ORIGINAL RESEARCH

Association Between Blood PLT and RBC Related Indices and Disease Activity in Patients with Rheumatoid Arthritis

Li Xue [ID][1]
Li Tao[1]
Haifeng Sun[2]
Yan Wang[1]
Yanping Zhang[1]
Na Lei[1]
Zeshi Liu[1]
Hua Zhang[1]
Li Jin[1]
Ting Zhang[1]
Jing Zhang[1]
Hao Meng[1]
Fang Huang[1]
Yan Geng[1]
Ming Li[3]

[1]Department of Clinical Laboratory, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710004, People's Republic of China; [2]Third Department of Medical Oncology, Shaanxi Provincial Cancer Hospital Affiliated to Medical College of Xi'an Jiaotong University, Xi'an, 710061, People's Republic of China; [3]Department of Cardiovascular Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, People's Republic of China

Correspondence: Yan Geng
Department of Clinical Laboratory, The Second Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, People's Republic of China
Email gengyanjyk@126.com

Ming Li
Department of Cardiovascular Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, People's Republic of China
Email minglil@126.com

Background: Platelet (PLT) and red blood cell (RBC) have been demonstrated to play a critical role in inflammatory processes. This study aimed to evaluate the association of blood PLT and RBC related parameters with the disease activity in rheumatoid arthritis (RA) patients, and also to investigate the role of these indices in differentiating among RA patients with different disease activity.

Methods: Clinical data from RA patients were retrospectively analyzed. RA patients were divided into inactive group and active group according to DAS28-CRP. The relationship between blood PLT and RBC counts-related indices and DAS28-CRP was detected by Spearman correlation. ROC curve was used to assess the diagnostic value of these indices in differentiating active RA from inactive RA.

Results: Active RA patients exhibited higher level of PLT counts but significantly lower levels of RBC counts, hemoglobin (Hb), red blood cells-platelet ratio (RPR) and hemoglobin-platelet ratio (HPR) compared with inactive RA. PLT counts were positively but RBC counts, Hb, RPR and HPR were negatively related with DAS28-CRP.

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 autoimmune disease characterized by synovial hyperplasia, pannus formation, and progressive damage of articular cartilage and bone.[1] 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.[2] 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.[3] It was reported that CCP rules are not useful in identifying a proportion of early unclassified RA patients.[4] Both anti-CCP and RF are members of the autoantibodies family. Anti-CCP has high

specificity but relatively low sensitivity for RA, while RF is strongly sensitive but lacks specificity for RA patients.[5] Therefore, there is a need for establishing new serological biomarkers to realize the early diagnosis of RA.

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.[6] 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.[7,8] 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.[9] It is reported that inflammatory cytokines may suppress maturation of red blood cell (RBC).[10,11] Therefore, it has been suggested that RBC-related parameters such as red blood cell distribution width (RDW) and hemoglobin (Hb) contents may be used as inflammatory indicators for predicting the severity of several autoimmune diseases including systemic lupus erythematosus,[12,13] primary Sjögren's syndrome,[14] and autoimmune hepatitis.[15] 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
Study Population
This study included one hundred and seventy-eight RA patients who were admitted to the Department of Rheumatology and Immunology of the Second Affiliated Hospital of Xi'an Jiaotong University during the period from September 2017 to April 2020. Patients fulfilled the 2010 ACR/EULAR criteria for RA.[16] 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 of Human Investigation of Xi'an Jiaotong University Health Science Center and 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 $\pm$ standard deviation. Non-normally distributed data were presented as median (interquartile 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 indice. The optimal cut-

Table 1 Comparison of Clinical Characteristics Between RA Patients and Controls

	RA (N=178)	Control (N=164)	*P*-value
Age (years)	57.11±14.17	54.86±10.59	0.122
Gender (F/M)	132/46	126/38	0.616
BMI (kg/m^2)	25.6±3.1	26.1±3.3	0.376
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(23.2–426.00)	4.87(3.10–15.70)	< 0.001
Anti-CCP (U/mL)	246.3 (38.1–400.0)	13.2(5.7–19.3)	< 0.001
WBC (10^9/L)	6.21±2.77	6.19±2.54	0.955
RBC (10^{12}/L)	4.06±0.93	4.62±0.74	< 0.001
Hb (g/L)	115.20± 28.08	136.18±21.67	< 0.001
HCT (%)	35.45±8.59	41.03±5.84	< 0.001
RDW	14.16±4.42	13.45±2.42	0.075
PLT(10^9/L)	240.59± 73.28	205.05±53.05	< 0.001
PDW	12.42±4.41	12.97±3.90	0.263
RPR	0.019±0.0065	0.024±0.0072	< 0.001
HPR	0.55±0.21	0.727±0.23	< 0.001

