Volume 3, Issue 7, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

HEMATOLOGICAL MANIFESTATION OF JUVENILE ONSET LUPUS ERYTHROMATOSUS IN TERTIARY CARE HOSPITAL

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DOI: https://doi.org/10.5281/zenodo.17522881

Keywords
Juvenile-onset lupus, Hematological manifestations, Anemia, Thrombocytopenia, Cytopenia

Article History
Received: 10 July 2025
Accepted: 26 August 2025
Published: 02 September 2025

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Abstract

Background: Juvenile-onset systemic lupus erythematosus (JSLE) is a multisystem autoimmune disease with significant hematological involvement. Objective: This study aimed to determine the frequency and spectrum of hematological manifestations in children diagnosed with JSLE in a tertiary care hospital in Pakistan. Methodology: This cross-sectional study was conducted at the Department of Pediatric Medicine, The University of Child Health and The Children's Hospital, Lahore, from March 2025 to June 2025. A total of 116 children aged 1–12 years with confirmed JSLE were enrolled through non-probability consecutive sampling. Demographic, clinical, and hematologic data were collected, including complete blood count, reticulocyte count, ferritin, complement levels, and anti-dsDNA antibodies. Results: Among 116 patients, the mean age was 9.1 ± 2.8 years, with a female predominance (75%). The mean disease duration was 11.3 ± 6.7 months. Hematologic manifestations were observed in 92 (79.3%) patients. Anemia was the most common finding (78.4%), followed by leukopenia (34.5%), lymphopenia (27.6%), thrombocytopenia (18.1%), and pancytopenia (6.0%). Iron deficiency anemia (42.2%) and autoimmune hemolytic anemia (14.7%) were the leading subtypes. Low complement levels (C3, C4) and positive anti-dsDNA were significantly associated with cytopenias ($p < 0.05$). Infection and disease flare were the most frequent triggers. Conclusion: Hematologic abnormalities are highly prevalent in juvenile-onset lupus and closely linked with disease activity. Anemia and thrombocytopenia remain the most frequent manifestations in Pakistani children.

INTRODUCTION

Juvenile-onset systemic lupus erythematosus (JSLE) is a chronic, multisystem autoimmune disorder characterized by loss of immune tolerance and production of pathogenic autoantibodies against nuclear and cytoplasmic antigens. Hematologic abnormalities are among the most frequent clinical manifestations of JSLE and often represent the initial presentation before the diagnosis is established. These abnormalities reflect immune-mediated destruction or bone marrow suppression and can serve as important indicators of disease activity and prognosis. Lupus is a chronic, autoimmune multisystem inflammatory disease that is associated with sizable morbidity and mortality [1]. When lupus commences in an individual less than 18 years of age, it is commonly referred to as childhood-onset systemic lupus erythematous (cSLE) [2]. With a reported incidence of 0.3-0.9 per 100 000

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ISSN: (e) 3007-1607 (p) 3007-1593

children per year, and a prevalence of 3.3-24 per 100 000 children, cSLE is rare [3]. About 10%-20% of all patients with SLE are diagnosed during childhood. Typically, cSLE has a more severe clinical course than that seen in adults, with a higher prevalence of lupus nephritis, hematologic anomalies, photosensitivity, neuropsychiatric, and mucocutaneous involvement [4].

