

ORIGINAL ARTICLE

The Relationship between Erythrocyte Sedimentation Rate and Erythrocyte Sedimentation/Red Blood Cell Ratio and Disease Activity in Systemic Lupus Erythematosus

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SUMMARY

Background: The treatment options of systemic lupus erythematosus (SLE) patients in active and inactive phases are very different clinically, and the prognosis of patients with active SLE is much worse than inactive patients. However, the present indicators for diagnosis of SLE in activity are limited and inefficient.

Methods: Three hundred thirty patients with SLE were included. All patients are classified as SLEDAI (systemic lupus erythematosus disease activity index) > 4 as active and SLEDAI ≤ 4 as inactive. The linear correlation between variables was assessed by Pearson's correlation analysis. The difference between parameters in active and inactive patients was evaluated by the Mann-Whitney *U* test. The evaluation capacity of erythrocyte sedimentation/red blood cell (ERR) and red blood cell/albumin ratio (RAR) on SLE activity was determined by bivariate regression analysis. Sensitivity and specificity are assessed by receiver operating characteristic curve (ROC).

Results: Compared with the inactive SLE, ESR (52.97 ± 35.66 vs. 32.38 ± 29.16 $p < 0.001$), ERR (15.40 ± 12.41 vs. 8.19 ± 8.10 $p < 0.001$) and RAR (0.13 ± 0.10 vs. 0.11 ± 0.20 $p = 0.038$) are all elevated in active SLE (52.97 ± 35.66 vs. 32.38 ± 29.16 $p < 0.001$). ERR shows better correlation than RAR with ESR ($p < 0.001$ vs. $p = 0.911$). Patients with active SLE exhibited higher SLEDAI than those with inactive SLE (8.67 ± 2.67 vs. 3.27 ± 1.36 , $p < 0.001$). According to ROC analysis, when ESR levels > 58.5 and ERR levels > 13.18 , the sensitivity is 37.6% and 45.2%, the specificity is 83.0% and 83.2%.

Conclusions: ESR and ERR are potential indicators for diagnosis of active and inactive SLE.
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KEY WORDS

erythrocyte sedimentation rate, erythrocyte sedimentation/red blood cell, red blood cell/serum albumin ratio, systemic lupus erythematosus, activity

INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory disorder of systemic connective tissue characterized by auto-immunity and auto-antibody, which influences major systems and organs involving kidney, brain, heart, and nervous system [1-3]. According to statistics, the global average prevalence of SLE is 12 - 39/100,000, while in China it is 30.13 - 70.41/100,000 [4-7]. Although there are several options and drugs for SLE treatment, these medical interventions cannot achieve complete remission due to the unclear pathogenesis of SLE and lack of early prediction indicators [8,9].

In clinical practice, SLE patients are divided into active and inactive phase to determine the correct treatments. Most patients with SLE in active phase have systemic symptoms including fever, headache, butterfly erythema, painful ulcers in the mouth and nasal mucosa, serositis, arthritis, and mental disorders. Active SLE could further harm the kidney, cardiovascular system, blood system, and nervous system, etc., compared to the inactive phase. Multiple organ damage and infection are the leading causes of death in the acute phase of patients, which seriously affect the prognosis of patients with SLE and significantly reduce the survival rate. The treatment of SLE patients in active and inactive phases are significantly different in clinical practice [10]. So far, some previous studies have reported that elevated SLEDAI value shows positive correlation with disease activity of patients with SLE [11]. It is reported that the expression level of erythrocyte type 1 complement receptor (CR1) in SLE patients had significant correlation with disease activity, which could be used as the indicator for SLE disease activity [12]. ESR is the most widely used indicators of nonspecific inflammation for measuring acute phase response in SLE [13-17]. Serum albumin is a well-known acute reactive protein in the peripheral blood and is negatively correlated with systemic inflammation [18-20]. Erythrocyte immune function in patients with active SLE is lower than in inactive SLE [11] [21-23]. Hence, in the present study, we evaluated the correlation of ESR, ERR, and RAR with SLEDAI and their utility as an independent predictor of active SLE.

MATERIALS AND METHODS

We reviewed the medical records of 330 patients who were diagnosed with SLE at the Clinical Laboratory Medicine Center, Shenzhen Hospital of Southern Medi-

cal University between February 2015 and December 2017. Two hundred sixty-four patients with active SLE and 66 inactive patients were enrolled according to the revised American College of Rheumatology classification criteria [24]: 1) cheek erythema, 2) disc erythema, 3) photosensitization, 4) oral-ulcers, 5) arthritis, 6) serositis, 7) nephritis, 8) neurological disease, 9) hematological disease, 10) immunological diseases, 11) antinuclear antibody abnormality. SLE can be diagnosed when infection, tumor, and other connective tissue disease are excluded and four or more of eleven items are met [25-27]. Any other medical conditions with history of cancers, concomitant infectious or inflammatory disease such as liver or kidney disease, ulcerative colitis, cardiovascular disease, hematologic disorders other than anemia, autoimmune disease, and the virus infections were removed [28]. The activity of SLE was determined with SLEDAI [29-32]: 0 through 4 in remission; 5 through 9 in low activity; 10 through 14 in moderate activity; ≥ 15 in high activity. The study protocol was approved by the University Local Research Ethics Committee.