Abbreviations: F, female; M, male; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; HCT, red blood cell specific volume; RDW, red blood cell volume distribution width; PLT, platelet; PDW, platelet volume distribution width; RPR, red blood cells-platelet ratio; HPR, hemoglobin–platelet ratio.

off value, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy (AC) of the indices were assessed.

Results
Study Population
Clinical and laboratory characteristics of RA patients and healthy controls were shown in Table 1. 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 showed the clinical and laboratory characteristics of two groups of RA patients. 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).

Blood Counts of PLT, RBC and Other Related Parameters
As shown in Table 1, blood counts of PLT were elevated while RBC as well as levels of Hb, HCT, RPR and HPR were decreased in RA patients compared with healthy

controls (*P* < 0.001). There were no significant differences in PDW and RDW between the two 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 (*P* < 0.001 or *P* < 0.01, Table 2). No significant differences in PDW and RDW were observed between the active RA and inactive RA (*P* > 0.05, Table 2).

In order to evaluate the diagnostic performance of blood PLT, RBC, Hb, RPR and HPR, we further used ROC curve analysis. As shown in Table 3, 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 (*P* > 0.05, Figure 1).

Table 4 showed the ROC curve analysis for the active and inactive RA patients. The AUC of PLT, RBC, Hb, RPR and HPR was 0.666, 0.780, 0.786, 0.744 and 0.727 for active RA versus inactive RA (all *P* < 0.001). The optimal cutoff values of PLT, RBC, Hb, RPR and HPR between active RA and inactive RA groups were 243×10^9/L, 4.22×10^{12}/L, 121 g/L, 0.48 and 0.017. As shown in

Table 2 Comparison of Clinical Characteristics Between the Two RA Subgroups

	Inactive RA (N=88)	Active RA (N=90)	*P*-value
Age (years)	56.29±15.16	58.41±13.33	0.121
Gender (F/M)	67/21	68/22	0.928
BMI (kg/m^2)	25.5±3.1	24.7±2.3	0.325
Disease duration (years)	7.2±3.8	8.6±5.1	0.213
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(20.80–321.00)	261.29(32.56–910.00)	<0.01
Anti-CCP (U/mL)	255.7 (21.1–382.0)	302.2(88.3–500.0)	0.264
Ig G (g/L)	11.97±3.21	15.42±6.35	<0.05
Ig A (g/L)	2.36±1.37	3.19±1.93	<0.05
Ig M (g/L)	1.05±0.78	1.37±0.91	<0.05
WBC (10^9/L)	6.22±2.24	6.64±2.74	0.270
RBC (10^{12}/L)	4.37±0.50	3.87±0.58	<0.001
Hb (g/L)	127.83± 17.55	109.08±16.10	<0.001
HCT (%)	38.18±6.74	35.64±5.22	<0.01
RDW	14.40±4.11	14.66±2.54	0.662
PLT(10^9/L)	215.61± 60.95	257.00±76.27	<0.001
PDW	12.74±3.56	12.92±3.98	0.754
RPR	0.022±0.0068	0.017±0.0055	<0.001
HPR	0.64±0.22	0.48±0.18	<0.001

Notes: Patients in inactive group with a DAS 28-CRP score lower than 2.7; active patients with a DAS 28-CRP score of 2.7 and higher.
Abbreviations: DAS28-CRP, Disease Activity Score in 28 joints based on C-reactive protein; F, female; M, male; BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide; Ig G, immunoglobulin G; Ig A, immunoglobulin A; Ig M, immunoglobulin M; WBC, white blood cells; RBC, red blood cells; Hb, hemoglobin; HCT, red blood cell specific volume; RDW, red blood cell volume distribution width; PLT, platelet; PDW, platelet volume distribution width; RPR, red blood cells-platelet ratio; HPR, hemoglobin–platelet ratio.

