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ORIGINAL ARTICLES

Disease activity in systemic lupus erythematosus in relation to direct Coombs test positivity without haemolytic anaemia: a single-centre cross-sectional study

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ABSTRACT

Background: The prevalence of Direct Coombs test (DCT) positivity in systemic lupus erythematosus (SLE) ranges from 12.8% to 65.2%. Approximately 5-11% of people with SLE have autoimmune haemolytic anaemia (AIHA), characterised by autoantibodies against erythrocytes that cause haemolysis. In about half of the SLE patients, DCT positivity occurs even in the absence of AIHA, likely due to immune complexes binding to red blood cells via complement receptor 1 (CR1), suggesting a higher immune complex load.
Objectives: To determine the DCT positive rate in SLE patients without AIHA and its association with disease activity, as measured by the SLE Disease Activity Index 2000 (SLEDAI-2K) score.
Methods: This descriptive cross-sectional study was conducted at a tertiary care centre in South India from March 2023 to March 2025. SLE patients who met the 2019 ACR/EULAR classification criteria without AIHA were included. Disease activity was measured using the SLEDAI-2K. The DCT was performed using the standard antihuman globulin, and a reaction grade of 1+ or higher was considered positive. The study compared DCT-positive and DCT-negative groups using statistical analysis.
Results: The study included 92 SLE patients, most of whom were female (97.8%), with a mean age of 35.1 ± 9.49 years, and a mean disease duration of 4.56 ± 4.36 years. DCT positivity without AIHA was found in 33.6% of the patients. DCT-positive patients had a higher median SLEDAI-2K score than DCT-negative patients (8 [IQR 3.5–10.5] vs 0 [IQR 0–5]; $p < 0.001$). DCT positivity was also strongly associated with arthritis ($p < 0.001$) and with higher anti-double-stranded DNA antibody levels ($p = 0.008$).
Conclusion: In individuals with SLE, DCT positivity without AIHA was common and was associated with higher contemporaneous disease activity, arthritis, and elevated anti-double-stranded DNA antibody levels. These findings suggest that DCT positivity may reflect increased immune activity at a single point in time. However, its utility in predicting future flares or monitoring longitudinal disease activity remains uncertain and requires prospective validation.

Keywords: Lupus, Antiglobulin test; Autoimmune hemolytic anaemia; Complement activation; Immune complexes; Autoantibodies.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disorder characterized by immune dysregulation, autoantibody production, and impaired clearance of immune complexes[1]. The global incidence of SLE ranges from 1.4 to 15.13 per 100,000 person-years, and approximately 0.40 million new cases are diagnosed annually, with a substantial effect on individual and health care burden[2]. The formation and tissue deposition of immune complexes, along with complement activation, play a central role in the pathogenesis of organ damage involving the kidneys, skin, joints, and nervous system[3–5].

Among the hematologic manifestations in SLE, Autoimmune haemolytic anaemia (AIHA) occurs in around 5-11% of people with SLE[6–8]. In patients with AIHA, the autoantibodies bind to erythrocytes, which causes haemolysis, and are associated with the Direct Coombs test (DCT) positivity in more than 90% of patients[9,10].

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DCT positivity is observed in a substantial proportion of SLE patients without clinical or laboratory evidence of hemolytic anaemia, and the reported prevalence of DCT positivity in SLE ranges from 12.8% to 65.2%[11,12]. In about half of the SLE patients, DCT positivity occurs even in the absence of AIHA, suggesting mechanisms distinct from classical AIHA. One such mechanism is immune complexes binding to red blood cells via complement receptor 1 (CR1), suggesting a higher immune complex load[13].

The binding of circulating immune complexes to erythrocytes via complement receptor 1 (CR1; CD35), which is abundantly expressed on red blood cells and is responsible for the clearance of approximately 85% of immune complexes from the circulation[14]. When immune complexes attach to CR1 on red blood cells, this can be seen as a positive result on the DCT even if there are no anti-erythrocyte antibodies. Unlike AIHA, DCT positivity due to immune complexes does not cause haemolysis but rather indicates a high level of circulating immune complexes[13].

Despite these observations, the clinical significance of DCT positivity in SLE patients without AIHA remains incompletely understood. In particular, its relationship with global disease activity has not been consistently explored. Therefore, the present study aimed to determine the frequency of DCT positivity in SLE patients without AIHA and to evaluate its association with disease activity as assessed by the SLE Disease Activity Index 2000 (SLEDAI-2K)[15].

MATERIALS AND METHODS

This descriptive cross-sectional study was carried out at a tertiary care hospital in South India from March 2023 to March 2025, with institutional ethics committee approval. All study participants provided written informed consent prior to enrolment.

