Case Study

Correlation Between Rheumatoid Arthritis Activity with Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio: A Case-Control Study

Safinaz Hussein[1], Nabawia M Tawfik[2], Noha F Abdelrahman[2], Asmaa Abobakr[3], Rania Hafez[1], Marwa M Thabet[4]

[1]Department of Internal Medicine, Clinical Hematology Unit, Faculty of Medicine, Assiut University, Assiut, Egypt

[2]Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

[3]Clinical pathology department, National Cancer Institute, Cairo University, Cairo, Egypt,

[4]Department of Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt,

Abstract:

Background: Patients with Rheumatoid arthritis (RA) may suffer from joint deformity, due to the inflammatory process in active disease. Inflammation may lead to disability in patients with RA. The neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have been emerged as markers of many inflammatory diseases including RA. The aim of this study was to evaluate the role of NLR and PLR ratios in the evaluation of RA activity and their relation with DAS-28 that is already used for the assessment of RA disease activity.

Our patients were divided into group A (patients with active disease, DAS-28 > 2.6) and group B (patients with remission, DAS-28 < 2.6). The patients with active disease were subdivided into three subgroups (patients with high disease activity with DAS-28 > 5.1, moderate disease activity patients with DAS-28 > 3.2, and low disease activity patients with DAS-28 <3.2 and >2.6).

Results: NLR and PLR are significantly higher in patients with RA than in healthy people and higher in patients with active disease than those in remission and significantly positively correlated with RA activity.

Conclusion: Both NLR and PLR are two inflammatory markers that are useful in evaluating RA disease activity as they are simple, cheap, and objective markers.

Background:

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disorder characterized by synovial inflammation with cartilage destruction which follows a relapsing-remitting course (1), RA manifested by joint destruction and deformity that may results in severe and progressive disability of the patients if not treated appropriately (2). The main cause of disability in RA patients is inflammation (3). The inflammatory process in RA is associated with changes in the counts, shapes, and sizes of circulating blood cells, particularly those of the immune system including neutrophils and lymphocytes in addition to platelets, these cells are responsible for the production of different pro-inflammatory cytokines, which, in turn, contribute to the activation of the neutrophils and platelets (4).

Therefore, the features of circulating blood cell components can be used for the assessment of inflammatory activity in RA patients (5). Neutrophil count is an important reflector of the inflammatory conditions in the body (6), as neutrophils are responsible for the production of many cytokines that contributes to the progress of inflammation (7). Platelets, also

play an important role in inflammation as they have regulatory effects on the immune system (8). Lymphocytes are one of the most important cells in the immune response as they release inflammatory agents that involved in the pathogenesis, progression, and clinical prognosis of RA (9).

The assessment of disease activity in RA patients is crucial as it could affect their management. The assessment of disease activity in RA depends mainly on clinical symptoms, signs, laboratory investigations, and questionnaires (10). Disease activity score-28 (DAS-28) which measures number of tender and swollen joints is considered the most popular and well-established tool for RA disease activity assessment, it consists of the following four domains: (1) number of tender joints (28 counted), (2) number of swollen joints (28 counted), (3) Erythrocytes Sedimentation Rate (ESR), and (4) Visual Analog Scale (VAS). Some of these domains are subjective with variable interpretation between the observers (11); therefore, the need for other reliable markers for assessment of disease activity is important to predict the prognosis of some RA patients (12). Laboratory markers are much preferred due to the

advantage of having fewer observer variations. The most widely used markers and well-recognized inflammatory indices that have been implicated in RA disease activity assessments are ESR and C-reactive protein (CRP) **(13)**. Although, both of these markers are widely used but they have some limitations as the reflection of short-term inflammatory activity and low discrimination ability with other inflammatory conditions **(10)**. Parameters of complete blood cell count are also important in assessment of RA disease activity. The NLR is the ratio of the absolute neutrophil count to the absolute lymphocyte count and reflects a balance between innate (neutrophils) and adaptive (lymphocytes) immune responses **(14)**. (PLR) is the proportion of platelet count to absolute lymphocyte count **(15)**. Compared with DAS-28, the NLR and PLR are objective indices. This advantage makes NLR and PLR more preferred markers in clinical practice **(16)**.

