University Ethics Board (approval number: 2021/02-04-KA-20092, date: 02.04.2021). The study adhered to the ethical standards of the Declaration of Helsinki.

Informed Consent: All patients gave informed consent.

Footnotes

Authorship Contributions

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

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

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

References

1. Sieper J, Hu X, Black CM, Grootscholten K, van den Broek RWM, Kachroo S. Systematic review of clinical, humanistic, and economic outcome comparisons between radiographic and non-radiographic axial spondyloarthritis. Semin Arthritis Rheum. 2017;46:746-53.
2. Atzeni F, Nucera V, Galloway J, Zoltán S, Nurmohamed M. Cardiovascular risk in ankylosing spondylitis and the effect of anti-TNF drugs: a narrative review. Expert Opin Biol Ther. 2020;20:517-24.
3. Bhattad PB, Kulkarni M, Patel PD, Roumia M. Cardiovascular morbidity in ankylosing spondylitis: a focus on inflammatory cardiac disease. Cureus. 2022;14:e25633.

4. Nie A, Wang C, Song Y, Xie X, Yang H, Chen H. Prevalence and factors associated with disturbed sleep in outpatients with ankylosing spondylitis. Clin Rheumatol. 2018;37:2161-8.

5. Salari N, Sadeghi N, Hosseinian-Far A, et al. Prevalence of sleep disturbance in patients with ankylosing spondylitis: a systematic review and meta-analysis. Adv Rheumatol. 2023;63:33.

6. Karatas G, Bal A, Yuceege M, et al. Evaluation of sleep quality in patients with ankylosing spondylitis and efficacy of anti-TNF-α therapy on sleep problems: a polisomnographic study. Int J Rheum Dis. 2018;21:1263-9.

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

8. Melgarejo JD, Patil D, Mena LJ, et al. Association of variability and hypertensive loads in 24-h blood pressure with mortality and cardiovascular risk. Am J Hypertens. 2024;37:323-33.

9. Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. J Am Heart Assoc. 2018;7:e007621.

10. Birkenhäger AM, van den Meiracker AH. Causes and consequences of a non-dipping blood pressure profile. Neth J Med. 2007;65:127-31.

11. Mena LJ, Felix VG, Melgarejo JD, Maestre GE. 24-hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis. J Am Heart Assoc. 2017;6:e006895.

12. Li Z, Fu T, Wang Y, et al. Sleep disturbances in ankylosing spondylitis: a systematic review and meta-analysis. Psychol Health Med. 2019;24:911-24.

13. Batmaz İ, Sarıyıldız MA, Dilek B, Bez Y, Karakoç M, Çevik R. Sleep quality and associated factors in ankylosing spondylitis: relationship with disease parameters, psychological status and quality of life. Rheumatol Int. 2013;33:1039-45.

14. Song BW, Jeong HJ, Kim BY, et al. Bath ankylosing spondylitis disease activity index is associated with the quality of sleep in ankylosing spondylitis patients. J Rheum Dis. 2021;28:143-9.

15. Lao XQ, Liu X, Deng HB, et al. Sleep quality, sleep duration, and the risk of coronary heart disease: a prospective cohort study with 60,586 adults. J Clin Sleep Med. 2018;14:109-17.

16. Lo K, Woo B, Wong M, Tam W. Subjective sleep quality, blood pressure, and hypertension: a meta-analysis. J Clin Hypertens (Greenwich). 2018;20:592-605.

17. Liu RQ, Qian Z, Trevathan E, et al. Poor sleep quality associated with high risk of hypertension and elevated blood pressure in China: results from a large population-based study. Hypertens Res. 2016;39:54-9.

18. Loredo JS, Nelesen R, Ancoli-Israel S, Dimsdale JE. Sleep quality and blood pressure dipping in normal adults. Sleep. 2004;27:1097-103.

19. Capkin E, Karkucak M, Kiris A, et al. Anti-TNF-α therapy may not improve arterial stiffness in patients with AS: a 24-week follow-up. Rheumatology (Oxford). 2012;51:910-4.

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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2025.87609
Ulus Romatol Derg 2025;17(3):188-194

Frequency and determinants of calcium pyrophosphate dihydrate deposition in patients with rheumatoid arthritis: A radiologic study

Romatoid artritte kalsiyum pirofosfat dihidrat birikim sıklığı ve ilişkili faktörler: Radyolojik bir çalışma

Mete Pekdiker, Gezmiş Kimyon

Hatay Mustafa Kemal University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Hatay, Türkiye

Abstract

Objective: Previous joint injury predisposes to calcium pyrophosphate dihydrate deposition (CPPD). In this study, we aimed to identify the frequency and associated factors of radiographic CPPD signs in cases of rheumatoid arthritis (RA).

Methods: Adult patients with RA who were referred to our tertiary rheumatology department between January 2023 and December 2024 were included. Patients with secondary rheumatologic diseases and conditions predisposing to CPPD were excluded. Chondrocalcinosis, scapholunate advanced collapse, scaphoid-trapezium-trapezoid joint collapse, and hook-like osteophytes on hand X-rays were defined as the signs of CPPD. Radiographs were read by two blinded rheumatologists.

Results: We included a total of 1,318 patients; 83% of them were female. The mean age was 55.2 years, and the mean disease duration was 8.6 years. Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) positivity were 56.2% and 52.7%, respectively. 95.5% of the patients had RA-type erosive changes. We found the frequency of CPPD as 10.5% (n=139). The most common CPPD sign was chondrocalcinosis of distal interphalangeal joints (n=70), and hook-like osteophytes were the second (n=48). The mean age (p<0.001), disease duration (p=0.002), anti-CCP negativity (p<0.001), and RA-type serious joint involvement (p=0.008) were significantly higher in the CPPD+ group. In multivariate analysis, age (p<0.001), disease duration (p=0.007), and anti-CCP negativity (p=0.002) were the independent predictive factors for CPPD.

Conclusion: Our findings align with prior literature suggesting that joint damage in RA may predispose patients to CPPD. Moreover, CPPD is a clinical entity that should be kept in mind in the management of RA.

Keywords: Chondrocalcinosis, crystal arthropathies, hand, rheumatoid arthritis, risk factors

Özet

Amaç: Önceki eklem hasarı, kalsiyum pirofosfat dihdirat birikimine (CPPD) yatkınlık yaratır. Bu çalışmada eroziv bir eklem hastalığına sahip romatoid artrit (RA) olgularında radyografik CPPD bulgulagrının sıklığını ve ilişkili faktörleri tanımlamayı amaçladık.

Yöntem: Ocak 2023 ile Aralık 2024 tarihleri arasında üçüncü basamak romatoloji kliniğimize başvuran erişkin RA hastaları çalışmaya dahil edildi. Sekonder romatolojik hastalıklara ve CPPD hastalığı için predispozan hastalıklara sahip olan olgular çalışmadan dışlandı. Anteroposterior el radyografilerinde kondrokalsinozis, skafo-lunat eklemde kollaps ve skafoid-trapezyum-trapezoid eklemde kollaps ve kanca benzeri osteofitler "CPPD bulguları" olarak tanımlandı. Röntgenler, hastalara kör iki romatolog tarafından değerlendirildi.

Bulgular: Çalışmaya toplam 1.318 hasta alındı ve bunların %83'ü kadındı. Ortalama yaş 55,2 yıl, ortalama hastalık süresi ise 8,6 yıldı. Romatoid faktör ve anti-CCP pozitifliği sırasıyla %56,2 ve %52,7 idi. Hastaların %95,5'inde RA'ya özgü eroziv değişiklikler mevcuttu. Çalışma grubunda CPPD sıklığı %10,5 idi (n=139). En sık görülen CPPD bulgusu distal interfalangeal eklemlerde kondrokalsinozis (n=70) olup, ikinci en sık bulgu kanca benzeri osteofitlerdi (n=48). Yaşı (p<0,001), hastalık süresi (p=0,002), anti-siklik sitrüline peptit (CCP) negatifliği (p<0,001) ve RA tipi ciddi eklem tutulumu (p=0,008) CPPD+ grupta anlamlı olarak daha yüksektir. Çok değişkenli analizde ise yaş (p<0,001), hastalık süresi (p=0,007) ve anti-CCP negatifliğini (p=0,002) RA olgularında için bağımsız prediktif faktörler olarak saptadık.

Sonuç: Bulgularımız, RA olgularındaki eklem hasarının hastaları CPPD birikimine yatkın hale getirebileceğini öne süren önceki literatürle uyumludur. Ayrıca, CPPD, RA yönetiminde akılda tutulması gereken bir klinik antitedir.

Anahtar Kelimeler: Kondrokalsinozis, kristal artropatileri, el, romatoid artrit, risk faktörleri

Correspondence / İletişim: Mete Pekdiker Asst. Prof., Hatay Mustafa Kemal University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Hatay, Türkiye
E-mail: mete.pekdiker@hotmail.com **ORCID ID:** orcid.org/0000-0003-3089-1564
Received / Geliş Tarihi: 09.05.2025 **Accepted / Kabul Tarihi:** 19.08.2025 **Epub:** 27.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Pekdiker M, Kimyon G. Frequency and determinants of calcium pyrophosphate dihydrate deposition in patients with rheumatoid arthritis: a radiologic study. Ulus Romatol Derg. 2025;17(3):188-194

Introduction

Calcium pyrophosphate dihydrate deposition (CPPD) disease is a crystal arthropathy that is caused by CPP crystals. The prevalence of CPPD is 4-7% in Europe and the United States, which usually affects the elderly population, especially those over 60 years old. Although the pathogenesis of CPPD remains unclear, pre-existing cartilage injury is an important predisposing factor. As a result, CPPD disease often coexists with osteoarthritis (OA). The most common cause of CPPD disease is idiopathic, but some metabolic disorders are associated with it.[1]

The clinical presentation of CPPD varies widely, including forms such as asymptomatic chondrocalcinosis (CC), acute arthritis, chronic arthritis, and tumoral deposition.[2,3] The knee and shoulder are the most commonly affected joints in CPPD disease, but small joints such as metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints can also be involved.[2] Moreover, erosive arthritis may develop during the course of CPPD disease.[4] Despite the fact that a definitive diagnosis is based on determining the crystals in synovial fluid (SF), radiographic CC supports the diagnosis of CPPD disease.[5]

Rheumatoid arthritis (RA) is a multisystem inflammatory disease that affects peripheral synovial joints. The prevalence of RA is 0.5-1%, and it has a higher occurrence in females. This condition is one of the most frequently encountered rheumatic diseases in routine clinical practice. Both innate and adaptive immune responses drive the pathogenesis of RA; chronic synovitis leads to cartilage and bone erosions in the natural course of RA.[6] RA typically presents insidiously with initial involvement of the small joints of the hands, such as MCP and PIP, and large joint involvement, such as the knee or hip, is a finding of later stages of RA. Up to 90% of RA cases have hand involvement during the disease course.[7,8]

RA may create a conducive environment for the development of CPPD disease due to its erosive effects on bone and cartilage tissues. A national database study from the United States demonstrated a positive association between RA and CPPD.[9] However, the frequency and risk factors of hand CPPD in patients with RA remain unclear. To date, no studies have addressed this topic in the medical literature. In this study, we aimed to determine the frequency and associated factors of radiographic CPPD signs in hand joints of RA patients.

