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Original Article

Neutrophil-to-lymphocyte ratio and CD40 as diagnostic biomarkers for systemic lupus erythematosus and its disease activity

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Abstract: Objectives: To evaluate the diagnostic value of the neutrophil-to-lymphocyte ratio (NLR), CD40, and other clinical indicators in systemic lupus erythematosus (SLE). Methods: A retrospective study was conducted with 158 SLE patients treated at Xijing Hospital. The SLE group was divided into an active group (n = 95) and a low-activity group (n = 63). A control group consisting of 105 healthy individuals was also included. NLR, CD40, and other relevant clinical indicators were collected from the medical record system. The diagnostic or differential value of these indicators for SLE or disease activity (high vs. low) was assessed using ROC curves. Pearson correlation coefficients were used to examine the correlations between NLR, CD40, C-reactive protein (CRP), red blood cell distribution width (RDW), monocyte-to-lymphocyte ratio (MLR), and the SLE Disease Activity Index (SLEDAI) score. Results: NLR and CD40 levels were significantly elevated in the SLE group ($P < 0.001$), with respective AUC values for diagnosing SLE of 0.917 and 0.907. NLR and CD40 levels in the SLE group were positively correlated with CRP and RDW, and negatively correlated with MLR (both $P < 0.001$). Furthermore, NLR and CD40 levels in the active SLE group were significantly higher than those in the low-activity group ($P < 0.001$), with AUC values for diagnosing disease activity of 0.902 and 0.904, respectively. SLEDAI scores were positively correlated with NLR and CD40 levels ($P < 0.001$). Conclusions: Both NLR and CD40 demonstrate high diagnostic value for SLE and disease activity assessment, suggesting their potential for clinical application in SLE diagnosis and management.

Keywords: Neutrophil-to-lymphocyte ratio, CD40, systemic lupus erythematosus, diagnostic value

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with high heterogeneity across different patient types [1, 2]. Its typical characteristics include abnormal immune cell activation, complement dysfunction, and multi-organ involvement resulting from autoantibody production [3, 4]. Epidemiological data indicate that the incidence of SLE is higher in women than men, and the mortality risk for SLE patients is three times that of the general population [5]. The pathogenesis of SLE involves alterations in both innate and adaptive immune responses, alongside inflammatory processes triggered by immune dysregulation [6, 7]. The disease's latent onset and clinical variability complicate diagnosis, and early detection rates for SLE remain suboptimal [8]. Consequently, exploring diagnostic indicators linked to SLE pathogenesis is crucial for enhancing patient outcomes and quality of life.

The neutrophil-to-lymphocyte ratio (NLR) serves as a biological marker of systemic inflammation and disease progression, with growing recognition of its diagnostic value for disease activity in SLE [9-11]. Neutrophils play a key role in autoimmune responses in SLE, particularly through their extracellular traps, which contribute to the formation of SLE autoantigens in response to inflammatory stimuli [12, 13]. Conversely, lymphocytes reflect the state of both innate and adaptive immune responses [14]. The NLR, determined by the balance of neutrophils and lymphocytes, is increasingly used to assess inflammation and disease activity in SLE [15].

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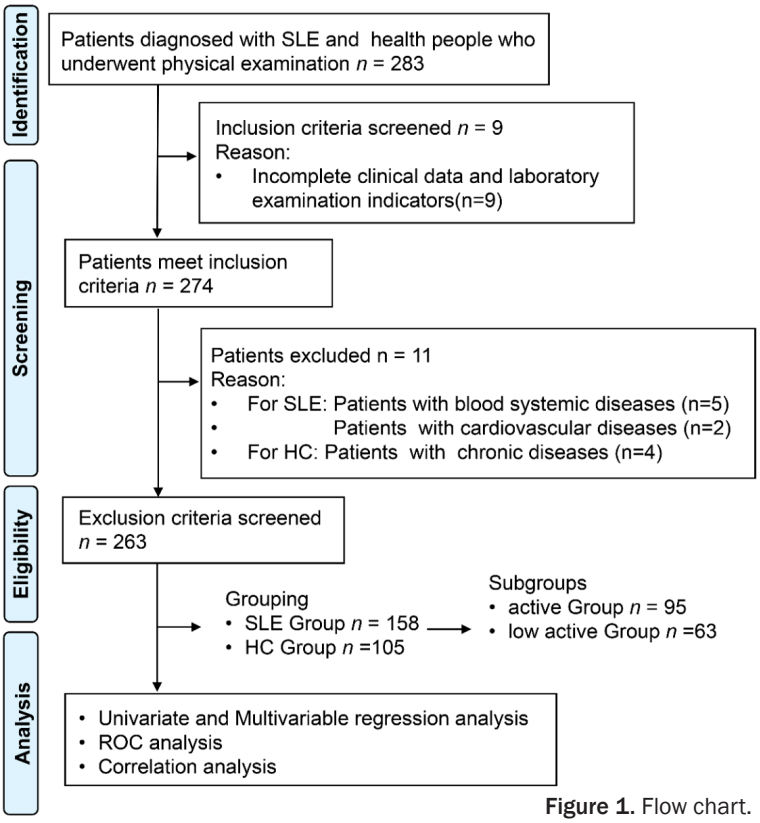

Figure 1. Flow chart.

