

# Application Value of Platelet-to-Lymphocyte Ratio as a Novel Indicator in Rheumatoid Arthritis: A Review Based on Clinical Evidence

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**Abstract:** Rheumatoid arthritis (RA) is a chronically progressive autoimmune disease with increasing age-standardized prevalence and incidence of RA worldwide. Its pathological features are persistent synovitis of the joint, accompanied by the release of a large number of inflammatory cytokines and cartilage and bone destruction. RA can lead to progressive joint damage, stiffness and swelling, vascular and bone-related complications, and irreversible disability, which seriously affects patients' life treatment. Early diagnosis and treatment can enhance the quality of life of RA patients. Platelet-to-lymphocyte ratio (PLR), as a common indicator in routine blood tests, has been proposed as an indicator of systemic inflammation in recent years. Its clinical detection is less invasive, economical, rapid and simple, and has been applied to the clinical evaluation of a variety of diseases. Of note, this indicator is important in assessing disease activity in RA, co-diagnosing RA, detecting subclinical complications, and monitoring responses to anti-inflammatory therapy. Therefore, this review summarizes the relationship between PLR and RA and the relevant mechanisms, further advancing the understanding of the clinical value of PLR.

**Keywords:** platelet-to-lymphocyte ratio, rheumatoid arthritis, inflammatory, blood platelets, lymphocytes

## Introduction

Rheumatoid arthritis (RA) is a common chronic progressive autoimmune disease among rheumatic diseases,<sup>1</sup> which clinically manifests as symmetric polyarthritis and is pathologically characterized by persistent synovitis and cartilage and bone destruction in the joints due to the release of massive inflammatory cytokines.<sup>2,3</sup> RA frequently occurs within all regions and ethnicities of the world. The global prevalence of RA has reached 0.27% according to a study based on the 2017 Global Burden of Disease data.<sup>4</sup> From 1990 to 2017, the global prevalence and incidence of RA both increased (age-standardized prevalence and incidence increased by 7.4% and 8.2%, respectively), and the mortality rate also rose due to many comorbidities of RA under the influence of persistent inflammation.<sup>5</sup>

Platelet-to-lymphocyte ratio (PLR) is the ratio of platelet (PLT) count to lymphocyte count, which has the advantage of simple, rapid, and inexpensive detection as it can be obtained during routine blood tests. As a composite indicator, PLR has a higher value in predicting the clinical outcomes of patients with systemic inflammation than single inflammatory markers. PLR was first proposed and used in clinical trials by Smith et al with favorable predictive performance.<sup>6,7</sup> PLTs, lymphocytes, and their interaction are responsible for the development of RA and immune-inflammatory responses. PLR has been established as an informative marker revealing changes in PLT and lymphocyte counts resulting from acute inflammatory and prothrombotic states.<sup>8</sup> When the body is subjected to inflammatory stimulation, a large number of platelets are released from megakaryocytes, which interact with inflammatory cells such as white blood cells and endothelial cells to release inflammatory factors and initiate and aggravate the

inflammatory response. Lymphopenia is due to the migration and infiltration of peripheral lymphocytes in RA inflamed synovium, which is exacerbated by the increase of early apoptotic markers. As a sensitive inflammatory response index, it is not affected by changes in physiological conditions and all other factors on the absolute value of leukocyte subtypes. It has been widely used in the diagnosis and treatment of various cancers,<sup>9</sup> cardiovascular diseases<sup>10</sup> and other diseases. It has been found in recent years that PLR can also be utilized for the diagnosis, activity prediction, and prognostic assessment of rheumatic diseases.<sup>11–15</sup>

In this study, we searched the association between PLR and RA, platelet and RA, lymphocyte and RA. In the process of literature reading and screening, we selected the literature in English in the past 10 years, integrated the data in the relevant literature, and sorted out a new table according to its correlation. In-depth study and reading of the literature related to the research topic of this paper were carried out to refine and summarize our views.

