ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Association Between Serum 25-Hydroxyvitamin D Levels and Inflammatory Markers and Disease Activity in Biologic-Treated Ankylosing Spondylitis Patients

Biyolojik Tedavi Alan Ankilozan Spondilit Hastalarında 25-Hidroksivitamin D'nin İnflamatuar Belirteçler ve Hastalık Aktivitesi ile İlişkisi

Selin Cilli Hayiroglu

Department of Rheumatology, Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Türkiye

ABSTRACT

Aim: *This study aims to evaluate the association between serum 25-hydroxyvitamin D [25(OH)D] levels and inflammatory markers as well as disease activity in patients with ankylosing spondylitis (AS) receiving biologic therapy, including TNF inhibitors, IL-17 inhibitors, and JAK inhibitors.*

Materials and methods: *This cross-sectional study includes 104 AS patients receiving biologic therapy for at least six months. Patients were categorized based on serum 25(OH)D levels: deficiency (<20 µg/L), insufficiency (20–30 µg/L), and sufficiency (>30 µg/L). Disease activity was assessed using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) scores. Laboratory parameters, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Group comparisons are performed using the Kruskal-Wallis test or one-way ANOVA, as appropriate, and the Chi-square test for categorical variables. Correlations between serum 25(OH)D levels and clinical or laboratory parameters are evaluated using Spearman's rank correlation analysis. Subgroup analyses are conducted according to biologic treatment class.*

Results: *Patients with vitamin D deficiency had significantly higher CRP levels (24.0 mg/L vs. 12.1 mg/L vs. 8.9 mg/L, p=0.001), elevated ESR (p=0.028), and higher BASDAI scores (8.0 vs. 6.7 vs. 5.3, p<0.001) compared to those with insufficiency and sufficiency. Serum 25(OH) D levels were inversely correlated with CRP (r=-0.304, p=0.002) and BASDAI (r=-0.335, p=0.001) in the overall cohort. Subgroup analyses revealed significant negative correlations between 25(OH)D and CRP (r=-0.426, p<0.001) and BASDAI (r=-0.317, p=0.008) in TNF inhibitor-treated patients, and between 25(OH)D and BASDAI (r=-0.609, p=0.001) in IL-17 inhibitor-treated patients.*

Conclusion: *Lower serum 25(OH)D levels are significantly associated with higher inflammatory markers and increased disease activity in biologic-treated AS patients. These findings suggest that vitamin D deficiency may be associated with increased inflammatory burden and disease activity in biologic-treated AS patients. Future prospective and interventional studies are needed to determine whether vitamin D supplementation improves clinical outcomes in this population.*

Key words: *ankylosing spondylitis; 25-hydroxyvitamin D; biological therapy; disease activity; bath ankylosing spondylitis disease activity index; c-reactive protein; inflammatory markers*

ÖZET

Amaç: *Bu çalışmanın amacı, TNF inhibitörleri, IL-17 inhibitörleri veya JAK inhibitörleri ile biyolojik tedavi alan ankilozan spondilit (AS) hastalarında serum 25-hidroksivitamin D [25(OH)D] düzeyleri ile enflamatuvar belirteçler ve klinik hastalık aktivitesi arasındaki ilişkiyi araştırmaktır.*

Gereç ve Yöntem: *Bu kesitsel çalışmaya, en az altı aydır biyolojik tedavi alan 104 AS hastası dâhil edilmiştir. Hastalar serum 25(OH)D düzeylerine göre üç gruba ayrılmıştır: eksiklik (<20 µg/L), yetersizlik (20–30 µg/L) ve yeterlilik (>30 µg/L). Hastalık aktivitesi Bath Ankilozan Spondilit Hastalık Aktivite Endeksi (BASDAI) ve Bath Ankilozan Spondilit Fonksiyonel Endeksi (BASFI) ile değerlendirilmiştir. C-reaktif protein (CRP) ve eritrosit sedimantasyon hızı (ESR) dâhil olmak üzere laboratuvar parametreleri ölçülmüştür. Grup karşılaştırmaları, uygun olduğu durumlarda Kruskal-Wallis testi veya tek yönlü ANOVA ve kategorik değişkenler için Ki-kare testi kullanılarak yapılmıştır. Serum 25(OH)D düzeyleri ile klinik ve laboratuvar parametreleri arasındaki korelasyonlar Spearman sıra korelasyon analizi ile değerlendirilmiştir. Biyolojik tedavi sınıfına göre alt grup analizleri gerçekleştirilmiştir.*

