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Original Research Article

Correlation of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio with Disease Activity in Patients with Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with unknown aetiology and has various clinical manifestations affecting different tissues. Chronic inflammation is an important pathological development in the disease process for autoimmune diseases.

Aims: To correlate NLR AND PLR with disease activity in SLE, lupus nephritis and with severity of SLE arthritis.

Materials & Methods: After obtaining institutional approval, a hospital based cross sectional study was conducted in Tertiary care centre – Rheumatology Clinic, Department of Internal Medicine, Government Medical College, Thiruvananthapuram for a period of one year. 80 SLE patients who were diagnosed using SLICC criteria were enrolled in the study. Severity of arthritis was assessed using DAS 28 scoring system.

Results: NLR and PLR values positively correlated with SLEDAI 2k scores with (r=0.863 and p<0.005) and (r=0.867 and p <0.001) respectively. On comparing NLR and PLR values in SLE patients with lupus nephritis and without lupus nephritis, it was found that both values were significantly increased in patients with lupus nephritis with p value <0.001. NLR and PLR also showed significant increase as severity of arthritis (assessed by DAS 28 score) increased with p value of 0.013 and 0.012 respectively. In the study we also compared NLR and PLR with CRP and ESR. There was significant positive correlation of NLR with ESR (r=0.804, p value <0.001) but not with CRP (r=0.099 and p=0.384). However there was statistically significant positive correlation of PLR with both ESR (r=0.711, p value<0.001) and CRP (r=0.308, p value=0.005).

Conclusion: NLR and PLR can also be used to assess the severity of arthritis in SLE. These markers can be easily calculated from routine blood counts and are less costly as compared to other inflammatory cytokines, these ratios are relatively stable as each WBCs count could be changed by dehydration/rehydration and diluted blood specimens.

Keywords: Neutrophil-to-lymphocyte ratio (NLR), Platelet-to-lymphocyte ratio (PLR), Disease activity in SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease with unknown etiology and has various clinical manifestations affecting different tissues. It is characterized by the deposition of immune complexes due to widespread loss of immune tolerance to nuclear self-antigens, as well as by excessive pro-inflammatory cytokine production, leading to damage of multiple organ systems. Chronic inflammation is an important pathological development in the disease process for autoimmune diseases. The chronic inflammatory process, which is triggered by auto-antigens and maintained by both environmental and genetic factors, is a common characteristic for all autoimmune diseases. Thus, inflammation plays an important role in SLE, although the pathophysiological process of SLE is complex.

Many different markers of inflammation, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interferon (IFN) and interleukin-6 (IL-6), have been used to assess inflammatory status in SLE. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been investigated as new prognostic indicators for a large number of malignancy studies. Many cancer survival studies have suggested that the NLR is a significant predictor of overall and disease-specific survival of patients. Moreover, previous studies have shown that NLR and PLR are associated with morbidity and mortality in many chronic diseases, such as hypertension, heart failure, infective endocarditis, acute coronary syndromes and type 2 diabetes.

In recent years, NLR has been a marker of subclinical inflammation, and has been used in combination with other inflammatory markers to determine inflammation in many diseases. As a novel marker for inflammation, NLR may be also useful to estimate the activity of autoimmune diseases. Previous studies have shown that NLR is associated with psoriasis and rheumatoid arthritis (RA). A recent study has also shown that NLR is increased in patients with systemic lupus erythematosus (SLE). PLR is also used as an index for differential diagnosis or prognostic prediction of diverse diseases such as cancer and inflammatory diseases.[1] Platelet system activation is a key event in the pathogenesis of SLE. Circulating immune complexes, anti-phospholipid antibodies and infectious agents such as virus are the main activators of platelets in SLE.

Aims & Objectives

To assess the correlation of Neutrophil-to-Lymphocyte ratio and Platelet-to-Lymphocyte Ratio with the disease activity in patients with systemic lupus erythematosus, with lupus nephritis and with severity of arthritis in SLE.

Materials & Methods

After obtaining clearance from Institutional Human Ethics Committee a hospital based cross sectional study was conducted in Tertiary care centre – Rheumatology Clinic, Department of Internal Medicine, Government Medical College, Thiruvananthapuram for a period of one year.

Inclusion criteria: All newly diagnosed cases of SLE satisfying the SLICC criteria for diagnosis of SLE attending rheumatology clinic in Government Medical college, Thiruvananthapuram, Kerala.

Exclusion criteria: Patients without SLE, malignancies, myocardial infarction, active infection, diabetic nephropathy, heart failure, other autoimmune disease like

sjogrens, RA, Hashimotos thyroiditis, recent tropical fever, hematological disorders.

After taking relevant history, physical examination and blood investigations, the disease activity was assessed using SLEDAI 2K scoring system. Severity of arthritis was assessed using DAS 28 scoring system.

Statistical Analysis: Data will be entered into excel sheet. Data analysis will be done using SPSS software. Categorical variables will be expressed as proportions and quantitative variables as mean and standard deviation. Association will be tested using Anova test. $p<0.05$ will be considered as statistically significant.

Results:

The observations and results were tabulated under the following tables and figures.

Age in years	**Frequency**	**Percent**
<30	24	30
31-40	29	36.3
41-50	15	18.8
>50	12	15
Total	80	100
Sex	**Frequency**	**Percent**
Male	8	10
Female	72	90
Total	80	100

Table 1: Distribution of patients according to age and sex and socioeconomic class

About 36 percent of patients were in the age group of 31-40 years, 30 % were under the age of 30 years, 18 % were in the age group of 41-50 years and 15 % were > 50 years. The mean age was found to be 36. Out of 80 patients, 72 were female and 8 were male. About 82 % patients belonged to lower socioeconomic class while 17 % patients belonged to upper-middle socioeconomic class.

Arthritis was the most common clinical manifestation present in 60 % of patients followed by acute cutaneous lupus in 45% patients and lupus nephritis in 37.5% patients. Other clinical manifestations included oral ulcer in 33.8%, alopecia in 30%, fever in 11%, pleurisy and psychosis in 10% patients each, pericarditis in 6% patients, seizure and chronic cutaneous lupus in 5 % patients each, lupus headache in 2.5%, organic brain syndrome in 1.3 % patients.

Patients were classified based on SLEDAI SCORE into MILD (0-5), MODERATE (6-10) and SEVERE activity (>10). 25 % patients had mild activity, 41 % patients had moderate and 33% had severe activity.