Biochemical and hematological measurements

Peripheral venous blood of subjects was gathered from an elbow vein of patients in the morning after 12 hours of fasting. The serum complement 3 and 4, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum albumin, globulin, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and urea nitrogen were analyzed from freshly separated serum in the clinical laboratory of the hospital by automatic biochemical analyzer. Platelet count, hemoglobin, leukocyte, erythrocyte, lymphocyte count, and neutrophil count were determined from anticoagulated blood samples by automatic blood routine analyzer. The disease activity in SLE patients was expressed by SLEDAI [33]. The normal range of erythrocytes is $3.8 - 5.1 \times 10^{12}/L$, serum albumin is 35.0 - 55.0 g/L, and ESR is 0 - 32 mm/hour. RAR and ERR were calculated respectively by the ratio of erythrocyte to serum albumin and the blood sedimentation rate to erythrocyte.

Collection of clinical data

Clinical variables related to SLE were collected, including skin rash, photosensitivity, erythema, oral-ulcers, arthritis, serositis, nephritis, neurological, hematological, immunological diseases, fever, lupus headache, etc.

Demographic data

The age, gender, and course of illness of the samples were recorded according to the demographic data.

Statistics

All the statistical data were processed by SPSS version 20.0. Values are expressed as mean \pm standard deviation or quantitative variables and counts or percentage for categorical variables. Differences between measured pa-

rameters in active SLE and inactive patients were analyzed by the Mann-Whitney *U* test. The evaluation of qualitative parameters was performed by analysis of variance test and Student's *t*-test. Pearson's correlation was used to assess the linear correlation between variables. Bivariate regression analysis (tau b(K) of Kendall) was used to judge whether ERR and RAR can serve as an independent predictor of disease activity. Sensitivity, specificity, and cutoff value were assessed by the ROC analysis. We considered statistically significant differences by *p*-value < 0.05. According to hospital standards all samples were examined within 2 hours after the collection.

RESULTS

Basic characteristics of patients with active and inactive SLE

Demographic data, clinical characteristics, and laboratory findings of 264 patients with active SLE and 66 patients with inactive SLE are presented in Table 1. The mean age of the patients is 31 years, with a gender distribution of 291 women (88.2%) and 39 men (11.8%). Patients with SLE had a mean disease duration of 4 years. In total, 264 (80%) patients were classified as active SLE, while 66 (20%) were classified as inactive SLE. There was no difference in age or gender between both groups.

Our results demonstrated that ESR levels in the patients with active SLE were significantly higher than the inactive group (*p* < 0.001). ERR and RAR were also markedly elevated in patients with active SLE compared with the inactive group (*p* < 0.001 and *p* < 0.05, respectively). On the contrary, erythrocytes and serum albumin levels of active patients were significantly lower than the inactive group (*p* < 0.001 and *p* < 0.001, respectively). In addition, hemoglobin and immunoglobulin G patients in active SLE were significantly lower than the inactive group (*p* < 0.001 and *p* < 0.05, respectively). No differences in other parameters such as CRP, platelet, leukocyte, lymphocyte, neutrophil, globulin, AST, ALT, and Cr were observed between the groups (Table 1).

Clinical characteristics including urinary protein, nephritis, erythema, skin rash, photosensitivity, arthritis, fever, hair-loss, neurological, hematological, and immunological diseases in active and inactive SLE show statistically significant differences (*p* < 0.001). Specifically, patients with active SLE accompanied with urinary protein, nephritis, erythema, arthritis, and fever were 227 (68.8%), 226 (68.5%), 114 (34.5%), 135 (40.9%), and 111 (33.6%), respectively.

The ROC curve analysis of ERR and RAR

ROC curve analysis was performed to determine the specificity and sensitivity of ERR and RAR in SLE activity prediction. The area under the curve (AUCs) of ERR, RAR, ESR, and CRP is 0.73, 0.58, 0.70, and 0.52,

respectively. There were statistically significant differences between ERR and RAR levels of AUCs with ESR (*p* < 0.001) (Figure 1A). However, there was no significant difference in the area under the curve of CRP, erythrocyte, and albumin (Figure 1B). The ERR levels of cutoff is 13.18 (sensitivity 45.2%, specificity 83.1%, AUCs 0.73 *p* < 0.001), the ESR level of cutoff is 58.50 (sensitivity 37.6%, specificity 83.0%, AUCs 0.70 *p* < 0.001), and RAR level of cutoff is 0.12 (sensitivity 39.2%, specificity 18.5%, AUCs 0.58 *p* = 0.035)

The cutoff values for ESR, ERR, and RAR were used to compare activity level and typical clinical manifestations of patients

