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Review Article

Serum lnc-DC and SOCS1 can be used as potential indicators for diagnosis and prognosis prediction of patients with systemic lupus erythematosus

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Abstract: This study aimed to investigate the diagnostic and prognostic value of serum lnc-DC and SOCS1 in patients with systemic lupus erythematosus (SLE). A total of 130 SLE patients admitted to the First Affiliated Hospital of Jinan University, were selected as SLE group, which were divided into active phase (n=78) and stationary phase (n=52). Meanwhile, 125 healthy persons who underwent physical examination at the same time were selected as control group (CG), and their clinical related indexes (C-reactive protein (CRP), complement C3, C4, anti-ds-DNA antibody (Anti-ds-DNA), immunoglobulin G (IgG), ESR, activity index (SLEDAI) score of systemic lupus erythematosus and correlation were detected. The serum lnc-DC and SOCS1 expression levels in SLE were dramatically lower than those in CG ($P < 0.05$), and the two in active patients in SLE group were dramatically lower than those in stable patients ($P < 0.05$). They can be used to diagnose SLE and distinguish active and stationary phases of SLE patients. Pearson analysis revealed that they were positively correlated with C3 and C4 of SLE patients, and obviously negatively correlated with IgG, CRP, ESR, Anti-ds-DNA and SLEDAI scores. After follow-up investigation, 39 SLE patients relapsed, with a relapse rate of 30.00%. The serum lnc-DC and SOCS1 of relapse patients were markedly lower than those of patients without relapse ($P < 0.05$). Those can be used to predict the recurrence of prognosis. Pearson analysis showed that serum lnc-DC and SOCS1 were remarkably positively correlated in active and stable SLE patients ($P < 0.001$). lnc-DC and SOCS1 are correlated in SLE, which can be used as biomarkers for diagnosis and prognosis prediction. And they have high research value in clinical practice.

Keywords: lnc-DC, SOCS1, systemic lupus erythematosus, diagnosis, prognosis

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with high heterogeneity. It is characterized by repeated attacks and alternate relief. Its clinical manifestations are mainly multi-system damages, including nervous system, cardiovascular system, respiratory system, skin diseases, etc. [1, 2]. It is more prevailing in women, and its death risk is three times that of ordinary people [3]. In Britain, 4.91 out of 100,000 people are sick every year and 97 out of 100,000 people are sick [4]. Serology of SLE is diversified clinically, and its immune pathogenicity abnormalities are constantly discovered. The clinical manifestations of individual patients are quite different and latent, which makes its diagnosis difficult [5]. At present, the SLE treatment mainly relies on non-steroidal anti-inflammatory drugs, glucocorticoids, hydroxychloroquine and immunosuppressive agents, which improves its prognosis greatly [6]. However, because the disease is easy to relapse and there are many adverse reactions to treatment, it is extremely crucial to find suitable biomarkers to improve SLE diagnosis and prognosis.

Circulating RNA in plasma or serum has become a new field of noninvasive diagnosis. Relevant studies have shown that long-chain non-coding RNA (lncRNA) is relatively stable in human plasma and can be used for diagnosis of various diseases [7, 8]. lnc-DC is a kind of lncRNA; it has been found that it can be expressed in dendritic cells (DC) and can mediate DC maturation through phosphorylated transcripts 3 and transcriptional activators

(STAT3) [9]. And the latest research shows that serum lnc-DC can be used as a potential biomarker for diagnosing multiple sclerosis [10]. Nevertheless, there is little research on serum lnc-DC in SLE. Suppressor of cytokine signaling 1 (SOCS1) is an inhibitor induced by relevant cytokines, which negatively regulates immune response by inhibiting the activity of JAK2 [11]. It is involved in the occurrence and development of various diseases. Relevant literature reports that it participates in the pathological process of SLE diseases, including the production of proinflammatory factors, activation of immune cells, occurrence of renal fibrosis and other processes [12]. But, whether lnc-DC and SOCS1 can be used as prognostic predictors of SLE still needs further research.

This study mainly explores the diagnostic and predictive value of lnc-DC and SOCS1 to SLE patients by examining their contents in serum, and analyzes the correlation between them.