Table 2: Clinical Manifestations

Clinical features	**Frequency**	**Percent**
Acute cutaneous lupus	36	45
Chronic cutaneous lupus	4	5
Oral ulcer	27	33.8
Alopecia	24	30
Arthritis	48	60
Pleurisy	8	10

Pericarditis	5	6.3
Fever	9	11.3
Seizure	4	5
Psychosis	8	10
Organic brain syndrome	1	1.3
Lupus headache	2	2.5
Lupus Nephritis	30	37.5

Distribution of patients according to SLEDAI score

Disease activity is determined using the SLEDAI 2K system.

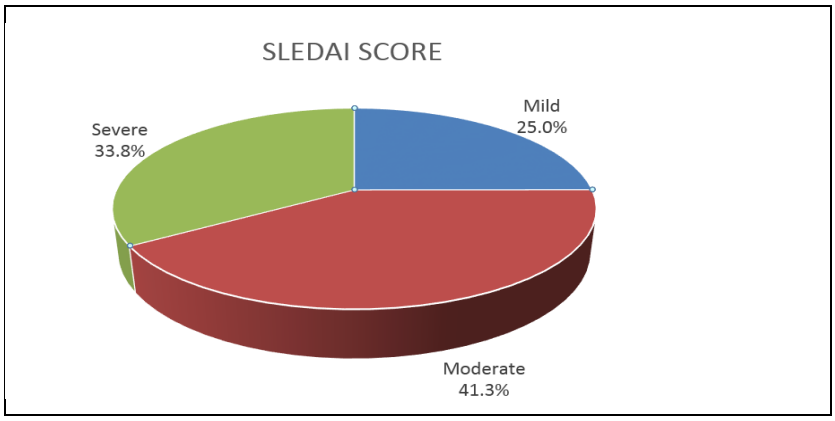


Figure 1: Distribution of patients according to SLEDAI SCORE

Lupus Nephritis

Table 3: Distribution of patients and lupus nephritis

Lupus Nephritis	Frequency	Percentage
Present	30	37.5
Absent	50	62.5

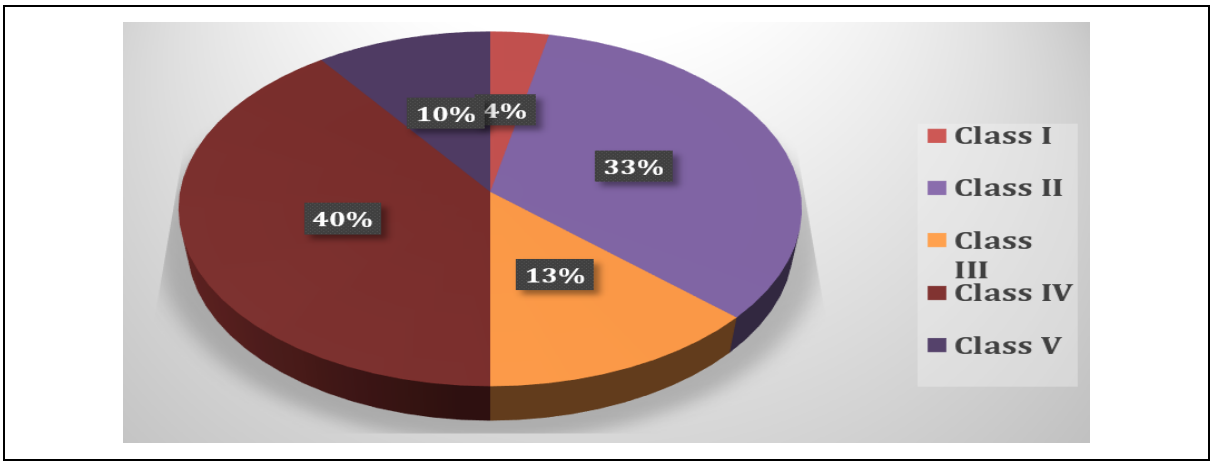


Figure 2: Class of lupus nephritis

Distribution of patients with arthritis based on DAS 28 score

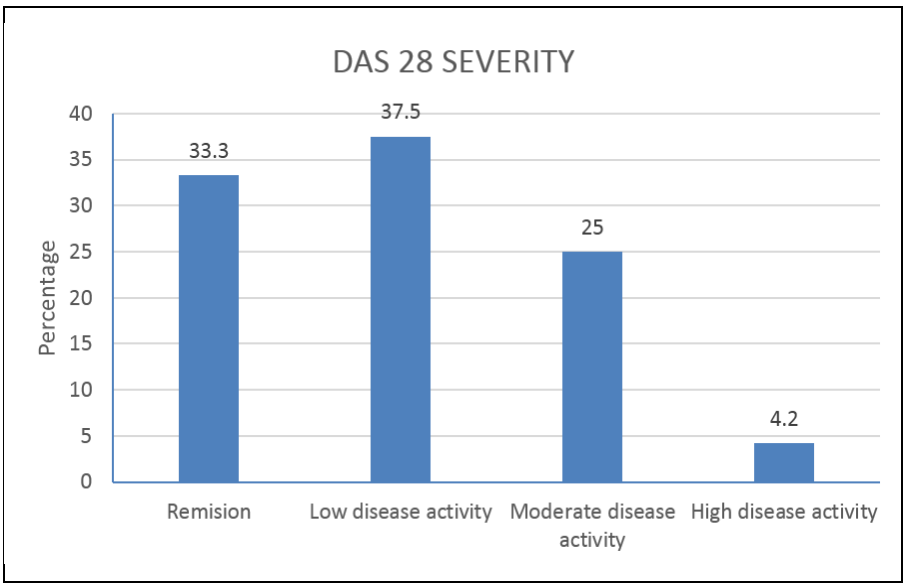


Figure 3: Classification of patients according to Severity of Arthritis based on DAS 28 score

