Case-controlled Study

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Systemic lupus erythematosus disease activity and neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: a cross-sectional case–control study

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Background: Systemic lupus erythematosus (SLE) is an autoimmune disease with unknown etiology. It involves multiple organs and presents as varying clinical manifestations such as renal involvement (nephritis) and hematological disorders.

Materials and Methods: One hundred sixty people, divided equally into two groups: SLE patients, diagnosed according to the 2010 American College of Rheumatology/European League Against Rheumatism criteria, and healthy controls matched in age and gender, attending the University Hospitals between April 2019 and January 2021. White blood cells count, neutrophils count, lymphocytes count, platelet count, erythrocyte sedimentation rate, C-reactive protein, serum complements (C3 and C4), anti-double-stranded deoxyribonucleic acid, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the SLE disease activity by using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was compared between the patient group and the control group. Demographic data were collected from all participants, and data on the disease, including disease durations and disease activity, were only collected from the patients.

Results: The age of the patients was 30.49 ± 10.979 years, while it was 34.54 ± 13.710 years in the control group ($P = 0.249$). In all, 90% were females and 10% were males in the patient's group, while 85% were female and 15% were males in the control group. NLR and PLR were significantly higher in SLE patients compared to healthy control. A significant relation was found between SLEDAI and NLR and PLR.

Conclusion: The NLR and PLR are correlated with disease activity while also being cost-effective.

Keywords: disease activity, NLR, PLR, SLE, SLEDAI

Background

Systemic lupus erythematosus (SLE) is an autoimmune disease with unknown etiology. It involves multiple organs and presents varying clinical manifestations such as renal involvement (nephritis) and hematological disorders[1]. There are simply available laboratory indicators that evaluate disease activity in SLE patients[2]. Lymphopenia, which is the most frequent white blood cell (WBC) abnormality in SLE was found in 93% of patients during the active phase of the disease[3]. Furthermore, neutrophils also highly increase due to the complement pathway's inability to clear the lupus neutrophils, thus resulting in their accumulation[4]. The changes in WBC components were studied to detect disease activity in autoimmune diseases[5]. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two of the parameters marked in a complete blood count (CBC). NLR elevation can be a marker for inflammation in some autoimmune diseases[6,7].

NLR and PLR are newly discovered and relatively inexpensive biomarkers, possessing diagnostic and predictive capabilities in SLE[8]. Our present study's main goal was to find or confirm a possible link between NLR and PLR and SLE disease, disease activity, and lupus nephritis.

HIGHLIGHTS

- A blood test can provide us with neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).
- NLR and PLR could be suitable markers for systemic lupus erythematosus (SLE) activity.
- Our study suggests that NLR and PLR could be good indicators of SLE activity.

Materials and methods

Study design and sample size

The sample size, when calculated with a confidence interval of 95% was 80 SLE patients.

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Our sample size was 160 participants who entered this cross-sectional case–control study, 80 SLE patients diagnosed according to the American College of Rheumatology and The European League Against Rheumatism (ACR/EULAR) criteria[9], and 80 healthy controls from the hospital staff were enrolled in the study. All the participants visited Rheumatology Departments at Damascus Hospital between April 2019 and January 2021.

Trials have been performed by the World Medical Association Declaration of Helsinki, and the Ethics Committee of Damascus University has approved this study. All adult patients, before participation, signed informed consent forms. Meanwhile, informed consent was obtained from the parents and legal guardians of patients under 16 years old.

The work has been reported in line with the STROCSS (strengthening the reporting of cohort, cross-sectional and case–control studies in surgery) guidelines[10].

Inclusion criteria

SLE patients were diagnosed according to ACR/EULAR 2010 criteria[9], and healthy controls were matched for age and gender. We have not had any cases diagnosed recently because our hospital closed the outpatient clinics and decreased admissions to the hospital by 50% for more than a year during the coronavirus disease 2019 (COVID-19) epidemic.

Exclusion criteria

Included are other autoimmune diseases, inflammatory arthritis, SLE patients with antiphospholipid syndrome, active infections, hematologic and lymphoproliferative disorders, malignancies, hepatosplenic diseases, cardiovascular disease, diabetes mellitus, thyroid disorders, renal diseases, iron deficiency anemia, blood transfusions during the last 6 months, pregnant women, and women who recently gave birth within the last 6 months.

