e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(1); 1255-1263

Original Research Article

A Hospital-Based Study to Assess the Association between Blood PLT and RBC Related Indices and Disease Activity in Patients with Rheumatoid Arthritis

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Received: 19-11-2022 / Revised: 06-12-2022 / Accepted: 28-01-2023

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Conflict of interest: Nil

Abstract

Aim: This study aimed to evaluate the association of blood PLT and RBC related parameters with the disease activity in rheumatoid arthritis (RA) patients.

Methods: This study included 200 RA patients who were admitted to the Department of General medicine at Nalanda Medical College and Hospital, Patna, Bihar, India for the period of one year.

Results: There were no differences in age and gender distribution, body mass index (BMI) and WBC between the two groups. Besides, CRP, ESR, RF and anti-CCP in RA patients were significantly higher than those in the control group ($P < 0.001$). Age, gender, BMI, disease duration, anti-CCP and WBC were similar between the two groups. The active RA patients had higher levels of ESR, CRP and RF compared with inactive RA groups ($P < 0.001$ or $P < 0.01$). The greater levels of Ig G, Ig A and Ig M were also observed in active RA groups as compared to those in inactive RA groups ($P < 0.05$). Patients with active RA showed higher levels of PLT counts but lower levels of RBC counts, HCT, RPR and HPR than those with inactive group. No significant differences in PDW and RDW were observed between the active RA and inactive RA.

Conclusion: Blood PLT and RBC related indices were significantly associated with RA disease activity. These indices may be used to distinguish active RA from inactive RA.

Keywords: Rheumatoid Arthritis, Platelets, Red Blood Cells, Hemoglobin.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by synovial inflammation, bone erosion, and cartilage destruction that led to joint damage and deformity, with a worldwide prevalence of approximately 1% of the general population. [1,2] Furthermore, RA causes increased risk of disability, mortality, and morbidity. Recent advanced understanding of pathogenesis and the development of new therapeutic agents and strategies for management in RA have improved clinical outcomes. In addition, the development and application of diverse disease activity measures have contributed to better clinical outcomes through tight monitoring of disease activity and treatment response. [3] In the routine clinical field, the most commonly used indices to evaluate disease activity in RA are Disease Activity Score 28 joints (DAS28) [4], the simplified disease activity index (SDAI) [5], and the clinical disease activity index (CDAI) [6], which are multidimensional instruments that utilize tender and swollen joints, patient and physician global health assessment of disease activity, and acute phase reactants (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]).

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial hyperplasia, pannus formation, and progressive damage of articular cartilage and bone. [7] RA patients are challenged to physical disabilities and a significant economic burden with disease progression. Previous studies revealed that early diagnosis and treatment could prevent bone destruction and joint deformities caused by RA, and thus contribute to a greater rate of remission in RA patient. [8] Therefore, early diagnosis and treatment are vital in improving the prognosis of RA. Currently, the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA has been widely used for diagnosis in clinical practice. The 2010 ACR/EULAR RA classification criteria place more emphasis on circulating anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF) and other serological biomarkers, in comparison with the 1987 ARA classification criteria. [9] It was reported that CCP rules are not useful in identifying a proportion of early unclassified RA patients. [10]

Recently accelerating studies have demonstrated the critical role of platelet (PLT) in inflammatory processes. For instance, PLT could participate in the regulation of leukocyte recruitment by releasing numerous inflammatory mediators. [11] P-selectin and several adhesion molecules expressed on PLT could contribute to the interaction between platelets and other leukocytes such as neutrophils, monocytes, T cells and so on. [12,13] Recent data indicate that anemia could occur in the setting of autoimmune diseases in that bone marrow function and iron metabolism could be influenced by inflammation. [14] It is reported that inflammatory cytokines may suppress maturation of red blood cell (RBC). [15,16]

However, there are few studies that have systematically assessed the association of PLT, RBC, Hb, red blood cells-platelet ratio (RPR) and hemoglobin-platelet ratio (HPR) with the disease activity of RA patients. And little is known about the diagnostic value of the peripheral blood PLT and RBC related indices in distinguishing between active RA and inactive RA. Therefore, this study aimed to investigate the correlation of hematological indices including PLT, RBC, Hb, RPR and HPR with RA disease activity. We also evaluated the diagnostic role of these indices in differentiating among RA patients with different disease activity.