Thus, the aim of this study was to evaluate the correlation of RA activity with NLR and PLR ratios and their relation with DAS-28 that is already used for the assessment of disease activity.

Patients and Methods:

This case control study, included 87 patients with RA as defined according to the American College of Rheumatology (2010) **(17)** and 87 healthy age and sex-matched controls. Patients and controls were evaluated by medical history and clinical examination, laboratory investigations, chest x-ray, and abdominal ultrasound. The detailed medical history of RA patients, including duration of disease, morning stiffness, type of treatment, family history, musculoskeletal examination and local clinical examination of affected joints. Plain x-rays of the small joints of the hands, wrists, feet, and other affected joints. Complete blood counts, including calculations of the NLR, which were done by dividing the absolute neutrophil count by the number lymphocyte count), calculation of the PLR which was done by dividing the absolute platelet count by the absolute lymphocyte count. **(6)**, which was followed by the construction of a platelet histogram to derive the MPV and the PDW that are both considered as markers of platelet activation, ESR, CRP, Rheumatoid factor (RF) which was considered positive at a cutoff value of 15 u/ml, Anti- Cyclic Citrullinated Peptide antibodies (Anti-CCP) with a cutoff point at 20 u/ml, also liver and kidney function tests were performed.

An assessment of disease activity and functional disability by 28 joint disease activity score calculator (DAS 28) was carried out for 28 joints (2 shoulders, 2 elbows, 2 wrists, 10 metacarpo-phalangeal joints, 10 proximal inter phalangeal joints, and 2 knees). We used the Disease Activity Score DAS 28-ESR (four variables) to assess inflammation in RA and calculated the DAS.28-ESR (four variables) score using this formula **(18)**:

DAS28-ESR (four variables) = $0.56\ VTJC + 0.28\ VSJC + 0.70\ (ESR) + 0.014(PG)$

Where: - TJc represents the number of tender joints. - SJc represents the number of swollen joints. - ESR represents the erythrocyte sedimentation rate (using Westergren's method in mm/first hour). PG represents the patient's global assessment on the VAS (0–100 mm), where 0

represents no activity and 100 represent the highest possible activity. **(19)**. The DAS 28-ESR is an index ranging from 0 to 9.4 in which: - Low disease activity is defined as an index of <3.2 and >2.6, Moderate disease activity is defined as an index of >3.2 to <5.1, and high disease activity is defined as an index of >5.1 **(20)**. Remission is defined as an index of <2.6 **(21)**.

Our Patients were divided into two groups according to the Disease Activity Score-28 DAS-28 **(18)**.

• Group A (patients with active disease) with DAS 28-ESR > 2.6.

• Group B (patients with remission) with DAS 28-ESR < 2.6.

Group A (patients with active disease) were subdivided into three subgroups (patients with high, moderate, and low activity) according to the DAS- 28 ESR score.

Statistical Analysis

Data entry and data analysis were done using the Statistical Package for the Social Sciences Version 24. Continuous data were expressed as mean values and standard deviations or median values and interquartile ranges while categorical data were expressed as frequencies and percentages. Categorical data were compared using the chi-square test while mean values of continuous data were compared using either Student's t-test (two groups) or the ANOVA test (more than two groups). The Spearman correlation coefficient was used to assess the correlation of the NLR, PLR, and MPV with other variables. ROC curves were used to determine the diagnostic accuracy of NLR and PLR as markers of disease activity in RA. P values ≤ 0.05 were considered statistically significant.

Results

This study included 87 RA patients ,70 females (80.5%) and 17 males (19.5%) with a mean age 40.0 ± 9.98 years) and 87 age matched and sex matched individuals as the control group (67 females (77.1%) and 20 males (22.9%) with mean age 38.42 ± 7.99 years).

RA patients were classified into 68 patients with active disease (active group), 15 males, 53 females with mean of age 39.95±10.15 years. and duration of diseases 4.75 ±1.57 years (DAS-28 4.20±0.95) and 19 patients with remission (Remission group), 6 males and 13 females with a mean age 40.71±8.38 years and duration of diseases 4.00 ±1.15 years (DAS-28 2.41±0.15).

