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

Original Article / Orijinal Araştırma

DOI: 10.4274/raed.galenos.2026.62681
J Turk Soc Rheumatol

Serum amyloid A and systemic immune-inflammation index for the evaluation of subclinical inflammation in attack-free familial Mediterranean fever: A real-life cohort study

Ataksız dönemdeki ailevi Akdeniz ateşi hastalarında subklinik enflamasyonun değerlendirilmesinde serum amiloid A ve sistemik immün-enflamasyon indeksi: Gerçek yaşam kohort çalışması

Emine Gözde Aydemir Gülöksüz, Serdar Sezer, Ayşe Bahar Keleşoğlu Dinçer, Müçteba Enes Yayla, Emine Uslu, Didem Şahin Eroğlu, Mehmet Levent Yüksel, Recep Yılmaz, Gülay Kınıklı, Aşkın Ateş, Tahsin Murat Turgay

Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye

Abstract

Objective: Familial Mediterranean fever (FMF) is characterized by episodic inflammation, but inflammatory activity may continue between clinically apparent attacks and contribute to complications such as amyloidosis. We aimed to identify clinical and laboratory variables associated with serum amyloid A (SAA) concentrations during attack-free periods and to examine the relationship between SAA and the systemic immune-inflammation index (SII).

Methods: We retrospectively analyzed data from 710 patients with FMF followed at a tertiary rheumatology center between January 2016 and December 2020. Demographic, clinical, genetic, treatment, and laboratory data were evaluated. SII was calculated as platelet count × neutrophil/lymphocyte ratio. Correlation and multivariable regression analyses were used to examine factors associated with SAA concentrations.

Results: SAA levels showed significant positive correlations with disease duration, leukocyte and neutrophil counts, proteinuria, C-reactive protein (CRP), erythrocyte sedimentation rate, fibrinogen levels, and SII (all $p<0.001$), while a negative correlation was observed with lymphocyte count. Higher SAA levels were detected in patients with amyloidosis and/or kidney disease and in those carrying the M694V mutation. In multivariable analysis, longer disease duration, higher CRP, and higher fibrinogen levels remained independently associated with SAA, whereas SII did not.

Conclusion: SAA remains a useful indicator of subclinical inflammatory activity in patients with FMF during attack-free periods. Although SII was positively correlated with SAA, it was not independently associated with

Özet

Amaç: Ailevi Akdeniz Ateşi (FMF), tekrarlayan enflamatuvar ataklarla karakterize bir hastalık olmakla birlikte, ataksız dönemlerde de subklinik enflamasyon persiste edebilmekte ve amiloidoz gibi uzun dönem komplikasyonlara katkıda bulunabilmektedir. Bu çalışmada, remisyondaki FMF hastalarında serum amiloid A (SAA) düzeyleri ile ilişkili klinik ve laboratuvar faktörlerin değerlendirilmesi ve SAA ile sistemik immün-enflamasyon indeksi (Sİİ) arasındaki ilişkinin araştırılması amaçlanmıştır.

Yöntem: Bu retrospektif gerçek yaşam kohort çalışmasına, Ocak 2016-Aralık 2020 tarihleri arasında üçüncü basamak bir romatoloji merkezinde takip edilen 710 FMF hastası dahil edilmiştir. Demografik özellikler, klinik bulgular, genetik mutasyonlar, tedavi verileri ve laboratuvar parametreleri analiz edilmiştir. Sistemik immün-enflamasyon indeksi, trombosit sayısı × nötrofil/lenfosit oranı formülü kullanılarak hesaplanmıştır. SAA düzeyleri ile bağımsız olarak ilişkili faktörleri belirlemek amacıyla korelasyon ve çok değişkenli regresyon analizleri yapılmıştır.

