

## RESEARCH ARTICLE

# Clinical significance of serum ferritin in patients with systemic sclerosis

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**Abstract**

**Objective:** The purpose of this study was to explore the clinical significance of serum ferritin (SF) in patients with systemic sclerosis (SSc).

**Methods:** The levels of SF were measured in 115 patients with SSc and 117 healthy controls (HCs). Clinical characteristics and laboratory indexes between the high ferritin SSc group and the normal ferritin SSc group were analyzed.

**Results:** The level of SF in SSc patients was significantly higher than that in HCs (319.78 [179, 554.33] ng/ml vs. 99 [49.03, 164.29] ng/ml,  $p < 0.01$ ). Compared with the normal ferritin SSc group, the high ferritin SSc group was more likely to develop skin diffuse cutaneous SSc, fingertip arthralgia, and cardiac involvement. In addition, the levels of glutamine transaminase (GGT), alanine aminotransferase (ALT), creatine kinase (CK), creatine kinase isoenzyme-MB (CK-MB), lactate dehydrogenase (LD), immunoglobulin G (IgG), immunoglobulin A (IgA), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and the positive rate of anti-Scl70 antibody in the high ferritin SSc group were significantly higher (each  $p < 0.05$ ). SF was positively correlated with GGT, ALT, CK, CK-MB, LD, IgA, CRP, and ESR (each  $p < 0.05$ ). Multiple linear regression analysis showed that cardiac involvement, ALT, and ESR were independent influencing factors of SF in SSc.

**Conclusion:** Our study shows that the level of SF in patients with SSc is increased, and the elevated SF is related to abnormal liver function, myocardial involvement, inflammatory status, and production of autoantibodies in SSc. Cardiac involvement, ALT, and ESR are independent factors affecting SF in SSc.

**KEYWORDS**

autoantibody, autoimmune diseases, inflammation, serum ferritin, systemic sclerosis

Yanting Jiang and Xi Li have contributed equally to this work and share first authorship.

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## 1 | BACKGROUND

Systemic sclerosis (SSc) is an autoimmune disease (AID) characterized by microangiopathy, inflammation, and fibrosis.<sup>1</sup> The pathogenesis of SSc is not fully clear. According to statistics, as a connective tissue disease, SSc has one of the highest mortality rates, and its standardized mortality ratio is between 1.39 and 5.10.<sup>2</sup> Interstitial lung disease (ILD), cardiac involvement, renal crisis, and infection are the main causes of death in SSc.<sup>3,4</sup> According to the LeRoy classification standard,<sup>5</sup> when skin thickening is limited to the facial/neck area and distal limbs in SSc patients, this is defined as skin limited cutaneous SSc (lcSSc), whereas skin thickening occurring in facial/neck area, distal proximal limbs, and trunk is described as skin diffuse cutaneous SSc (dcSSc).

Serum ferritin (SF) is the main storage protein for iron in the body; it is mainly present in the liver, spleen, bone marrow, and nucleus of the lateral pyramidal tract of brain.<sup>6</sup> Many diseases are related to iron deficiency or overload in the body. In these cases, the detection of SF levels can provide an crucial basis for the diagnostic and prognostic evaluation of diseases. Clinically, iron deficiency anemia is mainly diagnosed when a decrease in SF levels is observed. Some studies have confirmed that SF is increased in inflammation, chronic infection, and malignant tumors, and this is considered to be related to iron metabolism disorder in these diseases.

In recent years, studies have shown that SF levels in AID patients are significantly increased. A multi-centered research showed that in active adult Still's disease, SF was significantly increased and had diagnostic value for the disease.<sup>7</sup> Another study confirmed that SF is an excellent marker for evaluating systemic lupus erythematosus disease activity and renal dysfunction.<sup>8</sup> Ferreira et al.<sup>9</sup> reported that an increase in SF could aggravate the oxidative stress in patients with multiple sclerosis and promote the disease progression. These results suggest that elevated SF may be closely related to the occurrence and development of AID. Elevated inflammatory markers have been reported to be associated with SSc microangiopathy and fibrosis.<sup>10</sup> Despite being an acute-phase response protein with high sensitivity, SF has not been studied in SSc patients. Therefore, our aim is to explore the clinical significance of SF in SSc patients.