Active group (68 patients) was sub classified according to DAS-28 score into three groups (high active 17 patients, moderate active 40 patients and low active11 patients).

Complete blood count parameters in all the study groups showed that the hemoglobin level, MPV, and PDW in RA patients were significantly lower than the control group (P value < 0.001). Also, the neutrophil counts and platelet counts in RA patients were higher than those in the control group while the lymphocyte counts in RA patients were significantly lower than the control group (P value < 0.03) **(Table 1)**.

Table 1: Complete blood count parameters in all the study groups:

Item	RA group n = 87	Control group n = 87	P-value
1-Hb "g/dl"	10.74 ± 1.39	12.87 ± 1.34	P < 0.001
2-MPV "FL"	8.63 ± 1.00	9.71 ± 2.05	P < 0.001
3-PDW "FL"	9..79 ± 1.30	11.23 ± 1.30	P < 0.001
6-WBC "x10^9/L"	8.9 ± 2.14	6.2 ± 2.37	P < 0.001
7-Neutrophils"x10^9/L"	4.3 ± 1.87	3.3 ± 0.97	P < 0.04
8-lymphocytes"x10^9/L"	1.4 ± 0.24	1.9 ± 0.21	P < 0.03
9-platelets "x10^9/L"	281.55 ± 43.24	233.73 ± 42.31	P < 0.02

Hb Hemoglobin concentration; **MPV** Mean platelet volume; **PDW** platelet distribution width

MCV Mean corpuscular volume, **MCHC** Mean corpuscular Hemoglobin concentration

WBC white blood cell

* Significantly different at p value ≤ 0.05.

For the patients with active disease and those in remission, the hemoglobin level, MPV, and PDW in the active group were significantly lower than in the remission group (P value < 0.02, P value < 0.001, and P value < 0.001, respectively). The neutrophil and platelet count in the RA active group were significantly higher than patients in the remission group, while the lymphocyte counts in the RA active group were significantly lower than those in the remission group (P value < 0.04, P value < 0.03, and P value < 0.03).

The laboratory investigations & DAS28-ESR in RA patients showed that ESR, CRP levels, Anti-CCP, and the number of RF-positive people were significantly higher among patients with active RA than those in remission (P value < 0.001). Also, DAS28-ESR scores were significantly higher among patients with active RA than RA patients in remission (P value < 0.001) **(Table 2).**

Table 2: Complete blood count parameters and different laboratory investigations & DAS28-ESR in patients with RA

Item	RA patients "n = 87"		P-value
	Active group "n = 68"	Remission group "n = 19"	
1-Hb g/dl	10.65 ± 1.40	11.00 ± 2.16	P < 0.02
2-WBC	8.25 ± 2.14	7.5 ± 1.3	P < 0.03
3-Neutrophils	5.84 ± 1.42	3.47 ± 0.4	P < 0.04
4-Lymphocytes	1.14 ± 0.33	1.59 ± 0.57	P < 0.03
5-Plateletes	262.48 ± 15.49	246.47 ± 16.44	P < 0.03
6-MPV	7.63 ± 1.00	8.2	P < 0.001
7-PDW	9.59 ± 21	10.23 ± 34	P < 0.001
8—ESR "mm/h"	70.70 ± 3.49	20.0 ± 5.31	P < 0.001
9-CRP "mg/l"	13.05 ± 5.62	5.00 ± 3.41	P < 0.001
10-Anti-CCP	23.42 ± 1.22	15.85 ± 3.28	P < 0.001
11-DAS 28-ESR	4.20 ± 0.95	2.41 ± 0.15	P < 0.001
12-RF: - ve +ve	9(11.2%) 59(88.8%)	13(85.7) 6(14.3%)	P < 0.001

Hb Hemoglobin concentration, **MPV** Mean platelet volume, **PDW** platelet distribution width **MCV** Mean corpuscular volume, **MCHC** Mean corpuscular Hemoglobin concentration **WBC** White blood cell, **ESR** Erythrocyte sedimentation rate, **Anti-CCP** Anti-cyclic citrullinated peptide antibodies, **CRP** C-reactive protein **DAS-28** Disease activity score -28 **RF** Rheumatoid factor * Significantly different at p value ≤ 0.0