CD40, a member of the tumor necrosis factor receptor superfamily, is involved in enhancing immune cell anti-tumor activity and regulating B cell functions such as antibody production and proliferation. CD40 upregulation is observed in both immune and non-immune cells across various autoimmune diseases [16, 17]. Previous studies have demonstrated that CD40 and its ligand contribute to the pathogenesis of SLE, with gene polymorphisms and haplotypes linked to SLE susceptibility [18, 19].

Although NLR and CD40 are both associated with SLE pathogenesis, limited research has explored their combined diagnostic value. Most studies have focused on individual biomarkers or clinical indicators [15, 18]. However, comprehensive analysis of NLR and CD40, particularly in the context of disease activity and early diagnosis, is lacking. This study aims to fill this gap by evaluating the diagnostic and prognostic value of NLR and CD40 in SLE patients. The goal is to provide insights into the clinical application of these biomarkers, potentially enhancing early diagnosis rates, guiding personalized treatment, and improving patient outcomes.

Materials and methods

General information

From the medical records of Xijing Hospital, a total of 158 SLE patients admitted to Xijing Hospital were selected for this study, including 17 males and 141 females, with an average age of (40.3 ± 8.3) years. Based on the SLE Disease Activity Index (SLEDAI) score [20], the SLE group was divided into two subgroups: 95 patients with SLEDAI > 10 in the active group and 63 patients with SLEDAI ≤ 10 in the low-activity group. An additional 105 healthy individuals who underwent routine physical examinations were selected as the healthy control (HC) group, consisting of 16 males and 89 females, aged 19-61 years, with an average age of (38.9 ± 7.9) years. This study was approved by the Ethics Committee of Xijing Hospital (No. KY20202078-C-1).

Inclusion criteria: For the SLE group, patients were required to meet the diagnostic criteria for SLE according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) [21]. All patients had complete clinical data and laboratory examination results. For the HC group, individuals who underwent routine health examinations at Xijing Hospital during the same period were selected. Demographic and baseline clinical data for the HC group were matched with the SLE group in terms of age and gender.

Exclusion criteria: For the SLE group, patients with comorbid conditions that could confound the analysis were excluded, including but not limited to liver or kidney dysfunction, blood systemic diseases, malignancies, cardiovascular diseases, dermatomyositis, overlap syndrome, and systemic sclerosis. For the HC group, individuals with any chronic diseases or conditions that could affect immune system function, such as autoimmune diseases, liver or kidney disease, cardiovascular disease, or malignancies, were excluded (**Figure 1**).

Data extraction

All relevant clinical data and laboratory indicators were extracted from the electronic medical record system of Xijing Hospital. Two independent researchers performed data extraction to ensure accuracy and completeness. The extracted data included demographic information, clinical data, and laboratory examination results. Data validation was conducted by cross-checking with original medical records to ensure reliability.

Outcome measures

The primary outcome measures were the NLR and CD40. Secondary outcome measures included other blood cell parameters, specifically Neutrophil Count (NeuC), Lymphocyte Count (LymC), White Blood Cell Count (WBC), Hemoglobin (Hb), Red Blood Cell Distribution Width (RDW), and Monocyte-to-Lymphocyte Ratio (MLR).

Blood sample collection and analysis

A total of 3 mL of venous blood was collected from all subjects on an empty stomach after admission. The blood was placed in EDTA-K2 anticoagulation tubes and pro-coagulation tubes. Blood cell parameters, including NLR, were analyzed within 2 hours using the DxH600 blood cell analyzer (Beckman Coulter, China).

For CD40 analysis, 10 μL of human CD40-FITC antibody (Invitrogen™, Carlsbad, CA, USA, CD4001) and 50 μL of EDTA-K2 anticoagulant were mixed in a test tube. Additionally, 10 μL of mouse IgG2a-FITC antibody (Invitrogen™, Carlsbad, CA, USA, MG2A01) was added to another test tube. The samples were incubated in the dark for 15 minutes, followed by the addition of 8 mL of red blood cell lysate. The mixture was incubated at room temperature for 10 minutes until the liquid became clear. One mL of PBS buffer was added, mixed well, and after centrifugation, the supernatant was discarded. The final pellet was resuspended in 500 μL of PBS buffer, and 100 μL was placed in an EP tube for CD40 expression analysis using the CytoFLEX flow cytometer (Beckman Coulter, China).

Statistical analysis

SPSS 20.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis, and GraphPad 6 was used to generate figures. Data with a normal distribution were expressed as mean ± standard deviation (mean ± SD), and Student's t-test was used for comparisons. Data with non-normal distribution were expressed as median (P25-P75), and the Mann-Whitney U test was performed. Categorical data were expressed as frequency and percentage [n (%)], and chi-square tests were used for comparisons between groups. Pearson correlation tests were used for correlation analysis. The diagnostic value for SLE and disease activity was assessed using ROC analysis. A *P*-value of < 0.05 was considered statistically significant.