Materials and methods

General data collection

A total of 130 SLE patients admitted to the First Affiliated Hospital of Jinan University, from November 2016 to April 2018 were selected as the research subjects, and they were divided into two subgroups according to the activity index (SLEDAI) score [13] of systemic lupus erythematosus. Seventy-eight patients with SLEDAI score > 10 were in active phase, with an average age of (40.12±4.89) years and course of disease of (30.09±4.34) months. There were 52 patients with SLEDAI score ≤ 10 in stationary phase, with an average age of (39.87±5.98) years and course of disease of (29.87±4.11) months. Concurrently, 125 healthy persons who underwent physical examination at the same time were selected as the control group (CG), with an average age of (39.67±5.63) years. Inclusion criteria: those met SLE diagnostic criteria in the Systemic Lupus International Collaborating Clinics/the American College of Rheumatology (SLICC/ACR); those had good compliance, those were able to communicate in normal language; those were accompanied by their family when admitted to hospital. Exclusion criteria: those were complicated with other malignancies; those had a history of mental illness; those were unwilling to cooperate with the investigation.

The research was approved by the ethics committee. The patients and their families were informed in advance, and they agreed and signed informed consent forms.

Detection of serum lnc-DC and SOCS1

Early in the morning after admission, fasting venous peripheral blood was extracted from SLE patients and subjects in the CG, each 5 mL, and the contents of lnc-DC and SOCS1 mRNA in each group were detected by real-time fluorescence quantitative PCR (qRT-PCR). Total RNA was drawn based on the instructions of Trizol kit (Invitrogen), and the purity and concentration was measured by ultraviolet spectrophotometer (Beijing UP General Technology Co., Ltd.). It was then reverse transcribed into cDNA according to PrimeScript™ RT kit (Takara Bio Inc., Japan). Then, PCR experiments were conducted on ABI PRISM 7300 system (Applied Biosystems) using SYBR®Premix Ex Taq™ II (Takara Bio Inc.). PCR reaction conditions were as below: 95°C for 1 min, 95°C for 10 sec, 60°C for 30 sec, 72°C for 1 min, a total of 42 cycles. The primer sequence was designed and synthesized by Guangzhou Ribo Biotechnology Co., Ltd. The internal reference adopted GAPDH, SOCS1: F: 5'-ACCCCTCTCCCTTTGA-3', R: 5'-ATAAGCCAGACCCTCC-3'. LNC-DC: F: 5'-GAAACCTCTCCTGG-3', R: 5'-GAAACCTCTTCCCTGG-3', GAPDH: F: 5'-GGGAAACCTGTGGCGTGA3', R: 5'-GAGGTGTGTGTGTGTGTGTGTGGA-3'. Finally, the content was calculated by $2^{-\Delta\Delta Ct}$.

Detection of clinical indicators

The levels of serum C-reactive protein (CRP), complement C3 and C4 were detected by IMMAGE 800 automatic protein analyzer (Beckman Coulter, Fullerton, CA, USA). The concentration of plasma anti-dsDNA antibody (Anti-dsDNA) and immunoglobulin G (IgG) was determined by enzyme-linked immunosorbent assay (ELISA). The ESR was measured by Wechsler natural sedimentation method.

Statistical treatment

The experimental data were analyzed via SPSS 20.0 (IBM Corp., Armonk, NY, USA), and pictures were drawn via GraphPad 6. The counting data were expressed as [n (%)], and inter-group comparison was under chi-square test. The measurement data were expressed as (means

Table 1. Comparison of general clinical data per group

	SLE group			χ^2/F	P
	Active phase (n=78)	Stationary phase (n=52)	Control group (CG) (n=125)		
Gender				4.492	0.106
Female	51 (65.38)	39 (75.00)	73 (58.40)		
Male	27 (34.62)	13 (25.00)	52 (41.60)		
Average age (years)	40.12±4.89	39.87±5.98	39.67±5.63	0.162	0.851
BMI (kg/m^2)	23.17±2.76	22.98±2.18	22.87±2.39	0.354	0.702
Course of disease (month)	30.09±4.34	29.87±4.11	-	0.289	0.773
IgG (g/L)	20.18±7.87*	16.29±7.32	9.76±4.34	70.180	< 0.001
C3 (g/L)	0.60±0.22*	0.98±0.27	1.23±0.43	79.090	< 0.001
C4 (g/L)	0.18±0.09*	0.31±0.13	0.43±0.18	69.270	< 0.001
CRP (mg/L)	14.09±5.02*	10.28±4.12	3.68±1.78	216.030	<0.001
ESR (mm/h)	45.45±12.23*	40.09±10.11	9.87±3.10	507.190	< 0.001
Anti-ds-DNA (IU/ml)	302.28±71.28*	241.28±64.38	37.28±9.28	781.750	< 0.001
SLEDAI (score)	14.67±2.42*	7.57±2.13	-	17.180	< 0.001