The NLR and PLR were significantly higher in RA patients when compared with the control group (P value < 0.001, P value < 0.01). Also, they were significantly higher in active RA group than those in remission group (P value < 0.01 and P value < 0.006, respectively) **(Table 3).**

Table 3: NLR & PLR in all study groups:

	NLR %	PLR%
RA patients "n = 87"	2.67 ± 1.47	123.08 ± 34.46
Control group "n = 87"	1.74 ± 0.17	113.28 ± 6.98
P- value	P < 0.001***	P < 0.01*
Active "n = 68"	2.78 ± 1.48	126.05 ± 34.05
Remission "n = 19"	1.96 ± 0.22	111.24 ± 17.25
P- value	P < 0.01*	P < 0.006**

NLR Neutrophil lymphocyte ratio; **PLR** Platelet lymphocyte ratio

* Significantly different at p value ≤ 0.05.

Regarding the disease activity, patients with active RA disease had the highest NLR and PLR ratio (P value < 0.001 and p < 0.002, respectively) **(Table 4).**

Table 4: NLR & PLR in RA patients as regards disease activity

Item	RA in Remission n = 19	Active RA patients n = 68			P-value
		High active n = 17	Moderate active n = 40	Low active n = 11	
NLR	1.96 ± 0.22	4.25 ± 2.02	3.34 ± 1.03	2.61 ± 0.81	P < 0.001***
PLR	111.24 ± 17.25	144.61 ± 47.12	122.59 ± 30.46	113.67 ± 7.76	P < 0.002**

* Significantly different at p value ≤ 0.05.

Among RA patients, there were highly significant positive correlations between NLR & PLR with the DAS-28 score and CRP levels. The NLR was significant positive correlation with ESR and Anti CCP. Among the active RA group, there were significant positive correlations between NLR & PLR with DAS-28 scores & CRP **(Table 5).**

Regarding the sensitivity, specificity and accuracy of both NLR & PLR in all RA patients from ROC curve. At cutoff 2.5 of NLR the sensitivity equal 70.9%, specificity equal 96.8%

negative predictive value=69.5%, positive predictive value =100% and accuracy equal 78.73%. At cutoff 115.0 of PLR the sensitivity equal 65.6%, specificity equal 98.9%, negative predictive value=71.7%, positive predictive value =92.0% and accuracy equal 67.24%.

And for the sensitivity, specificity and accuracy of both NLR & PLR in active RA group from ROC curve. At cutoff 2.5 of NLR the sensitivity equal 79.8%, specificity equal 97.58% and accuracy equal 81.27%. At cutoff 115.0 of PLR the sensitivity equal 75.6%, specificity equal 97.5%, and accuracy equal 75.4%.

Discussion:

RA is an autoimmune inflammatory systemic disease, in which there is an infiltration of the synovia of the joints with immune cells which cause progressive damage of cartilage and bone. In this current study, in the group with active disease, females represent 78% and males represent 22% with a mean age of 39.95 years. The female predominance in our study may be attributed to the disease prevalence **(22)**, which is in agreement with the findings of **Mercan et al. (5) and Zhang et al. (6).**

In this study, regarding complete blood count parameters, RA patients had significantly lower hemoglobin levels, MPV and PDW values than healthy individuals in the control group (p < 0.001). This finding is in agreement with those of **Borah et al. (23),** who reported that anemia is a common extra-articular manifestation in RA patients. We also found a lower mean hemoglobin level in the active group (10.65 g/dL) than in the remission group (11.00 g/dL), which is in agreement with the findings of **Helal et al. (24),** who reported that hemoglobin levels were significantly lower in patients with active disease than in patients with inactive disease, and both mean levels were significantly lower than that of healthy controls.

Regarding MPV, our results are in agreement with **Gokmen et al. (25)** and **Kisacik et al. (16),** who found that MPV values in RA patients were significantly lower than healthy controls. In contrast with **Lee et al. (26),** who found no correlation between MPV and RA activity in their meta-analysis that included eleven RA patients. These findings also are in contrast with those of **Muddathir A et al. (27)** and **Yazici et al. (28),** which showed higher values of MPV and PDW in RA patients than controls in their study. This contrast might be explained by the fact that the ethnic background of our study participants is different from that of the participants in previous studies and the differences in methodology used to measure these parameters in these studies.

