Type of the Paper (Research Article)

Potential Value of Hematological Biomarkers in Assessment of Inflammatory Response and Disease Activity in Patients with Systemic Lupus Erythematosus

Maha H. Nassr[1]*, Heba E. Tolba[1], Othman M. Zaki[2], Hanan M Fathi[1]

[1]Rheumatology and Rehabilitation Department, Faculty of Medicine, Fayoum University, Fayoum 63514, Egypt.
[2] Clinical Pathology Department, Faculty of Medicine, Damietta University, Damietta, Egypt

* Correspondence: Maha H. Nassr, maha_nassr@yahoo.com, Tel: (002) 01202499442.

Received: 15 December, 2024 Reviewed: 3 January, 2025
Accepted: 3 May, 2025 Published online: 20 September 2025

Abstract:

Introduction: Remissions and relapses are hallmarks of systemic lupus erythematosus (SLE). The intricacy of SLE patients' clinical presentations causes erroneous assessment of disease progression. As disease activity indicators for SLE, blood indices like the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV).

Aim of the study: For the purpose of studying the relevance of NLR, PLR, and MPV to SLE patients' clinical outcomes and their correlation with SLE activity.

Subjects and Methods: The research included 63 individuals with SLE (58 females and 5 males) as well as 39 age and sex-matched controls. A complete clinical examination, laboratory investigations, and the SLE disease activity index (SLEDAI) were conducted on the patients. The NLR, PLR, and MPV were calculated from the CBC results. Estimation of serum procalcitonin (PCT) level by ELISA**.**

Results: The NLR and PLR values in SLE persons were substantially elevated than controls (2.5 vs. 1.52 and 189 vs. 108.5, respectively; $p \leq 0.0001$). PCT levels showed no significant difference ($p=0.174$). Both NLR and PLR correlated with SLEDAI scores (r=0.852, $p<0.0001$ and r=0.419, $p=0.001$, respectively). Individuals with nephritis exhibited significantly higher NLR and PLR ($p<0.0001$).

Conclusions: Both the NLR and the PLR were shown to be much greater in SLE patients than in healthy controls. Potentially helpful biomarkers for evaluating disease activity in SLE and lupus nephritis patients include the NLR and the PLR.

Keywords: SLE; Disease Activity; Hematological Biomarkers; Lupus Nephritis.

1. Introduction

There are a variety of clinical and laboratory features associated with systemic autoimmune illness known as systemic lupus erythematosus (SLE) [1]. The disease's progression, including remissions and relapses, is very unpredictable. Due to the intricacy of the illness, assessing disease progression appropriately is crucial [2].

Identifying easy-to-use laboratory markers that are accessible in the majority of healthcare institutions is crucial for monitoring disease activity in individuals with SLE [3]. Systemic inflammation causes changes in the circulating white blood cells (WBCs), namely a rise in neutrophils and a reduction in lymphocytes [4]. With a prevalence of up to 93%, lymphopenia is a widely frequent WBC anomaly in SLE [5]. Neutrophilia and lymphopenia may be more pronounced during a disease episode [6].

Because of the significant roles played by neutrophils and lymphocytes in inflammatory processes, the neutrophil to lymphocyte ratio (NLR) is a quickly accessible indicator that may be used as an investigative tool to provide crucial information on a patient's inflammatory activity [7]. SLE development is facilitated by the activation of the platelet system. Viruses, anti-phospholipid antibodies, and circulating immune complexes are the primary factors that activate platelets in SLE [8]. In connective tissue illnesses such as rheumatoid arthritis, SLE, and systemic sclerosis, peripheral blood components may identify disease activity [9,10]. Inflammation may be indicated by the platelet to lymphocytic ratio (PLR) in several disorders [11]. Several autoimmune illnesses have been examined using mean platelet volume (MPV) as a dependable inflammatory biomarker [12]. Nevertheless, its function as an indication of illness severity in SLE remains poorly understood [13].

In individuals with SLE, procalcitonin (PCT) may distinguish between bacterial infections and SLE flares [14].

This study investigated the correlation linking SLE illness severity and the practical value of NLR, PLR, and MPV.

2. Subjects and methods

2.1. Subjects

This investigation involved 63 adult SLE individuals fulfilling the 2019 European League Against Rheumatism /American College of Rheumatology classification criteria for SLE [15]. Another 39 of matched age were included as a control group

Exclusion criteria

Patients who have malignancies, lymphoproliferative disorders, hematologic diseases, hepatosplenic diseases, diabetic nephropathy, and other autoimmune diseases.

