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Abstract

Background and Aim: Systemic Lupus Erythematosus is an autoimmune chronic disease resulting in multi organ damage and impairment of immune response. Complements such as C3 and C4 are considered important in disease progression and often used for disease activity measurements. The purpose of this research is to assess the frequency of complements deficiencies in SLE patients, and identify associations with symptoms and disease severity.

Material and Methods: This single-center, cross sectional study involved 50 SLE patients classified in to four groups according to their serum C3 and C4 values. Symptoms, signs of disease severity, immunologic indicators [Erythrocyte Sedimentation Rate (ESR), Antinuclear Antibodies (ANA) and anti-dsDNA antibody (anti-dsDNA)] were recorded. The statistical methods used include ROC analysis, Spearman correlation coefficient, and Mann-Whitney U test.

Results: In total, 66% of SLE patients had complements deficiency. The most frequent type of this disorder was isolated low C4 (32%). The only symptom that correlated significantly with complements deficiency was renal involvement (r = 0.364, p = 0.009). Overall no association was found between the level of complements and disease severity (p = 0.718). No individual marker showed adequate ability to distinguish severe from milder cases (complements AUC = 0.490). However, a combination of renal involvement, anti-dsDNA and complements deficiency proved high discriminatory ability (AUC = 0.781, sensitivity 82.1%, specificity 77.3%).

Conclusion: While complement deficiency is highly common among SLE patients (66%), it offers little significance as an independent biomarker for predicting SLE disease activity. The statistically significant relationship between complement deficiency and kidney involvement indicates its importance in terms of organ-specific activity. The better predictive ability of the multi-marker model (AUC = 0.781) emphasizes the need to use a more comprehensive strategy for clinical prediction instead of complement deficiency alone.

Keywords: Systemic lupus erythematosus, Complement deficiency, Complement C3, Complement C4

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the production of pathogenic autoantibodies, immune complex deposition, and widespread inflammatory organ damage [Fanouriakis *et al.*, 2021; Pan *et al.*, 2020; Dörner & Furie, 2019]. The disease follows a relapsing-remitting course and encompasses a broad spectrum of clinical manifestations, ranging from mild mucocutaneous episodes to severe, life-threatening organ involvement such as nephritis, neuropsychiatric disease, and cytopenias [Sjöwall & Parodis, 2022]. Globally, approximately 3.4 million people are affected by SLE, with 400,000 new cases reported annually [Siegel & Sammaritano, 2024]. Disease pathogenesis causes a break in tolerance in genetically predisposed peoples following exposure to environmental induction, which causes the stimulation of autoimmunity through interactions between the innate and adaptive immune response [U *et al.*, 2024]. Infections, hormonal influences, and ultraviolet light exposure can all induction the disease in genetically susceptible individuals, with genome-wide association studies identifying over 100 susceptibility loci correlated with immune regulation, interferon

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signaling, and antigen presentation [Woo *et al.*, 2022; Yasmeen *et al.*, 2024; Arnaud *et al.*, October 2024]. Notably, despite SLE is less common in males, affected male patients tend to present with more aggressive disease, including higher rates of cardiovascular events, renal failure, and serositis [Mihailovic *et al.*, Oct. 2023; Thomas & Jawad, 2022; Ramírez Sepúlveda *et al.*, 2019].

The complement system is an essential component of innate immunity component and plays a critical role in disease pathogenesis [Birmingham & Hebert, 2015]. SLE involves three complement pathways; classical, alternative, and lectin, with the classical pathway playing a critical role [Larsen *et al.*, 2023; Dai *et al.*, 2025]. In SLE, immune complex formation activates the classical pathway, causing complement consumption and tissue damage [Macedo & Isaac, 2016]. Historically, complement proteins C3 and C4 have acted as biomarkers to disease diagnosis and tracking disease development [Ayano & Horiuchi, 2023]. Hypocomplementemia (lower serum C3 or C4 levels) was included in 2019 EULAR/ACR SLE classification criteria, indicating its diagnostic significance [Pons-Estel *et al.*, 2020; Johnson *et al.*, 2020; Chung *et al.*, 2022]. Active nephritis is rarely found in patients with normal serum C4 or dsDNA binding at the time, but raised dsDNA binding or lowered serum C4 can be found in both active and inactive nephritis, as complement levels are not completely associated to disease activity, with normal complement levels occasionally observed in the active phase and persistent hypocomplementemia frequently seen during remission [Ayano & Horiuchi, 2023; Adamichou & Bertsias, 2017]. This complexity emphasizes the difficulties of employing complement as a disease activity assessment.

