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Rheumatology and Arthritis/Romatoloji ve Artrit

Association Between Atherogenic Index of Plasma and Disease Activity in Ankylosing Spondylitis

Sibel Ösken[1], **Altuğ Ösken**[2]

[1] Department of Rheumatology, Istanbul Erenköy Physical Therapy and Rehabilitation Hospital, Istanbul, Türkiye

[2] Department of Cardiology, Istanbul Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center, Istanbul, Türkiye

Sibel Ösken
0000-0003-3052-609X

Altuğ Ösken
0000-0003-3018-339X

Correspondence: Sibel Ösken
Department of Rheumatology, Istanbul Erenköy Physical Therapy and Rehabilitation Hospital, Istanbul, Türkiye
Phone: +90 536 873 50 80
E-mail: sibeltos@yahoo.com

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ABSTRACT

Purpose: Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory disease associated with increased cardiometabolic risk. The atherogenic index of plasma (AIP), calculated as $\log_{10}$(triglyceride/high-density lipoprotein cholesterol), reflects atherogenic dyslipidemia. This study investigated the association between AIP and disease activity, assessed by the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP), in patients with AS.

Methods: In this retrospective cross-sectional study, consecutive adult patients with AS and lipid profile and ASDAS-CRP data were included. Patients were classified as having low (ASDAS-CRP <2.1) or high disease activity (≥2.1). Correlation analyses and multivariable logistic regression were performed to evaluate the association between AIP and disease activity.

Results: A total of 160 patients were included, of whom 102 (63.8%) had high disease activity. Compared with the low disease activity group, patients with high disease activity had a more atherogenic lipid profile and higher AIP values (0.20 ± 0.15 vs. 0.15 ± 0.11, p=0.004). AIP correlated positively with ASDAS-CRP (r=0.36, p=0.001), BASDAI (r=0.31, p=0.003), and BASFI (r=0.28, p=0.005). In multivariable analysis, AIP remained independently associated with high disease activity (adjusted OR per 0.1 increase: 1.42; 95% CI: 1.12–1.80; p=0.004). ROC analysis showed moderate discrimination (AUC 0.72; 95% CI: 0.64–0.80); the optimal AIP cut-off was 0.17, with 68% sensitivity and 65% specificity.

Conclusion: AIP is independently associated with higher disease activity in AS and may provide complementary information on the metabolic and atherogenic profile accompanying inflammatory activity rather than serving as a direct disease activity index.

Keywords: Ankylosing spondylitis; High-Density Lipoprotein; Inflammation; Triglyceride

ÖZET

Amaç: Ankilozan spondilit (AS), artmış kardiyometabolik risk ile ilişkili, kronik immün aracılı inflamatuvar bir hastalıktır. Trigliserid/yüksek yoğunluklu lipoprotein kolesterol oranının $\log_{10}$ dönüşümü ile hesaplanan aterojenik plazma indeksi (AIP), aterojenik dislipidemiyi yansıtmaktadır. Bu çalışmada, AS hastalarında AIP ile C-reaktif protein temelli Ankilozan Spondilit Hastalık Aktivite Skoru (ASDAS-CRP) kullanılarak değerlendirilen hastalık aktivitesi arasındaki ilişkinin araştırılması amaçlandı.

Yöntem: Bu retrospektif kesitsel çalışmaya, lipid profili ve ASDAS-CRP verileri bulunan ardışık erişkin AS hastaları dahil edildi. Hastalar düşük (ASDAS-CRP <2,1) ve yüksek (ASDAS-CRP ≥2,1) hastalık aktivitesi olarak sınıflandırıldı. AIP ile hastalık aktivitesi arasındaki ilişkiyi değerlendirmek amacıyla korelasyon analizleri ve çok değişkenli lojistik regresyon analizleri yapıldı.

Bulgular: Çalışmaya alınan 160 hastanın 102'sinde (%63,8) yüksek hastalık aktivitesi saptandı. Düşük hastalık aktivitesi grubuyla karşılaştırıldığında, yüksek hastalık aktivitesi olan hastalarda daha aterojenik bir lipid profili ve daha yüksek AIP değerleri bulundu (0,20 ± 0,15'e karşı 0,15 ± 0,11; p=0,004). AIP, ASDAS-CRP (r=0,36; p=0,001), BASDAI (r=0,31; p=0,003) ve BASFI (r=0,28; p=0,005) ile pozitif korelasyon gösterdi. Çok değişkenli analizde AIP, yüksek hastalık aktivitesi ile bağımsız olarak ilişkili bulundu (0,1 birimlik artış için düzeltilmiş OR: 1,42; %95 GA: 1,12–1,80; p=0,004). ROC analizi, AIP'nin yüksek hastalık aktivitesini ayırt etmede orta düzeyde performans gösterdiğini ortaya koydu (EAA=0,72; %95 GA: 0,64–0,80); optimal AIP kesim noktası 0,17 olup duyarlılık %68 ve özgüllük %65 olarak bulundu.

Sonuç: AIP, AS'de daha yüksek hastalık aktivitesi ile bağımsız olarak ilişkilidir ve doğrudan bir hastalık aktivitesi göstergesi olmaktan ziyade, inflamatuvar aktiviteye eşlik eden metabolik ve aterojenik profil hakkında tamamlayıcı bilgi sağlayabilir.