2.2.Study design

Participants underwent thorough history, clinical, and laboratory tests. The NLR, PLR, and MPV are CBC-derived. NLR and PLR are absolute count ratios: Neutrophils/lymphocytes are NLR, and platelets/lymphocytes are PLR.

The SLE disease activity index (SLEDAI) measured disease progression [16]. We give it a numerical value based on severity levels, and the sum shows how active the illness is overall (a greater number means the disease is more active). This index includes both dimensions: disease activity and disease severity [17].

A collection of 3ml of blood was done on a plain tube (without anticoagulant) for serum separation. The tube was centrifuged for 5 minutes. Separated serum was kept at a temperature of -20°C. Evaluation of PCT levels in blood using an enzyme-linked immunosorbent assay (ELISA) Product ID: 11270 (Glory Science, USA).

2.3. Statistical Methods We collected data on a standardized form and entered it into an electronic database. We addressed missing data and analyzed the variables using SPSS version 22. We compared the data using Chi-square or Mann-Whitney U tests and performed a Spearman correlation to identify any association between NLR, PLR, and MPV and the study parameters. The ROC curve was utilized to detect the discrimination value of NLR, PLR, and MPV for differentiating cases from controls and predicting nephritis. Dot graphs for NLR, PLR, and MPV levels were created using GraphPad Prism software, 6, 2012. Statistical significance was defined as a p-value below 0.05. These graphs compared controls to nephritis cases for sensitivity and specificity cut-off points. Scatterplots were also generated to investigate correlations.

3. Results

A case-control study was conducted, involving 63 SLE persons (mean age 32.9 ± 9.4 years, disease duration 5.2 ± 4.2 years) and 39 matched healthy controls. **Table 1** presents the clinical and laboratory characteristics of the SLE group.

Renal biopsy was performed for 22 cases. Half of them, 11/22 (50.0%), had class 4, followed by 8/22 cases (36.4%) for class 3. Only two cases (9.1) had class 5, and one case (4.5%) had class 1. (3.2%). A comparison was done between both study groups with different hematological biomarkers (**Table 2**).

Table 3 shows the associations between the research parameters and NLR, PLR, and MPV. Validity of NLR, PLR, and MPV for lupus nephritis prediction with AUC (95% CI); NLR 0.952(0.897-1.000) $p \leq 0.0001$ with a Cut- off point 2.55, Sensitivity % 100 and a Specificity 81.6, PLR 0.805 (0.692-0.912) $p \leq 0.0001$ with a Cut- off point 211.5, Sensitivity % 71.4% and a Specificity 85.7%. However, MPV was of a non-significant prediction for lupus

nephritis p =0.139. ROC curve for the prediction of nephritis among SLE patients by the differently assessed hematological biomarkers is seen in **Figure 1.**

Table 1: SLE individuals' clinical presentation, laboratory findings, and disease activity

Parameter	**SLE patients (n=63)**
Clinical manifestations	
Disease duration(years)	5.2±4.2
Mucocutaneous	62 (98.4)
Arthritis	23 (37.1)
Serositis	19 (30.2)
Lupus nephritis	28 (44.4)
Neuropsychiatric	43 (68.3)
laboratory investigations	
ESR (mm)	57.3±32.9
CRP (mg/l)	5.2±5.2
Hemoglobin (g/dl)	11.9±1.6
TLC (mm^3)	6.3±3.2
Platelets (mm^3)	260±77.5
Lymphocytes(mm^3)	4315±2987.8
Hemolytic anemia	2(3.2)
Leucopenia	16(25.4)
Thrombocytopenia	9(14.3)
Creatinine(mg/dl)	0.8±0.3
Proteinuria (mg/dl)	853.4±1039
Serum albumin(g/dl)	3.7±0.7
ALT(U/L)	26.2±6.7
AST(U/L)	32.1±54
RBS (mg/%)	116±25.9
ANA	63(100)
DNA	54(85.7)
Casts in urine analysis	23(36.5)
C3	99.4±31
C4	21.7±13.5
ANA	51 (98.1)
Anti-dsDNA	40 (76.9)
SLEDAI	15.6±9.6

