Correlation between neutrophil to lymphocyte and platelet to lymphocyte ratios and renal involvement in systemic lupus erythematosus in Central Vietnam

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Abstract

Background: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease with diverse clinical manifestations and relapsing - remitting disease course. Nephritis is a major cause of morbidity and mortality in patients with lupus. Many clinical parameters and laboratory markers can be used to evaluate disease activity and nephritis. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are positively associated with inflammatory disorders. **Objectives:** To evaluate the correlation between NLR and PLR in peripheral blood and renal involvement in systemic lupus erythematosus. **Methods:** 63 patients were diagnosed with SLE according to the criteria of the Systemic Lupus International Collaborating Clinics 2012 (SLICC 2012) and were treated at the Internal Medicine Department of Hue University of Medicine and Pharmacy Hospital, Thua Thien Hue province, in central Vietnam, from February 2020 to July 2021. This study included 41 SLE patients with lupus nephritis (LN) and 22 SLE patients without renal involvement. **Results:** The mean age of the study group was 31.67 ± 12.10. The most common age group was 21-50 years old, accounting for 69.8%. Females accounted for 90.5% and the female-to-male ratio stood at 9.5:1. Clinical and laboratory characteristics: acute cutaneous lupus 50.8%, subacute cutaneous lupus 11.1%, oral ulcers 27%, non - scarring alopecia 47.6%, arthritis 61.9%, pleural or pericardial effusion 30.2%, renal involvement 65.1%, neuropsychiatric damage 4.8%, anemia 81.0%, leukopenia 22.2%, neutropenia 11.1%, lymphopenia 41.3%, thrombocytopenia 15.9%, hemolytic anemia 15.9%, positive ANA antibody 61.9%, positive anti-ds DNA antibody 52.4%. Acute cutaneous lupus and arthritis in SLE patients without the nephritis group were higher than in the LN group ($p < 0.05$). Anemia, lymphopenia, thrombocytopenia, positive ANA, anti-ds DNA in the LN group were higher than SLE patients without nephritis ($p < 0.05$). SLE patients with LN had higher levels of NLR than those without nephritis. While PLR had no remarkable difference between these two groups. NLR was positively correlated with CRP, serum creatinine, and 24-hour urinary protein. PLR was positively correlated with the SLEDAI score. The best NLR to predict LN was 4.97 with a sensitivity of 51.2% and a specificity of 95.5% (AUC = 0.742, 95% CI, 0.617 - 0.866, $p = 0.002$). **Conclusion:** Most of the clinical manifestations in SLE patients according to SLICC 2012 criteria were lupus nephritis, arthritis, and acute cutaneous lupus. PLR was positively correlated with the SLEDAI score. NLR could predict renal involvement in SLE patients.

Keywords: *Lupus nephritis, ANA, anti-ds DNA, NLR, PLR.*

1. INTRODUCTION

SLE is a chronic autoimmune disease of the connective tissue characterized by the formation of autoantibodies which leads to immune complex deposition. The etiology of SLE is known to be multifactorial, involving genes, hormones, immune and environmental factors. This disease can affect different organs and it most frequently affects the kidneys. LN affects approximately 40 - 70% of SLE patients, leading to an increase in the risk of renal failure and cardiovascular diseases. This makes LN a major cause of morbidity and hospital admissions [1], [2]. Early diagnosis and rapid treatment of LN are crucial to improving survival in SLE patients.

In recent years, renal biopsy is still the standard investigation to diagnose LN. However, the renal biopsy carries some risks of complications, the majority of which are bleeding including perirenal hematoma, infection, and hypotension … [1], [3], [4] and difficult repeatability. In addition, 24-hour urinary protein and urinalysis also help to diagnose LN but these tests have limitations such as one-time-point measurement of proteinuria and sampling errors. Finding simple and repeatable tests that are available in most healthcare settings to assess disease activity and correlate with renal involvement

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is important. Recently, many domestic and foreign authors have applied the change of peripheral blood components such as NLR and PLR to detect disease activity in some connective tissue diseases including SLE [1], [5], [6] as well as correlation with LN [1], [7], [8]. Therefore, to better understand the value of NLR and PLR in LN, we carried out the topic: Correlation between NLR and PLR in peripheral blood and kidney involvement in systemic lupus erythematosus with Objective: To evaluate the correlation between NLR, and PLR in peripheral blood and kidney involvement in systemic lupus erythematosus.

