

## Original Research Article

# Aetiology and outcome of anemia in patients with systemic lupus erythematosus

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### ABSTRACT

**Background:** Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder that is greatly subject to the combined effect of genetic, environmental, demographic and geographical factors. Hematological manifestations are very common in SLE, with many patients presenting with anemia. The cause of Anemia could be varied, with Autoimmune hemolytic anemia, anemia of chronic disease, iron deficiency being the common causes. The aim of the present study was to estimate the proportion of patients with prevalence of different causes of anemia in SLE and its association between immunological and clinical parameters and to correlate the severity of anemia with SLEDAI score and SLICC/ACR score.

**Methods:** This was an observational and prospective study conducted on 52 patients satisfying ACR criteria for SLE and WHO definition of anemia. All patients underwent baseline investigations for hematological, biochemical parameters and immunological investigations for C3 and C4. Other special investigations were done as per the treating rheumatologists' opinion. Patients were followed up after three months to evaluate the response to therapy.

**Results:** In this study, most of the patients were in the age group between 20-50 years (94.22%) and female:male ratio was 13:1. At presentation 55.76% patients had severe anemia, 38.46% had moderate anemia and 5.78% had mild anemia. After therapy (three months) only 3.84% patients had severe anemia. The most common cause of anemia was AIHA (38.46%). Mean SLEDAI score at presentation was >20 but after three months therapy the score was reduced to 4. There was no correlation between anaemia and SLICC/ACR damage index.

**Conclusions:** Anaemia usually occurs at the onset of SLE and its recurrence rate will become low after three months of therapy. SLEDAI scores, SLICC/ACR damage index and serum complement levels (C3 and C4) acts as good indices for assessment and follow up of SLE.

**Keywords:** Anemia, Systemic lupus erythematosus, SLEDAI scores, SLICC/ACR damage index, Serum complement levels

### INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder, which most often affects the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. The course of the disease is unpredictable, with flares alternating with remissions. SLE is one of several diseases known as "the great imitators" because it often mimics or is mistaken for

other illnesses. Hematological manifestations of SLE are diverse and often they are the presenting manifestations of the disease.<sup>1-3</sup> The major hematologic manifestations of SLE are anemia, leukopenia, thrombocytopenia, and the antiphospholipid antibody syndrome (APLAS). It has been observed since the last two decades that many cases of SLE present with hematological abnormalities alone, without features of musculoskeletal, skin, or other system involvement.<sup>1</sup> In some of these cases presenting with

anemia, thrombocytopenia, pancytopenia, or thrombotic episodes, especially so in young females, the diagnosis may be delayed or initially missed if the index of suspicion is low or if there is improper and inadequate follow up.<sup>1</sup> Many cases which present initially with manifestations due to involvement of any one tissue or organ alone (autoimmune hemolytic anemia, lupus nephritis etc.) and some cases which are ANA negative do not satisfy the ACR criteria initially but do so on follow up. In most of these cases empirical treatment could be started, to the advantage of the patient, if there is any evidence of an autoimmune phenomenon, after ruling out other differential diagnoses. In such cases response to treatment or the development of other features of the disease on follow up confirms the diagnosis of SLE.

Hematological manifestations affecting one or more blood cell lineage are frequent in SLE and anemia is most common finding. Most studies have however examined hemolytic anemia.

Association of specific causes of anemia with specific immunological and clinical manifestations of SLE and their progress is well known from adequately sized studies. There are not many studies on association between severity of anemia and disease activity and damage index.

This study was conducted to estimate the proportion of patients with prevalence of different causes of anemia in SLE and its association between immunological and clinical parameters and to study correlation between severity of anemia and disease activity by (SLEDAI) score and to correlate severity of anemia with damage index by (SLICC/ACR) score.

## METHODS

Design of this study was an observational and prospective study, conducted in a major tertiary care hospital and Rheumatology clinic, Mumbai between January 2014 to January 2015. After obtaining institutional review board permission and written informed consent of patient (or guardian) who fulfill inclusion and exclusion criterion, subjects were recruited over the period of one year.

The sample size n and margin of error E are given by:

$$n = \frac{Z^2 \cdot r(100-r)}{E^2} \cdot \frac{N}{N-1}$$

$$E = \text{Sqrt} \left[ \frac{(N-n)x}{n(N-1)} \right]$$

where N is the population size, r is the fraction of response, and Z (c/100) is the critical value for the confidence level c.