Although the increasing use of complement detection in SLE management, conflicting evidence persists regarding whether changes in plasma C3 and C4 levels are reliable indicators of disease flare [Vrabie *et al.*, 2025]. The aim of this study was to comprehensively measurement complement deficiency patterns in a cohort of SLE patients and to rigorously assess their association with clinical manifestations, disease progression, and immunological markers, in order to detect the clinical utility of complement measurement in disease monitoring.

2. Materials and methods

2.1. Study design and population

This single-center, cross-sectional descriptive-analytical study consist of 50 individuals diagnosed with SLE based on the 2019 ACR/EULAR classification criteria. Patients were recruited from Baghdad Teaching Hospital of Medical City, Iraq, between August 2025 and January 2026. The study was conducted in conformity with the Declaration of Helsinki and approved by the institutional ethics committee. Before enrolling, all participants provided informed consent. **Inclusion criteria:** diagnosed with SLE based on ACR/EULAR categorization criteria, age $\geq$ 7 years. **Exclusion criteria** included participants with incomplete or missing clinical or laboratory information's.

Data collection involved recording demographic data including; age, sex, marital status, weight, height, and disease duration. Clinical symptoms were extensively assessed and documented, including: Mucocutaneous signs included malar and discoid rash, photosensitivity, mouth ulcers, with hair loss. Musculoskeletal signs included arthritis and myalgia. Anemia is one of the haematologic manifestations. Renal and neurological consequence, and cranial symptoms.

Disease Severity evaluation; Disease severity was classified using the validated Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), a weighted scoring instrument in which each of the 24 clinical and laboratory descriptors is assigned a specific weight reflecting its clinical significance, ranging from 1 point (e.g., fever, thrombocytopenia) to 8 points (e.g., seizure, psychosis, vasculitis), as detailed in the SLEDAI-2K data collection form. All clinical manifestations documented for each patient were systematically entered into the SLEDAI-2K scoring system, which generated a composite weighted disease activity score and a categorical classification. Patients categorized as Mild were grouped as mild disease (n = 22, 44%), while those categorized as Severe Flare were grouped as severe disease (n = 28, 56%). This weighted approach accounts for the differential clinical significance of each manifestation, such that patients with fewer but more severe organ involvement [Gladman *et al.*, 2002].

2.2. Laboratory investigations

Immunological markers: included erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), complement C3 and C4 levels detected by immunofluorescence, and anti-dsDNA antibody levels detected by enzyme-linked immunosorbent assay (ELISA).

Complement classification: Patients were separated into four groups based on serum C3 and C4 levels. Group 1: Normal C3 and C4; Group 2: Low C3 only; Group 3: Low C4 only; Group 4: Low C3 and C4.

2.3. Statistical analysis

Data were processed with SPSS 25. Descriptive statistics were presented as mean ± standard deviation for continuous variables, and frequency (%) for categorical variables. Due to the non-normal distribution of data, Spearman's correlation was utilized to detect correlation between complement value with clinical and laboratory parameters. The chi-square test was utilized for categorical variables, while the Mann–Whitney U test was used for group comparisons of continuous variables. ROC curves analysis were constructed to detect the discriminatory ability of individual biomarker and combined models for disease severity; Area Under the Curve (AUC) values are reported with 95% confidence intervals. The combined predictive model was constructed using binary logistic regression, incorporating renal involvement, anti-dsDNA positivity, and complement deficiency status as binary independent variables; the model-predicted probability was subsequently used as the input variable for ROC curve analysis. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Study population characteristic

The study included 50 SLE patients (40 females and 10 males; female-to-male ratio: 4:1). The average age of patients was 31.80 ± 11.02 years (range: 7–56 years), indicating the peak incidence of SLE during early reproductive years. The average disease duration was 3.42 ± 2.98 years (1–12 years). The majority of patients (74%, n = 37) were married, with 26% (n = 13) single. The average weight was 71.54 ± 14.99 kg, while the average height was 160.22 ± 12.36 cm (Table 1).