## 2 | MATERIALS AND METHODS

### 2.1 | Participants

One hundred and fifteen patients with SSc and 117 healthy controls (HCs) were recruited from the first affiliated Hospital of Guangxi Medical University from January 2021 to January 2022. The age and sex of the two groups were matched. According to American College of Rheumatology classification criteria,<sup>11</sup> all patients were diagnosed with SSc. Exclusion criteria: (1) patients with severe malnutrition/iron deficiency anemia, (2) patients who had been treated with iron, erythropoietin and blood transfusion in the past 6 months, (3) other

factors that could cause SF fluctuations, such as severe systemic infection, bleeding, malignant tumor, or pregnancy. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (approval number: 2016 (KY-E-060), and all patients signed informed consent forms.

### 2.2 | SF detection

After admission, 3 ml of fasting venous blood was collected and centrifuged at 2000g/min for 15 min. The supernatant was collected and stored in the refrigerator at  $-80^{\circ}\text{C}$ . The level of SF was detected by Abbott automatic immunoanalyzer, and the experimental operation was carried out strictly according to the instructions of the kit. According to the SF reference ranges by the Laboratory Department of the First Affiliated Hospital of Guangxi Medical University, which are 4.63–204 ng/ml for women and 21.8–274.66 ng/ml for men, we classified SSc patients with levels of  $>204$  ng/ml (women) and  $>274.66$  ng/ml (men) as the high ferritin SSc group and SSc patients in the reference range as the normal ferritin SSc group.

### 2.3 | Data collection

Demographic data include gender and age. Disease-related clinical data include disease subtypes (dcSSc and lcSSc), courses of disease, and clinical manifestations. The clinical manifestations include (1) ILD, which is defined using high-resolution computed tomography showing ground glass opacity under the pleura or at the base of the lung and showing honeycomb or reticular changes in both lungs; (2) pulmonary arterial hypertension (PAH), defined as a mean pulmonary artery pressure (mPAP)  $>25$  mmHg and pulmonary wedge pressure  $<15$  mmHg during cardiac catheterization; (3) Raynaud's phenomenon; (4) fingertip arthralgia; (5) fingertip ulcer/gangrene; (6) cardiac involvement, defined as cardiac systolic or diastolic dysfunction, pericardial effusion, constrictive pericarditis, or conduction defect with no other cause; (7) renal crisis, which is defined as at least two of the following: new hypertension, no other etiology, elevated creatinine, and new microvascular pathological hemolytic anemia; and (8) gastrointestinal system involvement, defined as esophageal or gastric mucosal abnormalities confirmed by gastroscopy and upper gastrointestinal radiography. The disease-related laboratory indexes are as follows: (1) liver function indexes: glutamine transaminase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP); (2) myocardial enzymes: creatine kinase (CK), creatine kinase isoenzyme-MB (CK-MB), and lactate dehydrogenase (LD); (3) renal function indexes: urea (UREA), creatinine (CREA), uric acid (UA); (4) inflammatory indicators: immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR); and (5) autoantibodies: antinuclear antibodies (ANA) and anti-Scl70 antibodies.

## 2.4 | Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics version 25.0 and GraphPad Prism 8. The measurement data in accordance with the normal distribution were expressed by mean  $\pm$  standard deviation, and the independent sample *t* test was used for the comparison between the two groups, while the skewed distribution measurement data were expressed by median (25th, 75th percentiles), and the Mann–Whitney U test or Kruskal–Wallis test was used for the comparison between groups. The counting data were expressed by frequency, and the chi-square test was used for comparison between groups. The correlation between SF and laboratory parameters was analyzed by Spearman correlation analysis. Multiple linear regression model was used to evaluate the relationship between laboratory indexes and SF in patients with SSc.  $p < 0.05$  was considered to be statistically significant.

## 3 | RESULTS

### 3.1 | Comparison of SF levels between SSc patients and HCs

A total of 115 SSc patients and 117 HCs were included in this study. There was no significant difference in sex and age between the SSc patients and HCs (each  $p > 0.05$ ). Figure 1 shows that the level of SF in the SSc group was significantly higher than that in the HCs (319.78 [179, 554.33] ng/ml vs. 99 [49.03, 164.29] ng/ml,  $p < 0.01$ ).