We reviewed the evidence on the association between PLR and RA to evaluate the effectiveness of PLR for clinical guidance, understand the molecular mechanism of PLR in RA, and provide some directions for future research. This article reviews the application of PLR in RA based on clinical evidence for the first time, and discusses its mechanism of action to a certain extent combined with existing studies. Based on the research of others, We systematically summarize the value of PLR in rheumatoid arthritis and present our views. This provides evidence for further exploration of the correlation between PLR and rheumatoid arthritis in the future and can be used as a reference for other researchers.

## Diagnosis of RA and PLR

Clinically, RA requires a comprehensive approach for its diagnosis and cannot be definitively diagnosed via single indicators at present. Available diagnostic modalities have some shortcomings. For instance, imaging is expensive. Additionally, the Disease Activity Score in 28 joints (DAS28) is cumbersome and easily influenced by subjective factors. Accordingly, it is urgent to find an objective, practical, and inexpensive clinical marker for the combined diagnosis of RA.

A meta-analysis in 2019,<sup>16</sup> which involved 8 PLR studies (380 RA patients and 305 healthy controls [HCs]), unraveled that PLR was significantly higher in RA patients than in HCs, indicating that PLR is associated with the development of RA. Further studies are needed, however, to evaluate the potential clinical use of this simple and relatively inexpensive marker in the diagnosis of RA. A cross-sectional study by Khan et al<sup>17</sup> showed that PLR was significantly high in 90 RA patients ( $P < 0.001$ ) and that PLR was positively correlated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), underscoring that in addition to the inflammatory markers ESR and CRP, PLR can be used as a complementary diagnostic indicator for RA patients. A prior study<sup>18</sup> investigating the value of PLR as a complementary diagnostic tool for RA exhibited that PLR was markedly higher in 1009 RA patients than in 245 hCs ( $P < 0.05$ ) and was positively correlated with rheumatoid factor (RF) ( $r = 0.139$ ,  $P < 0.01$ ), CRP ( $r = 0.297$ ,  $P < 0.01$ ), and ESR ( $r = 0.262$ ,  $P < 0.05$ ), highlighting that PLR may assist in the diagnosis of RA. Additionally, Zhou et al<sup>19</sup> measured PLR and aspartate aminotransferase (AST)-to-alanine aminotransferase (ALT) ratio in 215 RA patients and 303 hCs. The results revealed that PLR and AST/ALT ratio were dramatically higher in RA patients than in HCs ( $P < 0.05$ ) and that PLR + AST/ALT ratio had high sensitivity (91.1%) and moderate specificity (75.3%) in distinguishing between RA patients and HCs according to the receiver-operating characteristic (ROC) curve, illustrating that the combined detection of PLR and AST/ALT ratio was superior to the detection of the single indicators and can elevate the diagnostic efficiency of RA. A study by Peng et al<sup>20</sup> including 104 RA patients and 115 hCs reported that PLR in RA patients was prominently higher than that in HCs ( $P < 0.01$ ). In this study, the ROC curve was also used to assess the performance of ESR, RF, and PLR, which showed that a PLR value of  $> 115.7$  had a sensitivity of 82.5%, a specificity of 74.8%, and an area under the ROC curve (AUC) of 0.847 in the diagnosis of RA. These results suggest that PLR is associated with RA and may be an underlying indicator for chronic subclinical inflammation in RA patients.

The aforementioned studies are summarized in Table 1. Although the existing studies have determined that PLR cannot be used as the sole indicator for the diagnosis of RA, recent explorations have demonstrated its positive role in the diagnosis of RA. In the future, further studies are required to ascertain whether the early detection of PLR can be used for the early diagnosis of RA and which indicators, in combination with PLR, can increase the sensitivity and specificity of RA diagnosis.

