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RESEARCH

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# Platelet/lymphocyte, neutrophil/lymphocyte, and lymphocyte/monocyte ratios as biomarkers for rheumatoid arthritis: correlation with disease activity

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## Abstract

**Background** Assessment of disease activity in rheumatoid arthritis (RA) patients is essential for the adjustment of therapy. Inflammatory changes in lymphocytes, neutrophils, monocytes, and platelets supported the use of neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR) as markers of inflammation, we aimed to explore the clinical significance of PLR, NLR, and LMR in RA patients.

**Results** The study included 120 RA patients and 50 healthy matched controls. Clinical and laboratory data of the patients were assessed. Disease activity was measured using disease activity score (DAS28). Complete blood count (CBC) with differential count was used for the calculation of NLR, PLR, and LMR. Patients had significantly high NLR, and PLR ($p < 0.001$) and significantly low LMR ($p < 0.001$) when compared with the control group. Also, there were significant differences in the three ratios between patients in activity and those in remission ($p < 0.001$). Similarly, there were significant differences in all three ratios between patients with different degrees of disease activity. DAS28 score was positively correlated with NLR, PLR ($r = 0.666$, $p < 0.001$, $r = 0.586$, $p < 0.001$) and negatively correlated with LMR ($r = 0.761$, $p < 0.001$). Receiver operating characteristic (ROC) curve analysis revealed that NLR had the highest sensitivity (86.9%) for RA disease activity, followed by PLR (85.9%) then LMR (76.2%), and regarding the specificity, NLR had high specificity (81%) followed by LMR (78%) then PLR (67%).

**Conclusions** Given that NLR, PLR, and LMR were significantly different in patients when compared with the controls, also on comparing different degrees of disease activity and the three ratios were significantly correlated with DAS28 score, in addition to their good sensitivity and specificity for detection of RA disease activity, all this imply that they may be easy, reliable, cost-effective, and time-saving biomarkers when added to DAS28 score for the assessment of RA disease activity.

**Keywords** Disease activity, NLR, PLR, LMR

## Background

Rheumatoid arthritis is an autoimmune disease characterized by systemic inflammation with the synovial joints being the main target, leading to articular damage, disability, and increased mortality [1]. Autoimmune response to citrullinated proteins, activation of immune cells, and production of pro-inflammatory cytokines are the main pathological hallmarks for disease development [1].

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Inflammation is the major mechanism behind increased disability and mortality in patients with RA [2]; assessment of inflammation with a reliable marker is essential to predict disease outcome. The markers which are commonly used in daily practice are CRP and ESR [3], but they have some limitations as they reflect short term inflammation and cannot discriminate between different inflammatory conditions [4].

The detection of autoantibodies as rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein (anti-CarP) antibodies is important for patients' classification and prognosis [5] and disease activity assessment is essential for the adjustment of therapy in RA patients [6]; it depends mainly on pain, tender and swollen joints, C-reactive proteins (CRP) and visual analogue scale (VAS) [7]. Although CRP and ESR are commonly used to assess disease activity in clinical practice, they may be normal in patients with low disease activity [8] and they are reported to be weekly correlated with disease activity [8].

Blood cells interactions are important in the pathophysiology of immune response, inflammation, hemostasis, and oncogenesis [9]. Systemic inflammation is commonly accompanied with changes in the composition and quantity of circulating blood cells, so the characters of circulating blood cells can be used for the evaluation of inflammatory activity [10]. Elements of the immune system including platelets, neutrophils, and lymphocytes not only have a role in controlling inflammation but also they change in response to inflammation [11]. Neutrophils represent terminally differentiated cells, and when there is no inflammation, they present in the circulation for 24 to 48 h then return to the bone marrow and undergo apoptosis [12]. Cytokines, leukotrienes and bacterial lipopolysaccharides delay apoptosis of neutrophils during inflammation [13]. Neutrophils represent up to 90% of cells in the synovial fluid of RA patients; and they are also abundant at the junction of cartilage and pannus [14]. Dysregulated activation of neutrophils plays an important role in the pathogenesis of RA [15]. Early in RA, there is migration of neutrophils into joint cavity where they contribute to the initiation of inflammatory process [14]. Lymphocytes have an important role in the pathogenesis of RA, lymphopenia occurs in various hematological, autoimmune, and infectious diseases [16]. The NLR is the percentage between neutrophils which is an inflammatory activator, and lymphocytes which is an inflammatory regulator, so increased NLR is a sign of inflammation [17].

Platelets have a marked role in immune modulation and inflammation through the crosstalk between the inflammatory system and markers of coagulation. In RA platelets secrete pro-inflammatory particles that interact with leucocytes leading to inflammation [18]. Several studies reported the shifts in PLR for the evaluation of systemic inflammation, infections, and combined problems in autoimmune rheumatic diseases [19, 20]. High NLR values were recorded in patients with active Behcet's Disease and those with increased carotid intimal thickness [21], Selim [22] reported the association of each of NLR, MLR and PLR with different manifestations of Behcet's disease. NLR, LMR, and PLR are considered biomarkers of inflammation with a prognostic value in some types of cancers such as lung, colorectal, esophageal, and pancreatic cancer [20]. Since DAS28 score and other disease activity measures are multifactorial and time-consuming, it is necessary to search for an easy, reliable, and time saving marker for the assessment of RA disease activity, and it is beneficial to have objective data from the blood picture that correlate with RA disease activity. We aimed to evaluate the sensitivity and specificity of PLR, NLR, and LMR for the assessment of RA disease activity and their correlation with DAS28 score.