Results

Clinical data of the two groups

No significant differences were observed in gender, age, body mass index (BMI), NeuC, systolic blood pressure (SBP), diastolic blood pressure (DBP), immunoglobulin A (IgA), and other clinical data between the HC group and the SLE group ($P > 0.05$). However, significant differences were found in lymphocyte count (LymC), C3, C4, immunoglobulin G (IgG), immunoglobulin M (IgM), white blood cell count (WBC), hemoglobin (Hb), red blood cell distribution width (RDW), monocyte-to-lymphocyte ratio (MLR), C-reactive protein (CRP), NLR, CD40, and other clinical data (all $P < 0.05$). Further details are shown in **Table 1**.

Univariate and multivariable regression analysis

To evaluate the influence of various clinical indicators on SLE, univariate and multivariate logistic regression analyses were performed. The results revealed that several biomarkers, including NLR, CD40, LymC, C3, C4, IgG, IgM, WBC, Hb, RDW, MLR, and CRP, were significantly associated with SLE in univariate analysis (all $P < 0.05$). After adjusting for potential confounders in multivariate analysis, all of these biomarkers remained significantly associated with SLE (all $P < 0.05$), confirming their relevance as important factors influencing SLE status. Detailed results are presented in **Table 2**.

Diagnostic value of NLR, CD40, and clinical indicators in SLE

The levels of NLR and CD40 in the SLE group were significantly higher than those in the HC group ($P < 0.001$). ROC analysis revealed that the AUC for NLR in diagnosing SLE was 0.917 (95% CI: 0.885-0.950), with a cut-off value of 2.68, sensitivity of 81.01%, and specificity of

Table 1. Clinical data and laboratory examination indicators (means ± SD)/[n (%)]/[P_{50} (P_{25}-P_{75})]

Category	HC group (n = 105)	SLE group (n = 158)	$t/\chi^2/U$	*p*
Gender			1.153	0.283
Female	89 (84.76)	141 (89.24)		
Male	16 (15.24)	17 (10.76)		
Age (years)	38.9 ± 7.9	40.3 ± 8.3	1.365	0.173
BMI (kg/m^2)	22.7 ± 2.4	23.2 ± 2.1	1.785	0.075
Course of disease (month)	-	30.1 ± 3.9	-	-
NeuC (×10^9/L)	3.23 (1.62-7.01)	3.29 (0.67-12.57)		
LymC (×10^9/L)	2.15 ± 2.29	1.23 ± 0.57	7.422	< 0.001
SBP (mmHg)	113.36 ± 19.48	110.25 ± 22.69	1.151	0.251
DBP (mmHg)	79.54 ± 11.05	77.15 ± 10.24	1.796	0.074
C3 (g/L)	0.94 ± 0.17	0.86 ± 0.18	3.608	< 0.001
C4 (g/L)	0.26 ± 0.06	0.20 ± 0.07	7.199	< 0.001
IgG (g/L)	11.86 ± 1.50	13.75 ± 4.99	3.768	< 0.001
IgA (g/L)	1.93 ± 0.52	2.02 ± 0.75	1.070	0.286
IgM (g/L)	1.60 ± 0.39	1.28 ± 0.56	5.091	< 0.001
WBC (×10^9/L)	5.41 ± 1.04	4.76 ± 2.11	2.928	0.004
Hb (g/L)	136.81 ± 12.78	119.34 ± 18.34	8.485	< 0.001
RDW (%)	12.61 ± 0.42	14.36 ± 2.12	8.345	< 0.001
MLR	0.41 ± 0.21	0.22 ± 0.09	10.073	< 0.001
CRP (mg/L)	8.93 ± 1.32	10.33 ± 1.02	9.678	< 0.001
NLR	1.50 ± 0.88	4.47 ± 1.93	15.550	< 0.001
CD40	4.77 ± 1.76	8.61 ± 2.31	14.440	< 0.001

SLE: systemic lupus erythematosus; BMI: Body Mass Index; NeuC: Neutrophil Count; LymC: Lymphocyte Count; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; C3: Complement Component 3; C4: Complement Component 4; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; WBC: White Blood Cell Count; Hb: Hemoglobin; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40.

Table 2. Univariate and Multivariable regression analysis

Indicators	Univariate Analysis		Multivariate Analysis	
	OR	p	OR	p
NLR	6.344	< 0.001	5.983	< 0.001
CD40	7.215	< 0.001	6.897	< 0.001
LymC	0.567	0.003	0.615	0.009
C3	0.474	< 0.001	0.516	0.002
C4	0.311	< 0.001	0.352	0.005
IgG	1.984	< 0.001	1.872	0.004
IgM	0.428	0.009	0.455	0.018
WBC	0.483	0.031	0.522	0.042
Hb	0.596	0.005	0.636	0.010
RDW	2.456	< 0.001	2.317	0.001
MLR	0.180	0.002	0.211	0.007
CRP	1.892	0.008	1.756	0.012

SLE: systemic lupus erythematosus; NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40; LymC: Lymphocyte Count; C3: Complement Component 3; C4: Complement Component 4; IgG: Immunoglobulin G; IgM: Immunoglobulin M; WBC: White Blood Cell Count; Hb: Hemoglobin; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein.

