International Journal of Research in Medical Sciences
Hossen SI et al. Int J Res Med Sci. 2024 Nov;12(11):4081-4090
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20243354

Original Research Article

Role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as markers of disease activity in systemic lupus erythematosus patients with or without renal involvement

Sheikh Imran Hossen[1]*, Jyoti Vaskar Saha[1], Muhammad Saiful Ahsan Rana[1], Gul Jannat[1], M. Aminul Islam[1], M. Nazrul Islam[2]

[1]Department of Nephrology, Mugda Medical College Hospital, Dhaka, Bangladesh
[2]Department of Nephrology, Dhaka Medical College, Dhaka, Bangladesh

Received: 12 July 2024
Accepted: 25 September 2024

***Correspondence:**
Dr. Sheikh Imran Hossen,
E-mail: dr.s.imran.nephrology@gmail.com

ABSTRACT

Background: In systemic inflammation, white blood cells show neutrophilia and lymphopenia. The neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are emerging as key markers for systemic inflammation. This study aims to evaluate NLR and PLR as markers of disease activity in systemic lupus erythematosus (SLE) patients with or without renal involvement.
Methods: A cross-sectional study was conducted at Dhaka medical college and hospital (DMCH), national institute of kidney disease and urology (NIKDU), and Bangabandhu Sheikh Mujib medical university (BSMMU). It included 90 newly diagnosed SLE patients (with or without renal involvement) and 30 age- and sex-matched healthy controls. Patients were divided into two groups: active disease SLE disease activity index (SLEDAI score ≥8) and inactive disease (SLEDAI score <8). Data were analyzed using SPSS version 26.
Results: Results showed that both NLR and PLR were significantly higher in SLE patients compared to controls (both $p<0.001$) and were elevated in active disease (both $p<0.001$). NLR levels were higher in patients with renal involvement ($p<0.05$). NLR and PLR positively correlated with SLEDAI score, anti-dsDNA, and ESR, and negatively with C3 and C4. NLR differed significantly across lupus nephritis classes and correlated positively with activity index, while PLR did not. For predicting disease activity in SLE with renal involvement, NLR and PLR cut-off values were 2.41 (80% sensitivity, 51.1% specificity) and 178.4 (80% sensitivity, 57.8% specificity), respectively. For SLE without renal involvement, NLR was 2.23 (71.1% sensitivity, 52.02% specificity) and PLR was 159.6 (75.6% sensitivity, 73.3% specificity).
Conclusions: NLR and PLR are promising biomarkers for managing SLE patients, irrespective of renal involvement.

Keywords: SLE, NLR, PLR, SLEDAI

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown aetiology with various clinical manifestations affecting different organs and has diversity in its course of illness and prognosis.[1] The majority of SLE patients experience repeated exacerbations (flares) during the disease course which may adversely impact on short and long-term outcome.[2] Various SLE flare definitions have been developed in the context of clinical trials and are generally based on one or more of the following parameters: a) increase in disease activity score assessed by a validated index, b) appearance of new or worsening of disease manifestations, (e.g., increase in proteinuria in the case of renal flares), c) change in the physician's global assessment (PGA) scale towards more

active/severe disease, and d) need for treatment intensification (e.g., an increase of steroid dosage).[3] Lupus nephritis (LN) is an immune complex glomerulonephritis which involves about fifty percent of SLE patients.[4] Renal involvement is one of the main determinants of poor prognosis of SLE.[5] So early diagnosis and treatment of lupus nephritis is very important to improve survival in SLE patients.[6] Although pathogenesis of SLE is not clear completely, genetic, environmental and hormonal factors play important role in pathogenesis of SLE.[7,8] Unrestricted hyperactivation of the immune system may lead to the overproduction of autoantibodies, immune complex deposition, inflammatory cytokine release and eventually onset of disease and chronic inflammation also plays a key role in pathogenesis like pathological process involved in all autoimmune diseases.[9] Many laboratory parameters are used to check the disease activity such as low complement and increased anti-dsDNA.[10,11] Renal biopsy is still the gold standard investigation for evaluation of suspected flares in lupus nephritis which carries some risks, importantly bleeding resulting in perirenal hematoma and blood transfusion.[12,13] But all these require highly developed laboratory facility which is not available everywhere. So, finding some simple laboratory investigations that are available in almost every healthcare facility to evaluate disease activity in SLE patients is a crucial issue. Different white blood cells show some changes in systemic inflammation such as neutrophilia and lymphopenia and lymphopenia is seen in about ninety-three percent of cases in SLE.[14] Platelet system activation is an important factor in SLE.[15] Different studies showed that NLR can be used as an inflammatory marker in different autoimmune diseases such as rheumatoid arthritis (RA), psoriasis, primary Sjögren syndrome and ulcerative colitis.[16-20] NLR and PLR have recently been investigated as new prognostic indicators for a large number of malignancy studies.[21,22] Moreover, numerous previous studies have shown that NLR and PLR were associated with morbidity and mortality in different chronic diseases such as type 2 diabetes mellitus, acute coronary syndrome, heart failure, hypertension and infective endocarditis.[23-27] There are many studies showing that NLR is a good indicator of inflammation.[28] Platelets also play an active role in inflammation and have a regulatory effect on the immune system as well.[15,29] So the aim of this study is to evaluate the role of NLR and PLR as markers of disease activity in SLE patients with or without renal involvement. Disease activity measurement is a crucial issue in SLE patient's management. Early recognition of flares would reduce the long-term disease and drug-related comorbidities and adverse effects. The traditional markers of disease activity such as anti-dsDNA, complement level, ESR, activity index in renal biopsy are not available everywhere and also expensive. On the other hand, NLR and PLR are inexpensive and easily available tools. But there are very few studies on their role as disease activity markers in SLE patients. So, this study is to evaluate the role of NLR and PLR as disease activity markers in systemic lupus erythematosus patients with or without renal involvement so that these tools can be used in early detection and management of SLE flares and reduce the morbidity and mortality of SLE patients.