N is 60 in the present study as per indoor registry of the tertiary care center, r is 50%, c is 95%.

Using the above formula, the sample size of the present study was estimated as 52.

Detail physical examination including general and systemic examination was carried out and entered in the Proforma. All patients underwent baseline investigations for hematological and biochemical parameters. Immunological investigations for C3 and C4 were done. Other special investigations were done according to clinical indication.

### Inclusion criteria

- Age 12 years or more
- Patients satisfying ACR criteria for SLE
- Patients satisfying WHO definition of anemia, For Male  $\leq 13$  gms% and for female  $\leq 12$  gms%
- Patients willing to give consent.

### Exclusion criteria

- Hemoglobinopathies
- Overlap syndromes OR mixed connective tissue disorders
- Infections
- Pregnancy.

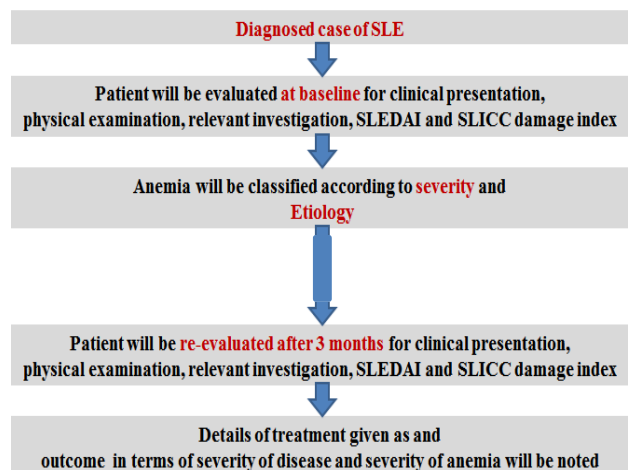


Figure 1: Study protocol.

After obtaining permission from institutional review board and written informed consent from the patients all the detailed information was entered in the proforma, 52 subjects were selected for the study.

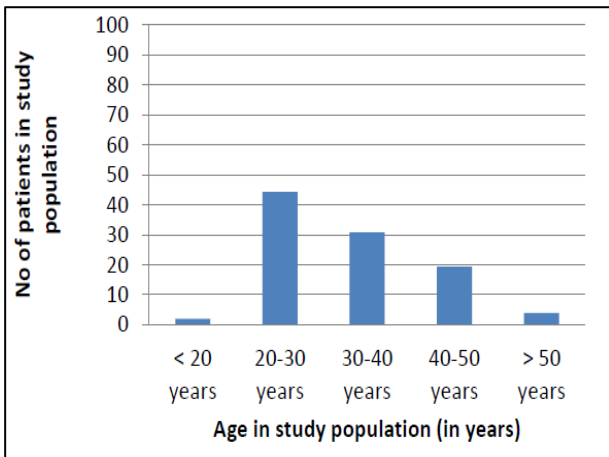
Comprehensive clinical examination including brief physical examination and systemic examination was carried out. Routine and special investigations available with these patients were entered in the Proforma. No special investigation was requested merely for the purpose of this study. All the investigations and treatment modalities were as per the discretion of treating rheumatologist.

**Statistical analysis**

All data collected was presented in mean and percentages. Data of immunological parameters, SLEDAI and SLICC/ACR SLE damage index were analysed using Chi-square test. A p value of <0.05 was considered significant.

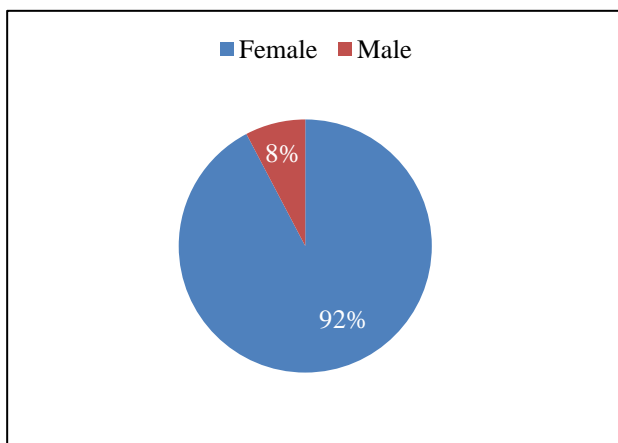
**RESULTS**

The reports of 52 subjects selected for the study were collected. The demographic data of the subjects are presented in Table 1. The result suggests that most of the patients were in the age group between 20-50 years (94.22%) and Female:Male= 13:1.