Neutrophil To Lymphocyte Ratio (NLR) and SLEDAI SCORE

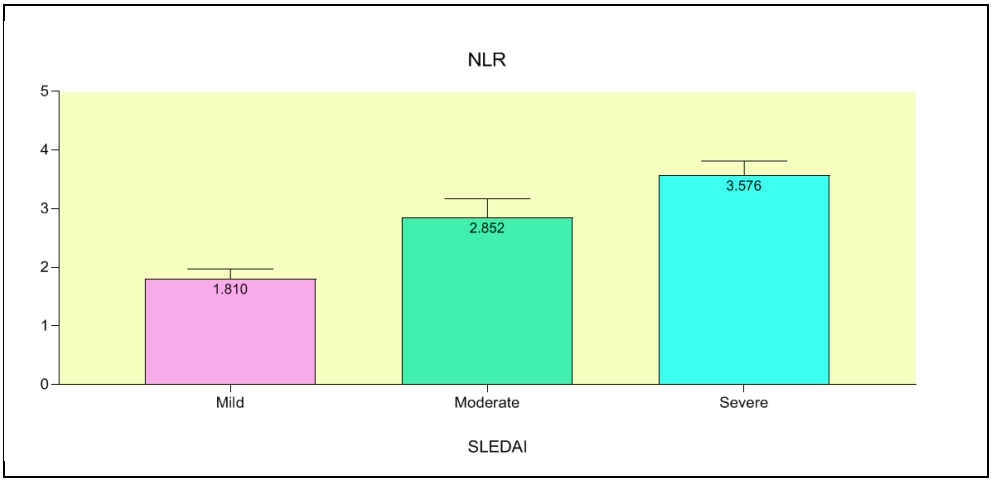


Figure 4: Comparison of NLR with mild, moderate and severe SLEDAI groups

Correlation between NLR and SLEDAI SCORE

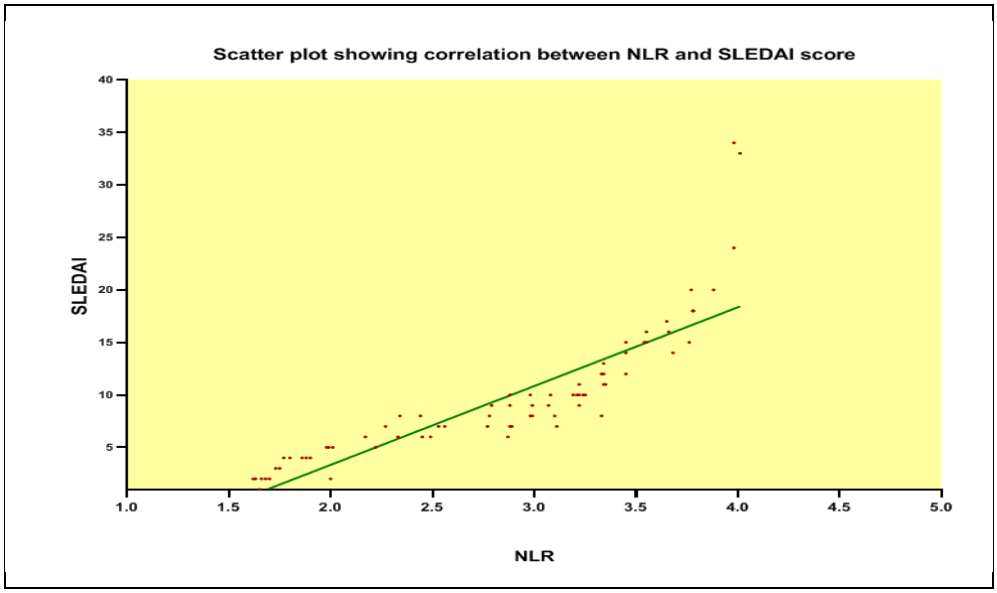


Figure 5: Correlation between NLR and SLEDAI SCORE