Objective

General objective

General objective was to evaluate of the role of NLR and PLR as disease activity marker in SLE patients with or without renal involvement.

Specific objectives

Specific objectives were to determine the association of NLR and PLR with SLEDAI score. To determine the association of NLR and PLR with other markers of disease activity e.g. ESR, serum C3, C4 and antids-DNA. To evaluate the relationship of NLR and PLR with different classes of lupus nephritis and activity and chronicity index in renal biopsy in case of SLE patients with renal involvement.

METHODS

Study design

This cross-sectional study was conducted at DMCH BSMMU, and the NIKDU from March 2020 to August 2021.

Study population

Group A: Diagnosed case of SLE patients with or without renal involvement having active disease.

Group B: Diagnosed case of SLE patients with or without renal involvement having inactive disease.

Group C: Age and sex matched healthy individual.

Sample size

Sample size was determined by power analysis for a single proportion. Formula for sample size determination for single proportion:

$$n=\frac{[Z_\beta\sqrt{P(1-P)}+Z_\alpha\sqrt{P_0(1-P_0)}]^2}{(P-P_0)^2}$$

P=Proportion under alternative hypothesis (HA) that is proposed to be detected P0=Proportion under null hypothesis (H0)

We hypothesized that sensitivity of NLR in the assessment of disease activity in systemic lupus erythematosus patients was 90.0% or greater. The sample size was calculated for a power level of 80% (where,

Zβ=0.84), an α error of 0.05 (95% confidence level, where Zα=1.96, two tail) and Qin et al revealed NLR had sensitivity of 74.7% for assessment of disease activity in SLE patients.[39]

Here, n=Sample size Zβ=0.84 26 Zα=1.96, p=91.0%=0.910 (alternative hypothesis in this study), P0=74.7%=0.747 (Qin et al).[39]

$N=\frac{[0.84\sqrt{0.91(1-0.91)}+1.96\sqrt{0.747(1-0.747)]^2}}{(0.91-0.747)^2}$=44.92 (estimated sample size)

Target sample size was 45 in group A, 45 in group B and 30 in C. Therefore, total sample was 120.

Sampling technique

It was a purposive sampling

Inclusion criteria

Patients with age ≥18 years, both male and female, newly diagnosed case of SLE (according to 2019 EULAR/ACR classification criteria of SLE) patients with or without renal involvement were included.

Exclusion criteria

Patients who have active infection, patients having malignancies and lymphoproliferative disorders. Patients with other autoimmune diseases, on drugs which can alter WBC count and pregnant women were excluded.

Study procedure

Approval for this study was initially obtained from the research review committee (RRC) of the department of nephrology, DMCH, followed by ethical approval from the ethical review committee (ERC) of Dhaka medical college. Due to DMCH being declared a COVID-19 dedicated hospital, additional approval was secured from the respective authorities to collect data from the department of nephrology, NIKDU, and the department of rheumatology, BSMMU, to ensure an adequate sample size. Patients presenting with clinical features of SLE, according to the 2019 EULAR/ACR classification criteria, were approached at DMCH, NIKDU, and BSMMU. After obtaining detailed histories, conducting clinical examinations, and performing relevant investigations, participants meeting the inclusion and exclusion criteria were enrolled. Written informed consent was obtained from each participant after explaining the study's aims and procedures. Patients with SLE (per 2019 EULAR/ACR criteria) exhibiting proteinuria >0.5 gm/day and/or active urine sediment were evaluated for renal biopsy suitability, and those without contraindications underwent the procedure. Ninety patients, confirmed to have SLE with or without renal involvement, were included and assessed for disease activity using the SLEDAI score. Based on their SLEDAI scores, they were categorized into two groups: Group A (active disease) and Group B (inactive disease). Additionally, 30 age- and sex-matched controls (Group C) were included for comparison.

Laboratory investigations, including urine analysis, CBC, ESR, serum creatinine, electrolytes, RBS, ECG, chest X-ray, and USG of KUB, were performed at DMCH, NIKDU, and BSMMU. Specific tests such as ANA, C3, C4, 24-hour urinary total protein (UTP), and anti-dsDNA were conducted at BSMMU, and renal histopathology was done at armed forces institute of pathology (AFIP).