Materials and Methods

This study included 200 RA patients who were admitted to the Department of General Medicine, at Nalanda Medical College and Hospital, Patna, Bihar, India for the period of one year. Patients who had hematologic diseases, other autoimmune inflammatory diseases, infections, malignancies, or had any history of other chronic diseases such as diabetes mellitus, dyslipidemia, thyroid dysfunction, severe liver or kidney impairment as well as those receiving treatment with corticosteroids within the last 3 months were excluded. One hundred and sixty-four healthy individuals were recruited from the health examination center of the same hospital, and matched with RA patients for age and gender. The study was conducted in accordance with the declaration of Helsinki and approved by the Research Committee. The written informed consent was given by all subjects. All methods were performed in accordance with the relevant guidelines and regulations.

Assessment of Disease Activity

Using the Disease Activity Score in 28 joints based on C-reactive protein (DAS 28-CRP),17,18 disease activity of RA patients can be described as low (DAS 28-CRP $\leq$ 2.7), moderate (2.7 < DAS 28-CRP $\leq$ 4.1) or high (DAS 28- CRP > 4.1), respectively. We define patients with moderate and high disease activity as active RA, whereas those with low disease activity were defined as inactive RA.

Clinical and Laboratory Parameters

Patients' characteristics, including age, gender, medical history, symptoms and signs, diagnosis, treatment, laboratory testing results were gathered from their electronic medical records. The laboratory testing results included PLT, platelet distribution width (PDW), white blood cells (WBC), lymphocytes, neutrophils, monocytes, RBC, Hb, red blood cell-specific volume (HCT), RDW, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), RF, anti-CCP. RPR and HPR were calculated.

Statistical Analysis

Continuous variables with the normal distribution were presented as mean values ± standard deviation. Non- normally distributed data were presented as median (inter quartile range). Categorical variables were expressed as frequencies or percentages. The differences of continuous variables were compared by The Student's t-test or Mann– Whitney U-test, while the chi-square test was performed to compare the differences of categorical variables. Spearman correlation analysis was used to detect the association between variables. Receiver operating characteristic (ROC) curves were plotted to distinguish RA patients from healthy individuals or to differentiate active RA from inactive group. The area under the curve (AUC) and 95% confidence interval (CI) were calculated to evaluate the diagnostic value of each indices. The optimal cut-off value, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy (AC) of the indices were assessed.

Results

Table 1: Comparison of Clinical Characteristics Between RA Patients and Controls

	RA (N=200)	Control (N=150)	P-value
Age (years)	57.11±14.17	54.86±10.59	0.120
Gender (F/M)	140/60	110/40	0.620
BMI (kg/m2)	25.6±3.1	26.1±3.3	0.375
CRP (mg/L)	18.35(6.75–52.41)	2.1(1.1–3.2)	< 0.001
ESR (mm/h)	37.0(15–79)	5.22(2.73–12.81)	< 0.001
RF (IU/mL)	167.31(23.2–	4.87(3.10–15.70)	< 0.001

Anti-CCP (U/mL)	426.00)	13.2(5.7–19.3)	< 0.001
WBC (109/L)	246.3 (38.1–400.0)	6.19±2.54	0.955
RBC (1012/L)	6.21±2.77	4.62±0.74	< 0.001
Hb (g/L)	4.06±0.93	136.18±21.67	< 0.001
HCT (%)	115.20± 28.08	41.03±5.84	< 0.001
RDW	35.45±8.59	13.45±2.42	0.070
PLT(109/L)	14.16±4.42	205.05±53.05	< 0.001
PDW	240.59± 73.28	12.97±3.90	0.260
RPR	12.42±4.41	0.024±0.0072	< 0.001
HPR	0.019±0.0065	0.727±0.23	< 0.001
	0.55±0.21		

There were no differences in age and gender distribution, body mass index (BMI) and WBC between the two groups. Besides, CRP, ESR, RF and anti-CCP in RA patients were significantly higher than those in the control group (P < 0.001).