Materials and Methods

Patient Selection

We surveyed patients with RA who were referred to the outpatient clinic of our tertiary rheumatology department between January 2023 and December 2024. Electronic medical records were reviewed retrospectively. Demographic, laboratory, and treatment data were documented. The inclusion criteria were: being aged ≥18 years, fulfilling the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) RA classification criteria,[10] and having an anteroposterior hand X-ray in the past year. The exclusion criteria were diagnosed with familial CPPD disease, having a bone fracture history at hand or wrist joints, having another rheumatic disease causing chronic synovitis at hand joints, such as psoriatic arthritis,[11] Sjögren's syndrome,[12] systemic sclerosis,[13] and having CPPD-associated metabolic disorders such as hyperparathyroidism, hemochromatosis, hypomagnesemia, Gitelman's disease, Bartter's disease, and, gout.[1,14] Patients with erosive OA and hand OA[15] were excluded from the study because of their strong association with CPPD disease. Patients with chronic kidney disease (CKD) were excluded because CKD is associated with CPPD.[9]

Assessments

Rheumatoid arthritis-type joint involvement (RJI) was defined as the presence of erosion or joint space narrowing (JSN) in any joint, as assessed using the modified sharp scoring (MSS) system,[16] "serious joint involvement (SJI) was characterized by an erosion score of ≥3 points or a JSN score of ≥4 points in any joint, as assessed by the MSS". The EULAR definition was employed to characterize the typical joint erosion of RA (as a cortical break).[17]

CC (which is the most common sign of CPPD disease), scapholunate advanced collapse/radiocarpal joint CC, scaphoid-trapezium-trapezoid joint collapse, and hook-like osteophytes on anteroposterior hand X-rays were accepted as signs of CPPD disease.[18] Radiological evaluations were independently conducted by two experienced rheumatologists (MP and GK), who were blinded to clinical data. In the event of disagreement between readers, the X-rays were re-evaluated, and a final consensus decision was reached through full agreement.

Rheumatoid factor (RF) was measured using a nephelometric method, and serum levels ≥14 IU/mL were considered positive. Anti-cyclic citrullinated peptide (CCP) antibody-2 IgG levels were assessed using an enzyme-linked immunosorbent assay, with values of ≥5 U/mL classified as positive. CKD was defined as a glomerular filtration rate below 60 mL/min/1.73 m², persisting for at least three months.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 22.0 (Chicago, IL). Data were presented as counts, frequencies, and percentages. Categorical variables and their associations were evaluated using the chi-square test and Fisher's exact test. Depending on the data distribution, group

comparisons were carried out using either the Mann-Whitney U test or the Independent Samples t-test. Multivariate analysis was employed to estimate the probabilities of the dependent variable and to classify outcomes based on these probability estimates. A 95% confidence interval (CI) was used for all analyses, and a p-value of less than 0.05 was considered statistically significant.

The study received ethical approval from the Ethics Committee of Hatay Mustafa Kemal University, where the study was conducted (approval date: 06.08.2024, protocol number: 08, decision number: 46).

Results

We consecutively reviewed 1,402 patients and included a total of 1,318 patients in our study. Figure 1 shows the data on the exclusion of the study population. Eighty-three percent of them were female, and the mean age was 55.2 years. The mean disease duration was 8.6 years. The frequency of smoking history (active or ex) was 32.2%. RF positivity was 56.2%, and anti-CCP positivity was 52.7%. The 95.5% of patients had RJI, and 25.8% had SJI. The 30.2% (n=399) of patients were being treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs). The frequency of CPPD was found to be 10.5% (n=139). Table 1 presents the characteristics of the study population.

The overall number of CPPD lesions was 201. The most common CPPD sign was the CC of distal interphalangeal (DIP) joints (n=70), and drooping osteophytes were the second most common (n=48). We detected CC at multiple joint levels, such as the wrist, MCP, PIP, and DIP joints. Table 2 presents the detailed radiographic analysis of hand CPPD. Figure 2 and Figure 3 show examples of hand CPPD in RA cases.

The CPPD+ group had a significantly higher mean age (p<0.001), longer disease duration (p=0.002), more frequent anti-CCP negativity (p<0.001), and more cases of SJI (p=0.008) compared to the CPPD- group. A multivariate analysis model (including age, disease duration, anti-CCP, and SJI) showed that age [odds ratio (OR)=1.89; 95% CI: 1.167-3.211; p<0.001], disease duration (OR=2.24; 95% CI: 1.418-3.612; p=0.007), and anti-CCP negativity (OR=2.13; 95% CI: 1.335-3.409; p=0.002) were the independent predictive factors of CPPD. Table 3 presents the comparison of two groups according to CPPD status.

Discussion

In this radiographic study, we first defined the freqeuncy, associated factors, and radiographic signs of hand CPPD in patients with RA in medical literature. We found 10.5% of RA cases had CPPD in hand joints. Age, disease duration, and anti-CCP negativity were the independent predictive factors of CPPD. According to our results, advanced age, long disease duration, anti-CCP negativity, and SJI were associated with CPPD in RA cases. Our findings are consistent with the pathogenesis of CPPD, as prolonged disease duration and SJI are likely to lead to greater joint damage. Our findings align with prior literature suggesting that joint damage in RA may predispose patients to CPPD deposition.

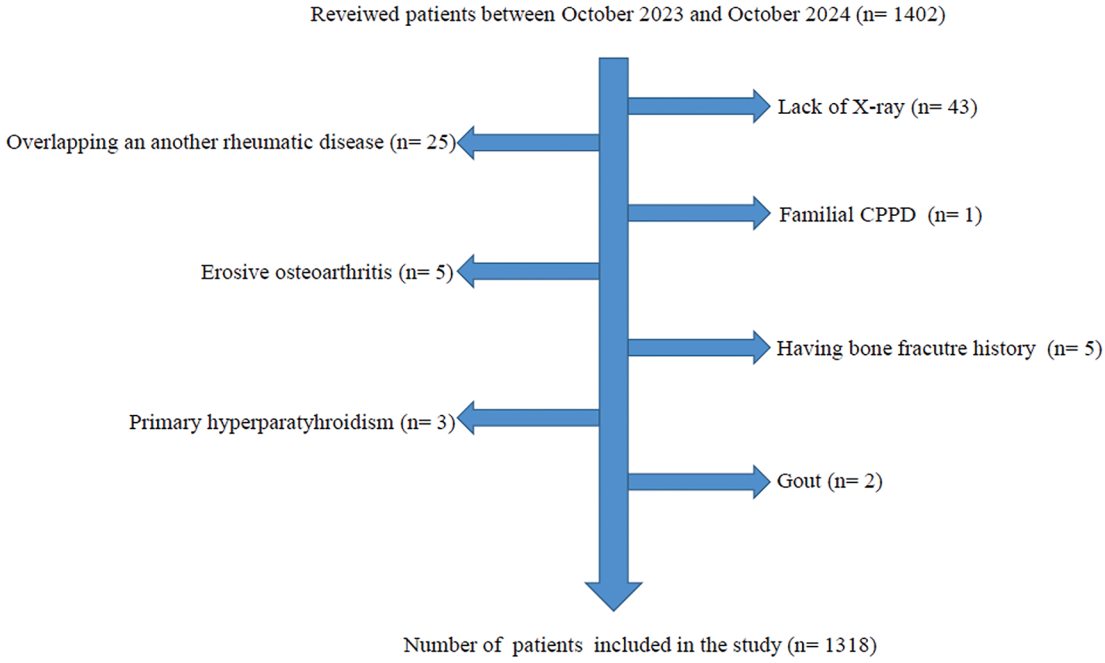

Figure 1. Flowchart of the study representing the criteria and number of patients from initial retrieval to the final study cohort
CPPD: Calcium pyrophosphate deposition

Table 1. Demographic, laboratory, and treatment characteristics of study population

Total patient, n	1,318
Age, mean ± SD, years	55.2±12.6
Disease duration, mean ± SD, years	8.6±7.5
Female sex, n (%)	1093 (83)
Male sex, n (%)	225 (17)
Smoking, n (%)	425 (32.2)
Hypertension, n (%)	390 (29.6)
Diabetes mellitus, n (%)	190 (14.4)
Coronary artery disease, n (%)	124 (9.4)
RF positivity, n (%)	741 (56.2)
Anti-CCP positivity, n (%)	695 (52.7)
b/tsDMARD use, n (%)	399 (30.2)
RJI, n (%)	1259 (95.5)
SJI, n (%)	341 (25.8)
CPPD, n (%)	139 (10.5)

Anti-CCP: Anti-cyclic citrullinated peptide, b/tsDMARD: Biologic/targeted synthetic disease modifying anti-rheumatic drugs, CPPD: Calcium pyrophosphate deposition, RF: Rheumatoid factor, RJI: Rheumatoid arthritis-type joint involvement, SD: Standard deviation, SJI: Serious joint involvement

Paalanen et al.[19] found the prevalence of radiographic CPPD to be 3.2% in 435 early seronegative RA patients. All patients with CPPD had CC at triangular cartilage. This study did not report CPPD findings other than triangular CC, and none of the patients with CPPD had typical RA-like erosions. The authors suggested that CPPD disease can mimic seronegative RA. In our cohort, the mean disease duration was 8.6 years, and 95.5% of patients had RJI, so clinical mimicry of CPPD was not observed. Sabchyshyn et al.[20] reported 21 patients with overlap syndrome between RA and CPPD, which was diagnosed by CC on X-rays. The authors reported that RA usually precedes CPPD disease and that CPPD disease can be a complication of established RA.