Measurements and parameters

(1) ACR/EULAR 2010 criteria to diagnose SLE: positive antinuclear antibody (ANA) $\geq 1:80$, and the presence of 10 points.
(2) SLEDAI[11], for assessment of disease activity.

Disease activity is classified according to points: as remission/mild disease (0–5 points), moderate disease (6–10 points), and severe disease (>10 points). Patients were diagnosed with lupus nephritis if their renal SLEDAI was greater than 8, as shown in Table 1, which is summarized by Gladman *et al*.[12]

Laboratory tests

Anemia was diagnosed if the hemoglobin level in males was less than 13 mg/dl, and less than 12 mg/dl in females, according to the definition by WHO[13].

Statistical analysis

We carried out SPSS version 23 for Windows (IBM Corporation, Armonk, New York, USA). The quantitative data were expressed as mean, SD, and range, while qualitative data were expressed as frequency and percentages. We used Student's *t* test for the difference between mean values of the studied parameters among the groups. Correlations between NLR and PLR were also assessed. *P* value less than 0.05 was considered statistically significant.

Results

Our sample size was 160 participants in this cross-sectional case–control study, which was conducted at the University Hospitals in Damascus, Syria, between October 2019 and June 2021. We had 80 SLE patients and 80 healthy people were selected from the two hospitals.

All parameters and relations were collected and analyzed the results.

Age and gender

The patient's age was 30.5 ± 10.979 years, while it was 34.4 ± 11.710 years, in the control group. In the patient's group, 90% were females and 10% were males, while, in the controls, 85% were females and 15% were males. The average duration of the disease was 5 ± 3.4 years, with a range of 1–9 years. Demographic data are shown in Table 2.

The clinical manifestations in SLE patients

The majority of our patient's clinical manifestations during the active disease was fever, arthritis, lupus headache, seizure, serositis, alopecia, butterfly rash, photosensitivity, and oral ulcers.

Epilepsy was found in 7 patients (5 patients, with active renal disease, and 2 patients, with vasculitis), the cerebral vascular accident was only found in 2 patients, and active renal disease (renal SLEDAI >8) was found in 10 patients with SLEDAI greater than 10.

The laboratory measurements

WBC, neutrophils, lymphocytes, platelet, NLR, and PLR, were analyzed in both groups. With SLEDAI greater than 18, four patients had leukopenia and thrombocytopenia, while leukopenia was alone found in one patient. The analyzed parameters data, without the exclusion of the patients with leukopenia, and/or thrombocytopenia are shown in Table 3.

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-ds DNA, and complements 3 and 4 (C3, C4) were analyzed in both groups (Table 4).

Proteinuria was found in five patients with inactive renal SLEDAI greater than 8, and with active disease (SLEDAI >10).

NLR value in both groups

NLR values in the control group were significantly decreased in comparison to SLE patients ($P = 0.000$).

PLR value in both groups

PLR values in the control group also significantly decreased in comparison to SLE patients ($P = 0.000$).

The SLEDAI

According to the SLEDAI score: 52 (65%) patients had a severe score, 14 (17.5%) patients had a moderate score, and only 14 (17.5%) patients had a mild/remission score. SLEDAI score was 15.713 ± 9.075, ranging from 0 to 38 (Table 5, Fig. 1).

The relationship between NLR, PLR, SLEDAI, ESR, and CRP

There was a significant relationship between NLR, PLR, and SLEDAI, as shown in Table 6.

Table 1

Disease activity classification.

SLEDAI-2K score	Descriptor	Definition
8	Seizure	Recent onset, exclude metabolic, infectious, or drug causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality
8	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function
8	Visual disturbance	Retinal changes
8	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves
8	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia
8	Cerebrovascular accident	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion)
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis
4	Urinary casts	Heme granular or red blood cell casts
4	Hematuria	>5 red blood cells/high power field. Exclude stone, infection, or other cause
4	Proteinuria	>0.5 g/24 h
4	Pyuria	>5 white blood cells/high power field. Exclude infection
2	Rash	Inflammatory type rash
2	Alopecia	Abnormal, patchy, or diffuse loss of hair
2	Mucosal ulcers	Oral or nasal ulcerations
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion or pleural thickening
2	Pericarditis	Pericardial pain with at least one of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation
2	Low complement	Decrease in CH50, C3, or C4
2	Increased DNA binding	Increased DNA binding by Farr assay
1	Fever	>38°C. Exclude infectious cause
1	Thrombocytopenia	$<100\,000$ platelets/$\times 10^9$/l, exclude drug causes
1	Leukopenia	<3000 white blood cells/$\times 10^9$/l, exclude drug causes

Summarized from Gladman *et al.*[12]

C3, complement protein 3; C4, complement protein 4; CH50, 50% hemolytic complement activity; DNA, deoxyribonucleic acid; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

There was a significant relationship between NLR, PLR, ESR, and CRP levels (Table 7).

