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ORIGINAL ARTICLE

The Significance of Blood Index and Biochemistry Index in Patients with Rheumatoid Arthritis

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SUMMARY

Background: **The aim of this study is to demonstrate the clinical significance of the platelet-to-lymphocyte ratio (PLR) and the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) in patients with rheumatoid arthritis (RA).**
Methods: **A total of 215 patients with RA, 115 patients with osteoarthritis (OA), and 303 healthy controls (HCs) were included in this study. Data on the AST and ALT levels were collected from liver function test reports, and data on the number of platelets and lymphocytes were obtained from a routine blood analysis. Moreover, all the laboratory parameters of patients with RA, patients with OA, and HCs were retrospectively analyzed.**
Results: **The results obtained in this study showed that patients with RA had the highest PLR and AST/ALT ratio, whereas HCs had the lowest ratios ($p < 0.05$). Receiver operating characteristic (ROC) analysis showed that PLR + AST/ALT can produce high sensitivity and moderate specificity, distinguishing patients with RA from HCs, with a sensitivity of 91.1%, specificity of 75.3%, and area under the ROC curve (AUC) of 0.907. Spearman's analysis showed the PLR is negatively correlated with the erythrocyte sedimentation rate and C-reactive protein levels ($p < 0.005$).**
Conclusions: **Combined detection of PLR and AST/ALT is better than each indicator individually and can improve the diagnostic efficiency of RA.**
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KEY WORDS

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune rheumatic disease of unknown etiology that severely affects the patient's quality of life and sometimes even causes disability. The prevalence of RA increases with age. For example, among middle-aged or older women, the prevalence of RA is significantly higher than in younger women [1,2]. According to several reports, the crude prevalence rate of RA among the whole population of China is 0.41%, with an age-adjusted prevalence of 0.28%. In Western countries, the prevalence of RA ranges between 0.5% and 1% among the adult popula-

tion [3], with the annual prevalence greatly varying with gender and age. RA is characterized by chronic synovial inflammation that may lead to joint destruction and bone erosion, causing significant pain and dysfunction [4,5]. In addition, RA has several extra-articular manifestations, including vasculitis, interstitial lung disease, cardiovascular disease, fragility fractures, and lymphoma [3].

Under normal circumstances, in patients with inflammatory arthritis, testing for rheumatoid factor or anti-citrullinated protein antibody or testing for elevated C-reactive protein (CRP) level or erythrocyte sedimentation rate (ESR) indicates the diagnosis of RA [6]. The initial laboratory evaluation should also include a complete blood count and assessment of differences in renal and liver function [7]. Several studies have shown that inflammation plays an important role in the development and progression of RA. Both the degree of metabolic changes and the types of metabolites observed may be good indicators of the cytokine-mediated inflammatory process associated with RA [8]. Regarded as simple, reliable, and inexpensive laboratory biomarkers for systemic inflammation, platelet-to-lymphocyte ratio (PLR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) have been introduced as prognostic or diagnostic methods of RA. Utilizing these routine examination results can provide doctors with a means to identify diseases more quickly. Recently, Sargin and Erre reported that PLR, LMR, and NLR can be used as biomarkers for the diagnosis and monitoring of RA. In their study, they found that the levels of PLR and NLR were significantly higher in patients with RA than in healthy controls (HCs), suggesting that PLR may be an indicator of chronic subclinical inflammation [9-11]. Moreover, in the study of Du and Fu, it was inferred that PLR, NLR, and LMR can be used as biomarkers for the diagnosis and monitoring of RA [12,13]. However, to our knowledge, only a few studies have evaluated the diagnostic ability of PLR and AST/ALT index for RA. Therefore, the aim of this study is to retrospectively analyze clinical data obtained from patients with RA, patients with osteoarthritis (OA), and HCs to determine whether the combination of these two parameters can be used in diagnostic evaluations.

MATERIALS AND METHODS

Study population

This retrospective study included 215 consecutively diagnosed patients with RA from the First Affiliated Hospital of Guangxi Medical University (Guangxi, China) from June 2016 to June 2020. All patients enrolled met the 2010 RA classification criteria [14]. Since in this study PLR and AST/ALT are inflammatory markers and enzymatic indicators, they may be affected by a variety of diseases or factors, such as obesity, smoking, and acute or chronic inflammation (hypertension, diabetes, infection, etc.). A total of 115 patients with OA, who were hospitalized, were randomly recruited as the disease control group, and 309 gender- and age-matched individuals were recruited as HCs. Both control groups had no history of autoimmune disease, hypertension, diabetes, cancer, cardiovascular disease, infection, or other inflammatory diseases. This study was approved by the Institutional Review Board of the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (Approval Number: 2021(KY-E013)).

