Original paper

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Assessment of hematologic indices for diagnosis in juvenile systemic lupus erythematosus

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Abstract

Introduction: The aim was to present effective approaches utilizing novel hematological parameters for early diagnosis of juvenile-onset systemic lupus erythematosus (jSLE).

Material and methods: Our study at Umraniye Training and Research Hospital involved a jSLE patient cohort from 2016 to 2022 and matched healthy controls aligning with sex and age. We use the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) for disease activity. Our approach was to analyze leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, along with ratios such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and monocyte-to-platelet ratio (MPR). We also explored novel indices: the systemic inflammatory index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) to identify relationships between systemic indices and jSLE activity.

Results: Upon comparative analysis with the healthy control group, systemic lupus erythematosus (SLE) patients exhibited significantly elevated levels of the hematological parameters NLR, SII, and SIRI (*p*-values: 0.010, 0.048, 0.025, respectively). Among SLE patients, neutrophil, lymphocyte, and platelet distribution width (PDW) values were notably higher, while hemoglobin, red blood cell distribution width (RDW), and procalcitonin (PCT) values were significantly lower. In comparison, C-reactive protein (CRP) and sedimentation values were markedly elevated in the SLE group in contrast to the healthy control cohort. Patients with significantly elevated disease activity had notably higher values of NLR ($p = 0.010$) and SII ($p = 0.048$). Among patients with positive antinuclear antibodies (ANA), elevated levels of NLR, SII, and SIRI were noted (*p*-values: 0.018, 0.021, 0.035).

Conclusions: In this study, the novel hematological markers SII, SIRI, and AISI were found to effectively reflect inflammation in SLE patients, exhibit associations with high disease activity, and demonstrate heightened sensitivity in detecting cases with high disease activity.

Key words: systemic indexes, hematologic indexes, systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder classified as a systemic connective tissue disease. It manifests with a wide range of clinical and laboratory symptoms affecting multiple organ systems. The underlying causes of SLE are believed to be complex, but a key characteristic is the production of autoantibodies. These autoantibodies lead to the formation of immune complexes, triggering inflammatory processes that can result in lasting organ damage [1]. Constitutional symptoms of SLE commonly affect the skin, joints, kidneys, central nervous system, and hematopoietic system [2]. However, it is important to note that while these clinical signs are indicative of SLE, they may also be related to other conditions. Therefore, it is crucial to carefully consider alternative diagnoses such as fibromyalgia, depression, infections, tumors, hormonal imbalances, or other connective tissue disorders during the initial assessment [1].

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The classification of SLE is based on the criteria established by the Systemic Lupus International Collaborating Clinics (SLICC) in 2012, as well as the guidelines provided by the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) in 2019 [3, 4].

Currently, the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score is a widely used tool for assessing disease activity in patients with SLE [5]. Traditional measures such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement components C3 and C4, and anti-double-stranded DNA (anti-dsDNA) titers have limitations in accurately reflecting the dynamic state of SLE activity [6–8]. This challenge has led to efforts to identify biomarkers that can predict SLE and quantify disease activity. However, the inherent heterogeneity of SLE makes it impractical to rely on a single biomarker to replace clinical evaluation.

Hematologic parameters that indirectly reflect subclinical inflammation have proven to be valuable in assessing or predicting disease activity in various medical conditions (i.e., Sjögren's syndrome, psoriasis, systemic vasculitis, and infectious diseases) [9–14]. In recent times, there has been a notable uptick in research focusing on the use of hematological parameters to evaluate SLE activity.

In this study, our primary objective was to evaluate the potential significance of novel hematological markers as indicators of inflammation in SLE. We aimed to complement the assessment by including traditional markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR). These newly explored markers, namely the systemic inflammatory index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI), were scrutinized to determine their relevance as indicators of inflammation in SLE. We also sought to investigate their association with disease activity and assess their sensitivity in detecting states of high disease activity.

Material and methods

In this retrospective cohort study, we included hospitalized individuals who developed SLE before the age of 18. These patients were recruited from the Department of Pediatric Rheumatology at Istanbul Health Science University, Umraniye Training and Research Hospital, spanning the years 2016 to 2022. As a comparative group, healthy individuals of matching age and sex who had undergone routine physical examinations at the same hospital during the same period were selected as the healthy control cohort.