Gerster et al.[21] conducted a study involving 93 patients with RA (the mean age and disease duration were 64.5 years and 12 years, respectively), and investigated CPPD by SF analysis of knee joints, finding a prevalence of 25.8%. Patients with CPPD had more joint prostheses than those in the CPPD-negative group, but there was no significant difference in disease duration between the groups. Theiler et al.[22] evaluated CC in the knees of RA patients using SF analysis via the cytospin technique. They reported a CPPD prevalence of 17.7%, with age identified as an independent predictive factor ($p<0.001$). Disease activity scores and serologic markers were not associated with CPPD. Galozzi et al.[23] investigated the frequency of CPP crystals in the SF of wrist and finger joints and reported prevelance rates 85.7%, 19.3%, 13.9%, and 0% in patients with RA, OA, psoriatic arthritis, and gout, respectively. The wrist was the most common site for CCP crystals, followed by MCP, PIP, and DIP joints. The higher frequency of CPP crystals in RA than OA, may suggest a potential link between the severity of inflammation and CPPD. Oliviero et al.[24] also analyzed the SF of patients with inflammatory joint disease, including 326 patients with RA (the mean age and disease duration were 58.8 years and seven years, respectively). They found the frequency of CPP crystals was 8.2% in patients with RA, and the CPP

Table 2. Radiographic analysis of CPPD findings

Total CPPD lesion count, n	203
-Hook-like osteophytes, n (%)	48 (23.9)
-Scapholunate advanced collapse/RC joint CC, n (%)	11 (5.4)
-Scaphoid-trapezium-trapezoid joint collapse, n (%)	6 (3)
-First carpometacarpal joint CC, n (%)	13 (6.4)
-DIP joint CC, n (%)	70 (34.9)
-MCP joint CC, n (%)	33 (16.4)
-PIP joint CC, n (%)	17 (8.5)
-Triangular cartilage CC, n (%)	3 (1.5)
Hook-like osteophytes, n (%)	
-2. MCP joint	10 (20.8)
-3. MCP joint	27 (56.3)
-4. MCP joint	5 (10.4)
-5. MCP joint	6 (12.5)
CC in DIP joints, n (%)	
-2. DIP joint	35 (50)
-3. DIP joint	20 (28.5)
-4. DIP joint	10 (14.3)
-5. DIP joint	5 (7.2)
CC in MCP joints, n (%)	
-1. MCP joint	1 (3)
-2. MCP joint	9 (27.3)
-3. MCP joint	10 (30.3)
-4. MCP joint	7 (21.2)
-5. MCP joint	6 (18.2)
CC in PIP joints, n (%)	
-2. PIP joint	2 (11.8)
-3. PIP joint	11 (64.7)
-4. PIP joint	4 (23.5)
-5. PIP joint	0

CC: Chondrocalcinosis, CPPD: Calcium pyrophosphate deposition, DIP: Distal interphalangeal, MCP: Metacarpophalangeal, PIP: Proximal interphalangeal, RC: Radiocarpal

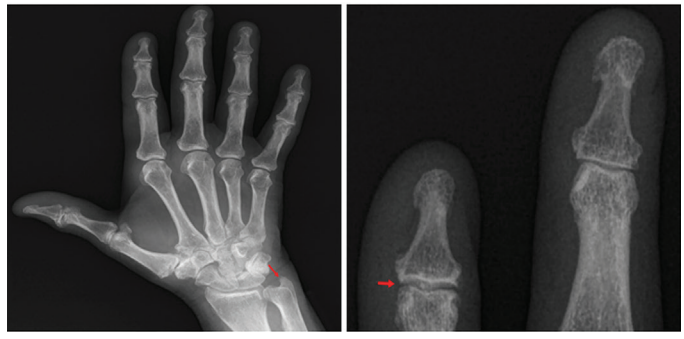

Figure 2. A 66 years old female patients with rheumatoid arthritis; erosion in the styloid process of ulna, and chondrocalcinosis in the second distal interphalangeal joint were shown with red arrows

crystal-positive group was significantly older (p<0.001) than the CPP crystal-negative group, but there was no difference in terms of disease duration.

Advanced age has been consistently identified as a significant risk factor for CPPD disease, a finding that is further corroborated by the results of our study.[25] We defined the disease duration as an independent predictive factor for CPPD disease, which may result from progressive cartilage and bone destruction during the course of RA. Anti-CCP is a commonly utilized test in clinical practice for the diagnosis of RA; it is included in the 2010 ACR/EULAR RA classification criteria.[10] The presence of anti-CCP antibodies is also observed in several immune-mediated inflammatory diseases, such as connective tissue diseases, psoriatic arthritis, Crohn's disease, and COVID-19, where citrullination processes are involved.[26] We defined the anti-CCP negativity as an independent predictive factor for CPPD. Therefore, we could hypothesize the absence of citrullination processes in the pathogenesis of CPPD. Krekeler et al.[27] also supported our results, finding that seronegative RA patients had a higher prevalence of CC compared to seropositive patients.

Another important issue is the difference in treatment strategies between RA and CPPD disease. The EULAR recommends conventional synthetic or biologic/targeted synthetic DMARDs in patients with RA, but none of the DMARDs are currently indicated for the treatment of CPPD disease. Moreover, colchicine, which is recommended for the treatment of crystal arthritis but not for RA, may be a beneficial option for patients with RA who have overlapping CPPD.[28,29] Furthermore, CPPD may present as acute or chronic arthritis and lead to overtreatment in patients with RA. In our cases, there was no notable statistical difference in b/tsDMARD use between the CPPD (+) and (-) groups (p=0.52).

Figure 3. A 58 years old female patients with rheumatoid arthritis; multiple joint space narrowing in wrist joints, and hook-like osteophytes in the fifth metacarpophalangeal joint were shown with red arrows

Table 3. Comparison of RA patients according to the CPPD status

Variable	CPPD+ group	CPPD- group	p-value
Age, mean ± SD, years	64.5±10.1	54.1±12.5	**<0.001**
Female sex, %	83.5	82.9	0.86
Disease duration, mean ± SD, years	11.1±9.5	8.3±7.1	**0.002**
Smoking history, %	28.1	32.7	0.26
RF positivity, %	48.9	57.1	0.06
Anti-CCP positivity, %	38.1	54.5	**<0.001**
Serious joint involvement, %	35.3	24.8	**0.008**
b/tsDMARD use, %	28.1	30.7	0.52

Anti-CCP: Anti-cyclic citrullinated peptide antibody-2 IgG, b/tsDMARD: Biologic or targeted synthetic disease modifying anti-rheumatic drugs, CPPD: Calcium pyrophosphate deposition, RA: Rheumatoid arthritis, RF: Rheumatoid factor, SD: Standard deviation

This study was a radiographic investigation, in which we identified the radiographic signs of CPPD rather than diagnosing CPPD disease in RA patients. We could not apply 'The 2023 ACR/EULAR classification criteria for CPPD disease' to our study population because that criteria includes the RA as an absolute exclusion criteria.[30] Additionally, our study population had low positivity rates of RF and anti-CCP antibodies according to the medical literature. This may be due to varying positivity rates of these autoantibodies among different populations with RA. A recent study from Türkiye reported RF and anti-CCP positivity rates of 40.3% and 35.6%, respectively, in patients with newly diagnosed RA.[31,32] We did not consider a diagnostic inaccuracy among RA patients because 95% of them had RJI.

Study Limitations

Despite unique results, our study had some limitations, such as a retrospective design, lack of a healthy control group, intra- and inter-observer variability, and the low sensitivity of conventional radiography, which may fail to detect CC, particularly in small joints.[33] Furthermore, hook-like osteophytes are not specific to RA and can be observed in patients with RA in remission.[34] Some of the patients with SJI had joint ankylosis, so we could not detect CC in these patients. Moreover, the absence of CC does not exclude the CPPD diagnosis.[5] Therefore, we suggest that the prevalence of hand CPPD in patients with RA may be higher than observed in our study. Ultrasound is more sensitive and less specific than conventional radiography; however, both imaging modalities demonstrate good diagnostic accuracy for CPPD.[35] Another important limitation is that primary CPPD can present with erosive arthritis even in the absence of RA.[2] Moreover, the CPPD may mimic a pseudo-RA pattern.[36] Although CPPD-related erosions are not clearly defined radiologically and 95% of our RA cases exhibited RA-type joint involvement, diagnostic challenges may still have occurred.

Conclusion

In conclusion, this is the first study to investigate radiographic hand CPPD in patients with RA. We identified the frequency of CPPD as 10.5%, with age, disease duration, and anti-CCP negativity emerging as independent predictive

factors. Additionally, we were the first to report radiographic signs of CPPD beyond CC. Rheumatologists should consider the possibility of CPPD in RA patients, particularly in the presence of the identified risk factors, to ensure optimal disease management. Prospective studies are needed to clarify the underlying mechanisms of this association and to enhance therapeutic strategies for affected individuals.

Ethics

Ethics Committee Approval: The study received ethical approval from the Ethics Committee of Hatay Mustafa Kemal University, where the study was conducted (approval date: 06.08.2024, protocol number: 08, decision number: 46).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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

References

1. Rosenthal AK, Ryan LM. Calcium pyrophosphate deposition disease. N Engl J Med. 2016;374:2575-84.
2. Dieppe PA, Alexander GJ, Jones HE, et al. Pyrophosphate arthropathy: a clinical and radiological study of 105 cases. Ann Rheum Dis. 1982;41:371-6.
3. Ishida T, Dorfman HD, Bullough PG. Tophaceous pseudogout (tumoral calcium pyrophosphate dihydrate crystal deposition disease). Hum Pathol. 1995;26:587-93.
4. Menkes CJ, Simon F, Delrieu F, Forest M, Delbarre F. Destructive arthropathy in chondrocalcinosis articularis. Arthritis Rheum. 1976;19:329-48.
5. Zhang W, Doherty M, Bardin T, et al. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis. 2011;70:563-70.
6. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.
7. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998;27:18-24.
8. Fleming A, Benn RT, Corbett M, Wood PH. Early rheumatoid disease. II. Patterns of joint involvement. Ann Rheum Dis. 1976;35:361-4.
9. Kleiber Balderrama C, Rosenthal AK, Lans D, Singh JA, Bartels CM. Calcium pyrophosphate deposition disease and associated medical comorbidities: a national cross-sectional study of US veterans. Arthritis Care Res (Hoboken). 2017;69:1400-6.
10. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580-8.
11. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H; CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006;54:2665-73.
12. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for primary Sjögren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Arthritis Rheumatol. 2017;69:35-45.
13. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum.2013;65:2737-47.
14. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatol. 2015;67:2557-68.
15. Zhang W, Doherty M, Leeb BF, et al. EULAR evidencebased recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis. 2009;68:8-17.
16. Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum. 1985;28:1326-35.
17. Knevel R, Lukas C, van der Heijde D, Rincheval N, Combe B, van der Helm-van Mil AH. Defining erosive disease typical of RA in the light of the ACR/EULAR 2010 criteria for rheumatoid arthritis; results of the data driven phase. Ann Rheum Dis. 2013;72:590-5.
18. Steinbach LS. Calcium pyrophosphate dihydrate and calcium hydroxyapatite crystal deposition diseases: imaging perspectives. Radiol Clin North Am. 2004;42:185-205.
19. Paalanen K, Rannio K, Rannio T, Asikainen J, Hannonen P, Sokka T. Prevalence of calcium pyrophosphate deposition disease in a cohort of patients diagnosed with seronegative rheumatoid arthritis. Clin Exp Rheumatol. 2020;38:99-106.
20. Sabchyshyn V, Konon I, Ryan LM, Rosenthal AK. Concurrence of rheumatoid arthritis and calcium pyrophosphate deposition disease: a case collection and review of the literature. Semin Arthritis Rheum. 2018;48:9-11.
21. Gerster JC, Varisco PA, Kern J, Dudler J, So AK. CPPD crystal deposition disease in patients with rheumatoid arthritis. Clin Rheumatol. 2006;25:468-9.
22. Theiler G, Quehenberger F, Rainer F, Neubauer M, Stettin M, Robier C. The detection of calcium pyrophosphate crystals in the synovial fluid of patients with rheumatoid arthritis using the cytospin technique: prevalence and clinical correlation. Rheumatol Int. 2014;34:137-9.
23. 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.