Note: *indicates comparison with stationary phase (*P < 0.05).

± SD), and multi-group analysis adpoted one-way analysis of variance. LSD-t test was used for post-event analysis, Pearson analysis was used for analysis of correlation of variables between both groups, and ROC was used for evaluating diagnostic or predictive value of indexes. P<0.05 indicates that the difference was statistically marked.

Results

Comparison of clinical general data

The basic clinical data of subjects in each group were collected, as shown in **Table 1**. There was no obvious difference in gender, average age and body mass index (BMI) between SLE group and CG (P > 0.05). Immunoglobulin G (IgG), CRP, ESR and Anti-ds-DNA in SLE group were remarkably higher than those in the CG (P < 0.001), while C3 and C4 were lower than those in the CG (P < 0.001). The IgG, CRP, ESR, Anti-ds-DNA and SLEDAI scores of active patients in SLE group were remarkably higher than those of stable patients, and C3 and C4 were lower than those of stable patients, with statistically obvious difference (P < 0.05).

Expression and diagnostic value of serum lnc-DC and SOCS1 in SLE

According to PCR detection, the serum lnc-DC and SOCS1 expression levels in SLE were remarkably lower than those in the CG (P < 0.05), and the serum lnc-DC and SOCS1 in active patients in the SLE group were remarkably lower than those in stable patients (P < 0.05) (**Figure 1**). The two could be used to diagnose SLE and distinguish active and stationary phases of SLE patients. More details were shown in **Table 2**.

Correlation between serum lnc-DC and clinical indicators

The correlation between serum lnc-DC and clinical indicators was observed under Pearson analysis (**Figure 2**), and serum lnc-DC was positively correlated with C3 and C4 of SLE patients (r=0.4431, 0.3877, P < 0.001). However, it was dramatically negatively correlated with SLE patients' IgG, CRP, ESR, Anti-ds-DNA and SLEDAI scores (r=-0.4026, -0.5379, -0.4119, -0.7413, -0.5259, P < 0.001).

Correlation between serum SOCS1 and clinical indicators

The correlation between serum SOCS1 and clinical indicators was observed under Pearson analysis (**Figure 3**), and serum SOCS1 was positively correlated with C3 and C4 of SLE patients (r=0.3987, 0.4602, P < 0.001). Nevertheless, it was dramatically negatively correlated with IgG, CRP, ESR, Anti-ds-DNA and SLEDAI scores of SLE patients (r=-0.4311, -0.4979, -0.4703, -0.7543, -0.5441, P < 0.001).