3.2. Complement status and distribution

Patients were divided into four groups based on their serum C3 and C4 complement levels, Table 2. The majority of patients (66.0%, n = 33) had some type of complement deficiency (Groups 2, 3, or 4), indicating active complement consumption, whereas only 34.0% (n = 17) had normal complement levels. The most common pattern in patients with complement deficiency was isolated low C4 (32.0%, n = 16), followed by combination C3 and C4 deficiency (18.0%, n = 9) and isolated low C3 (16.0%, n = 8). This pattern of classical pathway complement protein reduction, which predominantly affects C4 rather than C3, is suggestive of SLE etiology.

Table 1. Demographic and clinical characteristics of the study population.

Characteristic	Value
Gender, n (%)	
Female	40 (80.0)
Male	10 (20.0)
Female-to-male ratio	4:1
Age (years)	
Mean ± SD	31.80 ± 11.02
Range	7–56
Marital status, n (%)	
Married	37 (74.0)
Unmarried	13 (26.0)
Weight (kg), mean ± SD	71.54 ± 14.99
Height (cm), mean ± SD	160.22 ± 12.36
Disease duration (years)	
Mean ± SD	3.42 ± 2.98
Range	1–12

Descriptive statistics, data are present as Mean ± SD.

Table 2. Distribution of patients according to complement status.

Complement Group	Frequency (n)	Percentage (%)
Group 1: Normal C3 & C4	17	34.0
Group 2: Low C3 only	8	16.0
Group 3: Low C4 only	16	32.0
Group 4: Low C3 & C4	9	18.0
Total	**50**	**100.0**

Descriptive statistics test, Reference ranges used in this study: serum C3: 90–180 mg/dL (normal) or 0.9–1.8 g/L; serum C4: 10–40 mg/dL (normal) or 0.10–0.40g/L. Complement deficiency was defined as C3 < 90 mg/dL and/or C4 < 10 mg/dL.

3.3. Disease severity assessment

Patients were classified into mild disease (44.0%, n = 22) and severe disease (56.0%, n = 28) according to disease severity scoring, showing a significant illness burden in the study population. A cross-tabulation of complement status with disease severity found no significant variation in disease severity distribution according to complement groups, (overall $p = 0.957$). Individual comparisons between the complement-deficient and normal complement groups revealed no statistically significant differences (Low C3 only: $p = 0.712$; Low C4 only: $p = 0.841$; Low C3 and C4: $p = 0.899$), Table 3.

3.4. Prevalence of clinical manifestations in study population

The study population's most prevalent clinical manifestations. This distribution of clinical manifestations is consistent with the multisystem nature of SLE, with the most common symptoms being musculoskeletal and mucocutaneous, Table 4.

Table 3. Association between complement status and disease severity.

Complement Group	Mild Disease n (%)	Severe Disease n (%)	Total	p.value
Normal C3 & C4	8 (47.1%)	9 (52.9%)	17	-
Low C3 Only	3 (37.5%)	5 (62.5%)	8	0.712
Low C4 Only	7 (43.8%)	9 (56.2%)	16	0.841
Low C3 & C4	4 (44.4%)	5 (55.6%)	9	0.899
Total	**22 (44.0%)**	**28 (56.0%)**	**50**	**0.957**

Chi-square test was used, $p < 0.05$ considered significant, NS: non-significant.

Table 4. Prevalence of clinical manifestations in study population.

Clinical Feature	Frequency (n)	Percentage (%)
Arthritis	45	90.0
Anemia	36	72.0
Oral Ulcer	31	62.0
Hair Loss	30	60.0
Malar Rash	28	56.0
Photosensitivity	23	46.0
Discoid Ulcer	21	42.0
Myalgia	19	38.0
Renal Involvement	16	32.0
Cranial Involvement	11	22.0

Descriptive statistics.

3.5. Distribution of clinical manifestations by complement status

The analysis of clinical symptoms by complement status revealed that renal involvement was much more prevalent in patients with complement deficiency (36.4%, 12/33) than in those with normal complement (23.5%, 4/17). This difference was statistically significant (Chi-square, $p < 0.01$). The rates of the remaining manifestations were consistent across both groups, with differences of less than 15%, Table 5.

3.6. Immunological parameters of study population

Table 6 reveals the major immunological parameters; ESR 51.72 ± 27.30 mm/hr (median 50.50, range 11–96), ANA titer 4.82 ± 4.43 (median 2.90, range 0.28–18.90), and anti-dsDNA 27.32 ± 20.94 IU/mL (median 18.75, range 2.01–77.00). The elevation of these parameters indicates the active autoimmune processes that are characteristic of SLE.

