Indonesian Journal of Rheumatology

Journal Homepage: https://journalrheumatology.or.id/index.php/IJR

Hematological Parameters Comparison in Systemic Lupus Erythematosus Patients With and Without Nephritis

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ARTICLE INFO

Keywords:
Systemic lupus erythematosus, lupus nephritis, anemia, mean corpuscular hemoglobin concentration, Hasan Sadikin Lupus Registry.

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.66446/IJR.v18i1.1

A B S T R A C T

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disorder commonly complicated by hematological disorders and lupus nephritis (LN). Kidney impairment and chronic inflammation may affect erythropoiesis and red blood cell parameters. However, there is limited information on the short-term changes of hematological parameters in patients with and without LN. This study aimed to compare the short-term changes of hematological parameters between two clinical visits in patients with SLE with and without LN. **Methods:** This retrospective observational study used data from the Hasan Sadikin Lupus Registry in 2023. A total of 202 female patients with SLE aged 18 years and older with complete hematological data from two clinical visits were included. Hematological parameters included hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width coefficient of variation (RDW-CV). Comparison of changes in parameters between the first and second visits was done separately for patients with and without LN using the Wilcoxon Signed Rank Test. **Results:** In patients with LN, there was a statistically significant reduction in MCHC between the first and second visits, whereas there were no significant changes in hemoglobin, hematocrit, MCV, MCH, and RDW-CV. In patients without LN, small but statistically significant changes were noted in hemoglobin, MCV, and MCHC. The degree of change was small and remained within the normal range. **Conclusion:** The short-term hematological parameters in patients with SLE are generally stable between two clinical visits. Only MCHC showed a significant change in patients with LN, indicating a selective and subtle hematological change rather than a global effect of LN. These results indicate a cautious interpretation of the short-term hematological changes and suggest that MCHC may be used as an auxiliary parameter for hematological assessment in patients with SLE and LN.

1. Introduction

Systemic Lupus Erythematosus (SLE) is a long-lasting autoimmune condition distinguished by an improperly regulated immune system, continuous inflammation throughout the body, and the impact on several organs.[1] Hematological irregularities and kidney problems are two of the most prevalent and clinically important issues that arise from the wide range of clinical presentations it causes. Lupus nephritis (LN), a serious kidney-related symptom of SLE, arises in about 40–60% of those who have the disease as it advances and is still a major factor in illness and death over a long period.[2,3] Simultaneously, anemia stands out as the most typical blood-related irregularity observed in SLE, and it has consistently been linked to how active the disease is, how poorly the kidneys are functioning, and long-term inflammation.[4]

The intricate and varied connections between the disease mechanisms of LN and changes in blood cell

counts are not simple. Kidney problems in SLE result in inflammation and physical harm to the kidneys, which then hinders the creation of erythropoietin, a hormone made of protein and sugar that is vital for the growth and specialization of red blood cell precursors in the bone marrow.[2,5] Lowered creation of erythropoietin directly causes less red blood cell creation and the emergence of anemia where red blood cells are normal in size and color, a typical blood-related pattern seen in individuals with LNs.[6]

Anemia in SLE is significantly influenced by ongoing widespread inflammation throughout the body, in conjunction with a reduced ability to produce erythropoietin. Cytokines that promote inflammation, notably interleukin-6 (IL-6), stimulate the liver to generate hepcidin, which then diminishes iron uptake in the intestines and traps iron inside macrophages.[7] This disturbance of iron processing, caused by inflammation, gives rise to a condition where iron is not used effectively and red blood cell production is impaired, even when iron levels are normal or elevated, which worsens anemia in SLE patients who are actively affected, especially those with kidney problems.[4]