The relationship between NLR, PLR, and renal disease

We could not analyze this static correlation, as there were only 10 patients with active renal disease (SLEDAI >8) in our sample patients compared to 70 patients with nonactive renal disease, so statistically, the results will be incorrect. All the patients with active renal disease had SLEDAI greater than 10.

The treatment

No drug naïve patients were in our study. Predilone, hydroxychloroquine, and azathioprine were used in the majority of patients when they enrolled in the study. Predilone (7.5–80 mg/day) and hydroxychloroquine (200–400/day, related to the weight of the patients) were used in 100% of our patients. In all, 38 SLE patients were on azathioprine (50–150 mg/day, related to the weight of patients) treatment. Additionally. 14 SLE patients were on mycophenolate (500 mg twice/day), and 6 SLE patients were on intravenous (i.v.) cyclophosphamide (500–900 mg/month, according to the body surface). None of our patients had had biologics.

Proteinuria was found in 5 patients who were receiving mycophenolate (4 patients), cyclophosphamide (1 patient), and active renal disease was found in 10 patients, who were receiving mycophenolate. The four patients who had vasculitis were on cyclophosphamide treatment. One patient who had a cerebral vascular accident was on cyclophosphamide treatment.

Table 2

Demographic data of the two groups.

	Control group (80)	Patient group (80)
Age (years), mean ± SD	34.54 ± 11.710 (17–61)	30.49 ± 10.979 (14–59)
Gender		
Female (*n*, %)	68 (85)	72 (90)
Male (*n*, %)	12 (15)	8 (10)

The relationship between NLR, PLR, and treatment

Corticosteroids and hydroxychloroquine

We could not study this relationship as all of our patients were on prednisolone treatment with different doses and hydroxychloroquine.

Azathioprine

The NLR values were (1.844 ± 0.40) and (1.171 ± 2.221) in SLE patients with azathioprine treatment and SLE without azathioprine treatment, respectively. Meanwhile, the PLR values were (7.414 ± 1.996) and (11.774 ± 11.894) in SLE patients with azathioprine treatment and SLE without azathioprine, respectively.

No significant correlation was found between SLE patients with azathioprine treatment and SLE without azathioprine treatment, NLR ($P = 0.213$) and PLR ($P = 0.189$).

Mycophenolate and cyclophosphamide

We could not study this relation as 14/56 patients were on mycophenolate treatment and only 6/56 patients were on cyclophosphamide.

Table 3

WBC, hemoglobin, platelets, NLR, and PLR.

	Control group (80)	Patient group (80)
WBC ($\times 10^3/mm^3$), median (range)	6.935 ± 1.623 (4.68–9.03)	6.626 ± 4.481 (1.20–17.8)
Neutrophils ($\times 10^3/mm^3$), median (range)	58.605 ± 5.234 (49–65.6)	67.518 ± 13.631 (43–89)
Lymphocytes ($\times 10^3/mm^3$), median (range)	32.945 ± 5.607 (26.6–42)	22.815 ± 10.973 (6–45.6)
Hemoglobin (g/dl)	12.2 ± 1.3 (9.1–14.5)	8.8 ± 1.4 (6.1–11.2)
Platelets ($/mm^3$), median (range)	237.2 ± 47.28 (160–297)	195 ± 108.77 (24–420)
NLR: median (range)	1.844 ± 0.40 (1.160–2.430)	4.124 ± 2.942 (1.011–14.830)
PLR: median (range)	7.414 ± 1.996 (4.730–10.310)	11.774 ± 11.894 (0.730–48)

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; WBC, white blood cells.

Discussion

SLE is an autoimmune disorder characterized by nuclear antigens–antibodies, systemic inflammation, and several clinical manifestations, with relapsed and remitted course.