2. PATIENTS AND METHODS

In this cross-sectional study, we enrolled 63 patients with SLE who were recruited in the Internal Medicine Department of Hue University of Medicine and Pharmacy Hospital, Thua Thien Hue province, in central Vietnam from February 2020 to July 2021.

The participants were divided into the following groups:

Group I: 41 SLE patients with lupus nephritis.

Group II: 22 SLE patients without nephritis.

Inclusion criteria:

Patients with 4 or more out of the 11 revised classification criteria for SLE of the Systemic Lupus International Collaborating Clinics (SLICC 2012) were included in the study. We used the SLEDAI score to evaluate SLE disease activity. Patients with a score of over 4 were considered active. We confirmed the diagnosis of renal involvement in those patients by proteinuria > 0.5 g/24h. We did not perform kidney biopsy and urine sediment because it was not convenient.

Exclusion criteria:

Patients who had active infections, other connective tissue disease, malignancies, hematologic diseases without SLE-induced, or were using immunosuppressive drugs were excluded.

Data extraction

Data on patient demographics (age, gender), complete blood count (CBC), serum creatinine, 24-h proteinuria, ANA antibody, anti-ds DNA antibody, CRP, NLR, and PLR were recorded for each patient. SLE Disease Activity Index (SLEDAI) was used to assess disease activity based on the symptoms and laboratory findings as described.

Statistical analysis

We carried out statistical analysis via IBM SPSS version 20 for Windows (IBM Corporation, Armonk, NY, USA). We used Mann–Whitney U test to compare two independent groups according to distribution status. Furthermore, we used Chi-square test to show the association with variables for categorical data. We presented correlations between two variables using the Spearman correlation coefficient. We analyzed the receiver operating characteristic curve (ROC) to find the discrimination values of NLR and PLR for LN. A p-value less than 0.05 was considered to be statistically significant for all values.

3. RESULTS

Characteristics of the study subjects

The mean age of the study group was 31.67 ± 12.10. The most common age group was 21 - 50 years old, accounting for 69.8%. In this group, females accounted for 90.5% and the female-to-male ratio stood at 9.5:1.

Clinical characteristics of the two studied groups are given in Table 1. Systemic involvements were frequently observed in SLE patients were LN 65.1%, arthritis 61.9%, acute cutaneous lupus 50.8%, non-scarring alopecia 47.6%. Acute cutaneous lupus and arthritis in SLE patients without nephritis group were higher than the LN group (72.7% vs 39.0%, p = 0.011; 90.9% vs 46.3%, p = 0.001, respectively).

Table 2 shows the comparison of hematologic characteristics between SLE patients with and without nephritis. The incidence of anemia, leukopenia, neutropenia, lymphopenia, thrombocytopenia, hemolytic anemia in SLE patients was 81%, 22.2%, 11.1%, 41.3%, 15.9% and 15.9% respectively. We found that the LN group had a significantly higher rate of anemia, lymphopenia, and thrombocytopenia compared with SLE without nephritis ($p < 0.05$). In contrast, there was no statistical significance as leukopenia, neutropenia, hemolytic anemia as shown in Table 2.

Table 3 shows the comparison of immunological characteristics between SLE patients with and without nephritis. ANA and anti – ds DNA antibody was positive in 39 (61.9%), 33 (52.4%) respectively. The rate of ANA and anti-ds DNA antibody positive in LN patients was higher than in SLE without renal involvement. This difference was statistically significant with $p < 0.05$.