## Methods

One hundred-twenty RA patients were recruited from the rheumatology department. In addition, 50 sex and age-matched healthy subjects were included as a control group. All subjects in the study groups assigned a written informed consent prior to their inclusion in the study. Ethical approval was obtained from the university ethical committee. RA patients were classified according to ACR 2010 criteria [23]. Patients with other connective tissue diseases, systemic diseases, infections, and malignancy were excluded. Disease activity was evaluated using DAS28 score through counting of tender and swollen joints, ESR measurement, and VAS was used by the patients for scoring their pain with a range from 0 (no pain) to 100 (the worst imaginable pain). Patients were classified according to DAS28 score into; remission ($DAS28 \leq 2.6$), low disease activity ($2.6 < DAS28 \leq 3.2$), moderate disease activity ($3.2 < DAS28 \leq 5.1$), and high disease activity ($DAS28 > 5.1$) [24].

Blood samples were obtained from all patients for the assessment of ESR, CRP, and CBC with differential count, RF, and ACPA. PLR was calculated by dividing the platelet count by the absolute lymphocyte count. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. LMR was calculated by dividing the absolute lymphocyte count by the absolute monocyte count.

### Statistical analysis

SPSS (version 17) was used for statistical analysis of the data; we used numbers and percentages for presenting demographic and clinical data for the participants.

Mean ± SD was used for comparing numerical data. Pearson's correlation was used to correlate the parameters, and $p < 0.05$ was considered statistically significant. ROC curve analysis with estimation of the area under the curve (AUC) and 95% confidence interval (CI) was performed to determine the sensitivity and specificity of the studied parameters for RA disease activity.

## Results

Our study included 120 RA patients and 50 healthy individuals as a control group. The demographic, clinical, and medication characteristics of the participants are shown in Table 1; 90% of our patients had arthralgia, 47.5% had arthritis, 53.3% had morning stiffness, and 5% had extra-articular manifestations. Our patients had significantly ($p < 0.001$) very high serum levels of acute phase reactants (ESR, and CRP) significantly ($p = 0.003$) low serum level of hemoglobin in comparison to the control group. Despite there was no significant difference between patients and controls regarding total WBCs count, the differential count showed very high significant differences between patients and controls with decreased lymphocytes ($p < 0.001$), increased neutrophils ($p = 0.001$), and monocytes ($p < 0.001$) in the patients' group. Despite the patients having high platelet count compared with the controls, the difference was insignificant. On calculating the PLR, NLR, and LMR, we found that the patients had significantly high PLR ($p < 0.001$) and NLR ($p < 0.001$) and significantly low LMR ($p < 0.001$) in comparison to the control group, as shown in Table 2.

### The association of laboratory parameters with disease activity

Our patients were classified according to disease activity into active group ($n = 99$, DAS28 > 2.6), and remission group ($n = 21$, DAS28 ≤ 2.6). By comparing different laboratory parameters between the two groups, we found that the active group had significantly high acute phase reactants including ESR, and CRP ($p = 0.001$). Regarding the CBC parameters, active patients had high platelets ($p < 0.001$), monocytes ($p < 0.001$), neutrophils ($p < 0.001$), and low lymphocytes ($p < 0.001$) in comparison to the remission group. However, there was no significant difference between the two groups regarding hemoglobin and total WBCs count. The increased monocyte and neutrophil count and decreased lymphocyte count was associated with increased PLR ($p < 0.001$), NLR ($p < 0.001$), and decreased LMR ($p < 0.001$) in active patients compared with those in remission as shown in Table 3.

When we compared different disease activity groups, we found that patients with low disease activity had high neutrophils ($p = 0.028$), PLR ($p = 0.048$), NLR ($p = 0.028$), and low lymphocytes ($p = 0.041$) and LMR ($p < 0.001$) in comparison to those in remission. Patients with moderate disease activity had high, neutrophils ($p = 0.032$), monocytes ($p = 0.002$), PLR ($p = 0.045$), and NLR ($p = 0.009$), and low lymphocytes ($p = 0.023$) and LMR ($p < 0.001$) in comparison to those with low disease activity. In addition, high disease activity group patients showed increased ESR ($p < 0.001$), CRP ($p < 0.001$), neutrophils ($p = 0.005$), monocytes ($p < 0.001$), PLR ($p = 0.019$), and NLR ($p < 0.001$) and decreased lymphocytes ($p = 0.04$) and LMR ($p < 0.001$) in comparison to moderate disease activity group as shown in Table 4.