Women are affected in more than 90% of SLE patients, especially at the age of childbearing[1,14]. The median age of our SLE patients was 30.5 years, and the percentage of women was 90%.

Beyond genetic and environmental factors, cytokine imbalances trigger inflammation, which affects the hematopoiesis process[15,16]. Chronic inflammation can cause lymphopenia and/or neutrophilia, as they use up WBCs faster than they are produced[17,18]. Using absolute counts, NLR and PLR are calculated. These ratios have been used as a marker of inflammation in various diseases, such as connective tissue diseases, cardiovascular disease, malignancies, and others[19].

In SLE, inflammation causes lymphopenia and neutrophilia, and that can explain high NLR in SLE patients, especially with an active course[20,21]. Lymphopenia is associated with renal involvement, high doses of corticosteroids, and cyclophosphamide treatment, which means that it may be used as a marker for renal involvement[22].

The hematologic manifestations are common at the time of diagnosis and throughout the disease, including anemia, especially inflammatory-origin chronic anemia, pancytopenia, neutropenia, lymphopenia, thrombocytopenia, leukocytosis, hepatomegaly, splenomegaly, lymphadenopathy, and these disturbances maybe a manifestation of SLE, and/or caused by the treatment[1,23].

The hydration status and diluted blood samples can cause changes in WBCs count and subset[24]; for that, we analyzed the obtained blood samples of our results within the first hour.

Table 4

ESR, CRP, anti-ds DNA, C3, and C4 in both groups.

	Control group (80)	Patient group (80)
ESR (mm/h), mean ± SD	20.00 ± 0.00 (0–20)	36.34 ± 18.24 (20–72)
CRP (mg/l), median (range)	3 ± 0 (2–6)	7.4 (6–16)
Anti-ds DNA		
Negative (*n*, %)	80 (100)	65 (81.25)
Positive (*n*, %)	0 (0)	15 (18.75)
C3, median	115.50 (96.19–176.20)	79.50 (45–117.60)
Range	95–200	17–190
C4, median (IQR)	34.00 (29.00–45.00)	22.50 (10.00–34.00)
Range	22–69	3–60

Anti-ds DNA, anti-double-stranded DNA; C3, complement 3; C4, complement 4; CRP, C-reactive protein; ESR, erythrocyte sedimentation; IQR, interquartile range.

Compared with healthy individuals, the risk of mortality in SLE patients was found to be two to five times higher, and the most frequent causes of death were active SLE, thrombosis, and infections[25]; for that, the global score systems, and SLEDAI, which provides an overall measure of activity, and individual organ/system assessment scales have been developed[26].

As NLR and PLR are cost-effective easy-calculated markers of inflammation, recent studies have evaluated the relationship between these ratios and SLE and its correlation with disease activity[27].

NLR and PLR were significantly higher in patients with lupus as compared with healthy controls[1,19,21]. Furthermore, these ratios were also higher in lupus nephritis patients versus those without, and nonsignificant differences between naive and relapsing nephritis patients.

In some studies, a positive correlation was found between NLR and PLR, which were also higher in SLE patients with proteinuria, elevated CRP, elevated ESR, and elevated IL-6 in lupus nephritis[1], while other research did not reveal this correlation[19,27].

Table 5

The percent of SLEDAI.

	Percent (number)
0	2.5 (2)
2	2.5 (2)
4	3.8 (3)
5	8.8 (7)
6	2.5 (2)
8	10.0 (8)
10	5.0 (4)
11	2.5 (2)
12	2.5 (2)
14	2.5 (2)
16	1.3 (1)
17	10.0 (8)
18	15.0 (12)
20	10.0 (8)
21	3.8 (3)
24	2.5 (2)
25	1.3 (1)
29	2.5 (2)
30	2.5 (2)
31	2.5 (2)
32	3.8 (3)
38	2.5 (2)
Total	100 (80)

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

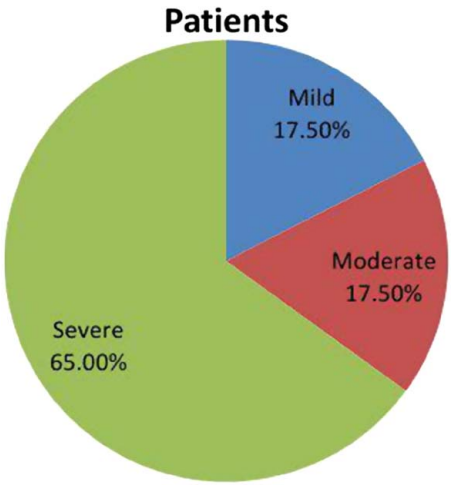

Figure 1. The percentage of Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

However, NLR and PLR are affected by age (>65 years) and sex[28]; for that reason, we did not study this correlation because the median age of our patients was 30.5 years and the majority of our patients were females.