Patients with SLE meeting the ACR/EULAR 2019 criteria[16], aged 18 to 60 years, who visited the Department of Clinical Immunology and Rheumatology, either as outpatients or inpatients, were included. Patients with haemolytic anaemia, defined as anaemia with laboratory evidence of increased red blood cell destruction, including elevated indirect bilirubin, high lactate dehydrogenase, and/or schistocytes on a peripheral blood smear were excluded.[17] Other exclusion criteria included a history of blood transfusion within the preceding month;[18] ongoing malignancies (haematological or solid tumours)[19], other autoimmune diseases, and the use of haemolytic drugs, such as methyldopa, second- or third-generation cephalosporins, or beta-lactamase inhibitors[20]. The sample size was calculated based on a reported prevalence of 5.8% for DCT positivity in patients with SLE without haemolytic anaemia, as described by Hanoka *et al.*[21] Using a 95% confidence interval, an absolute precision of 7%, and a 10% non-response rate, the final sample size, calculated using the formula as per the study by Daniel WW *et al.*,[22] was 92 patients.

Demographic information, disease duration, comorbidities, clinical characteristics, pertinent laboratory indicators, and treatment details were collected. The SLEDAI-2K score was used to assess disease activity at enrolment. For DCT testing, 3 mL of blood was collected in an EDTA anticoagulated tubes from each participant. Red blood cells were washed four times with saline to eliminate any unbound immunoglobulins and complement, after which polyspecific antihuman globulin reagent, which binds to both IgG (Immunoglobulin G) and C3 (complement 3) was added, and the sample was centrifuged. Agglutination was graded from 0 to 4+, with 1+ or higher considered DCT positive[23]. Quality control included regular equipment calibration, following standard procedures, and double-checking data entries. DCT positivity was analysed exclusively in patients without laboratory or clinical evidence of haemolytic anaemia and was compared with disease activity and individual SLEDAI-2K score components. Anti-dsDNA antibodies were measured by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's protocol. The results were recorded as a semi-quantitative variable. Values <100 IU/mL were considered negative, and ≥100 IU/mL as positive.

Statistical Analysis

Descriptive statistics were employed to summarize the baseline attributes. Categorical variables are presented as frequencies and percentages. Depending on the data, continuous variables are reported as means and standard deviations or medians with interquartile ranges. Categorical variables were compared using either the Chi-square test or Fisher's exact test. The Mann-Whitney U test was used. A two-tailed p-value of <0.05 was judged statistically significant. All statistical analyses were performed using SPSS version 26.

RESULTS

A total of 129 patients with SLE were screened; 9 were excluded due to AIHA, and 28 did not meet the inclusion or exclusion criteria or had incomplete data. The remaining 92 patients were included in the final analysis. The population studied was primarily female (90/92, 97.8%), with an average age of 35.10 ± 9.49 years. The median duration of the disease was 4.56 ± 4.36 years. Table I summarizes baseline demographics,

TABLE I. Baseline Demographic and Cumulative clinical characteristics of the study population (N=92)

Characteristics	Value
Demographic Characteristics	
Age (years), mean ± SD	35.10 ± 9.49
Female, n (%)	90 (97.8)
Disease duration (years), mean ± SD	4.56 ± 4.36
Comorbidities	
Any comorbidity, n (%)	42 (45.6)
Hypothyroidism, n (%)	27 (29.3)
Hypertension, n (%)	21 (22.8)
Diabetes mellitus, n (%)	9 (9.8)
Multimorbidity, n (%)	14 (15.2)
Cumulative Clinical Manifestations	
Mucocutaneous, n (%)	75 (81.5)
Arthritis, n (%)	71 (77.2)
Haematological, n (%)	62 (67.4)
Constitutional, n (%)	41 (44.6)
Renal involvement, n (%)	39 (42.4)
Neuropsychiatric manifestations, n (%)	13 (14.1)
Serositis, n (%)	18 (19.6)
Myositis, n (%)	7 (7.6)
Pregnancy morbidity†, n (%)	15 (16.3)
Antiphospholipid antibodies‡, n (%)	28 (30.4)
Lupus nephritis, Class III/IV ± V, n (%)	16 (64)
Lupus nephritis, Class V alone, n (%)	6 (24)
Lupus nephritis, Class II, n (%)	3 (12)
Current treatment profile	
Hydroxychloroquine, n (%)	84 (91.3)
Glucocorticoids (≤ 5mg/day), n (%)	65 (70.7)
Glucocorticoids (> 5mg/day), n (%)	9 (9.8)
Mycophenolate mofetil, n (%)	32 (34.7)
Methotrexate, n (%)	17 (18.5)
Tacrolimus, n (%)	16 (17.3)
Azathioprine, n (%)	14 (15.2)
Cyclophosphamide, n (%)	6 (6.5)
Rituximab, n (%)	2 (2.2)

†Pregnancy morbidity as defined by 2023 ACR/EULAR antiphospholipid syndrome classification criteria. ‡ Antiphospholipid antibodies include lupus anticoagulant, anticardiolipin, and anti-β2 glycoprotein I antibodies. Clinical manifestations represent cumulative manifestations since the time of diagnosis and are not limited to active disease at the time of assessment

comorbidities, organ system involvement, and current treatments.