The study included newly diagnosed patients who met the criteria for SLE according to the 2019 EULAR/ACR classification criteria and who were diagnosed before the age of 18 years at the tertiary care Pediatric Rheumatology Clinic [3].

Age- and sex-matched healthy individuals who underwent routine physical examinations at the same hospital during the same period were selected as the control group. Exclusion criteria included individuals who were concurrently diagnosed with other chronic inflammatory disorders, infections, or additional autoimmune diseases, as well as those who had received recent blood transfusions within the last 4 months at the time of their initial diagnosis.

Disease activity in SLE patients was assessed using the SLEDAI-2K. Subsequently, SLE patients were divided into two groups based on their disease activity levels: those with SLEDAI-2K scores of < 20 and those with scores of ≥ 20 [15, 16]. The following indices are derived from absolute leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts: NLR, PLR, MLR, monocyte-to-platelet ratio (MPR), systemic inflammatory index, lymphocyte fraction of platelet and neutrophil value (platelet × neutrophil-to-lymphocyte ratio), SIRI, lymphocyte fraction of neutrophil and monocyte value (neutrophil × monocyte-to-lymphocyte ratio), AISI, lymphocyte fraction of neutrophil, monocyte and platelet value (neutrophil × monocyte × platelet-to-lymphocyte ratio). The NLR was computed as the quotient of the absolute neutrophil count and the absolute lymphocyte count.

Statistical analysis

All data were subjected to analysis using the statistical software SPSS 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Continuous variables are reported as mean ± standard deviation (SD), while categorical variables are reported as frequency and percentage. Non-parametric variables between the various groups were assessed using the Mann-Whitney *U* test and Kruskal-Wallis test. The correlation between variables was investigated through Spearman's rank correlation coefficient. A significance level of $p < 0.05$ was deemed as statistically significant.

Bioethical standards

Ethical considerations were strictly adhered to in accordance with the principles of the Declaration of Helsinki (2013 revision). The study protocol received the necessary approval from the Research and Ethical Review Board of the Umraniye Training and Research Hospital in Istanbul (Protocol No: B.10.1.TKH.4.34.H.GP.0.01/159).

Results

Comparison of demographic and laboratory findings between systemic lupus erythematosus patients and healthy controls

The study included 44 SLE patients, 36 women (82%) and 8 men (18%), with a female to male ratio of 4.5 : 1. The median age at the time of diagnosis was 14.7 years, with a range of 3 to 18 years. There were no significant differences in the distribution of age and sex between the SLE patients and the healthy control group of 26 patients ($p = 0.103$ and $p = 0.913$, respectively). Upon comparative analysis with the healthy control group, SLE patients exhibited significantly elevated levels of the hematological parameters NLR, SII, and SIRI (p-values: 0.010, 0.048, 0.025, respectively). Among SLE patients, neutrophil, lymphocyte, and platelet distribution width (PDW) values were notably higher, while hemoglobin, red blood cell distribution width (RDW), and PCT values were significantly lower. Thrombocyte and mean platelet volume (MPV) levels were diminished in the SLE group, yet the discrepancy did not attain statistical significance. The SLE group presented higher levels of blood urea nitrogen (BUN) and creatinine. In comparison, CRP and sedimentation values were markedly elevated in the SLE group in contrast to the healthy control cohort (Table I).

Among the patient cohort, 5 individuals exhibited significantly elevated disease activity levels (SLEDAI-2K ≥ 20), while 39 patients demonstrated a less pronounced degree of disease activity. When stratifying patients based on disease activity, it was observed that patients with significantly elevated disease activity had notably higher values of NLR ($p = 0.010$) and SII ($p = 0.048$). However, there was no statistically significant difference concerning antinuclear antibodies (ANA) and anti-dsDNA positivity in relation to very high disease activity ($p > 0.05$). Laboratory findings based on disease activity for SLE patients are presented in Table II.

Assessment of hematological parameters in predicting very high disease activity was conducted using ROC curves. The area under the curve (AUC) values for NLR (0.699), SII (0.695), SIRI (0.681), and AISI (0.782) exceeded those of other parameters, demonstrating statistical significance (p-values: 0.031, 0.021, 0.004, 0.006, respectively) (Table III). Notably, NLR, SII, SIRI, and AISI exhibited the highest sensitivity; however, these indices cannot be confidently used as discriminators for assessing disease activity.