Study design and data collection

When a patient is first admitted to the hospital, all laboratory data are collected. Basic information about the participants, such as their age and gender, was first obtained. Moreover, their blood routine reports, including data on their white blood cell (WBC), red blood cell (RBC), platelet (PLT), lymphocyte (LYM), and neutrophil (NEU) levels, were obtained. Finally, AST and ALT values were obtained from their liver function reports. The following formulas were then used to calculate PLR and AST/ALT:

PLR = PLT count/LYM count

AST/ALT = aspartate aminotransferase level/alanine aminotransferase level

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 8 software (GraphPad Software, San Diego, CA, USA). The results are expressed as median and interquartile range. The chi-squared test was used for categorical variables, and one-way analysis of variance (ANOVA) was used to compare the characteristics of the participants. Summary data are expressed as median and interquartile range. Receiver operating characteristic (ROC) analysis was used to evaluate the sensitivity and specificity of PLR and AST/ALT before the intervention. A p-value of < 0.05 (two-sided) was considered statistically significant.

RESULTS

Comparison of the laboratory parameters of patients with RA, patients with OA, and HCs

Table 1 shows a comparison of parameters among patients with RA, patients with OA, and HCs. The results showed that the median serum PLT and AST in patients with RA were higher than those in patients with OA and HCs, whereas the median ALT and LYM in patients with RA were lower than in patients with OA and HCs. Comparison of the laboratory parameters (except for ALT) of the RA group with the OA group and HCs revealed statistically significant results (each $p < 0.001$; Figure 1). It was also observed in patients with RA that the WBC and NEU levels were elevated and the RBC levels were decreased.

Table 1. Comparison of the characteristics of subjects as well as other blood parameters among patients with RA, patients with OA, and HCs.

	RA (n = 215)	OA (n = 115)	HC (n = 303)	p-value
Gender (male/female)	58/157	31/84	88/215	0.846
Age (years)	55 (47, 64)	52 (48, 62)	54 (45, 65)	0.983
WBC (x 10^9/L)	7.82 (6.00, 10.00)	7.00 (6.00, 9.00)	6.31 (5.44, 7.56)	< 0.001
RBC (x 10^{12}/L)	4.00 (3.57, 4.50)	5.00 (4.29, 5.00)	4.88 (4.50, 5.27)	< 0.001
PLT (x 10^9/L)	323.00 (248.00, 407.80)	276.00 (223.00, 325.00)	245.30 (216.70, 292.00)	< 0.001
NEU (x 10^9/L)	5.00 (3.68, 7.00)	4.00 (3.13, 6.00)	3.56 (2.87, 4.36)	< 0.001
LYM (x 10^9/L)	1.51 (1.00, 1.83)	2.01 (2.00, 2.28)	2.13 (1.73, 2.55)	< 0.001
AST (μ/L)	25.00 (20.00, 32.00)	23.00 (18.00, 27.00)	19.00 (16.00, 24.00)	< 0.001
ALT(μ/L)	16.00 (11.00, 26.00)	21.00 (14.00, 28.00)	19.00 (13.00, 28.00)	0.288
PLR	248.79 (162.43, 352.67)	138.00 (106.45, 172.50)	117.77 (95.91, 142.00)	< 0.001
AST/ALT	1.43 (1.00, 2.00)	1.09 (0.78, 1.42)	1.00 (0.79, 1.29)	< 0.001

Data are expressed as median and interquartile range. RA - rheumatoid arthritis, OA - osteoarthritis, HCs - healthy controls, WBC - white blood cell, RBC - red blood cell, PLT - platelet, NEU - neutrophil, LYM - lymphocyte (absolute value), AST - aspartate aminotransferase, ALT - alanine aminotransferase, PLR - platelet-to-lymphocyte ratio.

Table 2. Correlation of laboratory parameters in RA.