Consistent with adult-onset disease, cSLE has a strong female preponderance; the female to male ratio is at 4:3 and 4:1 for disease onset in the first and second decades of life, respectively. The etiology of cSLE is multifactorial, involving genetic risk factors, epigenetic mechanisms, and environmental triggers [5]. SLE is thought to constitute a loss of tolerance in a genetically susceptible individual with progression to autoimmunity that is triggered by various environmental factors and infections [6]. Hematological abnormalities are frequently encountered in patients with SLE and are part of American Rheumatological Association Criteria for classifying the disease [7]. Anemia is the most common hematological abnormality seen in SLE, Autoimmune hemolytic anemia occurs in approximately 5-10% of SLE patients and it responds well to corticosteroid treatments. Neutropenia is relatively common and has been related to an increased risk of infection in patients with SLE. Although thrombocytopenia caused by peripheral immune destruction is common in SLE (20-40%), severe thrombocytopenia is comparatively rare (~5%). It is now recognized that lymphopenia is one of the most common hematological findings in SLE [8]. A study by Rouf MA et al. reported hematological manifestations anemia was the most common hematological abnormality detected (57.5%). Iron deficiency anemia (IDA) 60%, anemia of chronic disease (ACD) 26.9% and autoimmune hemolytic anemia (AIHA) 8.7 % were the most common cause of anemia detected [9]. Shamim et al. (2020) reported in children with juvenile-onset systemic lupus erythematosus (c-SLE), anemia was observed in 52.2% of cases, leukopenia in 13.0%, and thrombocytopenia in 13.0%. Additionally, proteinuria was present in 26.1% of the patients, hematuria in 8.7%, pyuria in 26.1%, and elevated ESR in 78.3% of the cases [10]. Sufian et al. (2017) reported that hematological manifestations among them anemia was most frequent in 77.5% patients followed by neutropenia (19.1%), lymphopenia (17.9%), thrombocytopenia (17.9%), autoimmune hemolytic anemia (AIHA) in 10.1% and pancytopenia in 5.6% patients [11]. Juvenile-onset systemic lupus erythematosus (c-SLE) is a significant health concern in pediatric populations due to its potential for severe hematological complications, yet there is limited data specifically addressing these manifestations in children within Pakistan. This study aims to fill this gap by systematically evaluating the hematological abnormalities such as anemia, leukopenia, lymphopenia, and thrombocytopenia in children with c-SLE.

Objective

To determine the frequency of hematological manifestations among childhood-onset systemic lupus erythematous patients.

Methodology

This Cross-sectional study was conducted at Department of Pediatric Medicine, The University of Child Health and the Children's Hospital, Lahore from March 2025 to June 2025. Data were collected through non-probability consecutive sampling technique. A total of **116 cases** were included in the study, taking a **95% confidence level, 7% margin of error**, and **expected percentage of thrombocytopenia as 17.9% [10].**

Inclusion Criteria:

- Children aged 1 to 12 years
- Both genders
- Diagnosed cases of juvenile-onset lupus erythematosus

Exclusion Criteria:

- Neonatal lupus and drug-induced lupus
- Syndromic children
- Parents or guardians refusing consent
- Patients lost to follow-up

Data Collection

After approval from the Institutional Ethical Review Board, this study was carried out in the Department of Pediatric Medicine. Patients meeting the inclusion and exclusion criteria

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ISSN: (e) 3007-1607 (p) 3007-1593

were enrolled after obtaining informed written consent from their parents or guardians. The diagnosis of juvenile-onset systemic lupus erythematosus (JSLE) was established based on defined operational and clinical criteria. Demographic data such as age, gender, and weight were recorded for all participants. Detailed hematological assessments were performed to identify specific manifestations. Blood samples were collected and analyzed in the hospital's central laboratory using standardized protocols. Tests included complete blood counts, reticulocyte counts, ferritin levels, and other relevant hematological investigations. Strict quality control measures were followed to ensure accuracy and reliability of results. To minimize bias, all tests were conducted within the same laboratory. Confounding variables were controlled through the exclusion criteria.

Data Analysis

All collected data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 25. Quantitative variables such as age, weight, hemoglobin levels, and disease duration were presented as mean ± standard deviation (SD). Qualitative variables, including gender, presence of JSLE, and hematologic manifestations such as iron deficiency anemia, hemolytic anemia, pancytopenia, leukopenia, lymphopenia, and thrombocytopenia, were expressed as frequencies and percentages. Data were stratified based on age, gender, disease duration, hemoglobin level, and weight to assess potential effect modifiers. The post-stratification chi-square test was applied to evaluate statistical associations, and a p-value ≤ 0.05 was considered statistically significant.

Results

Data were collected from 116 patients, mean age of participants was 9.1 ± 2.8 years, and most were female, accounting for 75% of the sample. The mean disease duration was 11.3 ± 6.7 months, and the mean body weight was 26.5 ± 6.9 kg. The mean hemoglobin level was 10.1 ± 1.8 g/dL, indicating that anemia was common among the participants. The most frequently reported symptoms included fatigue in 76% of cases and pallor in 72%, followed by fever in 55%, arthralgia in 61%, and photosensitivity in 43%. Lymphadenopathy was present in 38%, hepatosplenomegaly in 29%, and bleeding tendencies in 18%, reflecting widespread systemic and hematologic involvement in juvenile-onset lupus patients.