SLE: Systemic lupus erythematosus, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, TLC: total leucocytic count, AST: aspartate transaminase, ALT: alanine transaminase, RBS: random blood sugar, C3: complement 3, C4: complement 4, ANA: antinuclear antibody; anti-dsDNA: anti-double-stranded deoxyribonucleic

Table 2: Differences in NLR, PLR, and MPV in relation to study groups

Parameter	SLE (n =63)	Control (n=39)	p
NLR	3.44 ± 3.18	1.47 ± 0.23	<0.0001
	2.5 (0.65-22.5)	1.52 (1.08-1.8)	
PLR	215.17 ± 131.4	113.9 ± 20.64	<0.0001
	189 (51-836)	108.5 (90-170)	
MPV	9.77 ± 1.27	10.27 ± 0.79	0.224
	10 (7-11.8)	10.25 (8.7-11.8)	

NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio, MPV: mean platelet volume

Table 3: Correlations of a) NLR, b) PLR, and c) MPV with study parameters

Parameter	NLR r (p)	PLR r (p)	MPV r (p)
Onset of disease	-0.19 (0.143)	-0.13 (0.295)	-0.02 (0.868)
Disease duration	-0.23 (0.07)	0.03 (0.07)	-0.07(0.58)
CRP	0.018(0.89)	-0.1 (0.4)	-0.15 (0.25)
ESR	0.72 (<0.0001)	0.34 (0.006)	-0.149(0.244)
24 Hrs urinary protein	0.74(<0.0001)	0.45 (<0.0001)	-0.28 (0.02)
HB	-0.27(0.03)	-0.02 (0.85)	0.01 (0.93)
Platelets	0.25(0.052)	0.56(<0.0001)	0.19(0.137)
TLC	0.45 (<0.0001)	-0.12(0.33)	-0.09(0.48)
Lymphocytes	-0.497(<0.0001)	-0.73(<0.0001)	-0.73(<0.0001)
Neutrophils	0.64 (<0.0001)	0.02(0.897)	0.14(0.286)
Creatinine	0.099 (0.44)	-0.01(0.92)	-0.218(0.09)
Urea	0.43(<0.0001)	0.11 (0.40)	-0.18 (0.16)
Serum albumin	-0.676 (<0.0001)	-0.464(<0.0001)	0.23 (0.06)
ALT	0.367 (0.003)	0.176(0.17)	-0.07(0.58)
AST	0.37(0.003)	0.2(0.099)	-0.135(0.29)
RBS	0.36(0.004)	0.303(0.02)	-0. 05(0.71)
Procalcitonine	0.028 (0.83)	-0.025 (0.85)	-0.06 (0.61)
C3	-0.59(<0.0001)	-0.31 (0.01)	0.29 (0.02)
C4	-0.67 (<0.0001)	-0.4 (0.001)	0.24 (0.06)
SLEDAI	0.85(<0.0001)	0.419(0.0001)	-0.25(0.04)

SLE: Systemic lupus erythematosus, MPV: mean platelet volume, TLC: total leucocytic count, ESR: erythrocyte sedimentation rate, AST: aspartate transaminase, ALT: alanine transaminase, RBS: random blood sugar, C3: complement 3, complement 4, SLEDAI: SLE disease activity index

Table 4: Comparison between individuals with and without nephritis as regards NLR, PLR, and MPV

	Nephritis (N=28)	Non-Nephritis (N=35)	*P*-value[#]
NLR			
Mean ± SD	5.31± 3.97	1.95± 0.91	<0.0001*
Median (range)	4.06 (2.60-22.50)	1.70 (0.65-5.20)	
PLR			
Mean ± SD	280.21± 154.22	163.14± 79.66	<0.0001*
Median (range)	235.50 (100-836)	144.00 (51.00-469.00)	
MPV			

Mean ± SD	9.42± 1.46	10.04± 1.05	0.138
Median (range)	10.00 (7.00-11.20)	10.20 (8.00-11.80)	