Bulgular: SAA düzeyleri; hastalık süresi, lökosit ve nötrofil sayısı, proteinüri, C-reaktif protein (CRP), eritrosit sedimentasyon hızı, fibrinojen düzeyleri ve Sİİ ile anlamlı pozitif korelasyon göstermiştir (tüm $p<0,001$). Lenfosit sayısı ile ise negatif korelasyon saptanmıştır. Amiloidoz ve/veya renal tutulumu olan hastalarda ve M694V mutasyonunu taşıyanlarda SAA düzeyleri daha yüksek bulunmuştur. Çok değişkenli analizde; uzun hastalık süresi, yüksek CRP ve artmış fibrinojen düzeyleri yüksek SAA düzeylerinin bağımsız belirleyicileri olarak saptanırken, Sİİ düzeltme sonrası bağımsız ilişki göstermemiştir.

Correspondence / İletişim: Emine Gözde Aydemir Gülöksüz MD,
Ankara University Faculty of Medicine, Department of Internal Medicine, Division of Rheumatology, Ankara, Türkiye
E-mail: gzd_aydemir@hotmail.com **ORCID ID:** orcid.org/0000-0003-3619-476X
Received / Geliş Tarihi: 28.02.2026 **Accepted / Kabul Tarihi:** 02.11.2026 **Epub:** 03.11.2026

Cite this article as / Atıf: Aydemir Gülöksüz EG, Sezer S, Keleşoğlu Dinçer AB, et al. Serum amyloid A and systemic immune-inflammation index for the evaluation of subclinical inflammation in attack-free familial Mediterranean fever: a real-life cohort study. J Turk Soc Rheumatol. [Epub Ahead of Print]

Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of Turkish Society for Rheumatology.
This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

Abstract

SAA after multivariable adjustment. As a readily available and inexpensive index derived from routine blood tests, SII may provide complementary information; however, its clinical utility requires prospective validation.

Keywords: Familial Mediterranean fever, serum amyloid A, systemic immune-inflammation index

Özet

Sonuç: SAA, ataksız dönemdeki FMF hastalarında subklinik enflamatuvar aktivitenin değerlendirilmesinde yararlı bir gösterge olmaya devam etmektedir. Sİİ ile SAA arasında pozitif korelasyon saptanmakla birlikte, çok değişkenli analizde düzeltme yapıldıktan sonra Sİİ'nin SAA ile bağımsız bir ilişkisi gösterilememiştir. Rutin tam kan sayımı parametrelerinden kolaylıkla hesaplanabilen ve düşük maliyetli bir indeks olan Sİİ, tamamlayıcı bilgi sağlayabilir; ancak klinik kullanımının yararlılığının prospektif çalışmalarla doğrulanması gerekmektedir.

Anahtar Kelimeler: Ailevi Akdeniz ateşi, serum amiloid A, serum immün-enflamasyon indeksi

Introduction

Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent, self-limited inflammatory attacks involving serosal, articular, and cutaneous sites. During these episodes, systemic inflammation is commonly accompanied by neutrophilic leukocytosis and elevations in acute-phase reactants (APRs), including C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA), and erythrocyte sedimentation rate (ESR). Although these markers are not specific to FMF, SAA may be particularly sensitive to inflammatory activity and has been proposed as a useful parameter for guiding colchicine treatment and reducing the risk of AA amyloidosis.[1] Importantly, inflammatory activity may not resolve completely between clinically apparent attacks. Persistent SAA elevation during these periods is clinically relevant because SAA is the hepatic precursor of AA amyloid fibrils, and sustained SAA elevation has been associated with the development of AA amyloidosis.[1]

Several scoring systems are available for assessing disease activity and cumulative damage in FMF[2-5], while efforts continue to identify laboratory markers that may complement clinical assessment.[6] Systemic immune-inflammation index (SII), which integrates peripheral neutrophil, lymphocyte, and platelet counts, represents one such readily obtainable inflammatory index. Its prognostic value has been investigated predominantly in malignancies[7-10], but associations with clinical outcomes have also been reported in several non-malignant disorders, including cardiovascular and cerebrovascular diseases, osteoporosis, infective endocarditis, and interstitial lung disease.[11-15] Evidence regarding the clinical relevance of SII in rheumatological diseases, however, remains relatively limited.[16-18]

Accordingly, this study sought to characterize FMF patients during attack-free periods and to determine the clinical and laboratory factors associated with SAA concentrations, with particular emphasis on the relationship between SAA and SII.