NLR and PLR levels

We found that the LN group had significantly higher levels of NLR compared with SLE without nephritis ($p < 0.05$). Meanwhile, PLR had no significant difference between these 2 groups with $p > 0.05$ (Table 4).

In this study, NLR showed a positive correlation

with statistical significance with the following parameters: neutrophil, creatinine, 24-hour urinary protein, CRP, PLR ($p \leq 0.001$) for all. Besides, PLR showed a positive correlation with significance with the following parameters: platelet, NLR, SLEDAI (Table 5).

For predicting lupus nephritis, the ROC/AUC analysis showed a sensitivity of 51.2%, and a specificity of 95.5% when a cutoff value of 4.97 was used for NLR (AUC = 0.742, 95% CI, 0.617– 0.866, p = .0020. However, the AUCs for PLR are less than 0.7 (Fig.1)

Table 1. Comparison of clinical characteristics between patients with and without lupus nephritis.

Parameter	SLE patients N=63	LN patients N=41 (n, %)	SLE with no renal affection N =22 (n, %)	p
Fever	22 (34.9)	17 (41.5)	5 (22.7)	0.137
Non – scarring alopecia	30 (47.6)	22 (53.7)	8 (36.4)	0.190
Oral/nasal ulcers	12 (27)	9 (22.0)	8 (36.4)	0.219
Acute cutaneous lupus	32 (50.8)	16 (39.0)	16 (72.7)	0.011
Subacute cutaneous lupus	7 (11.1)	3 (7.3)	4 (18.2)	0.226
Neuropsychiatric	3 (4.8)	3 (7.3)	0	0.546
Pleural or pericardial effusion	19 (30.2)	19 (46.3)	0	0.000
Arthritis	39 (61.9)	19 (46.3)	20 (90.9)	0.001
Renal involvement	41 (65.1)	-	-	-

Table 2. Comparison of hematologic characteristics between SLE patients with and without nephritis

Parameter	SLE patients (N=63, %)	LN patients (n=41, %)	SLE with no renal affection (n=22, %)	p
Hemoglobin, g/dl Anemia (< 12 g/dl)	51 (81)	39 (95.1)	12 (54.5)	0.000
WBC, x 10^9/L Leukopenia (< 4 x 10^9/L)	14 (22.2)	10 (24.4)	4 (18.2)	0.753
Neutrophils, x 10^9/L Neutropenia (< 1.8 x 10^9/L)	7 (11.1)	5 (12.2)	2 (9.1)	1.000
Lymphocytes, x 10^9/L Lymphopenia (< 10^9/L)	26 (41.3)	22 (53.7)	4 (18.2)	0.006
Platelet, x 10^9/L Thrombocytopenia (< 100 x 10^9/L)	10 (15.9)	10 (24.4)	0	0.011
Hemolytic anemia	10 (15.9)	9 (22.0)	1 (4.5)	0.145

Table 3. Comparison of immunological characteristics between SLE patients with and without nephritis

Parameter	SLE patients (n = 63, %)	LN group (n = 41, %)	SLE with no renal affection (n = 22, %)	p
ANA				
Positive	39 (61.9)	29 (70.7)	10 (45.5)	**0.049**
Negative	24 (38.1)	12 (29.3)	13 (54.5)	
Anti-dsDNA				
Positive	33 (52.4)	29 (70.7)	4 (18.2)	**0.000**
Negative	30 (47.6)	12 (29.3)	18 (81.8)	

Table 4. NLR and PLR levels in SLE patients

Parameter	LN patients (n=41)	SLE patients with no renal affection (n=22)	p
NLR	4.97 (3.10 - 7.10)	2.87 (1.79 - 3.70)	**0.002**
PLR	155.32 (114.49 - 333.64)	137.41 (93.71 - 216.19)	0.299