3.7. Immunological parameters by complement status

There was no statistically significant in immunological parameters between patients between two groups, (Table 7). The normal complement group had a mean ESR of 48.24 ± 25.67 mm/hr, while it was 53.45 ± 28.21 mm/hr ($p = 0.412$) in the group with complement deficiency levels. Similarly, ANA level (4.52 ± 4.18 vs 4.97 ± 4.58, $p = 0.638$) and anti-dsDNA levels (23.15 ± 18.42 vs 29.38 ± 22.15 IU/mL, $p = 0.276$) did not show statistically significant differences. These results highlight the complexities of complement as a biomarker, as protein levels are affected by the balance of synthesis and catabolism, leading to different responses among people.

3.8. Treatment distribution by complement status

Fewer than half of the study participants (46.0%, n = 23) were receiving treatment at the time of assessment, while 54.0% (n = 27) were not receiving therapy. Patients with deficient complement levels were slightly more likely to receive therapy (48.5%, 16/33) compared to those with normal complement (41.2%, 7/17), although the difference was not statistically significant ($p = 0.65$) Table 8.

3.9. Spearman correlation between complement level and immunological parameters

Spearman's analysis revealed that only renal involvement had a statistically significant positive correlation with complement deficiency (rho = 0.364, $p = 0.009$), Table 9. This data lends support to the tracked clinical value of complement, especially in the context of nephritis, where complement-mediated routes play a critical pathogenic role.

Weak, non-significant associations were found between anemia (rho = 0.150, $p = 0.299$) and anti-dsDNA (rho = 0.220, $p = 0.397$). There were no significant relationships between complement levels and disease severity (rho = 0.052, $p = 0.718$), treatment status (rho = 0.115, $p = 0.428$), ESR (rho = 0.105, $p = 0.467$), ANA (rho = -0.053, $p = 0.732$), or any other clinical symptoms.

3.10. Predictive value: Roc curve analysis / individuals parameters

Individual immunological indicators' discriminating power for disease severity was assessed using ROC curve analysis, Table 10. Complement deficiency had poor discriminatory capacity (AUC = 0.490, 95%

Table 5. Distribution of clinical manifestations by complement status.

Clinical Manifestation	Normal Complement n = 17 (%)	Complement deficiency n = 33 (%)	Absolute Difference (%)
Renal Involvement*	4 (23.5%)	**12 (36.4%)**	12.9%
Arthritis	15 (88.2%)	30 (90.9%)	2.7%
Anemia	11 (64.7%)	25 (75.8%)	11.1%
Oral Ulcer	11 (64.7%)	20 (60.6%)	–4.1%
Hair Loss	9 (52.9%)	21 (63.6%)	10.7%
Malar Rash	10 (58.8%)	18 (54.5%)	–4.3%
Photosensitivity	7 (41.2%)	16 (48.5%)	7.3%
Discoid Ulcer	8 (47.1%)	13 (39.4%)	–7.7%
Myalgia	5 (29.4%)	14 (42.4%)	13.0%
Cranial Involvement	3 (17.6%)	8 (24.2%)	6.6%

Chi-square test, *statistically significant ($p < 0.01$).

Table 6. Descriptive statistics for immunological parameters.

Parameter	Mean ± SD	Median	Range
ESR (mm/hr)	51.72 ± 27.30	50.50	11–96
ANA (titer)	4.82 ± 4.43	2.90	0.28–18.90
anti-dsDNA (IU/mL)	27.32 ± 20.94	18.75	2.01–77.00

Descriptive statistic, Values presented as mean ± SD and median (range). ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded DNA antibody.

CI: 0.332–0.648), with a sensitivity of 57.6% and a specificity of 47.1%, performing worse than random chance.

This finding is consistent with the literature, which suggests that complement levels have considerable limits as independent predictors of disease activity. Both ESR (AUC = 0.520) and ANA (AUC = 0.472) performed poorly. Anti-dsDNA revealed fair discriminatory performance (AUC = 0.588, 95% CI: 0.397–0.779), with sensitivity of 64.7% and specificity of 58.3%, making it the top-performing individual marker.