92.38%. The AUC for CD40 in diagnosing SLE was 0.907 (95% CI: 0.871-0.942), with a cut-off value of 6.94, sensitivity of 76.58%, and specificity of 91.43%. ROC curves for LymC and other clinical indicators indicated diagnostic values of CRP, RDW, and MLR, with AUCs of 0.797, 0.784, and 0.783, respectively. More details are shown in **Figure 2** and **Table 3**.

Correlation of NLR and CD40 Levels with CRP, RDW, and MLR in the SLE group

To explore the relationships between key biomarkers and other markers of inflammation

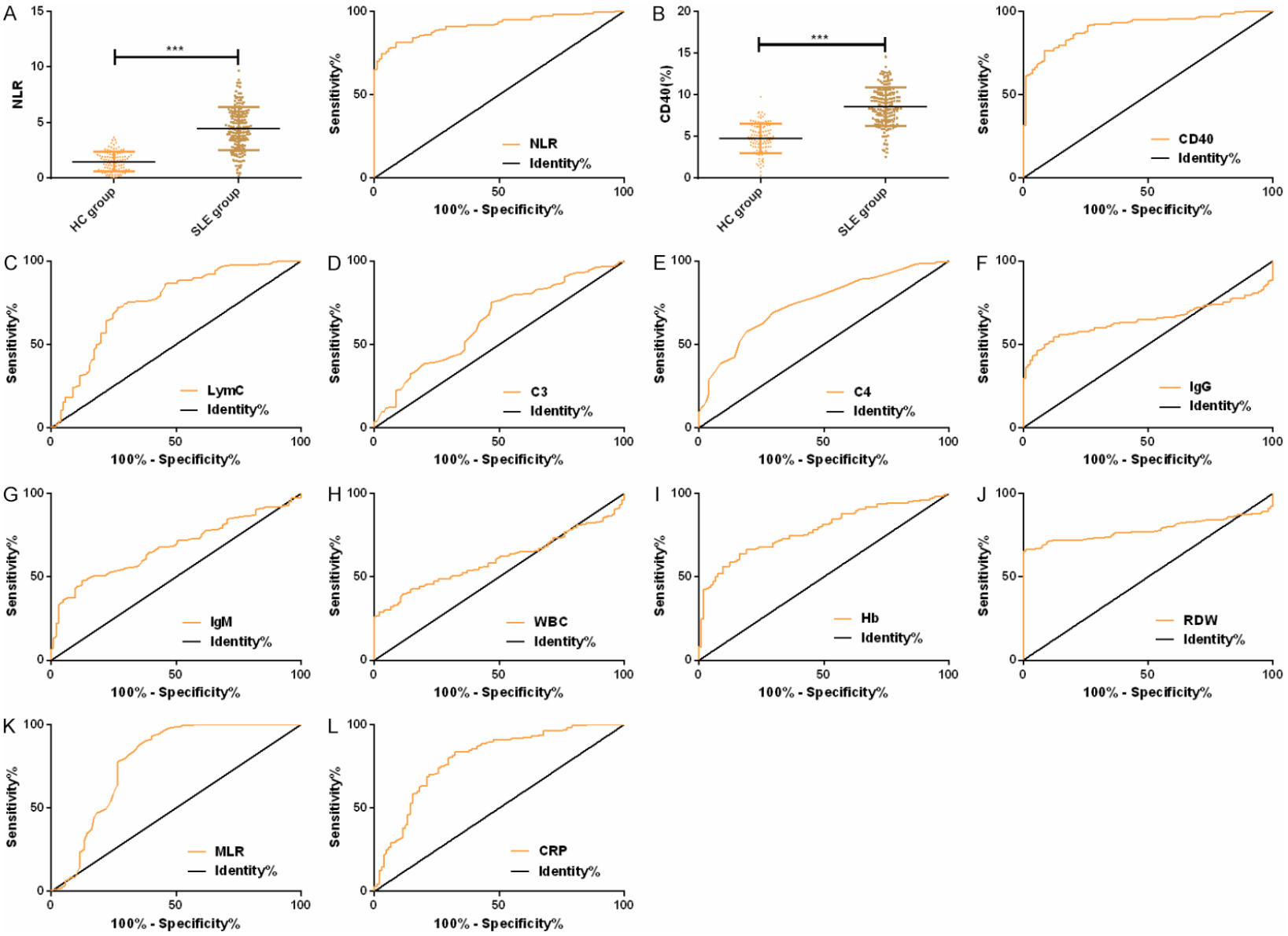
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Figure 2. Diagnostic value of peripheral blood NLR, CD40 and clinical indicators for SLE. A. The level of NLR in SLE group was significantly higher than that in the HC group, and AUC of diagnosing SLE through the level of NLR was 0.917. B. The level of CD40 in SLE group was significantly higher than that in the HC group, and AUC of diagnosing SLE through the level of CD40 was 0.907. C-L. ROC curve for diagnosis of SLE by various clinical indicators. SLE: systemic lupus erythematosus; NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40; LymC: Lymphocyte Count; C3: Complement Component 3; C4: Complement Component 4; IgG: Immunoglobulin G; IgM: Immunoglobulin M; WBC: White Blood Cell Count; Hb: Hemoglobin; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein. Note: ***$P < 0.001$.

