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Serum Amyloid A: A Potential Biomarker Assessing Disease Activity in Systemic Lupus Erythematosus

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to investigate the association between levels of serum amyloid A (SAA) and the activity of systemic lupus erythematosus (SLE).

Material/Methods: The study included 135 patients with SLE, including 52 patients with active SLE and 83 patients with inactive SLE and 149 healthy controls. The degree of activity of SLE was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K). Serum SAA levels were measured using a Cobas 8000 c702 modular analyzer.

Results: The levels of SAA were significantly increased in patients with active SLE compared with patients with inactive SLE (median IQR, 16.65 mg/L; range, 9.35–39.68 mg/L, and median IQR, 2.30 mg/L, range, 1.30–4.80 mg/L) ($p<0.001$). Levels of SAA were significantly correlated with the SLEDAI-2K scores, the erythrocyte sedimentation rate (ESR), and hypersensitive C-reactive protein (Hs-CRP) in patients with SLE ($r=0.726$, $p<0.001$; $r=0.631$, $p<0.001$; $r=0.774$, $p<0.001$, respectively). Multivariate logistic regression analysis showed that the SAA values were independently associated with active SLE when controlled for white blood cell (WBC) count, red blood cell distribution width (RDW), ESR, and Hs-CRP (OR=1.772; $p=0.01$; 95% CI, 1.101–2.851). Receiver operating characteristic (ROC) curve analysis for SAA was used to identify patients with active SLE with an area under the curve of 0.971, a sensitivity of 90.4%, and a specificity of 94.0%.

Conclusions: SAA levels were significantly correlated with disease activity in patients with SLE.

MeSH Keywords: Biological Markers • Lupus Vasculitis, Central Nervous System • Serum Amyloid A Protein

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, which results in multiple organ dysfunction [1,2]. SLE is characterized by the loss of immune tolerance to nuclear and cytoplasmic autoantigens, and is a common disease with an incidence of 1.4–24.0 per 100,000 person-years worldwide and predominantly affects women [1,2]. The evaluation of disease activity in patients with SLE mainly depends on laboratory testing, which is used to evaluate disease progression and the prognosis of patients with SLE. Previous studies have shown an association between the activity of SLE and some laboratory parameters, including interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) [3–5]. Recently, Hu et al. reported that increased red blood cell distribution width (RDW) was strongly correlated with SLE disease activity, indicating that RDW may be a useful inflammatory biomarker [6]. Also, a relationship between procalcitonin levels and the activity of SLE has previously been reported [7,8].

Serum amyloid A (SAA) has recently been identified as a novel inflammatory indicator that is significantly increased in patients with conditions including idiopathic pulmonary fibrosis, Familial Mediterranean Fever, and neonatal septicemia [9–11]. Also, increased levels of SAA have been reported in lung disorders that include chronic obstructive pulmonary disease (COPD), radiation pneumonitis, obstructive sleep apnea (OSA) syndrome, and lung cancer [12]. These previous findings indicate that this SAA may be an acute-phase protein with a role as a prognosis indicator [12]. Increased serum concentrations of SAA have been reported to be associated with rheumatoid arthritis, indicating that SAA may be an important biomarker in assessing the degree of inflammation in rheumatoid arthritis [13]. However, an association between SAA and SLE disease activity has not been previously determined. Therefore, this study aimed to investigate the association between levels of SAA and the activity of SLE.

Material and Methods

Study participants and study design

A total of 135 patients with systemic lupus erythematosus (SLE) and 149 healthy individuals were enrolled in this study. This study was approved by the Ethics Committee of the Affiliated Hospital of Guilin Medical University. Informed consent was obtained from the study participants. The SLE Disease Activity Index 2000 (SLEDAI-2k) scores were used to evaluate the activity of SLE in the patients [14]. The American College of Rheumatology (ACR) criteria were used to diagnose all patients with SLE [15]. Patients with co-morbidities, such as diabetes, hypertension, known liver disease, end-stage renal disease, hematological disorders, malignant tumors, and other systemic autoimmune diseases, were excluded from the study.