Bulgular: *Vitamin D eksikliği olan hastalarda, yetersizlik ve yeterlilik grubundakilere kıyasla anlamlı düzeyde yüksek CRP değerleri (24,0 mg/L'ye karşı 12,1 mg/L'ye karşı 8,9 mg/L, p=0,001), yüksek ESR (p=0,028) ve yüksek BASDAI skorları (8,0'a karşı 6,7'ye karşı 5,3, p<0,001) saptanmıştır. Tüm kohort değerlendirildiğinde, serum 25(OH) D düzeyleri CRP (r=-0,304, p=0,002) ve BASDAI (r=-0,335, p=0,001) ile anlamlı düzeyde ters korelasyon göstermiştir. Alt grup analizlerinde, TNF inhibitörü alan hastalarda 25(OH)D ile CRP (r=-0,426, p<0,001) ve BASDAI (r=-0,317, p=0,008) arasında, IL-17 inhibitörü alan hastalarda ise 25(OH)D ile BASDAI arasında (r=-0,609, p=0,001) anlamlı negatif korelasyonlar saptanmıştır.*

Sonuç: *Düşük serum 25(OH)D düzeyleri, biyolojik tedavi alan AS hastalarında yüksek enflamatuvar belirteçler ve artmış hastalık aktivitesi ile anlamlı şekilde ilişkilidir. Bu bulgular, vitamin D eksikliğinin biyolojik tedavi alan AS hastalarında artmış enflamatuvar yük ve hastalık aktivitesi ile ilişkili olabileceğine işaret etmektedir. Vitamin D takviyesinin bu popülasyonda klinik sonuçları iyileştirip iyileştirmediğini belirlemek için ileriye dönük ve müdahaleye dayalı çalışmalara ihtiyaç duyulmaktadır.*

Anahtar kelimeler: *ankilozan spondilit, 25-hidroksivitamin D, biyolojik tedavi, hastalık aktivitesi, bath ankilozan spondilit hastalık aktivite indeksi, C-reaktif protein, enflamatuvar belirteçler*

İletişim/Contact: *Selin Cilli Hayıroğlu, Department of Rheumatology, Istanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Istanbul, Türkiye* • ***Tel:*** *0537 269 29 39* • ***E-mail:*** *selincilli@hotmail.com.tr* • ***Geliş/Received:*** *05.02.2026* • ***Kabul/Accepted:*** *20.04.2026*

ORCID: *Selin Cilli Hayıroğlu: 0000-0002-9302-8437*

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease primarily affecting the axial skeleton, sacroiliac joints, and peripheral joints, leading to progressive spinal stiffness, functional impairment, and reduced quality of life (1). The pathogenesis of AS involves complex interactions between genetic predisposition, particularly HLA-B27 positivity, and dysregulated immune responses characterized by elevated pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-17) (2). Disease activity in AS is commonly assessed using clinical indices such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and laboratory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (3). The advent of biologic disease-modifying agents, particularly TNF-α inhibitors and IL-17 inhibitors, has revolutionized the management of AS by effectively suppressing systemic inflammation, reducing disease activity, and improving functional outcomes (4). Despite these therapeutic advances, a substantial proportion of patients continue to experience persistent inflammation and suboptimal treatment responses, suggesting that additional factors may influence disease activity and treatment efficacy (5).