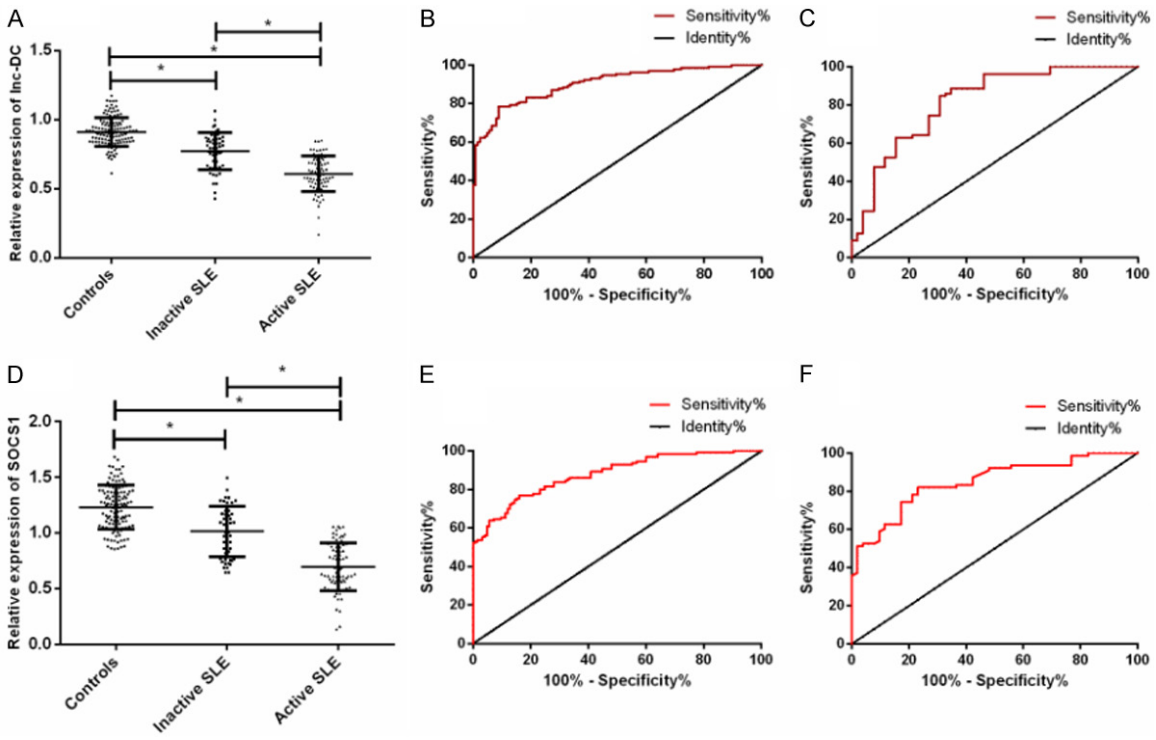

Figure 1. Expression and diagnostic value of serum lnc-DC and SOCS1 in SLE. A: Expression of LNC-DC in CG, SLE active and stationary phases. B: Diagnosis of SLE and normal persons by serum lnc-DC. C: Diagnosis of serum lnc-DC for SLE patients in active and stationary phases. D: Expression of SOCS1 in the CG, active and stationary phases of SLE. E: Diagnosis of SLE and normal persons by serum SOCS1. F: Diagnosis of serum SOCS1 in active and stationary phases of SLE patients. Note: *indicates the comparison between the two groups (*P < 0.05).

Table 2. ROC parameters

	AUC	95% CI	S.E	Cut-off	Sensitivity (%)	Specificity (%)
SLE-normal distinction						
lnc-DC	0.903	0.866-0.939	< 0.001	< 0.794	78.46%	91.20%
SOCS1	0.878	0.837-0.919	< 0.001	< 1.029	76.92%	84.00%
Distinction between active and stationary phases						
lnc-DC	0.818	0.742-0.895	< 0.001	< 0.741	84.62%	69.23%
SOCS1	0.848	0.783-0.913	< 0.001	< 0.867	82.05%	76.92%

Predictive value of serum lnc-DC and SOCS1 for prognosis

After follow-up investigation, 39 SLE patients relapsed, with a relapse rate of 30.00%. As shown in **Figure 4**, the serum lnc-DC and SOCS1 of patients with relapse were markedly lower than those of patients without relapse (P < 0.05). The serum lnc-DC can be used to predict the recurrence of prognosis (AUC: 0.833, sensitivity: 90.11%, specificity: 61.54%), and SOCS1 can be employed to predict the recurrence of prognosis (AUC: 0.869, sensitivity: 80.22%, specificity: 92.31%).

Correlation between serum lnc-DC and SOCS1

To further explore whether there is correlation between serum lnc-DC and SOCS1, Pearson analysis showed that they are obviously positively correlated in active and stationary phases of SLE patients (P < 0.001) (**Figure 5**).