Urine samples were collected following strict hygiene protocols, and venous blood samples were obtained with aseptic precautions for various tests. CBC was performed using an automated hematology analyzer, while other tests were conducted using appropriate methods and equipment. For 24-hour UTP estimation, patients collected urine over 24 hours, and samples were appropriately labeled and sent for analysis. Renal biopsies were performed under ultrasound guidance using a spring-loaded biopsy gun, and specimens were analyzed at AFIP for light microscopy and direct immunofluorescence. NLR and PLR calculated from CBC reports. Data were analyzed using SPSS version 26.

Data collection

Data were collected in a pre-tested questionnaire by taking history, examining the patients clinically and laboratory finding.

Analysis of the study

Data were collected, tabulated, and analyzed statistically using an IBM personal computer and the statistical package SPSS version 26 (Chicago, Illinois, USA). Two types of statistics were used. To express the quantitative data, mean and SD were used, whereas to express the qualitative data, frequency and percentage (%) were used. Unpaired T test was used to find out the presence of any significant difference between two groups for a normally distributed quantitative variable. Chi Square test was done to see significant difference between more than two qualitative variable and ANOVA test was done to see difference between more than two quantitative variables. Pearson's correlation was used to show an association between two quantitative variables. Receiver operating characteristic (ROC) curve was used to find the discrimination values of NLR and PLR for active and inactive SLE patients with or without. Renal involvement. A level of $p<0.05$ was considered statistically significant.

Ethical consideration

The researcher was duly concerned about the ethical issues related to the study. In this study the following criteria was followed to ensure maintaining the ethical

values. Formal approval was taken from RRC of department of nephrology, DMCH and ethical clearance was taken from the ethical review committee of Dhaka medical college for conducting the study. Confidentiality of the person and the information was maintained, observed and unauthorized persons didn't have any access to the data. C. Informed written consent was taken from the subject.

The content of the consent requirements was as such: Explanation of the nature and purpose of the study. Explanation of the procedure of study. Explanation that they have the right to refuse, accept and withdraw to participate in the study. The participants didn't gain financial benefit from this study.

RESULTS

In this study total 90 patients of SLE with or without renal involvement and 30 age and sex matched healthy control were included. Among 90 SLE patients, 45 patients had active disease (SLEDAI score ≥8) (group A) and another 45 patients had inactive disease (SLEDAI score <8) (group B). Thirty (30) age and sex matched healthy controls were labelled group C.

Table 1: Distribution of cases in group A and B, (n=90).

Renal involvement status	Group A, (n=45)		Group B, (n=45)	
	N	%	N	%
SLE with renal involvement	30	66.7	21	46.6
SLE without renal involvement	15	33.3	24	53.4

Table 1 shows the distribution of the SLE patients by renal involvement status. It was observed that about two third (66.7%) patients were SLE with renal involvement in group A and 21(46.6%) in group B.

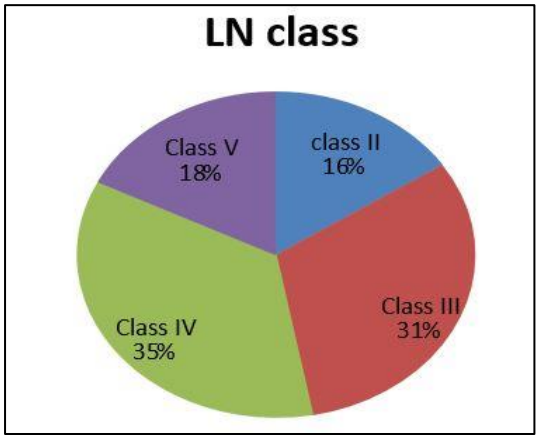

Figure 1: Distribution of the SLE patients with renal involvement by ISN/RPS classification of lupus nephritis.

Fifty one (51) SLE patients with renal involvement undergone renal biopsy. Among them 18(35%) were class IV, 16 (31%) were class III, 9 (18%) were class V and 8 (16%) were class II.

Table 2 shows the distribution of the study and control group by demographic profile. The mean age was 24.33±3.18 years in group A, 23.93±2.73 years in group B and 24.97±2.2 years in group C. Majority patients were female, 40 (88.9%) in group A, 43 (95.6%) in group B and 27 (90.0%) in group C. The difference of age and sex was not statistically significant (p>0.05) among three groups.

Table 3 shows comparison among study patients and control group by NLR and PLR. The mean NLR was 3.98±0.85 in group A, 2.25±0.41 in group B and 1.34±0.12 in group C. The mean PLR was 216.88±58.87 in group A, 139.09±21.11 in group B and 100.87±13.52 in group C. The difference of NLR and PLR were statistically significant (p<0.05) among three groups.

Table 4 shows comparison among study and control group regarding serological markers of disease activity. The mean C3 was 0.56±0.25 g/L in group A, 1.06±0.15 g/L in group B and 1.32±0.18 g/L in group C. The mean C4 was 0.07±0.02 g/L in group A, 0.15±0.09 g/L in group B and 0.3±0.06 g/L in group C. The mean ESR was 70.44±18.02 mm/h in group A, 46.13±10.97 mm/h in group B and 14.37±2.98 mm/h in group C. The mean anti-ds DNA was 209.73±31.64U/ml in group A, 145.82±22.09 U/ml in group B and 20.77±4.67 U/ml in group C. The difference of serological parameters was statistically significant (p<0.05) among three groups.