Materials and Methods

Study Design and Population

We reviewed the records of 710 adult patients with FMF who were followed at our center from January 2016 through December 2020. Patients were eligible if they were older than 18 years and met the Tel Hashomer diagnostic criteria. Those with an active infection at the time of evaluation or a history of solid or hematological malignancy were excluded.

Data Collection

Data extracted from the medical records included age, sex, age at diagnosis, genetic mutations, FMF-related treatments, comorbidities, and amyloidosis. Laboratory data included CRP, ESR, SAA, fibrinogen, complete blood count parameters, and proteinuria was assessed using the spot urine protein-to-creatinine ratio and/or 24-hour urinary protein excretion. Genetic data were available for 478 patients (67.32%); mutation results for the remaining patients were unavailable because of incomplete retrospective records.

Laboratory Measurements

Blood samples were obtained during routine outpatient visits while patients were clinically attack-free. The attack-free state was defined by the absence of symptoms consistent with an FMF attack and of clinical evidence of acute infection at the time of evaluation. SAA was measured by nephelometry in the hospital laboratory using 1 mL of serum (minimum volume, 0.5 mL), with a reference range of 0-10 mg/L.

Calculation of SII

SII was derived from complete blood count parameters and calculated as platelet count × neutrophil/lymphocyte ratio.

Ethical Approval

Ethical approval for the study was obtained from the Ankara University Human Research Ethics Committee (approval no: İ5-364-21, date: 25.06.2021). All study procedures were performed

in compliance with the principles of the 1964 Declaration of Helsinki and subsequent amendments.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Distributional characteristics of continuous variables were examined visually using histograms and Q-Q plots. Normally distributed continuous data are reported as mean ± standard deviation, whereas variables with non-normal distributions are summarized as median and interquartile range (Q1-Q3). Categorical data are presented as numbers and percentages.

Associations between SAA concentrations and continuous variables were examined using Spearman's rank correlation analysis, while between-group differences in SAA were assessed with the Mann-Whitney U test. Stepwise multiple linear regression was used to examine variables independently associated with SAA. Because of its skewed distribution, SAA was natural-log transformed before regression analysis. Variables significant in univariate analyses were considered for inclusion in the multivariable model. A two-sided p-value <0.05 was considered statistically significant.

Results

The study included 710 patients with FMF (461 women and 249 men), with a mean age of 41.87±12.70 years and a mean age at diagnosis of 25.73±13.46 years. Amyloidosis and/or kidney disease was present in 29 patients (4.08%), while 48 (6.76%) had a concomitant rheumatological disease. Genetic data were available for 478 patients (67.32%), and M694V was the most frequently identified mutation. Treatment data were available for 685 patients (96.48%). Median SAA was 3.8 (interquartile range, 1.5-10.8) (Table 1).

SAA concentrations correlated positively with disease duration (r=0.138; p<0.001), leukocyte count (r=0.200; p<0.001), neutrophil count (r=0.273; p<0.001), SII (r=0.288; p<0.001), proteinuria (r=0.219; p<0.001), CRP (r=0.918; p<0.001), ESR (r=0.411; p<0.001), and fibrinogen (r=0.526; p<0.001). Conversely, an inverse correlation was observed between SAA and lymphocyte count (r=-0.122; p=0.001). SAA was not significantly correlated with patient age, age at diagnosis, or platelet count (Table 2).

Receiver operating characteristic (ROC) analysis evaluated the ability of SII to discriminate patients with elevated SAA (≥5 mg/L), which was used as an indicator of subclinical inflammation. The area under the curve was 0.672 [95% confidence interval (CI): 0.632-0.713; p<0.001], indicating modest discrimination. The Youden index identified an SII threshold of 575, with 55.1% sensitivity, 70.8% specificity, and a positive likelihood ratio of 1.89 (Figure 1).

Patients with amyloidosis and/or kidney disease had significantly higher SAA concentrations (p=0.007). Similarly, SAA was higher among patients carrying the M694V mutation (p=0.001). In contrast, the presence of E148Q and other exon 2 mutations was associated with lower SAA concentrations compared with their respective counterparts (p=0.001 and p<0.001, respectively).