Discussion

The pathogenesis of SLE is relatively complicated. It is generally believed that on the basis of different genetic susceptibility, under the promotion of environment and virus infection, the body's immune system function is disor-

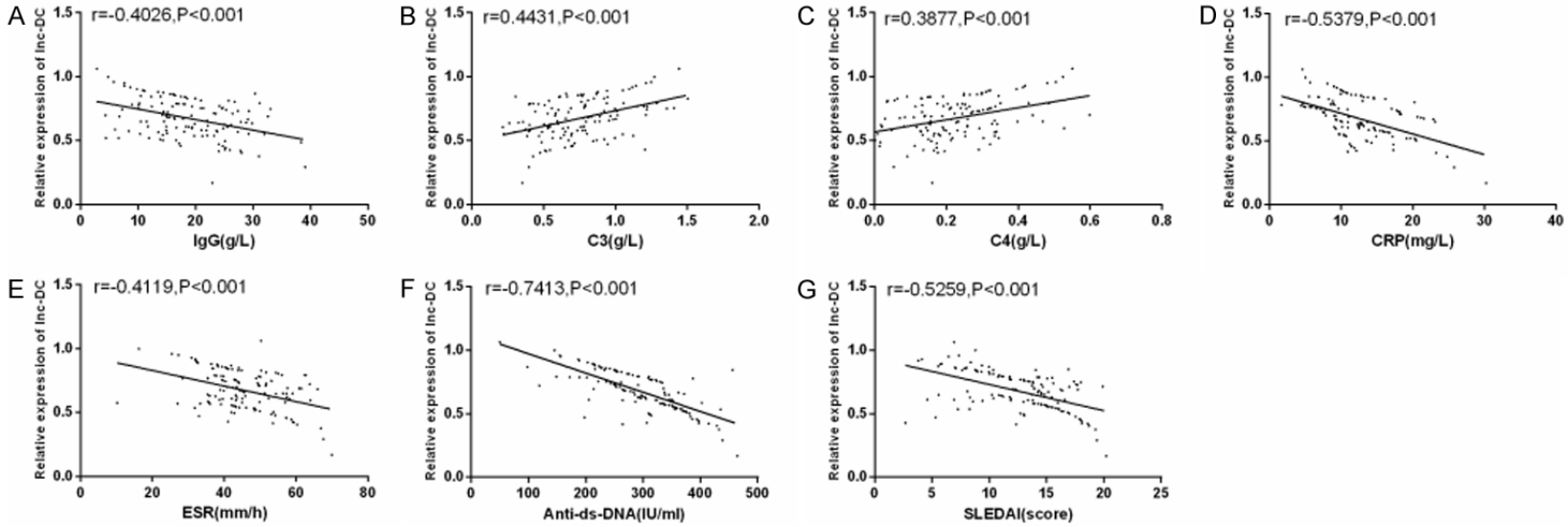

Figure 2. Correlation between serum lnc-DC and clinical indexes. A: Correlation between serum lnc-DC and IgG of SLE patients. B: Correlation between serum lnc-DC and C3 in SLE patients. C: C4 correlation between serum lnc-DC and SLE patients. D: Correlation between serum lnc-DC and CRP in SLE patients. E: ESR correlation between serum lnc-DC and SLE patients. F: Correlation between serum lnc-DC and Anti-ds-DNA of SLE patients. G: Correlation between serum lnc-DC and SLEDAI score of SLE patients.

