

Comparative Performance of CBC-Derived Inflammatory Indices for Detecting Persistent subclinical inflammation in Children with Familial Mediterranean Fever

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Research Article

Keywords: Familial Mediterranean fever, serum amyloid A, subclinical inflammation, systemic inflammation response index, SIRI, neutrophil-to-lymphocyte ratio, complete blood count, disease severity, ISSF, children

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11127335/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Subclinical inflammation may continue during clinical remission in children with familial Mediterranean fever (FMF), contributing to amyloidosis risk. Serum amyloid A (SAA) is a standardized marker of inflammation; however, its availability may be limited. Complete blood count (CBC)-derived indices are inexpensive surrogate biomarker, although their performance during remission remains uncertain.

Objective

To compare seven CBC-derived indices for identifying persistent subclinical inflammation and assess their independence from disease severity.

Methods

Clinical and laboratory data during remission were retrospectively analyzed in 182 children with FMF. Subclinical inflammation was defined as SAA > 10 mg/L. NLR, PLR, LMR, MLR, dNLR, SII, and SIRI were calculated from CBC. Disease severity was assessed using the International Severity Scoring System for FMF (ISSF).

Results

Sixty-nine children (37.9%) had elevated SAA. SIRI was higher in this group ($P = 0.027$) and showed the highest but modest discriminatory performance (AUC = 0.598; 95% CI, 0.514–0.681). Its association with elevated SAA became borderline after adjustment for disease severity (adjusted OR = 1.61; 95% CI, 0.99–2.63; $P = 0.055$), whereas disease severity was the only independent predictor (adjusted OR = 3.66; 95% CI, 1.73–7.76; $P = 0.001$).

Conclusion

SIRI showed the strongest overall performance but limited discriminatory accuracy and should not replace SAA. Disease severity was the principal independent determinant of persistent subclinical inflammation.

Introduction

Familial Mediterranean fever (FMF) is the most frequent autoinflammatory disease predominantly affecting populations originating from Mediterranean basin. It is characterized by recurrent, self-limited episodes of fever, abdominal pain, arthritis, and/or erysipelas-like rash. The disease is primarily caused by *MEFV* gene pathogenic variants which encode pyrin, a key protein in the innate immunity. Dysregulated stimulation of the pyrin inflammasome leads to caspase-1 activation and excessive production of interleukin-1 β (IL-1 β), which plays a pivotal role in the inflammatory manifestations of FMF

[1, 2]. Although MEFV genotype analysis has contributed greatly to knowledge of FMF, the diagnosis remains predominantly clinical [3, 4].

Although FMF attacks are typically separated by asymptomatic intervals, clinical remission does not necessarily indicate complete suppression of inflammation. Persistent elevation of acute-phase reactants during attack-free periods has been reported in a substantial proportion of patients, providing biochemical evidence of ongoing subclinical inflammation despite the absence of clinically apparent attacks [5, 6].

Persistent subclinical inflammation is clinically important because prolonged inflammatory activity increases the risk of AA amyloidosis. Serum amyloid A (SAA), an acute-phase protein induced primarily by inflammatory cytokines, is a sensitive marker of ongoing inflammation in FMF. Sustained SAA elevation promotes AA amyloid deposition, which can lead to progressive renal dysfunction and irreversible organ damage. Therefore, monitoring inflammatory activity during remission is an important component of long-term FMF management [7–9].

Current international recommendations emphasize regular assessment of disease activity and persistent inflammation during follow-up and recommend SAA, when available, for monitoring FMF patients [10]. However, SAA testing is not universally accessible and may be more costly than routine hematological investigations. This limitation highlights the need for inexpensive, readily available biomarkers that could help identify patients with subclinical inflammation who may benefit from confirmatory SAA testing or closer follow-up [11].

CBC-derived inflammatory indices have emerged as potentially useful surrogate markers because they are calculated from routinely available hematological parameters without additional testing. These include the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), monocyte-to-lymphocyte ratio (MLR), derived neutrophil-to-lymphocyte ratio (dNLR), systemic immune-inflammation index (SII), and systemic inflammation response index (SIRI). By integrating different circulating leukocyte populations, these composite indices may better reflect systemic inflammatory activity than individual blood-cell counts. Several studies have evaluated CBC-derived indices in FMF, with NLR reported to increase during acute attacks and associated with inflammation during attack-free periods in both children and adults. Other studies have examined traditional and composite indices in relation to disease severity, amyloidosis, and subclinical inflammation, but findings have been inconsistent across populations and clinical settings [12–17].

Recent studies have underscored the clinical importance of subclinical inflammation in FMF and the need for biomarkers that can detect ongoing inflammation despite clinical quiescence. Composite CBC-derived indices have consequently gained interest as accessible markers of systemic inflammatory activity [14–17]. However, their ability to discriminate children with persistent SAA elevation from those with biochemical remission, and whether they provide information independent of established measures of disease severity, remain unclear.

Aim

The present study aimed to compare the performance of seven CBC-derived inflammatory indices (NLR, PLR, LMR, MLR, dNLR, SII, and SIRI) in identifying persistent subclinical inflammation, defined as SAA > 10 mg/L, in children with FMF during attack-free remission. The study also assessed their correlations with continuous SAA concentrations and determined whether any index remained independently associated with elevated SAA after adjustment for disease severity, as assessed by the International Severity Scoring System for Familial Mediterranean Fever (ISSF).

Methods

Study population and data collection:

This retrospective, single-center study included 182 pediatric patients with FMF followed at the Pediatric Autoinflammatory Diseases Clinic, Alexandria University Children's Hospital, Alexandria, Egypt. FMF was diagnosed according to the Tel-Hashomer criteria [3]. Eligible patients were younger than 18 years and receiving regular colchicine therapy. Patients were excluded if they had malignancy or hematologic disease, acute or chronic infection, primary or secondary immunodeficiency, another rheumatologic disease, receiving corticosteroid or biologic therapy or had incomplete clinical or laboratory data. All eligible pediatric FMF patients registered in the clinic records between 2016 and June 2026 were included.

Demographic and clinical data were obtained from medical records, including age, sex, age at disease onset, disease duration, diagnostic delay, parental consanguinity, MEFV mutation status, colchicine dose, and disease severity. Disease severity was assessed using the International Severity Scoring System for Familial Mediterranean Fever (ISSF) [18].