### Correlation of DAS28 score, PLR, NLR, and LMR with laboratory parameters

We tested the correlations between different laboratory parameters and DAS28 score, we found that DAS28 score

**Table 1** Demographic and clinical data of the participants

| Item | RA patients (120) | Controls (50) |
|---|---|---|
| Age/years (mean ± SD) | 42.87 ± 9.77 | 40.56 ± 10 |
| Gender: (no. (%)) | | |
| Females | 108 (90%) | 44 (88%) |
| Males | 12 (10%) | 6 (12%) |
| Disease duration /years (mean ± SD) | 5.46 ± 2.93 | ..... |
| Arthralgia (no. (%)) | 108 (90%) | ..... |
| Arthritis (no. (%)) | 57 (47.5%) | ..... |
| Morning stiffness (no. (%)) | 64 (53.3%) | ..... |
| Extra-articular manifestations | 6 (5%) | ..... |
| DAS28 (mean ± SD) | 4.52 ± 1.38 | ..... |

**Table 2** Laboratory data of the patients and controls

| Item | Patients ($n = 120$) Mean ± SD | Controls ($n = 50$) Mean ± SD | *P* value |
|---|---|---|---|
| ESR | 50.73 ± 25.87 | 12.58 ± 5.32 | < 0.001 |
| CRP | 25.95 ± 16.40 | 2.68 ± 1.91 | < 0.001 |
| Hemoglobin | 11.53 ± 1.46 | 12.33 ± 1.75 | 0.003 |
| Platelets | 273.85 ± 40.26 | 263.38 ± 30.48 | 0.1 |
| WBCs | 7.16 ± 2.35 | 6.95 ± 1.68 | 0.573 |
| Lymphocytes | 1.77 ± 0.36 | 2.49 ± 0.615 | < 0.001 |
| Neutrophils | 3.77 ± 0.70 | 3.35 ± 0.742 | 0.001 |
| Monocytes | 0.49 ± 0.11 | 0.33 ± 0.06 | < 0.001 |
| PLR | 157.13 ± 50.03 | 111.00 ± 28.94 | < 0.001 |
| NLR | 2.19 ± 0.80 | 1.55 ± 0.60 | < 0.001 |
| LMR | 3.87 ± 1.54 | 7.77 ± 2.30 | < 0.001 |
| RF | 106.44 ± 103.08 | ..... | ..... |
| ACPA | 117.43 ± 98.73 | ..... | ..... |

Where: *PLR* is platelet/lymphocyte ratio, *NLR* is neutrophil/lymphocyte ratio, and *LMR* is lymphocyte/monocyte ratio

**Table 3** Comparison of laboratory parameters between active and inactive groups

| Item | Mean Difference | Std.error difference | *P* value | 95% CI | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| DAS28 | 2.34629 | 0.25 | < .001 | 1.83 | 2.85 |
| ESR | 19.59019 | 5.97 | .001 | 7.75 | 31.42 |
| CRP | 13.25844 | 3.76 | .001 | 5.80 | 20.71 |
| Hemoglobin | -0.58743 | 0.34 | .095 | -1.27 | 0.11 |
| Platelets | 42.48 | 8.9 | < .001 | 24.87 | 60.09 |
| WBCs | 0.03306 | 0.56 | .954 | -1.09 | 1.15 |
| Monocytes | 0.17743 | 0.03 | < .001 | 0.13 | 0.22 |
| Lymphocytes | -0.55580 | 0.08 | < .001 | -0.69 | -0.41 |
| Neutrophils | 1.09012 | 0.13 | < .001 | 0.82 | 1.36 |
| PLR | 75.37 | 9.88 | < .001 | 55.8 | 94.93 |
| NLR | 1.28668 | 0.15 | < .001 | 0.98 | 1.58 |
| LMR | -3.06332 | 0.24 | < .001 | -3.54 | -2.58 |

Where: *PLR* is platelet/lymphocyte ratio, *NLR* is neutrophil/lymphocyte ratio, and *LMR* is lymphocyte/monocyte ratio

was positively correlated with ESR ($r=0.666$, $p<0.001$), CRP($r=0.599$, $p<0.001$), PLT ($r=0.325$, $p<0.001$), neutrophils ($r=0.588$, $p<0.001$) and monocytes ($r=0.702$, $p<0.001$), and negatively correlated with hemoglobin ($r=-0.252$, $p<0.005$), and lymphocytes ($r=-0.573$, $p<0.001$) as shown in Table 5, also we found that DAS28 score was positively correlated with PLR ($r=0.586$, $p<0.001$), and NLR ($r=0.666$, $p<0.001$), and negatively correlated with LMR ($r=-0.761$, $p<0.001$) as shown in Fig. 1(a). Both PLR and NLR were positively correlated with ESR, CRP, neutrophils, monocytes and negatively correlated with lymphocytes, while LMR was negatively correlated with ESR, neutrophils and monocytes, and positively correlated with lymphocytes. RF and ACPA were not correlated with any of the studied parameters as shown in Table 5. A graphical summary outlines the main findings of the study is shown in Fig. 2.

### Receiver operating characteristic curve for detection of sensitivity and specificity of PLR, NLR, and LMR for disease activity

In the present work, ROC curve analysis revealed that PLR had an area under the curve (AUC = 0.841, $p<0.001$) with a sensitivity of 85.9% and a specificity of 67% at cut off 112.39, NLR had an AUC of 0.913, $p<0.001$ with a sensitivity of 86.9% and a specificity of 81% at cut-off 1.3, and LMR had an AUC of 0.873, $p<0.001$, with 76.2% sensitivity and 78% specificity at cut off 4.67 as shown in Fig. 1(b).