Platelet to lymphocyte ratio (PLR) and SLEDAI

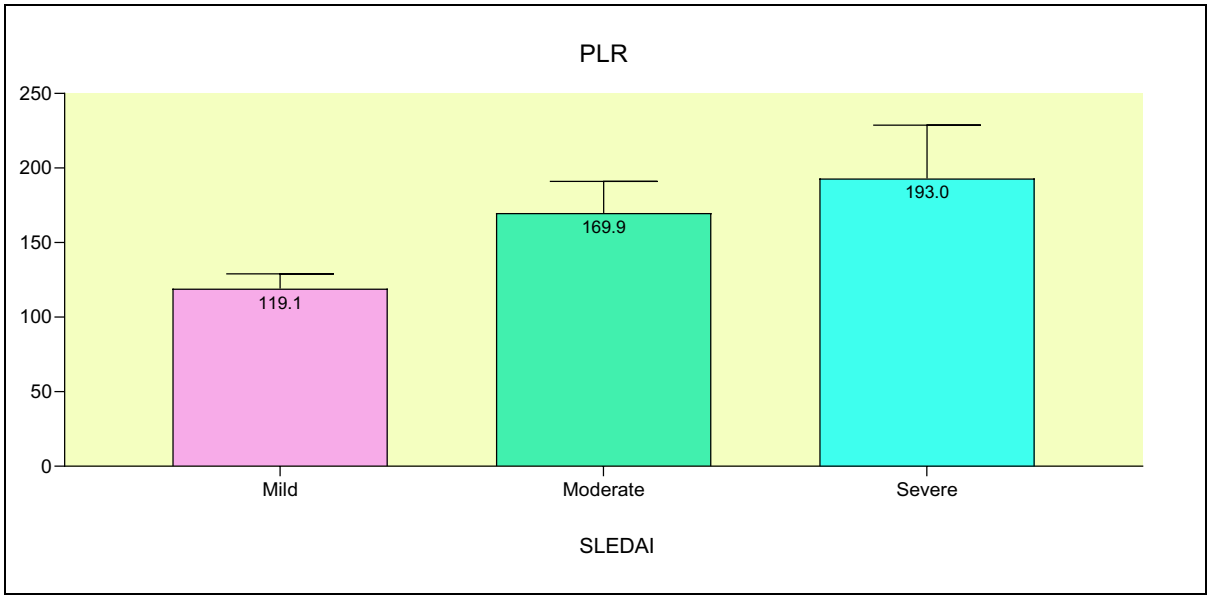


Figure 6 : Comparison of PLR with mild, moderate and severe SLEDAI groups

Correlation of PLR and SLEDAI SCORE

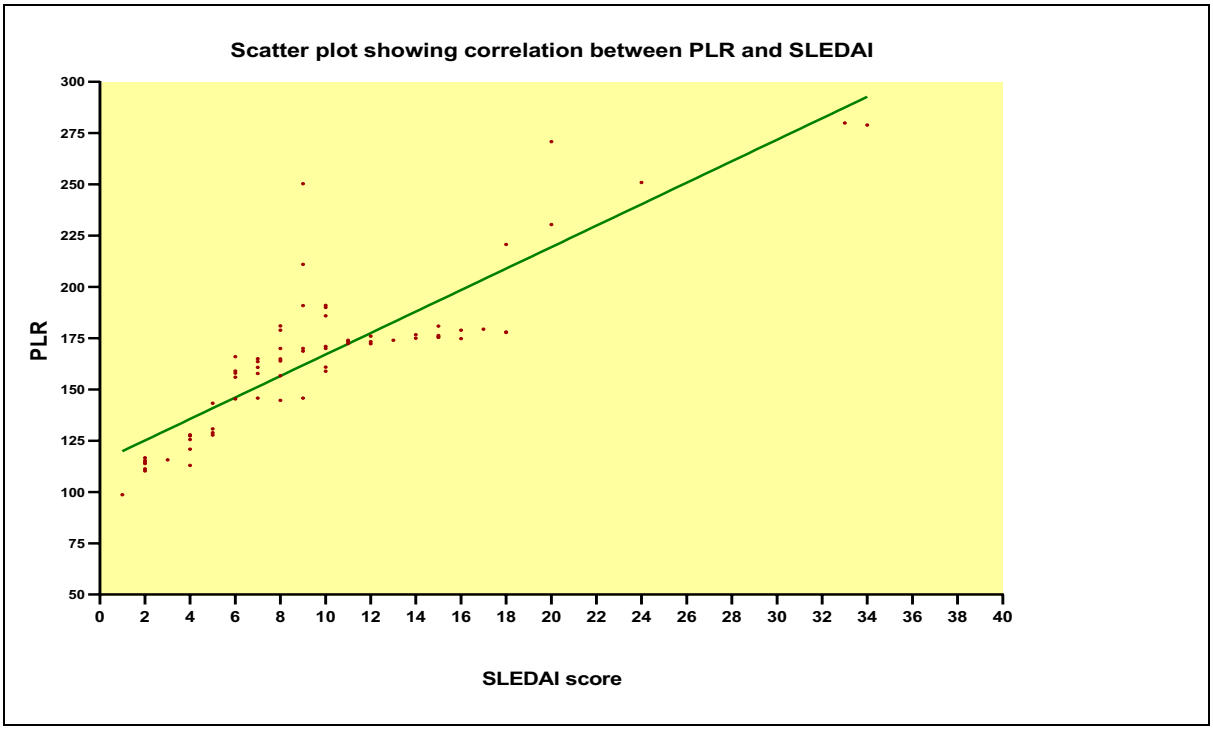
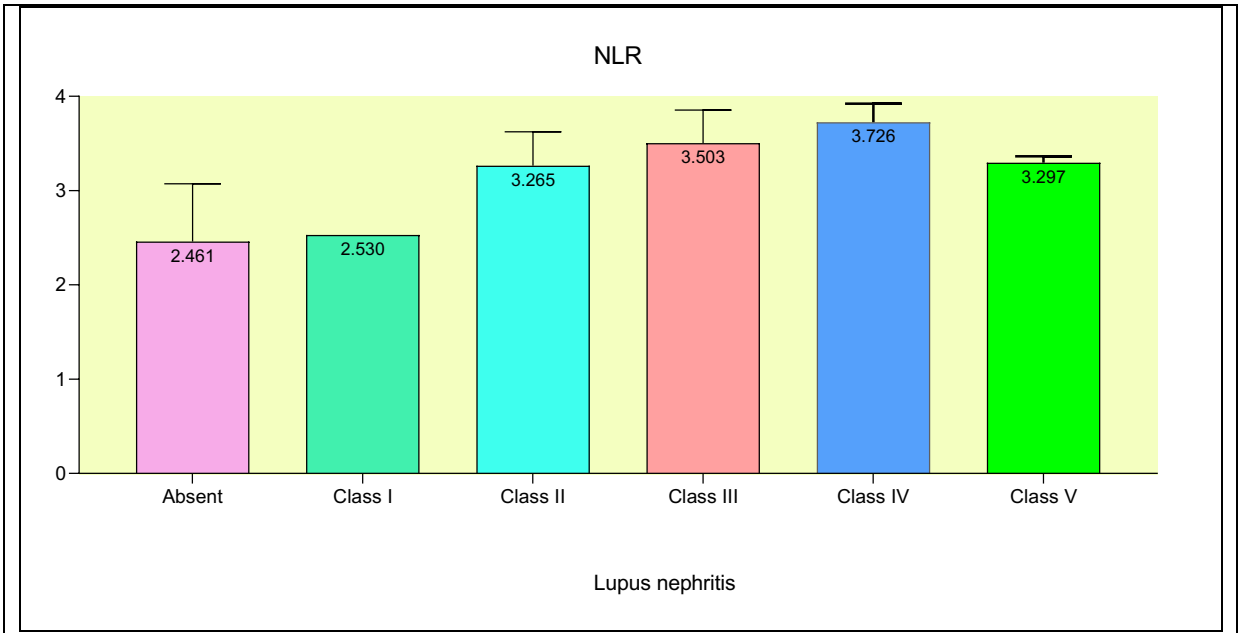