Laboratory assessments were performed during an attack-free remission period, defined as the absence of FMF-related manifestations for at least two weeks before assessment. A complete blood count (CBC) using an automated blood cell counter, and serum amyloid A (SAA) concentrations were measured by ELISA according to the manufacturer's instructions. CBC testing is routinely available at the clinic, whereas SAA testing is not available at the clinic laboratory and is relatively costly; therefore, SAA was requested when clinically indicated to assess disease activity and response to colchicine and to evaluate amyloidosis risk in patients with frequent attacks despite receiving the maximum tolerated colchicine dose.

Persistent subclinical inflammation was predefined as SAA > 10mg/L, consistent with the established treatment target of maintaining SAA < 10mg/L during attack-free periods to minimize the risk of AA amyloidosis. [10, 19] Accordingly, patients were categorized into two groups:

- Normal SAA: ≤ 10 mg/L
- Elevated SAA: > 10 mg/L

Seven CBC- derived inflammatory indices were calculated from absolute blood cell counts obtained from the same blood sample:

Index	Formula
Neutrophil-to-lymphocyte ratio (NLR)	ANC / ALC
Platelet-to-lymphocyte ratio (PLR)	Platelet count / ALC
Lymphocyte-to-monocyte ratio (LMR)	ALC / AMC
Monocyte-to-lymphocyte ratio (MLR)	AMC / ALC
Derived neutrophil-to-lymphocyte ratio (dNLR)	ANC / (WBC – ANC)
Systemic immune-inflammation index (SII)	Platelet × ANC / ALC
Systemic inflammation response index (SIRI)	ANC × AMC / ALC

Where ANC = absolute neutrophil count, ALC = absolute lymphocyte count, AMC = absolute monocyte count, and WBC = total white blood cell count.

Statistical analysis

Data were analyzed using IBM SPSS Statistics software package version 27.0 (IBM Corp., Armonk, NY, USA; released in 2020). Categorical variables were summarized as numbers and percentages, while quantitative variables were described using range (minimum and maximum), mean and standard deviation (SD), and median and interquartile range (IQR), as appropriate. Normality was assessed using the Shapiro–Wilk test and visual inspection of histograms and Q–Q plots. Comparisons between the two studied groups used the chi-square test or Fisher’s exact test for categorical variables, and the independent-samples Student’s t-test or Mann–Whitney U test for quantitative variables, as appropriate

Associations between continuous SAA concentrations and CBC-derived indices were assessed using Spearman’s rank correlation coefficient (rs). Receiver operating characteristic (ROC) curve analysis assessed the ability of each index to discriminate elevated SAA (> 10 mg/L) from normal SAA (≤ 10 mg/L) using the area under the ROC curve (AUC) with its 95% confidence interval (CI). The optimal cut-off value for each marker was determined, and the corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Binary logistic regression analysis was performed to identify predictors of elevated SAA. Univariable logistic regression analysis was conducted first and variables showing statistical significance, together with clinically relevant covariates, were entered into a multivariable model to determine their independent association with elevated SAA. Associations were expressed as odds ratios (ORs) with 95% CIs, with appropriate reference categories for categorical predictors. All statistical tests were two-tailed, and statistical significance was considered at $p \leq 0.05$.

Results

Distribution of serum amyloid A concentrations:

Among the 182 patients, 113 (62.1%) had normal SAA concentrations (≤ 10 mg/L), while 69 (37.9%) had elevated SAA concentrations (> 10 mg/L). In the elevated-SAA group, concentrations ranged from 10.8 to 177.0 mg/L, with a median of 40.0 mg/L (IQR, 21.2–95.0 mg/L). The overall distribution of SAA concentrations is presented in Table 1.

Table 1
Distribution of patients according to serum amyloid A (SAA) levels

SAA levels	No. (%)	Min. – Max.	Mean $\pm$ SD.	Median (IQR)
Normal SAA (≤ 10 mg/L)	113 (62.1%)	0.30–9.80	3.67 $\pm$ 2.14	3.0 (2.30–3.50)
Elevated SAA (> 10 mg/L)	69 (37.9%)	10.80–177.0	62.75 $\pm$ 51.90	40.0 (21.20–95.0)
Total	182 (100.0%)	0.30–177.0	26.07 $\pm$ 42.91	4.70 (3.0–27.0)
IQR: Inter quartile range SD: Standard deviation				

Patient characteristics

A total of 182 children with FMF in attack-free remission were included. The cohort comprised 103 males (56.6%) and 79 females (43.4%), with a median age of 10.0 years (IQR, 7.0–12.0 years). Consanguinity was reported in 71 patients (39.0%), and 151 (83.0%) had genetically confirmed MEFV mutations. Demographic and clinical characteristics, including age, age at symptom onset and diagnosis, diagnostic delay, sex, consanguinity, and MEFV mutation status, did not differ significantly between patients with normal and elevated SAA concentrations (all $P > 0.05$; Table 2)

Table 2
Demographic and disease characteristics of the two studied groups

	Total (n = 182)	SAA levels		Test of Sig	p
		Normal (≤ 10 mg/L) (n = 113)	Elevated (> 10 mg/L) (n = 69)		
Sex n (%)					
Male	103 (56.6%)	64 (56.6%)	39 (56.5%)	χ ² = 0.000	0.988
Female	79 (43.4%)	49 (43.4%)	30 (43.5%)		
Age (yrs)					
Min. – Max.	2.0–18.0	2.0–18.0	2.0–18.0	t = 1.053	0.294
Mean ± SD.	9.73 ± 3.70	9.50 ± 3.44	10.10 ± 4.09		
Median (IQR)	10.0 (7.0–12.0)	9.0 (7.0–12.0)	10.0 (7.0–12.0)		
Age of symptoms (yrs)					
Min. – Max.	0.16–13.0	0.16–11.0	0.25–13.0	U = 3662.500	0.491
Mean ± SD.	2.57 ± 2.03	2.63 ± 1.98	2.47 ± 2.11		
Median (IQR)	2.0 (1.0–3.80)	2.0 (1.0–3.80)	2.0 (1.0–3.0)		
Age of diagnosis (yrs)					
Min. – Max.	0.33–14.50	0.33–12.50	1.0–14.50	U = 3826.500	0.834
Mean ± SD.	5.01 ± 2.96	4.85 ± 2.69	5.28 ± 3.37		
Median (IQR)	4.25 (3.0–6.50)	4.0 (3.0–6.0)	5.0 (2.80–7.0)		
Delay of diagnosis (yrs)					
Min. – Max.	0.0–12.0	0.0–9.40	0.0–12.0	U = 3463.000	0.205
Mean ± SD.	2.42 ± 2.50	2.19 ± 2.21	2.80 ± 2.90		
Median (IQR)	1.50 (0.66–3.0)	1.50 (0.50–2.80)	1.60 (1.0–4.0)		
MEFV Mutation, n (%)					
Negative	31 (17.0%)	23 (20.4%)	8 (11.6%)	χ ² =	0.127
SD: Standard deviation #####					