SLE patients with ESR level higher than 58.5 had statistically significant higher CRP level (11.00 ± 20.18 vs. 6.49 ± 16.86 , *p* < 0.001) and SLEDAI level (8.45 ± 3.12 vs. 6.99 ± 3.28 , *p* < 0.001). On the contrary, the hemoglobin (101.69 ± 22.43 vs. 109.74 ± 21.60 , *p* = 0.001), erythrocyte (3.55 ± 0.74 vs. 3.95 ± 0.72 , *p* < 0.001), lymphocyte (1.89 ± 2.81 vs. 3.64 ± 8.01 , *p* = 0.009), and albumin (31.10 ± 8.55 vs. 33.99 ± 7.63 , *p* = 0.002) levels in patients with ESR levels higher than 58.5 were significantly lower than the group with ESR levels lower or equal than 58.5. However, there was no significant differences between patients with platelet (*p* = 0.177), neutrophil (*p* = 0.522), globulin (*p* = 0.373), C4 (*p* = 0.370), and IgG (*p* = 0.697) levels higher or lower than 58.5 in terms of clinical findings (Table 2). Using ERR as standard, patients with ERR levels higher than 13.18 had remarkably higher ESR (85.25 ± 27.03 vs. 25.20 ± 13.05 , *p* < 0.001), CRP (12.97 ± 24.47 vs. 4.51 ± 10.93 , *p* < 0.001), and SLEDAI (8.65 ± 3.00 vs. 6.90 ± 3.28 , *p* < 0.001) levels. On the contrary, the platelet (206.12 ± 90.73 vs. 228.48 ± 93.46 , *p* = 0.028), hemoglobin (99.98 ± 22.22 vs. 112.10 ± 20.76 , *p* < 0.001), erythrocyte (3.49 ± 0.74 vs. 4.05 ± 0.66 , *p* < 0.001), lymphocyte (1.92 ± 3.02 vs. 3.64 ± 8.01 , *p* < 0.001), and albumin (31.08 ± 8.40 vs. 34.45 ± 7.47 , *p* < 0.001) levels of patients with ERR level higher than 13.18 were significantly lower than the group with ERR levels lower than or equal to 13.18. However, when patients with ERR levels lower than or equal to 13.18, there were no significant differences between neutrophil (*p* = 0.371), globulin (*p* = 0.196), C4 (*p* = 0.691), and IgG (*p* = 0.494) levels higher or lower than 13.18 in terms of clinical findings (Table 3). Similarly, SLE patients with RAR levels higher than 0.12 had statistically significantly higher erythrocyte (4.10 ± 0.71 vs. 3.67 ± 0.72 , *p* < 0.001) and SLEDAI (8.15 ± 3.06 vs. 7.27 ± 3.37 , *p* = 0.016) levels. On the contrary, albumin (27.38 ± 7.57 vs. 36.38 ± 6.19 , *p* < 0.001) and globulin (26.07 ± 7.87 vs. 27.79 ± 7.87 , *p* = 0.040) levels of patients with RAR levels higher than 0.12 were significantly lower than the group with RAR levels lower than or equal to 0.12. However, there were no significant differences between patients with ESR (*p* = 0.536), CRP (*p* = 0.123), platelet (*p* = 0.311), hemoglobin (*p* = 0.311), lymphocyte (*p* = 0.199), neutrophil (*p* = 0.320), and

Table 1. Demographic, clinical, and laboratory data characteristics of patients with SLE.

	All patient n = 330	Active n = 264	Inactive n = 66	p-value
Female-gender	291 (88.2%)	230 (87.1%)	59 (89.4%)	< 0.001
Age (y)	31 ± 13.82	30 ± 13.45	33 ± 14.97	0.078
Duration (y)	4 ± 13.82	4 ± 3.81	4 ± 3.87	0.570
ESR, mm/hour	48.85 ± 35.40	52.97 ± 35.66	32.38 ± 29.16	< 0.001
CRP, mg/L	8.20 ± 19.12	7.42 ± 16.68	11.31 ± 26.69	0.671
Platelet, G/L	219.67 ± 92.90	218.45 ± 93.62	224.5 ± 90.51	0.465
Hemoglobin, g/L	107.33 ± 22.13	105.27 ± 22.50	115.5 ± 18.53	< 0.001
Leukocyte, G/L	6.82 ± 3.48	6.84 ± 3.55	6.77 ± 3.18	0.093
Erythrocyte, T/L	3.83 ± 0.75	3.75 ± 0.77	4.14 ± 0.54	< 0.001
Lymphocyte, G/L	3.11 ± 6.92	3.54 ± 7.67	1.43 ± 0.79	0.074
Neutrophil, G/L	29.18 ± 386.43	35.29 ± 432.00	4.74 ± 2.79	0.653
Albumin, g/L	33.09 ± 8.02	31.87 ± 8.11	38.01 ± 5.35	< 0.001
Globulin, g/L	27.15 ± 7.90	26.93 ± 7.32	28.11 ± 10.01	0.867
AST, IU/L	30.74 ± 75.27	32.50 ± 83.81	23.76 ± 15.48	0.653
ALT, IU/L	22.87 ± 23.24	22.96 ± 22.98	22.50 ± 24.43	0.873
Cr, μmol/L	92.16 ± 119.29	96.76 ± 131.24	73.82 ± 44.14	0.440
C4, g/L	0.14 ± 0.08	0.14 ± 0.08	0.75 ± 0.27	0.648
C3, g/L	1.08 ± 5.44	0.75 ± 0.27	1.16 ± 6.04	0.047
IgG, g/L	13.00 ± 9.44	12.64 ± 9.77	14.39 ± 8.00	0.035
RAR	0.13 ± 0.09	0.13 ± 0.10	0.11 ± 0.20	0.038
ERR	13.96 ± 12.02	15.40 ± 12.41	8.19 ± 8.10	< 0.001
PLR	0.02 ± 0.03	0.02 ± 0.04	0.01 ± 0.01	0.009
NLR	16.96 ± 237.00	20.16 ± 264.97	4.17 ± 3.78	0.198
SLEDAI scores	7.59 ± 3.28	8.67 ± 2.67	3.27 ± 1.36	< 0.001
Urine protein	227 (68.8%)	215 (81.4%)	13 (19.7%)	< 0.001
Nephritis	226 (68.5%)	199 (75.4%)	27 (40.9%)	< 0.001
Erythema	114 (34.5%)	85 (32.2%)	29 (43.4%)	< 0.001
Rash	42 (12.7%)	38 (14.4%)	4 (6.1%)	< 0.001
Photosensitization	28 (8.5%)	21 (8.0%)	7 (10.6%)	< 0.001
Blood system	42 (12.7%)	34 (12.9%)	8 (12.1%)	< 0.001
Arthritis	135 (40.9%)	122 (46.2%)	13 (19.7%)	< 0.001
Nervous system	13 (4.9%)	13 (4.9%)	0	< 0.001
Immune system	4 (1.2%)	3 (1.1%)	1 (1.5%)	< 0.001
Fever	111 (33.6%)	103 (39.0%)	8 (12.1%)	< 0.001
Alopecia	56 (17.0%)	52 (19.7%)	4 (6.1%)	< 0.001