Anahtar Kelimeler: Ankilozan Spondilit; İnflamasyon; Trigliserid; Yüksek Yoğunluklu Lipoprotein

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Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory disease primarily affecting the axial skeleton, characterized by structural damage, functional impairment, and systemic inflammation. AS is considered the radiographic form of axial spondyloarthritis (axSpA), characterized by definite radiographic sacroiliitis in the appropriate clinical setting. Beyond its musculoskeletal manifestations, accumulating evidence indicates that patients with AS carry an increased burden of cardiovascular morbidity and mortality compared with the general population (1). The mechanisms underlying this excess cardiovascular risk are complex and not fully elucidated, and are thought to involve persistent systemic inflammation, endothelial dysfunction, altered lipid metabolism, and traditional cardiometabolic risk factors (2).

Inflammation-related alterations in lipid metabolism have been increasingly recognized as a potential link between immune-mediated diseases and cardiovascular risk. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are known to modulate lipid pathways, leading to decreased high-density lipoprotein (HDL-C) levels, increased triglyceride (TG) concentrations, and qualitative lipid changes that may enhance atherogenicity (3). Accordingly, patients with inflammatory rheumatic diseases often exhibit a distinct lipid pattern, sometimes referred to as the lipid paradox, characterized by reduced HDL levels and functional alterations in lipoproteins despite relatively preserved total cholesterol levels (4).

The atherogenic Index of Plasma (AIP), calculated as log10(TG/HDL-C), has been proposed as a surrogate marker of small dense low-density lipoprotein (LDL) particles and a practical indicator of atherogenic dyslipidemia (5). Beyond its established role in cardiovascular risk stratification, AIP has been increasingly explored in relation to metabolic disturbances and systemic inflammatory states across various chronic conditions (6-10). Importantly, AIP should not be interpreted as a direct disease activity index. Rather, because it integrates triglyceride and HDL-C concentrations, it may provide complementary information on inflammation-associated lipid alterations and the cardiometabolic profile accompanying inflammatory activity. Given the close interplay between chronic inflammation, lipid metabolism, and cardiovascular risk in AS, examining the relationship between AIP and disease activity may therefore help characterize the metabolic component accompanying inflammatory activity in AS.

Among available disease activity measures, Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) is a validated composite index that incorporates both patient-reported outcomes and an objective inflammatory marker. However, data specifically addressing the relationship between AIP and validated composite disease activity measures in AS, particularly ASDAS-CRP, remain scarce and heterogeneous. Importantly, while prior studies have examined conventional lipid parameters in AS, fewer investigations have focused on integrative lipid indices that may provide additional information on the qualitative aspects of dyslipidemia in the context of inflammation. Whether AIP is associated with clinically relevant disease activity in AS, as assessed by a validated composite measure such as ASDAS-CRP, remains insufficiently characterized.

Because the present study has a cross-sectional design, any observed relationship between AIP and disease activity should be interpreted as an association rather than a causal relationship. In this context, a higher AIP may reflect the coexistence of a more atherogenic lipid profile during periods of greater inflammatory activity rather than serving as a direct measure or determinant of disease activity.

Therefore, the aim of this study was to evaluate the association between AIP and disease activity measured by ASDAS-CRP and to determine whether AIP is independently associated with high disease activity after adjustment for relevant clinical confounders.

Material and Methods

Study Design and Ethical Considerations

This single-center, retrospective, cross-sectional study was conducted in the rheumatology outpatient clinic of Erenköy Physical Therapy and Rehabilitation Hospital and was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to ensure methodological transparency and reproducibility. Medical records of patients evaluated between September 2024 and December 2025 were systematically reviewed. All clinical, laboratory, treatment, and disease activity data were obtained from existing medical records; no study-specific prospective data collection or follow-up was performed. The study protocol was approved by the Ethics Committee of Uskudar University (Approval Date: 27.02.2026;

Approval No: 61351342/020-118) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective design and the use of anonymized data, informed consent was waived. Given the cross-sectional nature of the analysis, AIP and disease activity were assessed at the same clinical evaluation, and no causal or temporal inferences were made.

Study Population

At the time of data extraction, a total of 214 patients with a diagnosis of AS were registered in the center's database. All patients who attended the outpatient clinic during the study period were screened consecutively without preselection to minimize selection bias. Of these, 198 patients had at least one eligible outpatient visit and were assessed for eligibility. Inclusion criteria were age ≥18 years, radiographic axial spondyloarthritis (ankylosing spondylitis) fulfilling the modified New York criteria for AS (11), rheumatologist-confirmed diagnosis, and availability of ASDAS-CRP and a complete lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) obtained during the same visit. After applying predefined exclusion criteria, 160 patients were included in the final analysis, of whom 102 (63.8%) had high disease activity (ASDAS-CRP ≥2.1).

Patients were excluded if they had missing or incomplete lipid parameters (particularly triglyceride or HDL values required for AIP calculation), absence of ASDAS-CRP or incomplete disease activity data, active infection or concurrent inflammatory conditions at the time of assessment, known active malignancy or malignancy under active surveillance, or chronic liver or renal disease affecting lipid metabolism. In addition, patients receiving lipid-lowering therapy (e.g., statins) and those with comorbid conditions requiring chronic lipid-lowering treatment, including coronary artery disease, diabetes mellitus, and familial hyperlipidemia, were excluded from the study. Overall, 38 patients were excluded during the selection process for these reasons, and the detailed study flowchart is presented in **Figure 1**.