In standard SLE assessments, the assessment of blood cells involves looking at red blood cell data, which offers vital insights into what causes anemia. Hemoglobin indicates how well blood can carry oxygen and is the main way to tell how bad the anemia is, whereas hematocrit shows the percentage of blood made up of red blood cells and is linked to the amount of hemoglobin present.[8] Mean Corpuscular Volume (MCV) measures the typical size of red blood cells and is helpful in determining whether the anemia is microcytic, normocytic, or macrocytic, which could be due to a lack of iron, ongoing inflammation, or issues with the bone marrow.[4]

The characteristics of erythrocytes regarding their hemoglobin levels and degree of hemoglobin saturation are further elucidated by Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC). The MCHC parameter is especially indicative of the hemoglobin density within the red blood cells, and research indicates its responsiveness to changes affecting the structural soundness of erythrocytes, as well as how iron is used in cases of long-term inflammation and kidney-related ailments.[9] The extent of variation in the size of red blood cells is determined by Red Cell Distribution Width coefficient of variation (RDW-CV), acting as an indicator of anisocytosis. This condition has been linked to the presence of inflammation, deficiencies in red blood cell production, disease progression, and unfavorable results in SLE.[10]

In individuals suffering from LN, these blood-related measurements might show different trends when contrasted with SLE patients who don't have kidney problems. Hemoglobin levels, along with MCHC and RDW-CV, could be mainly affected by decreased erythropoietin creation, constant swelling, and changed iron usage, but MCV and MCH might not change much based on how bad the illness is and what treatments are being used.[6,7,12] Nonetheless, blood-related changes in SLE can shift and alter as time passes, which highlights why it's crucial to monitor them regularly instead of just taking one measurement.[13,14]

Even though LN and blood-related signs in SLE have been studied a lot, most studies have looked at how common or serious anemia is, instead of watching how specific red blood cell numbers change over time.[11,3] There is not much information that compares how blood levels change in SLE patients with and without LN over many doctor visits, especially in normal clinical situations. This is a big hole in the research, since watching blood changes over time might show how the disease gets worse, how the kidneys are affected, and how well treatments are working.

This research, therefore, is designed to explore the shifting patterns of blood-related measurements like hemoglobin, hematocrit, MCV, MCH, MCHC, and RDW-CV across a pair of medical check-ups in individuals diagnosed with SLE, comparing those who also have LN to those who do not. By concentrating on the unique changes in each specific measurement and considering kidney involvement, the goal of this study

is to generate fresh, clinically useful information that will promote more accurate blood monitoring and care strategies for individuals with SLE**.**

2. Methods

This research used an analytical retrospective observational design with a quantitative approach to analyze dynamic changes of hematological values in SLE patients with and without LN. Data were collected from the Hasan Sadikin Lupus Registry, a hospital-based registry that systematically records demographic, clinical, laboratory, and disease activity information of SLE patients treated at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. Data collection was conducted from January to December 2023.

The study population was all female SLE patients (n = 258). Patients were eligible if they were ≥18 years old, had a confirmed diagnosis of SLE, and had complete hematological data available at two clinical visits during the study period of 3 months. Exclusion criteria included incomplete medical records, pregnancy, active infection, bleeding episodes, or incomplete hematological data at either visit. Using these criteria, 56 patients (21.7%) were excluded. A total of 202 patients were included in the final analysis, consisting of 124 patients with LN and 78 patients without LN.

All patients enrolled in this study had a confirmed diagnosis of SLE based on clinical assessment by rheumatologists and the fulfillment of internationally accepted classification criteria. The criteria were in accordance with the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria or the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) classification criteria, which are used in clinical practice at the study center.

The status of LN was defined based on the documented renal involvement as recorded in the registry. Patients were considered to have LN if there was a documented history of renal involvement due to SLE, as indicated by clinical and laboratory manifestations such as persistent proteinuria, hematuria, or impaired renal function, and/or histopathological confirmation by renal biopsy when performed. Because the registry was a retrospective study, renal biopsy results and histological classification were not always available for all patients. Consequently, the classification of patients with LN in this study was mainly based on the documented history of renal involvement, which was a common practice in large observational studies of patients with lupus. Patients who had no documented history of renal involvement throughout the course of their disease were considered to be non-lupus nephritis.