Table 5 shows the comparison of active SLE patients with renal involvement and without renal involvement by NLR and PLR. The mean NLR was 4.31±0.81 in SLE with renal involvement and 3.32±0.45 in SLE without renal involvement. The mean PLR was 228.20±45.77 in SLE with renal involvement and 194.25±75.69 in SLE without renal involvement. The difference of NLR was statistically significant (p<0.05) between two groups but no statistically significant difference in case of PLR.

Table 6 shows the comparison of NLR and PLR values depending on LN class. The mean NLR was 2.22±0.72 in class II, 3.68±0.88 in class III, 4.68±0.59 in class IV and 2.44±0.2 in class V. The difference of NLR was statistically significant (p<0.05) among four groups. The mean PLR was 187.03±29.46 in class 2, 191.29±43.64 in class 3, 202.02±36.1 in class 4 and 156.2±13.27 in class 5. The difference of PLR was not statistically significant (p>0.05) among four groups.

Pearson's correlation showed that NLR was positively significant correlated with SLEDAI score (r=0.772, p=0.001), Anti-ds DNA (r=0.815, p=0.001), ESR (r=0.481, p=0.002), Activity index (r=0.461, p=0.003), but not significant correlated with Chronicity index

(r=0.168, p=0.1001) and negatively significant correlated with C3 (r=-0.842, p=0.001) and C4 (r=-0.460, p=0.002). Pearson's correlation showed that PLR was positively significant correlated with SLEDAI score (r=0.682, p=0.001), Anti-ds DNA (r=0.718, p=0.001), ESR (r=0.373, p=0.003), but Activity index (r=0.371, p=0.057) and chronicity index (r=0.197, p=0.075) were not significantly correlated and it showed negatively significant correlation with C3 (r=-0.727, p=0.001) and C4 (r=-0.478, p=0.002).

Table 2: Comparison among study and control group regarding demographic data (n=120).

Demographic profile group	Group A (n=45)		Group B (n=45)		Group C (n=30)		P value
Age (in year)							
Mean±SD	24.33±3.18		23.93±2.73		24.97±2.2, 21,29		$^{a}0.291^{ns}$
Range (min, max)	19, 31		20, 29				
Sex							
Male	5	11.1	2	4.4	3	10.0	$^{b}0.483^{ns}$
Female	40	88.9	43	95.6	27	90.0	

*ns=not significant, [a]p value reached from ANOVA test, [b]p value reached from Chi-square test

Table 3: Comparison among study and control group regarding NLR and PLR (n=120).

Variables	Group A (n=45)	Group B (n=45)	Group C, (n=30)	P value
NLR				
Mean±SD	3.98±0.85	2.25±0.41	1.34±0.12	0.001^{s}
Range (min, max)	2.45, 5.74	1.35, 3.55	1.12, 1.56	
PLR				
Mean±SD	216.88±58.87	139.09±21.11	100.87±13.52	0.001^{s}
Range (min, max)	97.6, 316.3	88.1, 172.6	78.5,125.6	

*s=significant p value reached from ANOVA test.

Table 4: Comparison among study and control group regarding serological markers of disease activity (n=120).

Serological markers	Group A, (n=45)	Group B, (n=45)	Group C, (n=30)	P value
C3 (g/l)				
Mean±SD	0.56±0.25	1.06±0.15	1.32±0.18	0.001^{s}
Range (min,max)	0.23, 1.14	0.64, 1.21	0.94, 1.78	
C4 (g/l)				
Mean±SD	0.07±0.02	0.15±0.09	0.3±0.06	0.001^{s}
Range (min,max)	0.05, 0.14	0.07, 0.38	0.18, 0.39	
ESR (mm/h)				
Mean±SD	70.44±18.02	46.13±10.97	14.37±2.98	0.001^{s}
Range (min,max)	30,104	25, 68	8, 20	
Anti-ds DNA(U/ml)				
Mean±SD	209.73±31.64	145.82±22.09	20.77±4.67	0.001^{s}
Range (min,max)	134, 278	110, 198	12, 28	

*s=significant, p value reached from ANOVA test

Table 5: Comparison of active SLE patients with renal involvement and without renal involvement regarding NLR and PLR, (n=45).

Variables	SLE with renal involvement, (n=30)	SLE without renal involvement, (n=15)	P value
NLR			
Mean±SD	4.31±0.81	3.32±0.45	0.001^{s}
Range (min, max)	2.48, 5.74	2.45, 4.02	
PLR			
Mean±SD	228.20±45.77	194.25±75.69	0.067^{ns}
Range (min, max)	139.50, 316.30	97.6, 285.7	

*s=significant ns=not significant p value reached from unpaired t-test

Table 6: Comparison of NLR and PLR values depending on LN class, (n=51).