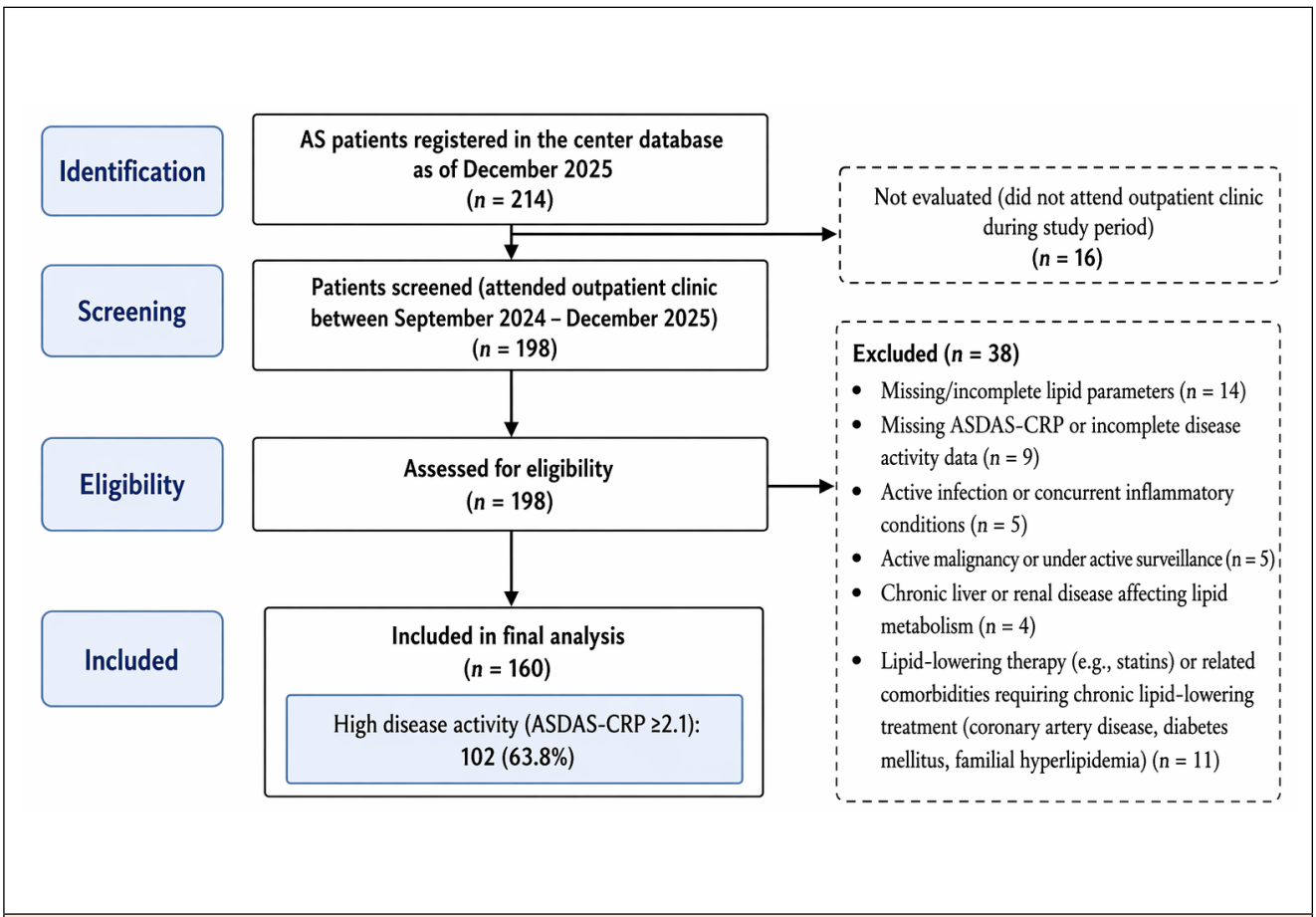

Figure 1. Flowchart of patient selection process
AS: ankylosing spondylitis; ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score based on C-reactive protein; AIP: atherogenic index of plasma.

Data Collection and Variables

Demographic and clinical data were extracted from electronic medical records, including age, sex, body mass index (BMI), smoking status (current smoker vs non-smoker), disease duration, diagnostic delay, human leukocyte antigen B27 (HLA-B27) status, and current treatment, including biologic disease-modifying antirheumatic drugs (bDMARDs), comprising TNF inhibitors and IL-17 inhibitors, and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), comprising Janus kinase (JAK) inhibitors.

All laboratory parameters were obtained from the same clinical visit at which disease activity was assessed, ensuring temporal alignment between exposure (lipid parameters) and outcome (disease activity). Laboratory measurements were performed using standardized automated assays in the hospital's central laboratory. All lipid parameters were measured in fasting blood samples obtained after an overnight fasting period of at least 8–12 hours, in order to minimize postprandial variability and ensure standardization of lipid-related indices.

Assessments were performed during routine outpatient visits rather than during acute infectious or inflammatory episodes. Measured laboratory parameters included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Disease activity was assessed using the ASDAS-CRP, a validated composite index incorporating both patient-reported outcomes and objective inflammatory markers. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were also recorded. Patients were categorized as having low disease activity (ASDAS-CRP <2.1) or high disease activity (ASDAS-CRP ≥2.1), in accordance with established cut-off values.

Lipid-Derived Indices

The AIP was calculated as log10(triglyceride/HDL cholesterol). AIP values were calculated using the *Atherogenic Index of Plasma Calculator* available through the AppCardio website (https://appcardio.com). Triglyceride and HDL values were expressed in consistent units prior to calculation to ensure accuracy. The triglyceride-to-HDL ratio (TG/HDL) was calculated as triglyceride divided by HDL cholesterol, and non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol.