## Discussion

The evaluation of RA disease activity is still challenging [25]. The assessment of inflammatory activity is of great importance to evaluate the efficacy of treatment, despite the current use of DAS28 score, CRP, and ESR to assess RA disease activity, but previous studies reported some limitations [26]. As the symptoms may not be typically presented in some patients, for example, patients may have low disease activity with CRP, ESR, CDAI, and DAS28 score at a cutoff value but still suffering from synovial inflammation with joint damage [27], despite the wide use of DAS28 score in clinical practice, it still has some drawbacks, as it is time-consuming and has subjective components, so it is essential to find an easy, reliable, time saving, objective method for the assessment of disease activity in RA patients.

Lymphocytes, neutrophils, and platelets have marked role in controlling inflammation in patients with RA, and their serum level can be used as a marker of disease activity [23]. Our findings revealed that despite there is no significant difference between patients and controls regarding total WBCs count, the differential count showed very high significant differences. Our patients had significantly decreased lymphocytes and increased neutrophils and monocytes; this agrees with Du and Tsukamoto [24, 25], who reported that the lymphocyte count was lower while the monocyte count was higher in RA patients than in healthy controls [26]. Suggesting that decreased lymphocytic count in RA patients may be due to the accumulation of lymphocytes in the inflamed joints and increased apoptotic elements such as caspase and heat shock protein. While Berezné [28] attributed lymphopenia to decreased production of lymphocytes and increased destruction secondary to immunosuppressive therapy or alterations in lymphocyte distribution. The role of neutrophils in the pathogenesis of RA is suggested by their involvement in the production of lytic enzymes and pro-oxidative mediators in the joints and activation of antigen-presenting cells, and the release of neutrophils extracellular traps which contain huge amounts of citrullinated proteins [29]. Reactive oxygen species and proteases derived from neutrophils are important in cartilage destruction and in post-translational modification of proteins and DNA [15]. In addition, cytokines and chemokines derived from neutrophils regulate the immune response and initiate autoantibodies production, and delay apoptosis of neutrophils in synovial joints leading to chronic inflammation [15].

According to our findings, RA disease activity had an impact on WBCs differential count as active patients revealed increased neutrophils and monocytes and decreased lymphocytes. DAS28 score was positively correlated with ESR, CRP, PLT, neutrophils, and monocytes,

**Table 4** laboratory parameters in different disease activity groups

| Item (Mean ± SD) | Remission (21) | Low (13) | Moderate (37) | High (49) | *P* value |
|---|---|---|---|---|---|
| DAS28 | 2.09 ± 0.5 | 3.05 ± 0.132 | 4.4 ± 0.545 | 5.83 ± 0.5 | P1 = 0.111<br>P2 < 0.001<br>P3 < 0.001 |
| ESR | 34.57 ± 11.83 | 27.38 ± 11.5 | 38.4 ± 11.78 | 73.16 ± 23.9 | P1 = 0.66<br>P2 = 0.22<br>P3 < 0.001 |
| CRP | 15.01 ± 7.23 | 16.07 ± 8.73 | 15.62 ± 5.49 | 41.06 ± 14.48 | P1 = 0.99<br>P2 = 0.1<br>P3 < 0.001 |
| Hemoglobin | 12.01 ± 1.27 | 11.96 ± 1.37 | 11.59 ± 1.5 | 11.16 ± 1.46 | P1 = 0.1<br>P2 = 0.86<br>P3 = 0.52 |
| Platelets | 238.8 ± 18.51 | 265.53 ± 39.04 | 281.44 ± 38.54 | 285.38 ± 40.56 | P1 = 0.11<br>P2 = 0. 66<br>P3 = 0.97 |
| WBCs | 7.13 ± 2.31 | 5.93 ± 1.42 | 6.89 ± 1.72 | 7.7 ± 2.82 | P1 = 0.46<br>P2 = 0. 57<br>P3 = 0.38 |
| Lymphocytes | 2.23 ± 0.26 | 1.97 ± 0.22 | 1.72 ± 0.31 | 1.56 ± 0.24 | P1 = 0. 041<br>P2 = 0.023<br>P3 = 0.04 |
| Neutrophils | 2.87 ± 0.68 | 3.38 ± 0.29 | 3.83 ± 0.17 | 4.21 ± 0.618 | P1 = 0. 028<br>P2 = 0.032<br>P3 = 0.005 |
| Monocytes | 0.034±0.035 | 0.4 ± 0.03 | 0.49 ± 0.08 | 0.58 ± 0.09 | P1 = 0. 24<br>P2 = 0.002<br>P3 < 0.001 |
| PLR | 94.95 ± 17.07 | 129.52 ± 38.22 | 162.32 ± 41.56 | 187.19 ± 39.8 | P1 = 0. 048<br>P2 = 0.045<br>P3 = 0.019 |
| NLR | 1.13 ± 0.26 | 1.66 ± 0.5 | 2.21 ± 0.48 | 2.77 ± 0.64 | P1 = 0. 028<br>P2 = 0.009<br>P3 < 0.001 |
| LMR | 6.39 ± 0.85 | 4.94 ± 0.718 | 3.58 ± 0.86 | 2.71 ± 0.61 | P1 < 0.001<br>P2 < 0.001<br>P3 < 0.001 |