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(10^9/L)	0.648	0.584–0.709	>237	82.26	46.55	72.41	60.61	64.41
RBC (10^{12}/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

Abbreviations: AUC, area under curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; AC, accuracy; RBC, red blood cells; Hb, hemoglobin; PLT, platelet; RPR, red blood cells-platelet ratio; HPR, hemoglobin–platelet ratio.

Figure 2, RBC and Hb had a higher AUC relative to ESR, RF and anti-CCP in distinguishing active RA from inactive RA ($P < 0.01$ or $P < 0.001$). There was no significant difference in the AUC between PLT and other indices including ESR, CRP, RF and anti-CCP for distinguishing active RA patients from inactive group ($P > 0.05$).

Correlation of Blood PLT and RBC Related Indices with Disease Activity and Laboratory Parameters

To further evaluate the relationship between blood PLT and RBC related indices and disease activity, we conducted a correlation analysis between blood levels of these indices and disease activity index DAS-28 CRP and laboratory parameters including CRP and ESR.

As shown in Table 5, 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, $P <$
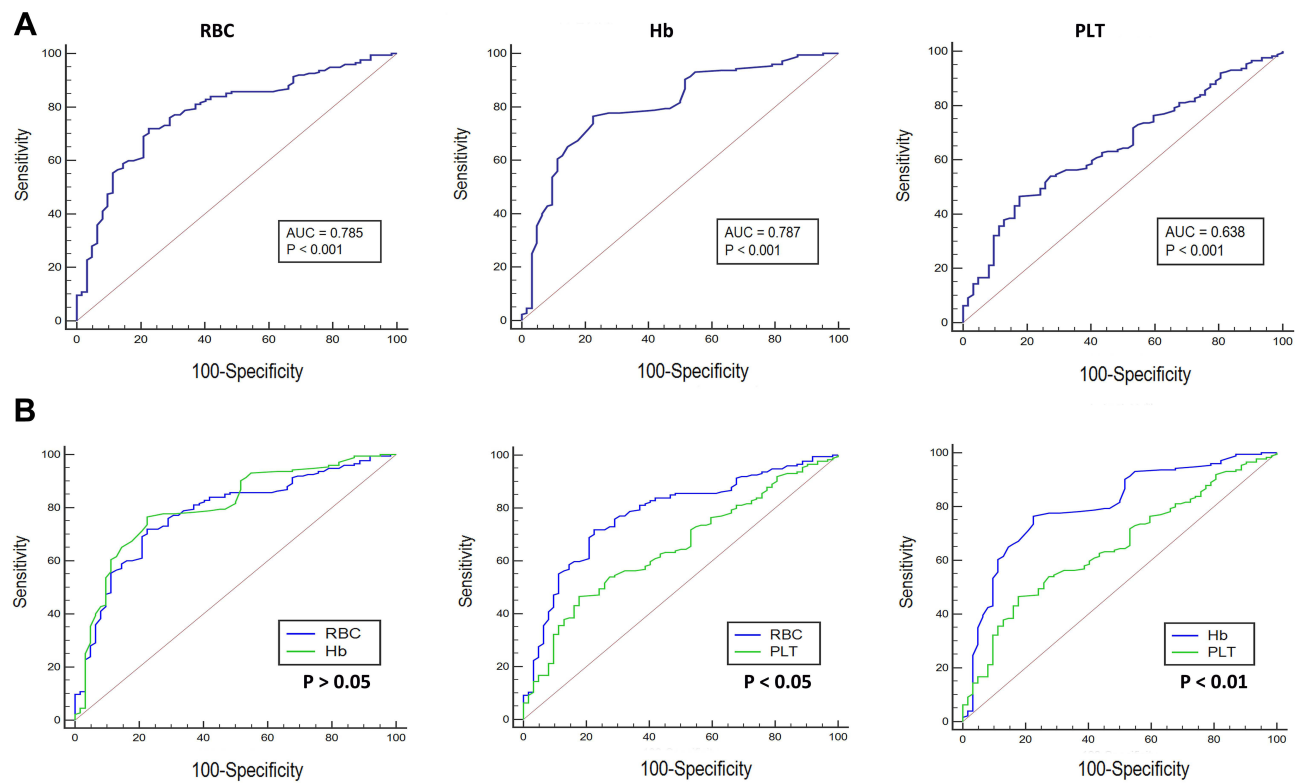
Figure 1 Performance of blood RBC, Hb, and PLT in discriminating RA patients from healthy controls. (**A**) The ROC curves of the three indices in differentiating RA patients from healthy controls. (**B**) Comparison of ROC curves among the three indices.

