

Reduced C3 Levels Link Dyslipidemia and Renal Involvement in Systemic Lupus Erythematosus

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Background: Dyslipidemia is more frequently observed in systemic lupus erythematosus (SLE) patients with hypocomplementemia, suggesting potential connections between immune dysregulation and lipid metabolism. This study aims to explore the association between complement components and lipid profiles, and investigate the influence in organ involvement among SLE patients.

Methods: A total of 935 patients diagnosed with SLE were enrolled and stratified based on their baseline lipid profiles. Logistic regression, stratified analyses and ROC curves analyses were employed to evaluate the predictive value of complements with other factors for dyslipidemia and organ involvement.

Results: Among the 935 enrolled SLE patients, 527 (56.4%) were diagnosed with dyslipidemia. Patients in the dyslipidemia group exhibited higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and lower complement 3 (C3) levels compared to those without dyslipidemia. Lower C3 levels were independently associated with an increased risk of dyslipidemia (OR = 0.29, 95% CI: 0.18–0.47, $P < 0.0001$) and renal involvement (OR = 0.21, 95% CI: 0.12–0.37, $P < 0.0001$). This association of dyslipidemia were further strengthened in patients with $C3 \leq 0.7$ g/L (OR = 0.08, 95% CI: 0.01–0.48, $P = 0.0061$). In addition, a predictive model for dyslipidemia risk among SLE patients was developed. Using criteria of $C3 (\leq 0.68$ g/L) and $ESR (\geq 33.65$ mm/h), the model achieved 64.1% sensitivity, 74.7% specificity, and an AUC of 0.71 for dyslipidemia prediction.

Conclusion: Reduced C3 levels serve as a significant independent risk factor for dyslipidemia and renal involvement. Furthermore, the combination of C3 and ESR enhances the identification of dyslipidemia.

Keywords: dyslipidemia, systemic lupus erythematosus, complement C3, immune dysregulation, lipid metabolism

Introduction

Systemic lupus erythematosus (SLE) is a complex, chronic autoimmune disease characterized by autoantibody production and immune complex deposition.¹ Clinically, patients with SLE frequently exhibit a special pattern of dyslipidemia.² Furthermore, this dyslipidemia typically accompanied disease flares and contribute to an elevated risk of cardiovascular disease (CVD) in SLE patients, potentially leading to mortality in severe cases.^{3,4}

Some traditional inflammatory markers, such as ESR and CRP, are susceptible to influences from external factors like infections and pregnancy, resulting in decreased specificity. Recent studies indicate that the complement system plays a central role in the pathogenesis of SLE.⁵ During the active phase of SLE, the complement system is activated by immune complexes, resulting in complement consumption. Low serum C3 levels are well-established indicators of SLE activity.^{6–8} Importantly, chronic immune system activation in SLE patients may partially contribute to the development of CVD.⁹ Although dyslipidemia is highly prevalent among individuals with SLE, indicating that it may play a critical role in CVD progression.^{10–12} Persistent dyslipidemia in systemic lupus erythematosus represents a critical driver of accelerated atherosclerosis and is robustly associated with substantially elevated long-term risks of myocardial infarction, stroke, and cardiovascular mortality.¹³ Complement activation may directly influence lipid metabolism through several interconnected mechanisms. The central component C3 is cleaved into C3a-desArg, which

regulates triglyceride synthesis and lipid storage in adipose tissue.¹⁴ In addition, complement activation products promote macrophage uptake of oxidized LDL and induce endothelial dysfunction via sublytic membrane attack complex deposition. Furthermore, complement system disruption, particularly reduced C3, is independently linked to impaired HDL cholesterol efflux capacity.¹⁵ These mechanisms collectively link immune activation to dyslipidemia and accelerated atherogenesis.¹⁶ However, assessing this “complement-lipid axis” clinically is complicated by treatments: HCQ improves lipid profiles and reduces organ damage,¹⁷ while long-term corticosteroids worsen dyslipidemia and accelerate atherosclerosis.¹⁸

The contribution of complement, particularly C3, to dyslipidemia has not yet been investigated. Given that SLE-related factors such as C3 may influence CVD pathogenesis,¹⁹ clarifying whether C3 can serve as a biomarker for predicting dyslipidemia in SLE patients is of particular importance.

Materials and Methods

Study Design and Participants

This study was designed as a cross-sectional analysis of baseline data derived from a prospectively maintained observational cohort established in 2004 at The First Affiliated Hospital, Shenzhen University, Shenzhen, China. This cross-sectional study included a total of 935 patients. Participants were stratified based on baseline lipid profiles into 2 groups: Non-Dyslipidemia (N=408) Dyslipidemia (N=527). Baseline demographic, clinical, and laboratory data were collected and compared across 2 groups.

In the current study, baseline information including clinical characteristics, biomarkers, and medications was used for analysis. Patients complicated with the following diseases were excluded: (i) missing lipid profile data; (ii) presence of malignant tumors; (iii) acute infections, such as tuberculosis or/and hepatitis. The baseline data of patients enrolled from Jan 2004 to Jan 2024 was extracted as the dataset. The investigation protocol was conformed with the Helsinki Declaration and approved by the Ethics Committee of The First Affiliated Hospital, Shenzhen University.