Where: *PLR* is platelet/lymphocyte ratio, *NLR* is neutrophil/lymphocyte ratio, and *LMR* is lymphocyte/monocyte ratio. P1 is the significance by comparing the remission with the low disease activity, p2 is the significance by comparing the low disease activity with the moderate disease activity, and p3 is the significance by comparing the moderate disease activity with the high disease activity

and negatively correlated with hemoglobin, and lymphocytes. This agrees with Cascao [30] who reported that patients with active disease had increased neutrophil and platelet count and decreased lymphocyte count, and he attributed the increased neutrophils due to enhanced secretion of anti-apoptotic cytokines and activation of myeloid cells and neutrophils by granulocyte colony-stimulating factor. Kouri [31] suggested that the role of neutrophils in increasing disease activity in RA is achieved through the secretion of prostaglandins, proteases, and reactive oxygen species to the joint cavity and stimulation of other cells through the secretion of B lymphocytes stimulator, IL-17, TNF-α, and other mediators of inflammation. Regarding platelets, active patients had high platelets count in comparison to the remission group and this is in agreement with Tekeoğlu [32] who found that RA patients may present with thrombocytosis during disease activity which decreases with disease remission. Platelets have a controversial role in the pathogenesis of RA [33]; Zamora [34], reported that platelets have an anti-inflammatory role mediated through leukocytes (macrophage, lymphocyte, monocyte) cell to cell interaction through platelet glycoprotein 1bα, p-selectin and CD40L while Biolard [35] suggested a pro-inflammatory role by the recruitment of leukocytes into the vascular synovium. Platelets have abundant pro-inflammatory agents that can release active micro particles, which are involved in the development of autoimmune diseases

**Table 5** Correlation of DAS28 score, PLR, NLR, and LMR with laboratory parameters

| | DAS28 | | PLR | | NLR | | LMR | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| **ESR** | 0.666** | < 0.001 | 0.291** | 0.001 | 0.398** | < 0.001 | -0.232* | 0.011 |
| **CRP** | 0.599** | < 0.001 | 0.222* | 0.015 | 0.302** | 0.001 | -0.16 | 0.081 |
| **Hemoglobin** | -0.252* | 0.005 | -0.131 | 0.154 | -0.175 | 0.056 | 0.082 | 0.373 |
| **Platelets** | 0.325* | < 0.001 | 0.469** | < 0.001 | 0.069 | 0.453 | -0.088 | 0.338 |
| **WBCs** | 0.167 | 0.06 | 0.124 | 0.178 | 0.09 | 0.331 | 0.004 | 0.965 |
| **Lymphocytes** | -0.573** | < 0.001 | -0.836** | < 0.001 | -.833** | < 0.001 | 0.746** | < 0.001 |
| **Neutrophils** | 0.588** | < 0.001 | 0.347** | < 0.001 | 0.733** | < 0.001 | -0.370** | < 0.001 |
| **Monocytes** | 0.702** | < 0.001 | 0.190* | 0.037 | 0.225* | 0.013 | -0.729** | < 0.001 |
| **RF** | 0.161 | 0.08 | 0.169 | 0.066 | 0.122 | 0.183 | -0.065 | 0.48 |
| **ACPA** | 0.129 | 0.161 | 0.04 | 0.661 | 0.115 | 0.21 | -0.139 | 0.13 |

Where: *PLR* is platelet/lymphocyte ratio, *NLR* is neutrophil/lymphocyte ratio, and *LMR* is lymphocyte/monocyte ratio