Figure 7: Correlation between PLR and SLEDAI SCORE

Correlation of NLR and PLR with lupus nephritis



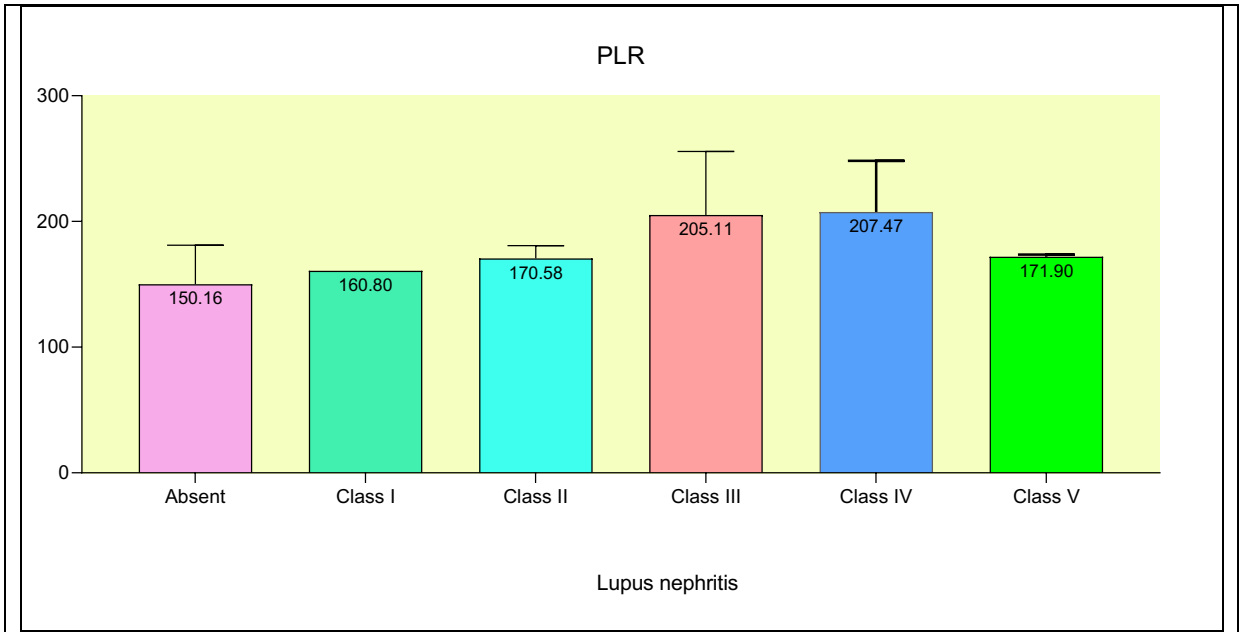


Figure 9: PLR and Lupus Nephritis

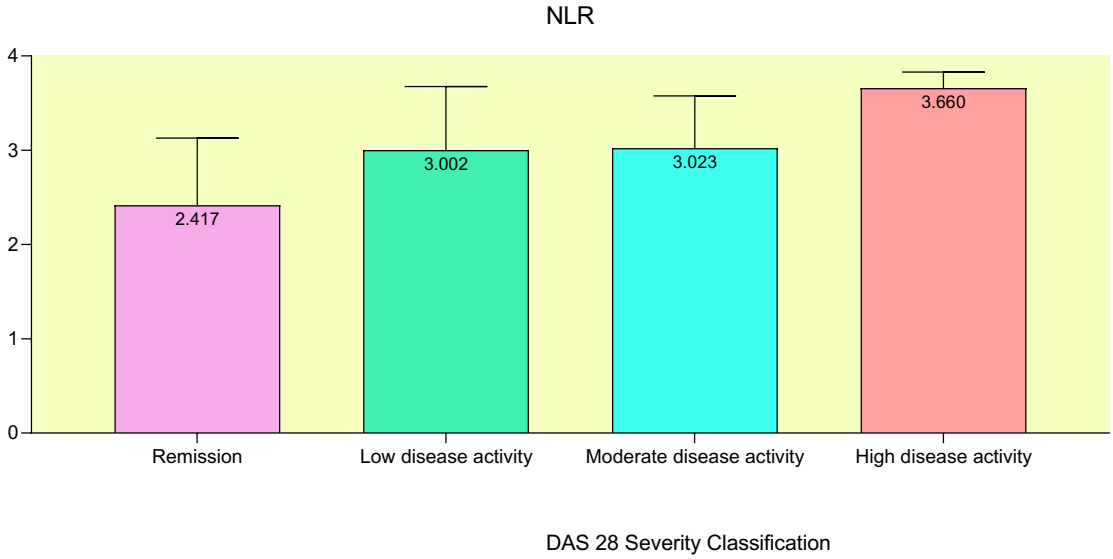


Figure 10: NLR and DAS 28 activity groups

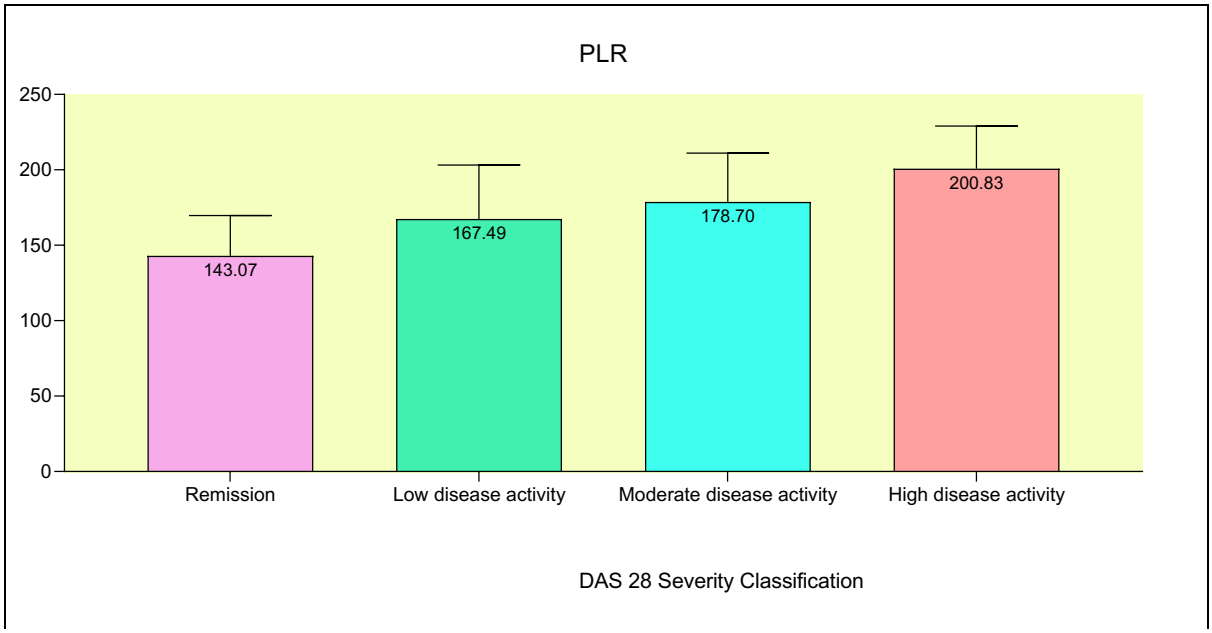


Figure 11: PLR and DAS 28 activity groups

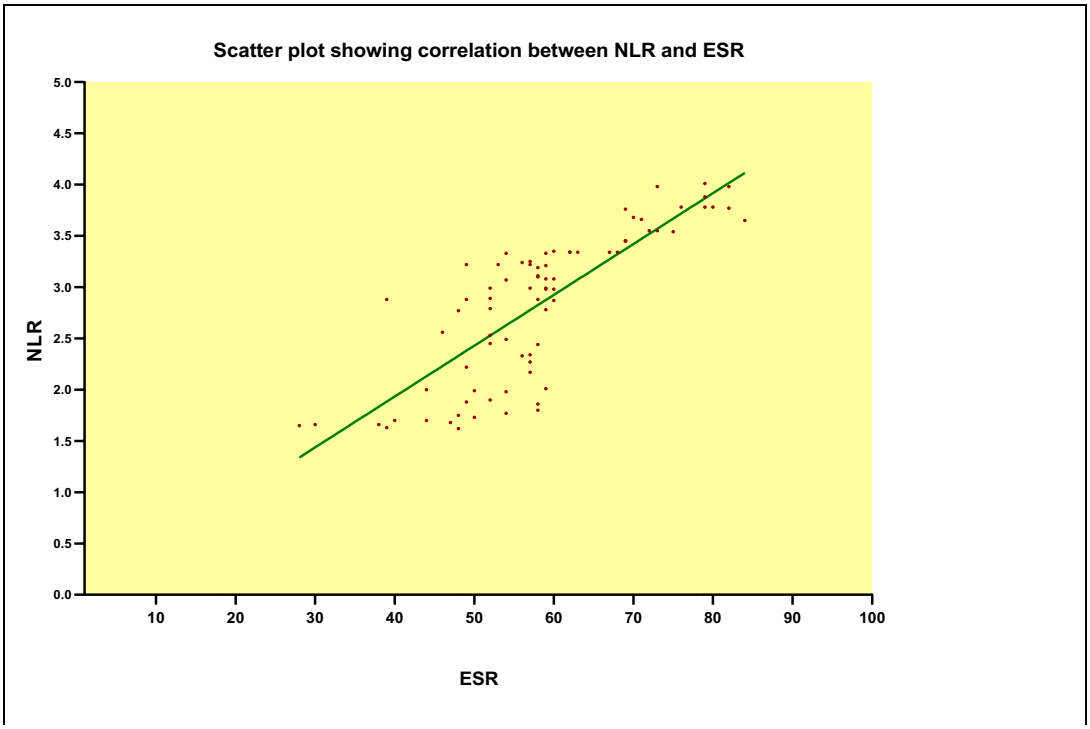


Figure 12: Correlation between NLR and ESR

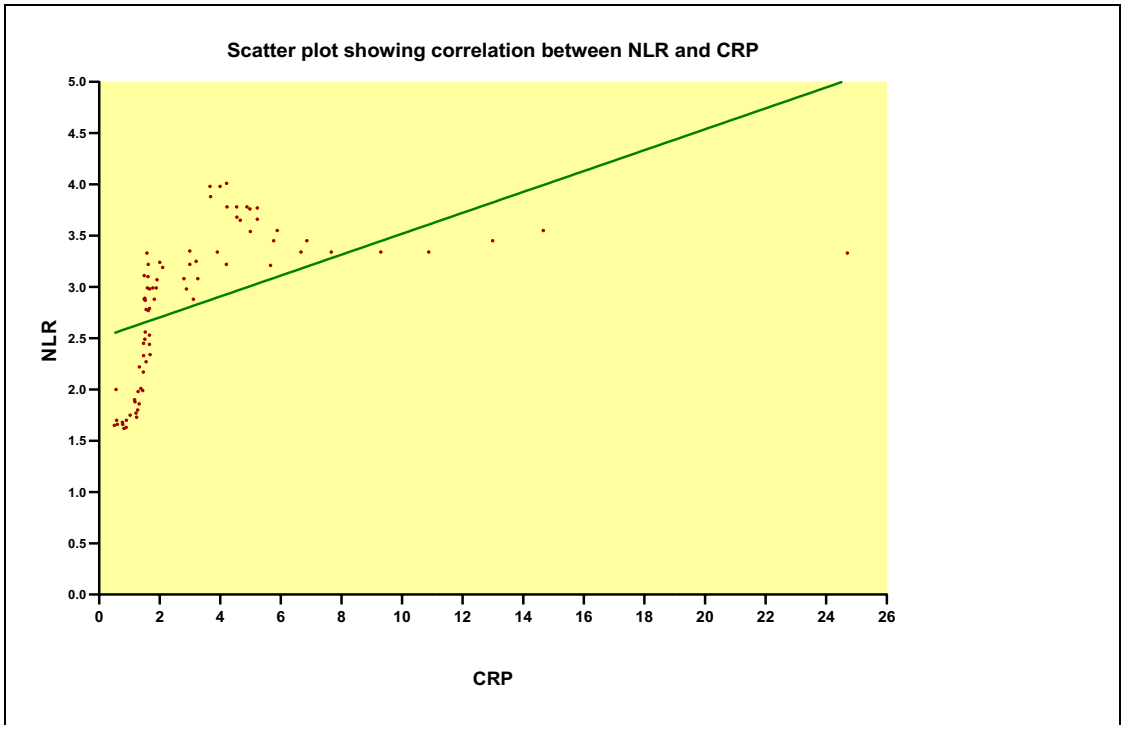


Figure 13: Correlation between NLR and CRP

CORRELATION OF PLR WITH ESR AND CRP

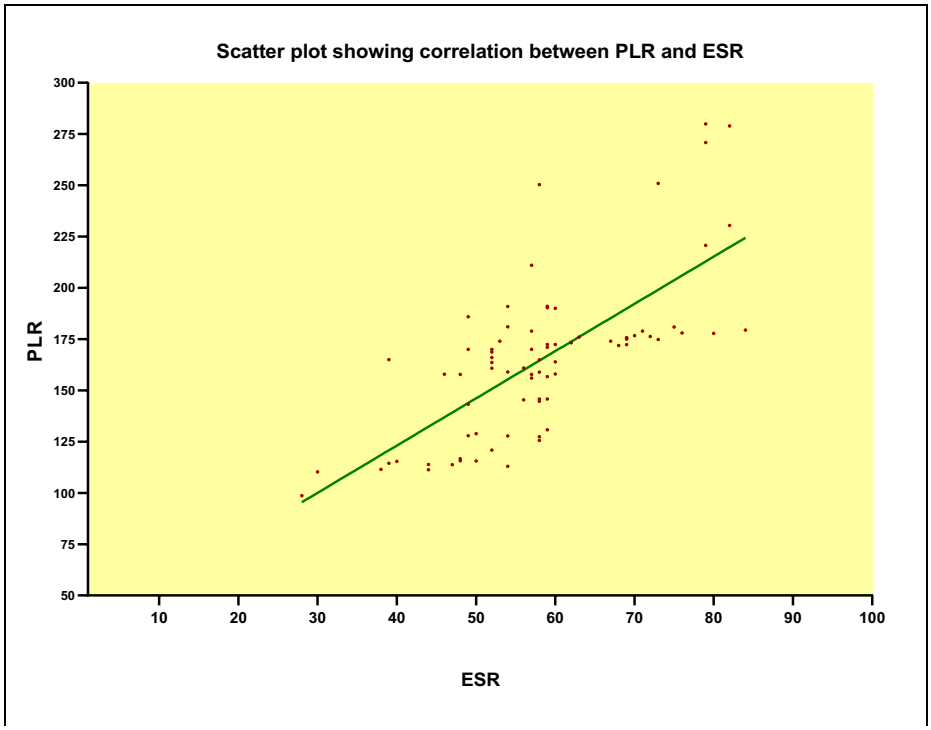


Figure 14: Correlation between PLR and ESR

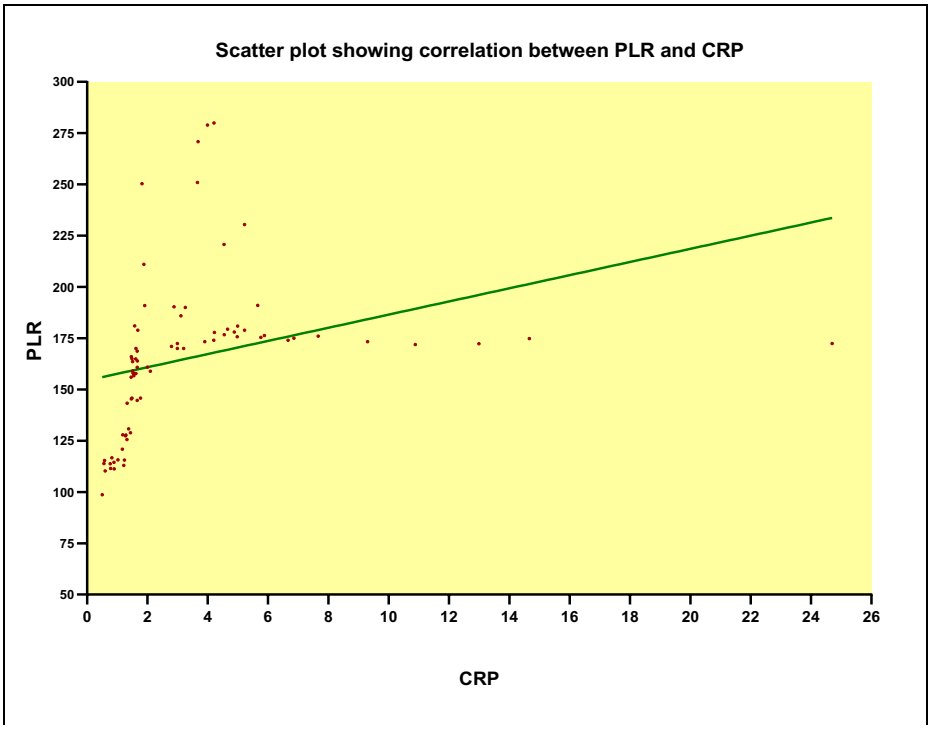


Figure 15: Correlation between PLR and CRP

30 patients (37.5 %) had lupus nephritis while 50 out of 80 patients (62.5%) were SLE without lupus nephritis.

Out of 30 patients with lupus nephritis, majority of them belonged to Class IV lupus nephritis (40%) followed by Class II (33%). 14 % patients belonged to Class III, 10 % belonged to Class IV and only 3 % patients had Class I lupus nephritis.

Arthritis was the most common clinical manifestation present in 48 patients (60 %). 40% patients did not have arthritis. Out of the 48 patients with arthritis 16 of them (33%) were in remission, 18 patients (37.5%) had low disease activity, 12 patients (25%) had moderate and 2 patients (4%) had high disease activity respectively.

