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Correlation between rheumatoid arthritis activity with neutrophil lymphocyte ratio and platelet lymphocyte ratio: a case-control study

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Abstract

Inflammation leads to disability in patients with rheumatoid arthritis (RA). The neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) have emerged as markers of many inflammatory diseases. 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. Eighty-seven RA patients and 87 age-matched and sex-matched controls, were recruited in the study. We assessed RA patients' activity by using DAS-28-erythrocyte sedimentation rate (ESR) (four variables) by using the 28-joint disease activity score software calculator. 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) . NLR and PLR are significantly higher in patients with active RA than in healthy people and those in remission and significantly positively correlated with RA activity. Both NLR and PLR are two inflammatory markers that are useful in evaluating RA disease activity as they are simple, cheap, and objective markers .

Keywords: neutrophil lymphocyte ratio, platelet lymphocyte ratio, Rheumatoid arthritis activity, Inflammatory markers.

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1. Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic disease in which there is synovial inflammation and joint destruction that follows a relapsing-remitting course [1-10], causing devastating joint destruction with severe disability if patients are not appropriately treated [11-22]. Inflammation is the main cause of disability in RA patients. Features of circulating blood cell components can be used for the assessment of inflammatory activity [23-34]. as systemic inflammation is associated with blood cells quantity and composition changes [35-41], especially those including immune system elements. Immune system elements that involve neutrophils, lymphocytes, and platelets have a role in the control of inflammation, and also undergo changes that are secondary to inflammation [32]. Hematological changes are a kind of feedback to systemic inflammation [15]. Disease activity assessment is important for RA management since it could greatly affect the clinical decision. Current RA disease activity assessment mainly depends on clinical symptoms, signs, laboratory tests, and questionnaires [6]. Currently, Disease activity score-28 (DAS-28) is the most well-established and popular RA disease activity assessment tool. It consists of the following four domains: (1) number of tender joints (28 counted), (2) number of swollen joints (28 counted), (3) ESR, and (4) Visual Analog. Scale (VAS); however, as some of these domains are subjective, the interpretation varies between observers [18]. therefore, the assessment of RA activity with reliable markers is important to predict the long-term outcome of a particular RA patient [9]. Laboratory markers are very much preferred due to their advantage of having fewer observer variations. The most commonly used markers for this purpose and well-recognized inflammatory indices that have been widely used for RA disease activity assessments are ESR and C-reactive protein (CRP) in daily practice [16]. However, both of these markers have some limitations such as the reflection of short-term inflammatory activity and low discrimination ability with other superimposed conditions [6]. 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 [13]. (PLR) is the proportion of platelet count to absolute lymphocyte count [21]. (21). Compared with DAS-28, the NLR and PLR are objective indices whose results are not subject to personal interpretation. This advantage makes NLR and PLR the preferred choices in clinical practice [19].

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

2. Patients and Methods

This case control study was conducted at the Internal Medicine Department and outpatient clinics, Assiut University Hospital. The study included 87 patients with RA as defined according to the American College of Rheumatology (2010) and 87 healthy age and sex-matched controls. All participants gave their written informed consent, this study was approved by the ethical committee of Assiut University. 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. [44]. 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, Anticyclic 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 metacarpophalangeal joints, 10 proximal interphalangeal 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 variable) score using this formula [29].

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 represents the highest possible activity. (2,29). 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 (37). Remission is defined as an index of <2.6 (8 .(Our Patients were divided into two groups according to the Disease Activity Score-28 DAS-28 [29].

- 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 .

2.1 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 .

3. Results

This study included 87 RA patients (70 females (80.5%) and17 males (19.5%) with a mean age 40.0 ± 9.98 years) and 87 normal persons 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 subclassified according to DAS-28 score into three groups (high active 17 patients, moderate active 40 patients and low active11 patients). Laboratory 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).