Where * means low correlation, and ** means high correlation

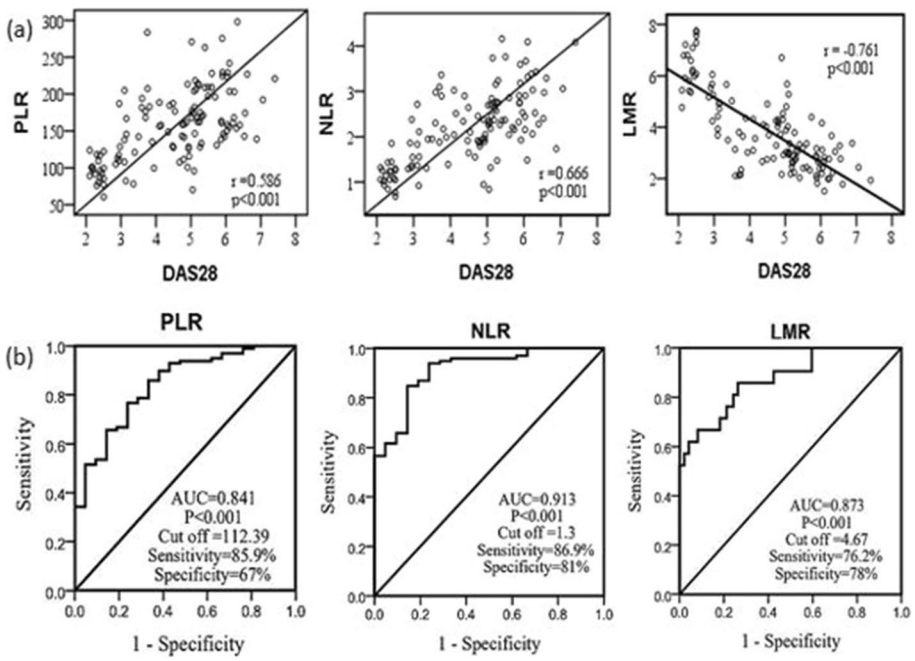


**Fig. 1** (**a**) Correlation of DAS28 score with PLR, NLR, and LMR, (**b**) ROC curve analysis of PLR, NLR, and LMR for the active RA patients compared with the remission group

[36]. The micro particles which are released by activated platelets interact with neutrophils through the expression of lipoxygenase and eicosanoid pathway activation [37].

The PLR is considered a good marker showing shifts in both platelet and lymphocyte count in response to prothrombotic and inflammatory states [20]. PLR and NLR are considered new inflammatory markers and they are reported to have a role in cardiovascular diseases and malignancy, but up to date limited studies with small sample size were found showing their role in RA [38]. In addition, the role of PLR and NLR as markers of disease activity in RA is still not properly investigated due to the limited number of studies and variation in cut-off values used [19]. LMR is an inflammatory marker for the development and progression of RA, but its role is still unclear [34]. Our study revealed that RA patients had significantly high PLR, NLR, and low LMR when compared with the control group and this is in agreement with Jin [39] who found that the PLR and NLR were higher in RA patients than healthy controls. Lee [40] had concluded in

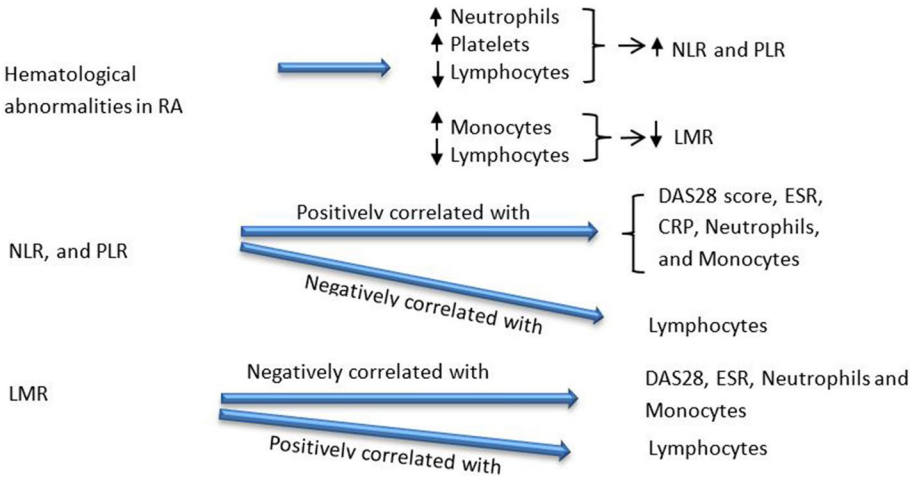


**Fig. 2** A graphical summary outlines the main findings of the study

his meta-analysis study that PLR and NLR were high in RA patients than healthy controls. Several studies supported the importance of PLR and NLR as diagnostic biomarkers in patients with rheumatic diseases especially RA [41, 42]. Du [34] found that LMR was lower in patients with RA than healthy controls.

According to our findings, active patients had high PLR, NLR and low LMR in comparison to those in remission and when we compared different disease activities groups, we found that increased disease activity was associated with increased PLR, NLR, and decreased LMR. In addition, we found that DAS28 score was positively correlated with PLR, and NLR and negatively correlated with LMR. Our findings are in agreement with Abd-Elazeem and Sargin [19, 43] who reported that PLR and NLR were high in RA patients with active disease and positively correlated with the DAS28 score. Lee [40] concluded that PLR and NLR were positively correlated with disease activity. Du [34] found that LMR was low in patients with active disease and negatively correlated with disease activity. In the work of Gaballah [44], NLR was not only significantly correlated with DAS28 but also with the findings of tenosynovitis on ultrasound in RA patients. So future work should focus on these ratios as biomarkers for articular as well as extra-articular inflammatory activity in RA patients.

ROC curve analysis revealed that NLR had the highest sensitivity for RA disease activity, followed by PLR then LMR. Regarding the specificity, NLR had the highest specificity, followed by LMR then PLR. Zhang [45] found that combining NLR with PLR is more accurate for distinguishing patients with active disease from those in remission according to ROC curve analysis. Our findings support that PLR, NLR, and LMR may be useful markers for the assessment of RA disease activity despite that they should not be used in isolation, it is important to consider other factors such as clinical, laboratory, and radiological findings to accurately assess disease activity and guide treatment decisions.

## Conclusions

Given that NLR, PLR, and LMR were significantly different in patients when compared with the controls, also on comparing different degrees of disease activity and the three ratios were significantly correlated with DAS28 score, in addition to their good sensitivity and specificity for detection of RA disease activity, all this imply that they may be easy, reliable, cost-effective, and time-saving biomarkers when added to DAS28 score for the assessment of RA disease activity.