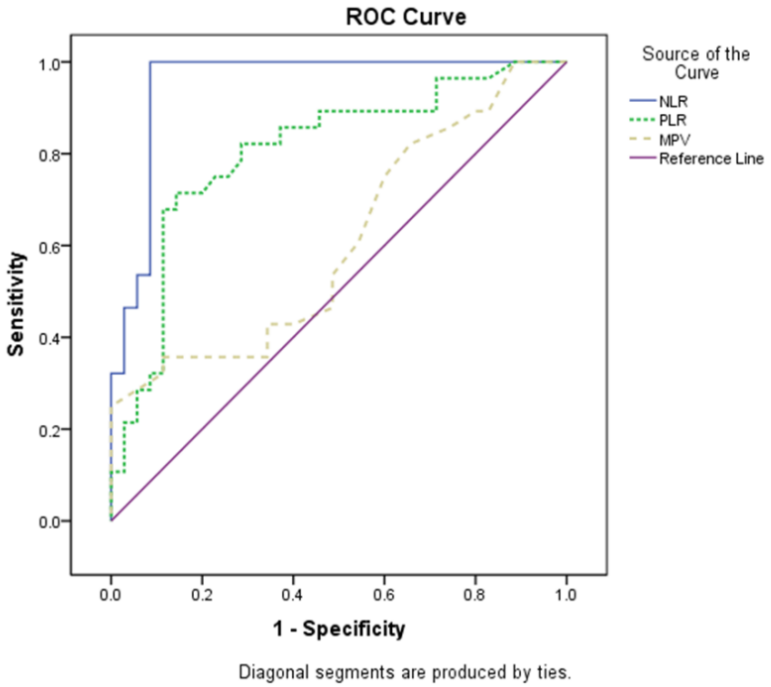

Figure 1: ROC curve for the prediction of lupus nephritis among patients by neutrophil lymphocytic ratio, platelet lymphocytic ratio, and mean platelet volume

4. Discussion

SLE follows a pattern of remission and relapse, making early flare detection vital. NLR and PLR ratios offer readily accessible and cost-effective measures of inflammation. Unlike individual white blood cell counts, these ratios remain stable and are unaffected by corticosteroids [7, 18]. Research indicates their significance as inflammatory markers in SLE disease activity [7,9,19,20,21].

A highly significant elevation in NLR was observed in SLE individuals than controls (p <0.0001). This finding aligns with a meta-analysis by Ma et al. (2019), which examined eleven studies encompassing 1246 SLE individuals and 976 healthy controls. Their analysis also demonstrated significantly increased NLR levels in SLE individuals (p <0.001) [19]

This study revealed a highly significant elevation of PLR in SLE

individuals than controls (p <0.0001), consistent with previous research. Qin et al. (2016) reported considerably superior PLR levels in SLE individuals versus healthy controls (155.64±91.69 vs. 123.01±39.07; p <0.01) [7]. A meta-analysis by Ma et al. (2019), encompassing 646 SLE individuals and 524 controls, further corroborated this finding, demonstrating a significantly increased PLR in SLE individuals (SMD=0.709, 95% CI=0.580–0.838; P <0.001) [19]

SLE patients may have an increase in NLR and PLR due to high levels of cytokines. This is a result of the inflammatory processes that involve inflammatory cells and molecules. The quantity, form, and size of cells in the bone marrow and the peripheral circulation may be altered by these mechanisms. Platelets and neutrophils generate these cytokines, which then activate them. When inflammation occurs, neutrophils, the most common kind of WBCs, become very active. Reduced lymphocyte and platelet counts are typical with SLE [12]. Furthermore, the current study found that MPV was lower in cases than controls, with a non-statistically significant value (p =0.22), and this agreed with a previous meta-analysis also, done by Lee &Song, 2017, who analyzed five comparative studies between MPV and SLE. The researchers discovered no indication of increased MPV in SLE persons (p =0.12) [13]. On the other hand, an investigation done by Qin et al. (2016) assumed that individuals with SLE have a rise in MPV compared to healthy controls (10.76±1.42 *vs.* 10.11±1.21) with p <0.01 [7].

A possible explanation for this discrepancy may be due to changes in platelet count among patients and clinical factors as the absence or presence of antiphospholipid syndrome, as Platelet-surface receptor interaction, receptor binding, and complement deposition promotion are all ways in which antiphospholipid antibodies (ApL) may directly activate platelets [22].

The research found a substantial increase in NLR in individuals than those without (p <0.0001). A considerable variation in PLR was seen concerning individuals with nephritis or not (p <0.0001). According to research by Qin et al. (2016), individuals with SLE with nephritis exhibited greater NLR and PLR levels than those without nephritis (p <0.01, p =0.03, respectively) [7]. Elsaid et al. (2022) recommended exploring these ratios with lupus nephritis [21].