Variables	Class II, (n=8)	Class III, (n=16)	Class IV, (n=18)	Class V, (n=9)	P value
NLR					
Mean±SD	2.22±0.72	3.68±0.88	4.68±0.59	2.44±0.2	0.001^{s}
Range (min, max)	1.65, 3.55	2.35, 4.85	3.53, 5.74	2.2, 2.65	
PLR					
Mean±SD	187.03±29.46	191.29±43.64	202.02±36.1	156.2±13.27	0.057^{ns}
Range (min, max)	102.3, 211.05	150.8, 310.2	187.5, 316.3	132.8, 168.8	

*s=significant ns=not significant, p value reached from ANOVA test

Table 7: Pearson's correlations of NLR and PLR with disease activity markers of SLE.

Clinical parameters	NLR		PLR	
	R value	P value	R value	P value
SLEDAI score	0.772	0.001^{s}	0.682	0.001^{s}
Anti-ds DNA	0.815	0.001^{s}	0.718	0.001^{s}
ESR (mm/h)	0.481	0.002^{s}	0.373	0.003^{s}
C3 (g/l)	-0.842	0.001^{s}	-0.727	0.001^{s}
C4 (g/l)	-0.460	0.002^{s}	-0.478	0.002^{s}
Activity index	0.461	0.003^{s}	0.371	0.057^{ns}
Chronicity index	0.168	0.1001^{ns}	0.197	0.075^{ns}

ns: not significant; s: significant.

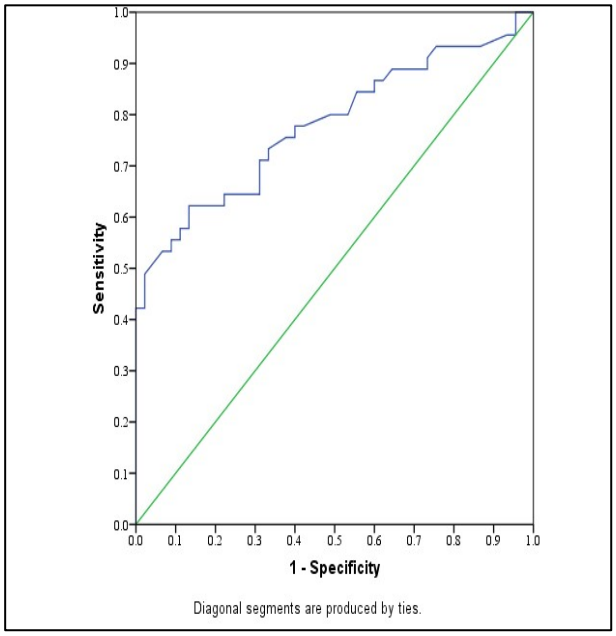

Figure 3: Receiver-operator characteristic curve of NLR for prediction of SLE with or without renal involvement status.

Based on the receiver-operator characteristic (ROC) curves NLR had area under curve 0.779. ROC was constructed by using NLR, which gave a cut off value 2.41 with 80.0% sensitivity and 51.1% specificity for prediction of disease activity in SLE with renal involvement. Based on the ROC curves PLR had area under curve 0.769. ROC was constructed by using PLR, which gave a cut off value 178.4 with 80.0% sensitivity and 57.8% specificity for prediction of disease activity in SLE patients with renal involvement.

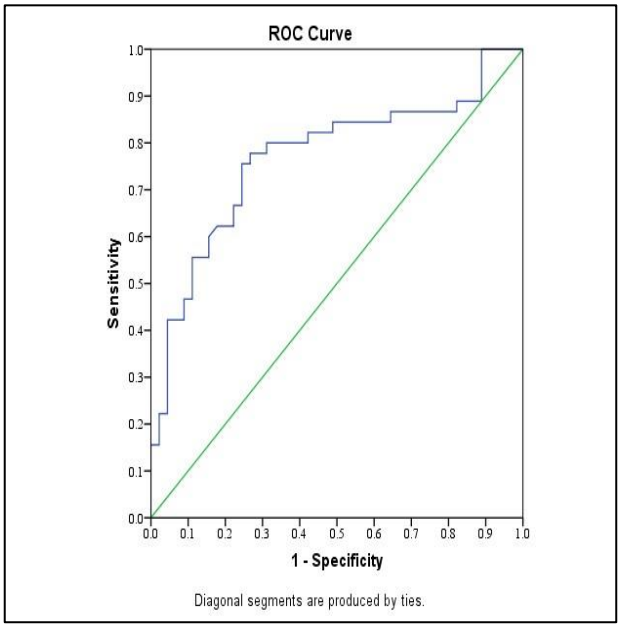

Figure 4: ROC curve of PLR for prediction of SLE with or without renal involvement status

Based on the ROC curves NLR had area under curve 0.779. ROC was constructed by using NLR, which gave a cut off value 2.23 with 71.1% sensitivity and 52.02% specificity for prediction of disease activity in SLE patients without renal involvement. Based on the ROC curves PLR had area under curve 0.769. ROC was constructed by using PLR, which gave a cut off value 159.6 with 75.6% sensitivity and 73.3% specificity for prediction of disease activity in SLE patients without renal involvement