AIP was analyzed both as a continuous variable and as a scaled variable (per 0.1-unit increase) in regression models to improve clinical interpretability and comparability with prior studies.

Statistical Analysis

Statistical analyses were performed using SPSS (version 25.0, IBM Corp., Armonk, NY, USA). Normality was assessed using Kolmogorov–Smirnov test. Continuous variables were presented as mean ± SD or median (IQR), as appropriate. Categorical variables were expressed as counts and percentages. Between-group comparisons (high vs low disease activity) were conducted using Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Spearman's correlation analyses was used to evaluate associations between AIP and disease activity parameters (ASDAS-CRP, BASDAI, BASFI, CRP, ESR). Correlation strength was interpreted using conventional thresholds (weak, moderate, strong) to facilitate clinical interpretation. Treatment categories (TNF inhibitors, IL-17 inhibitors, and JAK inhibitors) were evaluated separately in the descriptive analyses.

Regression modeling strategy

Binary logistic regression analysis was performed to determine whether AIP was independently associated with high disease activity (ASDAS-CRP ≥2.1). A pre-specified modeling strategy was employed to avoid data-driven overfitting. Model construction followed a parsimonious approach given the sample size (n=160) and number of events (n=102).

Variables were selected based on clinical relevance and prior literature, including age, sex, BMI, smoking status, disease duration, HLA-B27 positivity, and bDMARDs/tsDMARDs use. In the multivariable model, current use of any bDMARD or tsDMARD was entered as a binary covariate (yes/no), rather than entering TNF inhibitors, IL-17 inhibitors, and JAK inhibitors as separate treatment categories. This approach was chosen because the numbers of patients receiving IL-17 inhibitors and JAK inhibitors were relatively small, which could result in sparse data and unstable parameter estimates in

treatment-specific models. Treatment categories were nevertheless evaluated separately in the descriptive analyses.

Overall bDMARD/tsDMARD use was included as a clinically relevant covariate because treatment exposure may be associated with both disease activity and lipid parameters; however, this variable was not intended to estimate the differential effects of individual treatment classes on AIP.

CRP was not included in the multivariable model due to its incorporation into ASDAS-CRP, thereby avoiding redundancy and potential over-adjustment. Similarly, lipid parameters such as LDL, HDL, triglycerides, and TG/HDL ratio were not entered simultaneously with AIP to minimize multicollinearity.

Multicollinearity among covariates was assessed using variance inflation factors (VIF), with VIF values <5 considered indicative of no problematic multicollinearity, and model calibration was evaluated using goodness-of-fit statistics. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported.

Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminative performance of AIP for high disease activity (ASDAS-CRP ≥2.1), and the optimal cutoff value was determined by maximizing the Youden index.

Power Considerations

Given the number of outcome events (n=102 patients with high disease activity), the number of events was considered sufficient for the relatively parsimonious multivariable logistic regression model.

Accordingly, the number of events was considered sufficient for the relatively parsimonious model, while acknowledging that formal post hoc power calculations were not performed.

Results

Baseline Characteristics

A total of 160 patients were included, of whom 102 (63.8%) had high disease activity (ASDAS-CRP ≥2.1). Baseline demographic and clinical characteristics stratified by disease activity are presented in **Table 1**. The mean age was similar between the high and low disease activity groups (42.9 ± 11.8 vs 42.7 ± 9.4 years, p=0.899), and the proportion of male patients did not differ significantly (64.7% vs 55.2%, p=0.234).

No statistically significant differences were observed between groups with respect to BMI, disease duration, diagnostic delay, HLA-B27 positivity, or smoking status (all p>0.05), suggesting a broadly comparable clinical profile across disease activity strata.

Inflammatory markers were significantly higher in the high disease activity group. Median CRP and ESR levels were both elevated in patients with ASDAS-CRP ≥2.1 compared to those with ASDAS-CRP <2.1 (CRP: 9.9 [7.2–15.2] vs 7.1 [4.1–9.6] mg/L, p<0.001; ESR: 27 [22–37] vs 22.5 [16–28] mm/h, p<0.001). As expected, BASDAI and BASFI scores were also significantly higher in patients with high disease activity (both p=0.001), supporting internal consistency across disease activity measures.

In addition, the use of bDMARDs and tsDMARDs was significantly more frequent among patients with high disease activity than among those with low disease activity (66.7% vs. 36.2%, p<0.001), with TNF inhibitor use also being more frequent (44.1% vs. 25.9%, p=0.022).

Lipid Profile and AIP According to Disease Activity

Comparative lipid parameters according to disease activity are summarized in **Table 1**. Patients with high disease activity had significantly higher LDL cholesterol (132.8 ± 27 vs 117.7 ± 25.6 mg/dL, p=0.001), triglyceride levels (157.9 ± 46.3 vs 134.6 ± 31.3 mg/dL, p=0.001), and non-HDL cholesterol levels (147.7 ± 33.1 vs 125.5 ± 42.6 mg/dL, p=0.001).

In contrast, HDL cholesterol levels were significantly lower in the high disease activity group (44 ± 7.9 vs 49.9 ± 12.1 mg/dL, p=0.001). Total cholesterol levels were numerically higher in patients with high disease activity; however, this difference did not reach statistical significance (p=0.094).

Consistent with these findings, composite lipid indices reflecting atherogenic burden were significantly elevated in the high disease activity group, including TG/HDL ratio (4.59 ± 1.98 vs 3.34 ± 1.97, p<0.001) and AIP (0.20 ± 0.15 vs 0.15 ± 0.11, p=0.004).