Vitamin D, beyond its classical role in calcium homeostasis and bone metabolism, has emerged as a key immunomodulatory hormone with pleiotropic effects on both innate and adaptive immunity (6,7). Vitamin D receptors are expressed on various immune cells, including macrophages, dendritic cells, and T lymphocytes, and vitamin D has been shown to downregulate pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-17, while promoting anti-inflammatory pathways (8,9). Accumulating evidence suggests that vitamin D deficiency is highly prevalent in patients with chronic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, and AS (10). Several studies have investigated the relationship between serum 25-hydroxyvitamin D [25(OH)D] levels and disease activity in AS, with conflicting results. A recent meta-analysis by Chen et al. demonstrated that AS patients had significantly lower serum 25(OH) D levels compared to healthy controls and that vitamin D levels were inversely correlated with BASDAI, ESR, and CRP (11). Similarly, Cai et al. reported that higher serum vitamin D levels were associated with a decreased risk of AS and lower disease activity (12). However, other studies have failed to demonstrate a significant association between vitamin D concentrations and disease activity parameters, particularly BASDAI scores (13,14). These inconsistencies may be attributed to differences in study populations, geographic variations, seasonal fluctuations in vitamin D synthesis, and heterogeneity in treatment regimens.

Importantly, most previous studies have included mixed populations of AS patients receiving conventional nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), or biologic agents, making it difficult to isolate the specific relationship between vitamin D and disease activity in the context of biologic therapy. Given that biologic agents profoundly modulate systemic inflammation and immune responses, it remains unclear whether vitamin D status continues to influence disease activity in patients already receiving these potent immunosuppressive therapies. Therefore, the aim of this study is to evaluate the association between serum 25(OH)D levels and disease activity markers (CRP, ESR, and BASDAI) specifically in AS patients receiving biologic therapy, including TNF-α inhibitors and IL-17 inhibitors. We hypothesize that even in the setting of biologic treatment, vitamin D deficiency is inversely correlated with inflammatory markers and disease activity in this population.

Material and Methods

This cross-sectional study was conducted between May 2023 and June 2025 at the Department of Rheumatology, Istanbul Goztepe Prof. Dr. Suleyman Yalcin City Hospital, in accordance with the principles of the Declaration of Helsinki. The ethical approval was obtained from Medeniyet University Faculty of Medicine Research Ethics Committee (approval number: 14/2026). A total of 104 patients diagnosed with AS according to the modified New York criteria and receiving biologic therapy for at least six months were enrolled. Patients were excluded if they had concomitant systemic inflammatory diseases, active infections, malignancy, or severe renal/hepatic impairment. Demographic and clinical data, including age, gender, smoking status, and body mass index (BMI), were recorded. Disease activity was evaluated using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and functional status was assessed via the Bath Ankylosing Spondylitis Functional Index (BASFI), which are validated tools for monitoring AS patients. Laboratory parameters, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR),

and complete blood count, were measured using standard laboratory methods. Patients diagnosed with AS who had previously received only nonsteroidal anti-inflammatory drug therapy were included in the study. In cases where clinical and laboratory evaluations indicated persistent disease activity, biological treatment with JAK inhibitors or TNF inhibitors or IL-17 inhibitors were initiated at the discretion of the treating rheumatologist. Biologic treatment was prescribed in accordance with national reimbursement criteria. TNF inhibitors were used as first-line biologic therapy. IL-17 inhibitors and JAK inhibitors were initiated in patients with an inadequate response to or intolerance of at least one TNF inhibitor, consistent with the Turkish Social Security Institution reimbursement guidelines. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured, and patients were categorized into three groups based on established clinical thresholds: deficiency (<20 μg/L), insufficiency (20–30 μg/L), and sufficiency (>30 μg/L) (6). Serum 25-hydroxyvitamin D [25(OH)D] levels were measured using a chemiluminescence immunoassay (CLIA) on an automated analyzer in the hospital's central laboratory.

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation for normally distributed data or median (interquartile range [IQR]) for data that were not normally distributed. Categorical variables were expressed as frequencies and percentages. Differences between the groups were analyzed using the Kruskal-Wallis test for variables that were not normally distributed and one-way ANOVA for normally distributed variables. Categorical variables were compared using the Chi-square test. The relationship between serum 25(OH)D levels and disease activity markers (CRP, ESR, BASDAI, and BASFI) was evaluated using Spearman's rank correlation coefficient, consistent with methodologies used in similar rheumatological studies. A p-value of <0.05 was considered statistically significant. Additionally, subgroup analyses were performed according to biologic treatment class (TNF inhibitors, IL-17 inhibitors, and JAK inhibitors) to evaluate whether the association between 25(OH)D levels and disease activity differed by treatment type.