	Total (n = 182)	SAA levels		Test of Sig	p
		Normal (≤ 10 mg/L) (n = 113)	Elevated (> 10 mg/L) (n = 69)		
Sex n (%)					
Positive	151 (83.0%)	90 (79.6%)	61 (88.4%)	2.326	
- Homozygous	29 (19.2%)	20 (22.2%)	9 (14.7%)		
- Heterozygous	65 (43.0%)	51 (56.7%)	14 (22.9%)		
-Compound Heterozygous	40 (26.5%)	18 (20%)	22 (36%)		
-Triallelic E148 Q, I 692 del, V 726 A	17 (11.2%)	1 (1.1%)	16 (26.2%)		
- M694V mutation	14 (9.3%)	6 (6.7%)	8 (13.1%)		
Consanguinity n (%)					
Negative	111 (61.0%)	69 (61.1%)	42 (60.9%)	χ²=	0.979
Positive	71 (39.0%)	44 (38.9%)	27 (39.1%)	0.001	
SD: Standard deviation #####					

p: p value for comparing between the two studied groups

*: Statistically significant at $p \leq 0.05$

Comparison of CBC-derived inflammatory indices according to SAA status

CBC-derived inflammatory indices were compared between patients with normal and elevated SAA concentrations. Of the seven evaluated biomarkers, only SIRI differed significantly between the two groups, with higher values in patients with elevated SAA (median, 0.86 vs. 0.72; $P = 0.027$). NLR, PLR, MLR, LMR, dNLR, and SII showed no statistically significant differences between groups (all $P > 0.05$). The comparison of inflammatory indices according to SAA status is presented in Table 3, and the distribution of SIRI values is shown in Fig. 1.

Table 3
CBC-derived inflammatory indices of the two studied groups

	Total (n = 182)	SAA levels		U	p
		Normal (≤ 10 mg/L) (n = 113)	Elevated (> 10 mg/L) (n = 69)		
NLR					
Min. – Max.	0.28–4.39	0.28–3.50	0.38–4.39	3290.50	0.078
Mean ± SD.	1.37 ± 0.78	1.29 ± 0.74	1.50 ± 0.83		
Median (IQR)	1.21 (0.85–1.72)	1.10 (0.78–1.69)	1.33 (0.97–1.78)		
PLR					
Min. – Max.	32.17–344.0	46.0–344.0	32.17–333.6	3503.00	0.251
Mean ± SD.	125.6 ± 58.51	128.0 ± 56.82	121.6 ± 61.39		
Median (IQR)	114.3(85.37–150.2)	120.0(90.75–150.0)	103.1(80.94–151.4)		
LMR					
Min. – Max.	1.22–32.0	1.22–32.0	1.29–22.40	3393.00	0.143
Mean ± SD.	5.46 ± 4.0	5.73 ± 4.24	5.02 ± 3.55		
Median (IQR)	4.16 (3.16–6.48)	4.31 (3.29–6.67)	3.64 (3.02–6.07)		
MLR					
Min. – Max.	0.03–0.82	0.03–0.82	0.04–0.77	3393.00	0.143
Mean ± SD.	0.26 ± 0.14	0.25 ± 0.14	0.28 ± 0.15		
Median (IQR)	0.24 (0.15–0.32)	0.23 (0.15–0.30)	0.28 (0.16–0.33)		
dNLR					
Min. – Max.	0.21–4.0	0.21–4.0	0.31–3.18	3423.00	0.168
Mean ± SD.	0.97 ± 0.57	0.93 ± 0.55	1.03 ± 0.59		
Median (IQR)	0.82 (0.61–1.16)	0.80 (0.59–1.10)	0.89 (0.67–1.20)		
SII					

	Total (n = 182)	SAA levels		U	p
		Normal (≤ 10 mg/L) (n = 113)	Elevated (> 10 mg/L) (n = 69)		
NLR					
Min. – Max.	72.66–1932.2	72.66–1461.7	94.88–1932.2	3715.00	0.595
Mean $\pm$ SD.	444.3 $\pm$ 295.7	431.8 $\pm$ 277.1	464.7 $\pm$ 325.0		
Median (IQR)	393.2(235.4– 559.8)	376.0(235.4– 553.1)	401.8(242.7– 600.9)		
SIRI					
Min. – Max.	0.10–4.0	0.11–2.87	0.10–4.0	3138.00*	0.027*
Mean $\pm$ SD.	0.90 $\pm$ 0.66	0.81 $\pm$ 0.56	1.05 $\pm$ 0.78		
Median (IQR)	0.76 (0.42–1.18)	0.72 (0.37–1.09)	0.86 (0.53–1.20)		

IQR: **Inter quartile range** SD: **Standard deviation** U: **Mann Whitney test**

p: p value for comparing between the two studied groups

*: Statistically significant at $p \leq 0.05$ (All tests were two-tailed)

Correlation between inflammatory indices and serum amyloid A

In spearman correlation analysis, both NLR ($r_s = 0.158$, $P = 0.033$) and SIRI ($r_s = 0.156$, $P = 0.036$) showed weak positive correlations with continuous SAA concentrations, whereas PLR, LMR, MLR, dNLR, and SII were not significantly correlated with SAA (all $P > 0.05$). Correlation coefficients for all evaluated biomarkers are presented in Table 4.