Laboratory investigations & DAS28-ESR in RA patients showed that 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). ESR, the levels of CRP, 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). The NLR and PLR were significantly higher in RA patients when compared with the control group (P value < 0.001, P value < 0.01)

(Table 3). 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 4). 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 5) . 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 (Table 6). Among the active RA group, there were significant positive correlations between NLR & PLR with DAS-28 scores & CRP (Table 7). Table 8 showed 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%. Table 9 showed 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%.

4. Discussion

RA is an inflammatory disease in which the synovium is infiltrated with neutrophils, macrophages, lymphocytes, and dendritic cells that cause the progressive destruction of cartilage and bone [35]. resulting in joint deformity if patients are not appropriately treated [20]. Inflammation in RA causes changes in the numbers, shapes, and sizes of peripheral blood cells and the release of inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) that modulates erythropoiesis [15]. Therefore, the features of circulating blood cell components can be used for the assessment of inflammatory activity) [26]. Cytokines have a very significant role in the pathogenesis of a great number of inflammatory conditions. Neutrophils and platelets are involved in the production of these cytokines, which, in turn, contribute to the activation of these neutrophils and platelets [7]. Neutrophils account for 45%–75% of leucocytes in the peripheral blood circulation and the neutrophil count is an important reflector of the inflammatory condition of the body [44]. Neutrophils are the body's first line of defense. They are responsible for the production of many lytic enzymes, free oxygen radicals, and cytokines that contribute to the progress of inflammation [41]. Platelets play an active role in inflammation and also have regulatory effects on the immune system [4]. Lymphocytes are one of the most important actors in the cellular immune response as they release inflammatory agents that have major roles in the pathogenesis, progression, and prognosis of RA.(33) [33]. In the current study, females represent 81.2% and males represent 18.8% of participants in the active group with a mean age of 39.95 years, and 71.4% of females versus 28.6% of males with a mean age of 40.7 years in the remission group. The female predominance in our study may be attributed to the disease prevalence, which is in agreement with the findings of Mercan et al. and Zhang et.([44].

In this study, RA patients had significantly lower hemoglobin levels, MPV and PDW values than patients in the control group (p < 0.001). This finding is in agreement with those of Borah et al. [3]. who reported that anemia is a common multifactorial 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. [15]. 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. Also, in agreement with Gokmen et al. [12]. and Kisacik et al. [19]. who found that MPV values in RA patients were significantly lower than cotrols. In contrast with Lee et al. [23]. who found no correlation between MPV and RA activity in their meta-analysis that included 11 studies. In our results, we observed a significant difference in the mean MPV value between active patients and those in remission and noticed a negative correlation between MPV with NLR in the active group, which is consistent with the findings of Kisacik et al. [19]. (As they reported a negative correlation between MPV values and disease activity. Our findings are in contrast with those of Muddathir A et al. [27]. and Yazici et al. [43]. (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 platelet and neutrophil counts of RA patients were significantly higher 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 (34), and those could promote the maturation and release of neutrophils and platelets from the bone marrow [14]. This finding is in agreement with the findings of Quaiser et al. [31]. and Fu et al. [19]. On the other hand, Zhange et al. [44]. did 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. [31]. and in contrast with Helal et al. [15]. who did not find any significant difference in the lymphocyte count between patients with active disease, and patients in remission. In the present study, there were significantly higher platelet counts in RA patients than in controls and in active patients than those in remission. In consistent with the findings of Fu et al. [19]. who found significantly higher platelet counts in RA patients than in controls. It is also in line with the findings of Helal et al. [15]. who found that platelet counts were significantly higher in RA patients than in healthy controls. Our findings were not in line with those of Zhange et al. [44]. who found no significate difference in the platelet count between the patient group and the control group, which may be due to the difference in study design as theirs was a retrospective study .