NLR values were positively correlated with SLEDAI 2K scores (r=0.863, p <0.005). Mean value of NLR was 1.810 in patients with mild disease activity, 2.852 in those with moderate disease activity and 3.576 in patients with severe disease activity.

PLR and SLEDAI 2k scores showed positive correlation with r=0.867, p <0.001. On comparison, the mean value of PLR was found to be 119.12, 169.92 and 192.98 in patients with mild, moderate and severe disease activity respectively.

On comparing NLR values in SLE patients with lupus nephritis and without lupus nephritis, it was found that NLR was significantly increased in patients with lupus nephritis with p value <0.001. The mean value of NLR was 3.726 in Class IV lupus nephritis which was the highest value followed by 3.503 in Class III lupus nephritis. The mean value of NLR was 2.461 in patients without lupus nephritis, 2.530 in Class I ,3.265 in Class II and 3.297 in Class V lupus nephritis.

On comparing PLR values in SLE patients with lupus nephritis and without lupus nephritis, it was found that PLR was significantly increased in patients with lupus nephritis with p value <0.001. The mean value of PLR was 150.16 in SLE patients without nephritis whereas it was

160.80, 170.58, 205.11, 207.47 and 171.90 in Class I, Class II, Class III, Class IV and Class V lupus nephritis respectively.

Correlation of NLR and PLR with DAS 28 SCORE

On comparing NLR with different Das 28 severity groups, NLR showed significant increase as severity of arthritis increased. The mean value of NLR was 2.417 in those with remission, 3.002 in patients with low disease activity, 3.023 in patients with moderate disease activity and 3.660 in those patients with high disease activity. P value was 0.013.

On comparing PLR with different Das 28 severity groups, PLR showed significant increase as severity of arthritis increased. The mean value of PLR was 143.07 in those with remission, 167.49 in patients with low disease activity, 178.70 in patients with moderate disease activity and 200.83 in those patients with high disease activity. P value was 0.012.

Correlation of NLR with ESR and CRP

There was significant positive correlation of NLR with ESR (r=0.804, p value <0.001) but not with CRP (r=0.099 and p=0.384).

There was statistically significant positive correlation Of PLR with both ESR (r=0.711, p value<0.001) and CRP (r=0.308, p value=0.005).

Discussion

In recent years, NLR and PLR has been a marker of subclinical inflammation and has been used in combination with other inflammatory markers to determine inflammation in many autoimmune diseases and malignancies.

The mean age of our study population was 36 years with age distributed from 17 to 58 years. Out of 80 patients, 72 were female (90%) and 8 were male (10%).