In this research, MPV was smaller in nephritis patients than in controls, though not statistically significant (p =0.138). This matches other findings [8, 12]

This research found a substantial positive correlation across NLR and several study parameters, which included (ESR, 24 h urinary protein, blood urea, ALT, AST, RBS, TLC, Neutrophils, and SLEDAI score), with p <0.0001. These results came in concordance with Wu et al., 2016, on whose findings NLR displayed a favorable association with SLEDAI score and TLC, p <0.001 [6].

Research by Soliman et al. (2018) demonstrated a positive correlation between NLR and SLEDAI, ESR, serum urea, and proteinuria [9].

NLR and PLR demonstrate strong predictive capabilities for nephritis in SLE, with optimal cut-off values of 2.55 (100% sensitivity, 81.6% specificity) and 211.5 (71.4% sensitivity, 85.7% specificity), respectively. Another study reported a different NLR cut-off (2.26) with varying sensitivity (75%) and specificity (50%), and lower PLR sensitivity (42.3%) but comparable specificity (83.9%) [6]. Soliman et al. also suggested NLR and PLR cut-offs can predict SLE activity [9]. Conversely, MPV showed no significant value in distinguishing SLE cases from controls or predicting nephritis, a finding supported by a 2017 meta-analysis [12]. While one study suggested MPV (cut-off 8.5fl) could predict SLE activity with high sensitivity (92%) and specificity (100%), it lacked a comparison with healthy controls [13].

PCT effectively differentiates bacterial infection from SLE flares [14]. This investigation identified no significant SLE-control PCT difference (p =0.174), aligning with prior research showing no correlation between PCT and SLE activity [23, 24]. Elevated PCT in SLE necessitates investigation for underlying infections.

Study limitations were the smaller number of patients, the longitudinal study of SLE patients, and the control with a further follow-up study could help measure illness progression and drug effects.

5. Conclusion

It may be speculated that NLR and PLR were significantly higher in SLE than in healthy controls. Both NLR and PLR could be useful biomarkers for assessing disease activity in patients with SLE and lupus nephritis.

Ethical approval and consent to participate: The patients provided informed consents to participate, took local ethical committee research approval numbered (M456-session number 67), and the study was in accordance with the 1964 Helsinki declaration.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Conflicts of Interest: Non-declared.

AI declaration: Non-declared.

References

1. Ayna AB, Ermurat S, Coşkun BN, Harman H, PehlivanY. Neutrophil to lymphocyte ratio and mean platelet volume as inflammatory indicators in systemic lupus erythematosus nephritis. Archives of Rheumatology [Internet].2017 Aug [cited 2021 June 5];32(1):21–25. doi: 10.5606/ArchRheumatol.2017.5886
2. Safak S, Uslu AU, Serdal K, Turker T, Soner S, Lutfi A. Association between mean platelet volume levels and inflammation in SLE patients presented with arthritis. African health sciences. 2014 Dec;14:919–24. doi: 10.4314/ahs.v14i4.21
3. Carli L, Tani C, Vagnani S, Signorini V, Mosca M. Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact—A systematic literature review. Seminars in Arthritis and Rheumatism 2015;45(2):190-194. doi:10.1016/j.semarthrit.2015.05.009
4. Zahorec R. Ratio of neutrophil to lymphocyte counts – rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001 May;102(1): 5–14.
5. Donnelly S, Roake W, BrownS, Young P, Naik H, Wordsworth P., et al. Impaired recognition of apoptotic neutrophils by the C1q/calreticulin andCD91 pathway in systemic lupus erythematosus. Arthritis &Rheumatism 2006 May;54(5):1543-56. DOI: 10.1002/art.21783
6. Wu Y, Chena Y, Yang X, Chena L, Yang Y. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were associated with disease activity in patients with systemic lupus erythematosus. International ImmunoPharmacology 2016 Apr;36:94-9. DOI: 10.1016/j.intimp.2016.04.006
7. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Modern Rheumatology 2016 May;26(3):372–76. DOI: 10.3109/14397595.2015.1091136
8. Zhao CN, Mao YM, Wang P, Guan SY, Sam NB, Li XM., et al. Lack of association between mean platelet volume and disease activity in systemic lupus erythematosus patients: a systematic review and meta-analysis. Rheumatology international 2018 Sep;38(9):1635-41. doi.org/10.1007/s00296-018-4065-6
9. Soliman WM, Sherif NM, Ghanima IM, EL-Badawy MA. Neutrophil to lymphocyte and platelet to lymphocyte ratios in systemic lupus erythematosus: relation with disease activity and lupus nephritis.

