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Original Article

Red blood cell distribution width: a potential maker estimating disease activity of ankylosing spondylitis

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Abstract: Ankylosing spondylitis (AS) is a autoimmune disease, early and accurate detection is vital for effective treatment. Very recently, a large of novel laboratory index were found to diagnose AS. However, the correlation between red blood cell distribution width (RDW) and AS has been poorly discussed in previous study. Then, our aim was to focus on the association between RDW and AS. AS patients without drugs treatments and healthy individuals were incorporated in our study. Laboratory parameters including RDW tests were conducted consecutively on the entire cohort of AS patients and healthy individuals. AS patients with increased RDW showed significant difference compared to healthy individuals (13.66±0.77 vs. 12.77±0.47, $P<0.01$), similarly, difference of AS patients and heathy individuals stratified by sex was almost the same as that in two groups. Some significantly positive correlation were observed between RDW and CRP, ESR, IgG, BASDAI score in patients with AS (r=0.356, P=0.018; r=0.481, P=0.001; r=0.385, P=0.010; r=0.586, P<0.01), almost identical results were showed when AS patients was stratified by gender. Finally, receiver operating characteristic (ROC) curves of RDW levels to identify AS patients exhibited a statistically significant level (area under the curve of 0.853; sensitivity of 72.7%, specificity of 81.4%). The results suggested that increased RDW was associated with AS and may be used as a potential marker estimating disease activity of AS.

Keywords: Ankylosing spondylitis, red blood cell distribution width, C-reactive protein, erythrocyte sedimentation rate, Bath AS disease activity index

Introduction

Ankylosing spondylitis (AS), as a autoimmune disease, is a chronic and inflammatory disease involving sacroiliac joint and spine seen in 16-30 years old population mainly [1], historically males have been found to be more significantly affected than females, main symptoms includes joint pain, fatigue and eye inflammation [2]. The diagnosis for AS patients mainly depends on laboratory medicine and medical imaging in clinical work of which laboratory medicine plays an important role to diagnose patients with AS. A series of previous research have revealed that there were closely association between AS and some laboratory indicators including human leucocyte antigen-B27, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and proealcitonin (PCT) [3, 4]. Recently, Gökmen F [5] showed that neutrophil-lymphocyte ratio was associate with AS and was considered as a useful inflammatory indicator. Further, the correlation between AS and some novel biomarkers was observed, such as calprotectin and ERAP1 haplotype [6, 7].

Red blood cell distribution width (RDW) is a numerical measure that describes red blood cell (RBC) volume heterogeneity and serves as a component of complete blood count in the differential diagnosis of anemia [8]. In fact, previous a large of studies have shown that RDW was positive correlated with CRP and ESR in the cohort of unselected outpatients. Moreover, RDW, a well-known inflammatory markers, has

Table 1. Characteristics of participants

	AS patients	Healthy Controls	*P-value*
Gender (male/female)	30/14	82/31	0.585
Age (y)	35.98±16.24	33.87±7.88	0.423
C-reactive protein (mg/L)	22.9± 26.91	2.58±1.66	<0.01
Complement C3 (g/L)	1.14±0.20	0.92±0.67	<0.01
Immunoglobulin A (g/L)	3.07±1.64	1.80±0.77	<0.01
Immunoglobulin G (g/L)	14.05±4.47	10.83±1.70	<0.01
Immunoglobulin M (g/L)	1.44±0.55	1.14±0.43	0.001
Alanine aminotransferase (U/L)	22.71±15.59	24.35±12.65	0.496
Aspartate aminotransferase (U/L)	18.66±6.60	20.82±5.22	0.055
Alkaline phosphatase (U/L)	90.96±27.66	71.58±18.97	<0.01
Leukocyte ($\times 10^9$/L)	6.79±1.64	6.53±1.39	0.315
Neutrophil percent (%)	57.21±10.10	58.04±8.03	0.625
Lymphocyte ($\times 10^9$/L)	2.30±0.77	2.13±0.51	0.112
Erythrocyte sedimentation rate (mm/h)	38.82±18.40	7.39±3.94	<0.01
BASDAI score	5.52±2.32	-	-
RDW (%)	13.66±0.77	12.77±0.47	<0.01