Table 1. Descriptive statistics for variables	
Female	461 (64.93%)
Male	249 (35.07%)
Patient age, years	41.87±12.70
Age at diagnosis, years	25.73±13.46
Disease duration, years	14 (9-21)
Amyloidosis/kidney disease	29 (4.08%)
Diabetes mellitus	20 (2.82%)
Hypertension	21 (2.96%)
Genetic mutation data	
Available	478 (67.32%)
M694V heterozygous	119 (16.76%)
M694V homozygous	129 (18.17%)
M694V/E148Q	9 (1.27%)
M694V/M680I	32 (4.51%)
M694V/V726A	17 (2.39%)
M680I heterozygous	18 (2.54%)
M680I homozygous	9 (1.27%)
M680I/E148Q	2 (0.28%)
M680I/V726A	17 (2.39%)
M694I/E148Q	1 (0.14%)
V726A heterozygous	15 (2.11%)
V726A homozygous	12 (1.69%)
Others	98 (13.79%)
Not available	232 (32.68%)
Therapy	**685 (96.48%)**
Colchicine	681 (95.92%)
Anakinra	33 (4.65%)
Canakinumab	24 (3.38%)
Other	16 (2.25%)
Serum amyloid A	3.8 (1.5-10.8)
Leukocyte ($x10^3$)	7.19±1.90
Neutrophil ($x10^3$)	4.26±1.59
Lymphocyte ($x10^3$)	2.20±0.69
Platelet ($x10^3$)	276.53±72.09
SIII ($x10^3$)	497.83 (362.82-687.51)
Proteinuria	72 (57-105)
CRP	2.5 (1.0-6.4)
Sedimentation	8 (5-13)
Fibrinogen	3.14±0.87
CRP: C-reactive protein, SII: Systemic immune-inflammation index	

In the multiple linear regression model, longer disease duration (β=0.008; 95% CI: 0.000-0.016; p=0.045), higher CRP (β=0.152; 95% CI: 0.137-0.167; p<0.001), and higher fibrinogen levels (β=0.257; 95% CI: 0.164-0.350; p<0.001) remained independently associated with increased SAA concentrations (Table 3). No independent association with SAA was identified for sex (p=0.188), amyloidosis and/or kidney disease (p=0.952), M694V (p=0.141), E148Q (p=0.263), other exon 2 mutations (p=0.123), anakinra treatment (p=0.094), leukocyte count (p=0.056), neutrophil count (p=0.094), lymphocyte count (p=0.181), SII (p=0.102), proteinuria (p=0.639), or ESR (p=0.180).

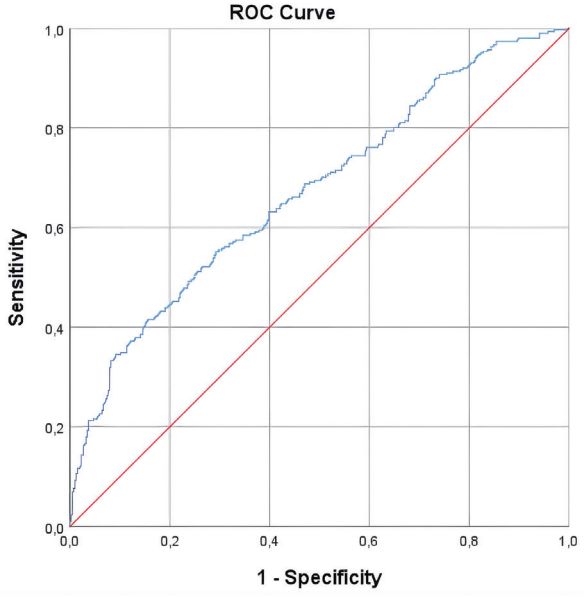


Figure 1. Receiver operating characteristic (ROC) curve evaluating the discriminatory performance of the systemic immune-inflammation index for elevated serum amyloid A (≥5 mg/L). The AUC was 0.672 (95% CI: 0.632-0.713; p<0.001)
AUC: Area under the curve, CI: Confidence interval