Thirty-one patients (33.6%) had DCT positivity without AIHA. Patients with DCT positivity had significantly higher disease activity, with a median SLEDAI-2K score of 8 (IQR 3.5–10.5) compared with 0 (IQR 0–5) in DCT-negative patients ($p< 0.001$) (Table II).

Similarly, the clinical SLEDAI-2K score was significantly higher in DCT-positive patients compared to DCT-negative patients (median 8 vs 2, $p<0.001$). Additionally, a higher proportion of DCT-positive patients had a clinical SLEDAI-2K score higher than zero (clinical SLEDAI-2K >0, 87% vs 50.8%) (Table III).

Among individual SLEDAI-2K components, DCT positivity was significantly associated with arthritis (12% vs 4.3%, $p< 0.001$) and higher levels of anti-dsDNA antibodies (16.3% vs 14.1%, $p = 0.008$). No significant associations were observed with other clinical or laboratory components of the SLEDAI-2K (Table IV).

DISCUSSION

In this cross-sectional study, the DCT positivity was seen in 33.6% of patients with SLE who did not have hemolytic anaemia. When compared to DCT-negative patients, these patients showed noticeably more disease activity, as shown by higher SLEDAI-2K scores. This result provides evidence for the hypothesis that DCT positivity may indicate increased immune activity in SLE even in the absence of obvious hemolysis.

The incidence of DCT positive among SLE cohorts varies widely, from roughly 12.8% to 65.2%, according to previous studies[11,12]. Among DCT-positive patients, AIHA has been described in 38–78.6%, demonstrating that a considerable number of SLE patients demonstrate DCT positivity without clinical haemolysis[11,24,25]. Thus, the sensitivity of the tube agglutination method in the direct Coombs test for detecting AIHA is 43%, while the specificity is 83%[26]. In the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria, the DCT positivity without AIHA was incorporated as one of the immunological parameters. This inclusion improved the sensitivity and statistical performance of the criteria[27]. Nevertheless, prior studies mostly examined DCT positivity in relation to

TABLE II. Comparison of SLEDAI-2K scores between DCT-positive and DCT-negative in SLE patients

Parameters	DCT-positive (n=31)	DCT-negative (n=61)	p-value
SLEDAI score (Median, IQR)	8 (3.5, 10.5)	0 (0, 5)	<0.001

Values are expressed as median (interquartile range). Comparisons were performed using the Mann–Whitney U test. DCT: Direct Coombs test; SLE: Systemic Lupus Erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

TABLE III. Comparison of SLEDAI-2K scores between DCT-positive and DCT-negative in SLE patients

Parameters	DCT-positive (n=31)	DCT-negative (n=61)	p-value
Clinical SLEDAI-2K (Median, IQR)	8 (4, 12)	2 (0, 4)	<0.001
Clinical SLEDAI-2K > 0, n (%)	27 (87%)	31 (50.8%)	<0.001

Clinical SLEDAI-2K score after excluding laboratory components from the SLEDAI-2K score. Values are expressed as median (interquartile range). Comparisons were performed using the Mann–Whitney U test. DCT: Direct Coombs test; SLE: Systemic Lupus Erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000.

TABLE IV. Comparison of Individual SLEDAI-2K components between DCT-positive and DCT-negative in SLE patients

SLEDAI-2K component	DCT positive, n (%)	DCT negative, n (%)	*p* value
Arthritis	11 (12.0)	4 (4.3)	**<0.001**
Low complements (C3, C4)	8 (8.7)	11 (12.0)	0.384
Myositis	2 (2.2)	1 (1.1)	0.262
Neuropsychiatric involvement+	3 (3.3)	2 (2.2)	0.331
Visual disturbance	1 (1.1)	0 (0)	0.337
Serositis‡	1 (1.1)	0 (0)	0.337
Mucosal ulcers	2 (2.2)	4 (4.3)	1.000
Fever	2 (2.2)	1 (1.1)	0.262
Leukopenia	7 (7.6)	8 (8.7)	0.245
Renal activity§	8 (8.7)	11 (12.0)	0.384
Vasculitis	0 (0)	3 (3.3)	0.548
New Rash	6 (6.5)	5 (5.4)	0.173
Positive dsDNA titers	15 (16.3)	13 (14.1)	**0.008**
Thrombocytopenia	5 (5.4)	6 (6.5)	0.498