Reumatologia clinica. 2018 Aug;1256:1-7. . DOI: 10.1016/j.reuma.2018.07.008

10. Fawzy RM, Said EA, Mansour AI. Association of neutrophil to lymphocyte ratio with disease activity indices and musculoskeletal ultrasound findings in recent onset rheumatoid arthritis patients. The Egyptian Rheumatologist 2017 oct;39:203-206. DOI: 10.1016/j.ejr.2017.05.001
11. Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. British Medical Journal Open. 2019 Jan; 25;9(1):e022896. DOI: 10.1136/bmjopen-2018-022896
12. Lee YH, Song GG. Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and mean platelet volume with systemic lupus erythematosus disease activity: a meta-analysis. Journal of rheumatic disease 2017 Oct ;24(5):279-86. doi: 10.1111/1756-185X.13404.
13. Khan A, Haider I, Ayub M, Khan S. Mean Platelet Volume (MPV) as an indicator of disease activity and severity in lupus. F1000 Research 2017Mar;6:1-16. doi: 10.12688/f1000research.10763.3.
14. Serio I, Arnaud L, Mathian A, Hausfater P, Amoura Z. Can procalcitonin be used to distinguish between disease flare and infection in patients with systemic lupus erythematosus: a systematic literature review. Clinical Rheumatology 2014 Oct;33:1209–15. DOI: 10.1007/s10067-014-2738-4
15. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramseygolden R., et al. European League Against Rheumatism /American College of Rheumatology classification criteria for systemic lupus erythematosus. Arthritis& Rheumatism 2019 Sep;71(9):1400-12. doi: 10.1136/annrheumdis-2020-219373.
16. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH, Austin A, et al. Derivation of the SLEDAI. A disease activity index for lupus patients. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1992 Jun;35(6):630-40. Doi: 10.1002/art.1780350606.
17. Lam G, Petri M. Assessment of systemic lupus erythematosus. Clinical and experimental Rheumatology 2005 Sep ;23(5):120-32.
18. Yu J, Xu B, Huang Y, Zhao J, Wang S, Wang H., et al. Serum procalcitonin and C-reactive protein for differentiating bacterial infection from disease activity in patients with systemic lupus erythematosus. Modern Rheumatology 2014 May;24(3):457-63. DOI: 10.3109/14397595.2013.844391
19. Ma L, Zeng A, Chen B, Chen Y, Zhou R. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio in patients with systemic lupus erythematosus and their correlation with activity: A meta-analysis. International Immunopharmacology 2019 Nov;76:105949. DOI: 10.1016/j.intimp.2019.105949
20. Abdulrahman MA, Afifi N, El-Ashry M. Neutrophil/lymphocyte and platelet/lymphocyte ratios are useful predictors comparable to serum IL6 for disease activity and damage in naive and relapsing patients with lupus nephritis. The Egyptian Rheumatologist. 2020 Apr;42(2):107-12. Doi.org/10.1016/j.ejr.2019.08.002
21. Elsaid N, El Adle S, Fathi HM. Clinical significance of platelet-lymphocyte ratio in systemic lupus erythematosus patients: relation to disease activity and damage. The Egyptian Rheumatologist 2022;44(3): 225-29. DOI: 10.1016/j.ejr.2021.12.005
22. Xie S, Chen X. Red blood cell distribution width-to-platelet ratio as a disease activity-associated factor in systemic lupus erythematosus. Medicine 2018

Sep;97(39): e12342. DOI:10.1097/MD.0000000000012342

23. Kim HA, Jung JY, Suh CH. Usefulness of neutrophil-to-lymphocyte ratio as a biomarker for diagnosing infections in patients with systemic lupus erythematosus. Clinical Rheumatology [Internet]. 2017 Nov [cited 2021 June 5];36(11):2479–85. doi: 10.1007/s10067-017-3792-5
24. Gheita TA, Sakr BR, Rabea RE, Abdel Hamid SM. Value of hematological indices versus VEGF as biomarkers of activity in Behçet‘s disease. Clinical Rheumatology 2019 Aug;38(8):2201-10. Available from:https://www.researchgate.net/publication/332060115. DOI: 10.1007/s10067-019-04513-5