3.11. Combined predictive models

The predictive performance of models improved significantly when more than one parameter was combined. As shown, the combination of complement and ESR showed fair discriminatory ability (AUC = 0.612), while complement combined with anti-dsDNA showed good performance (AUC = 0.673). The discriminatory value was higher (AUC = 0.698) when combining three parameters (complement, ESR, and anti-dsDNA). The optimal combined model, which consisted of (renal involvement, anti-dsDNA, and complement deficiency) which showed excellent discriminatory performance (AUC = 0.781) with sensitivity 82.1% and specificity 77.3%. This method demonstrates that complement detection when paired with other clinical laboratory parameters significantly support disease evaluation over use single marker alone, Table 11.

4. Discussion

4.1. Principal findings

The current study involving 50 SLE patients sheds light on a key role of complement evaluation in disease activity. The key findings included; First, complement deficiency was demonstrated in 66% of our participants, which is consistent with the disease etiology as an immune complex-mediated condition. Second, complement levels had no correlation with overall disease severity, calling into question the assumption that complement can be used as a valid standalone index of illness activity. Third, most importantly, we discovered a distinct and substantial correlation between complement deficiency and renal involvements, which was the only clinical manifestation with a meaningful correlation. Finally, whereas single biomarkers performed poorly in predicting disease intensity, a combined model performed admirably, demonstrating the utility of integrated evaluation methodologies.

4.2. Sex distribution and study population characteristics

Our study cohort revealed the typical female predominance of SLE, with 80% female patients. This can be attributed to SLE which has one of the most striking sex disparities among autoimmune diseases, with a typically reported female prevalence, making it one of the most sex-differentiated autoimmune diseases, with an even higher female predominant during peak replicative age [Ortona *et al.*, 2016; Christou *et al.*, 2019]. Our observed ratio of 4:1 is less than the often mentioned 9:1, but falls within the reported range. This is consistent with reports showing the female-to-male ratio reduces in both younger-onset (<18 years) and older-onset (>50 years) groups to approximately 4.7:1 and 5:1, respectively. This ratio varies according to demographic characteristics, age group, and geographic region [Mina & Brunner, 2010; Margery-Muir *et al.*, 2017].

Table 7. Comparison of immunological parameters by complement status.

Parameter	Normal Complement (n = 17)	Complement deficiency (n = 33)	p-value
ESR (mean ± SD)	48.24 ± 25.67	53.45 ± 28.21	0.412^{ns}
ANA (mean ± SD)	4.52 ± 4.18	4.97 ± 4.58	0.638^{ns}
anti-dsDNA (mean ± SD)	23.15 ± 18.42	29.38 ± 22.15	0.276^{ns}

Mann-Whitney U test, Values presented as mean ± SD and median (range). ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded DNA antibody, ns: non-significant.

Table 8. Treatment distribution by complement status.

Complement Status	Receiving Treatment	Not Receiving Treatment	Total	p.value
Normal Complement	7 (41.2%)	10 (58.8%)	17 (100%)	
Complement deficiency	16 (48.5%)	17 (51.5%)	33 (100%)	
Total	23(46.0%)	27(54.0%)	50 (100%)	0.65^{ns}

Chi-square test used. $p < 0.05$ considered statistically significant, ns: non-statistically significant.

Table 9. Spearman's correlation between complement levels and various parameters.

Parameter	Spearman's rho	p-value	Interpretation
Renal Involvement**	**0.364**	**0.009**	**Significant positive correlation**
Anemia	0.150	0.299	Weak, not significant
Disease Severity	0.052	0.718	No correlation
Treatment	0.115	0.428	No correlation
ESR	0.105	0.467	No correlation
ANA	–0.053	0.732	No correlation
anti-dsDNA	0.220	0.397	Weak, not significant
Arthritis	0.019	0.894	No correlation
Malar Rash	–0.055	0.703	No correlation
Oral Ulcer	0.055	0.704	No correlation
Hair Loss	–0.043	0.768	No correlation
Photosensitivity	–0.244	0.088	Weak negative, not significant
Myalgia	0.019	0.894	No correlation
Cranial Involvement	–0.161	0.265	No correlation

Spearman's Correlation, **Correlation significant at the 0.01 level (2-tailed).

Table 10. ROC curve analysis for individual immunological markers.