Table 2. Relationships between serum amyloid A and quantitative variables

	r	p
Patient age, years	0.042	0.260
Age at diagnosis, years	-0.070	0.062
Disease duration, years	0.138	**<0.001**
Leukocyte (x10^3)	0.200	**<0.001**
Neutrophil (x10^3)	0.273	**<0.001**
Lymphocyte (x10^3)	-0.122	**0.001**
Platelet (x10^3)	0.070	0.063
SII (x10^3)	0.288	**<0.001**
Proteinuria	0.219	**<0.001**
CRP	0.918	**<0.001**
Sedimentation	0.411	**<0.001**
Fibrinogen	0.526	**<0.001**

CRP: C-reactive protein, SII: Systemic immune-inflammation index

Discussion

Subclinical inflammatory activity may persist in patients with FMF even during clinically attack-free periods and may contribute to long-term complications such as amyloidosis. Reliable detection of this ongoing inflammatory burden is therefore important for long-term disease management. In the present study, we evaluated factors associated with SAA during attack-free periods, with particular emphasis on its relationship with SII. SAA was associated with disease duration, conventional inflammatory markers, leukocyte parameters, and proteinuria. Higher SAA levels were observed in patients with amyloidosis and in M694V carriers, whereas lower levels were found in patients with E148Q and other exon 2 mutations. Although SII correlated positively with SAA, this association did not remain significant in the multivariable analysis.

The biological characteristics of SAA support its value as a sensitive marker of inflammatory activity. Circulating SAA levels are normally very low in healthy individuals but may increase by up to 1000-fold within 24-48 hours after the onset of an acute-phase response.[19] This rapid increase is largely driven by inflammatory stimuli that promote *de novo* hepatic synthesis[20,21], with concentrations declining promptly as the inflammatory response resolves. Beyond reflecting acute-phase activity, SAA may also participate in the inflammatory process by promoting complement activation and pro-inflammatory cytokine responses.[22-24] It can enhance the expression of interleukin-6 (IL-6) and pro-IL-1β, while some SAA1-mediated effects involve signaling through TLR2 and TLR4.[19,25] SAA may also contribute to autoinflammatory pathways through direct activation of the NLRP3 inflammasome and subsequent caspase-1 activation.[23]

Clinical evidence further supports the value of SAA as a marker of inflammatory activity. A meta-analysis showed that SAA concentrations were higher in patients with rheumatological diseases than in healthy controls and were also higher during active disease than during remission.[26] In FMF, SAA increases together with other APRs during attacks. Its potential value in detecting residual inflammation has also been reported in other inflammatory conditions; for example, SAA has been proposed as an additional monitoring marker in patients with clinically quiescent inflammatory bowel disease, particularly when CRP concentrations are low.[27] In FMF, periodic assessment of SAA may be particularly relevant because it has been reported to be more sensitive than CRP and ESR for detecting residual inflammation during attack-free periods.[28]

Our findings are consistent with the potential role of SAA in identifying ongoing inflammation during clinically quiescent periods. SAA correlated positively with disease duration, leukocyte and neutrophil counts, proteinuria, CRP, ESR, and fibrinogen, whereas an inverse correlation was observed with

Table 3. Independent factors associated with serum amyloid A levels: multiple linear regression analysis						
	Unstandardized coefficient (B)	Standard error	Standardized coefficient (β)	p-value	95% CI for B	
(Constant)	-0.279	0.148		0.060	-0.570	0.012
Disease duration, years	0.008	0.004	0.058	0.045	0.000	0.016
CRP	0.152	0.008	0.650	<0.001	0.137	0.167
Fibrinogen	0.257	0.047	0.178	<0.001	0.164	0.350
CI: Confidence interval, CRP: C-reactive protein						

lymphocyte count. Mutation status was also associated with SAA levels: patients carrying M694V had higher levels than non-carriers, while E148Q and other exon 2 mutations were associated with lower levels. These findings suggest that variation in SAA during attack-free periods may reflect not only the current inflammatory burden but also differences associated with the underlying mutation profile.