Table 4
Correlations between inflammatory indices and SAA concentrations

	Serum Amyloid A (SAA)	
	r_s	p
NLR	0.158	0.033*
PLR	-0.045	0.548
LMR	-0.068	0.359
MLR	0.068	0.359
dNLR	0.117	0.116
SII	0.082	0.269
SIRI	0.156	0.036*

r: Spearman coefficient

*: Statistically significant at $p \leq 0.05$ (All tests were two-tailed)

Discriminatory performance of CBC-derived inflammatory indices

Receiver operating characteristic (ROC) curve analysis was performed to assess the ability of each CBC-derived inflammatory index to discriminate patients with elevated SAA concentrations ($> 10\text{mg/L}$). SIRI showed the highest discriminatory performance, with an area under the curve (AUC) of 0.598 (95% CI, 0.514–0.681; $P = 0.027$). However, its discriminatory ability was limited. None of the other indices showed statistically significant discriminatory performance (Table 5 and Fig. 2).

Table 5
Receiver operating characteristic (ROC) analysis of CBC-derived inflammatory indices for discriminating elevated SAA concentrations (SAA > 10 mg/L)

NLR	AUC	p	95% CI	Cut off[#]	Sensitivity	Specificity	PPV	NPV
	0.578	0.078	0.494–0.662	> 1.17	59.42	54.87	44.6	68.9
PLR	0.551	0.251	0.462–0.639	≤ 111.6	57.97	56.64	44.9	68.8
LMR	0.565	0.143	0.479–0.651	≤ 4.18	57.97	53.10	43.0	67.4
MLR	0.565	0.143	0.479–0.651	> 0.238	57.97	53.10	43.0	67.4
dNLR	0.561	0.168	0.476–0.646	> 0.810	56.52	52.21	41.9	66.3
SII	0.524	0.595	0.437–0.610	> 376	53.62	50.44	39.8	64.0
SIRI	0.598	0.027*	0.514–0.681	> 0.751	60.87	56.64	46.2	70.3

AUC: Area Under a Curve p value: Probability value CI: Confidence Intervals

NPV: Negative predictive value PPV: Positive predictive value

*: Statistically significant at $p \leq 0.05$

Predictors of subclinical inflammation

In univariable logistic regression analysis, higher SIRI values (OR = 1.736, 95% CI, 1.085–2.777; $P = 0.021$) and intermediate-to-severe disease severity (OR = 3.894, 95% CI, 1.849–8.199; $P = 0.001$) were significantly associated with elevated SAA concentrations. Variables meeting the predefined selection criteria and clinically relevant covariates were entered into the multivariable logistic regression model. After adjustment, intermediate-to-severe disease severity remained the only independent predictor of persistent subclinical inflammation (adjusted OR = 3.658, 95% CI, 1.725–7.757; $P = 0.001$). The association between SIRI and elevated SAA was attenuated and became borderline (adjusted OR = 1.612, 95% CI, 0.989–2.628; $P = 0.055$) (Table 6)

Table 6
Univariable and multivariable logistic regression analyses for predictors of elevated serum amyloid A (> 10 mg/L)

	Univariate		#Multivariate	
	p	OR (LL – UL 95%C.I)	p	OR (LL – UL 95%C.I)
NLR	0.086	1.402 (0.953–2.062)		
PLR	0.475	0.998 (0.993–1.003)		
LMR	0.251	0.952 (0.875–1.035)		
MLR	0.179	4.173 (0.520–33.466)		
dNLR	0.224	1.386 (0.819–2.345)		
SII	0.467	1.000 (0.999–1.001)		
SIRI	0.021*	1.736 (1.085–2.777)	0.055	1.612 (0.989–2.628)
Disease Severity				
Mild		1.000		
Intermediate & Severe	< 0.001*	3.894 (1.849–8.199)	0.001*	3.658 (1.725–7.757)
OR: Odds ratio				

C.I: Confidence interval LL: Lower limit UL: Upper Limit

#: All variables with $p < 0.05$ was included in the multivariate.

*: Statistically significant at $p \leq 0.05$

Discussion

Persistent elevation of serum amyloid A (SAA) during clinical remission is clinically important because ongoing inflammation in FMF contributes to long-term morbidity, particularly AA amyloidosis [9]. To our knowledge, this is the first pediatric FMF study to simultaneously compare a broad panel of CBC-derived inflammatory indices and specifically assess the relationship of the systemic inflammation response index (SIRI) with continuous SAA concentrations and SAA-defined persistent subclinical inflammation during attack-free remission.

In this cohort, 37.9% of children had SAA concentrations > 10 mg/L despite being clinically attack-free, indicating that biochemical inflammation persists in a substantial proportion of pediatric patients during apparent remission. This prevalence was consistent with that reported by Lachmann et al., who found that 35% of SAA measurements in FMF patients exceeded 10 mg/L, including 13% that exceeded 50 mg/L [6]. Lower prevalences of SAA elevation during attack-free periods were reported in other pediatric

cohorts by Çakan et al. (28.5%) and Bahçeci et al. (15.6%) [5, 7]. In contrast, a previous Egyptian study of children with FMF reported a substantially higher prevalence, with 78.9% of patients having SAA > 30mg/L [8]. Differences between studies may reflect variation in disease severity, MEFV genotype, colchicine adherence, duration of remission, patient characteristics, and the threshold used to define persistent inflammation. These findings reinforce the distinction between clinical remission and complete suppression of inflammation in FMF.

The principal finding was that SIRI showed the strongest overall performance among the seven evaluated indices. It was the only index significantly higher in children with elevated SAA and, together with NLR, showed a weak positive correlation with continuous SAA concentrations. SIRI also demonstrated the highest ROC performance (AUC = 0.598), although its discriminatory ability was limited. In univariable analysis, SIRI was significantly associated with elevated SAA; however, this association became borderline after adjustment for disease severity in multivariable analysis. This attenuation suggests that part of the observed relationship between SIRI and elevated SAA may be explained by underlying disease severity. More severe disease is associated with greater cumulative inflammatory burden, recurrent attacks, and sustained inflammatory signaling, which may contribute to both increased SAA concentrations and alterations in circulating leukocyte profiles [1, 2].