Abbreviations: ROC, receiver operating characteristic curve; AUC, area under the curve; RBC, red blood cells; Hb, hemoglobin; PLT, platelet.

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

In this retrospective study of one hundred and seventy-eight patients, we systematically analyzed the association of PLT, RBC, Hb, RPR and HPR with the disease activity in a cohort of Chinese patients with RA. We focused on the association of these indices with the current disease

Table 4 The Diagnostic Value of the Markers to Distinguish Active RA from Inactive RA

Parameters	AUC	95% CI	Optimal Cut-off Value	Specificity (%)	Sensitivity (%)	PPV (%)	NPV (%)	AC (%)
PLT(10^9/L)	0.666	0.591–0.736	>243	73.91	56.19	68.29	62.78	65.05
RBC (10^{12}/L)	0.780	0.711–0.839	<4.22	68.12	83.96	72.48	80.94	76.04
Hb (g/L)	0.786	0.717–0.844	<121	68.12	81.13	71.79	78.31	74.63
RPR	0.744	0.673–0.807	<0.017	68.12	74.29	69.97	72.60	71.21
HPR	0.727	0.654–0.791	<0.48	81.16	56.19	74.89	64.94	68.68
CRP (mg/L)	0.749	0.678–0.811	>6.56	89.86	59.81	85.50	69.10	74.84
ESR (mm/h)	0.643	0.552–0.727	>44	87.27	39.13	75.45	58.91	63.20
RF (IU/mL)	0.572	0.495–0.646	>101	76.47	43.40	64.84	57.47	59.94
Anti-CCP (U/mL)	0.544	0.455–0.631	>73.2	35.71	82.89	56.32	67.61	59.30