Laboratory investigations

The white blood cell (WBC) count, the platelet count, the red blood cell (RBC) count, hemoglobin level, hypersensitive C-reactive protein (Hs-CRP), red blood cell distribution width (RDW), erythrocyte sedimentation rate (ESR), and the serum amyloid A (SAA) levels of patients with SLE were retrospectively acquired from the electronic medical record. Complete blood counts were measured by using a Sysmex XN900 automated hematology analyzer (Sysmex, Kobe, Hyogo, Japan).

Statistical analysis

The normality of the distribution of continuous variables was analyzed using the Shapiro-Wilk test. Categorical variables were presented as counts and were compared using the chi-squared (χ^2) test. Continuous variables with a normal distribution were expressed as the mean±standard deviation (SD) and were compared using Student's t-test. Continuous variables with a non-normal distribution were presented as the median and interquartile range (IQR) and were compared using the Mann-Whitney U test. Spearman's rank correlation coefficient was used for correlation analysis. The least absolute shrinkage and selection operator (LASSO) method was utilized to select the key variables from the patients with SLE. Variables with non-zero coefficients, which were selected from the LASSO regression model, were entered into binary logistic regression analysis. The performance of SAA was evaluated by receiver operating characteristics (ROC) curve analysis. Statistical analysis was performed using SPSS version 16.0 (IBM, Chicago, IL, USA), MedCalc version 15.0, and R software version 3 .6.1 (*https://www.R-project.org*). P-values <0.05 indicated statistical significance.

Results

Patients with systemic lupus erythematosus (SLE) and healthy controls

A comparison of the demographic characteristics and clinical laboratory parameters between patients with SLE and healthy individuals is shown in Table 1. There were several significant differences between the two groups. The red blood cell (RBC) and platelet counts and the hemoglobin levels were significantly lower in the patients with SLE compared with the controls. In contrast with the controls, the levels of the red blood cell distribution width (RDW) and hypersensitive C-reactive protein (Hs-CRP) were higher in patients with SLE. The other laboratory parameters were not significantly different between patients with SLE and healthy controls.

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Table 1. Demographic characteristics and laboratory parameters of patients with systemic lupus erythematosus (SLE) and healthy individuals.

	Patients with SLE n=135	Healthy Controls n=149	P-value
Gender (Male/Female)	14/121	22/127	0.266
Age (years)	38.0 (29.0–47.0)	34.0 (26.0–44.0)	0.085
WBC (10^9/L)	5.90 (3.98–9.24)	6.68 (5.56–7.74)	0.059
RBC (10^{12}/L)	4.10±0.67	4.54±0.37	<0.001
Platelet count (10^9/L)	224.56±91.09	250.35±37.89	0.003
Hemoglobin (g/L)	116.0 (105.0–125.0)	133.0 (128.0–140.0)	<0.001
RDW (%)	13.80 (12.90–15.90)	12.20 (11.85–12.60)	<0.001
Hs-CRP (mg/L)	2.35 (0.44–7.71)	0.67 (0.58–0.99)	<0.001
ESR (mm/h)	18.0 (11.0–35.0)	–	–
SAA (mg/L)	4.90 (1.90–12.00)	–	–
SLEDAI-2k scores	7.0 (5.0–15.0)	–	–

WBC – white blood cell count; RBC – red blood cell; RDW – red blood cell distribution width; Hs-CRP – hypersensitive C-reactive protein; ESR – erythrocyte sedimentation rate; SAA – serum amyloid A; SLEDAI-2K – SLE Disease Activity Index 2000.

Table 2. Demographic and laboratory parameters in patients with systemic lupus erythematosus (SLE) with active disease and inactive disease.