## Limitation

Our study is a single center, small sample size study, so further studies with larger sample sizes and longer follow-up periods with monitoring patient's medications are needed to confirm the usefulness of these markers for the assessment of RA disease activity.

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**Authors' contributions**
Conceptualization and diagnosis: Sahar A. Elsayed and Mohamed A. Esmail; Material preparation, and data collection: Shereen M. Basily; Analysis, investigation, and writing: Sahar A. Elsayed and Ola Mounir; Review, editing and approval: All authors.

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**Availability of data and materialS**
The data of the current study is available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
This study was carried out in accordance with the ethical standards laid down in the Helsinki Declaration of 1975 and its later amendments in 2000 and approved by the Medical Research Ethics Committee, Faculty of Medicine, Sohag University, all patients included in this study gave written informed consent to participate in this research.

**Consent for publication**
All patients included in this research gave written informed consent to publish the data contained within this study.

**Competing interests**
The authors declare that they have no competing interests.

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**References**

1. Smolen J, Aletaha D, McInnes I (2016) Rheumatoid arthritis. Lancet Lond Engl 388:2023–2038
2. Zochling J, Braun J (2009) Mortality in rheumatoid arthritis and ankylosing spondylitis. Clin Exp Rheumatol 27:S127
3. Hobbs KF, Cohen MD (2012) Rheumatoid arthritis disease measurement: a new old idea. Rheumatology 51:vi21–vi27
4. Colglazier CL, Sutej PG (2005) Laboratory testing in the rheumatic diseases: a practical review. South Med J 98:185–191
5. Elsayed SA, Esmail MA, Ali RM, Mohafez OM (2019) Diagnostic and prognostic value of anti-CarP antibodies in a sample of Egyptian rheumatoid arthritis patients. Clin Rheumatol 38:2683–2689
6. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH (2016) 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 68:1–26
7. Chandrashekara S (2014) C-reactive protein: An inflammatory marker with specific role in physiology, pathology, and diagnosis. Int J Rheumatol Clin Immunol 2(S1)
8. Chandrashekara S, Mukhtar Ahmad M, Renuka P, Anupama K, Renuka K (2017) Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. Int J Rheum Dis 20:1457–1467
9. Scherlinger M, Guillotin V, Truchetet M-E, Contin-Bordes C, Sisirak V, Duffau P, Lazaro E, Richez C, Blanco P (2018) Systemic lupus erythematosus and systemic sclerosis: all roads lead to platelets. Autoimmun Rev 17:625–635
10. Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, Kiraz S, Ertenli I, Calguneri M (2008) Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. Joint Bone Spine 75:291–294
11. Rossaint J, Margraf A, Zarbock A (2018) Role of platelets in leukocyte recruitment and resolution of inflammation. Front Immunol 9:2712
12. McCracken JM, Allen L-AH (2014) Regulation of human neutrophil apoptosis and lifespan in health and disease. J Cell Death 7:JCD. S11038
13. Cross A, Moots RJ, Edwards SW (2008) The dual effects of TNFα on neutrophil apoptosis are mediated via differential effects on expression of Mcl-1 and Bfl-1. Blood 111:878–884
14. Chen W, Wang Q, Ke Y, Lin J (2018) Neutrophil function in an inflammatory milieu of rheumatoid arthritis. J Immunol Res
15. Fresneda Alarcon M, McLaren Z, Wright HL (2021) Neutrophils in the pathogenesis of rheumatoid arthritis and systemic lupus erythematosus: same foe different MO. Front Immunol 12:570
16. Miossi R, Fuller R, Moraes JC, Ribeiro ACM, Saad CG, Aikawa NE, Miraglia JL, Ishida MA, Bonfa E, Caleiro MTC (2013) Immunogenicity of influenza H1N1 vaccination in mixed connective tissue disease: effect of disease and therapy. Clinics 68:129–134
17. Ku JY, Roh J-L, Kim S-B, Choi S-H, Nam SY, Kim SY (2020) Prognostic value of neutrophil-to-lymphocyte ratio in older patients with head and neck cancer. J Geriatr Oncol 11:417–422
18. Harifi G, Sibilia J (2016) Pathogenic role of platelets in rheumatoid arthritis and systemic autoimmune diseases: perspectives and therapeutic aspects. Saudi Med J 37:354
19. Abd-Elazeem MI, Mohamed RA (2018) Neutrophil-lymphocyte and platelet-lymphocyte ratios in rheumatoid arthritis patients: Relation to disease activity. Egypt Rheumatol 40:227–231
20. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M, Kitas GD (2019) The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med 39:345–357
21. Elden MS, Hmmad G, Farouk H, Fawzy RM, Abdelwhaba B (2018) Neutrophil-to-lymphocyte ratio: relation to disease activity and carotid intima-media thickness in Behçet's disease. ERAR 45:133–139
22. Selim ZI, Mostafa NM, Ismael EO, Kamal D (2023) Platelet lymphocyte ratio, lymphocyte monocyte ratio, mean platelet volume, and neutrophil lymphocyte ratio in Behcet's disease and their relation to disease activity. ERAR 50:1
23. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD (2010) 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 62:2569–2581
24. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS (2005) Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 52:2625–2636
25. Coutant F, Miossec P (2020) Evolving concepts of the pathogenesis of rheumatoid arthritis with focus on the early and late stages. Curr Opin Rheumatol 32:57–63
26. Orr CK, Najm A, Young F, McGarry T, Biniecka M, Fearon U, Veale DJ (2018) The utility and limitations of CRP, ESR and DAS28-CRP in appraising disease activity in rheumatoid arthritis. Front Med 5:185
27. Yu X, Li Z, Ren M, Xi J, Wu J, Ji Y (2018) Superb microvascular imaging (SMI) for evaluating hand joint lesions in patients with rheumatoid arthritis in clinical remission. Rheumatol Int 38:1885–1890
28. Berezné A, Bono W, Guillevin L, Mouthon L (2006) Diagnosis of lymphocytopenia. Presse Medicale (Paris, France: 1983) 35:895–902
29. Corsiero E, Pratesi F, Prediletto E, Bombardieri M, Migliorini P (2016) NETosis as source of autoantigens in rheumatoid arthritis. Front Immunol 7:485
30. Cascao R, Rosário H, Souto-Carneiro M, Fonseca JE (2010) Neutrophils in rheumatoid arthritis: more than simple final effectors. Autoimmun Rev 9:531–535
31. Kouri V-P, Olkkonen J, Ainola M, Li T-F, Björkman L, Konttinen YT, Mandelin J (2014) Neutrophils produce interleukin-17B in rheumatoid synovial tissue. Rheumatology 53:39–47
32. Tekeoğlu İ, Gürol G, Harman H, Karakeçe E, Çiftçi İH (2016) Overlooked hematological markers of disease activity in rheumatoid arthritis. Int J Rheum Dis 19:1078–1082
33. Andia I (2017) The ins and outs of platelets in RA. Nat Rev Rheumatol 13:262–264
34. Du J, Chen S, Shi J, Zhu X, Ying H, Zhang Y, Chen S, Shen B, Li J (2017) The association between the lymphocyte-monocyte ratio and disease activity in rheumatoid arthritis. Clin Rheumatol 36:2689–2695
35. Boilard E, Nigrovic PA, Larabee K, Watts GF, Coblyn JS, Weinblatt ME, Massarotti EM, Remold-O'Donnell E, Farndale RW, Ware J (2010) Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. Science 327:580–583
36. Olumuyiwa-Akeredolu O-o O, Pretorius E (2016) Rheumatoid arthritis: notable biomarkers linking to chronic systemic conditions and cancer. Curr Pharm Des 22:918–924
37. Duchez A-C, Boudreau LH, Naika GS, Bollinger J, Belleannée C, Cloutier N, Laffont B, Mendoza-Villarroel RE, Lévesque T, Rollet-Labelle E (2015) Platelet microparticles are internalized in neutrophils via the concerted activity of 12-lipoxygenase and secreted phospholipase A2-IIA. Proc Natl Acad Sci 112:E3564–E3573
38. Li S, Zou J, Liu C, Jiao X, Gong J, Li J, Wang Z, Lu M, Lu Z, Shen L (2020) Baseline derived neutrophil-to-lymphocyte ratio as a prognostic