The renal function was indirectly indicated by the presence or absence of LN, as the specific parameters of renal function, such as the estimated glomerular filtration rate, were not consistently recorded in the registry. This was recognized, as the hematologic abnormalities in SLE are closely linked to renal dysfunction, particularly by the decreased production of erythropoietin.

The hematological information was gathered from two routine clinic visits for each patient. The first visit was considered to be the first visit in 2023 with comprehensive hematological information, while the second visit was considered to be a follow-up visit which was 3 months after. The time gap between the two visits was not fixed and ranged from a minimum of three months to a maximum of twelve months. This time gap was considered adequate to capture the changes in the hematological parameters, although it may not be representative of the long-term disease process.

The hematological variables considered in the analysis were hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width–coefficient of variation (RDW-CV). Hemoglobin and hematocrit were employed to determine the severity of anemia and the oxygen-carrying capacity. MCV was employed to determine the morphology of anemia, while MCH and MCHC described the hemoglobin content and concentration in erythrocytes, which could be compromised by the consequences of impaired erythropoiesis,

inflammation, and iron use in renal and autoimmune disorders. RDW-CV was employed to determine the variation in the size of red blood cells and was used as a marker of anisocytosis due to inflammation and disease activity.

Anemia was considered to be hemoglobin levels <12 g/dL, as per World Health Organization criteria for adult women. Disease activity was measured by the SLE Disease Activity Index 2000 (SLEDAI-2K). Scores ≥6 were considered to be active disease, and scores <6 were considered to be inactive disease.

Potential confounding variables that could affect hematological values, such as medication (corticosteroids, immunosuppressive drugs, and iron supplements), nutritional status, hemolytic anemia, and concomitant diseases like hypertension or diabetes mellitus, could not be controlled for in the registry because of the lack of complete information. These were cited as limitations of the study.

The clinical and laboratory information was abstracted from the registry by trained medical personnel and recorded as part of the routine patient care. The hematological variables were assessed using standardized automated hematology analyzers in the central laboratory of the hospital to ensure the accuracy and validity of the laboratory results.

The distribution of the data was determined using normality tests and was found to be non-normally distributed. The data was described using median and interquartile range for continuous variables, and frequency and percentage for categorical variables. Comparisons of the baseline characteristics between patients with and without LN were performed using the Chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Comparisons of hematological parameters within each group between the first and second clinical visits were performed using the Wilcoxon Signed Rank Test. All statistical analyses were conducted using the IBM Statistical Package for Social Sciences (SPSS) version 29.0 software, with statistical significance set at $p < 0.05$.

3. Results

Study Population

A total of 202 female patients with SLE were included in the final analysis, of which 124 patients (61.2%) had LN and 78 patients (38.8%) did not have LN. The majority of patients in both groups belonged to the 30-49 years age group. There were no statistically significant differences in the distribution of age and duration of disease between patients with and without LN. The baseline demographic and clinical variables of SLE patients with and without LN are shown in Table 1.

Table 1. The characteristics of Systemic Lupus Erythematosus patients registered at Hasan Sadikin Lupus Registry, with or without nephritis

Characteristics	With LN (n=124)	Without LN (n=78)	P value
Age (years); n (%)			
• 18-29 years	38 (30.6)	30 (38.5)	0.517
• 30-49 years	62 (50)	35 (44.9)	
• 50-69 years	24 (19.4)	13 (16.7)	
Duration of illness; mean±SD (years)	8.1±2.7	7.7±2.7	0.391
Organ involvement; n (%)			
- Renal	124 (100)	-	0.001*
- Hematology	101 (81.5)	43 (55.1)	0.001*
- Neurology	40 (32.3)	11 (14.1)	0.004*
- Musculoskeletal	36 (29)	15 (19.2)	0.118
- Vasculitis	20 (16.1)	18 (23.1)	0.219
- Pulmonary	15 (12.1)	9 (11.5)	0.905
- Heart	7 (5.6)	5 (6.4)	0.823