Table 3. Diagnostic value of peripheral blood NLR, CD40 and clinical indicators for SLE

Indicators	AUC	95% CI	S.E.	Cut-off	Sensitivity (%)	Specificity (%)	Delong Test
NLR	0.917	0.885-0.950	0.017	2.68	81.01	92.38	ns
CD40	0.907	0.871-0.942	0.018	6.94	76.58	91.43	ns
LymC	0.653	0.690-0.816	0.032	1.93	72.15	73.33	*, #
C3	0.640	0.571-0.708	0.035	0.96	75.32	53.33	*, #
C4	0.689	0.689-0.807	0.030	0.24	68.99	70.48	*, #
IgG	0.650	0.583-0.717	0.034	13.38	54.43	87.62	*, #
IgM	0.679	0.616-0.743	0.032	1.18	47.47	87.62	*, #
WBC	0.603	0.536-0.671	0.034	4.35	39.87	88.57	*, #
Hb	0.681	0.727-0.836	0.028	125.10	63.92	83.81	*, #
RDW	0.784	0.726-0.842	0.030	13.42	66.46	99.05	*, #
MLR	0.783	0.717-0.848	0.033	0.37	93.04	60.00	*, #
CRP	0.797	0.740-0.853	0.029	9.37	83.54	67.62	*, #

SLE: systemic lupus erythematosus; NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40; LymC: Lymphocyte Count; C3: Complement Component 3; C4: Complement Component 4; IgG: Immunoglobulin G; IgM: Immunoglobulin M; WBC: White Blood Cell Count; Hb: Hemoglobin; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein. Note: *: $P < 0.05$ compared with NLR; #: $P < 0.05$ compared with CD40; ns: No significant difference compared with NLR or CD40.

and disease activity, we analyzed the correlations of NLR and CD40 with CRP, RDW, and MLR in the SLE group. NLR and CD40 levels in the SLE group were positively correlated with CRP, RDW, and MLR (all $P < 0.001$), as shown in **Figure 3**.

Clinical data of SLE active and low activity groups

No significant differences were found in gender, age, BMI, disease duration, NeuC, SBP, DBP, IgG, IgA, WBC, and other clinical data between the SLE active and low-activity groups (all $P > 0.05$). However, significant differences were observed in LymC, C3, C4, IgM, Hb, RDW, MLR, CRP, NLR, CD40, SLEDAI, and other clinical data (all $P < 0.05$), as shown in **Table 4**.

Diagnostic value of NLR, CD40 and clinical indicators in SLE active and low activity groups

The levels of NLR and CD40 levels were significantly higher in the SLE active group than in the low-activity group (both $P < 0.001$). ROC curve analysis showed that the AUC for NLR in diagnosing SLE disease activity was 0.902 (95% CI: 0.856-0.947), with a cut-off value of 5.31, sensitivity of 87.30%, and specificity of 78.95%. The AUC for CD40 in diagnosing SLE disease activity was 0.904 (95% CI: 0.856-0.952), with a cut-off value of 9.88, sensitivity of 96.83%, and specificity of 76.84%. ROC curves for LymC, C3, C4, IgM, Hb, RDW, MLR, CRP, and other clinical indicators resulted in AUCs of 0.576, 0.698, 0.619, 0.616, 0.736, 0.643, 0.727, and 0.758, respectively. Among these, NLR, CD40, CRP, Hb, and MLR showed high diagnostic value for SLE disease activity. More details are shown in **Figure 4**.

Correlation between SLEDAI score, NLR and CD40

SLEDAI score was positively correlated with the levels of NLR and CD40 ($P < 0.001$), as shown in **Figure 5**.

Discussion

SLE is a complex and potentially fatal systemic inflammatory disease, primarily affecting fe-