In our study, the neutrophil count and the platelets of RA patients were significantly higher than control group, while their lymphocyte counts were significantly lower than controls and also higher in the active group than in the remission group. This finding could be attributed to the inflammation in RA that is characterized by increased serum levels of IL-6 and TNF and those could promote the maturation and release of neutrophils and platelets from the bone marrow **(29).**This finding is in agreement with the findings of **Quaiser and khan. (30), and Fu et al. (12).** On the other hand, **Zhange et al. (6)** who didn't not find any statistically significant difference in the neutrophil,

lymphocyte, or platelet counts between RA patients and the control group, which may be due to the different study design as theirs was a retrospective study.

Regarding the lymphocyte count, our results are consistent with the results of **Quaiser and Khan et al. (30),** and in contrast with **Helal et al. (24),** who did not find any significant difference in the lymphocyte count between patients with active disease, and patients in remission.

In the current study, we noticed that the ESR, CRP, Anti-CCP and RF levels in active RA patients were significantly higher than those in remission, which is in agreement with the findings of **Quaiser and Khan et al. (30), Helal et al. (24), and Zhang et al. (6),** who found that CRP and ESR levels significantly were significantly higher in patients with active disease than in those in remission.

In our study, the NLR and PLR of RA patients were significantly higher than controls, and this in agreement with the results of **Helal et al. (24), Fu et al. (12), and Uslu et al. (31),** who found significantly higher NLR and PLR among RA patients than among control group.

Regarding NLR, in contrast to our result **Abdelazeem and Mohamed et al. (32), who** found that there was no significant difference between patients and controls.

In the present study, the NLR and PLR of patients with active RA were higher than those of RA patients in remission, which is in agreement with the findings of **Uslu et al. (31),** who found that there were significant differences in NLR and PLR between patients with active RA and patients in remission .Also, we demonstrated that NLR and PLR were significantly higher among active RA patients according to the grade of activity than in patients in the remission group with the highest levels occurring in high active patients.

In the current study, we observed a highly significant positive correlation between NLR & PLR with DAS28-ESR and CRP in all RA patients. There was also a positive correlation between the NLR with ESR and Anti-CCP. We also noticed a significant positive correlation between the NLR & PLR with DAS28-ESR, CRP, and Anti-CCP in active RA patients and a non-significant difference between NLR & PLR with other variables in the remission group of patients. These results are consistent with the results of **Gokemen et al. (25), and Uslu et al. (31),** who noticed that the NLR and PLR had positive correlations with the ESR, CRP, and Anti-CCP., suggesting that NLR and PLR might be used as markers in the follow-up of disease activity.

In contrast to our results **Ibrahim et al. (33),** who found, in their study on 24 active RA patients, that there were only positive correlations between the NLR with ESR and inverse correlations with hemoglobin levels, and concluded that there was no correlation between the NLR with disease activity in RA patients

In our active RA patients, the ROC curve revealed that at the 2.5 cutoff point for the **NLR,** sensitivity was 79.8%, specificity was 97.1%, and accuracy was 81.77. Meanwhile, at the 115-cutoff point for the **PLR,** sensitivity was 75.6%, specificity was 97.5%, and accuracy was 67.24%.

In 2019, **Helal et al. (24),** demonstrated in their study on 30 active RA patients that at the 3.02 cutoff point for NLR, sensitivity was 90%, specificity was 85%, and accuracy was 86. Meanwhile, at the 112.59 cutoff for the PLR, sensitivity was 70%, specificity was 50%, and accuracy was 60%.

Limitations of the study:

The main limitation of this study was we did not conduct any power analysis to calculate the sample size selected for this study.

Conclusion

NLR and PLR are significantly higher in RA patients than in control participants, also in active patients than those in remission. They were significantly positively correlated with RA activity. So, both NLR and PLR could be used to evaluate RA activity as they are simple, cheap, and objective markers.

Recommendations

Financial support and sponsorship

Recommendations:

We recommend the use of both NLR and PLR for the assessment of disease activity in RA patients in clinical practice and evaluate the correlations of NLR and PLR with the radiological findings and medications of RA patients.

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