	PLR		AST/ALT	
	r	p	r	p
Gender	0.44	0.518	-0.079	0.250
Age (years)	-0.179	0.009	0.062	0.364
WBC (x 10^9/L)	0.119	0.081	-0.037	0.594
RBC (x 10^{12}/L)	0.012	0.865	0.028	0.684
PLT (x 10^9/L)	0.018	0.791	0.099	0.150
NEU (x 10^9/L)	0.105	0.124	-0.004	0.955
LYM (x 10^9/L)	-0.108	0.791	-0.030	0.662
AST (μ/L)	-0.098	0.153	-0.010	0.879
ALT(μ/L)	-0.023	0.742	0.029	0.669
PLR	-0.190	0.006	0.036	0.099
AST/ALT	-0314	0.005	0.134	0.242

Diagnostic efficacy of PLR and AST/ALT for distinguishing between patients with RA, patients with OA, and HCs

ROC analysis was used to evaluate the diagnostic ability of PLR and AST/ALT before the intervention and was performed on PLR, AST, and ALT to distinguish between patients with RA, patients with OA, and HCs. As shown in Figure 2A, compared with HCs, the sensitivity, specificity, and AUC of PLR for patients with RA were 90.76%, 73.95%, and 0.869, respectively, whereas those of AST/ALT were 67.99%, 67.91%, and 0.714, respectively. When PLR and AST/ALT were used in combination, the AUC, sensitivity, and specificity were found to be 0.907, 91.1%, and 75.3%, respectively, which can distinguish between patients with RA and HCs. As shown in Figure 2B, compared with patients with OA and HCs, the combination of PLR and AST/ALT produced an AUC of 0.654, which is different from the result obtained when comparing between patients with RA and HCs.

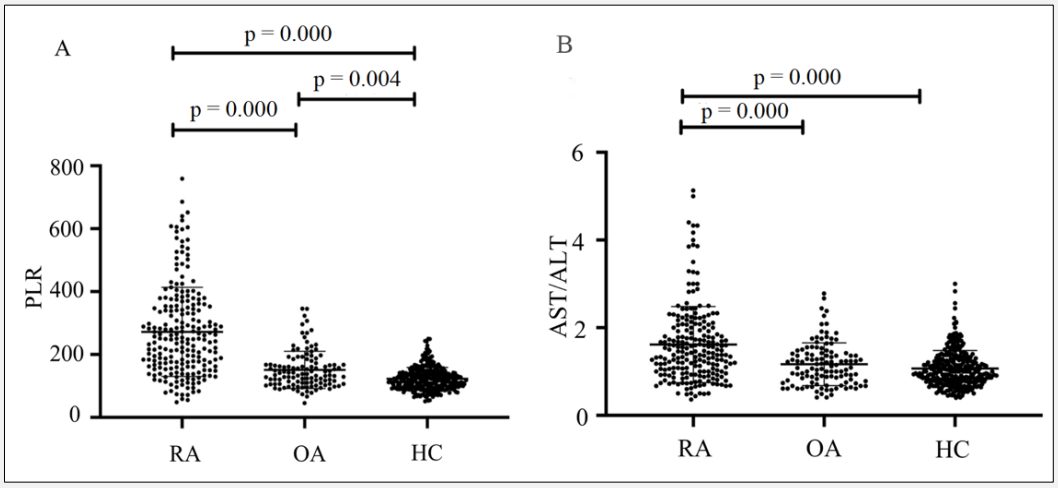
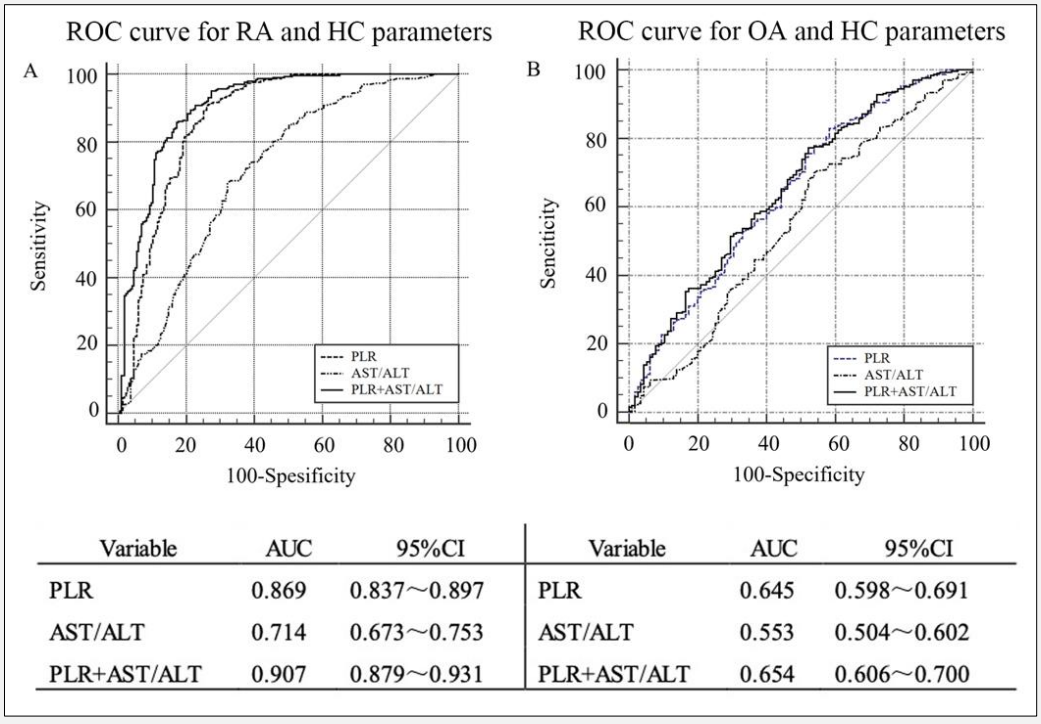