LN = lupus nephritis.
*Significant difference ($p<0.05$)

Patients with LN demonstrated significantly higher frequencies of hematological involvement (81.5% vs. 55.1%, p = 0.001) and neurological involvement (32.3% vs. 14.1%, p = 0.004) compared to patients without nephritis. No statistically significant differences were observed in musculoskeletal, vasculitis, pulmonary, or cardiac involvement between the two groups.

Anemia and Disease Activity

Although a higher proportion of patients with LN had a history of anemia compared to those without nephritis (51.6% vs. 38.5%), this difference did not reach statistical significance (p = 0.068). In contrast, disease activity assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) differed significantly between the two groups. Active disease (SLEDAI-2K ≥6) was observed in 29.8% of patients with LN compared to 9.0% of patients without nephritis (p = 0.001), with an odds ratio of 4.31 (95% CI: 1.8–10.2), indicating a substantially higher likelihood of active disease among patients with renal involvement.

The distribution of anemia history and disease activity among SLE patients with and without LN is presented in Table 2.

Table 2. Distribution of Anemia and Disease Activity among Visits in Systemic Lupus Erythematosus patients with and without Lupus Nephritis

Variable	With LN (n=124)	Without LN (n = 78)	p-value	OR (CI 95%)
Anemia; n (%)				
- Ever Anemia	64 (51.6)	30 (38.5)	0.068	
- Never Anemia	60 (48.4)	48 (61.5)		
Disease Activity; n (%)				
- Active	37 (29.8)	7 (9)	0.001*	4.31
- Inactive	87 (70.2)	71 (91)		(1.8 – 10.2)

LN = lupus nephritis; Ever anemia = had once or twice low Hb (Hb<12 gr/dL) each visit; Disease activity was determined by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), active (score ≥ 6) and inactive (score <6)
*Significant difference (p<0.05)

Dynamic Changes in Hematological Parameters

Dynamic changes in hematological parameters between the first and second clinical visits revealed different patterns between patients with and without LN. In patients with LN, no statistically significant changes were observed in hemoglobin, hematocrit, MCV, MCH, or RDW-CV. However, a statistically significant decline in MCHC was detected, decreasing from a median of 32.7 g/dL at the first visit to 32.2 g/dL at the second visit (p = 0.002) as presented in table 3.

Although the magnitude of MCHC reduction was modest and remained within the normal reference range (32–36 g/dL), this finding indicates a consistent temporal change in erythrocyte hemoglobin concentration among patients with LN, even in the absence of significant changes in hemoglobin levels.

In contrast, patients without LN demonstrated statistically significant changes in several hematological parameters. Hemoglobin levels decreased modestly between visits (p = 0.018), while MCV increased slightly (p = 0.026). A significant decline in MCHC was also observed (p < 0.001). The absolute increase in MCV was small (0.8 fL), suggesting limited clinical relevance despite statistical significance. These findings indicate that short-term hematological fluctuations in patients without renal involvement may be influenced by systemic disease activity or treatment-related factors rather than renal dysfunction.

4. Discussion

This study evaluated short term changes in hematological parameters among SLE patients with and without LN using registry based data. Overall, the findings demonstrate that most hematological parameters remained relatively stable over two clinical visits, with selective and modest changes observed

primarily in MCHC among patients with LN. These findings are consistent with the study objective to assess temporal hematological dynamics rather than cross sectional differences.