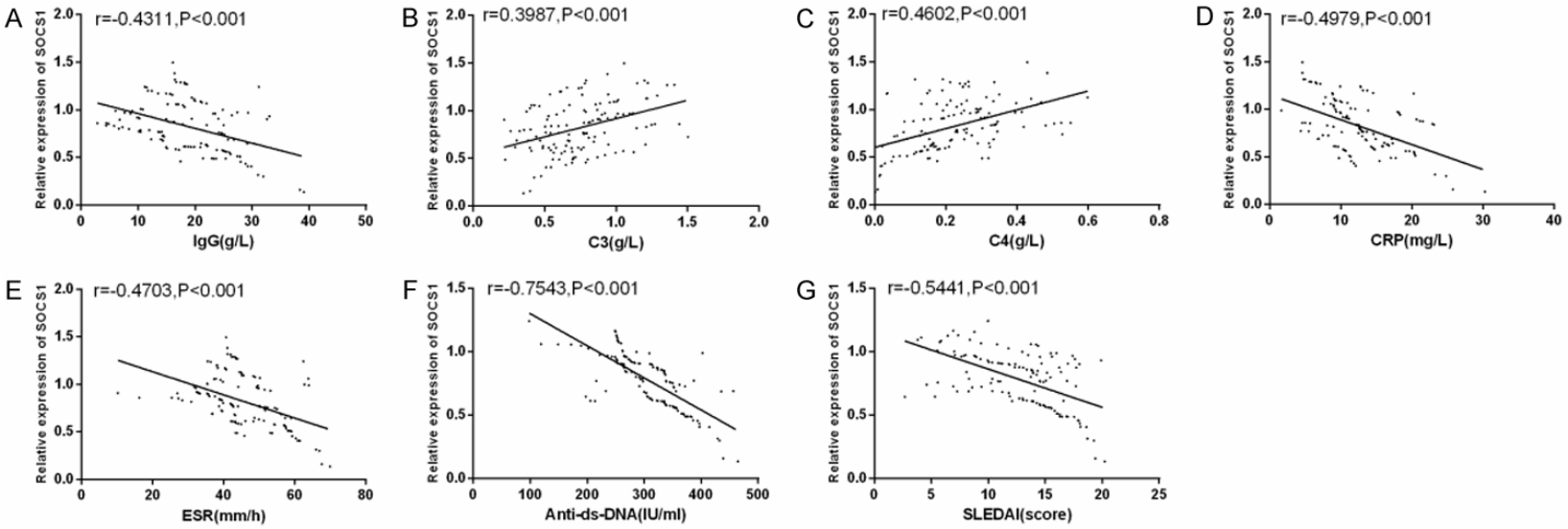

Figure 3. Correlation between serum SOCS1 and clinical indexes. A: Correlation between serum SOCS1 and IgG of SLE patients. B: C3 correlation between serum SOCS1 and SLE patients. C: C4 correlation between serum SOCS1 and SLE patients. D: Correlation between serum SOCS1 and CRP in SLE patients. E: ESR correlation between serum SOCS1 and SLE patients. F: Correlation between serum SOCS1 and Anti-ds-DNA of SLE patients. G: Correlation between serum SOCS1 and SLEDAI score of SLE patients.