Data Collection

Data were extracted from medical records, including demographics and clinical manifestations such as age, sex, smoking and alcohol history, as well as the presence or absence of fever, facial erythema, Raynaud phenomenon, oral ulcers, hair loss, joint pain, limb muscle weakness, edema, and psychiatric abnormalities. Comorbidities and signs included hypertension, diabetes mellitus, coronary heart disease, history of tumor, and qualitative urine protein (graded 0–4+ by dipstick). Laboratory parameters comprised white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), erythrocyte sedimentation rate (ESR), serum uric acid (UA), serum creatinine (Cr), and SLE Disease Activity Index (SLEDAI). Autoantibodies assessed were anti-Smith (Sm), anti-SSA, anti-SSB, and anti-double-stranded DNA (ds-DNA), evaluated by standard ELISA or immunofluorescence assays. Complement and immunoglobulins measured included serum C3, C4, IgG, IgA, and IgM using nephelometry. Inflammatory markers consisted of C-reactive protein (CRP) determined by immunoturbidimetry. Medication history documented the use of hydroxychloroquine (HCQ), methotrexate, azathioprine, leflunomide, mycophenolate mofetil, and systemic corticosteroids.

Definition

Dyslipidemia is characterized by abnormal blood lipid levels, defined by: 1. Total Cholesterol (TC): ≥ 200 mg/dL (≥ 5.18 mmol/L) 2. Low-Density Lipoprotein Cholesterol (LDL-C): ≥ 130 mg/dL (≥ 3.37 mmol/L) 3. Triglycerides (TG): ≥ 150 mg/dL (≥ 1.70 mmol/L) 4. High-Density Lipoprotein Cholesterol (HDL-C): < 50 mg/dL (< 1.29 mmol/L). Diagnosis is based on fasting lipid profile testing per AHA guidelines.²⁰

The study included patients diagnosed with Systemic Lupus Erythematosus (SLE). All enrolled patients fulfilled the 1997 revised classification criteria of the American College of Rheumatology (ACR) for SLE.²¹ Renal involvement was defined as the presence of any of the following clinical laboratory findings: (1) positive urine protein, (2) positive urine occult blood, or (3) persistent 24-hour proteinuria > 0.5 g.

Statistical Analysis

All statistical procedures were conducted using R (version 4.5.1) and GraphPad Prism 10.1.2. Continuous variables are presented as mean \pm standard deviation, whereas categorical variables are summarized as counts and corresponding proportions. Group differences were examined with Student's t-tests for continuous measures, while chi-square or Fisher's exact tests were applied for categorical data, depending on suitability.

To explore potential determinants of dyslipidemia, univariate logistic regression analyses were carried out initially. Variables that met the threshold of $P < 0.05$ or were deemed clinically important were subsequently entered into multivariable logistic regression models. Three models were generated: an unadjusted model; Model I, which accounted for sex, age, fever, edema, hemoglobin, CRP, and ESR; and Model II, which additionally incorporated ds-DNA, IgG, urine protein qualitative results, uric acid, and hydroxychloroquine usage.

An independent multivariable model was also constructed to assess the relationship between complement C3 and both dyslipidemia and renal involvement, adjusting for age, sex, fever, edema, hemoglobin, CRP, ESR, ds-DNA, and IgG. Pearson correlation tests were performed to examine associations between lipid parameters and selected clinical or laboratory indicators.

Stratified analyses were used to further evaluate potential effect modification on the association between C3 and dyslipidemia. Receiver operating characteristic (ROC) curves were generated to assess the predictive utility of C3 for identifying dyslipidemia. The area under the curve (AUC) and its 95% confidence interval were reported, and the optimal threshold value was determined using the Youden index. All effect estimates were expressed as odds ratios (ORs) with 95% confidence intervals. For other included covariates, the missing data rate was minimal ($< 5\%$), and these missing values were handled via multiple imputation. A two-tailed P-value of < 0.05 was regarded as statistically significant.

Result

Comparisons of Disease Characteristics Between Non-Dyslipidemia and Dyslipidemia Patients

As shown in Table 1, patients with dyslipidemia, compared to those without, were more likely to be male (12.33% vs. 6.37%, $P = 0.002$) and had higher rates of fever (31.31% vs. 18.14%, $P < 0.001$), Raynaud's phenomenon (9.30% vs. 5.15%, $P = 0.017$), and edema (29.98% vs. 11.27%, $P < 0.001$). Additionally, they had lower hemoglobin levels (107.48

Table 1 The Baseline Characteristics of SLE Patients in Relation to Dyslipidemia Status

Variable	Total (N=935)	Non-Dyslipidemia (N=408)	Dyslipidemia (N=527)	P-value
Age	37.34 \pm 13.40	37.24 \pm 13.39	37.42 \pm 13.42	0.843
Sex				0.002
Men	91 (9.73%)	26 (6.37%)	65 (12.33%)	
Women	844 (90.27%)	382 (93.63%)	462 (87.67%)	
Symptoms				
Fever	239 (25.56%)	74 (18.14%)	165 (31.31%)	<0.001
Facial Erythema	270 (28.88%)	105 (25.74%)	165 (31.31%)	0.062
Raynaud Phenomenon	70 (7.49%)	21 (5.15%)	49 (9.30%)	0.017
Oral Ulcer	73 (7.81%)	29 (7.11%)	44 (8.35%)	0.483
Hair Loss	212 (22.67%)	92 (22.55%)	120 (22.77%)	0.936
Joint Pain	359 (38.40%)	165 (40.44%)	194 (36.81%)	0.258
Limb Muscle Pain Weakness	46 (4.92%)	17 (4.17%)	29 (5.50%)	0.349
Edema	204 (21.82%)	46 (11.27%)	158 (29.98%)	<0.001
Psychiatric Abnormality	11 (1.18%)	2 (0.49%)	9 (1.71%)	0.087
Smoking	21 (2.25%)	5 (1.23%)	16 (3.04%)	0.064
Alcohol	10 (1.07%)	4 (0.98%)	6 (1.14%)	0.816

(Continued)

Table 1 (Continued).