	Patients with active SLE (n=52)	Patients with inactive SLE (n=83)	P-value
Gender (Male/Female)	6/46	8/75	0.725
Age (years)	38.1±13.9	38.2±13.0	0.978
WBC (10^9/L)	6.62 (4.33–10.22)	5.31 (3.82–9.00)	0.132
RBC (10^{12}/L)	4.01±0.65	4.16±0.68	0.210
Platelet count (10^9/L)	218.00 (153.50–302.50)	225.00 (166.00–274.00)	0.917
Hemoglobin (g/L)	111.0 (97.8–119.8)	119.0 (109.0–128.0)	0.019
RDW (%)	14.25 (13.20–17.08)	13.20 (12.60–14.80)	0.001
Hs-CRP (mg/L)	9.31 (6.14–24.04)	0.74 (0.27–1.82)	<0.001
ESR (mm/h)	49.0 (29.3–74.3)	12.0 (8.0–17.0)	<0.001
SAA (mg/L)	16.65 (9.35–39.68)	2.3 0 (1.30–4.80)	<0.001

WBC – white blood cell count; RBC – red blood cell; RDW – red blood cell distribution width; Hs-CRP – hypersensitive C-reactive protein; ESR – erythrocyte sedimentation rate; SAA – serum amyloid A.

Serum amyloid A (SAA) and the activity of SLE

All patients with SLE were classified into an active SLE group and an inactive SLE group, as shown in Table 2. There were no significant differences between the active SLE group and the inactive SLE group in terms of gender, age, white blood cell (WBC) counts, RBC counts, and platelet counts. The SAA levels were significantly higher in patients with active SLE compared with the patients with inactive SLE (Figure 1). Also, the RDW, Hs-CRP, and ESR levels were significantly higher in patients with active SLE compared with patients with inactive SLE. The hemoglobin levels in patients with active SLE were significantly lower than

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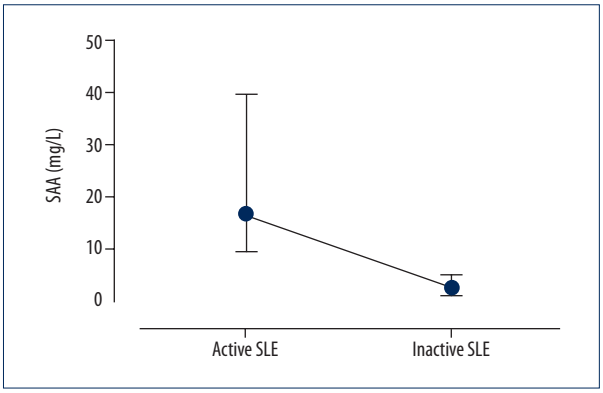

Figure 1. Serum amyloid A (SAA) in patients with active systemic lupus erythematosus (SLE) and patients with inactive SLE. P<0.001, Mann-Whitney U test.

those in patients with inactive SLE. The results of the correlation analysis showed that the SAA level was significantly correlated with WBC, RDW, ESR, and Hs-CRP in patients with SLE (r=0.230, p=0.007, r=0.280, p=0.001, and r=0.631, p<0.001 and r=0.774, p<0.001, respectively). SAA levels were significantly correlated with the SLE Disease Activity Index 2000 (SLEDAI-2K) scores in patients with SLE (r=0.726, p<0.001).

Parameter selection and binary logistic regression analysis

Based on the parameters with non-zero coefficients in the least absolute shrinkage and selection operator (LASSO) regression model, nine variables were reduced to five potential predictors of disease activity (Figure 2A, 2B). All potential predictors, including WBC, RDW, Hs-CRP, ESR, and SAA, were further analyzed using binary logistic regression analysis. The results of the explanatory covariables for the logistic regression analysis of WBC, RDW, Hs-CRP, ESR, and SAA are shown in Table 3. SAA was independently associated with active SLE when logistic regression analysis was conducted to detect potential variables associated with active SLE (OR=1.772; 95% CI, 1.101–2.851; p=0.01). The receiver operating characteristic (ROC) curve analysis of the SAA levels was performed to identify patients with active SLE, and the cut-off value for SAA was 7.2, with a sensitivity of 90.4% and a specificity of 94.0%. The area under the ROC curve (AUC) for SAA was calculated as 0.971 (95% CI, 0.926–0.992; p<0.001) (Figure 3).

Discussion

The aim of this study was to investigate the association between levels of serum amyloid A (SAA) and the activity of systemic lupus erythematosus (SLE). The findings showed that SAA values increased in patients with active SLE compared with inactive SLE patients. Also, SAA was positively correlated with the SLE Disease Activity Index 2000 (SLEDAI-2K) scores in patients with SLE. Multivariate logistic regression analysis showed that the serum levels of SAA were independently associated with SLE activity.