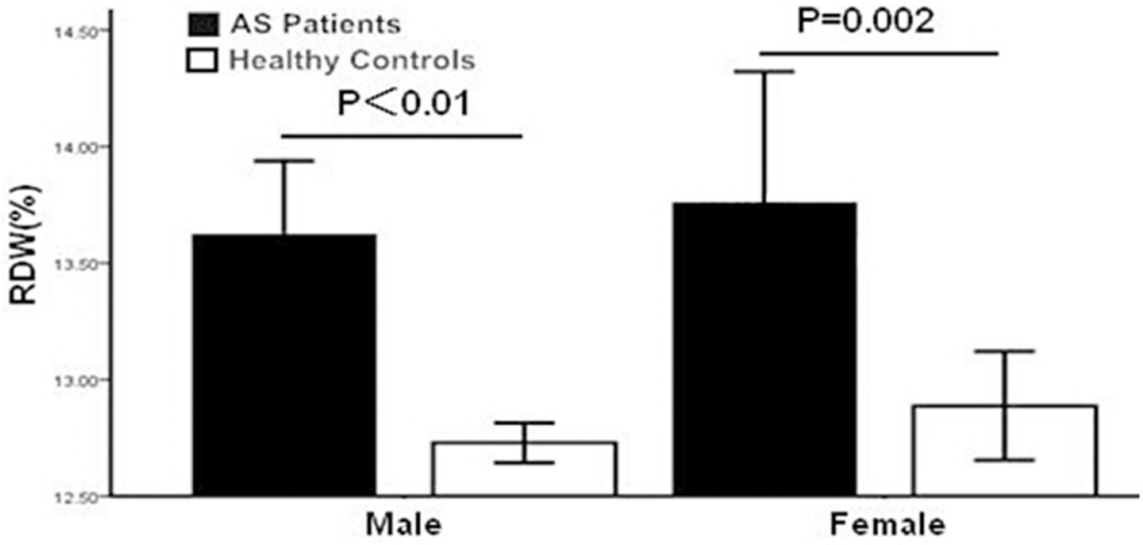

Figure 1. Increased RDW was observed when the AS patients and healthy individual was stratified by gender. Horizontal lines showed the *P* values. AS, Ankylosing spondylitis; RDW, Red blood cell distribution width.

been reported to be a strong and independently risk factor of many adverse events in general population [9-12], inflammatory status represented by increased RDW in the body possible contributes to explain the association [13]. Obviously, it could be speculated that RDW as a novel indicators for inflammation may be a participant in AS along with systematic inflammatory reaction. Then, our aim in this study was to examine whether RDW maintained relationship with AS.

Materials and methods

AS patients without drugs treatments who were recruited to *The First Affiliated Hospital of Xinjiang Medical University* from 2012 to 2014 were included in present study. The Bath AS disease activity index (BASDAI) score was used to evaluate disease activity of AS in this study. The diagnose for all patients with AS was based on the 1984 New York criteria. Meanwhile, patients were excluded if the presence of any

the following diseases and/or situations: (1) patients with other autoimmune diseases, such as systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and rheumatoid arthritis (RA); (2) patients with anemia, other hematologic disease or/and received blood transfusion during the past 6 months; (3) patients with diabetes, hypertension, cardiovascular disease and infectious diseases (4) presence of known chronic liver, kidney diseases, malignant diseases and mental illness. The healthy controls included 113 healthy individuals who were recruited for the research.

The data were obtained from recruited individuals who conformed to the inclusive criteria, including the medical history, the results of laboratory medicine and medical imaging information. Complement C3, immunoglobulin (IgA), immunoglobulin (IgG), immunoglobulin (IgM), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), leukocyte, neutrophil percentage, lymphocytes, CRP, ESR and RDW tests were carried out consecutively on the entire cohort of AS patients and healthy individuals.