Values are expressed as median (interquartile) or number (%).

The presence of clinical manifestation was evaluated according to the 1997 revised American College of Rheumatology classification criteria. SLE - systemic lupus erythematosus, Cr - creatinine, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein, AST - aspartate aminotransferase, ALT - alanine aminotransferase, C4 - serum complement 4, C3 - serum complement 3, IgG - immunoglobulin G, ERR - erythrocyte sedimentation/red blood cell ratio, RAR - red blood cell/albumin ratio, SLEDAI - systemic lupus erythematosus disease activity index, PLR - platelet to lymphocyte ratio, NLR - neutrophil to lymphocyte ratio.

Table 2. Comparing the activity level and typical clinical manifestations of patients up and down the critical value of ESR.

	ESR > 58.5	ESR ≤ 58.5	p-value
CRP, mg/L	11.00 ± 20.18	6.49 ± 16.86	< 0.001
Platelet, G/L	208.80 ± 89.72	224.32 ± 94.04	0.177
Hemoglobin, g/L	101.69 ± 22.43	109.74 ± 21.60	0.001
Erythrocyte, T/L	3.55 ± 0.74	3.95 ± 0.72	< 0.001
Lymphocyte, G/L	1.89 ± 2.81	3.64 ± 8.01	0.009
Neutrophil, G/L	7.95 ± 705.26	8.28 ± 14.53	0.522
Albumin, g/L	31.10 ± 8.55	33.99 ± 7.63	0.002
Globulin, g/L	27.77 ± 8.17	26.87 ± 7.77	0.373
C4, g/L	0.14 ± 0.09	0.14 ± 0.08	0.370
IgG, g/L	12.13 ± 6.75	13.36 ± 10.35	0.697
SLEDAI Scores	8.45 ± 3.12	6.99 ± 3.28	< 0.001

CRP - C-reactive protein, C4 - serum complement 4, IgG - immunoglobulin G, SLEDAI - systemic lupus erythematosus disease activity index, ESR - erythrocyte sedimentation rate.

Table 3. Comparing the activity level and typical clinical manifestations of patients up and down the critical value of ERR.

	ERR > 13.18	ERR ≤ 13.18	p-value
ESR, mm/hour	85.25 ± 27.03	25.20 ± 13.05	< 0.001
CRP, mg/L	12.97 ± 24.47	4.51 ± 10.93	< 0.001
Platelet, G/L	206.12 ± 90.73	228.48 ± 93.46	0.028
Hemoglobin, g/L	99.98 ± 22.22	112.10 ± 20.76	< 0.001
Erythrocyte, T/L	3.49 ± 0.74	4.05 ± 0.66	< 0.001
Lymphocyte, G/L	1.92 ± 3.02	3.89 ± 8.46	< 0.001
Neutrophil, G/L	61.05 ± 615.49	8.47 ± 14.83	0.371
Albumin, g/L	31.08 ± 8.40	34.45 ± 7.47	< 0.001
Globulin, g/L	28.44 ± 9.45	26.28 ± 6.53	0.196
C4, g/L	0.14 ± 0.09	0.14 ± 0.08	0.691
IgG, g/L	13.40 ± 8.19	12.75 ± 10.17	0.494
SLEDAI scores	8.65 ± 3.00	6.90 ± 3.28	< 0.001

CRP - C-reactive protein, C4 - serum supplement c4, IgG - immunoglobulin G, SLEDAI - systemic lupus erythematosus disease activity index, ESR - erythrocyte sedimentation rate.

C4 ($p = 0.457$) levels higher or lower than 0.12 in terms of clinical findings (Table 4).