Abbreviations: AUC, area under curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value; AC, accuracy; RBC, red blood cells; Hb, hemoglobin; PLT, platelet; RPR, red blood cells-platelet ratio; HPR, hemoglobin–platelet ratio; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide.
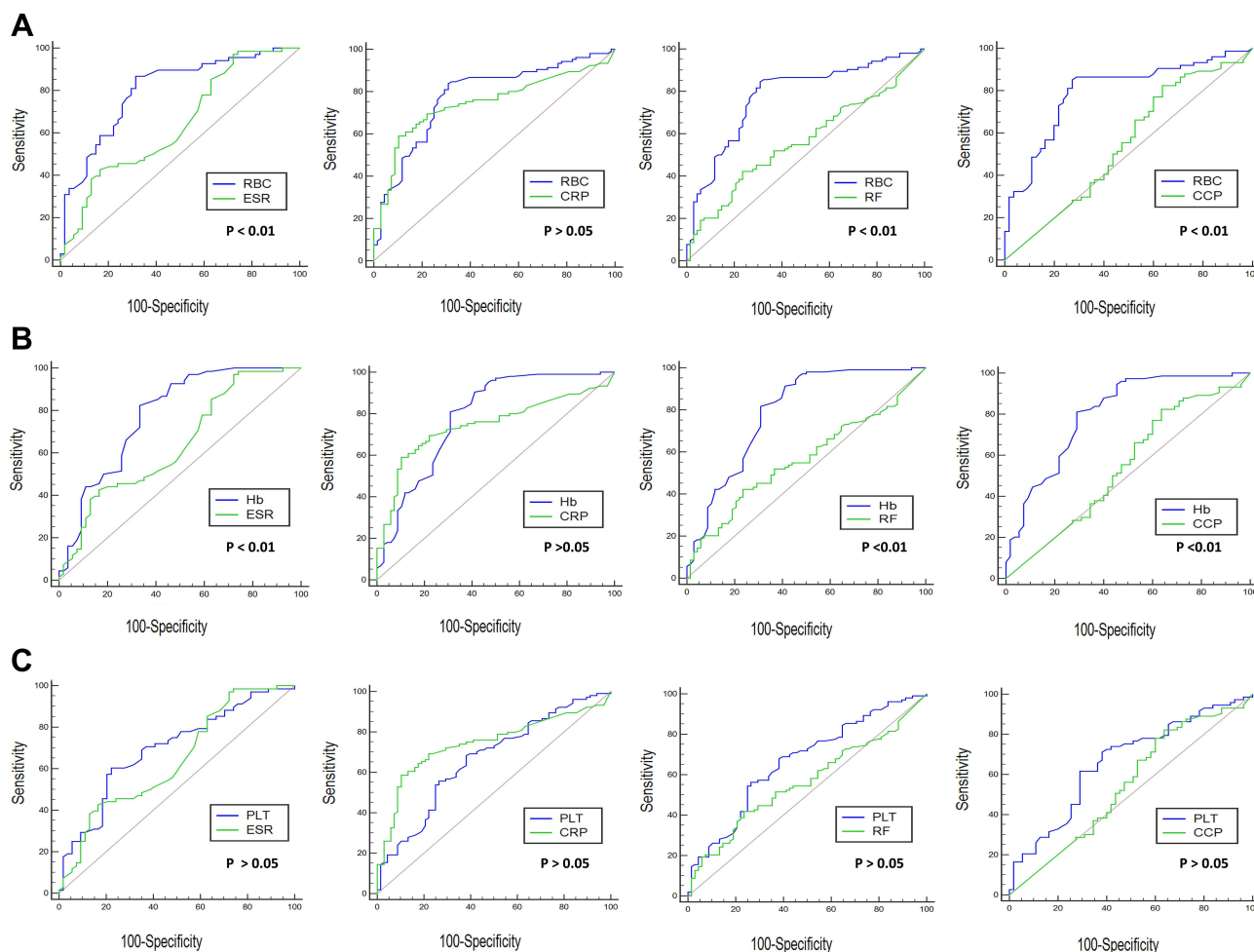
Figure 2 Performance of blood RBC, Hb, and PLT in discriminating active RA from inactive RA. Comparison of ROC curves between RBC (**A**), Hb (**B**) or PLT (**C**) and other parameters including ESR, CRP, RF and Anti-CCP in differentiating active RA from inactive RA.
Abbreviations: ROC, receiver operating characteristic curve; RBC, red blood cells; Hb, hemoglobin; PLT, platelet; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; Anti-CCP, anti-cyclic citrullinated peptide antibody.

activity of RA patients who were scheduled for blood test, and thus we could find some new indices to identify the disease activity of RA patients. In this study, we confirmed, for the first time, blood PLT and RBC related

indices RPR and HPR were significantly associated with the severity of RA.

Recently PLT has been demonstrated to be involved in the inflammatory process of RA.[19] The number of PLT

Table 5 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 (10^{12}/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(10^9/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

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28-CRP, Disease Activity Score in 28 joints based on C-reactive protein; RBC, red blood cells; Hb, hemoglobin; PLT, platelet; RPR, red blood cells-platelet ratio; HPR, hemoglobin–platelet ratio.

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 autoimmune pathways.[12,24] 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 microparticles (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] Notably, accelerating evidence revealed that RBC-derived microparticles (RMPs) could directly contribute to the pathogenesis of RA via their regulation on immune cell activation.[31] In our study, Hb concentration was decreased in RA patients as compared to the health controls, and the level of Hb concentration was lower in active RA patients than that in the inactive group. A finding similar to ours was observed in the study by Padjen et al[32] who identified that changes in Hb levels were strongly associated with disease activity of RA patients. 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.[33] 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.[14,34] 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.

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 178 patients with RA which were from a single center. Therefore, a multicenter prospective study with a large-scale sample is still required to confirm the accuracy of the results. Additionally, given the effect of disease-modifying antirheumatic drugs (DMARDs) on the disease activity of RA patients, we intend to investigate the association of these blood PLT and RBC related indices with the disease activity in newly diagnosed RA patients who have not received the treatment in our further study.

Conclusions

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.

Ethical Approval

The study was conducted in accordance with the declaration of Helsinki and approved by the Research Committee of Human Investigation of Xi'an Jiaotong University

Health Science Center and the written informed consent was obtained by all subjects.

Disclosure

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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