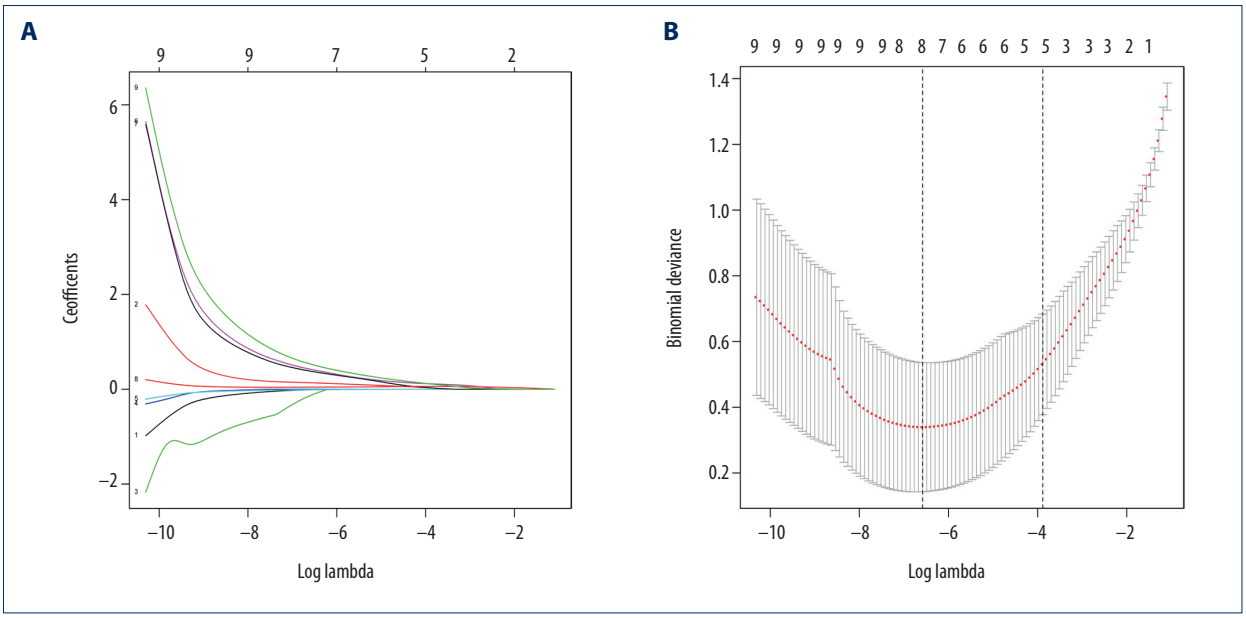

Figure 2. Selection of laboratory parameters by the least absolute shrinkage and selection operator (LASSO) binary logistic regression model. (**A**) The optimal parameter was selected based on fivefold cross-validation in the LASSO model. (**B**) LASSO coefficient profiles of the nine features. A coefficient profile plot was produced against the log (lambda) sequence. Fivefold cross-validation was used to draw a vertical line at the selected value, where optimal lambda identified five variables with non-zero coefficients. LASSO, least absolute shrinkage, and selection operator.

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Table 3. The potential factors associated with active systemic lupus erythematosus (SLE) evaluated by binary logistic regression analysis.

Variables	OR	95% CI	P-value
WBC (10^9/L)	1.006	0.651–1.555	0.980
RDW (%)	1.396	0.956–2.032	0.082
ESR (mm/h)	1.051	1.003–1.102	0.037
Hs-CRP (mg/L)	1.689	1.062–2.688	0.027
SAA (mg/L)	1.772	1.101–2.851	0.01

OR – odds ratio; CI – confidence interval; WBC – white blood cell; RDW – red blood cell distribution width; ESR – erythrocyte sedimentation rate; Hs-CRP – hypersensitive C-reactive protein; SAA – serum amyloid A.