Correlation between ESR, ERR, and RAR with disease activity assessments of SLE

Table 5 showed the correlation of ESR, ERR, and RAR with disease activity assessments of SLE. Bivariate re-

gression analysis (Kendall's tau b(K)) showed that ERR had significant correlation with SLEDAI ($r = 0.026$ $p < 0.001$). Similarly, ESR correlated well with SLEDAI in SLE patients ($r = 0.24$ $p < 0.001$). On the contrary, patients with RAR level had no statistically significant differences with disease activity of SLE ($r = 0.07$ $p = 0.094$). In addition, there was a remarkable

Table 4. Comparing the activity level and typical clinical manifestations of patients with RAR above and below the critical value.

	RAR > 0.12	RAR ≤ 0.12	p-value
ESR, mm/hour	49.05 ± 33.45	48.74 ± 36.54	0.536
CRP, mg/L	5.57 ± 9.53	9.14 ± 21.30	0.123
Platelet, G/L	228.87 ± 92.45	214.40 ± 92.97	0.311
Hemoglobin, g/L	109.66 ± 20.66	106.00 ± 22.87	0.311
Erythrocyte, T/L	4.10 ± 0.71	3.67 ± 0.72	< 0.001
Lymphocyte, G/L	3.81 ± 8.59	2.72 ± 5.72	0.199
Neutrophil, G/L	8.30 ± 14.32	41.11 ± 484.31	0.320
Albumin, g/L	27.38 ± 7.57	36.38 ± 6.19	< 0.001
Globulin, g/L	26.07 ± 7.87	27.79 ± 7.87	0.040
C4, g/L	0.13 ± 0.08	0.14 ± 0.08	0.057
IgG, g/L	12.21 ± 13.07	13.45 ± 6.50	< 0.001
SLEDAI scores	8.15 ± 3.06	7.27 ± 3.37	0.016

CRP - C-reactive protein, C4 - serum supplement c4, IgG - immunoglobulin G, SLEDAI - systemic lupus erythematosus disease activity index, ESR - erythrocyte sedimentation rate.

Table 5. Bivariate regression analysis was used to determine the ratio of sedimentation to red blood cells and the relationship between the ratio of red blood cells to albumin and the independent predictors of disease activity.

	ERR	RAR	SLEDAI
ERR	-	R = -0.05 p < 0.155	R = 0.26 p < 0.001
RAR	-	-	R = 0.07 p = 0.094
ESR	R = 0.87 p < 0.001	R = 0.01 p = 0.911	R = 0.24 p < 0.001

ESR - erythrocyte sedimentation rate, ERR - erythrocyte sedimentation/red blood cell ratio, RAR - red blood cell/albumin ratio, SLEDAI - systemic lupus erythematosus disease activity index.

correlation between ERR and ESR levels of patients with SLE ($r = 0.87$ $p < 0.001$). However, there were no significant differences between patients with ERR and RAR ($R = -0.05$ $p < 0.155$) (Table 5).

DISCUSSION

In this study, the correlation of ESR, ERR, and RAR with disease activity in patients with SLE are analyzed. Results of this study have demonstrated that ESR and ERR were remarkably increased in active SLE. This demonstrates that ESR and ERR may be potential indicators of the disease activity in patients with SLE. History studies had shown that neutrophils, lymphocytes, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are the most widely used nonspecific inflammatory indicators for assessing acute phase

in patients with SLE. However, they can only be used as markers of the response in the acute phase of inflammatory diseases, and show minimal effect in the detection and prediction of the disease activity of chronic phase or remission phase in patients with SLE [34]. ESR is commonly used to evaluate the activity and dynamic changes of rheumatic fever and tumors [21,23]. Studies had shown that high ESR in diffuse large B-cell lymphoma (DLBCL) patients indicated worse prognosis and high disease activity that may require alternative treatment regimens [35]. CRP is the most widely used indicator for evaluating acute phase response due to its reliability, effectiveness, repeatability, and lower cost [36]. However, CRP is only used to evaluate the acute phase of inflammation, and has significant limitations to assess the chronic phase of inflammation. Moreover, CRP is influenced by uncertain factors such as age, disease duration, anemia, kidney disease, and cancer [37].