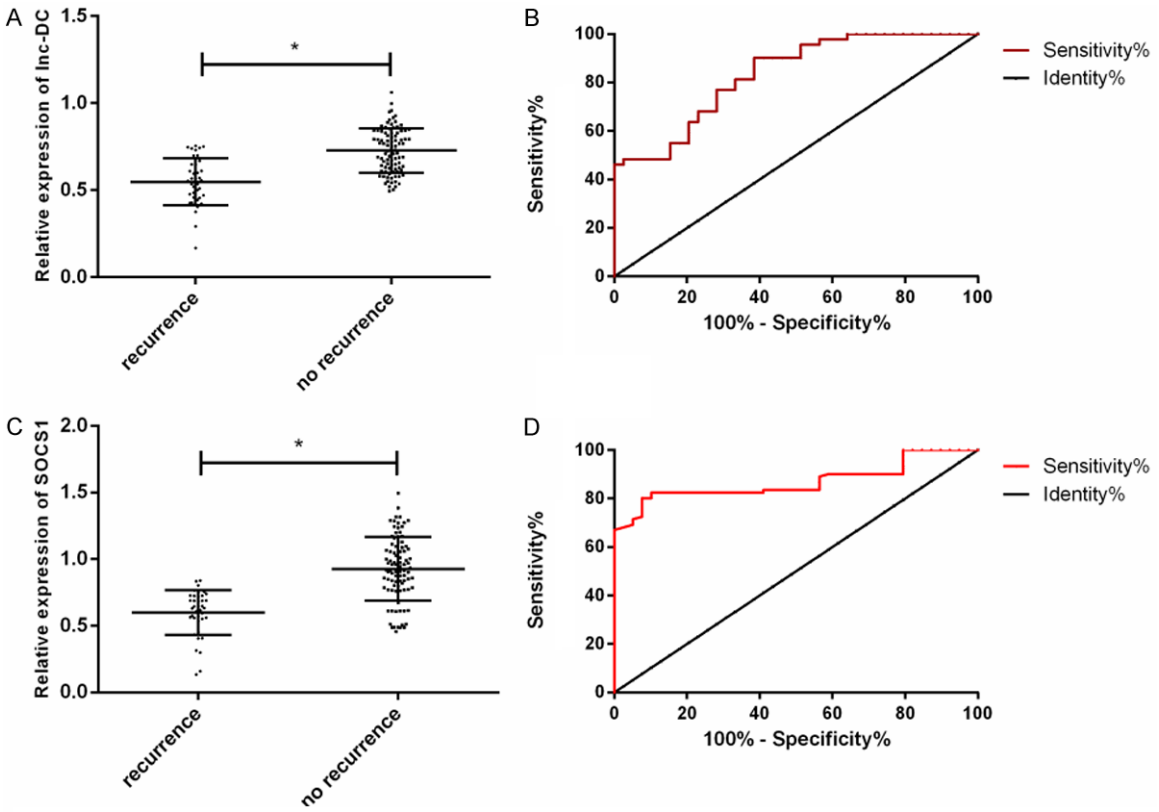

Figure 4. Predictive value of serum lnc-DC and SOCS1 for prognosis. A: LNC-DC expression in SLE patients with relapse and without relapse. B: Predictive value of lnc-DC for relapse in SLE patients. C: SOCS1 expression in SLE patients with relapse and without relapse. D: Predictive value of SOCS1 for relapse of SLE patients. Note: *indicates the comparison between the two groups (*P < 0.05).

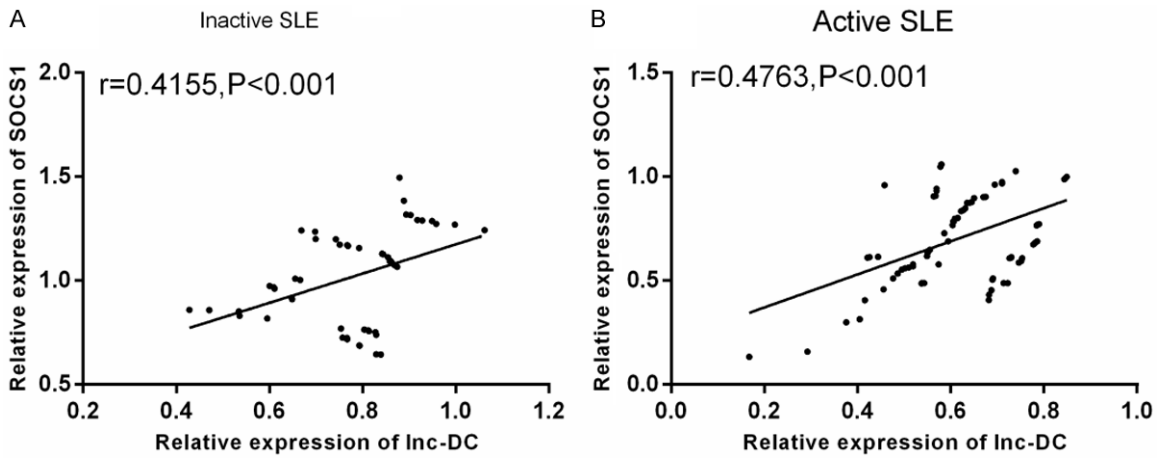

Figure 5. Correlation between serum lnc-DC and SOCS1. A: Correlation between lnc-DC and SOCS1 in active phase of SLE patients. B: Correlation between lnc-DC and SOCS1 in stationary phase of SLE patients.

dered and its immune tolerance is broken, thus causing multisystem lesions [14]. The induction, persistence and progression of the disease are a multi-step process that lasts for a long time and eventually leads to tissue and organ damage [15]. At present, SLE is mainly diagnosed according to clinical symptoms and combined detection of multiple autoantibodies. As the process of disease occurrence is accompanied by a large number of different kinds of autoantibodies and activated immune cells, immune damage will be caused to the whole body tissues and organs [16]. The degree of immune injury can also be used to reflect the disease activity of patients, and the evaluation of activity is the key to subsequent disease judgment and treatment scheme selection [17]. However, the degree of immune injury depends too much on the combined detection of autoantibodies, so there may be a risk of misjudgment.