Table 2: Comparison of Clinical Characteristics Between the Two RA Subgroups

	Inactive RA (N=98)	**Active RA (N=102)**	**P-value**
Age (years)	56.29±15.16	58.41±13.33	0.120
Gender (F/M)	65/33	70/22	0.928
BMI (kg/m2)	25.5±3.1	24.7±2.3	0.320
Disease duration	7.2±3.8	8.6±5.1	0.210
CRP (mg/L)	9.65(4.92–18.35)	32.07(9.13–55.72)	< 0.001
ESR (mm/h)	30.0(14–65)	54.0(19–87)	< 0.001
RF (IU/mL)	129.05(20.80–	261.29(32.56–	<0.01
Anti-CCP (U/mL)	321.00)	910.00)	0.260
Ig G (g/L)	255.7 (21.1–382.0)	302.2(88.3–500.0)	<0.05
Ig A (g/L)	11.97±3.21	15.42±6.35	<0.05
Ig M (g/L)	2.36±1.37	3.19±1.93	<0.05
WBC (109/L)	1.05±0.78	1.37±0.91	0.270
RBC (1012/L)	6.22±2.24	6.64±2.74	<0.001
Hb (g/L)	4.37±0.50	3.87±0.58	<0.001
HCT (%)	127.83± 17.55	109.08±16.10	<0.01
RDW	38.18±6.74	35.64±5.22	0.662
PLT(109/L)	14.40±4.11	14.66±2.54	<0.001
PDW	215.61± 60.95	257.00±76.27	0.754
RPR	12.74±3.56	12.92±3.98	<0.001
HPR	0.022±0.0068	0.017±0.0055	<0.001
	0.64±0.22	0.48±0.18	

Age, gender, BMI, disease duration, anti-CCP and WBC were similar between the two groups. The active RA patients had higher levels of ESR, CRP and RF compared with inactive RA groups (P < 0.001 or P < 0.01). The greater levels of Ig G, Ig A and Ig M were also observed in active RA groups as compared to those in inactive RA groups (P < 0.05). Patients with active RA showed higher levels of PLT counts but lower levels of RBC counts, HCT, RPR and HPR than those with inactive group. No significant differences in PDW and RDW were observed between the active RA and inactive RA.

Table 3: The Diagnostic Value of PLT, RBC, Hb, RPR and HPR for RA

Parameters	AUC	95% CI	Optimal Cut-off Value	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	AC (%)
PLT(109/L)	0.648	0.584–0.709	>237	82.26	46.55	72.41	60.61	64.41
RBC (1012/L)	0.785	0.727–0.835	<4.29	77.42	72.63	76.28	73.88	75.03
Hb (g/L)	0.787	0.730–0.837	<128	77.42	73.74	76.56	74.67	75.58
RPR	0.747	0.687–0.801	<0.018	90.32	55.17	85.07	66.83	72.75
HPR	0.738	0.677–0.793	<0.54	83.87	55.75	77.56	65.46	69.81

The AUC of PLT, RBC, Hb, RPR and HPR was 0.648, 0.785, 0.787, 0.747 and 0.738 respectively (all $P < 0.001$)for RA patients versus healthy controls. There were significant differences in the AUC between PLT and RBC as well as between Hb and PLT for distinguishing RA patients from healthy controls ($P < 0.05$ or $P < 0.01$, Figure 1). And no significant difference was observed in the AUC between RBC and Hb for distinguishing RA patients from healthy controls.

Table 4: Correlations of RBC, Hb, PLT, RPR and HPR with Indices of Disease Activity in RA Patients

Parameters	CRP (mgL)		ESR (mm/h)		DAS28-CRP	
	r	P-value	r	P-value	r	P-value
RBC (1012/L)	−0.289	<0.001	−0.481	<0.001	−0.428	<0.001
Hb (g/L)	−0.341	<0.001	−0.569	<0.001	−0.489	<0.001
PLT(109/L)	0.284	<0.001	0.331	<0.001	0.327	<0.001
RPR	−0.397	<0.001	−0.329	<0.001	−0.310	<0.001
HPR	−0.402	<0.001	−0.362	<0.001	−0.293	<0.001

PLT was positively associated with DAS-28 CRP ($r = 0.327$, $P < 0.001$), CPR ($r = 0.284$, $P < 0.001$) and ESR ($r = 0.331$, $P < 0.001$). RBC was negatively associated with DAS-28 CRP ($r = −0.428$, $P < 0.001$), CRP ($r = −0.289$, $P < 0.001$) and ESR ($r = −0.481$, $P < 0.001$). Hb was negatively associated with DAS-28 CRP ($r = −0.489$, $P < 0.001$), CRP ($r = −0.341$, $P < 0.001$) and ESR ($r = −0.569$, $P < 0.001$). RPR was negatively associated with DAS-28 CRP ($r = −0.310$, $P < 0.001$), CRP ($r = −0.397$, $P < 0.001$) and ESR ($r = −0.329$, $P <0.001$). HPR was negatively associated with DAS-28 CRP ($r = −0.293$, $P < 0.001$), CRP ($r = −0.402$, $P < 0.001$) and ESR ($r = −0.362$, $P < 0.001$). Notably, the correlation between Hb and disease activity parameters such as ESR and DAS-28 CRP was the strongest.