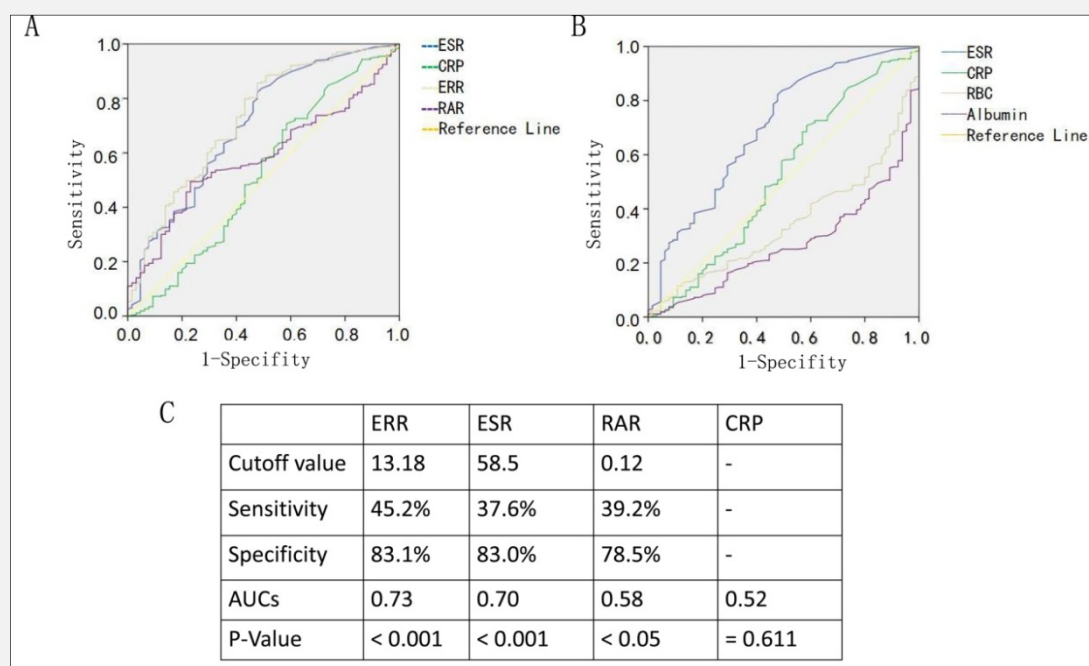


Figure 1. The ROC curve analysis of ESR, CRP, ERR, RAR, RBC, albumin.

(A) The ROC curve analysis of ESR, CRP, ERR, and RAR. (B) The ROC curve analysis of ESR, CRP, RBC, and albumin. (C) Statistical data obtained from the ROC curves of ERR, ESR, RAR, and CRP.

AUCs - area under the curve, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein, ERR - erythrocyte sedimentation/red blood cell ratio, RAR - red blood cell/albumin ratio < 0.001.

In our study, we observed that ESR and ERR showed no significant differences in patients with different gender, disease duration, and other factors.

In addition, others studies found that the neutrophil to lymphocyte ratio (NLR), the lymphocyte to platelet ratio (PLR), mean platelet volume (MPV), and erythrocyte type 1 complement receptor (CR1) were used as indicators of the disease activity in patients with SLE [38-41]. Previous study demonstrated that NLR and PLR both increased in patients with SLE, and positively correlated with SLEDAI scores and disease activity [42]. NLR and PLR may potentially be useful inflammatory parameters of systemic inflammation in patients with SLE, and even as new inflammatory markers for indicating disease activity in patients with SLE [35]. Our results indicated that PLR might be potentially useful inflammatory parameters in patients with SLE ($p < 0.01$, Table 1), However, NLR showed no difference between active and inactive SLE ($p > 0.05$, Table 1). Moreover, it is also reported that these markers had good correlation with tumor development due to inflammatory mechanism [43,44]. However, we should pay more attention to the study of inflammatory markers of chronic disease for more precise disease treatment and

prevention in patients. At present, some articles have introduced the treatment and prognosis of SLE [33,45, 46]. Our study demonstrates that ERR is elevated in active SLE, which indicated that ERR might be a predictor of disease activity in patients with SLE.

Our study has several limitations. First, our experiment is a retrospective study. We cannot avoid some errors due to subjectivity of data collection and processing. Second, the lack of information also led to inaccurate results such as serum globulin, IgA, IgG levels, etc. Although we demonstrated that ESR and ERR were independent predictors of active SLE, to avoid the errors caused by above problems, further prospective studies investigating ESR and ERR on a large number of patients are needed.

CONCLUSION

Our results demonstrate that ESR and ERR might be indicators of disease activity in patients with SLE. However, the utility of this simple tool in prediction of long-term prognosis merits further investigations.

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Declaration of Interest:

No potential conflicts of interest about the research, authorship, and publication of this article were disclosed.

References:

- Lopez P, Rodriguez-Carrio J, Martinez-Zapico A, Caminal-Montero L, Suárez A. Circulating microparticle subpopulations in systemic lupus erythematosus are affected by disease activity. *Int J Cardiol* 2017;236:138-44 (PMID: 28279502).
- Chen D Y, Chen Y M, Wen M C, Hsieh TY, Hung WT, Lan JL. The potential role of Th17 cells and Th17-related cytokines in the pathogenesis of lupus nephritis. *Lupus* 2012 Nov;21(13):1385-96 (PMID: 22892208).
- Elsharawy M, Hasan M, Abdul-Rahman IS, Al-Dhairy B, Elsaïd A. Extensive vascular occlusions as initial presentations of systemic lupus erythematosus. A case report and review of literature. *Avicenna J Med* 2015 Apr-Jun;5(2):42-5 (PMID: 25878966).
- Ocampo-Piraquive V, Nieto-Aristizabal I, Canas C A, Tobón GJ. Mortality in systemic lupus erythematosus: causes, predictors and interventions. *Expert Rev Clin Immunol* 2018 Dec;14(12):1043-53 (PMID: 30338717).
- Azizoddin D R, Jolly M, Arora S, Yelin E, Katz P. Patient Reported Outcomes Predict Mortality in Lupus. *Arthritis Care Res (Hoboken)* 2019 Aug;71(8):1028-35 (PMID: 30144293).
- Torrente-Segarra V, Salman M T, Rua-Figueroa I, et al. Relationship between damage and mortality in juvenile-onset systemic lupus erythematosus: Cluster analyses in a large cohort from the Spanish Society of Rheumatology Lupus Registry (RELESSER). *Semin Arthritis Rheum* 2019 Jun;48(6):1025-9 (PMID: 30344081).
- Rossides M, Simard J F, Svenungsson E, et al. Mortality and Functionality after Stroke in Patients with Systemic Lupus Erythematosus. *J Rheumatol* 2017 Nov;44(11):1590-6 (PMID: 28916550).
- Carroll M. Innate immunity in the etiopathology of autoimmunity. *Nat Immunol* 2001 Dec;2(12):1089-90 (PMID: 11725293).
- Su DL, Lu ZM, Shen MN, Li X, Sun LY. Roles of pro- and anti-inflammatory cytokines in the pathogenesis of SLE. *J Biomed Biotechnol* 2012;2012:347141 (PMID: 22500087).
- Schneider M. Target Therapy in SLE. *Autoimmun Rev* 2019 Jan;18(1):21-4 (PMID: 30408579).
- Schafer VS, Weiss K, Krause A, Schmidt WA. Does erythrocyte sedimentation rate reflect and discriminate flare from infection in systemic lupus erythematosus? Correlation with clinical and laboratory parameters of disease activity. *Clin Rheumatol* 2018 Jul;37(7):1835-44 (PMID: 29656375).
- Singh V, Mahoney JA, Petri M. Erythrocyte C4d and complement receptor 1 in systemic lupus erythematosus. *J Rheumatol* 2008 Oct;35(10):1989-93 (PMID: 18709693).
- Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol* 2015 Mar;110(3):444-54 (PMID: 25732419).
- Assasi N, Blackhouse G, Campbell K, et al. Comparative Value of Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) Testing in Combination Versus Individually for the Diagnosis of Undifferentiated Patients With Suspected Inflammatory Disease or Serious Infection: A Systematic Review and Economic Analysis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health, 2015 (PMID: 26677507).
- Alper A, Zhang L, Pashankar DS. Correlation of Erythrocyte Sedimentation Rate and C-Reactive Protein With Pediatric Inflammatory Bowel Disease Activity. *J Pediatr Gastroenterol Nutr* 2017 Aug;65(2):e25-e27 (PMID: 27741061).
- Ganesan V, Brown RD, Jimenez JA, De S, Monga M. C-Reactive Protein and Erythrocyte Sedimentation Rate Predict Systemic Inflammatory Response Syndrome After Percutaneous Nephrolithotomy. *J Endourol* 2017 Jul;31(7):638-44 (PMID: 28462592).
- Dai C, Jiang M, Sun MJ. The utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol* 2015 Aug;110(8):1242-3 (PMID: 26263364).
- Nasif WA, Mukhtar MH, El-Emshaty HM, Alwazna AH. Redox State of Human Serum Albumin and Inflammatory Biomarkers in Hemodialysis Patients with Secondary Hyperparathyroidism During Oral Calcitriol Supplementation for Vitamin D. *Open Med Chem J* 2018 Oct 18;12:98-110 (PMID: 30450134).
- Wani TA, Bakheit AH, Al-Majed AA, Bhat MA⁴, Zargar S. Study of the Interactions of Bovine Serum Albumin with the New Anti-Inflammatory Agent 4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-N'-[(4-ethoxy-phenyl)methylidene] benzo hydrazide Using a Multi-Spectroscopic Approach and Molecular Docking. *Molecules* 2017;22(8) (PMID: 28749443).
- Frederick ED, Hausburg MA, Thomas GW, Rael LT, Brody E, Bar-Or D. The low molecular weight fraction of human serum albumin upregulates COX2, prostaglandin E2, and prostaglandin D2 under inflammatory conditions in osteoarthritic knee synovial fibroblasts. *Biochem Biophys Rep* 2016 Aug 12;8:68-74 (PMID: 28955943).
- Dima A, Opris D, Jurcut C, Baicus C. Is there still a place for erythrocyte sedimentation rate and C-reactive protein in systemic lupus erythematosus? *Lupus* 2016 Oct;25(11):1173-9 (PMID: 27256317).
- Buyon J, Furie R, Putterman C, et al. Reduction in erythrocyte-bound complement activation products and titres of anti-C1q antibodies associate with clinical improvement in systemic lupus erythematosus. *Lupus Sci Med* 2016 Sep 30;3(1):e000165 (PMID: 27752336).
- Littlejohn E, Marder W, Lewis E, et al. The ratio of erythrocyte sedimentation rate to C-reactive protein is useful in distinguishing infection from flare in systemic lupus erythematosus patients presenting with fever. *Lupus* 2018 Jun;27(7):1123-9 (PMID: 29546774).
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40(9):1725 (PMID: 9324032).