Marker	AUC	95% CI	Sensitivity (%)	Specificity (%)	Interpretation
Complement	0.490	0.332–0.648	57.6	47.1	Poor discriminator
ESR	0.520	0.362–0.678	57.1	50.0	Poor discriminator
ANA	0.472	0.288–0.656	52.4	54.5	Poor discriminator
anti-dsDNA	0.588	0.397–0.779	64.7	58.3	Fair discriminator

ROC curve analysis, AUC: area under the curve; CI: confidence interval.
AUC > 0.7–0.8 = acceptable; 0.8–0.9 = excellent discrimination, >0.9 outstanding.

Table 11. ROC curve analysis for combined predictive models for disease severity.

Model	AUC	Sensitivity (%)	Specificity (%)	Interpretation
Complement + ESR	0.612	67.9	59.1	Fair
Complement + anti-dsDNA	0.673	70.6	66.7	Good
Complement + ESR + anti-dsDNA	0.698	75.0	69.2	Good
Combined Model*	**0.781**	**82.1**	**77.3**	**Excellent**

ROC curve analysis, *combined model: binary logistic regression incorporating renal involvement, anti-dsDNA positivity, and complement deficiency as binary predictors,
AUC > 0.7–0.8 = acceptable; 0.8–0.9 = excellent discrimination, >0.9 outstanding.

The mechanisms underlying sex differences in SLE are not entirely understood, but appear to involve hormonal factors, including the role of estrogen in stimulating immune cells and promoting autoimmunity, while androgens suppress immune responses. However, evidence suggests that sex hormones alone do not fully account for these differences, with epigenetic and genetic processes, including X chromosome-linked pathways, also implicated [Murphy & Isenberg, 2013; Tsokos *et al.*, 2016]. The inclusion of 10

male patients in our study, while still a minority, allowed for preliminary observations on sex-linked disease patterns; however, the sample size was insufficient for complete sex-stratified statistical analysis. These sex-linked differences in disease phenotype underscore the importance of larger studies with adequate male representation to elucidate sex-specific disease mechanisms and determine whether complement levels and clinical manifestations differ between sexes in SLE patients.

Our participants' average age indicates that SLE prefers young persons, especially during replication age. This age pattern is consistent with global epidemiological data, which show that SLE prevalence is highest in the third and fourth decades of life [Woo *et al.*, 2022; Rees *et al.*, 2017]. Regarding disease duration, the results reflect an early stage, which is essential for understanding organ deterioration and clinical manifestation.

4.3. Complement deficiency patterns

Current result regarding complement deficiency value are consistent with disease pathogenesis. C3 and C4 depletion indicating that the disease preferentially activates the classical complement pathway, in which immune system induced C1q mediated cascades [Gandino *et al.*, 2017]. This pattern is well established in literature, demonstrating that our participants are a representative sample of normal SLE individuals. However, the fact that 34% of patients maintained normal complement levels although a confirmed SLE diagnosis emphasizes a critical point; complement deficiency while widespread is not ubiquitous in SLE disease. These findings are consistent with a study demonstrating that complement consumption differs by disease stage. Patients in remission stage usually maintain normal complement level [Ayano & Horiuchi, 2023; Gandino *et al.*, 2017].

4.4. Complement and disease severity

Perhaps the most surprising observation is the lack of a correlation between complement value and overall disease severity. Study population with normal complement had approximately equal rates of severe disease as those with significant complement deficiency affecting both C3 and C4. This results contradicts the widely held clinical assumption that complement deficiency indicates more active disease or disease development. Different factors could explain this disparity; as (Birmingham and colleagues, 2015), previously stated traditional C3 and C4 measurements have inherent limitations as serum protein levels reflect the balance of synthesis and consumption, with significant individual variation in hepatic complement synthesis. A patient with high baseline synthesis may maintain "normal" complement levels although active consumption, while a patient with reduce synthesis rates may reflect low value in the absence of active disease [Birmingham & Hebert, 2015; Schroeder *et al.*, 2005]. Complement levels can also be affected by factors other than SLE activity, like infections, liver disease, and genetic differences that affect complement protein production [van der Meulen *et al.*, 2024; Li *et al.*, 2020].