24. 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.

25. Neame RL, Carr AJ, Muir K, Doherty M. UK community prevalence of knee chondrocalcinosis: evidence that correlation with osteoarthritis is through a shared association with osteophyte. Ann Rheum Dis. 2003;62:513-8.

26. Ciesielski O, Biesiekierska M, Panthu B, Soszyński M, Pirola L, Balcerczyk A. Citrullination in the pathology of inflammatory and autoimmune disorders: recent advances and future perspectives. Cell Mol Life Sci. 2022;79:94.

27. Krekeler M, Braliakos X, Tsiami S, Braun J. High prevalence of chondrocalcinosis and frequent comorbidity with calcium pyrophosphate deposition disease in patients with seronegative rheumatoid arthritis. RMD Open. 2022;8:e002383.

28. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis. 2023;82:3-18.

29. Parperis K, Papachristodoulou E, Kakoullis L, Rosenthal AK. Management of calcium pyrophosphate crystal deposition disease: a systematic review. Semin Arthritis Rheum. 2021;51:84-94.

30. Abhishek A, Tedeschi SK, Pascart T, et al. The 2023 ACR/EULAR classification criteria for calcium pyrophosphate deposition disease. Ann Rheum Dis. 2023;82:1248-57.

31. Bergstra SA, Chopra A, Saluja M, et al. Evaluation of the joint distribution at disease presentation of patients with rheumatoid arthritis: a large study across continents RMD Open. 2017;3:e000568.

32. Pekdiker M, Oğuzman H. The first involved joints and associated factors in patients with rheumatoid arthritis Arch Rheumatol. 2024;39:274-84.

33. Miksanek J, Rosenthal AK. Imaging of calcium pyrophosphate deposition disease. Curr Rheumatol Rep. 2015;17:20.

34. Cabral AR, Loya BL, Alarcón-Segovia D. Bone remodeling and osteophyte formation after remission of rheumatoid arthritis. J Rheumatol. 1989;16:1421-7.

35. Cipolletta E, Filippou G, Scirè CA, et al. The diagnostic value of conventional radiography and musculoskeletal ultrasonography in calcium pyrophosphate deposition disease: a systematic literature review and meta-analysis. Osteoarthritis Cartilage. 2021;29:619-32.

36. McCarty DJ. Calcium pyrophosphate dihydrate crystal deposition disease--1975. Arthritis Rheum. 1976;19:275-85.

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

Letter to the Editor / Editöre Mektup

DOI: 10.4274/raed.galenos.2025.07108
Ulus Romatol Derg 2025;17(3):195-197

Evaluating sleep quality in elderly rheumatoid arthritis: Strengths and shortcomings

Yaşlı romatoid artritte uyku kalitesinin değerlendirilmesi: Güçlü ve zayıf yönler

Selin Cilli Hayıroğlu

İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Rheumatology, İstanbul, Türkiye

Keywords: Rheumatoid arthritis, sleep quality, quality of life, disease activity, elderly patients
Anahtar Kelimeler: Romatoid artrit, uyku kalitesi, yaşam kalitesi, hastalık aktivitesi, yaşlı hastalar

Dear Editor,

I read with great interest the article "Sleep problems in elderly patients with rheumatoid arthritis: Contributing factors and quality of life implications" published in the Ulusal Romatoloji Dergisi.[1] This study makes a valuable contribution to our understanding of the prevalence of sleep disturbances in rheumatoid arthritis (RA) patients and the impact of these disturbances on patients' quality of life. However, several aspects of the article warrant critical evaluation.

The study's strengths are immediately apparent in its methodical approach. The authors clearly defined their objective: to identify factors contributing to poor sleep quality in elderly RA patients and to assess the impact of sleep quality on their quality of life. To achieve this, they employed a cross-sectional design, recruiting patients aged 65 years and older from a rheumatology outpatient clinic. This focus on an older population is particularly commendable, given the increasing prevalence of RA with age and the unique challenges faced by elderly individuals with chronic conditions.[2] The choice of assessment tools further underscores the study's rigor. The Pittsburgh sleep quality index (PSQI), a widely validated instrument, was used to evaluate sleep quality. This allowed for a standardized and quantifiable measure of sleep disturbances. Disease activity in RA was assessed using the disease activity score-C-reactive protein score, a standard clinical measure, ensuring that disease severity was accurately accounted for. Quality of life was evaluated with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, providing a comprehensive assessment of various domains of well-being. The inclusion of these validated tools strengthens the reliability and validity of the study's findings. The statistical analysis was also appropriate and well-executed. The authors used both descriptive and inferential statistics to analyze their data. They appropriately employed parametric and non-parametric tests based on the distribution of the data. Most notably, the use of multivariate regression analysis to identify independent predictors of poor sleep quality is a significant strength. This sophisticated statistical technique allowed the researchers to control for potential confounders and isolate the factors that most strongly influence sleep quality in this population. The findings of the study have important clinical implications. The identification of older age, being single, active RA, and depression as independent risk factors for poor sleep quality highlights the need for clinicians to proactively assess and manage these issues in elderly RA patients. The study also demonstrates the significant impact of poor sleep quality on various domains of quality of life, including physical,

Correspondence / İletişim:
Selin Cilli Hayıroğlu MD, İstanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Rheumatology, İstanbul, Türkiye
E-mail: selincilli@hotmail.com.tr **ORCID ID:** orcid.org/0000-0002-9302-8437
Received / Geliş Tarihi: 27.04.2025 **Accepted / Kabul Tarihi:** 24.07.2025 **Epub:** 03.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Cilli Hayıroğlu S. Evaluating sleep quality in elderly rheumatoid arthritis: strengths and shortcomings. J Turk Soc Rheumatol. 2025;17(3):195-197

emotional, and role functioning. This underscores the importance of addressing sleep disturbances not only to improve sleep itself but also to enhance patients' overall well-being.

Despite its strengths, the study is not without limitations that warrant critical evaluation. The most significant limitation is the cross-sectional design. As the authors themselves acknowledge, this design provides a snapshot of the relationship between sleep quality and other variables at a single point in time. Consequently, it is impossible to determine the direction of causality. For example, while the study found a strong association between depression and poor sleep quality, it cannot tell us whether depression causes sleep disturbances or whether sleep disturbances contribute to depression. Longitudinal studies, which follow patients over time, are needed to elucidate these causal relationships. The generalizability of the findings is another concern. The study was conducted at a single tertiary healthcare institution, and the sample size (n=77) was relatively small. Patients attending a tertiary centre may have more severe or complex RA than those managed in primary care settings.[3] Furthermore, the study population's demographic characteristics may not be representative of all elderly RA patients. Therefore, caution is warranted when extrapolating these findings to broader populations. While the authors briefly mention the role of inflammation and neuroendocrine dysregulation, a concise discussion of key cytokines such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6 could have enriched the mechanistic context. These pathways may represent important targets for therapeutic interventions aimed at improving sleep quality in RA.[4] Understanding these mechanisms could lead to the development of targeted therapies for sleep disturbances in RA.[5] The assessment of sleep quality relied solely on the PSQI, a subjective measure. While PSQI is a valuable tool, it is susceptible to recall bias and may not fully capture the complexity of sleep disturbances.[6] For instance, Fabbri et al.[6] emphasized that subjective instruments like the PSQI often diverge from objective measurements such as actigraphy and polysomnography, potentially limiting their diagnostic precision. The inclusion of objective measures of sleep, such as polysomnography or actigraphy, could have provided a more comprehensive and accurate assessment of sleep quality. Finally, the study could have benefited from a more in-depth analysis of the relationship between RA treatment and sleep quality, as this aspect was not comprehensively addressed in the published article. While the authors mention the medications used by the patients, they do not extensively discuss the potential impact of these medications on sleep. This is particularly important given that corticosteroids, such as dexamethasone, have been shown to induce dose-dependent sleep disturbances, as demonstrated in recent experimental studies.[7] Corticosteroids, for example, are known to cause insomnia, while other RA medications may have different effects on sleep.[7] A detailed analysis of how specific medications influence sleep quality in this population would be clinically relevant.

In conclusion, the study by Kayahan Satış and Satış[1] provides valuable insights into the prevalence of sleep disturbances and their impact on quality of life in elderly RA patients. The authors are to be commended for their rigorous methodology and the clinical relevance of their findings. However, the limitations of the cross-sectional design, the small sample size, the lack of mechanistic exploration, the reliance on subjective sleep measures, and the limited analysis of treatment-related effects on sleep should be acknowledged. Future research should address these limitations to further advance our understanding of sleep disturbances in RA. Longitudinal studies are needed to establish causal relationships. Larger, multi-centre studies with more diverse patient populations would enhance the generalizability of the findings. Mechanistic studies exploring the specific inflammatory and neurobiological pathways involved in sleep disturbances in RA are warranted. The inclusion of objective sleep measures, such as polysomnography and actigraphy, would provide a more comprehensive assessment of sleep quality. Finally, a detailed analysis of the impact of RA treatments on sleep is crucial for optimizing patient care. By addressing these limitations and pursuing further research, we can gain a more comprehensive understanding of sleep disturbances in RA, and develop more effective strategies to improve the sleep and overall well-being of affected individuals.

Footnotes

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

Financial Disclosure: The author declared that they received no financial support.

References

1. Kayahan Satış N, Satış H. Sleep problems in elderly patients with rheumatoid arthritis: contributing factors and quality of life implications. Ulus Romatol Derg. 2025;17:45-52.
2. Pavlov-Dolijanovic S, Bogojevic M, Nozica-Radulovic T, Radunovic G, Mujovic N. Elderly-onset rheumatoid arthritis: characteristics and treatment options. Medicina (Kaunas). 2023;59:1878.
3. Inchingolo F, Inchingolo AM, Fatone MC, et al. Management of rheumatoid arthritis in primary care: a scoping review. Int J Environ Res Public Health. 2024;21:662.

4. Krueger JM. The role of cytokines in sleep regulation. Curr Pharm Des. 2008;14:3408-16.

5. Garbarino S, Lanteri P, Bragazzi NL, Magnavita N, Scoditti E. Role of sleep deprivation in immune-related disease risk and outcomes. Commun Biol. 2021;4:1304.

6. Fabbri M, Beracci A, Martoni M, Meneo D, Tonetti L, Natale V. Measuring subjective sleep quality: a review. Int J Environ Res Public Health. 2021;18:1082.