25. Amezcua-Guerra LM, Higuera-Ortiz V, Arteaga-Garcia U, Gallejos-Nava S, Hübbe-Tena C. Performance of the 2012 Systemic Lupus International Collaborating Clinics and the 1997 American College of Rheumatology classification criteria for systemic lupus erythematosus in a real-life scenario. *Arthritis Care Res (Hoboken)* 2015 Mar;67(3):437-41 (PMID: 25073545).
26. Hartman E, van Royen-Kerkhof A, Jacobs J, Welsing PMJ, Fritsch-Stork RDE. Performance of the 2012 Systemic Lupus International Collaborating Clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-analysis. *Autoimmun Rev* 2018 Mar;17(3):316-22 (PMID: 29366725).
27. Cerovec M, Anic B, Padjen I, Cikes N. Prevalence of the American College of Rheumatology classification criteria in a group of 162 systemic lupus erythematosus patients from Croatia. *Croat Med J* 2012 Apr;53(2):149-54 (PMID: 22522993).
28. Spinella R, Sawhney R, Jalan R. Albumin in chronic liver disease: structure, functions and therapeutic implications. *Hepatol Int* 2016 Jan;10(1):124-32 (PMID: 26420218).
29. Sato JO, Corrente JE, Saad-Magalhaes C. Correlation between the Modified Systemic Lupus Erythematosus Disease Activity Index 2000 and the European Consensus Lupus Activity Measurement in juvenile systemic lupus erythematosus. *Lupus* 2016 Nov;25(13):1479-84 (PMID: 27230556).
30. Gladman DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002 Feb;29(2):288-91 (PMID: 11838846).
31. Touma Z, Urowitz MB, Taghavi-Zadeh S, Ibañez D, Gladman DD. Systemic lupus erythematosus disease activity Index 2000 Responder Index 50: sensitivity to response at 6 and 12 months. *Rheumatology (Oxford)* 2012 Oct;51(10):1814-9 (PMID: 2271868).
32. Touma Z, Urowitz MB, Gladman DD. Systemic lupus erythematosus disease activity index 2000 responder index-50 website. *J Rheumatol* 2013;40(5):733 (PMID: 23637378).
33. Stanescu II, Calenic B, Dima A, et al. Salivary biomarkers of inflammation in systemic lupus erythematosus. *Ann Anat* 2018 Sep;219:89-93 (PMID: 29621567).
34. Goodnow CC. Multistep pathogenesis of autoimmune disease. *Cell* 2007 Jul 13;130(1):25-35 (PMID: 17632054).
35. Wu S, Zhou Y, Hua H Y, et al. Inflammation marker ESR is effective in predicting outcome of diffuse large B-cell lymphoma. *BMC Cancer* 2018 Oct 19;18(1):997. (PMID: 30340560).
36. Delongui F, Lozovoy MAB, Iriyoda TMV, et al. C-reactive protein +1444CT (rs1130864) genetic polymorphism is associated with the susceptibility to systemic lupus erythematosus and C-reactive protein levels. *Clin Rheumatol* 2017 Aug;36(8):1779-88 (PMID: 28567557).
37. Mittal S, Agarwal P, Wakhlu A, Kumar A, Mehrotra R, Mittal S. Anaemia in Systemic Lupus Erythematosus Based on Iron Studies and Soluble Transferrin Receptor Levels. *J Clin Diagn Res* 2016 Jun;10(6):EC08-11 (PMID: 27504292).
38. Hartmann LT, Alegretti AP, Machado ABMP, et al. Assessment of Mean Platelet Volume in Patients with Systemic Lupus Erythematosus. *Open Rheumatol J* 2018 Aug 31;12:129-38 (PMID: 30258502).
39. Uyar S, Abanonu GB, Pehlevan SM, et al. Elevated beta-thromboglobulin and mean platelet volume levels may show persistent platelet activation in systemic lupus erythematosus patients. *Adv Clin Exp Med* 2018 Sep;27(9):1279-83 (PMID: 29790695).
40. Zhao CN, Mao YM, Wang P, et al. Lack of association between mean platelet volume and disease activity in systemic lupus erythematosus patients: a systematic review and meta-analysis. *Rheumatol Int* 2018 Sep;38(9):1635-41 (PMID: 29845430).
41. Soliman WM, Sherif NM, Ghanima IM, El-Badawy MA. Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Systemic Lupus Erythematosus: Relation With Disease Activity and Lupus Nephritis. *Reumatol Clin* 2018 (PMID: 30166230).
42. Kim HA, Jung JY, Suh CH. Usefulness of neutrophil-to-lymphocyte ratio as a biomarker for diagnosing infections in patients with systemic lupus erythematosus. *Clin Rheumatol* 2017 Nov;36(11):2479-85 (PMID: 28840341).
43. Malaer JD, Marrufo AM, Mathew PA. 2B4 (CD244, SLAMF4) and CS1 (CD319, SLAMF7) in systemic lupus erythematosus and cancer. *Clin Immunol* 2019 Jul;204:50-6 (PMID: 30347240).
44. Fang L P, Xu X Y, Ji Y, Huang PW. The Prognostic Value of Preoperative Neutrophil-to-Lymphocyte Ratio in Resected Patients with Pancreatic Adenocarcinoma. *World J Surg* 2018 Nov;42(11):3736-45 (PMID: 30014292).
45. Grieshober L, Graw S, Barnett MJ, et al. Methylation-derived Neutrophil-to-Lymphocyte Ratio and Lung Cancer Risk in Heavy Smokers. *Cancer Prev Res (Phila)* 2018 Nov;11(11):727-34 (PMID: 30254071).
46. Grilz E, Posch F, Konigsbrugge O, et al. Association of Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio with the Risk of Thromboembolism and Mortality in Patients with Cancer. *Thromb Haemost* 2018 Nov;118(11):1875-84 (PMID: 30296815).