Table 1. Baseline characteristics according to ASDAS-CRP disease activity

	ASDAS-CRP ≥2.1 (n=102)	ASDAS-CRP <2.1 (n= 58)	p-value[a]
Age, years	42.9 ± 11.8	42.7 ± 9.4	0.899
Male sex, n (%)	66 (64.7)	32 (55.2)	0.234
BMI, kg/m^2	25.7 ± 3.2	24.9 ± 3.9	0.172
Current smoker, n (%)	49 (48)	21 (36.2)	0.147
Disease duration, years	9.1 ± 5.3	7.8 ± 4.4	0.079
Diagnostic delay, years	4 ± 2.4	3.4 ± 2.5	0.144
HLA-B27 positive, n (%)	71 (69.6)	33 (56.9)	0.105
CRP, mg/L	9.9 (7.2-15.2)	7.1 (4.1-9.6)	**<0.001**
ESR, mm/h	27 (22-37)	22.5 (16-28)	**<0.001**
BASDAI	4.5 (4.1-4.9)	3.5 (3-3.9)	**0.001**
BASFI	2.7 (2.4-3.6)	1.9 (1.6-2.3)	**0.001**
Total cholesterol, mg/dL	183.6. ± 33.5	173.7 ± 38.8	0.094
LDL cholesterol, mg/dL	132.8 ± 27	117.7 ± 25.6	**0.001**
HDL cholesterol, mg/dL	44 ± 7.9	49.9 ± 12.1	**0.001**
Triglycerides, mg/dL	157.9 ± 46.3	134.6 ± 31.3	**0.001**
Non-HDL cholesterol, mg/dL	147.7 ± 33.1	125.5 ± 42.6	**0.001**
TG/HDL ratio	4.59 ± 1.98	3.34 ± 1.97	**<0.001**
AIP, log10(TG/HDL cholesterol)	0.20 ± 0.15	0.15 ± 0.11	**0.004**
bDMARDs/tsDMARDs use	68 (66.7)	21 (36.2)	**<0.001**
TNF inhibitor use, n (%)	45 (44.1)	15 (25.9)	**0.022**
IL-17 inhibitor use, n (%)	11 (10.8)	3 (5.2)	0.227
JAK inhibitor use, n (%)	12 (11.8)	3 (5.2)	0.169

[a] *Values with $p < 0.05$ are shown in bold.*

Abbreviations: *AIP, Atherogenic Index of Plasma (log10 TG/HDL); ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMI, body mass index; CRP, C-reactive protein; bDMARDs,biologic disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; HLA-B27, human leukocyte antigen B27; JAK, Janus kinase; LDL, low-density lipoprotein; Non-HDL, non–high-density lipoprotein cholesterol; TG, triglycerides; TNF, tumour necrosis factor; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs*

Overall, these findings indicate a more atherogenic lipid profile in patients with higher disease activity, without implying a causal or directional relationship.

Correlation Analysis

The relationships between AIP and disease activity parameters are presented in **Table 2**. AIP demonstrated a moderate positive correlation with ASDAS-CRP (r=0.36, p=0.001) and BASDAI (r=0.31, p=0.003), as well as with BASFI (r=0.28, p=0.005).

In addition, weaker but statistically significant correlations were observed with CRP (r=0.27, p=0.004) and ESR (r=0.21, p=0.011).

These findings indicate consistent positive correlations between AIP and multiple clinical and laboratory measures of disease activity.

Table 2. Correlation analysis between AIP and disease activity parameters

	Spearman's rho	p-value[a]
ASDAS-CRP	0.36	**0.001**
BASDAI	0.31	**0.003**
BASFI	0.28	**0.005**
CRP	0.27	**0.004**
ESR	0.21	**0.011**

[a] *Values with p < 0.05 are shown in bold.*

Abbreviations: *AIP, Atherogenic Index of Plasma; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.*

Table 3. Multivariable logistic regression analysis for high disease activity (ASDAS-CRP ≥2.1)

	Adjusted OR (95% CI) *	p-value[a]
AIP (per 0.1- increase)	1.42 (1.12–1.80)	**0.004**
Age (per year)	1.00 (0.97–1.03)	0.91
Male sex	1.28 (0.66–2.45)	0.46
BMI	1.06 (0.97–1.16)	0.18
Smoking	1.58 (0.82–3.04)	0.17
HLA-B27 positivity	1.52 (0.78–2.95)	0.21
Disease duration	1.04 (0.98–1.10)	0.15
bDMARDs/tsDMARDs use	3.21 (1.62-6.34)	**0.001**

[a] *Values with p < 0.05 are shown in bold.*

Abbreviations: *AIP, Atherogenic Index of Plasma; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-reactive protein; BMI, body mass index; bDMARDs,biologic disease-modifying antirheumatic drugs; CI, confidence interval; HLA-B27, human leukocyte antigen B27; OR, odds ratio; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs*

**Adjusted for age, sex, BMI, smoking status, HLA-B27, disease duration, and bDMARDs/tsDMARDs use.*

Multivariable Logistic Regression Analysis

Results of the multivariable logistic regression analysis are presented in **Table 3**. After adjustment for age, sex, BMI, smoking status, HLA-B27 positivity, disease duration, and bDMARDs/tsDMARDs use, AIP remained independently associated with high disease activity.

Specifically, each 0.1-unit increase in AIP was associated with a 42% higher odds of high disease activity (adjusted OR 1.42, 95% CI 1.12–1.80, p=0.004). This association remained significant after adjustment for the prespecified covariates included in the model.