Table 1. Baseline Demographic and Clinical Characteristics of Study Population (n = 116)

Variable	n (%) / Mean ± SD
Age (years)	9.1 ± 2.8
Gender	
Male	29 (25%)
Female	87 (75%)
Duration of disease (months)	11.3 ± 6.7
Weight (kg)	26.5 ± 6.9
Mean Hemoglobin (g/dL)	10.1 ± 1.8
Common Symptoms	
Fatigue	88 (76%)
Pallor	84 (72%)
Fever	64 (55%)
Lymphadenopathy	44 (38%)
Bleeding tendencies	21 (18%)
Hepatosplenomegaly (HSM)	34 (29%)
Arthralgia	71 (61%)
Oral ulcers	39 (34%)
Photosensitivity	50 (43%)

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Hematologic manifestations were found in the majority of cases, with anemia being the most frequent abnormality (78.4%). Among anemic patients, iron deficiency anemia accounted for 42.2%, autoimmune hemolytic anemia for 14.7%, and anemia of chronic disease for 21.5%. Other abnormalities included leukopenia in 34.5%, lymphopenia in 27.6%, and thrombocytopenia in 18.1% of cases. Pancytopenia was less frequent, observed in 6% of patients, while thrombotic microangiopathy and macrophage activation syndrome or hemophagocytic lymphohistiocytosis were rare, occurring in 2.6% and 3.4% respectively

Table 2. Spectrum and Severity of Hematological Manifestations in JSLE Patients (n = 116)

Hematological Manifestations	**n** (%)
Anemia (total)	91 (78.4%)
• Iron Deficiency Anemia	49 (42.2%)
• Autoimmune Hemolytic Anemia (AIHA)	17 (14.7%)
• Anemia of Chronic Disease	25 (21.5%)
Leukopenia	40 (34.5%)
Lymphopenia	32 (27.6%)
Thrombocytopenia	21 (18.1%)
Pancytopenia	7 (6.0%)
Thrombotic Microangiopathy (TMA)	3 (2.6%)
MAS/HLH	4 (3.4%)
Severity of Cytopenia	
Mild	37 (32%)
Moderate	41 (35%)
Severe	14 (12%)

The average hemoglobin level was 10.1 ± 1.8 g/dL, and the mean white blood cell count was 4,200 ± 1,050 per microliter, while platelet counts averaged 148,000 ± 58,000 per microliter, indicating mild thrombocytopenia in some cases. Reticulocyte counts were elevated (2.4 ± 1.1%), along with increased LDH levels (520 ± 140 U/L) and bilirubin (1.7 ± 0.6 mg/dL), consistent with hemolysis. The direct antiglobulin test was positive in 9.5% of cases. Complement levels were reduced, with mean C3 and C4 values of 56 ± 21 mg/dL and 11 ± 5 mg/dL respectively, and anti-dsDNA antibodies were positive in 75.8% of patients, reflecting active disease. Peripheral smear examination showed normocytic patterns in 39.6%, microcytic hypochromic features in 31%, schistocytes in 8%, and spherocytes in 6%.

Table 3. Key Laboratory Findings in Patients with Hematologic Manifestations

Parameter	**Mean ± SD / n**(%)
Hemoglobin (g/dL)	10.1 ± 1.8
WBC (/µL)	4,200 ± 1,050
Platelets (/µL)	148,000 ± 58,000
Reticulocyte count (%)	2.4 ± 1.1
Direct Antiglobulin Test (DAT)	Positive in 11 (9.5%)
LDH (U/L)	520 ± 140
Bilirubin (mg/dL)	1.7 ± 0.6
C3 (mg/dL)	56 ± 21
C4 (mg/dL)	11 ± 5
Anti-dsDNA	Positive in 88 (75.8%)
Peripheral smear – Normocytic	46 (39.6%)
Peripheral smear – Microcytic hypochromic	36 (31%)

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Schistocytes present	9 (8%)
Spherocytes present	7 (6%)
Bone marrow examination done	18 (15.5%)
• Erythroid hyperplasia	9 (7.7%)
• Hypocellular marrow	4 (3.4%)
• Hemophagocytosis	3 (2.6%)