Results

The study population consisted of 104 AS patients, divided into three groups based on vitamin D status: deficiency (n=39), insufficiency (n=44), and sufficiency (n=21). Baseline demographic and clinical characteristics, including age, gender, BMI, HLA-B27 positivity, and smoking status, were similar across all groups (p>0.05 for all). Furthermore, the distribution of biologic agents, including TNF inhibitors (n=70), IL-17 inhibitors (n=25), and JAK inhibitors (n=9), did not differ significantly between the groups (p>0.05). Laboratory analysis revealed that patients in the vitamin D deficiency group had significantly higher CRP levels [24.0 (15.7–30.4) mg/L] than those in the insufficiency [12.1 (7.5–24.2) mg/L] and sufficiency [8.9 (2.4–12.4) mg/L] groups (p=0.001). Similarly, ESR levels were significantly elevated in the deficiency group (p=0.028). Regarding clinical indices, BASDAI scores showed a significant inverse relationship with vitamin D status, with the highest scores observed in the deficiency group [8.0 (7.4–8.4)] and the lowest in the sufficiency group [5.3 (5.0–7.1)] (p<0.001). However, BASFI scores did not differ significantly across groups (p=0.291).

Correlation analysis for the entire cohort demonstrated that serum 25(OH)D levels were significantly and inversely correlated with CRP (r=-0.304, p=0.002) and BASDAI scores (r=-0.335, p=0.001), while no significant correlation was found with ESR or BASFI. In subgroup analyses based on treatment type, 25(OH)D levels in patients receiving TNF inhibitors were negatively correlated with both CRP (r=-0.426, p<0.001) and BASDAI (r=-0.317, p=0.008). For patients on IL-17 inhibitors, a strong negative correlation was identified between 25(OH)D and BASDAI scores (r=-0.609, p=0.001). In the JAK inhibitor group, no significant correlations were observed (p>0.05).

Discussion

In this cross-sectional study, we evaluated the association between serum 25-hydroxyvitamin D levels and inflammatory markers and clinical disease activity in biologic-treated patients with ankylosing spondylitis. Our main finding was that lower 25(OH)D levels were significantly associated with higher CRP values and higher BASDAI scores. Although ESR levels were significantly elevated in the vitamin D deficiency group compared to other groups, no significant correlation was found between 25(OH)D and ESR in the overall cohort correlation analysis. This distinction suggests that ESR may

Table 1. *Baseline demographic, clinical, and laboratory characteristics of ankylosing spondylitis patients according to vitamin D status*