Table 1: Laboratory 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 < 0.000
2-MPV "FL"	8.63 ± 1.00	9.71 ± 2.05	P < 0.000
3-PDW "FL"	9..79 ± 1.30	11.23 ± 1.30	P < 0.000
6-WBC "x10^9/L"	8.9 ± 2.14	6.2 ± 2.37	P < 0.000
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

Table 2: 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	9(11.2%)	13(85.7)	P < 0.001
+ve	59(88.8%)	6(14.3%)	

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

Table 3: NLR & PLR in all study groups

Item	RA patients "n = 87"	Control group "n = 87"	P-value
1- NLR% **2- PLR%**	2.67 ± 1.47 123.08 ± 34.46	1.74 ± 0.17 113.28 ± 6.98	P < 0.001*** P < 0.01*

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

Table 4: NLR & PLR in RA patients (active group and remission group)

Item	Remission	Active	P-value
	"n = 19"	**"n = 68"**	
1-NLR	1.96 ± 0.22	2.78 ± 1.48	P < 0.01*
2-PLR	111.24 ± 17.25	126.05 ± 34.05	P < 0.006**

Table 5: NLR & PLR in RA patients as regards disease activity

Item	RA in Remission n = 19	Active RA patient n = 68			P-value
		High active n = 17	Moderate active n = 40	Low active n = 11	
1- NLR **2- PLR**	1.96 ± 0.22 111.24 ± 17.25	4.25 ± 2.02 144.61 ± 47.12	3.34 ± 1.03 122.59 ± 30.46	2.61 ±0.81 113.67 ± 7.76	P < 0.001*** P < 0.002**

Table 6: Correlation of NLR and PLR with all the study variables among RA patients

Item	NLR		PLR	
	R	P	R	P
MPV	−.053	.626	−.141	.193
PDW	.165	.126	.149	.170
DAS-.28	**.469****	**.000**	**.386****	**.000**
ESR	**.224***	**.037**	.076	.485
Anti-CCP	**.241***	**.025**	.066	.541
dis. Duration	−.119	.273	−.015	.889
CRP	**.427**	**.001**	**.376**	**.03***

Table 7: Correlation of NLR and PLR with all study variables among active RA patients

Item	NLR		PLR	
	R	P	R	P
Age	−.053	.641	.122	.283
DAS.28	**.406**	**.000**	**.297**	**.007**
ESR	.271	.015	.114	.316
MPV	−.077	.496	−.172	.128
PDW	.149	.188	.148	.190
Dis. Duration	−.166	.140	−.056	.625
Anti-CCP	.199	.076	.010	.932
Hb	−.036	.752	.011	.924
CRP	**.343**	**.002**	**.250**	**.025***

Table (8): Sensitivity, specificity and accuracy of NLR &PLR in all RA patients

Item	NLR	PLR
1- Cutoff	2.5	115.0
2-Sensitivity	70.9%	65.6%
3-Specificity	96.8%	98.9%
4- NPV	69.5%	71.7%
5-PPV	100%	92.0%
6-Accuracy	78.73%	67.24%
7-AUC	0.741	0.689
p-value	P<0.001**	P<0.02*

NPV Negative predictive value, **PPV** positive predictive value, **AUC** Area under curve

Table 9: Sensitivity, specificity, and accuracy of NLR & PLR in patients with active RA

Item	NLR	PLR
1-Cutoff	2.5	115.0
2-Sensitivity	79.81%	75.6%
3-Specificity	97.1%	97.5%
4- NPV	67.5%	72.6%
5-PPV	100%	94.0%
6-Accuracy	81.27%	75.48%
7-AUC	0.762	0.721
p-value	P < 0.001**	P < 0.01*

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. [31]. Helal et al. [15]. and Zhang et al. [44]. 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, which is in agreement with the results of Helal et al. [15]. Fu et al. [19]. and Uslu et al. [36]. 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. [1]. who found that there was no significant difference between patients and control . 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. [36]. 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 . The NLR and PLR can be considered as inflammatory markers due to changes that occur in the numbers of neutrophils, lymphocytes, and platelets as a result of inflammation [23]. The NLR and PLR can serve as indicators of the severity of RA [44].

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. [12]., and Uslu et al. [36]. 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. [17]. 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. [15]. 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% .

5. Conclusions

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

•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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Conflicts of interest

There are no conflicts of interest

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