Among biopsy-confirmed cases ($n = 25$), 82% ($n = 21$) were diagnosed with lupus nephritis (LN). No significant disparities in hematological parameters were observed between those with and without LN. Notably, sex differences were observed among patients with renal involvement, with male SLE patients demonstrating a significantly higher prevalence of kidney involvement ($p = 0.023$). No significant differences were identified in age at diagnosis or hematological parameters regarding hematological involvement, renal involvement, and neurological involvement. A higher frequency of renal involvement was observed among individuals with positive anti-dsDNA ($p = 0.047$).

Associations of hematological parameters in systemic lupus erythematosus patients

Disease activity in SLE patients was assessed utilizing the SLEDAI-2K. Within each patient, a comprehensive assessment encompassing NLR, MLR, PLR, SII, SIRI, and AISI markers was conducted. While a correlation was observed between MLR and disease activity, this correlation was not evident in relation to CRP and ESR. Significant associations were identified between sedimentation rate and both NLR and MLR (p-values respectively 0.047, 0.010). Among patients with positive ANA, elevated levels of NLR, SII, and SIRI were noted (p-values were respectively: 0.018, 0.021, 0.035). Conversely, in cases where ds-DNA was positive, a substantial elevation in MLR was observed compared to those with negative anti-dsDNA status ($p = 0.012$). Furthermore, individuals with decreased complement levels exhibited higher MLR compared to those with normal complement levels (Table IV).

Comparison of marker averages across different organ damage manifestations induced by SLE was conducted. No significant differences were observed among patients with mucocutaneous involvement, hematological involvement, renal involvement, neurological involvement, acute cutaneous lupus, acute pericarditis, and pleural effusion with pericarditis, compared to those without (Table V). Among patients with musculoskeletal involvement, MLR was higher when compared to those without ($p = 0.055$), but this difference was not significant. No significant association was observed between LN and kidney involvement with the newly identified markers platelet-to-neutrophil ratio (PNR), platelet-to-monocyte ratio (PMR), and neutrophil-to-monocyte ratio (NMR) (Table VI). Although SII, SIRI and AISI values, which are systemic indices, are higher in LN patients, no statistically significant difference was detected.

Discussion

In recent years, there has been growing interest in the role of hematological markers in the assessment of SLE activity, with studies indicating that neutrophil, basophil, eosinophil, monocyte, and platelet parameters, represented by lymphocyte ratios (NLR, BLR, ELR,

Table I. Comparison of demographic data and laboratory findings between SLE patients and healthy controls

Parameters	Patients (n = 44)	Controls (n = 26)	p-value
Age at diagnosis [years], [median (min–max)]	14.7 (2.5–18.5)	12.7 (4.9–17.9)	0.103
Sex			
Female [n, (%)]	36 (81.8)	21 (80.8)	0.913
Male [n, (%)]	8 (18.2)	5 (19.2)	
Hematological markers	Median (min–max)		
NLR	2.04 (0.75–8.46)	1.27 (0.65–2.12)	0.01
PLR	128.11 (15.36–300)	113.46 (66.18–223.6)	0.409
MLR	0.2 (0.01–0.63)	0.17 (0.1–0.27)	0.187
MPR	0 (0–0.01)	0 (0–0)	0.442
SII	581.87 (69.72–1989.02)	342.81 (190.58–699.88)	0.048
SIRI	0.72 (0.07–5.43)	0.51 (0.26–1.74)	0.025
AISI	191.43 (2.79–1399.8)	141.09 (78.14–524.67)	0.238
Complete blood count (CBC) parameters	Median (min–max)		
Leukocyte [10^3/mm^3]	6.85 (2.76–16.73)	6.37 (4.76–10.9)	0.415
Neutrophil [10^3/mm^3]	4.21 (1.52–12.63)	3.25 (1.93–6.47)	0.016
Lymphocyte [10^3/mm^3]	1.96 (0.54–4.94)	2.62 (1.54–4.14)	0.009
Monocyte [10^3/mm^3]	0.36 (0.04–1.76)	0.43 (0.25–0.87)	0.231
Hemoglobin [g/dl]	12.25 (7.9–14.9)	13.05 (11.8–16.7)	0.032
RDW [%]	14.35 (12–28)	13.45 (12–14.6)	0.005
PCT [%]	0.24 (0.03–0.4)	0.28 (0.17–0.4)	0.033
Platelet [10^3/mm^3]	270 (33–535)	296 (194–463)	0.095
MPV [fl]	8.95 (5.75–12)	9.05 (7.7–15)	0.584
PDW [%]	16.15 (13.6–18.7)	15.8 (15–17.3)	0.025
Biochemical parameters	Median (min–max)		
BUN [mg/dl]	23.85 (13–81.32)	16.63 (3.6–27.5)	0
Creatinine [mg/dl]	0.6 (0.35–0.84)	0.53 (0.41–0.78)	0.01
ALT [U/l]	16 (6–192)	12.5 (7–20)	0.126
AST [U/l]	18 (6–102)	19 (14–31)	0.761
Acute phase reactants	Median (min–max)		
CRP [mg/l]	0.2 (0.1–8.2)	0.2 (0.1–1.8)	0.004
ESR [mm/h]	14 (0–77)	8 (2–22)	0.003