Statistical analysis

Continuous variables were displayed as mean ± standard, normal distribution were examined with the Kolmogorov-Smirnov test. Two independent sample t-test, Mann-Whitney U test and X^2 test were used for the comparison between AS patients and healthy controls. Correlations between RDW and continuous variables were analyzed using Spearman and Pearson correlation analysis. Finally, the receiver operating characteristic (ROC) curves was used to measure the performance of the variables. The data used SPSS16.0 (SPSS Inc, Chicago, IL, USA) statistical software for statistical analysis. The P value of <0.05 was considered as significant.

Results

According to the criteria, a total of 44 eligible AS patients who included 3 juvenile ankylosing spondylitis (JAS) were incorporated in our study. Characteristics of 44 AS patients used in this study and 113 healthy individuals were presented in (**Table 1**). At baseline, the mean RDW values was 13.7% in patients with AS and 12.8% in the healthy controls, AS patients with high RDW values presented significant difference compared to healthy individuals (13.66±0.77 vs. 12.77±0.47, P<0.01). Similarly, difference of AS patients and heathy individuals stratified by sex was almost the same as that in two groups (**Figure 1**).

In patients with AS, some significantly correlation were observed between RDW and inflammatory markers, including both CRP (r=0.358, P=0.018) and ESR (r=0.481, P=0.001). Of note, the BASDAI score and serum IgG showed a positive correlation with RDW in AS patients (r=0.586, P<0.01; r=0.358, P=0.010) (**Figure 2**), almost identical results also were showed when AS patients was stratified by gender, however, RDW was not correlated with age, CRP, ESR, complement C3,serum IgA, serum IgM, serum IgG, ALT, AST, ALP, leukocyte, neutrophil percentage and lymphocyte in healthy controls (**Table 2**).

The ROC curves of RDW levels was used to identify patients with AS, the sensitivity of 72.7% and specificity of 81.4% for RDW was observed in the study with a cutoff value of 13.15 and area under the curve (AUC) of 0.853 (**Figure 3**).

Discussions

In this study, even though we only incorporated AS patients without drugs treatments to avoid potential impact from drugs. However, our results showed that increased RDW had a close relation with AS patients compared with healthy controls.

Chronic inflammatory process that is triggered by interaction between autoantibodies, genetic factors and environment serves as significantly factors in autoimmune diseases including AS [14]. The evidence of spinal inflammation associated with AS was confirmed by MRI [15]. Further, a series of studies have shown that inflammation was associated with tumor necrosis factor (TNF) and interleukin-6 (IL-6), these cytokines were found in the tissues of sacroiliac joint of patients with AS by pathological biopsy [16, 17], which revealed inflammatory response possibly was participator in the pathogenesis of AS. RDW reflects the variability in circulating RBC size, with larger values hinting greater variability, it is based on the width of the RBC volume distribution curve [18]. RDW