	Vitamin D deficiency 25(OH)D <20 µg/L n=39	Vitamin D insufficiency 25(OH)D 20–30 µg/L n=44	Vitamin D sufficiency 25(OH)D >30 µg/L n=21	P value
Age, years (median [IQR])	53 (31–60)	50 (44–60)	55 (44–62)	0.175
Male sex, n (%)	19 (48.7)	23 (52.3)	8 (38.1)	0.559
Married, %	25 (64.1)	32 (72.7)	16 (76.2)	0.554
First-degree family history of ankylosing spondylitis, %	10 (25.6)	16 (36.4)	8 (38.1)	0.483
Hypertension, %	11 (28.2)	11 (25.0)	4 (19.0)	0.730
Diabetes Mellitus, %	10 (25.6)	11 (25.0)	8 (38.1)	0.520
Smoking, %				
Smoker	10 (25.6)	18 (40.9)	8(38.1)	0.314
Ex-smoker	6 (15.4)	9 (20.5)	5 (23.8)	0.704
Non-smoker	23 (59.0)	17 (38.6)	8 (38.1)	0.126
Body mass index, kg/m^2	25.7±3.9	26.8±3.4	27.4±7.5	0.351
HLA-B27 positivity, n (%)	21 (53.8)	18 (40.9)	11 (52.4)	0.452
Extra-articular manifestations, %	9 (23.1)	12 (27.3)	4 (19.0)	0.753
Biologic agents				
Jak inhibitors	3 (7.7)	3 (6.8)	3 (14.3)	0.584
TNF inhibitors	23 (59.0)	34 (77.3)	13 (61.9)	0.167
IL-17 inhibitors	13 (33.3)	7 (15.9)	5 (23.8)	0.177
Laboratory variables				
Hb (g/dl)	13.9 (12.5 – 15.2)	13.6 (12.6 – 15.1)	13.5 (13.0 – 14.1)	0.313
Lymphocytes (×10^9/L)	2.5 (1.7 – 3.3)	2.2 (1.8 – 2.5)	2.4 (1.9 – 2.7)	0.109
Monocytes	0.5 (0.4 – 0.7)	0.5 (0.3 – 0.6)	0.5 (0.4 – 0.6)	0.226
Neutrophils (×10^9/L)	5.3±1.8	5.1±1.3	5.2±1.2	0.835
Platelet count (×10^9/L)	281±116	296±69	297±58	0.698
Creatinine (mg/dL)	0.8 (0.7 – 0.9)	0.8 (0.7 – 0.9)	0.7 (0.6 – 0.9)	0.373
Urea (mg/dL)	29 (25–38)	29 (24–37)	30 (24–35)	0.967
AST	29 (13–33)	16 (14–19)	15 (12–18)	0.125
ALT	23 (11–29)	16 (13–17)	15 (9–27)	0.219
Albumin (g/dl)	43 (41–47)	43 (42–45)	43 (41–45)	0.729
CRP, mg/L (median [IQR])	24.0 (15.7 – 30.4)	12.1 (7.5 – 24.2)	8.9 (2.4 – 12.4)	0.001
ESR, mm/h (median [IQR])	19.0 (9.0 – 32.0)	17.0 (14.0 – 29.0)	12.0 (9.0 – 14.0)	0.028
Morning stiffness, minute	60 (30–120)	50 (30–90)	60 (40–80)	0.213
BASDAI score (median [IQR])	8.0 (7.4 – 8.4)	6.7 (6.2 – 7.2)	5.3 (5.0 – 7.1)	<0.001
BASFI score (median [IQR])	7.0 (6.2 – 8.0)	7.1 (5.0 – 7.8)	6.0 (5.9 – 7.4)	0.291

Data are presented as median (interquartile range) or n (%).
ALT: alanine aminotransferase; AST: aspartate aminotransferase; 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; Hb: hemoglobin; HLA-B27: human leukocyte antigen B27; IQR: interquartile range; IL-17: interleukin-17; JAK: janus kinase; SD: standard deviation; TNF: tumor necrosis factor.

reflect broader group-level inflammatory differences rather than a direct linear relationship with vitamin D status. These data suggest that vitamin D status may contribute to the residual inflammatory burden and disease activity in AS, even in the biologic era.

The biological plausibility of this association is supported by extensive experimental and clinical evidence. Vitamin D exerts immunomodulatory effects through its receptor, which is expressed on T cells, B cells, antigen-presenting cells, and other immune cells, thereby regulating both innate and adaptive immune responses (7,8). It has been shown to downregulate key proinflammatory cytokines, including TNFα, IL1, IL6, and IL17, and to promote a more tolerogenic immune

Table 2. *Spearman rank correlation coefficients between serum 25(OH)D levels and disease activity markers in all patients and by biologic treatment subgroup*

	All Patients 25(OH)D	TNF Inhibitors 25(OH)D	IL-17 Inhibitors 25(OH)D	JAK Inhibitors 25(OH)D
CRP				
r	-0.304	-0.426	0.309	0.471
p	0.002	<0.001	0.133	0.201
ESR				
r	-0.170	-0.193	0.018	-0.277
p	0.084	0.110	0.931	0.470
BASDAI				
r	-0.335	-0.317	-0.609	0.305
p	0.001	0.008	0.001	0.425
BASFI				
r	-0.141	-0.188	0.136	-0.682
p	0.153	0.118	0.516	0.083