AISI – aggregate index of systemic inflammation, ALT – alanine aminotransferase, AST – aspartate aminotransferase, BUN – blood urea nitrogen, CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, MLR – monocyte-to-lymphocyte ratio, MPR – monocyte-to-platelet ratio, MPV – mean platelet volume, NMR – neutrophil-to-monocyte ratio, NLR – neutrophil-to-lymphocyte ratio, PDW – platelet distribution width, PLR – platelet-to-lymphocyte ratio, PMR – platelet-to-monocyte ratio, PNR – platelet-to-neutrophil ratio, RDW – red blood cell distribution width, SII – systemic inflammatory index, SIRI – systemic inflammation response index.

MLR, and PLR), indirectly reflect subclinical inflammation [17, 18]. In this study, in addition to hematological indicators such as NLR, PLR, and MLR, novel hematological markers including SII, SIRI, and AISI were evaluated in SLE patients. The investigation aimed to establish the association of these parameters with SLE disease activity and to explore their sensitivity in predicting high disease activity. Our study demonstrated that NLR, SII, and SIRI were significantly elevated in SLE patients compared to the healthy control group.

Recent emphasis has been placed on early diagnosis of disease flares and monitoring disease activity in SLE. While the SLEDAI-2K score is widely used for this purpose [5, 17], its complexity may hinder routine clin-

Table II. Comparison of demographic data and laboratory findings among SLE patients based on disease activity

Parameters		SLEDAI-2K < 20	SLEDAI-2K ≥ 20	*p*-value
		(*n* = 39)	(*n* = 5)	
Age at diagnosis [years], [median (min–max)]		14.6 (2.5–18)	14.9 (1.6–16)	0.747
Sex				
Female [*n*, (%)]		32 (82.1)	4 (80)	0.911
Male [*n*, (%)]		7 (17.9)	1 (20)	
Hematological markers		Median (min–max)		
NLR		1.99 (0.75–8.46)	2.36 (0.81–3.87)	0.01
PLR		130.99 (15.36–300)	101.3 (26.83–198.66)	0.409
MLR		0.2 (0.01–0.63)	0.21 (0.07–0.32)	0.187
MPR		0 (0–0.01)	0 (0–0)	0.442
SII		592.5 (69.72–1989.02)	220.37 (96.85–699.28)	0.048
SIRI		0.84 (0.07–5.43)	0.46 (0.26–0.6)	0.25
AISI		263.42 (2.79–1399.8)	76.92 (13.56–141.04)	0.238
Complete blood count (CBC) parameters		Median (min–max)		
Leukocytes [10^3/mm^3]		7.18 (2.99–16.73)	5.02 (2.76–6.59)	0.415
Neutrophils [10^3/mm^3]		4.54 (1.52–12.63)	2.83 (1.86–3.61)	0.016
Lymphocytes [10^3/mm^3]		2.02 (0.92–4.94)	1.49 (0.54–3.01)	0.009
Monocytes [10^3/mm^3]		0.38 (0.04–1.76)	0.14 (0.11–0.74)	0.231
Hemoglobin [g/dl]		12.7 (7.9–14.9)	9.8 (9.1–12)	0.032
RDW [%]		14.4 (12–28)	14.3 (12.5–19)	0.005
PCT [%]		0.24 (0.03–0.4)	0.19 (0.08–0.28)	0.033
Platelets [10^3/mm^3]		279 (41–535)	234 (33–296)	0.095
MPV [fl]		8.7 (5.75–12)	9.3 (7.91–10.2)	0.584
PDW [%]		16.1 (13.6–18.7)	16.9 (15.7–18.5)	0.025
Biochemical parameters		Median (min–max)		
BUN [mg/dl]		24 (13–81.32)	23.54 (21–26.85)	0
Creatinine [mg/dl]		0.6 (0.35–0.84)	0.59 (0.53–0.71)	0.01
ALT [U/l]		16 (6–71)	30 (7–192)	0.126
AST [U/l]		18 (6–45)	46 (9–102)	0.761
Acute phase reactants		Median (min–max)		
CRP [mg/l]		0.2 (0.1–8.2)	0.2 (0.2–0.8)	0.004
ESR [mm/h]		15 (0–76)	13 (13–77)	0.003
ANA	Negative	5 (12.8)	0 (0)	0.395
	Positive	34 (87.2)	5 (100)	
dsDNA	Negative	22 (56.4)	1 (20)	0.125
	Positive	17 (43.6)	4 (80)	
DC	Negative	26 (66.7)	2 (40)	0.243
	Positive	13 (33.3)	3 (60)	