Laboratory-derived inflammatory indices have gained increasing attention as practical tools for assessing systemic inflammatory activity.[29] Although much of the available evidence concerns autoimmune diseases, SII has also been reported to be elevated in adult-onset Still's disease, an autoinflammatory disorder.[16] As SII is derived solely from routine complete blood count parameters, it offers a simple and inexpensive measure that can be readily obtained in clinical practice. In our cohort, SII correlated positively with SAA during attack-free periods. This association is biologically plausible given the contribution of its cellular components to inflammatory responses: SAA correlated positively with neutrophil counts and negatively with lymphocyte counts, while neutrophils are key early participants in the inflammatory response.

Beyond their established roles in thrombosis and hemostasis, platelets also participate in inflammatory and immune responses.[30] These functions are mediated partly through interactions with innate immune cells, including neutrophils, monocytes, and macrophages. Platelet-expressed TLRs contribute to thromboinflammatory signaling[30,31], while TLR2 and TLR4 have also been implicated in the pathogenesis of FMF.[32-34] These mechanisms provide a biological basis for the contribution of platelet count to SII.

Platelet-neutrophil interactions represent another important link between hemostatic and inflammatory pathways and contribute to the regulation of immune responses.[35] Their reciprocal activation under both physiological and pathological conditions may sustain thromboinflammatory responses, creating a self-amplifying cycle.[36] Platelet activation is also associated with the release of pro-inflammatory cytokines, including tumor necrosis factor-α, IL-1β, IL-6, and IL-8.[37] Among these mediators, IL-1β is particularly relevant to FMF because of its central role in autoinflammatory pathways. Taken together, these mechanisms provide a biological rationale for investigating SII as a marker reflecting inflammatory activity in FMF.

Despite its positive correlation with SAA, SII did not remain independently associated with SAA in the multivariable analysis. The very strong correlation between SAA and CRP may have introduced multicollinearity into the regression model, reflecting the substantial overlap between these inflammatory markers. This may have attenuated the independent contribution of SII and should be considered when interpreting the regression findings. Further studies are needed to clarify the relationship of SAA and SII with clinical characteristics, including mutation status, during attack-free periods.

Study Limitations

Several limitations should be considered when interpreting our findings. The retrospective, single-center design may restrict their generalizability, while the cross-sectional assessment of SAA and SII during attack-free periods precluded evaluation of their longitudinal relationship with clinical outcomes. In addition, the absence of a control group limits conclusions regarding the specificity of these markers for FMF-related inflammation, as both may be influenced by other inflammatory conditions. Residual confounding related to the retrospective design also cannot be excluded.

The SII cut-off identified by ROC analysis should be interpreted cautiously, as the cross-sectional design does not allow a definitive threshold for clinical use to be established. Incomplete genetic and treatment data may also have introduced selection bias and affected the subgroup analyses and regression modeling. In addition, the attack-free state was determined clinically without a standardized interval from the preceding attack or a requirement for complete normalization of APRs, which may have influenced the assessment of subclinical inflammation. Prospective studies with well-defined clinical outcomes are therefore needed to validate clinically meaningful cut-off values for SII and SAA. Despite these limitations, the large sample size and comprehensive assessment of clinical, laboratory, and genetic characteristics represent important strengths of the study.

From a clinical perspective, our findings support the potential utility of SAA for identifying subclinical inflammatory activity during attack-free periods. SII, as a readily available and

inexpensive index derived from routine laboratory parameters, may provide complementary information. However, the SII cut-off identified in this study should be interpreted cautiously and should not be directly applied to clinical decision-making without prospective validation. Prospective studies are needed to establish clinically relevant cut-off values and determine the optimal frequency of SAA and SII assessment in routine FMF follow-up.

Conclusion

In conclusion, SAA remains a useful marker of subclinical inflammatory activity during attack-free periods in FMF. Although SII was positively correlated with SAA, it was not independently associated with SAA in the multivariable analysis, suggesting that its potential role may be complementary rather than independent. As a readily available and inexpensive index derived from routine laboratory parameters, SII may provide additional information alongside established inflammatory markers; however, its clinical utility requires further prospective validation.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ankara University Human Research Ethics Committee (approval no: İ5-364-21, date: 25.06.2021).