**Table 1** Studies of PLR as an Adjuvant in the Diagnosis of RA

Research Type	Researchers	Group 1: The RA Group			Group 2: The Control Group			P Value
		n	Partial Parameters in the Study	PLR	n	Partial Parameters in the Study	PLR	
Cross-sectional comparative study	Sumbal Khan et al <sup>15</sup>	90	HG: 11.8 ± 1.9 ESR: 31.9 ± 22.5 NLR: 2.7 ± 0.9	152.8 ± 69.7	60	HG: 12.9 ± 2.3 ESR: 8.0 ± 2.7 NLR: 1.4 ± 0.6	102.5 ± 42.8	P < 0.001
Retrospective study	Zihan Jin et al <sup>16</sup>	1009	CRP: 13.55 (10.37–50.93) ESR: 50.50 (28.25–79.00) RF: 129.00 (41.85–394.00)	168.68 (124.45–239.57)	245	CRP: 2.30 (1.50–3.01) ESR: 24.00 (17.00–31.00) RF: 8.00 (4.40–14.30)	113.77 (92.97–144.95)	P < 0.05
Retrospective study	Wei Zhou et al <sup>17</sup>	215	AST/ALT: 1.43 (1.00, 2.00) PLT (× 10 <sup>9</sup> /L): 323.00 (248.00, 407.80) LYM (× 10 <sup>9</sup> /L): 1.51 (1.00, 1.83)	248.79 (162.43, 352.67)	303	AST/ALT: 1.00 (0.79, 1.29) PLT (× 10 <sup>9</sup> /L): 245.30 (216.70, 292.00) LYM (× 10 <sup>9</sup> /L): 2.13 (1.73, 2.55)	117.77 (95.91, 142.00)	P < 0.001
Cross-sectional study	You-Fan Peng et al <sup>18</sup>	104	CRP: 32.01 ± 41.80 ESR: 43.47 ± 22.65 RF: 463.69 ± 734.82	192.85 ± 101.78	115	CRP: 2.24 ± 1.48 ESR: 8.04 ± 4.41 RF: 33.35 ± 53.85	103.49 ± 28.68	P < 0.01

**Abbreviations:** RA, rheumatoid arthritis; HG, hemoglobin; ESR, erythrocyte sedimentation rate; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; RF, rheumatoid factor; PLT, platelet; LYM, lymphocyte; AST/ALT, aspartate aminotransferase/alanine aminotransferase.

## RA Disease Activity and PLR

DAS28 was calculated from 4 metrics, including swollen joint count, tender joint count, ESR, and visual analogue scale (VAS)-general health.<sup>21</sup> SDAI<sup>22</sup> is a scoring system that integrates multiple parameters, including number of tender joints, number of swollen joints, VAS, physician's global assessment of patient disease activity (PhGA), and measures of acute response such as CRP or ESR. CDAI<sup>23</sup> is similar to SDAI but typically does not contain acute-phase reactants and is more focused on clinical assessment. DAS28, SDAI, CDAI, ESR, CRP, and RF have been extensively used to assess disease activity in RA patients.<sup>24–26</sup> Yet, these indicators have the disadvantages of complex calculation, slow clinical detection, and susceptibility to the interference of other extraneous factors, which to a certain extent may affect the efficiency of assessment. Therefore, more convenient indicators need to be identified to help assess the disease activity of RA, which is vital for understanding disease progression and refining clinical decision-making for RA. Previous studies have reported that PLR is associated with the poor prognosis of various inflammation-related diseases, which may be attributed to the association of PLR with inflammatory states.<sup>27–29</sup> Given these findings, we hypothesized that PLR may also be associated with disease activity in RA. A study<sup>30</sup> showed that the area under the curve (AUC) of PLR for predicting disease activity was 0.921 (95% CI: 0.863–0.979,  $P=0.000$ ). At the best cut-off value of 2.56, the sensitivity and specificity were 81% and 77%, respectively.