DISCUSSION

SLE is a chronic inflammatory autoimmune disease with diverse clinical manifestations affecting various organs.[30] Most SLE patients experience repeated exacerbations (flares) that negatively impact their prognosis.[31] Different SLE flare definitions are based on parameters such as increased disease activity scores, new or worsening symptoms, and changes in the physician's global assessment (PGA).[32] The study aimed to evaluate the role of NLR and PLR as disease activity markers in SLE patients with or without renal involvement. Ninety SLE patients and 30 age- and sex-matched healthy controls were divided into three groups: Group A (active SLE), group B (inactive SLE), and group C (controls). The mean ages were 24.33±3.18 years for active SLE, 23.93±2.73 years for inactive SLE, and 24.97±2.2 years for controls. Maximum and minimum ages were 34 and 19 years, respectively. Similar mean ages were found in a study by Abd-Elhafeez et al while Cuenco et al reported higher mean ages.[33,34] SLE predominantly affects women, with 88.9% females in group A, 95.6% in group B, and 90.0% in group C, consistent with Cuenco et al and Cojocaru et al.[34,35]

The female-to-male ratio is 8-15:1 due to the complex effects of sex hormones on the immune system.[36,37] NLR was significantly higher in group A compared to groups B and C, and in group B compared to group C. SLE patients with renal involvement and active disease had higher NLR (4.31±0.81) than those without renal involvement (3.32±0.45) and both groups had higher NLR than inactive patients and controls (1.34±0.12), consistent with studies by Wu et al, Qin et al, and Soliman et al but contrasting with Yolbas et al.[38-41] High NLR in active SLE is due to systemic inflammation, immune dysregulation, and increased cytokine production.[38,42,43] PLR was significantly higher in group A compared to groups B and C, and in group B compared to group C. SLE patients with renal involvement and active disease had higher PLR (228.20±45.77) than those without renal involvement (194.25±75.69), with both groups showing higher PLR than inactive patients and controls (100.87±13.52). These results align with studies by Wu et al, Qin et al, Cuenco et al and Soliman et al but differ from Abd-Elhafeez et al.[33,38-40]

High PLR in active SLE is due to the decline in lymphocyte count relative to platelet count.[44] Anti-dsDNA levels were significantly higher in active SLE patients, especially those with renal involvement (217.30±27.85), compared to those without renal involvement (194.60±34.24), inactive patients (145.82±22.09), and controls (20.77±4.67), corresponding to studies by Yavuz et al and Luo et al.[45,46] High anti-dsDNA levels in active SLE are due to increased dsDNA binding by autoantibodies.[34] C3 and C4 levels were significantly lower in active SLE patients compared to inactive patients and controls, with lower levels in those with renal involvement (C3: 0.46±0.21; C4: 0.07±0.02) than those without renal involvement (C3: 0.76±0.20; C4: 0.08±0.02). These findings are consistent with studies by Wu et al, Qin et al, Yavuz et al, Cuenco et al, and Luo et al but contrast with Elwy et al.[34,38,39,45-47] Low complement levels are due to active consumption during immune complex deposition in active disease.[34,48,49,50]

Renal biopsy showed that 35% of patients had class IV lupus nephritis, 31% had class III, 18% had class V, and 16% had class II, consistent with Soliman et al.[40] NLR showed significant differences among lupus nephritis classes and positive correlation with activity index, while PLR did not, consistent with Soliman et al.[40] The best NLR cut-off value to predict disease activity in SLE with renal involvement was 2.41 (80% sensitivity, 51.1% specificity), and the best PLR cut-off value was 178.4 (80% sensitivity, 57.8% specificity), similar to Cuenco et al.[34] ROC curve analysis showed NLR cut-off of 2.23 (71.1% sensitivity, 52.02% specificity) and PLR cut-off of 159.6 (75.6% sensitivity, 73.3% specificity) for differentiating active SLE without renal involvement from inactive cases. NLR cut-off of 2.2 (90% sensitivity, 50% specificity) and PLR cut-off of 132.9 (95% sensitivity, 50% specificity) for predicting SLE activity.[40]

ESR was significantly higher in active SLE, especially with lupus nephritis, consistent with Wu et al and Huang et al but not with Ayna et al.[38,51,52] ESR variations may be due to factors unrelated to inflammation, such as age, sex, anemia, and renal failure.[53] NLR and PLR were positively correlated with SLEDAI score, anti-dsDNA, and ESR, and negatively correlated with C3 and C4, with significant correlations consistent with Cuenco et al, Farouk et al, and Soliman et al except for C3 in the latter.[34,40,54] Wu et al and Yolbas et al also reported significant correlations, but Huang et al and Qin et al showed varying results.[38,39,41,51] Differences in methodologies, patient characteristics, and drug use may explain these variations.

Limitations

The study's limitations include a relatively small sample size, which may restrict the generalization of findings in SLE patients, and the analyses were based on a single measurement of WBC counts, potentially not reflecting the relationship over time. Additionally, the cross-sectional design limited the ability to infer causal relationships between NLR, PLR, and disease activity. Furthermore, the influence of treatment on NLR and PLR was not investigated.

CONCLUSION

This study showed that both NLR and PLR were significantly higher in SLE patients with active disease than inactive disease and higher value for patients with renal involvement than without renal involvement. Moreover, it showed significant correlation of NLR and

PLR with SLEDAI score and other markers of disease activity. So NLR and PLR can be used as two new markers of disease activity for management of SLE patients with or without renal involvement.