### 3.2 | Comparison of clinical characteristics between the high ferritin SSc group and the normal ferritin SSc group

Among 115 patients with SSc, 74 patients with elevated SF were defined as the high ferritin SSc group and 41 patients with normal SF as the normal ferritin SSc group. Comparison of clinical characteristics between the high ferritin SSc group and the normal ferritin SSc group are shown in Table 1. There were 57 patients with dcSSc, 12 patients with lcSSc, and five patients with unclassified

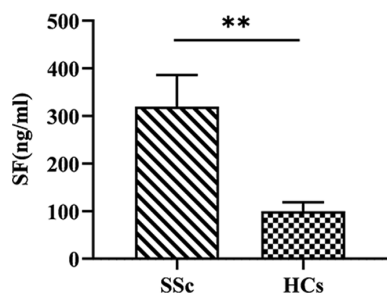


FIGURE 1 Comparison of SF levels between SSc patients and HCs.  $**p < 0.01$

SSc (because of a lack of clinical data) in the high ferritin SSc group. There were 21 patients with dcSSc, 18 patients with lcSSc, and two patients with unclassified SSc (because of a lack of clinical data) in the normal ferritin SSc group. Patients with high ferritin SSc were more likely to develop dcSSc (82.6% vs. 53.8%,  $p = 0.001$ ), whereas patients with normal ferritin SSc were more likely to exhibit lcSSc (17.4% vs. 46.2%,  $p = 0.001$ ). Compared with the normal ferritin SSc group, fingertip arthralgia (48.65% vs. 24.39%), and cardiac involvement (41.89% vs. 14.63%) were more common in the high ferritin SSc group (each  $p < 0.05$ ). There was no significant difference in age, sex, course of disease, ILD, PAH, Raynaud's phenomenon, fingertip ulcer/gangrene, renal crisis, or gastrointestinal involvement between the two groups.

### 3.3 | Comparison of laboratory indexes between the high ferritin SSc group and the normal ferritin SSc group

In Table 2, the liver function indexes, myocardial enzymes, renal function indexes, other inflammatory indexes, and autoantibodies were compared between the high ferritin SSc group and the normal ferritin SSc group. Compared with the normal ferritin SSc group, the levels of GGT, ALT, CK, CK-MB, LD, IgG, IgA, CRP, ESR, and the positive rate of anti-Scl70 antibody were higher in the high ferritin SSc group (each  $p < 0.05$ ). There was no significant difference in the levels of AST, ALP, UREA, CREA, UA, IgM, or the positive rate of ANA between the two groups.

### 3.4 | Correlation between SF and laboratory indexes in SSc patients

Next, Spearman correlation test was used to analyze the potential correlation between SF level and GGT, ALT, CK, CK-MB, LD, IgA, CRP, and ESR. The results demonstrated that SF and GGT (Figure 2A,  $R = 0.310$ ,  $p = 0.001$ ), ALT (Figure 2B,  $R = 0.241$ ,  $p = 0.009$ ), CK (Figure 2C,  $R = 0.295$ ,  $p = 0.003$ ), CK-MB (Figure 2D,  $R = 0.289$ ,  $p = 0.002$ ), LD (Figure 2E,  $R = 0.437$ ,  $p = 0.001$ ), IgA (Figure 2F,  $R = 0.228$ ,  $p = 0.022$ ), CRP (Figure 2G,  $R = 0.495$ ,  $p = 0.001$ ), and ESR (Figure 2H,  $R = 0.428$ ,  $p = 0.001$ ) were positively correlated in SSc patients.

### 3.5 | Multiple linear regression analysis of SF levels and clinical characteristics and laboratory indicators in SSc patients

Disease subtype, fingertip arthralgia, cardiac involvement, GGT, ALT, CK, CK-MB, IgG, IgA, CRP, ESR, anti-Scl-70 positivity, and other indicators were included in multiple linear regression analysis by the step method. Table 3 shows that cardiac involvement, ALT, and ESR were independent influencing factors of SF in SSc patients.