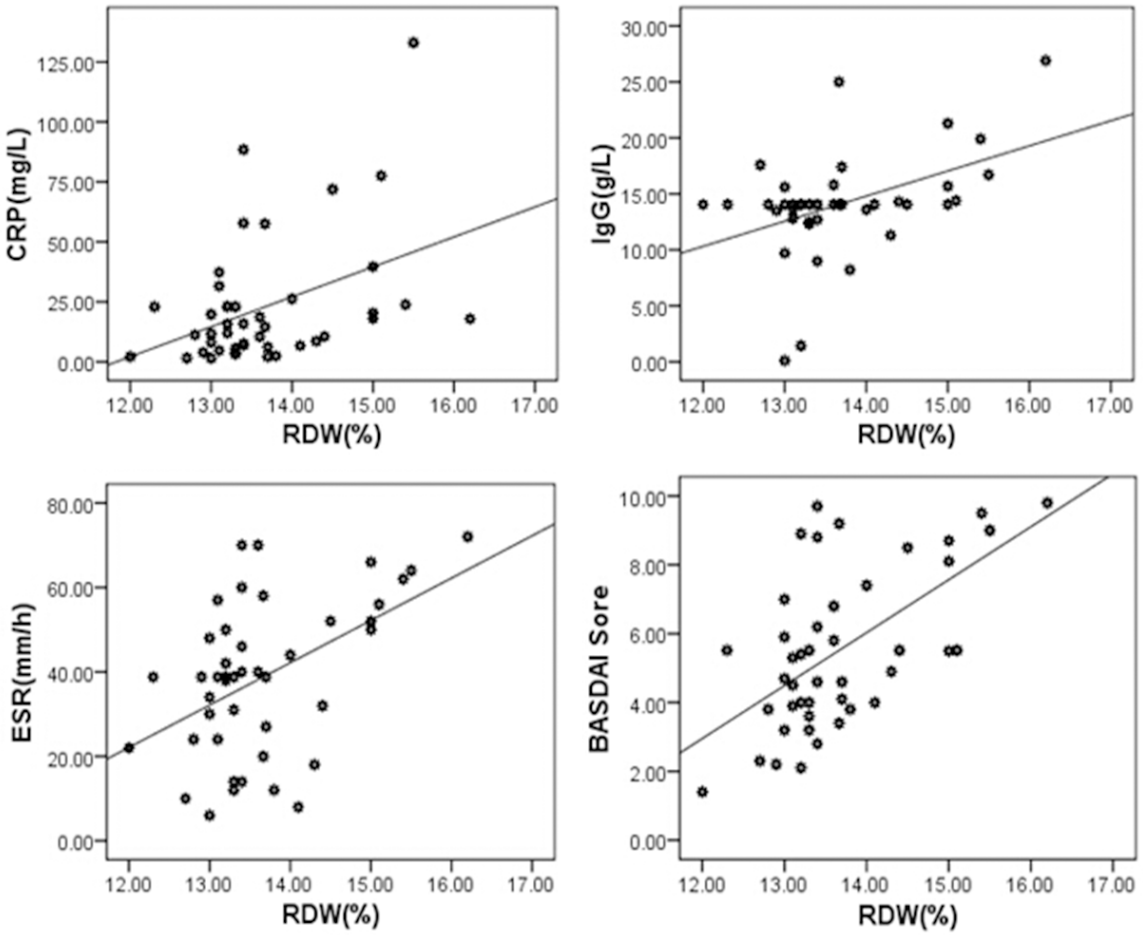

Figure 2. Scatter plot presents the correlation between RDW and clinical indicators in patients with AS. AS, Ankylosing spondylitis; RDW, Red blood cell distribution width.

presented a strong and graded association with inflammatory markers, it was a novel inflammatory indicator and was independent of sex, age and haematological variation [19], Very recently, however, a strong independently association between higher levels of RDW and ESR, CRP has been demonstrated in SEL and RA [20, 21]. Interesting, our study found that RDW was positive associated with CRP, ESR in AS patients, previous studies have shown that ESR and CRP were higher in patients with AS and have been considered as traditional index to estimate disease activity of AS [22]. However, the ESR and CRP that seem to be reliable might be disordered by outcome of recent infection and is unspecific to estimate inflammation states [23], which potentially induce a misconception to assess the activity of AS patients with acute infection through values of ESR and CRP, obviously it is adverse to monitor disease activity of AS. It is generally known that the lifespan of RBC is approximately 120 days, then, the fast alteration of RDW values possibly could be avoided in AS patients with acute infection compared with ESR and CRP, it is speculated that RDW contributing to evaluate chronic inflammatory states may be more remarkable than performance of CRP and ESR for AS patients. At present, the pathophysiologic mechanisms of AS possibly remains unclear. The long-term chronic inflammation possible help to explain potentially correlation between RDW and CRP, ESR in patients with AS. AS patients involves chronic inflammation referring to IL-6, TNF from tendon and attachment points of ligament, which impacts mature of RBC, production of glycoprotein, iron metabolism, the lifespan of RBC and sensitivity of erythropoietin [13, 24-25], contributing to increase RDW. In the past decades, BASDAI score has been one of reference to estimate the activity of AS, whereas the performance of