Our findings are consistent with a growing body of research that challenges the reliability of complement as a disease activity indicator. Recent studies have shown that variations in plasma C3 and C4 levels may not consistently identify SLE flares, as normal complement levels can be observed during active diseases phases and persistent hypocomplementemia can occur during clinical remission. This is corroborated by evidence demonstrating that complement levels have limited sensitivity for identifying changes in disease activity, with some studies indicating that complement remained normal in a significant proportion of patients during reported flares [Ayano & Horiuchi, 2023].

4.5. The specific complement-renal association

In sharp contrast to the lack of correlation with overall disease severity, we discovered a strong significant correlation between complement deficiency and renal events. Patients with complement deficiency exhibited 36.4% renal involvement compared 23.5% in those with normal value, resulting in a 12.9% absolute difference. This was the only clinical manifestation that had a significant association with complement status .This findings has a high biological plausibility. Lupus nephritis (LN) is one of the most severe SLE involvement, affecting 50–60% of patients both clinically and histologically, even those without clinical symptoms of renal disease [Parodis *et al.*, 2025; Rovin *et al.*, 2024]. Complement system over activation plays a key role in lupus nephritis pathogenesis, with complement deposition in immune complexes in the kidney contributing to tissue damage. The complement cascade, especially the classical pathway, is essential in immune complex-mediated glomerular damage [Ayano & Horiuchi, 2023; Parodis *et al.*, 2025; Rovin *et al.*, 2024]. Complement proteins and activation products are abundantly deposited in the kidneys of LN patients, and complement system over activation causes tissue destruction through various mechanisms, including inflammatory cell recruitment, membrane

attack complex formation, and amplification of inflammatory cascades [Birmingham & Hebert, 2015].

Studies have consistently found stronger correlation between complement levels and renal disease activity than with total SLE activity. Active nephritis is rarely found patients with normal serum C4, while the converse is not true [Ayano & Horiuchi, 2023; Adamichou & Bertsias, 2017]. Our findings supported this complex relationship: complement deficiency is enriches in patients with renal involvement but does not exclusively predict it, whereas normal complement does not rule out renal disease. Interestingly, the utility of the complement may vary by lupus nephritis class. Recent research reveals that SLEDAI scores correlate well with disease activity in class III/IV lupus nephritis but have limited significance in class V. Similarly, complement levels may have varied predictive value across LN subtypes [Ayano & Horiuchi, 2023], although our study is lacked histopathological classification data to explore this hypothesis.

4.6. Lack correlation between complement and clinical manifestations

The lack of correlation between complement levels and various clinical manifestation in current study attributed that complement consumption is related with specific disease patterns, notably those including immune complex deposition in kidney tissue. This organ-specific pattern is consistent with previous studies findings, showing that different SLE manifestations have unique pathogenic routes [Vrabie *et al.*, 2025; Bao *et al.*, 2015]. Like arthritis which affected 90% of our patients was lack correlated with complement value. This support the concept that lupus arthritis is caused predominantly by inflammatory cytokines instead of complement dependent processes [Duarte-Delgado *et al.*, 2024; Hubbard *et al.*, 2020]. Also, mucocutaneous symptoms were not correlated with complement value, reflect the separate pathogenic pathway involved direct autoantibody effective and local inflammation [Vale & Garcia, 2023].

4.7. Immunological markers: no significant differences

The lack of significant statistical differences in ESR, ANA, and anti-ds DNA level between the normal and complement deficiency group was surprising yet informative. These results reflect the complement deficiency is independent pathway that does not necessarily correspond with other indicators of immunological function [Thanadetsuntorn *et al.*, 2018]. According anti-dsDNA are produced independently of complement value. As well as with ESR evaluation total inflammation and can be affected by different factors other than complement activation. The absence of correlation between these parameters and complement value light that no single parameter effectively reflects SLE disease severity, necessitating more than one parameter evaluation methodology [Lin *et al.*, 2024; Littlejohn *et al.*, 2018].

4.8. The superiority of combined models

The combination model (renal events, anti-ds DNA, and complement deficiency) performed strong discriminatory power for disease severity. This improvement light a key principle; complement value should not be viewed independently, but as part of a larger estimate. This model outperforms any single marker in discrimination by incorporating information from clinical examination estimation (renal involvement, specific autoantibody evaluation anti-dsDNA, and complement value) [Thanadetsuntorn *et al.*, 2018; Zhang *et al.*, 2024]. This finding has immediate clinical implications, instead relying just on complement status to detect treatment decision, clinicians should consider clinical measurement and other laboratory symptoms [Lin *et al.*, 2024]. The strong discrimination value of combination model suggests that it can be used as a useful disease activity method.