A meta-analysis in 2023<sup>31</sup> displayed that in 18 studies (2122 patients with active RA and 1071 patients with nonactive RA), PLR was higher in patients with active RA. Choe et al<sup>32</sup> analyzed the correlation between PLR and disease activity in RA, which also unveiled that PLR was substantially higher in RA patients than in controls ( $P = 0.046$ ) and was only correlated with CRP ( $P = 0.025$ ), but not with other parameters of inflammatory activity. In a multicenter retrospective study,<sup>33</sup> RA patients showed greatly higher PLR than controls, and PLR was highly accurate in distinguishing between RA patients and HCs (ROC analysis;  $P < 0.001$ ) and was positively correlated with ESR, CRP, DAS28-ESR, and DAS28-CRP (correlation analysis).

The above studies are listed in Table 2. It is of great significance to monitor disease activity in RA patients for the improvement of their quality of life. In summary, PLR, as a new comprehensive indicator, has been widely studied in RA patients and has certain clinical value for effectively grasping the current status of RA. Nevertheless, PLR also has limitations. Accordingly, additional large-sample clinical trials are needed to verify the effective use and critical value of PLR.

## Comorbidity of RA and PLR

RA can involve multiple organs and systems other than joints, manifesting as many comorbidities such as interstitial lung disease (ILD), rheumatoid nodules, osteoporosis (OP), and Sjögren's syndrome.<sup>34,35</sup> As reported, PLR has great clinical value in predicting comorbidities in RA.

A study<sup>36</sup> involving 198 RA patients and 103 RA-ILD patients revealed that PLR was different between the RA and RA-ILD groups ( $P < 0.05$ ) and the AUC of PLR in differentiating RA-ILD from RA was 0.650, the best cut-off value was 144.625, the sensitivity was 75.73%, and the specificity was 53.98% ( $P < 0.001$ ), indicating that PLR can be used as a predictive and diagnostic biomarker for RA-ILD. Another single-center retrospective cohort study<sup>37</sup> analyzed whether PLR was associated with the occurrence of OP and vertebral fractures in RA patients by including 413 postmenopausal RA patients and 200 hCs. The results showed that PLR was significantly higher in RA patients than in HCs, and the

**Table 2** Studies of the Association Between PLR and Disease Activity in RA

Research Type	Researchers	Group 1: The RA Group			Group 2: The Control Group			P Value
		n	Age	PLR	n	Age	PLR	
Retrospective study	Jung-Yoon Choe et al <sup>27</sup>	257	60.7 ± 8.7	158.2 ± 93.6	71	60.4 ± 7.5	134.9 ± 55.2	$P = 0.046$
Multicenter retrospective study	Xu Y et al <sup>28</sup>	1499	60.03 ± 12.31	198.51 ± 110.48	366	58.87 ± 12.33	118.41 ± 36.86	$P < 0.001$

**Abbreviations:** RA, rheumatoid arthritis; PLR, platelet-to-lymphocyte ratio.

multivariate Cox proportional risk regression model revealed that high baseline PLR (hazard ratio = 1.96,  $P = 0.024$ ) was independently associated with a higher risk of incidental vertebral fractures in RA patients, illustrating PLR as a potential marker for systemic bone loss in RA patients.

The above-mentioned studies are displayed in Table 3. PLR as a potential marker in comorbidities of RA has been intensively studied in recent years, which enables improved prediction of comorbidities in RA in the clinical setting. Notably, since RA has numerous comorbidities, involving multiple organs and systems, the existing studies fail to completely present the clinical value of PLR in all comorbidities of RA, which calls for persistent research.

## Treatment Effect of RA and PLR

ESR and CRP can predict the severity of inflammation in RA but are difficult to predict therapeutic efficacy. PLR has been extensively utilized to assess the inflammation degree and efficacy of rheumatic diseases, tumors, cardiovascular diseases, and respiratory diseases as it has the advantages of affordability and availability and can better reflect systemic inflammation.<sup>38–41</sup>