biomarker for non-colorectal gastrointestinal cancer patients treated with immune checkpoint blockade. Clin Immunol 212:108345
39. Jin Z, Cai G, Zhang P, Li X, Yao S, Zhuang L, Ren M, Wang Q, Yu X (2021) The value of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as complementary diagnostic tools in the diagnosis of rheumatoid arthritis: a multicenter retrospective study. J Clin Lab Anal 35:e23569
40. Lee YH (2018) Association between the neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio and rheumatoid arthritis and their correlations with the disease activity: a meta-analysis. J Rheum Dis 25:169–178
41. Yang Z, Zhang Z, Lin F, Ren Y, Liu D, Zhong R, Liang Y (2017) Comparisons of neutrophil-, monocyte-, eosinophil-, and basophil-lymphocyte ratios among various systemic autoimmune rheumatic diseases. APMIS 125:863–871
42. Zengin O, Onder M, Kalem A, Bilici M, Türkbeyler I, Ozturk Z, Kisacik B, Onat A (2018) New inflammatory markers in early rheumatoid arthritis. Z Rheumatol 77:144–150
43. Sargin G, Senturk T, Yavasoglu I, Kose R (2018) Relationship between neutrophil-lymphocyte, platelet-lymphocyte ratio and disease activity in rheumatoid arthritis treated with rituximab. Int J Rheum Dis 21:2122–2127
44. Gaballah AEA, Elsawy NA, El Gendy WM, Afifi AH, Hanafi MSM (2022) Hematological markers and ultrasound 7-joint inflammation score as add-on tools in the assessment of inflammation in rheumatoid arthritis patients. ERAR 49:25
45. Zhang Y, Yin Y, Kuai S, Shan Z, Pei H, Wang J (2016) Combination of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as diagnostic biomarker for rheumatoid arthritis. Int J Clin Exp Med 9:22076–22081

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