However, the persistence of an adjusted odds ratio > 1 (adjusted OR = 1.61), with a *P* value close to the conventional threshold for statistical significance (*P* = 0.055), suggests a residual association despite reduced statistical certainty. This should not be interpreted as evidence that SIRI lacks biological relevance; rather, it suggests that SIRI provides limited independent information beyond the broader inflammatory phenotype captured by disease severity. Persistent inflammation during remission is multifactorial and may also be influenced by MEFV genotype, arthritis, colchicine responsiveness and adherence, disease duration, treatment optimization, and host-related factors that cannot be adequately captured by a single hematological index. Adjustment for a comprehensive clinical measure such as disease severity would therefore be expected to reduce the apparent contribution of SIRI [5, 6].

The superior performance of SIRI is biologically plausible. FMF is driven by dysregulated pyrin inflammasome activation, leading to excessive caspase-1 activation and IL-1 β -mediated innate immune responses. Although neutrophils are major effector cells during acute attacks, persistent inflammation during clinically quiescent periods may involve more complex interactions among neutrophils, monocytes, and lymphocytes. By integrating all three cellular components, SIRI may capture a broader inflammatory profile than indices that predominantly reflect neutrophil or platelet-related responses. However, circulating monocyte counts should not be interpreted as direct measures of inflammasome activation [2, 20, 21].

These findings are biologically consistent with observations from other immune-mediated diseases, including rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, and Behçet disease. In these conditions, composite indices such as SIRI have been associated with inflammatory activity or disease severity and have shown diagnostic or prognostic value, supporting their potential as

broad indicators of systemic inflammatory burden [22–25]. Nevertheless, these findings cannot be directly extrapolated to FMF because of differences in disease mechanisms and clinical contexts.

The limited performance of the remaining indices is also noteworthy. In the present study, NLR showed a weak positive correlation with SAA but did not significantly distinguish between patients with normal and elevated SAA. In contrast, NLR has been reported as a marker of systemic inflammation during acute FMF attacks, with higher values also described during attack-free periods as an indicator of subclinical inflammation [11–14]. Other studies have reported higher NLR values in patients with amyloidosis and suggested its potential role in predicting amyloidosis [15, 16, 26]. These discrepancies emphasize that an index capable of distinguishing patients with FMF from healthy controls or reflecting general inflammatory activity may not necessarily discriminate persistent SAA elevation during remission. Similarly, the lack of significant discriminatory value for dNLR may reflect its substantial overlap with conventional NLR. Normalization of neutrophil counts during remission may further limit the ability of both indices to detect low-grade persistent inflammation.

PLR and SII also failed to demonstrate significant associations with elevated SAA. Both indices incorporate platelet counts, which may be less informative during attack-free remission than during acute inflammatory states. Previous FMF studies have shown that PLR may increase during acute attacks but is not consistently associated with subclinical inflammation [13, 14, 16]. Likewise, the absence of significant associations for LMR and MLR may indicate that absolute monocyte counts do not adequately reflect functional monocyte activation during remission. Both ratios are also influenced by lymphocyte counts which may remain relatively stable during clinically quiescent periods.

Overall, the potential utility of CBC-derived inflammatory indices as accessible markers of residual inflammatory activity in FMF has been highlighted by several studies, although their performance varies according to the index and inflammatory outcome. Özer et al. reported that NLR, PLR, MPV, and RDW could reflect subclinical inflammatory activity during symptom-free periods [11]. In contrast, Dinçer et al. found that NLR, but not PLR or MPV, was associated with subclinical inflammation during attack-free periods, suggesting that neutrophil-lymphocyte imbalance may reflect residual inflammatory activity [14]. Similarly, Ocak et al. found that the pan-immune-inflammation value (PIV), another composite CBC-derived index incorporating neutrophils, lymphocytes, monocytes, and platelets, was associated with amyloidosis and moderate-to-severe disease in adults with FMF assessed during an attack-free interval [16]. More recently, Cure et al. evaluated several hematologic inflammatory indices, including NLR, MLR, PLR, SII, and SIRI, alongside SAA in attack-free FMF patients. Although these indices did not differ significantly between FMF patients and controls, SAA-defined subclinical inflammation was associated with higher Growth Differentiation Factor-15 (GDF-15) levels, which showed moderate discriminatory ability for subclinical inflammation (AUC = 0.74) [17]. In this context, our finding that SIRI showed the strongest association among the evaluated CBC-derived indices extends the existing evidence, while its modest discriminatory performance indicates that SIRI should be considered a complementary rather than replacement biomarker for SAA.

An important finding of the present study was that intermediate-to-severe disease severity, assessed using the ISSF, was the only independent predictor of persistent subclinical inflammation. This suggests that standardized disease severity captures the cumulative inflammatory phenotype more comprehensively than any CBC-derived index measured at a single time point. Our finding is consistent with the recently published pediatric cohort by Bahçeci et al., which also identified higher ISSF scores, arthritis, earlier disease onset, and biallelic exon 10 *MEFV* mutations as important predictors of persistent subclinical inflammation [5]. This further supports the multifactorial nature of persistent inflammation and may explain why the apparent association between SIRI and SAA was attenuated after adjustment for disease severity.

Clinically, these findings suggest a potential integrated approach in which children with more severe disease undergo closer biochemical surveillance, with SIRI potentially serving as an inexpensive complementary screening marker when SAA testing is unavailable. However, the modest AUC and loss of independent statistical significance after adjustment do not support using a specific SIRI cutoff to guide treatment decisions. SAA should therefore remain the confirmatory biomarker [7, 10].

The major strengths of this study are its focus on attack-free remission, evaluation of seven CBC-derived inflammatory indices within the same pediatric FMF cohort, and use of a predefined SAA threshold as the biochemical reference outcome. In addition, the combined use of correlation analysis, ROC analysis, and multivariable logistic regression enabled assessment of both the relative performance and independent contribution of the evaluated indices after adjustment for disease severity. The study is further strengthened by its comparative assessment of SIRI and other CBC-derived inflammatory markers in relation to SAA-defined persistent inflammation in pediatric FMF.

Several limitations should be acknowledged. The study design precludes conclusions regarding temporal relationships and does not establish whether SIRI predicts future attacks, colchicine resistance, treatment escalation, or AA amyloidosis. The single-center tertiary-care setting may limit generalizability, and serial SAA and CBC measurements were unavailable. In addition, genetic heterogeneity, colchicine adherence, and treatment responsiveness may influence persistent inflammation. Future prospective multicenter studies should incorporate longitudinal SAA and SIRI measurements together with *MEFV* genotype and treatment-related variables.