Recommendations

Further studies with larger sample sizes are recommended to better understand the relationship between NLR, PLR, and disease activity in SLE patients. Additionally, research is needed to explore the causal relationship between NLR and PLR and disease activity, as well as to assess the impact of treatment on these ratios.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Hepburn AL, Narat S, Mason JC. The management of peripheral blood cytopenias in systemic lupus erythematosus. Rheumatology (Oxford). 2010;49(12):2243-54.
2. Petri M, Genovese M, Engle E, Hochberg M. Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. Am J Med. 1991;91(2):135-44.
3. Petri M, Buyon J, Kim M. Classification and definition of major flares in SLE clinical trials. Lupus. 2005;14(9):690-4.
4. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients with Lupus Nephritis, 1971 to 2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis Rheumatol. 2016;68(6):1432-41.
5. Suzuki K, Nagasawa K, Masukawa H. Prognosis and prognostic factors of patients with lupus nephritis. Nihon Rinsho Meneki Gakkai Kaishi. 2008;31(5):295-302.
6. Grande JP. Immunoglobulin A nephropathy and systemic lupus erythematosus nephritis. Curr Opin Nephrol Hypertens. 2011;20(1):38-42.
7. Carroll MC. The lupus paradox. Nat Rev Immunol. 2001;1(1):1-5.
8. Su DL, Lu ZM, Shen MN, Li XL, Sun LY. Roles of pro- and anti-inflammatory cytokines in the pathogenesis of SLE. J Biomed Biotechnol. 2012;2012:347141.
9. Goodnow CC. Multistep pathogenesis of autoimmune disease. Cell. 2007;130(1):25-35.
10. Liu CC, Ahearn JM, Manzi S. Complement activation in systemic lupus erythematosus: an update. Ann N Y Acad Sci. 2004;1051:302-12.
11. Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, et al. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford). 2005;44(7):902-6.
12. Giannico G, Fogo AB. Lupus nephritis: is the kidney biopsy currently necessary in the management of lupus nephritis? Clin J Am Soc Nephrol. 2013;8(1):138-45.
13. Chen TK, Estrella MM, Fine DM. Predictors of kidney biopsy complications in patients with systemic lupus erythematosus. Lupus. 2012;21(8):848-54.
14. Carli L, Tani C, Spera V, Vagelli R, Baldini C, Mosca M. Leukopenia and autoimmune diseases. Clin Rev Allergy Immunol. 2015;50(2):192-202.
15. Boilard E, Fortin PR, Lande R, Gerald FMW, Jonathan SC, Michael EW, et al. Platelets amplify inflammation in arthritis via collagenspecific immune complexes. J Immunol. 2010;184(9):5381-90.
16. Yazici S, Yazici M, Erer B, Erer B, Calik Y, Ozhan H, et al. The platelet-lymphocyte ratio: a simple, inexpensive and rapid prognostic marker for rheumatoid arthritis. Platelets. 2010;21(3):239-44.
17. Mercan R, Bitik B, Tufan A, Utku BB, Nuh A, Mehmet AO, et al. The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis. J Clin Lab Anal. 2016;30(5):597-601.
18. Sen BB, Rifaioglu EN, Ekiz O, Mehmet UI, Tugba S, Nihat S. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutan Ocul Toxicol. 2014;33(3):223-7.
19. Hu ZD, Sun Y, Guo J, Yuan-Lan H, Bao-Dong Q, Qian G, et al. Red blood cell distribution width and neutrophil to lymphocyte ratio are correlates of disease activity in primary Sjogren's syndrome. Clin Biochem. 2014;47(18):287-9.
20. Celikbilek M, Dogan S, Ozbakir S, Gökmen Z, Hamit K, Sebnem G, et al. Neutrophil-lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal. 2013;27(1):72-6.
21. Templeton AJ, McNamara MG, Seruga B, Francisco EV-B, Priya A, Alberto O, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 2014;106(6):dju124.
22. Templeton AJ, McNamara MG, Šeruga B, Francisco EVB, Priya A, Alberto O, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Treat Rev. 2014;40(7):919-28.
23. Tamhane UU, Aneja S, Montgomery D, Eva-Kline R, Kim AE, Hitinder SG, et al. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102(6):653-7.
24. Guasti L, Dentali F, Castiglioni L, Lorenzo M, Franca M, Alessandro S, et al. Neutrophils and clinical outcomes in patients with acute coronary