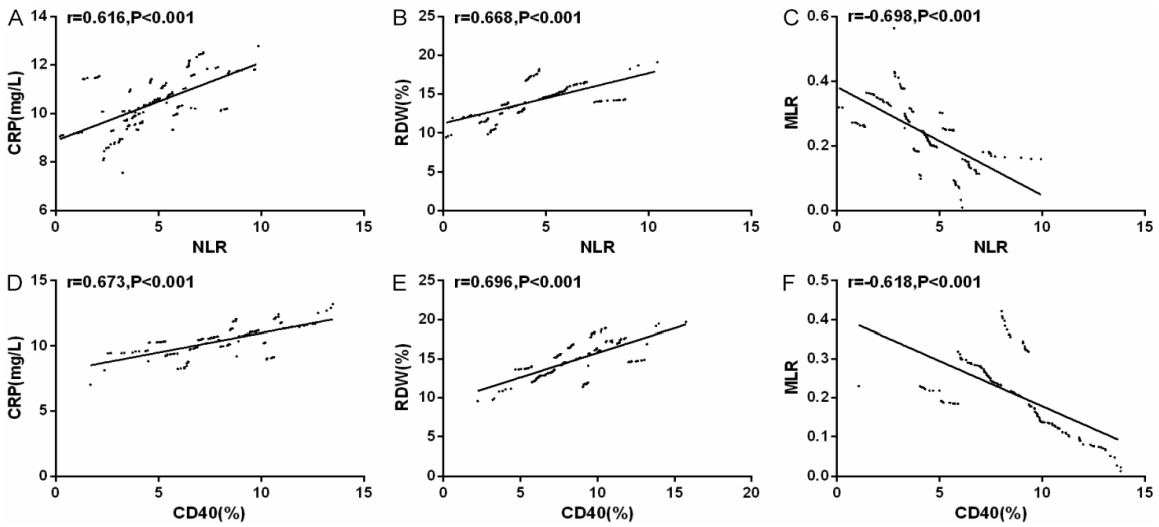

Figure 3. Correlation between the levels of NLR and CD40 with CRP, RDW and MLR. A-C. Correlation between the level of NLR and CRP, RDW and MLR ($P < 0.001$). D-F. Correlation between the level of CD40 and CRP, RDW and MLR ($P < 0.001$). NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein.

Table 4. Clinical data and laboratory examination indicator in SLE active and low activity groups (means ± SD)/[n (%)]/[P_{50} (P_{25}-P_{75})]

Category	Active group (n = 95)	Low activity group (n = 63)	$t/\chi^2/U$	*p*
Gender			0.410	0.522
Female	86 (90.53)	55 (87.30)		
Male	9 (9.47)	8 (25.40)		
Age (years)	39.5 ± 7.6	41.9 ± 8.7	1.834	0.069
BMI (kg/m^2)	23.0 ± 2.2	23.5 ± 1.7	1.526	0.129
Course of disease (month)	30.4 ± 3.7	29.6 ± 4.1	1.274	0.205
NeuC ($\times 10^9$/L)	3.32 (0.73-12.57)	3.24 (0.67-12.28)		
LymC ($\times 10^9$/L)	1.12 ± 0.55	1.29 ± 0.49	1.985	0.049
SBP (mmHg)	109.96 ± 21.57	112.43 ± 23.88	0.675	0.501
DBP (mmHg)	76.21 ± 11.54	78.58 ± 9.13	1.370	0.173
C3 (g/L)	0.73 ± 0.23	0.87 ± 0.14	4.326	< 0.001
C4 (g/L)	0.18 ± 0.09	0.21 ± 0.06	2.324	0.021
IgG (g/L)	13.89 ± 5.12	13.48 ± 4.78	0.506	0.614
IgA (g/L)	2.15 ± 0.68	1.96 ± 0.82	1.583	0.116
IgM (g/L)	1.06 ± 0.41	1.26 ± 0.59	2.515	0.013
WBC ($\times 10^9$/L)	4.48 ± 1.86	4.83 ± 2.28	1.057	0.292
Hb (g/L)	110.23 ± 16.90	126.88 ± 20.11	5.617	< 0.001
RDW (%)	14.55 ± 2.30	13.49 ± 1.55	3.205	0.002
MLR	0.18 ± 0.07	0.25 ± 0.10	5.176	< 0.001
CRP (mg/L)	11.16 ± 1.45	9.91 ± 1.04	5.906	< 0.001
NLR	6.92 ± 1.91	4.00 ± 1.26	10.685	< 0.001
CD40	11.61 ± 2.83	7.14 ± 1.81	11.114	< 0.001
SLEDAI (score)	14.83 ± 2.37	7.21 ± 2.03	20.927	< 0.001

SLE: systemic lupus erythematosus; BMI: Body Mass Index; NeuC: Neutrophil Count; LymC: Lymphocyte Count; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; C3: Complement Component 3; C4: Complement Component 4; IgG: Immunoglobulin G; IgA: Immunoglobulin A; IgM: Immunoglobulin M; WBC: White Blood Cell Count; Hb: Hemoglobin; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40.