In addition, bDMARDs/tsDMARDs use was independently associated with high disease activity (OR 3.21, 95% CI 1.62–6.34, p=0.001).

Other covariates, including age, sex, BMI, smoking status, HLA-B27 positivity, and disease duration, were not significantly associated with disease activity (all p>0.05).

No problematic multicollinearity was identified among the covariates, with all VIF values <5.

ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative ability of AIP for identifying high disease activity (ASDAS-CRP ≥2.1). The analysis demonstrated that AIP had a moderate discriminatory performance, with an area under the curve (AUC) of 0.72 (95% CI: 0.64–0.80, p < 0.001) (**Figure 2**).

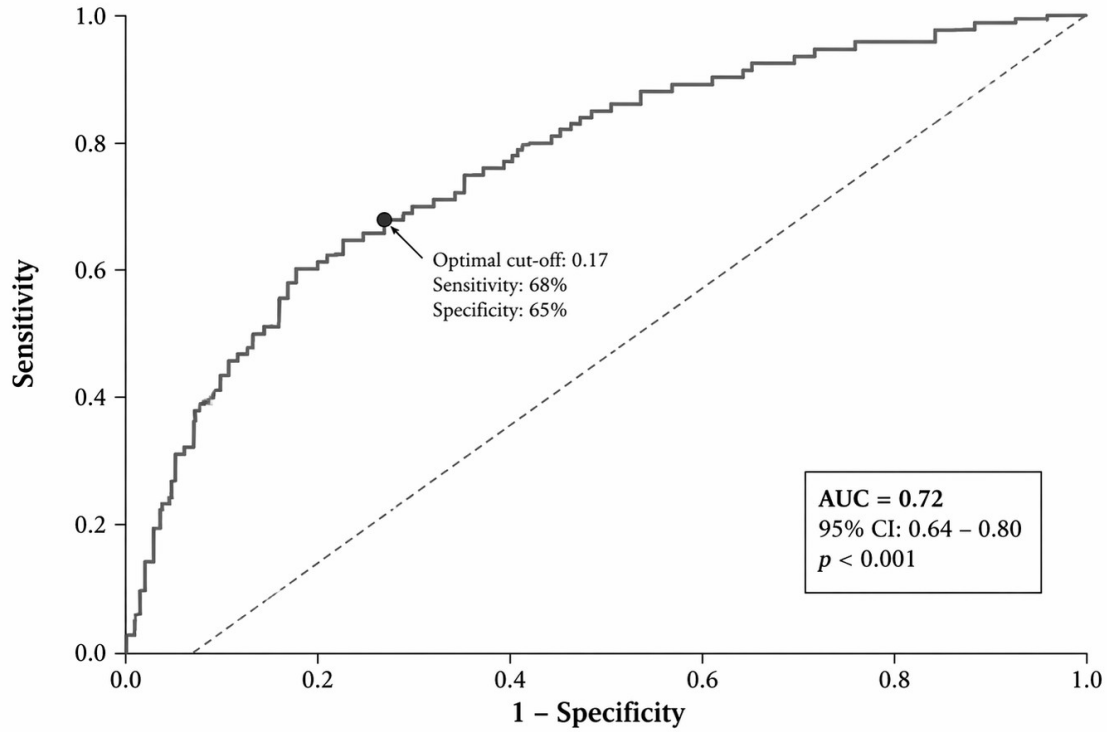

Figure 2. ROC curve of AIP for predicting high disease activity (ASDAS-CRP ≥2.1).

Figure 2. ROC curve analysis of AIP for high disease activity (ASDAS-CRP ≥2.1)

The optimal cutoff value for AIP was identified as 0.17, yielding a sensitivity of 68% and a specificity of 65% for high disease activity.

Discussion

In this retrospective cross-sectional study of patients with AS, we found that the AIP was independently associated with higher disease activity as assessed by ASDAS-CRP, even after adjustment for key clinical confounders. Specifically, each 0.1-unit increase in AIP was associated with a 42% higher odds of high disease activity. Patients with high disease activity exhibited a distinctly more atherogenic lipid profile, characterized by elevated triglycerides, reduced HDL cholesterol, and higher TG/HDL ratio and AIP values. In addition, AIP demonstrated consistent correlations with composite disease activity indices (ASDAS-CRP, BASDAI), functional status (BASFI), and inflammatory markers, supporting a consistent association between lipid-derived indices and overall disease activity measures. These findings are in line with previous studies in inflammatory rheumatic diseases, where elevated AIP has been associated with increased cardiovascular risk and disease-related inflammatory burden (12,13). The observed association between AIP and disease activity is biologically plausible. AIP reflects the balance between triglyceride-rich lipoproteins and protective HDL cholesterol and is considered a surrogate marker of small dense LDL particles, which are highly atherogenic and pro-inflammatory. Prior studies have demonstrated that patients with inflammatory arthritis exhibit a shift toward a more atherogenic lipoprotein phenotype, including smaller and denser LDL particles (14). Chronic systemic inflammation in AS may promote dyslipidemia through cytokine-mediated pathways, including TNF-α and IL-6–driven alterations in hepatic lipid metabolism. In addition to quantitative lipid changes, inflammation may also impair HDL functionality, reducing its anti-inflammatory and antioxidative properties.