7. Kato T, Okawa G, Tanaka KF, Mitsukura Y. Dexamethasone induces sleep disturbance in a dose-dependent manner in mice. PLoS One. 2023;18:e0296028.

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

Letter to the Editor / Editöre Mektup

DOI: 10.4274/raed.galenos.2025.77699
Ulus Romatol Derg 2025;17(3):198-199

The emerging role of climate modeling in understanding rheumatic disease burden

Romatizmal hastalık yükünün anlaşılmasında iklim modellemesinin ortaya çıkan rolü

Cennet Nur Erdoğdu[1], Beyza Öztürk[2], Burcu Hazer[1], Fatih Bağcıer[1]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Haseki Training and Research Hospital, İstanbul, Türkiye

Keywords: Rheumatic diseases, climate change, weather and health
Anahtar Kelimeler: Romatolojik hastalıklar, iklim değişikliği, hava durumu ve sağlık

Dear Editor,

Rheumatic diseases such as rheumatoid arthritis (RA), osteoarthritis (OA), systemic lupus erythematosus, and ankylosing spondylitis are lifelong conditions characterized by pain, inflammation, and fluctuating disease activity.[1] Genetics, immune dysfunction, and lifestyle factors are the cornerstones of our understanding of these diseases. However, environmental conditions, particularly climate-related variables, are often underappreciated despite their substantial effects on symptom severity.[1] Many patients report that changes in weather, humidity, and air pollution exacerbate pain and stiffness.[1] Nevertheless, clinical practice has not yet systematically incorporated these environmental triggers into disease management.

Nvidia recently introduced its advanced artificial intelligence-based climate modeling platform, "Climate in a Bottle", which is capable of predicting environmental changes with remarkable precision.[1] Although designed primarily for global climate simulations, this technology holds significant potential in healthcare, particularly rheumatology. By forecasting temperature fluctuations, humidity levels, barometric pressure shifts, and air quality patterns, such models could help anticipate periods when patients with rheumatic diseases are likely to experience symptom flare-ups.

The existing literature has already established associations between climate factors and rheumatic disease activity.[2] Sudden temperature drops, increased humidity, and decreased barometric pressure are frequently associated with heightened joint pain and swelling, especially in patients with RA and OA.[2] Moreover, air pollution, particularly fine particulate matter, has been shown to increase systemic inflammation, thereby aggravating autoimmune processes.[3] To date, clinicians have lacked the tools to provide patients with advance warnings of these environmental changes. Climate modeling may enable the anticipation of such triggers, allowing clinicians to counsel patients before symptoms intensify.

It is clear that weather conditions influence patient behaviour. During periods of extreme cold or hot weather, outdoor activity typically declines, resulting in reduced physical exercise.[3] For patients with rheumatic diseases, maintaining an active lifestyle is essential to preserving joint mobility and reducing stiffness. Anticipating adverse weather

Correspondence / İletişim: Cennet Nur Erdoğdu MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Physical Medicine and Rehabilitation, İstanbul, Türkiye
E-mail: cennetnur17@gmail.com **ORCID ID:** orcid.org/0009-0004-9068-2208
Received / Geliş Tarihi: 10.07.2025 **Accepted / Kabul Tarihi:** 18.09.2025 **Epub:** 02.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Erdoğdu CN, Öztürk B, Hazer B, Bağcıer F. The emerging role of climate modeling in understanding rheumatic disease burden. J Turk Soc Rheumatol. 2025;17(3):198-199

could therefore allow clinicians to recommend indoor exercise regimens and make timely treatment adjustments to maintain disease control.

In addition to physical factors, psychosocial variables influence how patients perceive and respond to climate-related risks. Recent machine learning studies have demonstrated that beliefs about climate change –and by extension, health behaviours– are shaped by both individual characteristics and broader cultural contexts. Integrating environmental forecasts with patient-specific disease patterns, activity levels, and psychosocial factors is essential for delivering truly personalized care plans.[3]

While existing literature has described associations between climate factors and rheumatic disease activity, much of this evidence remains observational or anecdotal, with limited validation from controlled trials or meta-analyses. Advancing the scientific foundation will require identifying specific, testable biological mechanisms such as inflammatory cytokine responses, immune cell activation, or epigenetic modifications- that can directly link environmental exposures to disease pathology.

It is also important to acknowledge limitations of large-scale climate models, which were originally designed for global or regional applications. These models cannot yet account for patient-specific factors such as genetics, comorbidities, lifestyle, and treatment regimens, all of which are crucial for personalized disease forecasting. Consequently, their most immediate utility in rheumatology may lie in identifying population-level risk periods (e.g., seasonal flare-up trends) rather than providing precise individual forecasts. To advance toward clinical integration, initial pilot studies should be conducted, followed by the resolution of implementation challenges, and ultimately the development of a structured framework for clinical adoption. Future progress will rely on combining climate modeling with personalized health data and rigorous clinical validation, paving the way for precision-based patient care.

In conclusion, rheumatologists must seize the opportunity to incorporate advanced climate modeling into patient care, shifting from a reactive to a preventive approach.[4] Tools such as those exemplified by "Climate in a Bottle" could allow prediction of environmentally driven disease flare-ups and enable proactive treatment planning. Collaboration among rheumatologists, climate scientists, and public health experts will be essential to refine and validate these models for clinical use. This forward-looking approach has the potential to substantially improve the quality of life for millions of individuals living with rheumatic diseases worldwide.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.N.E., B.Ö., B.H., F.B., Concept: C.N.E., B.Ö., B.H., F.B., Design: C.N.E., B.Ö., B.H., F.B., Data Collection and Processing: C.N.E., B.Ö., B.H., F.B., Analysis or Interpretation: C.N.E., B.Ö., B.H., F.B., Literature Search: C.N.E., B.Ö., B.H., F.B., Writing: C.N.E., B.Ö., B.H., F.B.

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

Financial Disclosure: The authors declared that they received no financial support.

References

1. Sangha O. Epidemiology of rheumatic diseases. Rheumatology (Oxford). 2000;39(Suppl 2):3-12.
2. Latman NS. Influence of atmospheric factors on the rheumatic diseases. Experientia. 1987;43:32-8.
3. Katsumoto TR, Stolyar L, Dandeniya CL, et al. Impact of climate change on rheumatic diseases: a scoping review. The Journal of Climate Change and Health. 2024;19:100338.
4. Mruthyunjaya P, Sondur S, Ahmed S, Grainger R. The climate emergency for rheumatologists: where do we stand? Clin Rheumatol. 2025;44:573-82.

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

Case Report / Olgu Sunumu

DOI: 10.4274/raed.galenos.2025.15238
Ulus Romatol Derg 2025;17(3):200-203

Stevens-Johnson syndrome triggered by cyclophosphamide: A rare clinical observation

Siklofosfamid ile tetiklenen Stevens-Johnson sendromu: Nadir bir klinik gözlem

Muzaffar Bindroo[1], Mushtaq Dangroo[1], Farah Sameem[2], Danish Mushtaq Shah[1], Aadil Bashir[1]

[1]Sheri Kashmir Institute of Medical Sciences, Department of Rheumatology, Srinagar, India
[2]Skims Medical College, Department of Dermatology, Srinagar, India

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are rare, life-threatening mucocutaneous hypersensitivity reactions, predominantly triggered by medications such as antibiotics, antiepileptics, and non-steroidal anti-inflammatory drugs. Cyclophosphamide, though extensively used in autoimmune diseases and malignancies, is infrequently implicated in adverse reactions or complications. We report a rare case of SJS induced by cyclophosphamide in a patient with systemic lupus erythematosus and lupus nephritis. This case underscores the need for heightened clinical vigilance for rare but severe adverse drug reactions while managing patients with severe autoimmune diseases. Prompt recognition and withdrawal of the offending drug are essential for favorable outcomes.

Keywords: Stevens-Johnson syndrome, cyclophosphamide, systemic lupus erythematosus, adverse drug reaction

Özet

Stevens-Johnson sendromu (SJS) ve toksik epidermal nekroliz, nadir görülen ve hayatı tehdit eden mukokutanöz aşırı duyarlılık reaksiyonlarıdır. Bu reaksiyonlar çoğunlukla antibiyotikler, antiepileptikler ve steroid olmayan anti-enflamatuvar ilaçlar gibi ilaçlar tarafından tetiklenir. Otoimmün hastalıklar ve malignitelerde yaygın olarak kullanılan siklofosfamid ise nadiren bu reaksiyonlara sebep olmaktadır. Biz, lupus nefritli sistemik lupus eritematozus hastasında siklofosfamid kaynaklı nadir bir SJS olgusunu sunuyoruz. Bu olgu, ağır otoimmün hastalıkların tedavisinde nadir fakat ciddi ilaç yan etkilerine karşı klinik dikkat ve farkındalığın artırılması gerektiğini vurgulamaktadır. Suçlu ilacın hızlı tanınması ve kesilmesi, olumlu sonuçlar için hayati öneme sahiptir.

Anahtar Kelimeler: Stevens-Johnson sendromu, siklofosfamid, sistemik lupus eritematozus, advers ilaç reaksiyonu

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe mucocutaneous hypersensitivity reactions, most frequently induced by medications. It is characterized by widespread epidermal necrosis, skin detachment, and involvement of multiple mucosal sites. Common culprits include antibiotics, antiepileptics, and non-steroidal anti-inflammatory drugs (NSAIDs).[1] Early diagnosis and immediate discontinuation of the offending drug are critical. SJS is considered a medical emergency. Cyclophosphamide, an alkylating agent widely used in the treatment of autoimmune diseases and malignancies, is not commonly associated with SJS. Reports of cyclophosphamide-induced SJS are exceedingly rare in the literature. We present a unique case of SJS in a patient with systemic lupus erythematosus (SLE) and lupus nephritis, caused by cyclophosphamide, underscoring the need for heightened clinical awareness even with less commonly implicated agents.