Table II. Cont.

Parameters		SLEDAI-2K < 20	SLEDAI-2K ≥ 20	*p*-value
		(*n* = 39)	(*n* = 5)	
LA	Negative	33 (86.8)	5 (100)	0.388
	Positive	5 (13.2)	0 (0)	
C3	Low	10 (25.6)	4 (80)	0.014
	Normal	29 (74.4)	1 (20)	
C4	Low	21 (53.8)	4 (80)	0.37
	Normal	18 (46.2)	1 (20)	

AISI – aggregate index of systemic inflammation, ALT – alanine aminotransferase, ANA – antinuclear antibody, AST – aspartate aminotransferase, BUN – blood urea nitrogen, C3 – complement C3, C4 – complement C4, CRP – C-reactive protein, DC – direct Coombs, dsDNA – double stranded DNA, ESR – erythrocyte sedimentation rate, LA – lupus anticoagulant, MLR – monocyte-to-lymphocyte ratio, MPR – monocyte-to-platelet ratio, MPV – mean platelet volume, NLR – neutrophil-to-lymphocyte ratio, NMR – neutrophil-to-monocyte ratio, PDW – platelet distribution width, PLR – platelet-to-lymphocyte ratio, PMR – platelet-to-monocyte ratio, PNR – platelet-to-neutrophil ratio, RDW – red blood cell distribution width, SII – systemic inflammatory index, SIRI – systemic inflammation response index, SLEDAI-2K – Systemic Lupus Erythematosus Disease Activity Index 2000.

Table III. ROC analysis for evaluating the cut-off value in predicting high disease activity (SLEDAI-2K > 20) in SLE patients

Hematological markers	AUC	Cut-off	95% confidence interval (CI)	Sensitivity (%)	Specificity (%)	*p*-value
NLR	0.699	2.8	0.665–0.812	61.20	71.30	0.031
PLR	0.585	0.19	0.496–0.711	89.40	33.40	0.336
MLR	0.514	161.8	0.417–0.691	0.48	69.40	0.665
MPR	0.478	0.09	0.125–0.651	15.50	68.80	0.474
SII	0.695	415	0.663–0.871	85.00	76.10	0.021
SIRI	0.681	2.56	0.533–0.951	83.00	69.70	0.004
AISI	0.782	328	0.438–0.786	78.00	58.10	0.006

AISI – aggregate index of systemic inflammation, AUC – area under the curve, MLR – monocyte-to-lymphocyte ratio, MPR – monocyte-to-platelet ratio, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, SII – systemic inflammatory index, SIRI – systemic inflammation response index.

ical application. Conventional markers such as ESR and CRP are not fully congruent with SLE activity [6, 7]. Thus, identifying biomarkers capable of predicting SLE and quantifying disease activity has garnered substantial interest, although a single biomarker is unlikely to replace clinical evaluation due to the heterogeneous nature of the disease [4]. Intensive efforts are underway to identify markers capable of predicting SLE flares and indicating flare manifestations in specific organs.