Importantly, these mechanisms may operate not only during persistent chronic inflammation but also during relatively short-term increases in inflammatory activity. Pro-inflammatory cytokines can rapidly influence lipoprotein lipase (LPL) activity, hepatic lipid handling, and

HDL composition and functionality, potentially increasing triglyceride-rich lipoproteins and reducing the protective properties of HDL. Thus, even acute fluctuations or surges in inflammatory activity may shift the TG/HDL balance toward a more atherogenic profile and consequently increase AIP. This provides a plausible biological bridge between short-term inflammatory activity and the lipid alterations captured by AIP, although the present cross-sectional study cannot establish the temporal sequence of these processes.

Conversely, atherogenic lipoproteins may be linked to inflammatory pathways through endothelial dysfunction and oxidative stress, suggesting a potential association between lipid abnormalities and inflammatory activity rather than a strictly causal relationship. This is in line with population-based studies reporting an association between AIP and arthritis prevalence (15). Accordingly, the relationship observed in our study should be interpreted as the coexistence of a more atherogenic lipid profile with higher inflammatory disease activity rather than evidence that AIP directly drives disease activity or that increased disease activity necessarily causes an increase in AIP.

Consistent with the group comparisons, CRP and ESR were significantly higher in patients with high disease activity, reinforcing the validity of ASDAS-CRP–based stratification. However, it is important to note that acute-phase reactants may still incompletely capture the complexity of chronic inflammatory burden, particularly in treated populations. Previous studies have shown that targeted therapies may modify lipid parameters independently of conventional inflammatory markers (16,17). Accordingly, composite indices such as ASDAS-CRP and lipid-derived inflammatory markers like AIP may provide a more integrated reflection of systemic inflammatory and metabolic status.

Our correlation analysis further supports the relationship between metabolic and disease activity pathways. AIP showed moderate correlations with ASDAS-CRP (r=0.36) and BASDAI (r=0.31), as well as with BASFI (r=0.28), and weaker but significant correlations with CRP (r=0.27) and ESR (r=0.21). The consistency of these associations across a composite inflammatory disease activity measure, a patient-reported disease activity measure, a functional index, and conventional inflammatory markers suggests that the relationship between AIP and disease burden is not restricted to a single disease activity construct. Nevertheless, the correlation coefficients were moderate rather than strong, indicating that AIP captures only one component of the complex inflammatory and clinical phenotype of AS.

Our findings are also broadly consistent with observations from other inflammatory rheumatic diseases. In rheumatoid arthritis, Roy et al have reported associations between AIP and composite disease activity measures such as DAS28-CRP, suggesting that atherogenic lipid alterations may accompany greater inflammatory activity (18). Although RA and AS differ in their predominant clinical manifestations and inflammatory pathways, these findings support the broader concept that systemic inflammation and lipid metabolism may interact across immune-mediated rheumatic diseases (19). Importantly, these cross-disease observations should be interpreted as supportive biological evidence rather than direct equivalence between disease activity measures.

Consistent with our findings, AIP and related atherogenic indices have been associated with subclinical atherosclerosis and/or increased cardiovascular risk across several chronic inflammatory diseases within or related to the spondyloarthritis spectrum, including AS, psoriatic arthritis, Behçet disease, and familial Mediterranean fever (20–25). In AS, Min et al. reported that treatment with TNF-α inhibitors was associated with changes in lipid profiles and AIP during a 2-year follow-up, highlighting the potential interaction between systemic inflammation, lipid metabolism, and atherogenic risk in axial spondyloarthritis (20). Similarly, Cure et al. demonstrated that AIP was associated with carotid intima-media thickness, suggesting that this lipid-derived index may reflect subclinical atherosclerotic burden in patients with AS (21). These findings are particularly relevant to our results, as they support the concept that AIP may capture cardiometabolic and vascular alterations that accompany chronic inflammation in AS, beyond individual lipid parameters alone.

Similar observations have been reported in psoriatic arthritis, another spondyloarthritis-spectrum disease characterized by chronic systemic inflammation and an increased cardiometabolic burden. Tecer et al. evaluated several atherogenic indices in patients with psoriatic arthritis and found that these indices, including AIP, were associated with markers of subclinical atherosclerosis, supporting their potential utility in identifying patients with increased vascular risk (22). Importantly, the relevance of AIP extends beyond the classical spondyloarthritis

spectrum. In Behçet disease, Cure et al. reported that AIP was associated with subclinical atherosclerosis and suggested that it may serve as a useful predictor of vascular involvement in this chronic inflammatory vasculitic disease (23). Likewise, in familial Mediterranean fever, Icli et al. demonstrated an association between AIP and carotid atherosclerosis, suggesting that persistent or recurrent systemic inflammation may be accompanied by adverse lipid-related vascular changes even in the absence of conventional cardiovascular risk factors (24). Taken together, these findings across pathogenetically related inflammatory diseases support the biological plausibility of our observation that higher AIP is associated with greater disease activity in AS and suggest that AIP may represent an integrated marker linking inflammatory burden, altered lipid metabolism, and vascular risk.

In addition, ROC curve analysis demonstrated that AIP had a moderate ability to discriminate high disease activity, with an AUC of 0.72. The identified cutoff value of 0.17 provided a balanced sensitivity and specificity, suggesting that AIP may serve as a supportive marker for identifying patients with elevated disease activity. However, the moderate discriminative performance and the cross-sectional nature of the study indicate that this cutoff should not be interpreted as a diagnostic or disease activity threshold. AIP alone may not be sufficient for clinical decision-making and should be interpreted in conjunction with established disease activity indices.