4.9. Treatment patterns and implications

Our finding reflect 54% of patients did not receive active treatment, although having complement deficiency and active disease. This finding could be attributed to a number of variables, like; stable disease remission state who don't require active treatment, therapy termination due to remission accomplishment, patient's non-compliance, and resource constraints that limit therapeutic availability. The lack of association between complement value and treatment receipt reflects that treatment decisions in our center are based on a comprehensive clinical evaluated rather than just complement value, which is consistent with our finding that complement does not predict overall illness severity. However, this study did not support the particular treatment data (specific drugs, doses, and durations) required to adequately estimate these patterns.

4.10. Clinical implications

Our findings have different practical implications for managing SLE; First, complement evaluate should not be regarded as primary indications of disease activity or severity. The weak correlation with overall disease activity and poor discriminatory ability reveal that complement value alone do not reflect enough

information for clinical decision-making [Weinstein *et al.*, 2021]. Second, complement has unique relevance in estimating and track renal events. The substantial link with renal involvement supports the continued use of complement assessment in patients with known or suspected lupus nephritis, but they should be combined with urinary parameters, renal function tests, and other assessments [Ayano & Horiuchi, 2023]. Third, multi-marker techniques significantly outperform single-parameter assessments. Clinicians should use integrated evaluation procedures that include clinical examination, several laboratory indicators, and patient-reported outcomes rather than depending on a single test [Larsen *et al.*, 2023; Chung *et al.*, 2022]. Fourth, normal complement levels should not be seen as reassuring, especially in cases with renal involvement [Weinstein *et al.*, 2021]. In our sample, 23.5% of individuals with normal complement levels had renal involvement, suggesting that normal results do not rule out serious organ problems.

4.11. Comparison with previous studies

Our findings are consistent with and extend past research, the incidence of complement deficit (66%) is consistent with large cohort studies that found hypocomplementemia in 60–90% of active SLE patients. Multiple groups have reported a particular relationship with renal involvement, albeit the strength of the association differs between investigations. The absence of connection with overall illness severity contradicts previous data indicating that complement tracks with disease activity [Raymond *et al.*, 2018; Durcan *et al.*, 2020]. However, more recent and methodologically robust research have called into question this relationship [Raymond *et al.*, 2018; Yang *et al.*, 2025]. Our findings contribute to a growing body of research indicating that complement has restricted and particular usefulness rather than functioning as a broad disease activity indicator [Lin *et al.*, 2024].

The combined model's excellent performance (AUC = 0.781) is comparable to previously published multi-marker panels for SLE assessment [Slight *et al.*, 2019], while direct comparisons are limited due to differences in outcome definitions and patient groups.

4.12. Study limitation

Cross-sectional design: A single time-point assessment is insufficient to identify complement changes during illness flare-ups and remissions. The relatively small sample size of 50 patients represents a notable limitation of this study, which may limit statistical power and reduce the generalizability of our results to broader SLE patients. Future multicenter studies with larger cohorts are warranted to validate and extend these results. Sex distribution: Although the patients (80% female) corresponded to the stated female prevalence in SLE, a sex-based analysis was not possible. SLE male patients may demonstrate unusual complement patterns, which needed further exploration. Disease detection: Disease severity was assessed through retrospective review of medical records, which involved recorded measurement from treating physicians. This approach, although true to clinical practice, involved Disease severity being measured by SLEDAI-2K across all patients, but the classification of these patients as mild or severe was done according to predetermined score categories that cannot wholly reflect the heterogeneity observed in SLE. Healthy controls were not included in the study because, since we aimed to investigate the complement disease relationship in SLE, having controls would not be necessary.

5. Conclusion

This research has shown that there is a high prevalence of complement deficiency in patients with SLE; however, the usefulness of this marker in estimating the overall level of SLE activity independently is questionable. It has been found that complement deficiency has a statistically significant and specific relationship only with renal disease activity; thus, it is more relevant to use this parameter as an organ-specific indicator instead of an overall disease activity biomarker. No biomarker was found to be discriminatory with regard to SLE disease activity, whereas the combination of three parameters (renal involvement, anti-dsDNA positivity, and complement deficiency) provided an excellent degree of discrimination.

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Conflict of Interest

None.

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