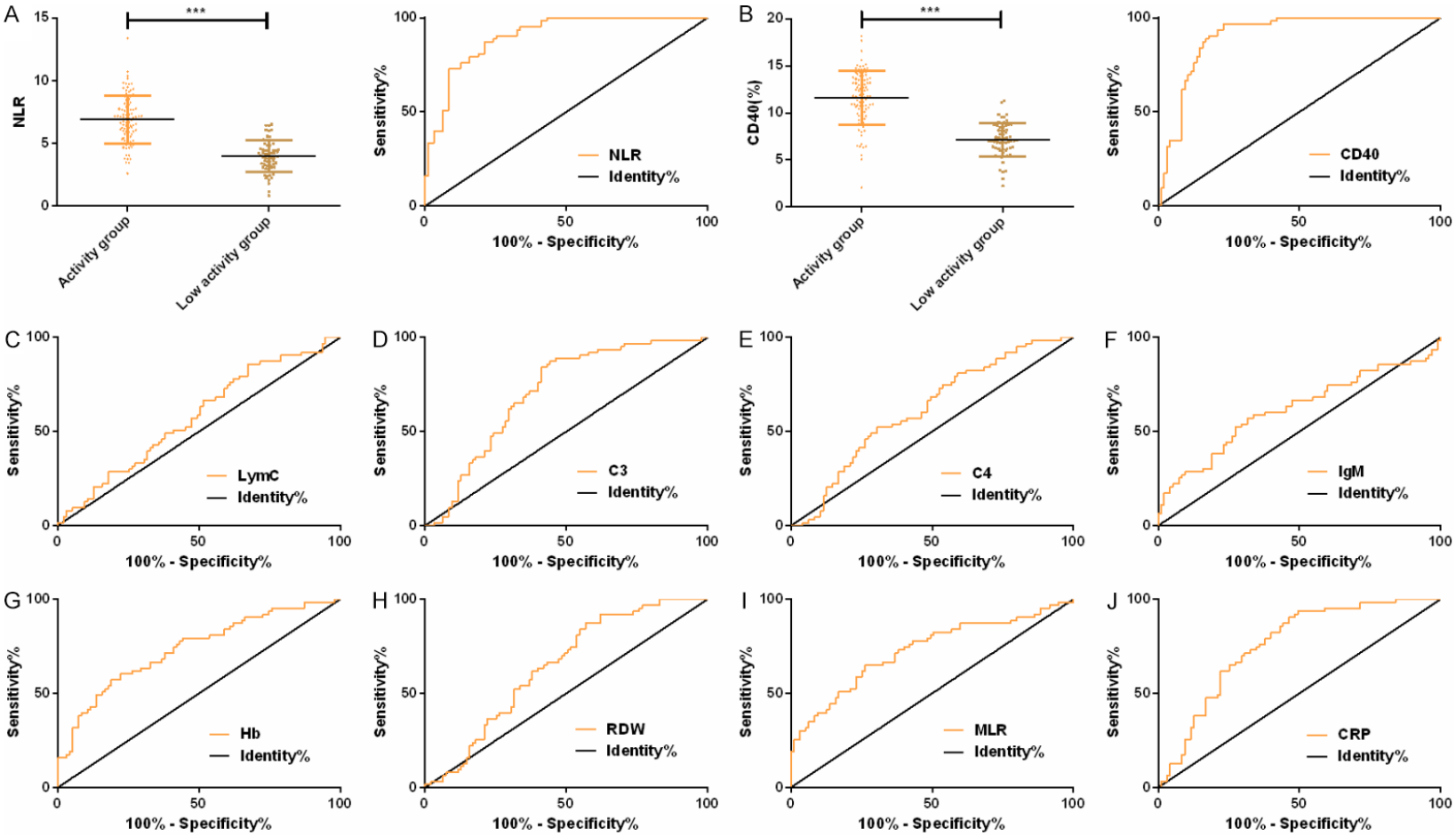

Figure 4. Diagnostic value of peripheral blood NLR, CD40 and clinical indicators for SLE active and low activity groups. A. The level of NLR was significantly higher in SLE active group than in low activity group, and AUC for diagnosing SLE disease activity through the level of NLR was 0.902. B. The level of CD40 in SLE group was significantly higher than that in the HC group, and AUC for diagnosing SLE disease activity through the level of CD40 was 0.904. C-J. ROC curve of various clinical indicators in diagnosing SLE disease activity. SLE: systemic lupus erythematosus; NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40; LymC: Lymphocyte Count; C3: Complement Component 3; C4: Complement Component 4; IgM: Immunoglobulin M; Hb: Hemoglobin; RDW: Red Blood Cell Distribution Width; MLR: Monocyte-to-Lymphocyte Ratio; CRP: C-Reactive Protein. Note: ***$P < 0.001$.

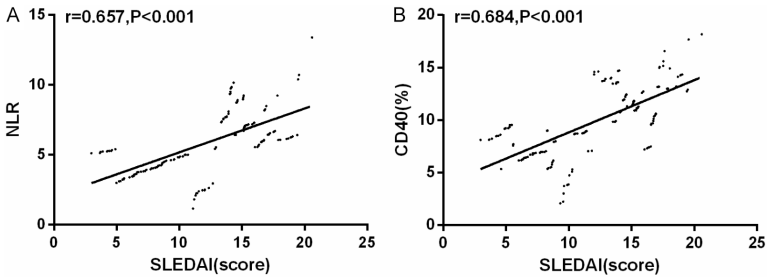

Figure 5. Correlation of SLEDAI score with NLR and CD40. A. SLEDAI score was positively correlated with NLR ($P < 0.001$). B. SLEDAI score was positively correlated with CD40 ($P < 0.001$). NLR: Neutrophil-to-Lymphocyte Ratio; CD40: Cluster of Differentiation 40; SLEDAI: systemic lupus erythematosus Disease Activity Index.

males between puberty and menopause [22]. Delayed diagnosis of SLE increases the risk of damage to vital organs, which may include functional impairment of the skin, joints, kidneys, and central nervous system [23, 24]. While current laboratory indicators, such as complement C3, C4, ANA, and dsDNA, show potential for diagnosing SLE, their sensitivity and specificity remain suboptimal [25, 26]. Therefore, identifying new and reliable diagnostic markers for SLE is not only a challenge but also crucial for improving the early detection of SLE patients.