Conclusion

SIRI was the most informative of the evaluated CBC-derived inflammatory indices for identifying persistent SAA-defined subclinical inflammation during attack-free remission in children with FMF. However, its modest discriminatory performance and attenuation after adjustment for disease severity indicate that SIRI should be interpreted as a complementary marker of inflammatory burden rather than an alternative to SAA. Intermediate-to-severe disease severity remained the strongest independent predictor of persistent SAA elevation, supporting the integration of standardized clinical severity assessment with biochemical monitoring. Prospective studies should determine whether serial SIRI

measurements can improve prediction of persistent inflammation and clinically relevant long-term outcomes.

Abbreviations

ALC

Absolute lymphocyte count

AMC

Absolute monocyte count

ANC

Absolute neutrophil count

AUC

Area under the curve

CBC

Complete blood count

CI

Confidence interval

dNLR

Derived neutrophil-to-lymphocyte ratio

FMF

Familial Mediterranean fever

IL-1 β

Interleukin-1 β

IQR

Interquartile range

ISSF

International Severity Scoring System for FMF

LMR

Lymphocyte-to-monocyte ratio

MLR

Monocyte-to-lymphocyte ratio

NLR

Neutrophil-to-lymphocyte ratio

NPV

Negative predictive value

ORs

Odds ratios

PLR

Platelet-to-lymphocyte ratio

PPV

Positive predictive value
ROC
Receiver operating characteristic
SAA
Serum amyloid A
SD
Standard deviation
SII
Systemic immune-inflammation index
SIRI
Systemic inflammation response index
WBC
Total white blood cell count

Declarations

Consent for publication:

Retrospectively collected data from medical records in the clinic and informed consent was obtained from the parents or legal guardians of all patients for publication of anonymous patients' data.

Competing interests:

The authors declare that they have no competing interests.

Author Contribution

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Availability of data and material:

All data generated or analyzed are available upon reasonable request.

References

1. Ben-Chetrit E (2024) Old paradigms and new concepts in familial Mediterranean fever (FMF): an update 2023. *Rheumatology (Oxford)* 63(2):309–318. <https://doi.org/10.1093/rheumatology/kead439>
2. Kislak E, Kocak E, Kocak N, Gul U (2024) Familial Mediterranean Fever in Childhood. *Turk Arch Pediatr* 59(6):527–534. <https://doi.org/10.5152/TurkArchPediatr.2024.24188>
3. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T et al (1997) Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 40(10):1879–1885. <https://doi.org/10.1002/art.1780401023>
4. Grateau G, Pêcheux C, Cazeneuve C, Cattani D, Dervichian M, Goossens M et al (2000) Clinical versus genetic diagnosis of familial Mediterranean fever. *QJM* 93(4):223–229. <https://doi.org/10.1093/qjmed/93.4.223>
5. Bahçeci O, Aydın F, Taş Aslan Ö, Sarisoğlu D, Erorhan E, Özçakar ZB (2026) Subclinical inflammation in pediatric familial Mediterranean fever: predictors and follow-up results of a retrospective single-center cohort study. *Clin Rheumatol* 45(6):3667–3674. <https://doi.org/10.1007/s10067-026-08133-8>
6. Lachmann HJ, Sengül B, Yavuzşen TU, Booth DR, Booth SE, Bybee A et al (2006) Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. *Rheumatology (Oxford)* 45(6):746–750. <https://doi.org/10.1093/rheumatology/kei279>
7. Çakan M, Karadağ ŞG, Tanatar A, Sönmez HE, Ayaz NA (2021) The Value of Serum Amyloid A Levels in Familial Mediterranean Fever to Identify Occult Inflammation During Asymptomatic Periods. *J Clin Rheumatol* 27(1):1–4. <https://doi.org/10.1097/rhu.0000000000001134>
8. Lofty HM, Marzouk H, Farag Y, Nabih M, Khalifa IA, Mostafa N et al (2016) Serum Amyloid A Level in Egyptian Children with Familial Mediterranean Fever. *Int J Rheumatol* 2016:7354018. <https://doi.org/10.1155/2016/7354018>
9. Papa R, Lachmann HJ (2018) Secondary, AA, Amyloidosis. *Rheum Dis Clin North Am* 44(4):585–603. <https://doi.org/10.1016/j.rdc.2018.06.004>
10. Ozen S, Sağ E, Oton T, Gül A, Sieiro Santos C, Bayraktar D et al (2025) EULAR/PRoS endorsed recommendations for the management of familial Mediterranean fever (FMF): 2024 update. *Ann Rheum Dis* 84(6):899–909. <https://doi.org/10.1016/j.ard.2025.01.028>
11. Özer S, Yılmaz R, Sönmezgöz E, Karaaslan E, Taşkın S, Bütün İ et al (2015) Simple markers for subclinical inflammation in patients with Familial Mediterranean Fever. *Med Sci Monit* 21:298–303. <https://doi.org/10.12659/msm.892289>
12. Ahsen A, Ulu MS, Yuksel S, Demir K, Uysal M, Erdogan M et al (2013) As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. *Inflammation* 36(6):1357–1362. <https://doi.org/10.1007/s10753-013-9675-2>