	High ferritin SSc group (n = 74)	Normal ferritin SSc group (n = 41)	t/X <sup>2</sup> /Z	p Value
Sex (male/ Female)	29/45	13/28	0.637	0.425
Age, years ± SD	53.73 ± 9.85	49.15 ± 15.07	1.968	0.085
Course of disease (years)	1.0 (0.58, 5.0)	1.1 (0.7, 4.0)	-0.354	0.724
Disease subtypes				
dcSSc	57(82.6%)	21(53.8%)	10.28	0.001
lcSSc	12(17.4%)	18(46.2%)		
Clinical manifestations				
ILD	54 (72.97%)	31 (75.61%)	0.095	0.758
PAH	15 (20.27%)	13 (31.71%)	1.874	0.171
Raynaud's phenomenon	55 (74.32%)	30 (73.17%)	0.018	0.893
Fingertip arthralgia	36 (48.65%)	10 (24.39%)	6.469	0.011
Fingertip ulcer/gangrene	15 (20.27%)	11 (26.83%)	0.649	0.421
Cardiac involvement	31 (41.89%)	6 (14.63%)	8.982	0.003
Renal crisis	7 (9.46%)	2 (4.88%)	0.768	0.381
Gastrointestinal system involvement	5 (6.76%)	2 (4.88%)	0.163	0.687

Abbreviations: dcSSc, diffuse cutaneous SSc; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

TABLE 1 Comparison of clinical characteristics between the high ferritin SSc group and the normal ferritin SSc group

	High ferritin SSc group (n = 74)	Normal ferritin SSc group (n = 41)	t/X <sup>2</sup> /Z	p Value
GGT (U/L)	20 (13, 35)	15 (11, 20.5)	2.035	0.046
ALT (U/L)	19 (12, 32)	14 (11, 22)	2.796	0.006
AST (U/L)	30(23, 44)	26(21, 31)	1.365	0.178
ALP (U/L)	64(54, 77)	57(46, 76)	0.385	0.169
CK (U/L)	181.5 (58.5, 322.25)	79 (49, 144)	3.030	0.003
CK-MB (U/L)	20.5(15, 32.25)	17.5 (12.75, 22.25)	2.899	0.004
LD (U/L)	265 (208, 360)	215 (15.75, 310.25)	3.500	0.001
UREA(mmol/L)	5.9 ± 4.85	4.94 ± 2.24	1.448	0.150
CREA (μmol/L)	62 (48.5, 91.5)	61 (48, 73.5)	1.497	0.138
UA (μmol/L)	337.75 ± 155.91	302.13 ± 98.23	1.320	0.190
IgG (g/L)	17.35 ± 7.25	14.58 ± 4.53	2.074	0.041
IgA (g/L)	2.86 ± 1.33	2.26 ± 1.03	2.376	0.019
IgM (g/L)	1.33 ± 0.68	1.54 ± 0.69	-1.527	0.130
CRP (mg/L)	9.6 (3.9, 18.58)	2.5 (1.1, 5.35)	3.930	0.001
ESR (mm)	34 (22.5, 63.25)	14 (10, 26)	6.387	0.001
ANA	69 (93.24%)	36 (87.80%)	0.983	0.322
anti-Scl70	62 (83.78%)	25 (60.97%)	7.451	0.006

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase isoenzyme-MB; CREA, creatinine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GGT, glutamine transaminase; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; LD, lactate dehydrogenase; SSc, systemic sclerosis; UA, uric acid; UREA, urea.