Informed Consent: Because the study was designed retrospectively no written informed consent form was obtained from the patients.

Footnotes

Authorship Contributions

Concept: E.G.A.G., D.Ş.E., Design: E.G.A.G., S.S., A.B.K.D., D.Ş.E., M.L.Y., G.K., A.A., T.M.T., Data Collection and Analysis: E.G.A.G., S.S., A.B.K.D., M.E.Y., E.U., R.Y., Analysis or Interpretation: E.G.A.G., A.B.K.D., D.Ş.E., G.K., A.A., T.M.T., Literature Search: E.G.A.G., S.S., E.U., R.Y., Writing: E.G.A.G., M.L.Y., G.K., T.M.T.

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. Lachmann HJ, Sengül B, Yavuzşen TU, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford). 2006;45:746-50.
2. Demirkaya E, Acikel C, Hashkes P, et al.; FMF Arthritis Vasculitis and Orphan disease Research in pediatric rheumatology (FAVOR). Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). Ann Rheum Dis. 2016;75:1051-6.
3. Piram M, Frenkel J, Gattorno M, et al.; EUROFEVER and EUROTRAPS networks. A preliminary score for the assessment of disease activity in hereditary recurrent fevers: results from the AIDAI (Auto-Inflammatory Diseases Activity Index) Consensus Conference. Ann Rheum Dis. 2011;70:309-14.
4. Piram M, Koné-Paut I, Lachmann HJ, et al.; EUROFEVER, EUROTRAPS and the Paediatric Rheumatology International Trials Organisation (PRINTO) networks. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis. 2014;73:2168-73.
5. Ter Haar NM, Annink KV, Al-Mayouf SM, et al. Development of the autoinflammatory disease damage index (ADDI). Ann Rheum Dis. 2017;76:821-30.
6. 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.
7. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of systemic immune-inflammation index in cancer: a meta-analysis. J Cancer. 2018;9:3295-302.
8. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20:6212-22.
9. Huang Y, Gao Y, Wu Y, Lin H. Prognostic value of systemic immune-inflammation index in patients with urologic cancers: a meta-analysis. Cancer Cell Int. 2020;20:499.
10. Ji Y, Wang H. Prognostic prediction of systemic immune-inflammation index for patients with gynecological and breast cancers: a meta-analysis. World J Surg Oncol. 2020;18:197.
11. Yang YL, Wu CH, Hsu PF, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50:e13230.
12. Trifan G, Testai FD. Systemic Immune-Inflammation (SII) index predicts poor outcome after spontaneous supratentorial intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2020;29:105057.
13. Fang H, Zhang H, Wang Z, Zhou Z, Li Y, Lu L. Systemic immune-inflammation index acts as a novel diagnostic biomarker for postmenopausal osteoporosis and could predict the risk of osteoporotic fracture. J Clin Lab Anal. 2020;34:e23016.
14. Agus HZ, Kahraman S, Arslan C, et al. Systemic immune-inflammation index predicts mortality in infective endocarditis. J Saudi Heart Assoc. 2020;32:58-64.
15. Ruta VM, Man AM, Alexescu TG, et al. Neutrophil-to-lymphocyte ratio and systemic immune-inflammation index-biomarkers in interstitial lung disease. Medicina (Kaunas). 2020;56:381.
16. Kim JW, Jung JY, Suh CH, Kim HA. Systemic immune-inflammation index combined with ferritin can serve as a reliable assessment score for adult-onset Still's disease. Clin Rheumatol. 2021;40:661-8.
17. Kim Y, Choi H, Jung SM, Song JJ, Park YB, Lee SW. Systemic immune-inflammation index could estimate the cross-sectional high activity and the poor outcomes in immunosuppressive drug-naïve patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton). 2019;24:711-7.
18. Wu J, Yan L, Chai K. Systemic immune-inflammation index is associated with disease activity in patients with ankylosing spondylitis. J Clin Lab Anal. 2021;35:e23964.
19. Sack GH Jr. Serum amyloid A - a review. Mol Med. 2018;24:46.
20. Morrow JF, Stearman RS, Peltzman CG, Potter DA. Induction of hepatic synthesis of serum amyloid A protein and actin. Proc Natl Acad Sci U S A. 1981;78:4718-22.