In a former study<sup>30</sup> involving 98 patients with active RA, PLR in RA patients was positively correlated with the levels of high-sensitivity CRP (hs-CRP), ESR, interleukin-6 (IL-6), DAS28-ESR, anti-cyclic citrullinated peptide (CCP) antibody, and RF before and after tofacitinib treatment, and 6 months of tofacitinib treatment markedly reduced the levels of hs-CRP, ESR, IL-6, anti-CCP antibody, RF, and DAS28-ESR in RA patients. In addition, ROC analysis demonstrated that the AUC of PLR in assessing disease activity in tofacitinib-treated RA patients was 0.921 (95% confidence interval = 0.863–0.979,  $P = 0.000$ ), with a sensitivity of 81% and a specificity of 77% at the optimal cutoff value of 2.56. These results underlined that PLR can be used to assess the disease activity of tofacitinib-treated RA patients. Another study<sup>42</sup> including 38 RA patients elucidated that PLR, CRP, ESR, and DAS28-ESR levels were greatly lowered in RA patients after 6 months of rituximab treatment and that a significant correlation existed between the levels of DAS28-ESR and PLR before and after treatment, illustrating that PLR may be a potent indicator to assess the efficacy of rituximab. Zhou et al<sup>43</sup> recruited 52 RA patients treated with tocilizumab and followed them for 6 months for detecting

**Table 3** Studies of PLR in Predicting Comorbidities of RA

Research Type	Researchers	Groups	Group 1			Group 2			P Value
			n	Partial Parameters in the Study	PLR	n	Partial Parameters in the Study	PLR	
Cross-sectional study	Qiang Chen et al <sup>31</sup>	Group 1: the RA group Group 2: the RA-ILD group	198	DAS28: 4.63 ± 0.81	190.69 ± 98.75	103	DAS28: 5.08 ± 1.05	241.83 ± 158.74	$P < 0.001$
Retrospective cohort study	Byung-Wook Song et al <sup>32</sup>	Group 1: the postmenopausal RA group Group 2: the control group	413	CRP: 0.26 (0.07–0.91)  BMD in the lumbar spine: 0.94 ± 0.16 Osteoporosis in the lumbar spine, n (%): 102 (24.7) Osteoporosis at any site of the body, n (%): 132 (32)	139.8 (108–186.3)	200	CRP: 0.04 (0.02–0.08)  BMD in the lumbar spine: 1.11 ± 0.19 Osteoporosis in the lumbar spine, n (%): 14 (7) Osteoporosis at any site of the body, n (%): 16 (8)	122.8 (102.1–146)	$P < 0.001$

**Abbreviations:** RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; CRP, C-reactive protein; BMD, bone mineral density.

hemoglobin, PLT, neutrophil-to-lymphocyte ratio (NLR), and PLR in RA patients. The results displayed that changes in NLR ( $\Delta$ NLR) and PLR ( $\Delta$ PLR) showed an obvious correlation with changes in the Clinical Disease Activity Index ( $\Delta$ CDAI) ( $\Delta$ NLR:  $r = 0.30$ ,  $P = 0.03$ ;  $\Delta$ PLR:  $r = 0.31$ ,  $P = 0.03$ ), which suggested that  $\Delta$ PLR, combined with  $\Delta$ PLT and  $\Delta$ NLR, and  $\Delta$ NLR can be used to monitor  $\Delta$ CDAI in RA patients following tocilizumab treatment. Ayşegül Yetişir et al<sup>44</sup> found that inflammatory biomarkers were measured in RA patients before and after treatment with TNF- $\alpha$ . Consistent with other common inflammatory markers, changes in PLR had detailed statistical significance. Similarly, another study<sup>45</sup> also showed that baseline PLR is a useful marker for predicting the outcome of anti-Tnf- $\alpha$  therapy in RA patients.

The above studies are detailed in Table 4. In conclusion, PLR has been used to assess the therapeutic efficacy of RA, with clearly positive outcome feedback, and monitoring PLR has certain positive significance in determining the therapeutic efficacy of RA, which increases the confidence in future research on PLR in evaluating the therapeutic efficacy of RA.