There has been increasing research on the role of the NLR in autoimmune diseases. For example, studies by Fu et al. [27] on NLR in rheumatoid arthritis (RA) showed that NLR was significantly elevated in RA patients and positively correlated with CRP, ESR, and disease activity scores, making it a useful tool for evaluating disease activity. In their study on NLR in SLE, Oehadian et al. [28] demonstrated that NLR could serve as an inflammatory marker for SLE, reflecting the inflammatory status of SLE patients. Regarding NLR's diagnostic value for SLE, Li et al. [29] found that NLR had a specificity of 92.6% in distinguishing SLE without nephritis from lupus nephritis, with an AUC of 0.757, indicating its potential to reflect renal involvement in SLE. In our study, we observed significantly elevated NLR levels in the SLE group, demonstrating its strong diagnostic performance. These findings are consistent with previous studies, further confirming NLR as a valuable biomarker for diagnosing SLE and differentiating it from healthy controls. The high sensitivity and specificity observed in our analysis reinforce the potential of NLR as an early diagnostic marker for SLE. Elevated NLR levels in SLE patients likely reflect ongoing immune dysregulation and inflammation, contributing to the pathogenesis of the disease. Increased neutrophil counts and reduced lymphocyte counts suggest heightened inflammatory responses and impaired immune regulation, both characteristic of SLE [28]. Although the SLEDAI is used to assess disease activity, it lacks sensitivity for detecting changes in disease improvement or deterioration [30]. Therefore, this study focused on distinguishing between SLE activity and low activity, without analyzing diagnostic value in detail. We found that NLR was upregulated in the active SLE group, with an AUC of 0.902 for diagnosing SLE disease activity. This was positively correlated with the SLEDAI score, suggesting that NLR could also reflect disease activity in SLE patients, indicating its potential clinical value. The correlation analysis in our study revealed that NLR was positively correlated with CRP and RDW but negatively correlated with MLR. In contrast, Qin et al. [31] reported a positive correlation between NLR, CRP, ESR, and SLEDAI, which could indicate inflammation and disease activity in SLE patients, differing from our findings.

CD40 is a receptor on antigen-presenting cell that plays a key role in maintaining humoral and cell-mediated immune responses. Studies have shown that anti-CD40 therapy can reverse glomerular and renal tubular damage in mice by targeting the key pathogenic mechanisms of SLE, highlighting CD40 as a potential therapeutic target for SLE [32]. CD40 is overexpressed in the epithelium, leukocytes, and vascular endothelium of patients with autoimmune diseases such as RA and SLE, suggesting its involvement in the onset and progression of autoimmune diseases [33]. In a study on CD40 in SLE patients in Egypt, Mousa et al. [34] demonstrated that CD40 gene expression plays a crucial role in SLE adaptive immunity, with 98% sensitivity and 96% specificity for distinguishing SLE patients from healthy subjects, suggesting CD40's potential as a clinical marker for early diagnosis. In our study, CD40 levels were significantly elevated in the SLE group,

with a high AUC for diagnosing SLE, indicating that CD40 could serve as an independent marker for distinguishing SLE patients from healthy controls. CD40's role in promoting B-cell activation and autoantibody production highlights its involvement in the autoimmune response characteristic of SLE. Elevated CD40 levels may contribute to the sustained activation of immune cells, leading to chronic inflammation and tissue damage in SLE [33]. We also analyzed CD40's role in SLE disease activity. The level of CD40 in the active SLE group was significantly higher than in the low-activity group, with an AUC of 0.904 for diagnosing SLE disease activity. This was positively correlated with the SLEDAI score, indicating that CD40 could also be used as an effective marker for diagnosing SLE disease activity. Additionally, our research revealed that CD40 levels were positively correlated with CRP, RDW, and negatively correlated with MLR.

This study has several limitations. The retrospective design limits our ability to establish causality between NLR/CD40 levels and disease progression. Furthermore, the relatively homogeneous patient population may reduce the generalizability of our findings to broader populations. Although this study confirmed that NLR and CD40 could serve as independent markers for diagnosing SLE and evaluating disease activity, there is room for improvement. First, basic experiments and animal SLE models could be conducted to investigate the specific regulatory effects of NLR and CD40 on SLE pathogenesis. Second, increasing the sample size would improve the accuracy of the results. We hope that future studies will address these limitations and improve upon the findings of this research.

Disclosure of conflict of interest

None.

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