Case Presentation

A 23-year-old male with a history of vitiligo since childhood, initially presented with polyarthritis involving the small joints of the hands, wrists, knees, and ankles in a

Correspondence / İletişim:
Muzaffar Bindroo MD, Sheri Kashmir Institute of Medical Sciences, Department of Rheumatology, Srinagar, India
E-mail: bindroomuzaffar@gmail.com **ORCID ID:** orcid.org/0000-0002-6317-840X
Received / Geliş Tarihi: 27.05.2025 **Accepted / Kabul Tarihi:** 06.10.2025 **Epub:** 27.10.2025 **Publication Date / Yayın Tarihi:** 28.11.2025

Cite this article as / Atıf: Bindroo M, Dangroo M, Sameem F, Shah DM, Bashir A. Stevens-Johnson syndrome triggered by cyclophosphamide: a rare clinical observation. J Turk Soc Rheumatol. 2025;17(3):200-203

bilaterally symmetrical pattern, along with fever (recorded between 100-101 °F) and a skin rash over the malar eminences. These symptoms had been present for the past three months. On evaluation, he was found to have an elevated erythrocyte sedimentation rate (55 mm/hr), high C-reactive protein (23 mg/dL), negative rheumatoid factor, negative anti-cyclic citrullinated peptide antibody, and positive anti-nuclear antibody (by indirect immunofluorescence assay) (titer 1:160, homogeneous pattern). He was admitted for further evaluation. Subsequent investigations revealed high levels of anti-dsDNA, low complement levels (C3 and C4), and significant proteinuria on 24-hour urinary protein estimation (2.2 g/day). A kidney biopsy was performed, which revealed Class IV lupus nephritis with poor prognostic features, including crescents and fibrinoid necrosis (Figure 1). In view of these findings, he was treated with pulse methylprednisolone (500 mg daily for three consecutive days) along with the first dose of cyclophosphamide (15 mg/kg body weight). He was also started on hydroxychloroquine and angiotensin-converting enzyme inhibitors. The patient improved clinically with resolution of joint pain, subsidence of fever, and disappearance of the malar rash. He was discharged on oral prednisolone 60 mg daily and advised to continue monthly cyclophosphamide infusions. However, two weeks later, he developed generalized weakness, fatigue, malaise, fever, and new-onset skin rashes involving the face and trunk (Figures 2 and 3), which were associated with oral ulcerations. He was readmitted and re-evaluated for disease activity and other possible causes of the rash. Laboratory investigations revealed negative anti-dsDNA, normal C3 and C4 levels, and negative infectious work-up, including viral serologies for herpes and CMV. A dermatology consult was obtained, and a skin biopsy was performed. Histopathology revealed hydropic degeneration of the basal layer with spongiosis, apoptotic keratinocytes, dermoepidermal clefting, epidermal necrosis, and moderate dermal inflammation with pigment incontinence. Direct immunofluorescence was negative for immunoglobulin (Ig)

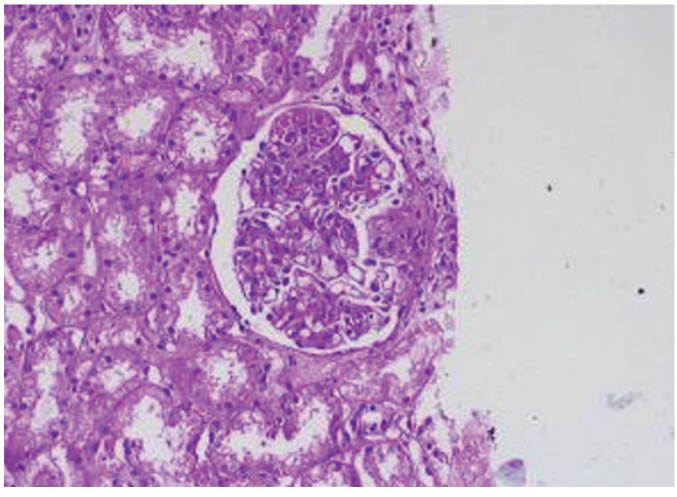

Figure 1. Kidney biopsy showing features of class IV lupus nephritis

Figure 2. Showing erythematous raised rashes with dusky centers, over anterior body surface with vitiligo patches

Figure 3. Showing erythematous macular raised rashes with dusky centers over head & neck area

M, IgG, C3, C1q, and IgA. These findings were consistent with SJS (Figure 4). The patient was again treated with pulse methylprednisolone (500 mg daily for three days) and intravenous Ig (IVIg) was planned. His condition improved, with resolution of fever and marked improvement in skin lesions. Cyclophosphamide was discontinued, and he was switched to Mycophenolate Mofetil and Tacrolimus. On follow-up visits, there was complete resolution of skin and mucosal lesions. At the three-month follow-up, oral steroids were tapered to 15 mg/day, and his proteinuria had decreased to 800 mg/24 hours. Currently, his disease remains in remission, and he has been advised to continue regular follow-up every 2-3 months.

Discussion

SJS/TEN is a rare, severe mucocutaneous reaction characterized by extensive necrosis and detachment of the epidermis. It is most commonly triggered by medications such as sulfonamides, anticonvulsants, and NSAIDs.[2] While cyclophosphamide is widely used as an immunosuppressive agent in various autoimmune conditions, reports of cyclophosphamide-induced SJS are exceedingly rare.[2] In the presented case, a 23-year-old male with SLE, and biopsy-proven Class IV lupus nephritis developed erythematous skin rashes following the administration of cyclophosphamide. The initial impression was that the skin rash was likely related to either active lupus disease or an infective cause, given the use of strong immunosuppressants, including cyclophosphamide and high-dose steroids. However, his infectious work-up was negative.[3,4] To our surprise, skin biopsy findings were suggestive of SJS. A literature review revealed that cyclophosphamide-induced SJS is extremely rare. Jarret et al.[5] reported SJS in a male patient with breast carcinoma who was treated with docetaxel and cyclophosphamide, who developed SJS after the fourth chemotherapy cycle. Unfortunately, their patient died due to severe complications despite receiving steroids, IVIg, and supportive care. In contrast, our patient survived, possibly due to early recognition and discontinuation of the offending drug. Another case was reported by Chowdhury et al.[6] in a patient with seronegative rheumatoid vasculitis who received cyclophosphamide. Assier-Bonnet et al.[7] reported two cases of SJS linked to cyclophosphamide: a 55-year-old woman with Wegener's granulomatosis and a 53-year-old woman with polymyositis, both of whom developed severe skin eruptions that resolved after discontinuing cyclophosphamide, thereby confirming it as the likely cause. The uniqueness of our case lies in the relatively mild involvement of mucosal surfaces compared to extensive skin involvement, with no classical blistering or skin detachment. Additionally, there are case reports describing SLE itself presenting as SJS.[8] However, in our patient, the resolution of skin rashes following the discontinuation of cyclophosphamide along with close follow-up strongly suggested a drug-induced reaction rather than primary lupus activity. In previous case reports, oral cyclophosphamide was used, whereas our case involved intravenous administration. Additionally, the mild mucosal involvement in our patient could have been easily mistaken for SLE manifestations. The management of SJS primarily involves immediate cessation of the offending agent and supportive care, which includes fluid and electrolyte management, meticulous wound care, and prevention of secondary infections. The use of systemic corticosteroids in SJS remains controversial. Some studies suggest that early administration may help halt disease progression and reduce mortality. In our case, the patient received pulse methylprednisolone therapy, which led to significant clinical improvement. As alternative immunosuppressive therapy, the patient was switched to mycophenolate mofetil and tacrolimus. These agents have demonstrated efficacy in inducing and maintaining remission in lupus nephritis while avoiding the risk of severe cutaneous adverse drug reactions.[9] Biologic agents such as etanercept have also been reported as potential therapeutic options in severe SJS/TEN, particularly when initiated early in the disease course.[10] However, these treatments require further validation through controlled clinical studies. Prompt recognition, immediate withdrawal of the offending drug, and early intervention are crucial to improving patient outcomes.[11]

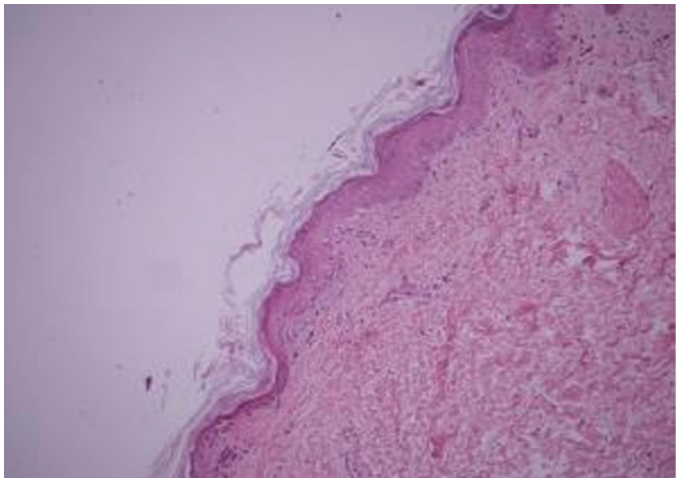

Figure 4. Showing hydropic degeneration of basal layer with spongiosis, dermoepidermal clefting, apoptotic keratinicytes

Conclusion

This case underscores the importance of vigilance for rare but potentially life-threatening adverse drug reactions,

such as SJS, in patients receiving cyclophosphamide. Clinicians should maintain a high index of suspicion when patients develop mucocutaneous symptoms following drug administration. Clinicians should remain vigilant for cutaneous adverse drug reactions, even with medications not commonly associated with SJS, to ensure timely diagnosis and management.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Concept: M.B., M.D., F.S., D.M.S., A.B., Design: M.B., M.D., F.S., D.M.S., A.B., Data Collection or Processing: M.B., M.D., F.S., D.M.S., A.B., Analysis or Interpretation: M.B., M.D., F.S., D.M.S., A.B., Literature Search: M.B., M.D., F.S., D.M.S., A.B., Writing: M.B., M.D., F.S., D.M.S., A.B.

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

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

References

1. Harr T, French LE. Stevens-Johnson syndrome and toxic epidermal necrolysis. Dermatol Clin. 2013;31:587-600.
2. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331:1272-85.
3. Mockenhaupt M. The current understanding of Stevens–Johnson syndrome and toxic epidermal necrolysis. Expert Rev Clin Immunol. 2011;7:803-15.
4. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129:92-6.
5. Jarrett B, Ghazala S, Chao J, Chaudhary S. Case of Steven-Johnson syndrome in a male with breast cancer secondary to docetaxel/cyclophosphamide therapy. BMJ Case Rep. 2016;2016:bcr2016217255.
6. Chowdhury AC, Misra DP, Patro PS, Agarwal V. Toxic epidermal necrolysis due to therapy with cyclophosphamide and mesna. A case report of a patient with seronegative rheumatoid arthritis and rheumatoid vasculitis. Z Rheumatol. 2016;75:200-2.
7. Assier-Bonnet H, Aractingi S, Cadranel J, Wechsler J, Mayaud C, Saiag P. Stevens-Johnson syndrome induced by cyclophosphamide: report of two cases. Br J Dermatol. 1996;135:864-6.
8. Lee HY, Tey HL, Pang SM, Thirumoorthy T. Systemic lupus erythematosus presenting as Stevens-Johnson syndrome and toxic epidermal necrolysis: a report of three cases. Lupus. 2011;20:647-52.
9. Yang Y, Xu J, Chen Y, et al. Successful treatment of severe lupus nephritis with mycophenolate mofetil and tacrolimus. Ren Fail. 2014;36:1523-7.
10. Paradisi A, Abeni D, Bergamo F, Ricci F. Etanercept therapy for toxic epidermal necrolysis. J Am Acad Dermatol. 2014;71:278-83.
11. Sharma VK, Sethuraman G, Kumar B. Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme: clinical pattern in India. Int J Dermatol. 1996;35:523-7.