## In-Depth Research of PLR Changes in RA

Although the association between PLR and RA has been established, the mechanism of the association remains to be further investigated. In RA, elevated PLR is mainly characterized by an increase in PLT count and a decrease in lymphocyte count. Reportedly, PLTs and lymphocytes may play different roles in the immune response during RA. Therefore, this article discusses the mechanisms behind the correlation between PLR and RA from the following two aspects.

### Mechanisms of Increased PLT Count

PLTs are the smallest blood cells derived from the proliferation and differentiation of bone marrow megakaryocytes.<sup>46,47</sup> PLTs play a role in inflammation in addition to hemostasis and coagulation.<sup>48,49</sup> It has been reported that PLTs may maintain and exacerbate inflammation in the pathogenesis of RA.<sup>50,51</sup> PLTs are difficult to detect in the joints of RA patients when their condition is stable, but PLT proteins are significantly increased in synovial fluids and serum during the active disease RA.<sup>52</sup> Elevated PLT count is strongly associated with acute phase reactants and pro-inflammatory substances.<sup>53–55</sup> During the progression of RA, PLTs increase in response to the release of inflammatory cytokines such

**Table 4** Studies of PLR in Assessing the Therapeutic Efficacy of RA

Research Type	Researchers	Before Treatment			After Treatment			P Value
		n	Partial Parameters in the Study	PLR	n	Partial Parameters in the Study	PLR	
Retrospective study	Juan Tang et al <sup>37</sup>	98	DAS28-ESR: 6.60 (5.82, 7.27) ESR: 148.49 $\pm$ 49.90 hs-CRP: 58.84 (2.6–207.29) IL-6: 17.69 (1.3–56.91) CCP: 178.11 $\pm$ 135.23	278.45 $\pm$ 124.63	98	DAS28-ESR: 3.89 (3.13, 4.82) ESR: 50 (12, 92) hs-CRP: 23.45 (0.2, 142) IL-6: 23.45 (0.2, 142) CCP: 65.14 $\pm$ 47.93	148.49 $\pm$ 49.90	$P < 0.01$
Retrospective study	Gokhan Sargin et al <sup>38</sup>	38	DAS28-ESR: 7.6 (5.2–8.9) ESR: 41.5 (5–96) CRP: 9.2 (0.6–181.5)	179.4 $\pm$ 92.7	38	DAS28-ESR: 3.7 (2.1–5.4) ESR: 33.5 (6–81) CRP: 5.7 (0.6–71.7)	129.7 $\pm$ 69.0	$P < 0.01$
Prospective study	Li Zhou et al <sup>39</sup>	52	Hemoglobin: 11.74 $\pm$ 1.78 Platelets: 292.12 $\pm$ 85.39 NLR: 3.75 $\pm$ 2.19	192.03 $\pm$ 90.96	52	Hemoglobin: 13.15 $\pm$ 1.74 Platelets: 216.35 $\pm$ 57.60 NLR: 2.37 $\pm$ 1.6	128.81 $\pm$ 63.65	$P < 0.01$
Prospective study	Ayşegül Yetişir et al <sup>40</sup>	207	CRP: 14.50 $\pm$ 32.7 ESR: 37.61 $\pm$ 23.1	179.9 $\pm$ 85.5	207	CRP: 5.68 $\pm$ 11.3 ESR: 29.66 $\pm$ 21.5	129.2 $\pm$ 54.6	$P < 0.01$

**Abbreviations:** RA, rheumatoid arthritis; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; CCP, cyclic citrullinated peptide; HG, hemoglobin; NLR, neutrophil-to-lymphocyte ratio.

as IL-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and the production of thrombopoietin and granulocyte colony-stimulating factor (CSF).