13. Babak Sandoghchian S, Faramarz A-K, Fatemeh A, Leila M (2024) Comparison of neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and red blood cell distribution width during the attack phase of familial Mediterranean fever with the silent phase of the disease in patients referred to the emergency department. *Front Emerg Med* 8(3):e25. <https://doi.org/10.18502/fem.v8i3.16332>
14. Dinçer ABK, Gülöksüz EGA, Sezer S, Yılmaz R, Turgay TM, Ateş A et al (2022) Neutrophil/lymphocyte ratio but not platelet/lymphocyte ratio and mean platelet volume can be an indicator of subclinical inflammation in patients with Familial Mediterranean Fever. *Egypt Rheumatol* 44(3):215–218. <https://doi.org/10.1016/j.ejr.2021.11.005>
15. Uslu AU, Deveci K, Korkmaz S, Aydın B, Senel S, Sancakdar E et al (2013) Is neutrophil/lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with familial Mediterranean fever? *Biomed Res Int* 2013:185317. <https://doi.org/10.1155/2013/185317>
16. Ocak T, Görünen A, Coşkun BN, Yağız B, Ozemri Sağ S, Ocakoğlu G et al (2024) Pan-Immune-Inflammation Value Could Be a New Marker to Predict Amyloidosis and Disease Severity in Familial Mediterranean Fever. *Diagnostics (Basel)* 14(6):634. <https://doi.org/10.3390/diagnostics14060634>
17. Cure O, Huner Yigit M, Uzun H, Zihni HC, Yigit E (2026) Growth differentiation factor-15 as a potential biomarker in subclinical inflammation in familial mediterranean fever. *Clin Rheumatol* 45(6):3645–3656. <https://doi.org/10.1007/s10067-026-08064-4>
18. Demirkaya E, Acikel C, Hashkes P, Gattorno M, Gul A, Ozdogan H et al (2016) Development and initial validation of international severity scoring system for familial Mediterranean fever (ISSF). *Ann Rheum Dis* 75(6):1051–1056. <https://doi.org/10.1136/annrheumdis-2015-208671>
19. Stankovic Stojanovic K, Hentgen V, Fellahi S, Georgin-Lavialle S, Amselem S, Grateau G et al (2017) Concordance between CRP and SAA in familial Mediterranean fever during attack-free period: A study of 218 patients. *Clin Biochem* 50(4–5):206–209. <https://doi.org/10.1016/j.clinbiochem.2016.11.008>
20. Qi Q, Zhuang L, Shen Y, Geng Y, Yu S, Chen H et al (2016) A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer* 122(14):2158–2167. <https://doi.org/10.1002/cncr.30057>
21. Chae JJ, Cho YH, Lee GS, Cheng J, Liu PP, Feigenbaum L et al (2011) Gain-of-function Pyrin mutations induce NLRP3 protein-independent interleukin-1 β activation and severe autoinflammation in mice. *Immunity* 34(5):755–768. <https://doi.org/10.1016/j.immuni.2011.02.020>
22. Okutan İ, Aci R, Keskin Â, Bilgin M, Kızılet H (2024) New inflammatory markers associated with disease activity in rheumatoid arthritis: pan-immune-inflammation value, systemic immune-inflammation index, and systemic inflammation response index. *Reumatologia* 62(6):439–446. <https://doi.org/10.5114/reum/196066>
23. Ozdemir A, Baran E, Kutu M, Celik S, Yılmaz M (2023) Could systemic immune inflammation index be a new parameter for diagnosis and disease activity assessment in systemic lupus erythematosus? *Int Urol Nephrol* 55(1):211–216. <https://doi.org/10.1007/s11255-022-03320-3>

24. Cesaro N, Valvano M, Monaco S, Stefanelli G, Fabiani S, Vernia F et al (2025) The role of new inflammatory indices in the prediction of endoscopic and histological activity in inflammatory bowel disease patients. *Eur J Gastroenterol Hepatol* 37(1):24–32.
<https://doi.org/10.1097/meg.0000000000002842>
25. Kılıç J, Yamancan G, Doğan Y, Şahin S, Gündüz İ, Alakuş ÖF et al (2026) Inflammatory Indices as Markers of Vascular and Organ Involvement in Behçet's Disease. *J Clin Med* 15(4):1535.
<https://doi.org/10.3390/jcm15041535>
26. Tezcan ME, Acer Kasman S, Şen N, Osken S, Yılmaz-Oner S (2023) Importance of hematological markers in familial Mediterranean fever in terms of disease severity and amyloidosis. *Rheumatol Int* 43(7):1313–1321. <https://doi.org/10.1007/s00296-023-05290-w>