Our study found increasing levels of NLR and PLR in SLE patients when compared to healthy controls. Besides, active SLE patients had higher levels of both ratios than patients without disease activity, and these ratios were correlated with CRP, ESR, and SLEDAI scores. Our results are in accordance with Lee and Song[19] and Qin *et al.*[27], who found higher levels of NLR and PLR in SLE patients as compared to healthy controls. Besides, active SLE patients had higher levels of both ratios than patients without disease activity, and these ratios were correlated with SLEDAI scores; meanwhile, NLR was positively correlated with CRP and ESR. Moreover, Wu *et al.*[21], Abdulrahman *et al.*[29], and Soliman *et al.*[1] found higher NLR and PLR in patients compared to those of the controls. SLEDAI scores positively correlated with NLR and PLR. Furthermore, SLE patients with nephritis had higher NLR levels found in lupus nephritis compared to those without nephritis. Yolbas *et al.*[30] found NLR and PLR to be higher in SLE patients as compared to healthy control. We could not analyze the correlation of NLR, and PLR between SLE patients with active renal disease, and SLE patients with nonactive renal disease, as there were only 10 patients with active renal disease (SLEDAI >8) in our sample patients compared to 70 patients with nonactive renal disease, so statically the results will be incorrect. No significant correlation was found between SLE patients with azathioprine treatment, SLE without azathioprine treatment, NLR, and PLR. We had not studied the NLR and PLR correlation with the other used treatment in our study. We did not find any study that compared this ratio and the SLE treatment.

Table 6
NLR and PLR correlation with SLEDAI scores.

	NLR ratio		PLR ratio	
	R	*P*	*R*	*P*
SLEDAI	0.384	0.000	0.721	0.000

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Table 7
The relationship between NLR, PLR, and ESR and CRP levels.

	NLR ratio		PLR ratio	
	R	*P*	*R*	*P*
ESR	0.525	0.001	0.512	0.001
CRP	0.371	0.021	0.361	0.023

CRP, C-reactive protein; ESR, erythrocyte sedimentation; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

As this study was mostly enrolled during the COVID-19 quatrain, only patients with severe symptoms attended our hospitals, and our results may change with a different sample of SLE patients.

Our study had some limitations. Firstly, the relatively small sample size was taken from the two University hospitals because the time of the study was during the COVID-19 quatrain. Secondly, we did not study the influence of active renal lupus on NLR and PLR. The main advantages we can get from our results are that NLR and PLR can be easily calculated from routine blood counts and are less costly as compared to other inflammatory cytokines. In addition, these ratios are relatively stable as each WBCs count could be changed by dehydration–rehydration and diluted blood specimens.

Conclusion

The NLR and PLR are useful indicators of disease activity while also being cost-effective. Future large follow-up studies are required to better assess this correlation through an evaluation of these ratios in the same patient over time.

Ethical approval

Trials have been performed in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was given by the ethics committee of the Faculty of Medicine, Damascus University.

Patient consent

Written informed consent was obtained from adult patients. Written informed consent was obtained from the parents and legal guardians of patients under 16 years old.

Consent for publication

Not applicable.

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Author contribution

S.A.: reviewed the literature, designed the study, collected data, and wrote the results section; N.K.: reviewed the literature and wrote the discussion section; B.A.-G.: the corresponding author, reviewed the literature and wrote the article's abstract, introduction, and

conclusion sections; M.K.: the supervisor, reviewed the literature and wrote the discussion section. All authors accepted and approved the final manuscript.

Conflicts of interest disclosure

The authors have reported no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Systemic lupus erythematosus disease activity and neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: a cross-sectional case-control study.
2. Unique identifying number or registration ID: researchregistry8331.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-the-registry#home/registrationdetails/6328d5302aa1c5002127cd2f/

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Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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