Table 2. The correlation between RDW and parameters

	Correlation coefficients					
	AS Patients			Healthy Controls		
	All	Male	Female	All	Male	Female
Age (y)	-0.041	-0.067	-0.038	-0.062	0.118	-0.292
C-reactive protein (mg/L)	0.356*	0.383*	0.616*	-0.049	-0.040	-0.026
Complement C3 (g/L)	0.177	0.050	0.553*	0.095	0.014	0.277
Immunoglobulin A (g/L)	0.109	0.100	0.148	0.000	0.015	-0.090
Immunoglobulin G (g/L)	0.358*	0.419*	0.584*	-0.039	0.085	-0.190
Immunoglobulin M (g/L)	0.105	-0.019	0.035	0.035	0.002	0.127
Alanine aminotransferase (U/L)	0.231	0.330	0.026	-0.018	0.102	-0.083
Aspartate aminotransferase (U/L)	0.167	-0.257	0.149	0.008	0.121	-0.405*
Alkaline phosphatase (U/L)	-0.014	0.269	0.129	-0.022	-0.061	-0.440*
Leukocyte ($\times 10^9$/L)	-0.275	-0.492*	0.044	-0.010	-0.124	0.266
Neutrophil percentage (%)	0.002	-0.063	0.150	0.089	0.024	0.154
Lymphocyte ($\times 10^9$/L)	-0.304*	-0387*	-0.087	-0.044	-0.028	-0.022
Erythrocyte sedimentation rate (IU/L)	0.481*	0.394*	0.648	0.010	0.023	-0.178
BASDAI score	0.58 6*	0.511*	0.791*	-	-	-

*P<0.05 with compare to healthy controls.

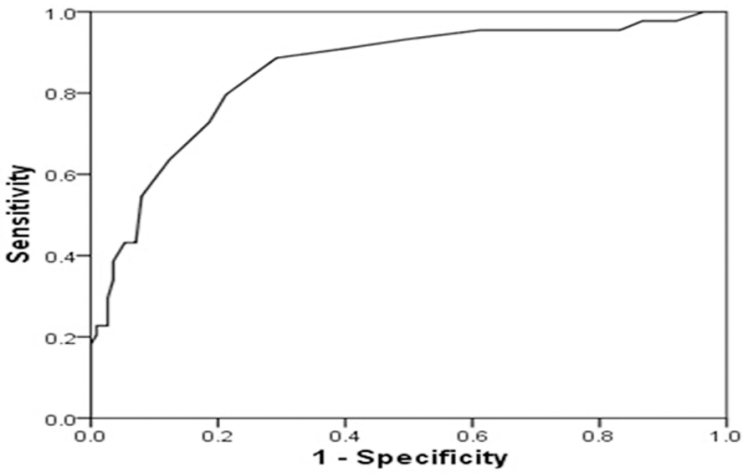

Figure 3. Receiver Operating Characteristics of the Red Blood Cell Distribution Width for AS patients. AS, Ankylosing spondylitis.

BASDAI score is impaired easily by the subjective factors from judge and patients. As shown in the present study, our study found that RDW was positive related with BASDAI score, RDW is easily measured with standardized methods and is routinely used in the clinical setting, the objective and measured RDW possible is more advantage than BASDAI to appraise the activity of AS and is considered as underlying indicators estimating activity of AS to some extent. Nevertheless, further investigation should be implemented whether RDW could be a useful indicator. In addition, a additional positive correlation between RDW and serum IgG was observed in patients with AS. Indeed, a number of studies have shown that serum IgG was associated with CRP, ESR and played a role in inflammation response, serum IgA and serum IgM were not correlate with CRP even though it were increased frequently in AS patients [26, 27], a pathway participated by serum IgG in the pathogenesis of inflammatory process may exists in AS. On the other hand, increased serum IgG that implies chronic inflammation seem similar to RDW to a certain extent, the relationship between RDW and serum IgG seemly could be interpreted. The possible mechanism, however, for this correlation requires further investigation.

There are several underling limitations that should be considered in this study. First, our study is limited by small sample due to the lower prevalence of AS in the region. Second, RDW values, as a cross-sectional study, were not observed dynamically whether RDW was heightened stepwise when condition of AS patients was deteriorated progressively. Finally, the samples were collected and measured

from a single laboratory, the values of RDW possibly has been slightly different in the different population and region. However, our research suggested that increased RDW was associated with AS although individuals of AS-related treatment were not included in this study. These findings suggest a mechanism by which higher levels of RDW possibly could contribute to a potential marker estimating disease activity of AS.

Disclosure of conflict of interest

None.

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