21. Uhlar CM, Whitehead AS. The kinetics and magnitude of the synergistic activation of the serum amyloid A promoter by IL-1 beta and IL-6 is determined by the order of cytokine addition. Scand J Immunol. 1999;49:399-404.

22. Yuste J, Botto M, Bottoms SE, Brown JS. Serum amyloid P aids complement-mediated immunity to Streptococcus pneumoniae. PLoS Pathog. 2007;3:1208-19.

23. Ather JL, Ckless K, Martin R, et al. Serum amyloid A activates the NLRP3 inflammasome and promotes Th17 allergic asthma in mice. J Immunol. 2011;187:64-73.

24. De Buck M, Gouwy M, Wang JM, et al. The cytokine-serum amyloid A-chemokine network. Cytokine Growth Factor Rev. 2016;30:55-69.

25. Li W, Wang W, Zuo R, et al. Induction of pro-inflammatory genes by serum amyloid A1 in human amnion fibroblasts. Sci Rep. 2017;7:693.

26. Zinellu A, Mangoni AA. The potential role of serum amyloid A as biomarker of rheumatic diseases: a systematic review and meta-analysis. Clin Exp Med. 2024;24:141.

27. Stute M, Kreysing M, Zorn M, Michl P, Gauss A. Serum amyloid A as a potential biomarker in ınflammatory bowel diseases, especially in patients with low c-reactive protein. Int J Mol Sci. 2024;25:1177.

28. 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.

29. Yang Z, Zhang Z, Lin F, et al. Comparisons of neutrophil-, monocyte-, eosinophil-, and basophil- lymphocyte ratios among various systemic autoimmune rheumatic diseases. APMIS. 2017;125:863-71.

30. Mandel J, Casari M, Stepanyan M, Martyanov A, Deppermann C. Beyond hemostasis: platelet ınnate immune interactions and thromboinflammation. Int J Mol Sci. 2022;23:3868.

31. Aslam R, Speck ER, Kim M, et al. Platelet Toll-like receptor expression modulates lipopolysaccharide-induced thrombocytopenia and tumor necrosis factor-alpha production in vivo. Blood. 2006;107:637-41.

32. Ozen S, Berdeli A, Türel B, et al. Arg753Gln TLR-2 polymorphism in familial mediterranean fever: linking the environment to the phenotype in a monogenic inflammatory disease. J Rheumatol. 2006;33:2498-500.

33. Karakose MZ, Yapali S, Salman E, Aksu K, Karakose S, Akarca US. TLR2 and TLR4 gene expression levels and associated factors during acute attack and attack-free periods in familial Mediterranean fever. Clin Rheumatol. 2015;34:785-90.

34. Soylu A, Ateş H, Cingöz S, et al. TLR polymorphisms in FMF: association of TLR-2 (Arg753Gln) and TLR-4 (Asp299Gly, Thre399Ile) polymorphisms and myeloid cell TLR-2 and TLR-4 expression with the development of secondary amyloidosis in FMF. Inflammation. 2011;34:379-87.

35. Silvestre-Roig C, Braster Q, Ortega-Gomez A, Soehnlein O. Neutrophils as regulators of cardiovascular inflammation. Nat Rev Cardiol. 2020;17:327-40.

36. Caillon A, Trimaille A, Favre J, Jesel L, Morel O, Kauffenstein G. Role of neutrophils, platelets, and extracellular vesicles and their interactions in COVID-19-associated thrombopathy. J Thromb Haemost. 2022;20:17-31.

37. Kaplanski G, Farnarier C, Kaplanski S, et al. Interleukin-1 induces interleukin-8 secretion from endothelial cells by a juxtacrine mechanism. Blood. 1994;84:4242-8.