Variable	Total (N=935)	Non-Dyslipidemia (N=408)	Dyslipidemia (N=527)	P-value
Signs				
Hypertension	161 (17.22%)	58 (14.22%)	103 (19.54%)	0.032
Diabetes	28 (2.99%)	8 (1.96%)	20 (3.80%)	0.103
Coronary heart disease	14 (1.50%)	9 (2.21%)	5 (0.95%)	0.116
Tumor	19 (2.03%)	6 (1.47%)	13 (2.47%)	0.434
Urine Protein Qualitative				<0.001
0	562 (60.11%)	293 (71.81%)	269 (51.04%)	
1	181 (19.36%)	62 (15.20%)	119 (22.58%)	
2	72 (7.70%)	23 (5.64%)	49 (9.30%)	
3	75 (8.02%)	19 (4.66%)	56 (10.63%)	
4	45 (4.81%)	11 (2.70%)	34 (6.45%)	
WBC (10 ⁹ /L)	6.14 ± 3.75	6.11 ± 3.76	6.16 ± 3.74	0.861
Hb (g/L)	111.07 ± 21.74	115.71 ± 18.21	107.48 ± 23.52	<0.001
PLT (10 ⁹ /L)	195.60 ± 87.45	201.71 ± 81.23	190.86 ± 91.77	0.06
ESR (mm/h)	37.65 ± 32.08	26.11 ± 25.63	46.59 ± 33.70	<0.001
UA (μmol/L)	335.84 ± 109.82	302.06 ± 85.82	362.00 ± 118.94	<0.001
Cr (μmol/L)	90.97 ± 256.41	96.13 ± 372.36	86.97 ± 97.06	0.588
SLEDAI	9.36 ± 6.26	7.48 ± 4.95	10.82 ± 6.77	<0.001
Autoantibodies				
SM	181 (19.36)	53 (12.99%)	128 (24.29%)	<0.001
SSA	599 (64.06%)	270 (66.18%)	329 (62.43%)	0.236
SSB	152 (16.26%)	66 (16.18%)	86 (16.32%)	0.953
ds-DNA	459 (49.09%)	153 (37.50%)	306 (58.06%)	<0.001
Immunity-related markers				
CRP (mg/L)	9.33 ± 19.46	6.06 ± 13.27	11.86 ± 22.83	<0.001
C3 (g/L)	0.73 ± 0.28	0.79 ± 0.24	0.69 ± 0.31	<0.001
C4 (g/L)	0.13 ± 0.10	0.14 ± 0.08	0.12 ± 0.11	0.065
IgG (g/L)	14.93 ± 7.14	14.23 ± 6.10	15.48 ± 7.81	0.008
IgA (g/L)	2.69 ± 2.35	2.56 ± 1.13	2.79 ± 2.97	0.142
IgM (g/L)	1.14 ± 0.85	1.14 ± 1.00	1.13 ± 0.71	0.863
Medication history				
Hydroxychloroquine	639 (68.34%)	314 (76.96%)	325 (61.67%)	<0.001
Methotrexate	63 (6.74%)	35 (8.58%)	28 (5.31%)	0.048
Azathioprine	30 (3.21%)	15 (3.68%)	15 (2.85%)	0.475
Leflunomide	28 (2.99%)	11 (2.70%)	17 (3.23%)	0.637
Mycophenolate Mofetil	230 (24.60%)	103 (25.25%)	127 (24.10%)	<0.001
Steroids	788 (84.28%)	336 (82.35%)	452 (85.77%)	0.155
Renal involvement	527 (56.36%)	188 (46.08%)	339 (64.33%)	<0.001

± 23.52 vs. 115.71 ± 18.21 g/L, $P < 0.001$), higher ESR values (46.59 ± 33.70 vs. 26.11 ± 25.63 mm/h, $P < 0.001$), elevated uric acid levels (362.00 ± 118.94 vs. 302.06 ± 85.82 μmol/L, $P < 0.001$), and higher SLEDAI scores (10.82 ± 6.77 vs. 7.48 ± 4.95, $P < 0.001$). IgG levels were higher in the dyslipidemia group (15.48 ± 7.81 vs. 14.23 ± 6.10 g/L; $P = 0.008$), indicating augmented humoral immune activation.

Furthermore, patients in the dyslipidemia group patients had higher positivity rates for SM (24.29% vs. 12.99%, $P < 0.001$) and ds-DNA (58.06% vs. 37.50%, $P < 0.001$), lower C3 levels (0.69 ± 0.31 vs. 0.79 ± 0.24 g/L, $P < 0.001$), and higher CRP (11.86 ± 22.83 vs. 6.06 ± 13.27 mg/L, $P < 0.001$). They were less likely to use HCQ (61.67% vs. 76.96%, $P < 0.001$), and had a higher prevalence of renal involvement was more prevalent (64.33% vs. 46.08%, $P < 0.001$).

The Relationships Between Complements and Other Biomarkers with Dyslipidemia

Univariate logistic regression analysis in Table 2 demonstrated that lower C3 levels were strongly associated with an increased risk of dyslipidemia (OR = 0.29, 95% CI: 0.18–0.47, $P < 0.0001$). This association persisted in multivariable models after adjusting for potential confounders. In Model I, which accounted for sex, age, fever, edema, CRP, ESR, and Hb, the OR for C3 was 0.34 (95% CI: 0.19–0.60, $P = 0.0002$). In Model II, which further adjusted for additional factors including ds-DNA, IgG, qualitative urine protein, uric acid, and hydroxychloroquine use, the OR for C3 became 0.50 (95% CI: 0.26–0.95, $P = 0.0332$).