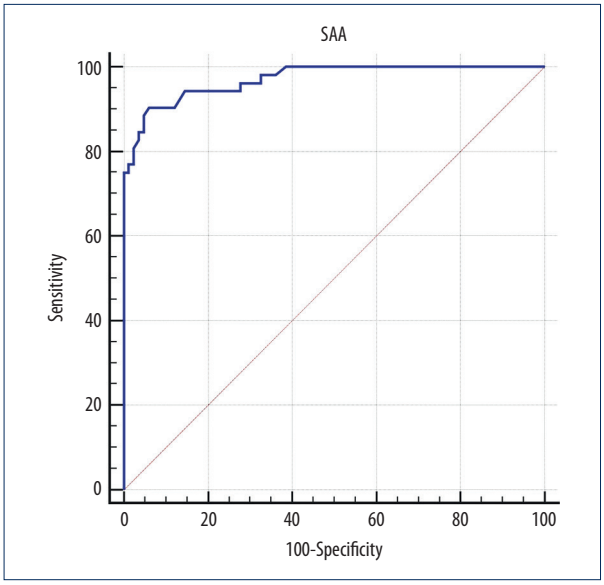

Figure 3. The receiver operating characteristics (ROC) curve analysis of serum amyloid A (SAA) to identify patients with active systemic lupus erythematosus (SLE). The sensitivity of SAA levels for the detection of the activity of SLE was 90.4%, and the specificity was 94.0%, with the area under the ROC curve (AUC) of 0.971(95% CI, 0.926–0.992; p<0.001).

The rapid, sensitive, and specific evaluation of disease activity in patients with SLE are important for short-term and long-term treatment planning. Previous studies have shown that inflammatory factors, including tumor-necrosis factor-α (TNF-α), complement C3, complement C4, the mean platelet volume, the neutrophil to lymphocyte ratio, IL-6, and IF-34, were associated with the severity of SLE [3,16–19]. The findings from these previous studies support that inflammatory cytokines play an essential role in the pathogenesis and etiology of SLE.

Recently, SAA has been shown to be a novel inflammatory factor found in several diseases, including rheumatoid arthritis, neonatal septicemia, and diabetic kidney disease [11,13,20]. Hwang et al. [21] reported that an increased SAA level was associated with disease activity in patients with rheumatoid arthritis and was a better indicator of disease activity than C-reactive protein (CRP). A previous study identified SAA as a key biomarker in proinflammatory and proatherogenic disease activity and involved in atherosclerosis development [22]. In another study, the level of SAA was found to be significantly higher in women with polycystic ovary syndrome (PCOS) than in controls [23]. In a case-control study undertaken by Dev et al. [24], serum SAA levels were significantly increased in patients with juvenile idiopathic arthritis compared with healthy controls. Also, increased SAA levels have been associated with pulmonary infections in patients with SLE [25]. Consistent with these previous findings, the findings from the present study showed that SAA values were significantly higher in patients with active SLE than in patients with inactive SLE. The level of SAA was independently associated with disease activity in patients with SLE. In other studies, a strong association between increased SAA values and CRP, ESR, and the percentage of peripheral CD4+ lymphocytes has been shown in patients with polycystic ovary syndrome (PCOS), juvenile idiopathic arthritis, and lung transplantation with acute rejection [23,24,26]. The findings from the present study also showed that increased SAA levels were significantly associated with ESR, Hs-CRP, and SLEDAI-2k scores in patients with SLE.

However, this study had several limitations. This study included a small sample size, especially for patients with active SLE. Second, the SAA concentrations were not evaluated in patients with SLE undergoing treatment with anti-inflammatory drugs. The degree of SLE activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) in this study, but other inflammatory cytokines, such as IF-34, TNF-α, and IL-6, should also be considered in assessing disease activity in future studies.

Conclusions

This study aimed to investigate the association between levels of serum amyloid A (SAA) and the activity of systemic lupus erythematosus (SLE). SAA levels were significantly correlated with disease activity in patients with SLE, with SAA levels significantly associated with active SLE at a sensitivity of 90.4% and a specificity of 94.0%. Therefore, the measurement of SAA may be a useful and cost-effective biomarker to evaluate disease activity in patients with SLE.

Conflict of interest

None.

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