Table 5. Correlations of NLR, PLR with other variables of the studied group

Parameter	NLR		PLR	
	R	p	R	p
Hemoglobin	-0.329	**0.008**	-0.072	0.575
WBC	0.119	0.354	-0.392	**0.002**
Neutrophil	0.370	**0.003**	-0.232	0.067
Lymphocytes	-0.652	**0.000**	-0.612	**0.000**
Platelet	-0.034	0.793	0.457	**0.000**
Creatinine	0.400	**0.001**	-0.059	0.647
24h urinary protein	0.414	**0.001**	0.041	0.750
CRP	0.360	**0.004**	0.228	0.073
SLEDAI	0.202	0.112	0.334	**0.007**
ANA		0.954		0.898
Anti –ds DNA		0.063		0.099
NLR			0.495	**0.000**
PLR	0.495	**0.000**		

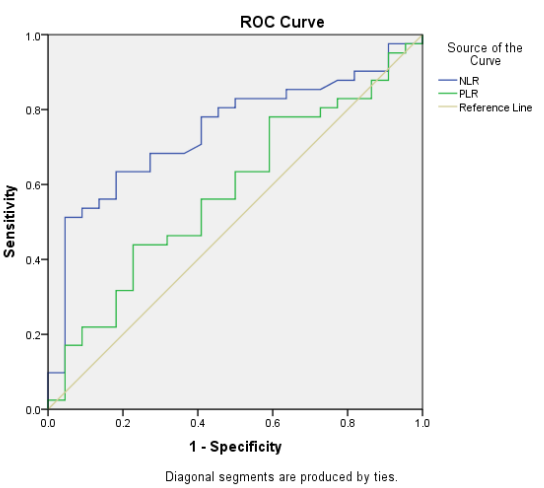

Figure 1. Receiver Operating Characteristic curve (ROC) analysis of NLR and PLR to predict lupus nephritis. The ROC/AUC analysis showed a sensitivity of 51.2%, and a specificity of 95.5% when a cutoff value of 4.97 was used for NLR (AUC = 0.742, 95% CI, 0.617 - 0.866, p = .002). However, the AUCs for PLR is less than 0.7.

4. DISCUSSION

Lupus is a syndrome that primarily affects young women. Its phenotypic variability makes every lupus patient unique with different clinical and laboratory characteristics. In this study, systemic involvements are frequently observed in SLE patients were renal involvement, arthritis, acute cutaneous lupus, and non-scarring alopecia, while neuropsychiatric manifestations were the least common.

Dermatological manifestations are one of the

most typical symptoms in SLE and features that help clinicians to guide the disease. Acute cutaneous lupus such as malar rash and photosensitivity accounted for 50.8%, which is similar to the study of Nguyen Thi Kim Thanh (57.6%) [9], but lower than the study of Huynh Thi Nhu Hang (69.2%) [10]. Non-scarring alopecia accounted for 47.6%, lower than the study of Hoang Thi Phuong Thao (60%) [11]. In this study, we recorded the rate of oral or nasal ulcers at 27%, equivalent to the study Huynh Van Khoa [12].

Musculoskeletal manifestations, which are very common in SLE patients and mainly appear in small joints, do not cause joints destruction. Our research showed that there was 61.9% of patients with arthritis at the time of examination, equivalent to the study of Huynh Van Khoa (66.1%) [12], lower than the study of Petri M et al., (79%) [13]. According to the literature, characteristics usually range from 53% to 95% [2]. This can be explained by the fact that when the patients had joint pain, they had self-treated with corticosteroids or analgesic drugs at home, so the arthritis symptoms had been reduced significantly when they came hospital.

Lupus nephritis is common with an incidence of 40-70% and it is a major cause of hospitalization and death in SLE patients [2]. It accounted for 65.1%, equivalent to the study of Hoang Thi Phuong Thao [11]. Ramji Wichaniun who conducted a similar study in Thailand in 2019 on 100 SLE patients reported this rate was 66% [14]. In general, LN is very common and is related to the prognosis of the disease. It is necessary to carefully screen for renal involvement at the time of diagnosis and monitor the disease through urinalysis and kidney function tests.