PLTs have been reported to function as an active regulator of intrinsic and adaptive immune responses.<sup>56,57</sup> Inflammatory mediators secreted from PLTs promote inflammation and recruit immune and inflammatory cells to tissue sites.<sup>58,59</sup> These recruited cells release chemokines to amplify and repeatedly exacerbate inflammation. Meanwhile, activated PLTs are involved in the onset and progression of RA by producing pro-inflammatory microparticles in the circulation and synovium.<sup>60,61</sup> These PLT microparticles are unique markers because they not only bear the characteristic hallmarks of apoptosis but also contain specific proteins and receptors on the PLT surface.<sup>62,63</sup> Of note, these microparticles are capable of expressing antigens and forming pro-inflammatory immune complexes, further driving the development of synovitis.<sup>64</sup> In addition, they stimulate cytokine responses from fibroblast-like synoviocytes, thus causing damage to joints by mediating the action of IL-1 $\beta$ .<sup>65</sup> Likewise, they also can foster inflammatory signaling by activating the complement system.<sup>66</sup> In vitro studies have unraveled that PLT-expressed P-selectin can interact with neutrophil-expressed P-selectin glycoprotein ligand-1, which favors the rolling of neutrophils at sites of inflammation or deposition on damaged endothelial cells<sup>56</sup> and increases the formation of circulating PLT-neutrophil aggregates,<sup>67</sup> enhancing the inflammatory activity of neutrophils. P-selectin-mediated PLT-T-lymphocyte interactions also repress lymphocyte proliferation. Additionally, PLTs not only secrete prostaglandins to result in synovial inflammation but also release 5-hydroxytryptamine, permeability factors, and chemokines that can drive the differentiation of Th1, Th17, and Treg cells through direct cell-to-cell contact and multiple soluble mediators. Notably, PLTs present antigens by expressing MHC I classes, regulating T cell responses.<sup>68,69</sup> PLTs induce the differentiation of monocytes into the pro-inflammatory phenotype M1 via the CD147 pathway, enabling the formation of platelet-monocyte aggregates, as well as inducing neovascularization in the hypoxic environment of RA.<sup>70,71</sup>

### Mechanisms of Lymphocyte Decline

Lymphocytes are the smallest white blood cells. This review focuses on T and B lymphocytes, which have irreplaceable roles in the immune response of the body.<sup>72,73</sup> Specifically, T lymphocytes can activate other immune cells to enhance the immune response,<sup>74</sup> and B lymphocytes predominantly produce antibodies, present antigens, and secrete cytokines to participate in immunomodulation.

Decreased lymphocytes are the result of sustained migration and infiltration of peripheral lymphocytes in the inflamed synovium of RA, while the upregulation of early apoptotic markers in peripheral blood lymphocytes may initiate an apoptotic cascade response, elevating lymphocyte apoptosis in RA patients.<sup>75,76</sup> Lymphocyte subpopulations have an essential pathogenic role in RA.<sup>77,78</sup> For example, Th0 cells can be transformed into Th1 cells that secrete interferon (IFN)- $\gamma$ , TNF- $\alpha$ , and lymphotoxin (LT)- $\beta$  to be involved in the pathogenesis of RA. Upon stimulation with TNF- $\alpha$  and IL-6, Th0 cells can be transformed into Th22 cells that participate in the pathogenesis of RA by releasing TNF- $\alpha$ , IL-13, and IL-22. Under transforming growth factor- $\beta$  (TGF- $\beta$ ) stimulation, Th0 cells are converted into Treg cells that are implicated in the pathogenesis of RA by secreting TGF- $\beta$ . Following stimulation with some cytokines, Th0 cells are converted to Th17 cells that secrete IL-17, TNF- $\alpha$ , IL-21, IL-22, granulocyte-macrophage-CSF, and receptor activator of nuclear factor- $\kappa$ B ligand (RANKL) for the development of RA. An earlier study<sup>79</sup> disclosed that Th17/Treg cell imbalance encouraged the progression of RA by producing proinflammatory/anti-inflammatory cytokines. Th17 cells can be induced by cytokines in synovial joints to recruit neutrophils and activate B lymphocytes, thereby facilitating osteoclast formation, and activated T lymphocytes migrate to the local synovium to interact with macrophages, dendritic cells, synoviocytes, and osteoclasts. In addition, diverse T cell subpopulations can recruit monocytes/macrophages and promote osteoblast differentiation and inflammatory cytokine production.<sup>80</sup>