Figures

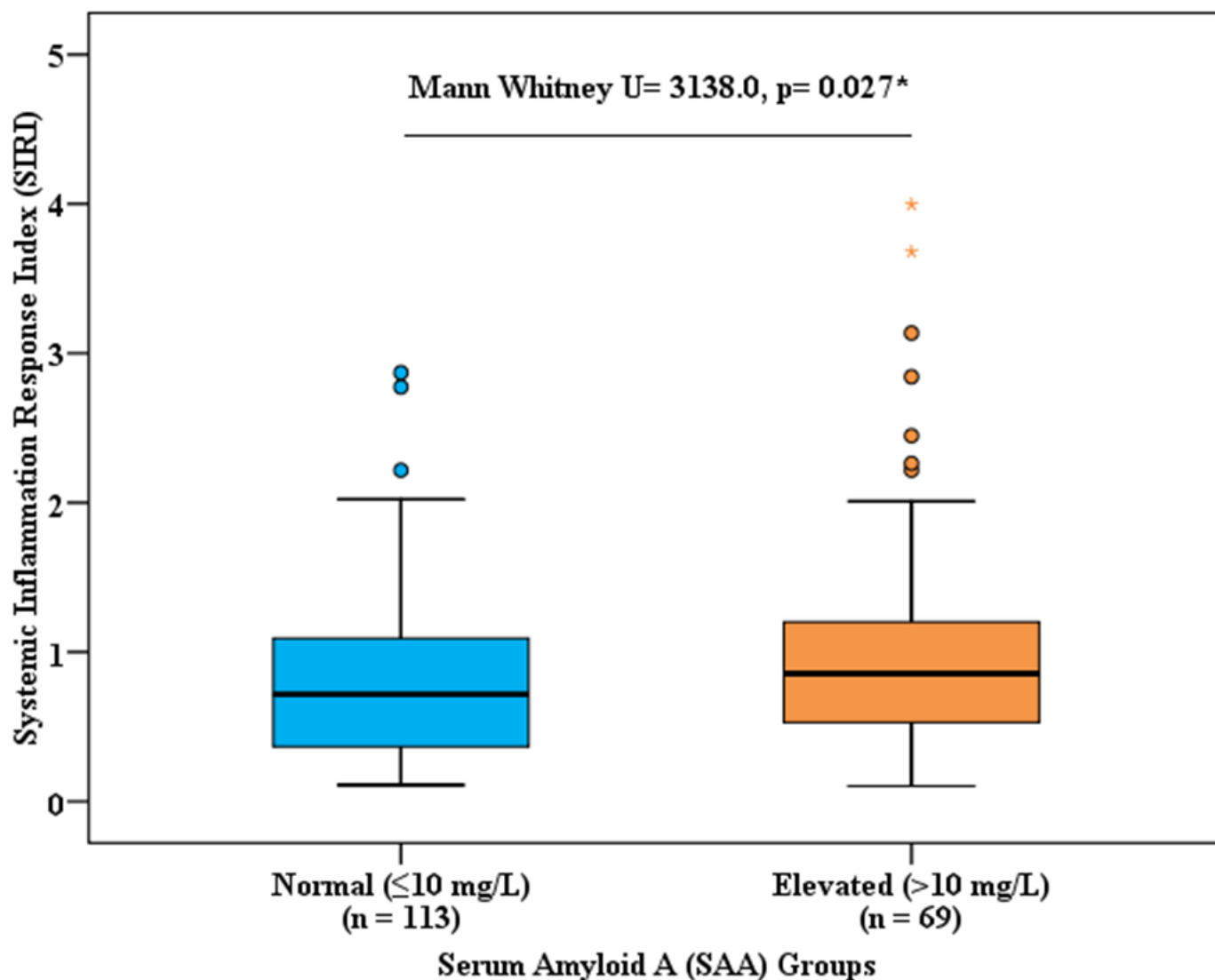


Figure 1

Distribution of systemic inflammation response index (SIRI) according to serum amyloid A (SAA) status during attack-free remission in children with familial Mediterranean fever

Legend: Box-and-whisker plot showing the median, interquartile range, and overall distribution of SIRI values in patients with normal SAA (≤ 10 mg/L) and elevated SAA (>10 mg/L). Individual patient values are displayed as overlaid data points. Patients with elevated SAA demonstrated significantly higher SIRI values compared with those with normal SAA (Mann–Whitney U test, $P=0.027$), supporting the association between SIRI and persistent subclinical inflammation during attack-free remission

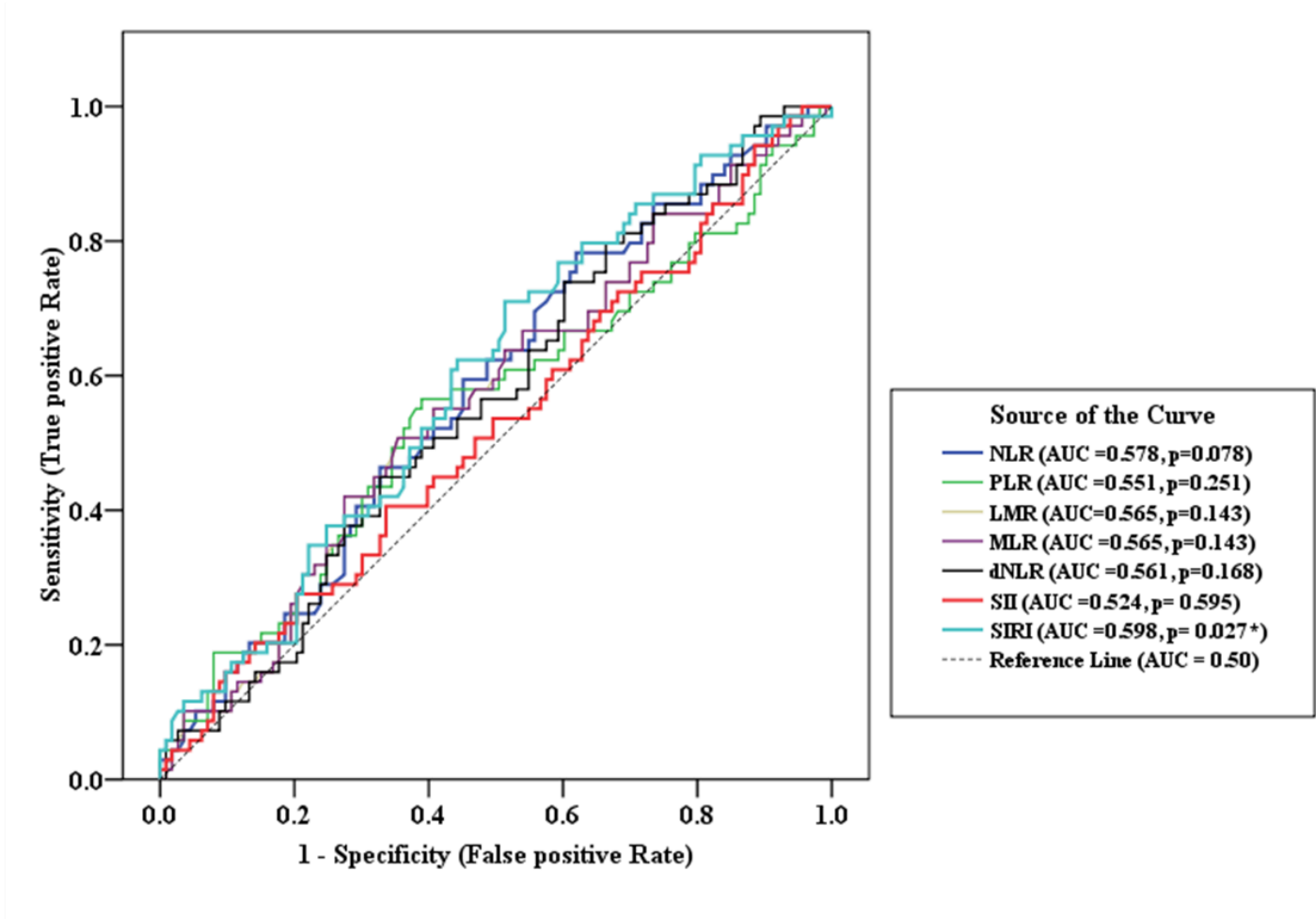


Figure 2

Receiver operating characteristic (ROC) curves of CBC-derived inflammatory indices for identifying persistent subclinical inflammation

Legend: SIRI demonstrated the highest area under the curve (AUC=0.598, 95% CI 0.514–0.681; $P=0.027$) and was the only index that achieved statistical significance, whereas NLR, PLR, LMR, MLR, dNLR, and SII showed limited discriminatory performance.