Neuropsychiatric and serosal manifestations are relatively uncommon in SLE patients. In our study, there were 3 cases of neuropsychiatric disorder, accounting for 4.8%, pleural or pericardial effusion 30.2%. This result was equivalent to the study of Nguyen Thi Kim Thanh with seizure (5.9%) [9].

Acute cutaneous lupus and arthritis in group II SLE patients without nephritis were higher than group I ($p < 0.05$). This was in agreement with Nguyen Thi Kim Thanh (9) and Cervera et al., [15].

Anemia is the most common hematological disorder. In our study, it accounted for 81%, in which immune hemolytic anemia was 15.9%, higher than the study of Mai Thu Huyen (70.8%, 4.2%) [16], Nguyen Thi Kim Thanh (44.1%, 13.6%) (9). Anemia was higher in group I than group II with statistical significance ($p < 0.001$). This was in agreement with Josep et al., [15], Nguyen Thi Kim Thanh [9]. This n be explained by chronic inflammatory damage of the glomeruli that reduces the secretion of erythropoietin, and some other reasons.

Leukopenia which is less common but often reflects disease activity, maybe due to adaptive immune mechanisms, use of drugs such as cyclophosphamide or azathioprine, bone marrow dysfunction, or hypersplenism. In this study, the rate of leukopenia, neutropenia, and lymphopenia accounted for 22.2%, 11.1%, and 41.3%, respectively. This was similar to Mai Thu Huyen [16], Hoang Thi Phuong Thao [11]. Lymphopenia was higher in group I than group II with statistical significance ($p = 0.006$). This was in agreement with Nguyen Thi Kim Thanh [9], [17]. From the above study results, there was a reduction in WBC count in the peripheral blood. But the most obvious reduction was the number of lymphocytes due to the suppression of T lymphocytes, especially in the active disease stage.

Thrombocytopenia is defined as a platelet count less than 100.000/mm^3. The most common cause of thrombocytopenia in SLE is immune-mediated platelet destruction, but increased platelet consumption may also occur due to microangiopathic hemolytic anemia or hypersplenism. Impaired platelet production secondary to medications is another contributing factor. In our study, it accounted for 15.9%, equivalent to the study of Mai Thu Huyen (18.8%) [16], Hoang Thi Phuong Thao (16.4%) [11], Nguyen Thi Kim Thanh (13.6%) [9]. Thrombocytopenia was higher in group I than group II with statistical significance ($p < 0.05$). This was in agreement with Nguyen Thi Kim Thanh [9].

ANA and anti-ds DNA antibodies are very valuable immunoassays in the diagnosis of SLE. ANA antibody is considered the best screening test because of its high sensitivity (95%) and simplicity. Whereas, anti-ds DNA antibody has high specificity, allowing assessment of disease activity. The results of our study showed that the rate of ANA and anti-ds DNA antibody was positive 61.9% and 52.4%, respectively, lower than the study of Nguyen Thi Kim Thanh (98%, 72.9%) [9], Hoang Thi Phuong Thao. (96.4%, 89.1%) [11]. This could be explained by differences in sample size, ethnicity, laboratory-specific testing. Another explanation is that some treated patients with loss of ANA reactivity become serologically negative over time or in the early stages of the disease. The positive rate of these antibodies in group I was higher than group II with statistical significance $p < 0.05$. This result was in contrast to Nguyen Thi Kim Thanh [9], who showed no difference between the two groups. Because we

mainly sampled inpatients, LN patients were higher than SLE patients without nephritis.