BASDAI: bath ankylosing spondylitis disease activity index; BASFI: bath ankylosing spondylitis functional index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IL-17: interleukin-17; JAK: janus kinase; TNF: tumor necrosis factor; 25(OH)D: 25-hydroxyvitamin D.

profile (9). Given that TNFα and IL17 play central roles in the pathogenesis of axial spondyloarthritis (2), deficiency of vitamin D may favor a proinflammatory milieu that persists despite targeted cytokine inhibition. Our findings are consistent with several clinical studies and meta-analyses that have reported lower serum 25(OH)D concentrations in AS patients and demonstrated inverse correlations between vitamin D levels and disease activity indices, including BASDAI, CRP, and ESR (11,12). Beyond AS, several studies in rheumatoid arthritis and other autoimmune conditions have demonstrated that vitamin D deficiency is associated with higher disease activity and worse functional outcomes, further supporting a generalized immunomodulatory role of vitamin D in chronic inflammatory rheumatic diseases (15). The subgroup analyses in our cohort provide additional insights. We found that the inverse correlations were particularly evident in patients receiving TNF inhibitors and IL17 inhibitors. Similar observations have been reported in recent literature, in which low vitamin D levels were associated with an inadequate response to TNF inhibitors or with higher residual disease activity in patients with spondyloarthritis (16). While our study design does not allow causal inference, it raises the possibility that optimizing vitamin D status might enhance or stabilize response to biologic therapy in AS.

The lack of significant correlations in the JAK inhibitor subgroup in our study is likely attributable to limited statistical power rather than a true absence of association. These findings should therefore not be interpreted as evidence against a relationship between vitamin D status and disease activity in JAK inhibitor-treated patients; larger studies with adequate sample sizes are needed to evaluate this subgroup. In addition, BASFI did not differ significantly across vitamin D categories. This may reflect the fact that functional impairment in AS is strongly influenced by structural damage and long-standing disease, which may be less reversible and less directly affected by short-term fluctuations in vitamin D levels (17). Furthermore, it is important to consider that patients with more active disease may have reduced outdoor physical activity and sun exposure, potentially leading to lower vitamin D synthesis, which may be a consequence rather than a cause of high disease activity (18). Disease duration was not recorded as a variable in this study, which may be considered a limitation, as it could influence disease activity, treatment response, and vitamin D levels. The cross-sectional design precludes any causal interpretation of the observed associations. It cannot be determined from these data whether vitamin D deficiency contributes to higher disease activity, or conversely, whether higher disease activity leads to lower vitamin D levels through mechanisms such as reduced sun exposure, decreased physical activity, or increased metabolic consumption of vitamin D. Longitudinal and interventional studies are required to establish the directionality of this relationship.

Despite these limitations, our findings strengthen the hypothesis that vitamin D deficiency is associated with higher inflammatory activity in AS, even in patients receiving biologic treatments. Given the high prevalence

of hypovitaminosis D in patients with chronic inflammatory rheumatic diseases and in the general population, routine screening and correction of vitamin D deficiency may represent a simple, low-cost, and safe adjunct to current therapeutic strategies. Future longitudinal and randomized controlled trials are warranted to determine whether vitamin D supplementation can improve disease outcomes or optimize response to biologic therapy in ankylosing spondylitis.

Conclusion

This study demonstrates a significant inverse association between serum 25-hydroxyvitamin D levels and CRP and BASDAI scores among patients with ankylosing spondylitis receiving biologic therapy. While ESR levels were significantly elevated in the vitamin D deficiency group, a consistent correlation between 25(OH)D and ESR was not observed across all analyses. Subgroup analyses revealed significant associations in TNF inhibitor- and IL-17 inhibitor-treated patients, whereas no significant correlations were identified in the JAK inhibitor subgroup, possibly due to the limited sample size (n=9). These findings suggest that vitamin D deficiency may contribute to residual inflammatory burden in selected patient groups; however, larger prospective and interventional studies are required to confirm these observations and determine whether vitamin D supplementation can provide additional therapeutic benefits alongside biologic treatments.

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