**Figure 2: Age distribution in study.**

Table 1 shows the clinical manifestations of study population and most common clinical manifestation were constitutional and hematological symptoms followed by mucocutaneous symptoms.



**Figure 3: Distribution of study population as per gender (n=52).**

Some hematological parameters are presented in Table 2. At presentation 55.76% patients had severe anemia

and 5.78% had mild anemia. After therapy (three months) only 3.84% patients had severe anemia. 21.11% patients had thrombocytopenia and after therapy no one had thrombocytopenia. At presentation 93.34% patients had raised ESR and at three months 71.11% had normal ESR.

**Table 1: Clinical manifestations of study population at presentation and at three months (n=52).**

Symptoms	At presentation	At 3 months
Constitutional	52 (100%)	4 (7.69%)
Musculoskeletal	47 (90.38%)	1 (1.92%)
Renal	41 (78.84%)	3 (5.76%)
Gastrointestinal	5 (9.61%)	1 (1.98%)
Neurological	22 (42.30%)	1 (1.98%)
Mucocutaneous	48 (92.30%)	4 (7.69%)
Hematological	52 (100)	7 (13.46)

**Table 2: Hematological parameters at presentation and at three months (n=52).**

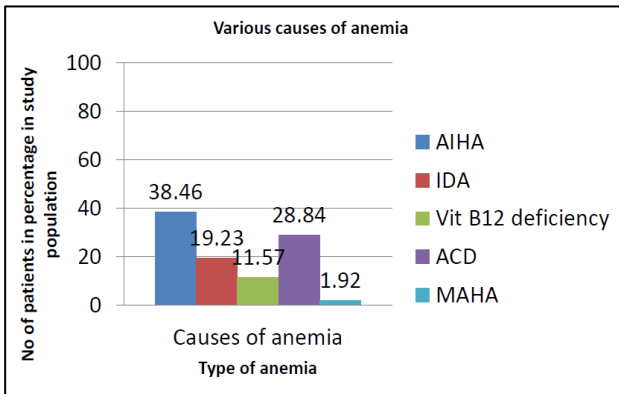
	No. of patient at presentation	No. of patient at three months
<b>Hemoglobin level (grams)</b>		
Hb >12 (F)	0 (0%)	3 (5.78%)
>13 (M)		
Hb 11-12 (F)	3 (5.78%)	34 (65.39%)
11-12.9(M)		
Hb 10.9-8	20 (38.46%)	13 (25%)
b <8	29 (55.76%)	2 (3.84%)
<b>White blood cells (cmm)</b>		
>11000	10 (19.23%)	2 (3.85%)
11000-3000	39 (75%)	50 (96.15%)
<3000	3 (5.77%)	0 (0%)
<b>Platelet count (lakhs)</b>		
>4	4 (7.69%)	7 (13.46%)
4-1	42 (71.15%)	45 (86.55%)
<1	10 (21.11%)	0 (0%)
<b>Erythrocyte sedimentation rate (mm at the end of one hour)</b>		
>20	42 (93.34%)	13 (28.89%)
0-20	3 (6.66%)	32 (71.11%)

**Table 3: Different causes of anemia of study population at presentation (n=52).**

Causes of anemia	No. of patients
Autoimmune hemolytic anemia(AIHA)	20 (38.46%)
Iron deficiency anemia(IDA)	10 (19.23%)
Vitamin B <sub>12</sub> deficiency	6 (11.57%)
Anemia of chronic disease(ACD)	15 (28.84%)
Microangiopathic hemolytic anemia (MAHA)	1 (1.92%)

Different causes of anemia of study population at presentation are tabulated in Table 3. The most common

cause of anemia was AIHA (38.46%) followed by nutritional and ACD.



**Figure 4: Distribution of different causes of anemia.**

Some hematological parameters at presentation are shown in Table 4. The results revealed 55.76% patients were having lower MCV (i.e. Microcytic Anemia) which indicated microcytic anemia was more common. Almost 46.15% patients had raised Serum LDH levels. 36.53% patients had DCT positive. 51.93% patients had retic

count of >2, 48.07% had retic count between 0.5-2 and no one had retic count <0.5.