Abdurrahman Tufan
Adem Ertürk
Amra Adrovic
Aslıhan Avanoğlu Güler
Atalay Doğru
Ayşe Cefle
Ayten Yazıcı
Belkıs Nihan Coşkun
Berivan Bitik
Berna Yurttaş
Betül Sözeri
Burak İnce
Cemal Bes
Didar Uçar
Dilek Solmaz
Döndü Üsküdar Cansu
Duygu Ersözlü
Ebru Atalar
Ediz Hüseyin Dalkılıç
Emel Gönüllü
Fatih Yıldız
Gerçek Can
Gezmiş Kimyon
Gökçe Kenar Artın
Gökhan Keser
Gökhan Sargın
Gözde Kübra Yardımcı
Hakan Apaydın
Hakan Emmungil
Hamit Küçük
Handan Yarkan
Hazan Karadeniz
İsmail Sarı
Kenan Barut
Levent Kılıç
M. Nedim Taş
Mehmet Akif Öztürk
Mehmet Derya Demirağ
Mehmet Engin Tezcan
Mehmet Soy
Mehmet Yıldız
Melike Ersoy
Mete Pekdiker
Murat Bektaş
Mustafa Özmen
Ömer Karadağ
Rıdvan Mercan
Rıza Can Kardaş
Sadettin Uslu
Sema Kaymaz Tahra
Sezgin Şahin
Ufuk İlgen
Veli Yazısız
Yeşim Özgüler
Yüksel Maraş

Hazırlayan: Gülay Koca

2024 ve 2025 yılından HABERLER

XVIII. Romatoloji Uzmanlık Öğrencileri ve Uzmanları İçin Eğitim Kursu & X. Romatolojide Yaklaşımlar ve Profesörler ile Yuvarlak Masa Toplantıları

• 4-7 Ocak 2024 tarihleri arasında Dr. Umut Kalyoncu, Dr. Timuçin Kaşifoğlu ve Dr. Cemal Bes başkanlığında, Antalya'da düzenlenen kursa 46 konuşmacı ve 120 katılımcı katkıda bulundu.

• Bu yıl 16-19 Ocak 2025 tarihleri arasında Antalya'da düzenlenen kursa ise 46 konuşmacı ve 103 katılımcı katkıda bulunmuştur.

TRD YAZ OKULU

• 10-12 Mayıs 2024 tarihleri arasında Dr. Umut Kalyoncu, Dr. Timuçin Kaşifoğlu ve Dr. Cemal Bes başkanlığında, Eskişehir'de düzenlenen kursa 34 konuşmacı ve 83 katılımcı katkıda bulundu..

* Bu yıl 23-25 Mayıs 2025 tarihleri arasında Ankara'da düzenlenen kursa 62 konuşmacı ve 80 katılımcı katkıda bulunmuştur.

ULUSAL ROMATOLOJİ KONGRESİ (2024-2025)

• "*24. Ulusal Romatoloji Kongresi*" 26-30 Ekim 2024 tarihleri arasında Dr. Cemal Bes ve Dr. Timuçin Kaşifoğlu başkanlığında 716 katılımcı ve 5'i yabancı olmak üzere toplam 155 konuşmacı ile Fethiye/Muğla'da düzenlenmiştir.

• "*25. Ulusal Romatoloji Kongresi*" *bu yıl 12-16 Kasım 2025 tarihleri arasında Dr. Murat İnanç başkanlığında* 691 katılımcı ve 6'sı yabancı olmak üzere toplam 187 konuşmacı ile Antalya'da düzenlenmiştir.

Dr. Christopher Denton ve Dr. Murat İnanç

• Dr. Christopher Denton ve Dr. Aladdin Mohammad'a Türkiye Romatoloji Derneği Onursal üyeliğine kabul edilmişler ve 25. Ulusal Romatoloji Kongresi'nde Onursal Üyelik Sertifikaları verilmiştir.

Dr. Aladdin Mohammad ve Dr. Ahmet Gül

TRD Genel Kurul Toplantısı 27 Nisan 2025 tarihinde İstanbul'da yapılmıştır.

2025-2027 dönemi TRD Yönetim Kurulu üyeleri

Dr. Ahmet Gül (Yönetim Kurulu Başkanı)

Dr. Murat İnanç (Başkan Yardımcısı)

Dr. G. Nevsun İnanç (Genel Sekreter)

Dr. Bahar Artım Esen (Sayman)

Dr. Cemal Bes(Sayman)

Dr. Süleyman Özbek (Üye)

Dr. Ahmet Omma (Üye)

Dr. H.Ediz Dalkılıç (Üye)

Dr. Adem Küçük (Üye)

2025-2027 dönemi TRD Denetleme Kurulu üyeleri

Dr. İzzet Fresko

Dr. Sedat Kiraz

Dr. A. Gökhan Keser


TÜRKİYE
ROMATOLOJİ
DERNEĞİ
25


TÜRKİYE
ROMATOLOJİ
DERNEĞİ

2024 ve 2025 yıllarında profesörlük ve doçentlik unvanı alan üyelerimizi tebrik eder, akademik yaşamlarında başarılar dileriz.			
Prof. Dr.	Ahmet	Omma	SBÜ Ankara Bilkent Şehir Hastanesi (SUAM)
Prof. Dr.	Ali	Akdoğan	Hacettepe Üniversitesi Tıp Fakültesi
Prof. Dr.	Sait Burak	Erer	Memorial Hastanesi
Prof. Dr.	Songül	Çildağ	Adnan Menderes Üniversitesi Tıp Fakültesi
Prof. Dr.	Rıdvan	Mercan	Namık Kemal Üniversitesi Tıp Fakültesi
Prof. Dr.	Atalay	Doğru	Süleyman Demirel Üniversitesi Tıp Fakültesi
Prof. Dr.	Servet	Yolbaş	İnönü Üniversitesi Tıp Fakültesi
Prof. Dr.	Gonca	Karabulut	Ege Üniversitesi Tıp Fakültesi
Prof. Dr.	Yasemin	Yalçınkaya	İ.Ü. İstanbul Tıp Fakültesi
Prof. Dr.	Yüksel	Maraş	SBÜ Ankara Bilkent Şehir Hastanesi
Prof. Dr.	Gökhan	Sargın	Adnan Menderes Üniversitesi Tıp Fakültesi
Prof. Dr.	Mehtap	Tınazlı	Yakındoğu Üniversitesi Tıp Fakültesi
Doç. Dr.	Sadettin	Uslu	Celal Bayar Üniversitesi Tıp Fakültesi
Doç. Dr.	Mete	Pekdiker	Hatay Mustafa Kemal Üniversitesi Tıp Fakültesi
Doç. Dr.	Esra	Kayacan	Ankara Bilkent Şehir Hastanesi
Doç. Dr.	Rabia	Deniz	Kars Harakani Devlet Hastanesi
Doç. Dr.	Emine	Sarıyıldız	Etlik Şehir Hastanesi
Doç. Dr.	Müçteba Enes	Yayla	Ankara Üniversitesi Tıp Fakültesi
Doç. Dr.	Tuğba	Demirci Yıldırım	İzmir Şehir Hastanesi
Doç. Dr.	Özlem	Özdemir Işık	Kocaeli Şehir Hastanesi
Doç. Dr.	Ali	Ekin	Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi
Doç. Dr.	Hatice Ecem	Konak	SBÜ Ankara Bilkent Şehir Hastanesi
Doç. Dr.	Gökçe	Kenar	Dokuz Eylül Üniversitesi Tıp Fakültesi
Doç. Dr.	Erdal	Bodakçi	Eskişehir Şehir Hastanesi
Doç. Dr.	Derya	Yıldırım	Sincan E.A.H.
Doç. Dr.	Senem	Tekeoğlu	Bezmiâlem Vakıf Üniversitesi
Doç. Dr.	Bahar	Özdemir Ulusoy	Ankara Gaziler FTR E.A.H.
Doç. Dr.	Adem	Ertürk	Afyon Sağlık Bilimleri Üniversitesi

2024 ve 2025 yıllarında profesörlük ve doçentlik unvanı alan üyelerimizi tebrik eder, akademik yaşamlarında başarılar dileriz.			
Doç. Dr.	Aslıhan	Avanoğlu Güler	Ağrı Eğitim ve Araştırma Hastanesi
Doç. Dr.	Burcu	Yağız	Uludağ Üniversitesi Tıp Fakültesi
Doç. Dr.	Ebru	Atalar	SBÜ Ankara Bilkent Şehir Hastanesi (SUAM)
Doç. Dr.	Emre	Bilgin	Sakarya Üniversitesi Tıp Fakültesi
Doç. Dr.	Fatih	Yıldız	Kahramanmaraş Sütçü İmam Üniversitesi
Doç. Dr.	Hakan	Apaydın	Ankara Etlik Şehir Hastanesi
Doç. Dr.	Hazan	Karadeniz	SBÜ-Gülhane Tıp Fakültesi
Doç. Dr.	İsmail	Doğan	Yıldırım Beyazıt Üni. Ankara Şehir Hast.
Doç. Dr.	Murat	Bektaş	İstanbul Sağlık ve Teknoloji Üniversitesi
Doç. Dr.	Mustafa	Erdoğan	Marmara Üniversitesi Tıp Fakültesi
Doç. Dr.	Ufuk	İlgen	Heidelberg University, Almanya
Doç. Dr.	Sinem Nihal	Esatoğlu	İ.Ü.C.-Cerrahpaşa Tıp Fakültesi
Doç. Dr.	Yeşim	Özgüler	İ.Ü.C.-Cerrahpaşa Tıp Fakültesi

2024 ve 2025 yılında emekli olan üyelerimize, Romatoloji Bilim Dalı'nın gelişmesine ve Derneğimize yapmış oldukları değerli katkılar nedeniyle teşekkür eder, sağlıklı, mutlu bir emeklilik dönemi dileriz.

Prof. Dr. Fatoş Önen
(Dokuz Eylül Üniversitesi Tıp Fakültesi)

Prof. Dr. Nurullah Akkoç
(Celal Bayar Üniversitesi Tıp Fakültesi)

Prof. Dr. Yasemin Kabasakal
(Ege Üniversitesi Tıp Fakültesi)

Prof. Dr. Şeminur Haznedaroğlu
(Gazi Üniversitesi Tıp Fakültesi)

Derneğimiz Tarafından 2024-2025 yıllarında Verilen Ödüller

Türkiye Romatoloji Derneği'nin 2004 yılından bu yana her 2 yılda bir verdiği Hulusi Behçet Ödülü bu yıl Japonya'dan Mitsuhiro Takeno ve Türkiye'den Prof. Gülen Hatemi'ye verilmiştir. Ödüller 18-20 Eylül 2024 tarihinde Marrakech'te yapılan 20. Uluslararası Behçet Hastalığı Kongresi'nde Türkiye Romatoloji Derneği yönetim kurulu adına Prof. Dr. Ahmet Gül tarafından verilmiştir. Ödül kazanan araştırıcıları tebrik eder, çalışmalarında başarılar dileriz.