Values are expressed as number (%). Comparisons were performed using Fischer's exact test or Chi-square test, as appropriate. Anti-dsDNA was analysed as a categorical variable (positive vs negative) based on semi-quantitative reporting.
+ Neuropsychiatric involvement includes seizure or psychosis as defined by SLEDAI-2K
‡ Serositis includes pleuritis or pericarditis.
§ Renal activity defined as proteinuria >500 mg/24 h and/or active urinary sediment (casts, hematuria, or pyuria).
DCT: Direct Coombs test; SLE: Systemic Lupus Erythematosus, SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; dsDNA: double-stranded DNA; C3/C4: complement components.

AIHA, with relatively little assessment of its importance in individuals without hemolytic anaemia[11,12,28].

DCT or direct antiglobulin test utilizes anti-human globulin to induce a visible agglutination reaction in the presence of complement or antibodies attaching to red blood cell membranes[23]. There are three forms of anti-human reagents, which are poly-specific, which binds to both IgG and C3, and monospecific, which binds to either IgG or C3. In this study we used poly-specific serum and conventional tube agglutination method. Other methods include gel test, flow cytometry, which can be performed by automated systems[29].

Abou Assalie *et al.* observed DCT positivity in approximately 20% of SLE patients, of whom only 38% had AIHA[30]. Patients with AIHA were more likely to have neuropsychiatric and renal symptoms in that cohort, but the health consequences of isolated DCT positivity were not thoroughly investigated. Earlier investigations by Edwards *et al.*, Dohlstrom *et al.*, and Isenberg *et al.*, similarly confirmed DCT positivity in SLE at rates of 65.2%, 50%, and 20%, respectively, but did not specifically examine disease activity or stratify patients by the presence of haemolytic anaemia[12,31,32].

Mendes IC *et al.*, observed clinical and laboratory profile of DCT positive patients, among the subgroup of SLE patients, 77.2% had DCT positivity without AIHA[24]. Similarly, Kerkar AS *et al.*, and Worlledge SM *et al.*, observed 41.9% and 44.4% DCT positivity, respectively, without AIHA in the SLE patients[28,33]. According to Skare *et al.*, 12.8% of SLE patients had DCT positive, and around half of them did not have AIHA. AIHA, anti-RNP, and anti-La antibodies were independently linked to DCT positivity in multivariate analysis; however, DCT positivity in the absence of hemolytic

anaemia was not independently evaluated in relation to disease activity[11]. Hanaoka *et al.* performed a more targeted assessment, focusing on SLE patients who tested positive for DCT without hemolytic anaemia. Significant correlations with increased anti-dsDNA titers, hypocomplementemia, lower renal response to treatment, and higher SLEDAI scores were seen in that study[21]. The current results support the idea that DCT positivity may reflect enhanced immune complex formation and complement activation rather than erythrocyte destruction alone, especially the correlation between DCT positivity and increased disease activity[13,14,34].

Interestingly, our research revealed a strong correlation between arthritis and DCT positivity, a finding not consistently reported in other studies[11,21]. During periods of high disease activity, this finding might result from enhanced immune complex deposition or Fc receptor-mediated inflammation within the synovial tissues. This connection is biologically plausible based on experimental studies showing that IgG deposition induces arthritis in lupus, but clinical confirmation necessitates validation in larger, longitudinal cohorts[35].

Differences in disease activity at enrollment, disease duration, ethnic or regional variables, and study design may be contributing factors to the increased prevalence of DCT positivity without hemolytic anaemia found in our study compared with certain previously reported results[11,21]. Disease activity has been demonstrated to impact complement receptor expression on erythrocytes and immune complex load, which may significantly affect DCT outcomes across cohorts[13,14,34].

There are several limitations to this study. Assessing temporal or causal links between DCT positivity and disease activity is not possible given the cross-sectional design. A deeper understanding of alterations in immune activity over time may be possible with serial DCT data. Furthermore, the study's single-center design may have limited its generalizability. Long-term renal outcomes and complement functional assays, such as CH50, were not assessed, which could have further elucidated the prognostic implications of isolated DCT positivity.

In conclusion, among individuals with SLE, DCT positivity in the absence of AIHA was relatively common and was significantly associated with higher anti-dsDNA antibody levels, arthritis, and increased disease activity in our study. However, its role as a longitudinal biomarker remains uncertain. Further prospective studies are required to evaluate temporal changes in DCT status and to determine its association with disease activity.

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