The absence of statistically significant changes in most hematological parameters, including hemoglobin, hematocrit, MCV, MCH, and RDW-CV, may be explained by the relatively short observation period and the heterogeneous nature of renal involvement in LN. Previous studies have shown that substantial hematological deterioration in SLE is more commonly observed in patients with advanced or prolonged renal disease rather than during early or stable phases of nephritis.[2,3,15,16,17,18] In patients with preserved or partially preserved renal function, erythropoietin production may remain sufficient to maintain stable erythropoiesis over a limited follow up period, which could explain the stability of most red blood cell indices observed in this study.[19,20]

The selective decline in MCHC observed in patients with LN, despite stable hemoglobin levels, represents a key finding of this study. MCHC reflects the concentration of hemoglobin within erythrocytes and has been suggested to be more sensitive to early disturbances in erythropoiesis and iron utilization than absolute hemoglobin values. Inflammatory processes in SLE, particularly in the presence of renal involvement, promote cytokine mediated upregulation of hepcidin, which impairs iron availability for hemoglobin synthesis and leads to ineffective erythropoiesis.[4,7] Similar patterns have been reported in patients with chronic kidney disease and inflammatory disorders, where reductions in MCHC may precede the development of overt anemia.[6,5] Although the magnitude of MCHC reduction in the present study remained within the normal reference range, its consistent temporal change suggests that MCHC may reflect subtle subclinical hematological alterations in LN.

In contrast, patients without LN demonstrated statistically significant but clinically modest changes in hemoglobin, MCV, and MCHC. The small increase in MCV and slight decrease in hemoglobin are unlikely to indicate clinically meaningful anemia progression. Previous studies have shown that fluctuations in red blood cell indices among SLE patients without renal involvement may be influenced by systemic inflammation, disease activity, or treatment related factors rather than intrinsic renal dysfunction.[8,4] This finding underscores the importance of distinguishing statistical significance from clinical relevance, particularly when absolute changes are small.

There are a number of potential confounding variables which must be taken into account when considering the results of these findings. Medications which are commonly used in the treatment of SLE, including corticosteroids, hydroxychloroquine, and immunosuppressive medications, are known to affect hematologic variables as a consequence of their impact on bone marrow activity, inflammation, and iron metabolism. Furthermore, infections, nutritional factors, iron deficiency, and hemolytic anemia are common in SLE patients and may independently affect red blood cell variables. Because the data was retrospective, these confounding variables could not be controlled for and may have mitigated or obscured the hematologic effects of LN alone.

Despite the above limitations, the results of this study still have clinical significance. Most of the previous studies on hematological abnormalities in SLE and LN were cross-sectional in nature and mainly focused on the prevalence or severity of anemia. By assessing the changes over two clinical visits, this study has given a temporal perspective on the stability of hematological parameters and the slight changes in the parameters, especially the less frequently highlighted parameter of MCHC. Although the changes were slight, the data suggest that the monitoring of MCHC and hemoglobin levels may provide supplementary information for the early assessment of erythropoietic changes in patients with LN.

There are a number of limitations to this study. The retrospective nature of the study makes it difficult to establish causality and control for confounding variables. The observation period may be too short to reflect the long-term hematological and renal changes. Additionally, the severity of LN and histopathological

category were not stratified, which could have masked differences between patients with different levels of renal disease. The unequal number of patients in each group could affect the comparison.

5. Conclusion

This study demonstrates that short term hematological parameters in SLE patients are largely stable, with selective and modest changes observed in MCHC among patients with lupus nephritis. Although these changes are subtle and of limited immediate clinical impact, they support the potential role of MCHC as a sensitive parameter for hematological monitoring in SLE with renal involvement. Future prospective studies with longer follow up, comprehensive adjustment for confounding variables, and stratification by LN severity are needed to further clarify the clinical significance of these findings.

Conflict of Interest

There is no conflict of interest regarding the publication of this article.

Author's Contribution

AMS generated the idea, supported by ES and LH. LH supervised clinical data. AMS wrote the first draft, supervised by ES and LH. All authors discussed the results and contributed to the final manuscript.

Funding

This study financially funded by Internal Research Grant of Universitas Padjadjaran.

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