24. Ulusal Romatoloj Kongresine gönderilen bildiriler arasından TRD BİLDİRİ ödüllerini almaya hak kazanan çalışmalar;

BİRİNCİLİK ÖDÜLÜ

"BEHÇET HASTALIĞI AYIRICI TANISINDA NÖROFİLAMENT ORTA SEROLOJİK İMMÜNOREAKTİVİTENİN DUYARLILIĞI VE ÖZGÜLLÜĞÜNÜN ARAŞTIRILMASI"

Tayfun Hilmi Akbaba[1], Buket Dönmez Demir[2], Ayşe İlksen Çolpak[3], Yeliz Z Akkaya Ulum[1], Gizem Ayan[4], Şefik Evren Erdener[2], Aslı Tuncer[3], Umut Kalyoncu[4], Banu Balcı Peynircioğlu[1], Turgay Dalkara[5]

[1]Tıbbi Biyoloji Anabilim Dalı, Hacettepe Üniversitesi, Sıhhiye, Ankara, Türkiye
[2]Nörolojik Bilimler ve Psikiyatri Enstitüsü, Hacettepe Üniversitesi, Sıhhiye, Ankara, Türkiye
[3]Nöroloji Anabilim Dalı, Hacettepe Üniversitesi, Sıhhiye, Ankara, Türkiye
[4]İç Hastalıkları AnabilimDalı Romatoloji Bilim Dalı, Hacettepe Üniversitesi, Sıhhiye, Ankara, Türkiye
[5]Sinirbilim ve Moleküler Biyoloji ve Genetik Bölümleri, Bilkent Üniversitesi, Ankara, Türkiye

İKİNCİLİK ÖDÜLÜ

"BAMBU OMURGASI VE KLASİK ANKİLOZAN SPONDİLİT İÇİN GENETİK BİR ARKA PLAN TANIMLANMASI"

Kerem Abacar[1], Şeyma Çolakoğlu Özkaya[2], Yunus Emre Dilek[3], Günseli Bayram Akçapınar[3], Pamir Atagündüz[1], Can Erzik[2]

[1]Marmara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul
[2]Marmara Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, İstanbul
[3]Acıbadem Üniversitesi Tıp Fakültesi, Medikal Biyoloteknoloji Departmanı, İstanbul

ÜÇÜNCÜLÜK ÖDÜLÜ

"KOLŞİSİN TEDAVİSİ KESİLEN BEHÇET SENDROMU HASTALARINDA MUKOKUTANÖZ HASTALIK AKTİVİTESİ"

Başak Şirin Ünal[1], Sinem Nihal Esatoğlu[2], Hasan Yazıcı[3], Gülen Hatemi[2]

[1]İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, İç Hastalıkları Ana Bilim Dalı, İstanbul
[2]İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, İç Hastalıkları Ana Bilim Dalı, Romatoloji Bilim Dalı,İstanbul
[3]Academic Hospital, Romatoloji Kliniği, İstanbul

25. Ulusal Romatoloj Kongresine gönderilen bildiriler arasından POSTER SUNUM TEŞVİK ve TRD BİLDİRİ ödüllerini almaya hak kazanan çalışmalar;

Poster Sunum Teşvik Ödülleri

BİRİNCİLİK ÖDÜLÜ

"IDİYOPATİK ENFLAMATUVAR MİYOPATİLERDE KANTİTATİF 18FFDG PET/BT ANALİZ İLE YENİ KAS TUTULUM PATERNLERİN GÖSTERİLMESİ VE PROGNOSTİK GÖSTERGELER"

Fatma Başıbüyük[1], Melih Yigithan Bahadır[2], Gökçe Kenar Artın[1], Amaç Kiray[3], Recep Bekıs[2], İsmail Sarı[1]

[1]Dokuz Eylül Üniversitesi Hastanesi, İç Hastalıkları Kliniği, Romatoloji Bölümü, İzmir
[2]Dokuz Eylül Üniversitesi Hastanesi, Nükleer Tıp Anabilim Dalı, İzmir [3]Dokuz Eylül Üniversitesi Tıp Fakültesi, Anatomi Anabilim Dalı, İzmir

İKİNCİLİK ÖDÜLÜ

"STİLL HASTALIĞINDA ENFEKSİYONLA İLİŞKİLİ OLMAYAN PROKALSİTONİN YÜKSEKLİĞİ VE KLİNİK ÖNEMİ: MAKROFAJ AKTİVASYON SENDROMUNUN BELİRTECİ OLABİLİR Mİ? "

Erdem Bektaş[1], Burcu Ceren Uludoğan[2], Büşra Fırlatan Yazgan[3], Özgür Can Kılınç[4], Beste Acar[4], Oğuzhan Kızılkaya[4], Ayşenur Yılmaz[1], Büşra Yüce[5], Reşide Börçe Aydın[6], Meliha Meriç Koç[6], Serdal Uğurlu[7], Umut Kalyoncu[3], Timuçin Kaşifoğlu[2], Cemal Bes[1]

[1]Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Şehir Hastanesi, Romatoloji Kliniği, İstanbul
[2]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Eskişehir
[3]Hacettepe Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara
[4]İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, İstanbul
[5]Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Şehir Hastanesi, İç Hastalıkları Kliniği, İstanbul
[6]Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Şehir Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, İstanbul
[7]İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul

ÜÇÜNCÜLÜK ÖDÜLÜ

"TAKAYASU ARTERİTİNDE BAŞLANGIÇ GLUKOKORTİKOİD DOZUNUN RELAPS VE DOZ AZALTMA SÜRECİNE ETKİLERİ"

Ayşenur Yılmaz[1], Fatih Yıldırım[1], Feyyaz Hazar Yağmur[2], Fatih Taştekin[3], Muhammet Emin Kutu[4], Senar Şan[5], Tuğba Ocak[6], Hasan Kocaayan[7], Sema Işık[8], Burcu Ceren Uludoğan[9], Ayşe Çefle[5], Ayten Yazıcı[5], Yavuz Pehlivan[6], Servet Akar[7], Ahmet Omma[8], Şule Yaşar Bilge9, Kenan Aksu[3], Gökhan Keser[3], Cemal Bes[1], Nilüfer Alpay Kanıtez[10]

[1]Sağlık Bilimleri Üniversitesi, Başakşehir Çam ve Sakura Şehir Hastanesi, İç Hastalıkları Kliniği, Romatoloji Bölümü, İstanbul
[2]Koç Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, İstanbul
[3]Ege Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir
[4]Sağlık Bilimleri Üniversitesi, Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi, İç Hastalıkları Kliniği, Romatoloji Bölümü, İstanbul
[5]Kocaeli Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Kocaeli
[6]Uludağ Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Bursa
[7]İzmir Katip Çelebi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir
[8]Sağlık Bilimleri Üniversitesi, Ankara Bilkent Şehir Hastanesi, İç Hastalıkları Kliniği, Romatoloji Bölümü, Ankara
[9]Eskişehir Osmangazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Eskişehir
[10]Koç Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul

TRD Bildiri Ödülleri

BİRİNCİLİK ÖDÜLÜ

"AİLESEL AKDENİZ ATEŞİNDE PANOPTOZ: İNFLAMAZOM VE NEKROPTOZ YOLAKLARININ AĞ ANALİZİ"

Rıza Can Kardaş, İbrahim Vasi, Rahime Duran, İbrahim Yahya Çakır, İbrahim Karaduman, Esma Eseroğlu, Burak Karakaya, Ertuğrul Çağrı Bölek, Abdulsamet Erden, Hamit Küçük, Berna Göker, M. Akif Öztürk, Abdurrahman Tufan

Gazi Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, Ankara

İKİNCİLİK ÖDÜLÜ

"PRİMER SJÖGREN SENDROMU HASTALARINDA YENİ BİR TANI YÖNTEMİ OLARAK TÜKÜRÜK SIVISINDA AKIM SİTOMETRİSİ İLE LENFOSİT ALT GRUPLARININ TESPİT EDİLMESİ VE MİNÖR TÜKÜRÜK BEZİ BİYOPSİ BULGULARI İLE KARŞILAŞTIRILMASI"

Kerem Abacar[1], Şeyma Çolakoğlu Özkaya[2], İmren Aydın Tatlı[3], Özge Karakök[4], Sıdıka Tapşın Güllüoğlu[5], Şükrü Güllüoğlu[2], Can Erzik[6], Leyla Cinel[7], Pamir Atagündüz[4]

[1]Marmara Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İstanbul; Leeds Üniversitesi, Leeds Romatizma ve Kas-İskelet Sistemi Tıbbı Enstitüsü, Leeds, Birleşik Krallık
[2]Marmara Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, İstanbul
[3]Marmara Üniversitesi Tıp Fakültesi, Hematoloji ve İmmünoloji Anabilim Dalı, İstanbul
[4]Marmara Üniversitesi Tıp Fakültesi, Romatoloji Anabilim Dalı, İstanbul
[5]Marmara Üniversitesi Tıp Fakültesi, İmmünoloji Anabilim Dalı, İstanbul
[6]Marmara Üniversitesi, Sağlık Bilimleri Enstitüsü, Tıbbi Biyoloji ve Genetik Anabilim Dalı, İstanbul [7]Marmara Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, İstanbul

ÜÇÜNCÜLÜK ÖDÜLÜ

"ANKİLOZAN SPONDİLİT VE AKUT ANTERİOR ÜVEİTTE HLA-B*27 PEPTİDOMUNUN BİYOİNFORMATİK KARAKTERİZASYONU: BAĞLANMA GÜCÜ, MOLEKÜLER TAKLİT VE PATOJENİK MEKANİZMALAR"

Nazlı Mert Özüpek[1], Gökçe Kenar Artın[2], Gerçek Şen[2], Gizem Çalıbaşı Koçal[1], Yasemin Başbınar[1], İsmail Sarı[2]

[1]Dokuz Eylül Üniversitesi Onkoloji Enstitüsü, Translasyonel Onkoloji Anabilim Dalı, İzmir
[2]Dokuz Eylül Üniversitesi Tıp Fakültesi, İç Hastalıkları Anabilim Dalı, Romatoloji Bilim Dalı, İzmir

2026 yılında düzenlenecek olan Ulusal ve Uluslararası Etkinlikler

“21st International Conference on Behçet’s Disease” 25-27 Haziran 2025 tarihleri arasında Dr. Ahmet Gül başkanlığında İstanbul’da düzenlenecektir.

“LVV-PMR 2026 –Large Vessel Vasculitis and Polymyalgıa Rheumatica Conference” 1-2 Ekim 2026 tarihleri arasında Dr. R. Haner Direskeneli başkanlığında İstanbul’da düzenlenecektir.

26. Ulusal Romatoloji Kongresi 25-29 Kasım 2026 tarihlerinde Prof. Dr. Süleyman Özbek başkanlığında Antalya'da düzenlenecektir.