In addition, B lymphocytes have also been increasingly evidenced to play an integral role in the development of RA.<sup>81,82</sup> For instance, B lymphocytes can present antigens to CD4<sup>+</sup> T cells to generate IL-21, which drives the maturation and differentiation of lymphocytes and the production of autoantibodies.<sup>83,84</sup> B lymphocytes can produce immune complexes formed by autoantibodies such as RF and anti-citrullinated protein antibodies to activate the complement pathway and cause the production of C5a and membrane attack complexes, consequently damaging to the joints. Likewise, B lymphocytes are involved in bone destruction by secreting TNF- $\alpha$ , IFN- $\gamma$ , IL-6, IL-1 $\beta$ , and IL-17.<sup>85</sup>

Activated B cells can propagate bone density loss through the release of RANKL.<sup>86</sup> Breg cells suppress the progression of RA by releasing IL-10, TGF- $\beta$ , and IL-35,<sup>87,88</sup> and the reduced number of Breg cells is associated with increased disease activity.

Conclusively, PLTs and lymphocytes play indispensable roles in the pathogenesis and progression of RA and regulate disease progression through a series of complex mechanisms. Accordingly, combined detection of PLTs and lymphocytes can not only monitor the immune-inflammatory response in RA from multiple perspectives and in an all-round manner but also provide a deeper understanding of the mechanism of RA and more comprehensive and accurate information for the diagnosis and treatment of RA, thus allowing for better control of the condition of RA.

## Conclusions and Prospects

To summarize, PLR is a simple and reliable biomarker for systemic inflammation. In RA, PLR can be used as an auxiliary indicator for the combined diagnosis of RA. Additionally, PLT has a certain correlation with the disease activity of RA, which helps to determine disease activity in RA, to detect various complications at early clinical stages for early interventions, and to monitor responses to anti-inflammatory therapy. Meanwhile, PLR has a predictive value for the outcomes of RA treatment. These observations provide novel guidance for RA-related clinical research. However, the laboratory results of PLT may be affected by multiple factors such as the physiological state of patients, sampling time, and detection time, which calls for the standardization of the detection process of PLT to reduce the error and increase the accuracy of results. Future studies should deeply explore the mechanism of the association between PLR and RA, therefore providing more scientific support for the early diagnosis and treatment of RA. Additionally, large sample, multicenter, and prospective studies are warranted to complement the results through rich research approaches.

## Abbreviations

RA, rheumatoid arthritis; PLR, platelet-to-lymphocyte ratio; PLT, platelet; DAS28, disease activity score in 28 joints; HCs, healthy controls; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ROC, receiver-operating characteristic; AUC, area under the ROC curve; VAS, visual analogue scale; ILD, interstitial lung disease; OP, osteoporosis; hs-CRP, high-sensitivity CRP; IL-6, interleukin-6; CCP, cyclic citrullinated peptide; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; CSF, colony-stimulating factor; TGF- $\beta$ , transforming growth factor- $\beta$ ; RANKL, receptor activator of nuclear factor- $\kappa$ B ligand; PhGA, patient disease activity.

## Consent for Publication

This paper is our original work. We certify that this manuscript has not been published in part or whole elsewhere in any language, and it has not been submitted to any other journal for reviews.

We certify that all authors named deserve authorship, and that all authors have agreed to be so listed and have read and approved the manuscript.

## Author Contributions

All authors contributed significantly to the work reported, whether in conception, study design, execution, data acquisition, analysis and interpretation, or in all of these areas; Participated in the drafting, revision or critical review of the article; To give final approval to the version to be published; The journal to which the manuscript will be submitted has been agreed; And agree to be accountable for all aspects of the work.

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The authors declare that they have no conflicts of interest regarding the publication of this paper.

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