syndromes and/or cardiac revascularization. Thromb Haemost. 2011;106(4):733-43.
25. Uthamalingam S, Patvardhan EA, Subramanian S, Waleed A, William M, Marilyn D, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol. 2011;107(3):433-8.
26. Afsar B. Neutrophil-lymphocyte ratio as a prognostic marker in systemic lupus erythematosus. J Coll Physicians Surg Pak. 2014;24(8):556-9.
27. Sunbul M, Gerin F, Durmus E, Tarik K, Ibrahim S, Kursat T, et al. Neutrophil to lymphocyte and platelet to lymphocyte ratio in patients with dipper versus non-dipper hypertension. Clin Exp Hypertens. 2014;36(4):217-21.
28. Ahsen A, Ulu MS, Yuksel S, Kasım D, Mukremin U, Mujgan E, et al. As a new inflammatory marker for familial Mediterranean fever: neutrophil-to-lymphocyte ratio. Inflammation. 2013;36(6):1357-62.
29. Choi JH, Kim EJ, Cho YS. Platelet activation and interaction with leucocytes in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2014;53(10):1849-58.
30. Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929-39.
31. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(26):2110-21.
32. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.
33. Abd-Elhafeez H, Saber-Ayad M, Basyouni H, Fahim HH. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in systemic lupus erythematosus patients: Correlation with disease activity and nephritis. Egypt Rheumatol. 2017;39(2):69-75.
34. Cuenco CA, Yang Q, Luo Y. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in lupus nephritis: Correlation with disease activity and renal biopsy class. Int J Rheum Dis. 2020;23(5):717-26.
35. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Manifestations of systemic lupus erythematosus. Maedica (Bucur). 2011;6(2):138-43.
36. Lu LJ, Wallace DJ, Ishimori ML, Scofield RH, Weisman MH. Review: Male systemic lupus erythematosus: a review of sex disparities in this disease. Lupus. 2010;19(2):119-29.
37. Wasef SZ. Gender differences in systemic lupus erythematosus. Gend Med. 2004 Apr;1(1):12-17.
38. Wu Y, Chen Y, Yang X, Chen L, Yang Y, Wei Y, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in lupus nephritis: correlation with disease activity and renal biopsy class. Int J Clin Exp Med. 2016;9(6):11836-41.
39. Qin B, Ma N, Tang Q, Wei T, Yang Z, Zhong R. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) as risk factors for evaluating systemic lupus erythematosus: a meta-analysis. Rheumatol Int. 2016;36(5):763-71.
40. Soliman WM, Sherif NM, Ghaly MS, Ghonaim R. Neutrophil to lymphocyte and platelet to lymphocyte ratios in systemic lupus erythematosus: Relation with disease activity and lupus nephritis. Reumatol Clin (Engl Ed). 2020;16(2):76-81.
41. Yolbas S, Yildirim A, Yildirim MS. The relationship between neutrophil-to-lymphocyte ratio and disease activity in patients with systemic lupus erythematosus. Gazz Med Ital-Arch Sci Med. 2016;175(3):127-32.
42. Zahorec R. Ratio of neutrophil to lymphocyte counts-rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102(1):5-14.
43. Li Z, Li X, Chen Q. Circulating cytokines and growth factors in systemic lupus erythematosus. Arthritis Res Ther. 2015;17:221.
44. Ma J, Wang R, Fang X, Sun Z, Hu Y. Platelet to lymphocyte ratio in the differential diagnosis of active lupus nephritis and lupus nephritis in remission. Iran J Kidney Dis. 2019;13(1):25-31.
45. Yavuz S, Karakus S, Demir G. The diagnostic and predictive role of anti-dsDNA, anti-C1q, and other serological markers in systemic lupus erythematosus: A comparative study. Int J Rheum Dis. 2014;17(6):606-12.
46. Luo Y, Li H, Ma R, Fu J, Guo H, Wei R, et al. Predictive role of anti-C1q antibodies in renal involvement and disease activity of systemic lupus erythematosus: A study of 109 Chinese patients. Immunol Invest. 2017;46(7):727-34.
47. Elwy HM, Nashaat EH, Abdelhamid HM. Evaluation of anti-C1q antibodies and C3, C4 levels in lupus nephritis patients. Egypt J Immunol. 2010;17(1):17-23.
48. Sandhu S, Quan H. Rheumatoid arthritis, lupus, and vasculitis. In: Silverstein A, et al., editors. Handbook of systemic autoimmune diseases. Elsevier. 2017;103-26.
49. Sturfelt G, Sjöholm AG. Complement components, complement activation, and acute phase response proteins in systemic lupus erythematosus. Arthritis Rheum. 1984;27(2):142-9.
50. Talstad I, Haugen A, Berntzen HB. The acute-phase response in rheumatoid arthritis: The effects of surgical stress and glucocorticoid treatment. Scand J Rheumatol. 1983;12(1):40-6.
51. Huang X, Quach A, Ly N. Evaluation of a new screening method for SLE using antinuclear antibody HEp-2 indirect immunofluorescence and enzyme immunoassays. Lupus. 2015;24(9):934-41.
52. Ayna TK, Sezer I, Demir S, et al. Neutrophil to lymphocyte ratio as an indicator of disease activity in patients with systemic lupus erythematosus. Osteoarthr Cartil. 2013;21(1):10.
53. Farouk H, Zayed HS, Alsayed Z. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in

patients with systemic lupus erythematosus: The relationship with disease activity. Egypt Rheumatol. 2017;39(4):193-8.
54. Esheba GE, El-Deen AM, Hussein RR. Renal biopsy in systemic lupus erythematosus: Correlation between the histopathologic classes and the clinical and laboratory data. Egypt J Intern Med. 2018;30(1):7-12.

Cite this article as: Hossen SI, Saha JV, Rana MSA, Jannat G, Islam MA, Islam MN. Role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as markers of disease activity in systemic lupus erythematosus patients with or without renal involvement. Int J Res Med Sci 2024;12:4081-90.