**Table 4: Hematological parameters at presentation.**

Hematological parameters	No. of patients at presentation
<b>Mean corpuscular volume (MCV)</b>	
>96 (Macrocytic)	8 (15.38%)
80-96 (Normocytic)	15 (28.84%)
<80 (Microcytic)	29 (55.76%)
<b>Serum LDH levels (U/L)</b>	
<280	28 (53.85%)
>280	24 (46.15%)
<b>Direct Coombs test (DCT)</b>	
Positive	19 (36.53%)
Negative	33 (63.47%)
<b>Retic count</b>	
>2	27 (51.93%)
0.5-2	25 (48.07%)
<0.5	0

**Table 5: Correlation of immunological parameter with anemia at presentation and at three months (n=52).**

	At presentation (Mean±SD)	After 3 months follow up (Mean±SD)	P value
Hemoglobin female	7.96±1.70	11.18±1.26	0.0001
Hemoglobin male	8.4±1.68	11.67±0.57	0.035
C3 (80-180)	50.59±23.53	88.08±20.68	0.0001
C4 (10-40)	13.72±9.57	24.65±9.28	0.0001
ESR	82.66±16.35	11±1	0.0001

The mean hemoglobin level for female was 7.96±1.70 gm/dl and for male was 8.4±1.68 gm/dl at presentation and after therapy for female was 11.18 ± 1.26 gm/dl and for male was 11.67±0.57gm/dl (Table 5).

(7.70%) patients thus showing a significant reduction in disease activity with treatment.

**Table 6: Disease activity according to SLEDAI score at presentation (n=52).**

SLEDAI score	No. of patients at presentation
>20	30 (57.79%)
11-19	19 (36.53%)
6-10	3 (5.76%)
1-5	0 (0%)
0	0 (0%)

**Table 7: Disease activity according to SLEDAI score at three months (n=52).**

SLEDAI score	No. of patients at three months
>4	4 (7.69%)
≤4	35 (67.3%)
0	13 (25%)

Table 6 and 7 shows SLEDAI score at presentation and at three months respectively. The results revealed that 57.79% patients had SLEDAI score of >20 and no one had SLEDAI score <5 at presentation. After therapy at three months in present study the SLEDAI score was 0 in 13 (25%) patients, ≤4 in 35 (67.30%) patients and >4 in 4

**Table 8: Correlation between severity of anemia with disease activity by SLEDAI score (n=52).**

Type of anemia	SLEDAI ≤19	SLEDAI ≥20
Mild (11-12.9)	3 (5.76%)	0 (0%)
Moderate (8-10.9)	12 (23.07%)	10 (19.23%)
Severe (<8)	7 (13.46%)	20 (38.46%)
Total	22 (42.30%)	30 (57.69%)

Correlation between severities of anemia with disease activity by SLEDAI score is presented in Table 8. Patients with higher SLEDAI scores ( $\geq 20$ ) had more severe anemia than those with lower SLEDAI scores. This difference was found to be statistically significant (p value=0.01).

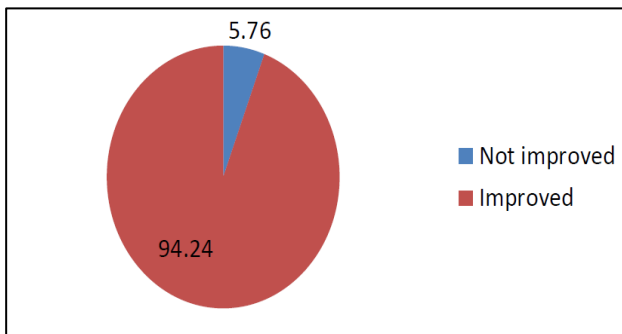
**Table 9: SLICC/ACR SLE Damage index at presentation (n=52).**

SLICC/ACR SLE Damage index	No. of patients at presentation
4	1 (1.9%)
3	7 (13.46%)
2	6 (11.53%)
1	13 (25%)
0	25 (48.07%)

Table 10 shows the correlation between the severity of Anemia and SLICC/ ACR Damage index. Patients with more severe anemia were found to have higher SLICC / ACR Damage index score but the difference was not statistically significant (p value -0.27, by ANOVA test).