Table 2 Univariate and Multivariable Logistic Regression Models Between Various Factors and Dyslipidemia

Univariate logistic Regression Models (Y= Dyslipidemia)			
Variable	Univariable Odds Ratios	95% CI	P-value
Age	1	(0.99, 1.01)	0.8431
Sex			
Men			
Women	0.48	(0.30, 0.78)	0.0027
Symptoms			
Fever	2.06	(1.51, 2.81)	<0.0001
Facial Erythema	1.32	(0.99, 1.75)	0.0625
Raynaud Phenomenon	1.89	(1.11, 3.20)	0.0183
Oral Ulcer	1.19	(0.73, 1.94)	0.4834
Hair Loss	1.01	(0.74, 1.38)	0.9361
Joint Pain	0.86	(0.66, 1.12)	0.258
Limb Muscle Pain Weakness	1.34	(0.73, 2.47)	0.3503
Edema	3.37	(2.35, 4.82)	<0.0001
Psychiatric Abnormality	3.53	(0.76, 16.41)	0.1081
Signs			
Smoking	2.52	(0.92, 6.95)	0.0732
Alcohol	1.16	(0.33, 4.15)	0.8158
Hypertension	1.47	(1.03, 2.08)	0.033
Diabetes	1.97	(0.86, 4.52)	0.1089
Coronary heart disease	0.42	(0.14, 1.28)	0.1273
Tumor	1.69	(0.64, 4.50)	0.2896
Urine Protein Qualitative			
0			
1	1.73	(1.29, 2.31)	0.0002
2	4.6	(2.39, 8.86)	<0.0001
3	3.98	(2.10, 7.56)	<0.0001
4	5.07	(1.69, 15.19)	0.0038
WBC	1	(0.97, 1.04)	0.861
Hb	0.98	(0.98, 0.99)	<0.0001
ALT	1.01	(1.00, 1.01)	0.011
AST	1.02	(1.01, 1.02)	<0.0001
PLT	1	(1.00, 1.00)	0.0604
ESR	1.02	(1.02, 1.03)	<0.0001
UA	1.01	(1.00, 1.01)	<0.0001
Cr	1	(1.00, 1.00)	0.5964
SLEDAI	1.1	(1.08, 1.13)	<0.0001

(Continued)

Table 2 (Continued).

Autoantibodies				
SM		2.15	(1.51, 3.05)	<0.0001
SSA		0.85	(0.65, 1.11)	0.2364
SSB		1.01	(0.71, 1.43)	0.9534
ds-DNA		2.31	(1.77, 3.01)	<0.0001
Immunity-related markers				
CRP		1.02	(1.01, 1.03)	<0.0001
C3		0.29	(0.18, 0.47)	<0.0001
C4		0.27	(0.07, 1.10)	0.0681
IgG		1.03	(1.01, 1.05)	0.0086
IgA		1.06	(0.98, 1.16)	0.1629
IgM		0.99	(0.85, 1.15)	0.8624
Medication history				
Hydroxychloroquine		0.48	(0.36, 0.64)	<0.0001
Methotrexate		0.6	(0.36, 1.00)	0.0502
Azathioprine		0.77	(0.37, 1.59)	0.4762
Leflunomide		1.2	(0.56, 2.60)	0.6379
Mycophenolate Mofetil		0.94	(0.70, 1.27)	0.6865
Steroids		1.29	(0.91, 1.84)	0.1554
Multivariable Logistic Regression Models (Y= Dyslipidemia)				
Variable		Odds Ratios	95% CI	P-value
C3 (per 1 g/L increase)	Non-adjusted model	0.29	(0.18, 0.47)	<0.0001
C3 (per 1 g/L increase)	Adjust I model	0.34	(0.19, 0.60)	0.0002
C3 (per 1 g/L increase)	Adjust II model	0.5	(0.26, 0.95)	0.0332
Multivariable Logistic Regression Models (Y= Renal Involvement)				
		Odds Ratios	95% CI	P-value
C3 (per 1 g/L increase)	Non-adjusted model	0.1	(0.04, 0.24)	<0.0001
C3 (per 1 g/L increase)	Adjust model	0.13	(0.04, 0.42)	0.0006

Notes: Adjust model I adjust for: Sex; Age; Fever; Edema; Hb; CRP; ESR; Adjust model II adjust for: Sex; Age; Fever; Edema; Hb; CRP; ESR; ds-DNA; IgG; Urine Protein Qualitative; UA; Hydroxychloroquine; Adjust model adjust for: Sex; Age; Fever; Edema; Hb; CRP; ESR; ds-DNA; IgG.

These findings indicate that lower serum C3 levels are strongly and independently associated with dyslipidemia among SLE patients, even after controlling for inflammatory markers and disease activity, suggesting that C3 may serve as a potential biomarker or mechanistic link in lupus-related lipid metabolism disturbances.

Smooth curve fitting revealed a non-linear negative association between C3 levels and the probability of dyslipidemia in patients with SLE (Figure 1A). Patients with lower C3 levels exhibited a markedly higher risk of dyslipidemia, indicating a potential link between hypocomplementemia and abnormal lipid metabolism. Violin plots further demonstrated that C3 levels were significantly reduced in patients with dyslipidemia compared with those without ($P < 0.0001$), and similarly, patients with renal involvement had significantly lower C3 levels than non-LN patients ($P < 0.0001$) (Figure 1B), suggesting that complement depletion is associated with both disease activity and organ involvement.