Infections were the most common triggers of hematologic events, occurring in 14.6% of patients, followed by disease flare without an external trigger in 20.6%, new drug exposure in 5.2%, and post-vaccination events in 1.7%. Corticosteroids were the main therapeutic agents used, with 37% receiving intravenous methylprednisolone and 63% on oral prednisolone. Immunosuppressants such as azathioprine and mycophenolate mofetil were prescribed in 33.6% and 29.3% of cases, while cyclophosphamide was used in 13.8%, rituximab in 6.9%, and IVIG in 7.8%. Blood transfusions were required in 19% of patients, with an average of 1.6 units transfused. Following treatment, 52.6% of patients achieved complete remission, 25% had partial response, 10.3% showed no improvement, and 12% experienced relapse. After an average follow-up of 10.8 ± 5.3 months, 76.7% of patients were alive in remission, 17.2% had active disease, and 6% died, primarily due to sepsis, macrophage activation syndrome, or multi-organ failure.

Table 4. Triggers, Management, and Outcomes (n = 116)

Parameter	**n (%) / Mean ± SD**
Triggers	
Infection	17 (14.6%)
New Drug Exposure	6 (5.2%)
Post-vaccination	2 (1.7%)
Lupus Flare (No external trigger)	24 (20.6%)
Treatment Modalities	
IV Methylprednisolone	43 (37%)
Oral Prednisolone	73 (63%)
Azathioprine (AZA)	39 (33.6%)
Mycophenolate mofetil (MMF)	34 (29.3%)
Cyclophosphamide (CYC)	16 (13.8%)
Rituximab (RTX)	8 (6.9%)
Intravenous Immunoglobulin (IVIG)	9 (7.8%)
Transfusion Required	22 (19%)
Mean Units Transfused	1.6 ± 0.7
Treatment Outcome	
Complete Response	61 (52.6%)
Partial Response	29 (25%)
No Response	12 (10.3%)
Relapse	14 (12%)
Follow-up Duration (months)	10.8 ± 5.3
Final Status	
Alive – Remission	89 (76.7%)
Active Disease	20 (17.2%)
Died	7 (6%)
Causes of Death	Sepsis (3), MAS (2), Multi-organ failure (2)

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Patients with hematologic involvement had a longer mean disease duration of 12.5 ± 7.1 months compared to 8.1 ± 4.8 months in those without abnormalities, a statistically significant difference. Fever at presentation was more common among patients with cytopenias (60.9%) than those without (33.3%). Significant laboratory associations included low complement levels, elevated LDH, and raised bilirubin, all indicating increased disease activity and hemolysis. Low C3 and C4 were observed in 77.2% and 67.4% of patients with hematologic abnormalities compared to 41.7% and 33.3% of those without, respectively. Elevated LDH and bilirubin were also strongly correlated with cytopenias, while renal involvement was more frequent among affected patients (53.3% versus 29.2%).

Table 5. Association Between Hematological Manifestations and Clinical/Laboratory Parameters in JSLE (n = 116)

Parameter	With Hematologic Abnormality (n = 92)	Without Hematologic Abnormality (n = 24)	p-value
Mean Age (years)	9.4 ± 2.6	8.7 ± 3.1	0.26
Gender			
Female	70 (76.1%)	17 (70.8%)	0.58
Male	22 (23.9%)	7 (29.2%)	
Mean Duration of Disease (months)	12.5 ± 7.1	8.1 ± 4.8	0.04*
Fever at Presentation	56 (60.9%)	8 (33.3%)	0.03*
Hepatosplenomegaly (HSM)	30 (32.6%)	4 (16.7%)	0.12
Arthralgia	59 (64.1%)	12 (50%)	0.23
Photosensitivity	43 (46.7%)	7 (29.2%)	0.15
Anti-dsDNA Positive	73 (79.3%)	15 (62.5%)	0.09
Low C3 (<90 mg/dL)	71 (77.2%)	10 (41.7%)	0.01*
Low C4 (<10 mg/dL)	62 (67.4%)	8 (33.3%)	0.02*
Elevated LDH (>250 U/L)	69 (75%)	6 (25%)	<0.001*
Raised Bilirubin (>1.2 mg/dL)	54 (58.7%)	5 (20.8%)	0.002*
Presence of Schistocytes / Spherocytes	14 (15.2%)	0	0.04*
Renal Involvement (Lupus Nephritis)	49 (53.3%)	7 (29.2%)	0.05*
Neurological Involvement	13 (14.1%)	3 (12.5%)	0.84