Some studies use NLR and PLR values as biomarkers to reflect inflammation in various diseases such as malignancies, ischemic lesions, cardiovascular diseases, and infections. SLE is a chronic autoimmune disease that follows relapsing - remitting courses. Early recognition of flares would reduce the long-term disease and drug-related co-morbidities. Renal involvement is one of the main determinants of the poor prognosis of SLE. Thus, early diagnosis and management of LN are highly desirable for SLE patients via urinalysis and kidney function. In addition, anti-ds DNA antibody and complement are often used but this test has not been popularized in primary health care. Non-invasive, simple, available biomarker seems to be necessary. Recently, some authors have studied the value of NLR, PLR in SLE with renal involvement.

This study recorded higher values of NLR in SLE patients with nephritis (4.97 (3.10 - 7.10)) than SLE patients without nephritis (2.87 (1.79 - 3.70)). This was in agreement with Soliman et al., [1], Ayna A. et al., [7], Tang D. et al., [18], Nguyen Thi Kim Thanh [9] who stated that NLR differed significantly between two groups. In contrast, there was no significant difference in PLR values between these groups.

Recently, the authors Qin B. et al., [5], Ayna A. et al., [7] showed NLR and PLR as inflammatory markers in SLE disease such as VSS and CRP tests. In our study, NLR showed positive correlations with CRP ($r = 0.360$, $p=0.004$). This was similar to the study of Qin B. et al., [5], Ayna A. et al., [7], Soliman et al., [1], Nguyen Thi Kim Thanh [9]. Meanwhile, PLR showed no significant correlations with this parameter. NLR showed positive correlations with serum creatinine and 24-h urinary protein ($p \leq 0.001$) for all. While no statistically significant difference was found between them and PLR with $p > 0.05$, respectively. This was similar to the study of Soliman et al., [1]. PLR showed a positive correlation with the SLEDAI score with $r = 0.334$ and $p = 0.007$. This was in agreement with Qin B. et al., [5], [6], Wu Y. et al., [6]. However, there was no correlation between NLR and this score.

For predicting lupus nephritis, the ROC/AUC analysis showed a sensitivity of 51.2%, and a specificity of 95.5% when a cutoff value of 4.97 was used for NLR (AUC = 0.742, 95% CI, 0.617 - 0.866, $p = .0020$). These results were in agreement with Li et al., who suggested that NLR can predict LN with a cutoff value of 4.4 for NLR (sensitivity 0.64, specificity 0.91) [19]. Tang D. et al., showed that NLR was useful in the diagnosis and severity of renal involvement in SLE with a sensitivity of 65.9% and a specificity of 86.3% when a cutoff value 5.44 was used (AUC = 0.785, 95% CI, 0.708–0.862) [18]. Ayna B. et al. showed that a cutoff NLR value of 1.93 had 83% sensitivity and 54% specificity in differentiating SLE patients with or without nephritis [7]. While Soliman et al. used a cutoff value of 2.2 and reported 74.4% sensitivity and 77.5% specificity for prediction of SLE nephritis [1]. The domestic study of Nguyen Thi Kim Thanh used a cutoff value of 2.04 and reported 77.9% sensitivity and 76% specificity [9]. However, the AUCs for PLR are less than 0.7 so it was not valid in predicting LN. This was agreed in Soliman et al., [1], Nguyen Thi Kim Thanh [9]. The reasons for the difference in values of NLR, PLR in predicting LN were relative changes in leukocytes such as neutropenia, lymphopenia in system inflammation and cellular immune response, small sample size, short study period, and most of the patients in our study used corticosteroids that could affect CBC results.

Limitations of the study:

- It was a single-center study with a cross-sectional design. Therefore, its ability to infer a causal relation between NLR and renal involvement in SLE was limited.

- The study was based on a single measurement of CBC that may not reflect the relation over time. Otherwise, each WBC count could be changed by dehydration/rehydration and diluted blood specimens.

- The sample size was relatively small.

- In the study, some patients have undergone treatment that resulted in a change in WBC count.

5. CONCLUSION

- NLR in predicting lupus nephritis: a sensitivity of 51.2% and a specificity of 95.5% when a cutoff value of 4.97.

- PLR has no value in the prediction of lupus nephritis.

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