Heatmap analysis integrating C3 (high/low), CRP (positive/negative), and ESR (high/low) status revealed that patients with low C3 combined with elevated CRP or ESR had the highest prevalence of dyslipidemia (Figure 1C). The cutoff values were determined based on the cutoff points from the ROC curves (Figure 1D), supporting the hypothesis of a synergistic effect between inflammatory activity and complement consumption on lipid abnormalities.

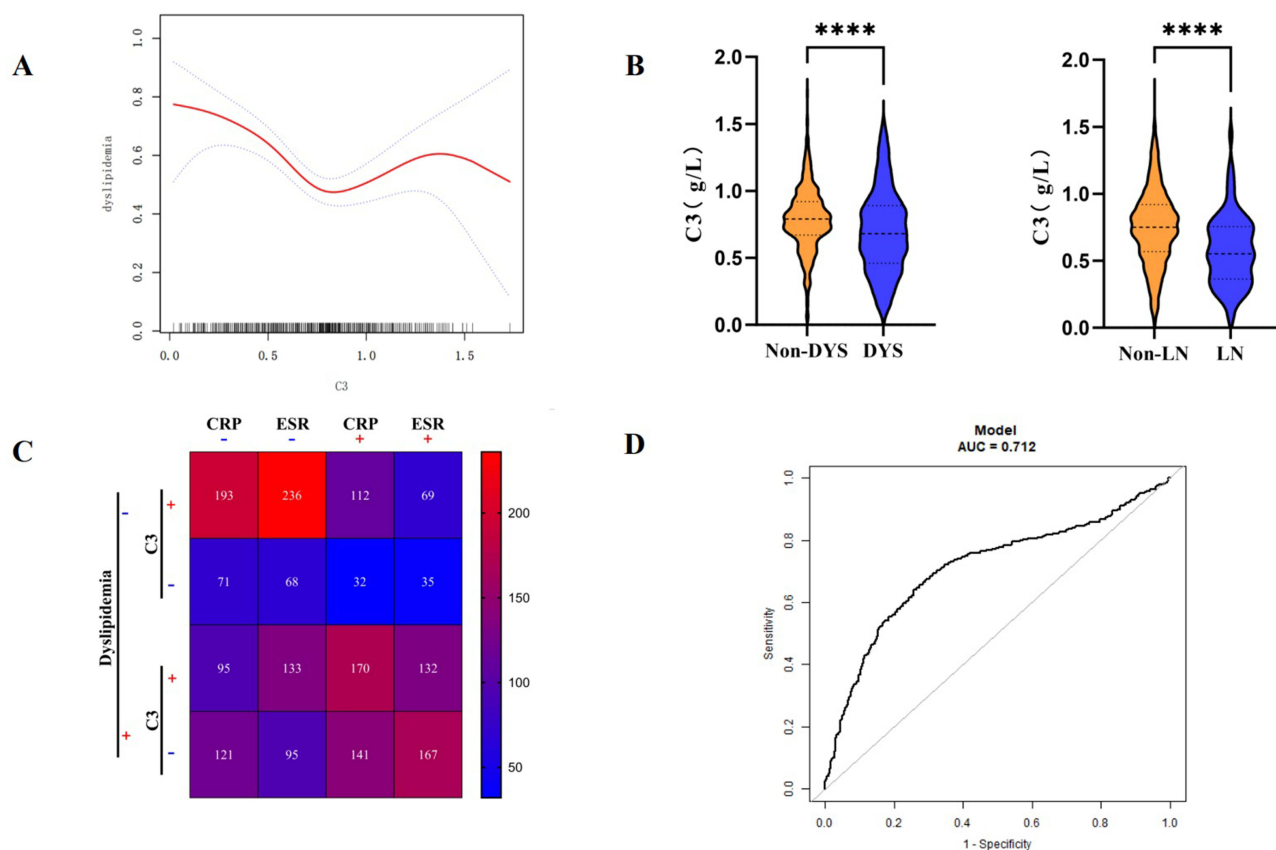


Figure 1 The value of C3 in identifying Dyslipidemia and Organ Involvement. **(A)** Smooth curve fitting C3 for dyslipidemia. **(B)** The distribution of C3 in different patients. **(C)** The summary of C3, CRP, ESR, and dyslipidemia in different subgroups based on the cut-off value. “+” (high) and “-” (low) denote values above or below optimal thresholds determined by smooth curve fitting. **(D)** The ROC curve of C3 to distinguish dyslipidemia.

Cluster and Stratified Analysis of Associations Between Various Factors and Dyslipidemia

Stratified analyses in [Table 3](#) revealed that the association between lower C3 levels and dyslipidemia was particularly pronounced in specific subgroups.

The stratified analysis examining the associations between various factors and dyslipidemia is presented in [Table 3](#). The analysis was adjusted for sex, age, fever, edema, CRP, ESR and Hb. In the C3 categorical subgroup analysis, significant associations were observed for specific C3 levels. For C3 levels ≤ 0.7 , the odds ratio (OR) for dyslipidemia was 0.08 (95% CI: 0.01–0.48, $P = 0.0061$), indicating a strong and significant inverse association. However, for C3 levels between > 0.7 and ≤ 1.4 , the OR was 1.62 (95% CI: 0.39–6.81, $P = 0.5069$), suggesting no significant association with dyslipidemia.