This results parallels with Malaviya et al [2], who studied 1366 SLE patients across India and found out that SLE affects predominantly women in their reproductive years and the median age of onset in Indian SLE is 24.5 years [3]. As regard sex distribution, SLE is an autoimmune disease affecting primarily in women. Our finding agrees with Houman etal.[4] They noticed that women were 92% and men 8%. Also, Khanfir et al. [5] showed that women were 90.3% and men were 9.7%, with an average age of SLE onset at 30.66 years.

In our study, 82.5% patients belonged to lower socioeconomic class and 17.5% patients belonged to upper middle class. A study by Erin E Carter et al found that poverty, low educational attainment, lack of health insurance, poor social support and poor treatment compliance are all associated with unfavourable disease outcomes, both independent of and in combination with, ethnic influences. [6] The treatment of SLE incurs high direct costs, and sometimes even higher indirect costs; costs are influenced by disease severity and organ manifestations.

Arthritis was the most common clinical manifestation present in 60% of patients followed by acute cutaneous lupus in 45% patients and lupus nephritis in 37.5% patients. Other clinical manifestations included oral ulcer in 33.8%, alopecia in 30%, fever in 11%, pleurisy and psychosis in 10% patients, pericarditis in 6% patients, seizure and chronic cutaneous lupus in 5% patients, lupus headache in 2.5%, organic brain syndrome in 1.3% patients.

Our study results paralleled with the study conducted by Malaviya et al in which 1366 SLE patients in India were studied. Arthritis (60%) was the most common clinical manifestation followed by fever in 50% and skin lesions in 45%. However, lupus nephritis was present only in 17% in

the study. Other manifestations were present in comparable proportions. [2]

Borchers et al. stated that SLE is a systemic autoimmune disease with manifold clinical manifestations and immunological abnormalities.[7] Houman et al. observed that among their SLE patients 78% had articular involvement, 53% photosensitivity, 63% malar rash, and 45% had serositis.[4]

Santos MJ et studied 544 patients with SLE in a Portuguese population. The most common clinical features was musculoskeletal (91%), followed by cutaneous and mucous membrane (90%), and haematological involvement (58%). In a study by Villamin et al, arthritis [8] (68%) was the most common manifestation followed by malar rash (49%), renal involvement (47%), photosensitivity (33%), and oral ulcers (33%).

Disease activity of SLE was determined using SLEDAI 2K score. Patients were categorised into mild, moderate and severe activity groups. SLEDAI score of 1-5 was categorised as mild, score of 6-10 as moderate and score of >10 as severe activity groups.

In our study, 25 % patients belonged to mild, 41% patients belonged to moderate and 34 % patients belonged to severe activity groups.

Lupus nephritis was present in 30 % patients in our study. Out of 30 patients with lupus nephritis, majority of them belonged to Class IV lupus nephritis (40%) followed by Class II (33%). 14 % patients belonged to Class III, 10 % belonged to Class IV and only 3 % patients had Class I lupus nephritis. There was no patient with Class VI disease. Mean age was 35 years.

Arthritis was the most common clinical manifestation present in 48 patients (60%). 40% patients did not have arthritis. Patients were categorised based on Das 28 score into those in remission, low, moderate and high disease activity groups. Out of the 48 patients with arthritis 16 of them (33%) were in remission, 18 patients (37.5%) had low disease activity, 12 patients (25%) had moderate and 2 patients(4%) had high disease activity respectively.

In the Hopkins lupus cohort study conducted by Petri et al [9], arthritis was present in 78.3% of lupus patients at the time of the presentation.

NLR values were positively correlated with SLEDAI 2K scores ($r=0.863$, $p<0.005$). Mean value of NLR was 1.810 in patients with mild disease activity, 2.852 in those with moderate disease activity and 3.576 in patients with severe disease activity. PLR and SLEDAI 2k scores showed positive correlation with $r=0.867$, $p<0.001$. On comparison, the mean value of PLR was found to be 119.12, 169.92 and 192.98 in patients with mild, moderate and severe disease activity respectively.

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On comparing NLR with different Das 28 severity groups, NLR showed significant increase as severity of arthritis increased. The mean value of NLR was 2.417 in those with remission, 3.002 in patients with low disease activity, 3.023 in patients with moderate disease activity and 3.660 in those patients with high disease activity. P value was 0.013. PLR also showed significant increase as severity of arthritis increased. The mean value of PLR was 143.07 in those with remission, 167.49 in patients with low disease activity, 178.70 in patients with moderate disease activity and 200.83 in those patients with high disease activity. P value was 0.012.

There was significant positive correlation of NLR with ESR (r=0.804, p value <0.001) but not with CRP (r=0.099 and p=0.384). However, there was statistically significant positive correlation Of PLR with both ESR (r=0.711, p value<0.001) and CRP (r=0.308, p value=0.005).

Our results are in accordance with Qin et al [10] who observed increased levels of NLR and PLR in SLE patients as compared to healthy controls. In that study, NLR was positively correlated with CRP, ESR, and SLEDAI score. PLR was positively correlated with SLEDAI score. In addition, NLR level of 2.06 was determined as a predictive cut off value for the development of SLE, and NLR level of 2.66 as a predictor of LN.

For instance, the study of Wu et al [11] showed that NLR and PLR levels were much higher in SLE patients as compared to healthy control group. Both ratios were significantly associated with SLE Disease Activity index 2000 (SLEDAI-2K). Only NLR was significantly increased in SLE patients with nephritis. The best NLR cut-off value to predict SLE patients with severe disease was 2.26 with 75% sensitivity and 50% specificity, where the best PLR cut-off value for the severe disease was 203.85 with 42.3% sensitivity and 83.9% specificity.

A study by Soliman et al [12] demonstrated NLR and PLR were positively correlated with SLEDAI score and acute phase reactants (ESR and CRP levels). Also, both ratios showed a significant negative correlation with C4. Another important finding was that NLR was significantly increased in SLE patients with nephritis. Additionally, NLR showed positive correlations with BUN, serum urea, serum creatinine, and 24 h urinary protein. Meanwhile, PLR showed no significant correlations with those parameters. Moreover, he found a statistically significant difference between LN patients in different renal biopsy classes as regards NLR. NLR was found to be increased as histological stages of LN get more advanced.

Conclusions

In conclude NLR and PLR are two new inflammatory markers that can be used to assess the disease activity in SLE. It can be easily calculated from routine blood counts and are less costly as compared to other inflammatory cytokines, these ratios are relatively stable as each WBCs count could be changed by dehydration/rehydration and diluted blood specimens. It could reflect renal involvement in SLE patients as it is correlated to Lupus Nephritis. It can also be used to assess the severity of arthritis in SLE.

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