The SII has been found to be significantly elevated in conditions such as cancer, infectious diseases, and cardiovascular diseases [19–22]. The AISI has been recognized as a prognostic factor in idiopathic pulmonary fibrosis [23]. Moreover, AISI, SII, and SIRI indices have been suggested to reflect disease severity and intensive care needs in COVID-19 infections [24–26]. These indices have previously been evaluated as inflammatory markers in rheumatoid arthritis patients [25]. While SII ratios did not differ significantly between rheumatoid arthritis patients and healthy controls, SII values were higher in the former group and associated with disease activity [26]. It is well established that systemic inflammation induces relative changes in blood composition, notably characterized by neutrophilia, lymphopenia, and anemia [27]. The NLR has been used in combination with other inflammatory markers to assess systemic inflammation in both autoimmune and non-autoimmune diseases [28]. Accumulating evidence suggests that NLR serves as a reliable inflammation indicator [17, 29, 30].

In line with previous studies, our investigation confirmed a positive correlation between NLR and SLEDAI-2K, an extensively utilized indicator for assessing SLE disease activity, as well as ESR and CRP, inflammatory markers often employed to gauge SLE activity [28]. Our

Table IV. Comparison of complement levels according to hematological parameters in SLE patients

Hematological markers	Low complement Median (min–max)	High complement Median (min–max)	*p*-value
NLR	2.43 (0.94–6.12)	1.85 (0.75–8.46)	0.112
PLR	145.54 (26.83–300)	112.06 (15.36–242.27)	0.121
MLR	0.22 (0.07–0.63)	0.18 (0.01–0.32)	0.049
MPR	0 (0–0.01)	0 (0–0)	0.405
SII	594.9 (96.85–1872.5)	413.91 (69.72–1989.02)	0.305
SIRI	0.82 (0.26–5.43)	0.63 (0.07–3.1)	0.31
AISI	253.57 (13.56–1399.8)	161.48 (2.79–1235.59)	0.352

AISI – systemic inflammation aggregate index, MLR – monocyte-to-lymphocyte ratio, MPR – monocyte-to-platelet ratio, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, SII – systemic inflammatory index, SIRI – systemic inflammation response index.

Table V. Comparison of hematological indices according to different clinical and laboratory findings in SLE patients

Parameter	NLR	MLR	PLR	MPR	SII	SIRI	AISI
Hematological involvement	0.242	0.419	0.847	0.427	0.876	0.306	0.197
Renal involvement	0.743	0.331	0.836	0.329	0.734	0.560	0.466
Neurological involvement	0.089	0.347	0.082	0.943	0.069	0.971	0.802
Alopecia	0.548	0.647	0.548	0.909	0.274	0.548	0.510
Oral ulcer	0.772	0.579	0.614	0.495	0.821	0.605	0.668
Subacute discoid lupus	0.987	0.628	0.493	0.934	0.828	0.431	0.582
Acute cutaneous lupus	0.778	0.541	0.280	0.317	0.981	0.549	0.707
Musculoskeletal involvement	0.911	0.055	0.833	0.472	0.512	0.747	0.990
Serositis	0.179	0.687	0.687	0.917	0.823	0.800	0.988
Acute pericarditis	0.517	0.747	0.914	0.943	0.277	0.311	0.177
ANA positivity at onset	0.018	0.693	0.858	0.943	0.021	0.035	0.075
dsDNA positivity at onset	0.613	0.012	0.481	0.295	0.769	0.733	0.751
Low C3	0.251	0.623	0.147	0.143	0.364	0.990	0.450
Low C4	0.135	0.099	0.173	0.383	0.325	0.407	0.374

AISI – systemic inflammation aggregate index, ANA – antinuclear antibody, C3 – complement C3, C4 – complement C4, dsDNA – double stranded DNA, MLR – monocyte to lymphocyte ratio, MPR – monocyte to platelet ratio, NLR – neutrophil-to-lymphocyte ratio, PLR – platelet to lymphocyte ratio, SII – systemic inflammatory index, SIRI – systemic inflammation response index.