Table 3 Stratified Analysis of Associations Between Various Factors and Dyslipidemia

Stratified Analysis				
Variable	Dyslipidemia			
C3 Subgroup	N	Odds Ratios	95% CI	P-value
C3 Categorical				
≤ 0.7	408	2.09	(1.52, 2.86)	< 0.001
$> 0.7, \leq 1.4$	517	Ref		

Notes: Adjust for: Sex; Age; Fever; Edema; CRP; ESR; Hb.

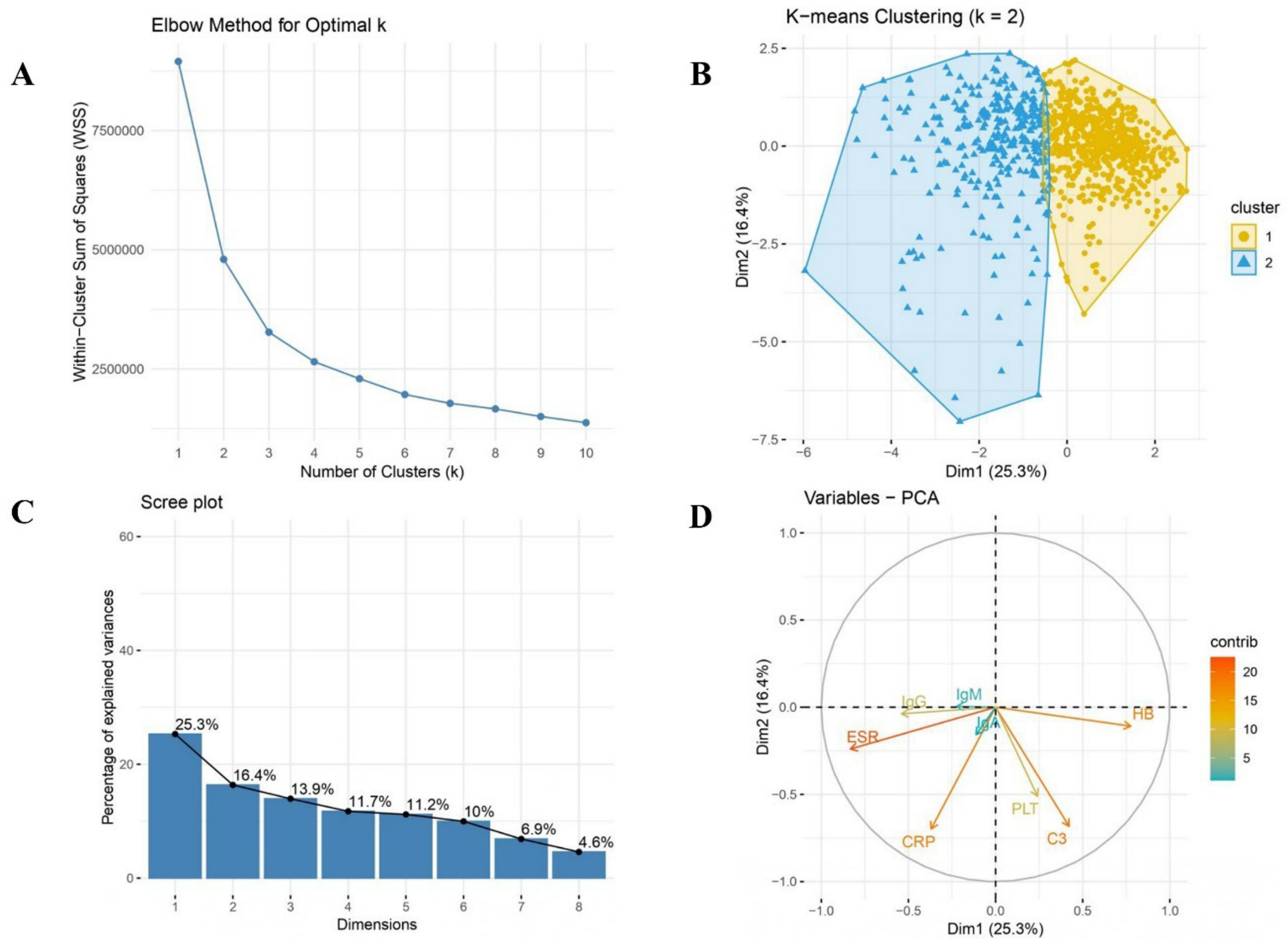


Figure 2 Elbow Method, K-means Clustering, and PCA Analysis of Dyslipidemia in SLE Patients. **(A)** Elbow plot: WSS shows an elbow at $k=2$, indicating optimal clustering into normal and dyslipidemia groups. **(B)** K-means ($k=2$): Scatter plot clusters, convex hulls show distribution. **(C)** Scree plot: Dim1 (25.3%) and Dim2 (16.4%) explain 41.7% of variance. **(D)** Variables-PCA: CRP and HB contribute $>15\%$ to Dim1 and Dim2, linking inflammation to lipid metabolism.

To explore the multidimensional relationships between clinical variables and dyslipidemia status, we applied unsupervised clustering and PCA. The elbow method identified $k = 2$ as the optimal number of clusters (Figure 2A), corresponding to patients with normal lipid profiles and those with dyslipidemia. K-means clustering with $k = 2$ achieved clear separation between these two groups (Figure 2B), showing high concordance with the clinical diagnosis.

PCA results indicated that the first two principal components (PC1 25.3%, PC2 16.4%) explained 41.7% of the total variance (Figure 2C). Variable contribution plots showed that CRP and HB contributed more than 15% to both PC1 and PC2, while C3, platelet count (PLT), and ESR also exhibited substantial contributions (Figure 2D). Notably, C3 loaded separately from the inflammatory cluster of CRP and ESR, highlighting its distinct variance profile within the dataset.