From a clinical perspective, our findings highlight AIP as a simple, cost-effective, and readily available lipid-derived marker that may provide complementary information regarding the metabolic profile accompanying inflammatory activity. Given the increased cardiovascular morbidity observed in axial spondyloarthritis, integrating lipid-derived inflammatory indices may play a role in supporting risk assessment and provide additional insight beyond traditional lipid parameters. However, AIP should not be regarded as a substitute for validated disease activity measures such as ASDAS-CRP, nor should it be interpreted as a direct disease activity index. Rather, its potential clinical value may lie in simultaneously reflecting an aspect of atherogenic lipid metabolism in patients with greater inflammatory disease activity.

Moreover, treatment exposure represents an important consideration when interpreting the relationship between AIP and disease activity. In our study, overall bDMARD/tsDMARD use was more frequent among patients with high disease activity and remained independently associated with high disease activity in the multivariable model. This finding should be interpreted cautiously, as it most likely reflects confounding by indication, whereby patients with more active or refractory disease are more likely to receive advanced therapies, rather than a direct effect of treatment on disease activity. Anti-inflammatory therapies may also alter both inflammatory activity and lipid metabolism, and these effects may differ according to treatment class. In particular, JAK inhibitors have been associated with increases in lipid parameters, including HDL-C and triglycerides, whereas the effects of TNF and IL-17 inhibitors on lipid profiles may differ (25). For this reason, TNF inhibitor, IL-17 inhibitor, and JAK inhibitor use were distinguished in the descriptive analyses and reported separately in Table 1. However, because the numbers of patients receiving IL-17 inhibitors and JAK inhibitors were relatively small, treatment was represented as overall bDMARD/tsDMARD use in the multivariable model. Longitudinal studies have demonstrated that biologic therapies, particularly TNF-α inhibitors, can influence lipid profiles and AIP levels (26,27), further emphasizing the dynamic interaction between treatment, inflammatory control, and lipid metabolism.

Overall, our findings support an association between AIP and disease activity in AS but do not establish whether inflammatory activity alters AIP, whether atherogenic lipid alterations contribute to inflammatory activity, or whether both are influenced by shared biological and treatment-related factors. Prospective longitudinal studies with repeated lipid measurements, detailed treatment exposure, and validated disease activity assessments are therefore needed to clarify the temporal relationship between AIP and inflammatory activity.

Limitations

This study has several limitations. First, its cross-sectional and retrospective design precludes causal inference and limits the ability to determine the temporal directionality between lipid alterations and disease activity. Second, single-center recruitment may limit generalizability to broader and more diverse patient populations, particularly across different treatment settings and ethnic backgrounds.

Third, although we adjusted for major confounders, residual confounding cannot be excluded, especially from unmeasured factors such as dietary habits,

physical activity, and detailed cardiovascular risk profiles, including blood pressure, insulin resistance, and measures of subclinical atherosclerosis. Thyroid function status and thyroid-related medication use were also not systematically available in the retrospective medical records and therefore could not be adequately assessed as potential confounders of lipid metabolism. Furthermore, imaging-based measures of disease activity and structural damage were not available; therefore, the relationship between AIP and objective radiographic or magnetic resonance imaging findings could not be assessed.

In addition, the observed association between bDMARD/tsDMARD use and higher disease activity should be interpreted with caution, as this likely reflects confounding by indication rather than a causal relationship. Moreover, treatment exposure was modeled as a binary variable representing overall bDMARD/tsDMARD use rather than individual treatment classes because of the limited number of patients in some treatment categories; therefore, potential differential effects of TNF, IL-17, and JAK inhibitors on lipid parameters and AIP could not be separately evaluated. Exclusion of patients receiving lipid-lowering therapy and those with major cardiometabolic comorbidities may have improved internal validity for assessing the relationship between AIP and disease activity but may limit generalizability to the broader AS population.

Additionally, lipid parameters were assessed at a single time point, which may not fully reflect long-term metabolic status or intra-individual variability over time, particularly in the context of fluctuating inflammatory activity. Similarly, AIP was calculated from single measurements, which may limit its ability to capture dynamic changes in lipid metabolism.

Finally, although bDMARD/tsDMARD was included in the regression model, detailed treatment duration and response data were not available, precluding a more granular evaluation of treatment effects on the relationship between AIP and disease activity. Future studies incorporating longitudinal lipid measurements, treatment-spesific analyses, and treatment response trajectories would provide more robust insights into these relationships.

Conclusion

In conclusion, AIP is independently associated with higher disease activity in AS and correlates with both clinical and functional disease measures. Each incremental increase in AIP was associated with a significantly higher likelihood of high disease activity, supporting its role as an independent metabolic marker of disease burden.

These findings support the concept that atherogenic dyslipidemia is closely linked to the inflammatory and functional burden of disease in AS. Given its simplicity, accessibility, and integrative nature, AIP may provide complementary information to conventional disease activity measures in routine clinical practice; however, its role should be interpreted within the broader clinical context.

Declarations

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Conflict of interest

The authors declare that they have no competing interests.

Ethics Approval

The study was approved by the Ethics Committee of Uskudar University (Approval Date: 27.02.2026; Approval No: 61351342/020-118). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee. All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki and its subsequent amendments.

Availability of Data and Material

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

Sibel ÖSKEN (SO) contributed to study conception and design, data collection, statistical analysis, interpretation

of the data, and drafting of the manuscript. Altuğ ÖSKEN (AO) contributed to study supervision, critical revision of the manuscript, and interpretation of the findings. All authors read and approved the final manuscript.

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