Table VI. Comparison of LN according to hematological markers in SLE patients

Hematological markers	Patients without LN Median (min–max)	Patients with LN Median (min–max)	*p*-value
PNR	76.11 (7.16–178.33)	59.06 (9.14–84.09)	0.121
PMR	773.68 (238.24–3357.14)	521.64 (179.55–2690.91)	0.099
NMR	10.18 (2.51–117.29)	13.03 (3.05–32)	0.403
NLR	1.85 (0.75–8.46)	2.84 (0.94–5.88)	0.252
PLR	145.54 (15.36–267.5)	113.71 (26.83–300)	0.460
MLR	0.18 (0.01–0.63)	0.22 (0.07–0.46)	0.209
MPR	0 (0–0)	0 (0–0.01)	0.239
SII	458.08 (69.72–1989.02)	648.29 (96.85–1872.5)	0.301
SIRI	0.62 (0.07–4.02)	0.89 (0.26–5.43)	0.109
AISI	168.59 (2.79–977.58)	284.1 (13.56–1399.8)	0.146

AISI – aggregate index of systemic inflammation, LN – lupus nephritis, MLR – monocyte-to-lymphocyte ratio, MPR – monocyte-to-platelet ratio, NLR – neutrophil-to-lymphocyte ratio, NMR – neutrophil-to-monocyte ratio, PLR – platelet-to-lymphocyte ratio, PMR – platelet-to--monocyte ratio, PNR – platelet-to-neutrophil ratio, SII – systemic inflammatory index, SIRI – systemic inflammation response index.

study further revealed a correlation between NLR and MLR scores and SLEDAI-2K scores.

A meta-analysis demonstrated the positive clinical value of NLR in diagnosing active SLE and LN [31]. Similar to NLR, PLR is a widely used inflammatory index in routine blood tests that reflects changes in inflammation and cytokine concentrations. While lymphocyte and platelet count generally decrease in SLE patients, PLR fluctuates only with changes in disease activity [32]. Qin et al. [28] reported an association between PLR and SLE disease activity, observing higher PLR values in LN patients. While the literature frequently evaluates NLR and PLR in monitoring SLE activity, studies assessing a combination of the 5 hematological markers NLR, MLR, BLR, ELR, and PLR are scarce [2]. In our study, NLR, SII, SIRI, and AISI exhibited higher sensitivity in detecting high disease activity in SLE patients compared to other hematological indices.

Furthermore, our findings suggest that each novel hematological marker can serve as both an indicator of inflammation and a "high disease activity marker" in SLE. We also investigated the relationship between hematological markers and other parameters indicating disease activity. Positive correlations were observed between ESR and NLR, as well as MLR, as well as between anti-dsDNA positivity and MLR. Notably, MLR was elevated in cases with complement deficiency. These data collectively support the notion that new hematological parameters are associated with well-established markers such as ESR, CRP, anti-dsDNA positivity, and complement deficiency, indicating their potential use as indicators of SLE activity. We also explored differences in hematological markers according to the presence or absence of organ involvement. For instance, MLR levels were significantly higher in cases with neurological or psychiatric involvement, while SII and AISI were elevated in patients with renal involvement.

In cases of major organ involvement, particularly neuro-psychiatric and renal, the elevated levels of these markers in affected individuals may signify their potential utility as indicators of organ involvement. As far as we know, this study is the first to evaluate novel hematological biomarkers in SLE, investigating their relationship with disease activity. Additionally, our study uniquely evaluated almost all hematological indices in SLE patients and compared their utility in detecting high disease activity.

Nevertheless, certain limitations warrant consideration. Firstly, the study design was retrospective in nature. Secondly, the sample size was relatively modest. Lastly, the study was conducted at a single center. Future investigations, preferably encompassing multicenter collaborations, are imperative to delineate the utility of peripheral blood cell ratios in juvenile-onset systemic lupus erythematosus (jSLE). To summarize, our findings underscore the correlations between NLR and PLR with serological markers, suggesting their potential to predict organ involvement, particularly pertaining to cutaneous, articular, serosal, and hematological manifestations, in jSLE.

Study limitations

The sample size of our study, as it is based on single-center experience, may be considered relatively small. This may limit the statistical power and generalizability of our results to broader populations. Future studies with larger and more diverse cohorts could provide a more comprehensive understanding of the use of new hematologic indexes for the prognosis of jSLE. Despite these limitations, this is the first study to analyze a total of six hematological indices, three of which are novel, collectively in jSLE patients.

Conclusions

In this study, the novel hematological markers SII, SIRI, and AISI were found to effectively reflect inflammation in SLE patients, exhibit associations with high disease activity, and demonstrate heightened sensitivity in detecting cases with high disease activity.

Disclosures

Conflict of interest: *The authors declare no conflict of interest.*
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Data availability: *The data that support the findings of this study are available on request from the corresponding author (G.Ö.B.).*

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