Correlation Between Serum Lipid Levels and Clinical Indices

Correlation analyses between serum lipid levels and clinical indices are presented in Table 4. Serum C3 levels were negatively correlated with triglyceride (TG) levels ($r = -0.1506$, $P < 0.0001$) and positively correlated with high-density lipoprotein (HDL) levels ($r = 0.1846$, $P < 0.0001$). These findings suggest that lower C3 levels are associated with unfavorable lipid profiles, particularly elevated TG and reduced HDL, which are hallmarks of dyslipidemia.

The analysis highlights a complex interplay between liver function, inflammation, immune response, and lipid metabolism. Liver enzymes (ALT, AST, GGT) and inflammatory markers (CRP, ESR) showed significant correlations with lipid profiles, particularly affecting TG and HDL levels. Immunological markers, notably C3 and IgG, exhibited

Table 4 Correlation Between Serum Lipid Levels and Clinical Index

	TG		TC		HDL		LDL		HCY	
	r	Pvalue	r	Pvalue	r	Pvalue	r	Pvalue	r	Pvalue
ALT	0.0449	0.1563	-0.0042	0.8950	-0.1369	0.0002*	-0.0120	0.7054	-0.0160	0.7685
AST	0.0890	0.0124*	-0.0241	0.4990	-0.1926	<0.0001*	-0.0244	0.4935	0.0203	0.7386
GGT	0.0974	0.0039*	-0.0257	0.4469	-0.1101	0.0052*	-0.0280	0.4077	0.0497	0.3621
LDH	0.1076	0.0332*	0.0047	0.9259	-0.0938	0.1053	-0.0102	0.8399	0.0891	0.2303
TP	-0.2400	<0.0001*	-0.3550	<0.0001*	-0.0756	0.0436*	-0.2986	<0.0001*	-0.0892	0.0995
ALB	-0.3253	<0.0001*	-0.2381	<0.0001*	0.2092	<0.0001*	-0.2288	<0.0001*	-0.1192	0.0275*
Urea	0.0357	0.2624	0.0229	0.4720	-0.0059	0.8764	0.0118	0.7122	0.5510	<0.0001*
Cr	0.0706	0.0268*	0.0221	0.4875	-0.0123	0.7453	-0.0018	0.9554	0.3603	<0.0001*
UA	0.2971	<0.0001*	0.1499	<0.0001*	-0.1912	<0.0001*	0.1268	0.0001*	0.3839	<0.0001*
IgA	0.0271	0.4101	-0.0104	0.7509	-0.0819	0.0323*	0.0001	0.9966	-0.0490	0.3762
IgM	0.0165	0.6161	-0.0146	0.6571	-0.0729	0.0571	-0.0047	0.8862	-0.1209	0.0288*
IgG	-0.0633	0.0412*	-0.3443	<0.0001*	-0.3784	<0.0001*	-0.2511	<0.0001*	-0.0338	0.5298
C3	-0.1506	<0.0001*	-0.0170	0.5844	0.1846	<0.0001*	-0.0256	0.4096	-0.0380	0.4809
C4	-0.1041	0.0015*	0.0623	0.0574	0.1950	<0.0001*	0.0188	0.5660	-0.0163	0.7685
CRP	-0.0312	0.3142	-0.1709	<0.0001*	-0.2305	<0.0001*	-0.1752	<0.0001*	0.0672	0.2119
WBC	0.0519	0.0945	0.1113	0.0003*	0.1892	<0.0001*	0.0496	0.1096	0.1428	0.0077*
ESR	0.2534	<0.0001*	-0.0429	0.1669	-0.4078	<0.0001*	-0.0428	0.1676	0.1267	0.0182*
D-dimer	0.1259	<0.0001*	0.0283	0.3615	-0.1291	0.0005*	0.0299	0.3347	0.0942	0.0799

Notes: Bold text and asterisk (*) indicate statistical significance ($P < 0.05$).

strong associations with multiple lipid parameters, suggesting a mechanistic link in dyslipidemia pathogenesis. Renal function markers, especially UA and CysC, also demonstrated significant correlations with lipid and metabolic profiles. These findings provide valuable insights into the multifactorial mechanisms underlying dyslipidemia in this patient cohort, emphasizing the roles of inflammation and immune activation in lipid dysregulation.

The Value of C3 and Other Biomarkers in Identifying Dyslipidemia and Organ Involvement in SLE

In the diagnostic test analysis, the optimal cut-off value for complement C3 in identifying dyslipidemia was 0.68 g/L, with a sensitivity of 51.0%, a specificity of 73.7%, and an area under the curve (AUC) of 0.61 (0.58–0.65). For erythrocyte sedimentation rate (ESR), the cut-off was 33.65 mm/h, with a sensitivity of 56.7%, a specificity of 74.5%, and an AUC of 0.70 (0.67–0.74). In comparison, the cut-off for C-reactive protein (CRP) was 3.16 mg/L, with a sensitivity of 59.0%, a specificity of 64.7%, and an AUC of 0.64 (0.602–0.674).

The diagnostic performance of the combined model incorporating C3 and ESR was evaluated by receiver operating characteristic (ROC) analysis, yielding an area under the curve (AUC) of 0.71 (95% CI: 0.68–0.75), indicating moderate discriminative power. Parallel testing of C3 and ESR improved sensitivity to 64.1% while maintaining specificity at 74.4%. In contrast, serial testing further enhanced specificity, albeit with a corresponding decrease in sensitivity, as suggested by the optimized threshold analysis in (Figure 1D).