**Table 10: Correlation of severity of anemia with SLICC/ACR SLE Damage index at presentation (n=52).**

Severity of anemia	Mean SLICC/ACR Damage index
Mild	0
Moderate	0.81±1.07
Severe	1.16±1.12



**Figure 5: Effectiveness of therapy on anaemia.**

**DISCUSSION**

In our study of 52 patients with SLE, 48 (92.3%) females and 4 (7.69%) males are there. The male:female ratio was 13:1. This female preponderance was almost similar with the studies of Sasidharan et al and Shaikh MA et al in which the male:female ratio was 9:1.<sup>4,5</sup> The increased frequency of SLE among females is thought to be due to hormonal effects.

Most of the patients (44.2%) involved in the study were under the age group of 21-30 years followed by 31-40

years (31.76) years and 41-50 years (19.2%). The mean age of the patients was found to be 33 years which is in accordance with the findings of Sasidharan et al and Shaikh MA et al.<sup>4,5</sup>

In the present study, the common clinical manifestation noted was constitutional and hematological symptoms (100%) followed by mucocutaneous symptoms (92.3%). Renal symptoms were also common. Two patients had ocular symptoms. On follow up after three months, there was decrease in the symptoms most probably due to therapy. These observations were comparably higher than the previous findings made by Saigal et al in which only 13.3% patients had cutaneous and renal symptoms.<sup>6</sup>

The mean hemoglobin level in present study was 7.96 mg/dL and 8.4 mg/dL in females and males respectively. This was lower than the previous findings of Sasidharan et al where as in study done by Saigal et al the mean haemoglobin level was 6.7 mg/dl.<sup>4,6</sup>

In the present study, most common cause of anemia is AIHA (38.46%) which is comparable with Domiciano et al, Oliveira et al.<sup>7,8</sup> Second most common cause was nutritional anemia (30.80%) followed by ACD (17.30%). In the present study, microcytic anemia was more common. This might be due to nutritional deficiency in most of the Indian population.

In the present study, most of the patient had severe anemia on presentation which is not comparable with previous study, this is because in earlier studies study population were both anemic and non-anemic patients.<sup>7</sup>

There are two major scoring systems to evaluate the activity of lupus in clinical studies. The most commonly being used was the SLE disease activity index (SLEDAI). It is a list of 24 items, 16 of which are clinical items such as seizure, psychosis, organic brain syndrome, visual disturbance, other neurological problems, hair loss, new rash, muscle weakness, arthritis, blood vessel inflammation, mouth sores, chest pain worse with deep breathing and manifestations of pleurisy and/or pericarditis and fever. Eight of the 24 items were laboratory results such as urinalysis testing, blood complement levels, increased anti-DNA antibody levels, low platelets, and low white blood cell count. These items are scored based on whether these manifestations are present or absent in the previous 10 days. The score can range from zero to 105. Higher scores indicate more severe disease activity. Patients with higher SLEDAI scores ( $\geq 20$ ) had more severe anemia than those with lower SLEDAI scores.<sup>9,10</sup>

In the present study there is no correlation between anemia and SLEDAI damage index. In this study, 57.79% patients had SLEDAI score of  $>20$  and after three months of therapy, the score was reduced to almost 4. These observations are comparable with the studies of Mirzayan et al.<sup>11</sup>

The Systemic Lupus International Collaborating Clinics (SLICC/ACR) damage index has been developed to assess irreversible damage in SLE patients, independently of its cause (SLE activity, therapy, comorbidities), but occurring after disease onset.<sup>12</sup> In the present study no correlation was found between anemia and SLICC/ACR damage index.

Serological tests are commonly used to assess the disease activity and expect lupus flare. During active disease, there is a fall in complement levels (C3 and C4) and a rise in anti-double stranded deoxyribonucleic acid (anti dsDNA) levels.<sup>13</sup> In the present study, all the patients had low C3 and C4 levels. The mean C3 level was 50.59±23.53 and C4 level was 13.72±9.57 and after therapy at three months the mean C3 and C4 levels was improved to 88.08±20.68 and 24.65±9.28 respectively. These results were in accordance with the findings of Narayanan et al.<sup>14</sup>

## CONCLUSION

Anaemia usually occurs at the onset of SLE and its recurrence rate will become low after three months of therapy. Monitoring SLEDAI scores, SLICC/ACR damage index and serum complement levels (C3 and C4) will be very advantageous for assessment and follow up of disease activity in SLE.

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*Ethical approval: The study was approved by the institutional ethics committee*

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