Current laboratory indicators, such as complement C3, C4, CRP, ESR and Anti-ds-DNA, are commonly used indicators for SLE clinical diagnosis [18, 19]. This study reveals that IgG, CRP, ESR and Anti-ds-DNA in the SLE group are remarkably higher than those in the CG, while C3 and C4 are lower than those in the CG, similar to previous studies. In addition, IgG, CRP, ESR, Anti-ds-DNA and SLEDAI scores of active patients in the SLE group were higher than those in stationary phase, while C3 and C4 were lower than those in stationary phase. As ESR and CRP are sensitive inflammatory indicators, and SLE is accompanied by systemic small vessel damage and inflammatory reaction, the increase of the two indicates that the body is in a state of stress and inflammation [19]. Specific immune reactions can form immune complexes and then activate complement. Complement is consumed in a large amount during this process, and C3 and C4 levels decrease, which is consistent with previous research results [20]. Most SLE patients suffer from blood system damage [21]. The Anti-ds-DNA concentration in active SLE patients in this study is much higher than that in stationary SLE patients, which indicates that the damage to blood system in active SLE is more severe.

More and more studies have confirmed the clinical value of serum biomarkers in SLE. For example, serum Tenascin C (TNC) can be used as a biomarker for specific diagnosis and prediction of SLE [22]. Serum miRNA-371B-5P and miRNA-5100 are abnormally expressed in SLE and are correlated with its clinical parameters, which can be used as diagnostic markers for active and inactive phases [23]. At the moment, there have been reports that compared with healthy controls, the lnc-DC level in plasma of SLE patients has decreased dramatically, and lnc-DC is presumed to be a potential biomarker of SLE [24], which provides some ideas for this study. To further confirm the lnc-DC value in SLE, this study discovered that the serum lnc-DC was low in SLE; it in active patients was lower than that of inactive patients ($P < 0.05$), and it can be used for SLE diagnosis, with AUC of 0.903, and its expression was obviously negatively correlated with SLEDAI score. Through ROC detection, it can be used to distinguish SLE patients from active and stationary states. Pearson analysis showed that serum lnc-DC was positively correlated with clinical indicators C3 and C4, and it was markedly negatively correlated with IgG, CRP, ESR and Anti-ds-DNA of SLE patients. The results suggest that serum lnc-DC can be used as a new biomarker for SLE diagnosis, similar to the results of Wu [24] and others. Currently, there are many studies that showed abnormal SOCS1 expression in SLE. QIU [25] and others suggested that the SOCS1 mRNA was abnormally expressed in peripheral blood mononuclear cells of SLE patients, suggesting that the SOCS1 imbalance might be tied to the pathogenesis of SLE. Recent literature has pointed out that the imbalance of SOCS1 signal is involved in SLE hematological abnormalities and various pathological processes of autoantibody production [11, 26]. In this research, the SOCS1 expression was down-regulated remarkably in SLE patients, and SOCS1 can be used for SLE diagnosis and differentiation of active phases, with high clinical value. Further correlation analysis shows that SOCS1 is correlated with various clinical index parameters, suggesting that it participates in inflammation occurrence and development, blood injury, immune regulation and other processes in SLE. The occurrence of SLE diseases often leads to poor prognosis. Li [27] and others have followed up the progression-free survival of SLE patients and found that the abnormal expression of miR-181a and miR-203 can be used to predict their prognosis and survival. Because SLE disease has high recurrence

rate, 39 patients have relapsed SLE after follow-up investigation, with a recurrence rate of 30.00%. Serum indexes were used for prediction, and it was found that serum lnc-DC and SOCS1 can be used for prediction of prognosis recurrence (AUC: 0.833 and 0.869). Previous studies on the role of lnc-DC and SOCS1 in regulating STAT3 in coronary heart disease and type 2 diabetes suggest that they may have certain correlation [28]. To further verify whether there is correlation between serum lnc-DC and SOCS1, Pearson analysis displays that they are remarkably positively correlated in active and stationary phases of SLE patients. It is suggested that the two are relevant to SLE.

This study confirmed the clinical value and correlation of serum lnc-DC and SOCS1 in SLE. However, there is still room for improvement. Animal SLE models can be established in future studies to explore the specific regulatory effects of lnc-DC and SOCS1 in SLE pathogenesis. What's more, the long-term prognosis and survival of patients can be explored to provide better research programs for clinical diagnosis and treatment.

To summarize, lnc-DC and SOCS1 are correlated with SLE, which can be used as biomarkers for diagnosis and prognosis prediction, and therefore with high clinical significance.

Disclosure of conflict of interest

None.

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