Discussion

To our knowledge, this is the first study to investigate the value of complement 3 in assessing dyslipidemia-related disease activity in SLE and to characterize the clinical profiles associated with lipid profile disturbances in these patients. In addition, we aim to construct a clinical prediction model integrating C3 with conventional biomarkers by using ROC curve analysis, thereby clarifying the associations between circulating C3 levels and common clinical complications in SLE patients. Our cohort demonstrated a robust association between dyslipidemia and markers of disease activity, including higher SLEDAI scores, elevated CRP and ESR, and increased renal involvement. These findings align with prior studies reporting an atherogenic lipid profile in SLE patients, particularly during active disease phases.^{2,22}

Moreover, Dyslipidemia in patients with systemic lupus erythematosus is more severe in those with active disease or lupus nephritis. In pediatric SLE, patients with biopsy-proven nephritis exhibit a significantly higher incidence of dyslipidemia at 79.9%, accompanied by markedly reduced complement C3 and C4 levels.²³

Clinically, we found that lupus patients often have lipid profile disorders. Our data indicate that low C3 is significantly associated with lipid profile disorders in lupus, demonstrating acceptable specificity as an adjunctive indicator. Its combined diagnosis with classic biomarkers is of great significance.

The risk of lipid profile disturbances has been reported in patients with active lupus.^{22,24} 50–89% of SLE patients have hypocomplementemia at diagnosis, and persistently low C3 is a risk factor for relapse.^{25,26} Our results extend this understanding by showing that low C3 not only signals inflammation but also identifies patients at risk for lipid derangements. In our models, C3 remained significantly inversely associated with dyslipidemia even after adjusting for CRP, ESR, and other confounders. Thus, monitoring C3 alongside standard markers could provide a dual benefit in managing SLE: guiding immunosuppression and flagging metabolic risk. In fact, EULAR guidelines now recognize “persistent serological activity” (low complement and/or high anti-dsDNA) as a risk factor for adverse outcomes,⁵ underscoring the need to integrate immunologic and metabolic surveillance in routine care.

Although direct studies on C3 and lipid metabolism are limited in the literature, several reports have demonstrated that dyslipidemia in SLE patients is associated with disease activity.^{24,27} There is a direct correlation between small HDL and complement (C3/C4/CH50), and complement activation can affect lipid metabolism through inflammation.²⁸ Our study revealed for the first time a significant correlation between C3 levels and parameters such as TG, TC or HDL-C, suggesting that the complement system is involved in the metabolic disorder mechanism of SLE.

Dyslipidemia in SLE arises from the convergence of multiple distinct yet tightly interrelated pathophysiological processes, most notably autoantibody mediated impairment of endothelial lipoprotein lipase activity and the hepatic overproduction of apolipoproteins secondary to renal protein loss.²⁹ Against this backdrop of immune metabolic dysregulation, the complement cascade assumes a central and mechanistically indispensable role.³⁰ Positioned at the obligatory nodal point where the classical, alternative, and lectin pathways intersect, C3 functions not merely as a sentinel marker of systemic immune activation but as a pivotal biological intermediary that couples innate immune dysregulation to downstream metabolic disturbance.^{31,32} Accordingly, beyond its canonical roles in innate immunity, including pathogen opsonization, anaphylatoxin driven leukocyte recruitment, and membrane attack complex mediated cytotoxicity,³³ complement signaling is now increasingly recognized as a critical regulator of lipid homeostasis, adipose tissue remodeling, and inflammation driven atherogenesis.³⁴

We suggest that tighter control of disease activity and complement normalization help prevent metabolic complications in SLE. Future research should explore whether interventions that modulate complement activation can favorably impact lipid profiles and cardiovascular risk in lupus.

Limitation

We acknowledge that hyperlipidemia can affect immunoturbidimetric C3 measurements. Residual interference from high lipid levels remains a potential limitation. The cross-sectional design precludes causal inference between C3 activation and lipid alterations. Additionally, C3 suggesting its utility as an adjunctive risk indicator rather than a standalone diagnostic tool. These findings should be validated in future prospective cohorts.

Conclusion

Our findings position serum complement C3 as a potential biomarker for dyslipidemia in SLE patients. Reduced C3 levels were significantly associated with adverse lipid profiles and organ involvement, independent of traditional inflammatory markers. The combination of C3 and ESR enhanced the identification of patients at metabolic risk. These results suggest that complement monitoring may serve a dual role in assessing both disease activity and cardiometabolic risk, facilitating more tailored disease management in SLE.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

The study was approved by the Ethics Committee of the First Affiliated Hospital of Shenzhen University (Approval No. 2024-209-01PJ). All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. All patients signed the informed consent.

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Author Contributions

Shuo Cheng: Conceptualization, Methodology, Data curation, Investigation, Formal analysis, Writing – original draft. Yi Jiang: Methodology, Validation, Writing – original draft. Zhanheng Hu: Methodology, Data curation, Formal analysis, Writing – original draft. Xue Guo: Investigation, Resources, Validation, Writing – original draft. Qin Lai: Data curation, Investigation, Resources, Writing – original draft. Cuiling Fan: Investigation, Resources, Methodology, Writing – original draft. Suo Zhang: Formal analysis, Data curation, Writing – original draft. Bing Yuan: Formal analysis, Writing – review & editing. Yushuang Wei: Validation, Writing – review & editing. Meiyang Wang: Project administration, Supervision, Writing – review & editing, Funding acquisition.

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests. The authors declare no competing interests. Specifically, no authors have any affiliations with or financial involvement in any pharmaceutical companies, diagnostic firms, or commercial entities developing complement-targeting therapies relevant to this study.

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