Figure 1. (A) Comparison of the PLR values in patients with RA, patients with OA, and HCs. (B) Comparison of the AST/ALT values in patients with RA, patients with OA, and HCs.

RA - rheumatoid arthritis, OA - osteoarthritis, HCs - healthy controls.



Variable	AUC	95%CI	Variable	AUC	95%CI
PLR	0.869	0.837～0.897	PLR	0.645	0.598～0.691
AST/ALT	0.714	0.673～0.753	AST/ALT	0.553	0.504～0.602
PLR+AST/ALT	0.907	0.879～0.931	PLR+AST/ALT	0.654	0.606～0.700

Figure 2. ROC analysis distinguishing between RA and OA.

(A) ROC curve for RA and HC parameters. (B) ROC curve for OA and HC parameters.

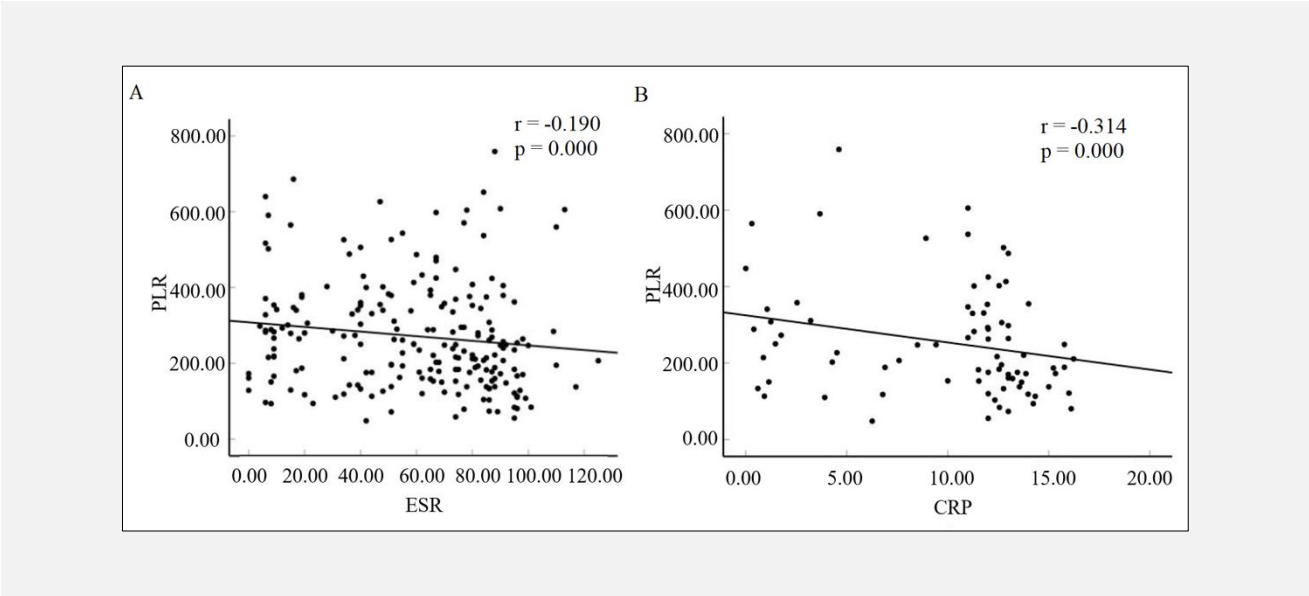


Figure 3. (A) Correlation analysis between ESR and PLR. (B) Correlation analysis between CRP and PLR.