Discussion

The population prevalence of rheumatoid arthritis (RA), the most common form of inflammatory polyarthritis, is up to 1%. [17,18] While the presence of overt clinical manifestations generally leads to a straightforward diagnosis and classification a significant number of patients with RA present with mild, non-specific signs and symptoms. [19]

Recently PLT has been demonstrated to be involved in the inflammatory process of RA. [19] The number of PLT was reported to be significantly higher in RA patients with high disease activity compared to

those with low to moderate disease activity. [20] Moreover, a previous study revealed that mean volume of PLT was significantly associated with RA disease activity. [21] PLT derived growth factor was indicated to be participated in the invasion of synovial membranes and angiogenesis that are the characteristics of RA. [22,23] PLT could function as delivering vehicles carrying major amounts of cytokines, chemokines, and growth factors which were important to sustain immune pathways. [24] Notably, a study from Knijff- Dutmer et al showed that PLT counts were similar in the three groups including active RA, inactive RA and healthy controls. [25] However, the levels of platelet-derived particles (PMPs) in RA patients were evidently higher than those in healthy controls. PMPs were also correlated with disease activity of RA. [25] Our results showed that there were significant difference in the number of blood PLT between RA patients and the healthy controls. Considering the significance of PMPs in RA inflammation, we will investigate the role of PMPs in RA patients in our further study.

The inflammatory milieu in RA has been demonstrated to modulate erythropoiesis. There are two main reasons responsible for inflammation-induced anemia in RA. Firstly, erythropoietin (EPO) gene transcription could be suppressed by proinflammatory cytokines such as IL-1, IL-6 and TNF-α. [26,27] Secondly, these proinflammatory cytokines could inhibit the effect of EPO on erythroid progenitors in bone marrow. [28] RA patients with early stage were reported to present anemia which was caused by IL- 6-induced suppression of erythropoiesis in bone marrow. [29] In addition, RBC in RA patients have been shown to be affected by the presence of generated free radicals and excessive amounts of proteins circulating in the blood. [30]

Our results demonstrated that blood Hb concentration was negatively correlated with the indices of RA disease activity such as DAS 28-CRP, CRP and ESR. The interaction between PLT and RBC bears a helpful understanding of RA pathophysiology, as it has been shown that RMPs were capable of inducing PLT hyperstimulation following collagen activation in an in vitro study. [31] These RMPs were also confirmed to induce ex vivo PLT–PLT aggregates. Moreover, some adhesion proteins have been identified to be involved in the direct contact between PLT and RBC. For example, as a family member of glycoproteins, adhesion molecule 4 (ICAM-4 or CD242) on RBC membranes could directly bind to the integrin αIIbβ3 of PLT, illustrating the direct effect of RBC on the activation of thrombotic and inflammatory pathways. [32] Given that interaction between PLT and RBC plays a role in the pathogenesis of chronic inflammation of RA, so we evaluated the association of RPR and HPR with the disease activity in RA. Our results showed that RPR and HPR were significantly related to the severity of RA. [33]

However, there were several limitations in this study. Firstly, this study was a retrospective analysis of the data on RA patients, and selection bias cannot be eliminated completely. The controls did not include patients with osteoarthritis or other autoimmune diseases with clinical manifestations similar to RA, such as gout arthritis and so on. Secondly, this study included only 200 patients with RA which were from a single center. Therefore, a multi- center prospective study with a large-scale sample is still required to confirm the accuracy of the results.

Conclusion

In summary, this study systematically investigated the role of PLT, RBC, Hb, RPR and HPR as biomarkers in determining the disease activity of RA. We found that PLT was elevated in RA patients and positively correlated with RA disease activity. RBC, Hb, RPR and HPR

were found to be decreased in RA patients and negatively correlated with RA disease activity.

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