*Significant at $p \leq 0.05$

Discussion

The objective of this study was the assessment of the range and frequency of hematologic expression of juvenile-onset systemic lupus erythematosus (JSLE) in patients who present to a tertiary care pediatric facility in Lahore, Pakistan. The results showed that hematologic abnormalities were very frequent and were present in about 79 percent of cases with anemia and thrombocytopenia being the most common. These findings agree with the international and regional research, highlighting that hematologic involvement is among the initial and most common systemic

manifestations in pediatric lupus. We found anemia in 78.4% of our cohort, which was not a low result in comparison to the Indian and Egyptian studies which found anemia prevalence to be between 70 and 85 percent [12]. Iron deficiency anemia (42%) prevails as a manifestation of the combined nutritional anemia and chronic inflammation that is observed in developing nations. Autoimmune hemolytic anemia (AIHA), which is found in approximately 15 percent of the cases, is

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ISSN: (e) 3007-1607 (p) 3007-1593

consistent with the results of Rouf MA et al., who found 17.9 percent in a comparable cohort of Pakistan. The prevalence of anemia of chronic disease (21.5) is an additional indication of the current inflammatory microclimate and cytokine imbalance that is typical of the activity of lupus [13].

Other frequent abnormalities were leukopenia (34.5%) and lymphopenia (27.6) and were mostly autoantibody mediated autoantigens of leukocytes and complement. Similar findings have been documented by Abdwani et al. (Oman, 2015) and Bader-Meunier et al. (France, 2008), as in 30-40% of pediatric cases of lupus, leukopenia was present. These results emphasize that JSLE is frequently followed by a combination of cytopenias as a result of generalized immune dysregulation and not a solitary hematologic flaw [14]. Thrombocytopenia was identified in 18.1% of patients, which compares to South Asian cohort reports (15-20) but is less than some Western studies which report rates as high as 25%. This disparity can be based on differences in the genetic predisposition, environmental stimuli, and access to health care in the region. Thrombocytopenia was mild and moderate in majority of our cases with only 12percent of the cases having severe cytopenias. This variability indicates variation in disease identification and times of referral. Pancytopenia was less prevalent (6 percent) but usually linked to end stage disease or macrophage activation syndrome (MAS), yet it occurred in 3.4 percent of the patients [15].

It was also revealed in the analysis that hematological abnormalities were more common among patients whose disease duration was long, whose complement levels are low, and whose anti-dsDNA antibodies were positive. These relationships support the idea that cytopenias can be parallel to disease activity and can be used as an early predictor of flares [16]. Patients with lupus had high LDH and bilirubin levels, which were also associated with the active hemolysis process, as it was demonstrated by Yeo et al. (Singapore, 2017), who also highlighted the importance of hemolytic indices in lupus monitoring. Mortality (6%) in our study was predominantly due to infection and MAS-both known fatal complications of JSLE with hematologic involvement [17]. Comparatively, our findings reaffirm that hematologic abnormalities in juvenile lupus are not only diagnostic but also prognostic. They can precede systemic manifestations and help clinicians anticipate flares, monitor therapy, and assess prognosis. In resource-limited settings like Pakistan, where diagnostic delays are common, early recognition of cytopenias through routine complete blood counts can significantly aid early diagnosis and improve survival [18-20].

Limitations of the study include its single-center cross-sectional design, which restricts the ability to establish causality or temporal trends between disease activity and hematologic changes. Moreover, advanced immunological assays (e.g., antiphospholipid antibody profiles, bone marrow flow cytometry) were not available for all patients, which may have led to underestimation of some specific etiologies like TMA or aplastic anemia. Despite these limitations, the relatively large sample size and detailed laboratory correlation strengthen the reliability of the findings.

Conclusion

It is concluded that hematological abnormalities are highly prevalent among patients with juvenile-onset systemic lupus erythematosus, representing a major component of disease morbidity in the pediatric population. In this study, nearly four out of five children exhibited at least one hematologic manifestation, with anemia and thrombocytopenia being the most common findings. These abnormalities were frequently associated with longer disease duration, elevated anti-dsDNA titers, low complement levels, and markers of active inflammation, underscoring their close relationship with lupus disease activity.

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Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

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