Correlation of parameters in Rheumatoid arthritis
Correlation analysis showed that ESR and PLR were negatively correlated ($r = -0.190$, $p = 0.006$; Table 2, Figure 3A) and that CRP and PLR were also negatively correlated ($r = -0.314$, $p = 0.005$; Table 2, Figure 3B). However, no significant correlation was found between AST/ALT and ESR and CRP.

DISCUSSION

Patients with RA usually experience a serious decline in the quality of life. Therefore, timely diagnosis and appropriate treatment can effectively control the occurrence of RA. Moreover, the symptoms of RA are clinically similar to those of OA. Therefore, identification and diagnosis of RA in clinical settings are becoming more and more important [15]. This study was designed to reveal the relationship between the two laboratory parameters of PLR and AST/ALT and RA.

The results showed that PLR and AST/ALT were the lowest in HCs, followed by the OA group, and the highest in the RA group. The ROC value of PLR used to distinguish between RA and HC is 0.869, whereas the ROC value of AST/ALT is 0.714. Interestingly, combining the two parameters of PLR and AST/ALT, the ROC value significantly increased to 0.907, improving the diagnostic efficacy for RA. According to Assayag et al. LYM is related to loci 17q21 and 6p21 in the Human Leukocyte Antigen (HLA) region, suggesting that PLR may be affected by genetic variations [16]. In a previous study by Peng et al. it was found that the PLR levels in patients with RA were significantly higher than in the control group [11], a finding that was also confirmed in our study. In our study, the PLR (median: 248.79) of patients with RA was found to be much higher than that of patients with OA (median: 138) and HCs (median: 117.77), suggesting that PLR has a diagnostic value for patients with RA. Remarkably, few studies have revealed a relationship between AST or ALT and RA. In this study, it was also found that the value of AST/ALT was higher in patients with RA than in those with OA and HCs. Therefore, combining PLR and AST/ALT can significantly improve the diagnostic efficacy of RA. It should be noted that RA is a common but complicated disease and that the exact mechanism of PLR and AST/AST in RA has not yet been determined [17]. Therefore, more research is needed to reveal such a relationship.

Other factors can also cause changes in PLR and AST/ALT in patients with RA. First, inflammation plays a vital role in the activity process of RA, whereas platelets, lymphocytes, and the like play a vital role in inflammatory and immune responses. Hence, patients with RA who have better mobility may have higher PLR and AST/ALT values. PLR may affect the activity and progress of RA by activating immune responses. Second, accumulation and persistence of lymphocyte infiltration in the rheumatoid synovium are characteristic of RA. During the inflammatory response to RA, lymphocytes are reduced by triggering an apoptotic cascade [18,19]. Such a decrease in the lymphocyte count in peripheral blood is considered to be due to the continuous accumulation of lymphocytes in inflammatory joints and may also be due to an increase in apoptotic markers, such as heat shock protein 70 and caspase-3/7, which in turn leads to an increase in PLR [20], a finding that has also been confirmed in this study. However, it

should be pointed out that lymphopenia is a common clinical manifestation induced by steroids and immunosuppressants in various autoimmune diseases [21-23]. The decrease observed in the PLR levels in the RA group may be due to the effects of treatment, such as methotrexate, leflunomide, and glucocorticoids. Third, patients with active RA may exhibit liver involvement, thereby increasing the AST and ALT values. In this study, it was confirmed that patients with RA have significantly higher AST/ALT levels than those of patients with OA and HCs, which can help distinguish those with RA from the control group.

Several traditional inflammatory parameters, such as ESR, CRP, and NLR, have been extensively studied and found to be closely related to the activity of RA [24-26]. However, the results obtained in this study showed that PLR and AST/ALT can be used as indicators of disease activity reflecting the degree of systemic inflammation. It should be noted, however, that there are some limitations in this study. First, this was a single-center retrospective study, which made it hard to avoid selection bias. Second, the sample size was small and many patients had incomplete information that could not be included in the study, posing potential bias. Therefore, the results obtained should be validated using a multicenter large-scale study.

CONCLUSION

In summary, this study revealed the potential of PLR and AST/ALT as diagnostic markers for RA. It was concluded that PLR and AST/ALT can be used as convenient and economic indicators to distinguish RA from OA and HC.

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Declaration of Interest:
The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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