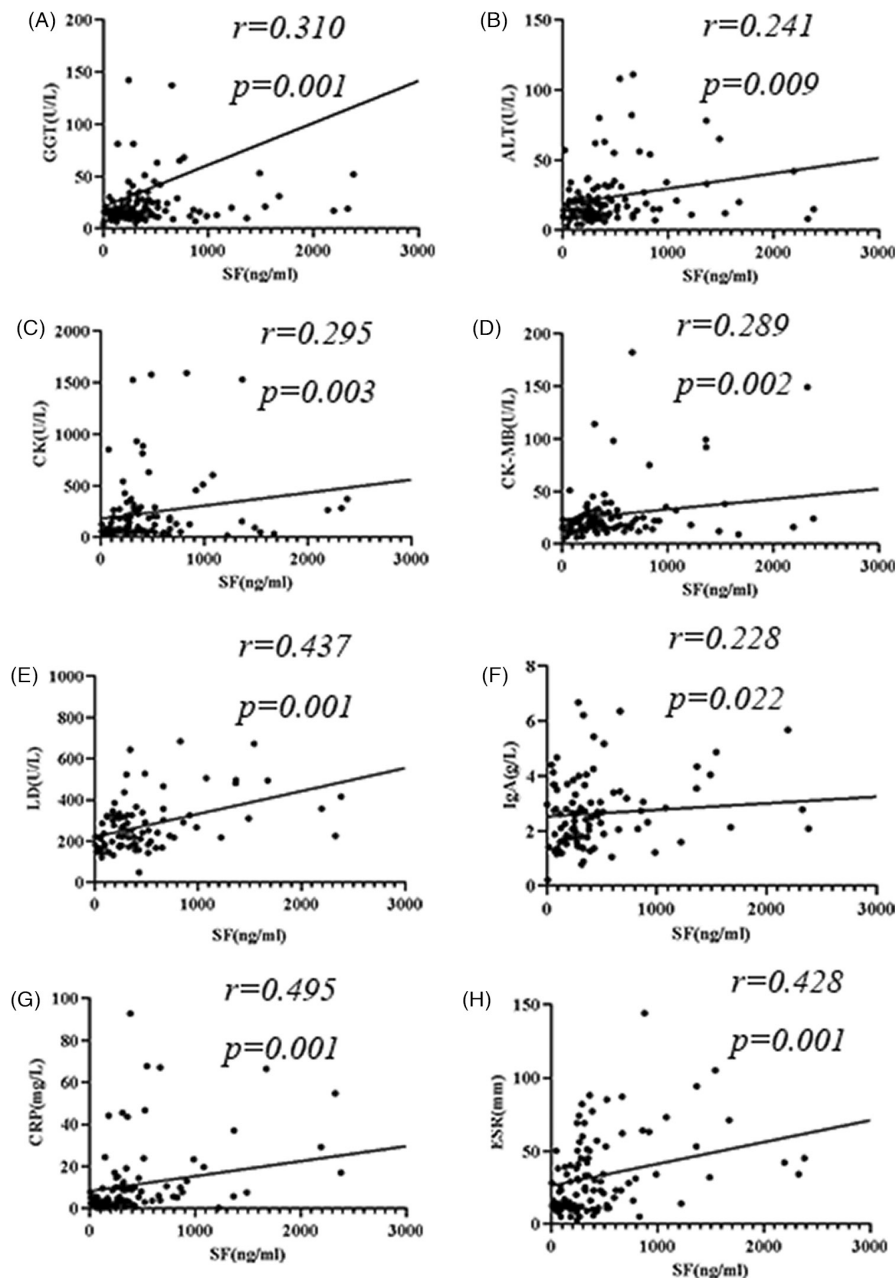
TABLE 2 Comparison of laboratory indexes between the high ferritin SSc group and the normal ferritin SSc group

## 4 | DISCUSSION

SSc is a kind of AID characterized by skin inflammation, thickening, and fibrosis. The age of onset is mostly between 30 and 50 years old. The incidence and prevalence rate of women is higher than that of

men, but male patients show more serious disease and lower survival rate.<sup>12,13</sup> SF is elevated in inflammatory diseases, so it is considered an acute-phase protein, representing the product of acute-phase reaction in vivo. Recently, studies have shown that the level of SF in patients with AID is increased, and it is related to disease activity.<sup>14,15</sup>

**FIGURE 2** Spearman correlation test was used to analyze the potential correlation between SF level and GGT, ALT, CK, CK-MB, LD, IgA, CRP, and ESR. (A) Shows SF and GGT. (B) Shows SF and ALT. (C) Shows SF and CK. (D) Shows SF and CK-MB. (E) Shows SF and LD. (F) Shows SF and IgA. (G) Shows SF and CRP. (H) Shows SF and ESR



**TABLE 3** Multiple linear regression analysis of SF levels and clinical characteristics and laboratory indicators in SSc patients

	$\beta$	SE	$t$	$p$ Value
Constant	-89.290	175.293	-0.509	0.612
cardiac involvement	456.095	200.122	2.279	0.026
ALT (U/L)	10.007	4.371	2.289	0.025
ESR (mm)	8.088	3.700	2.186	0.033

Abbreviations: ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate.

This suggests that SF can be used as a biomarker to monitor disease progression and to evaluate disease prognosis.

Our study found that SF in patients with SSc was significantly higher than that in HCs. We also analyzed the differences in clinical

characteristics between the high ferritin SSc group and the normal ferritin SSc group. We observed that compared with the normal ferritin SSc group, the high ferritin SSc group was more likely to develop dcSSc, and the high ferritin SSc patients with fingertip arthralgia and cardiac involvement were more common. Previous studies have shown that gastrointestinal, cardiopulmonary, kidney, and joint involvement are more common in dcSSc, so patients with dcSSc have a poorer prognosis and a lower survival rate.<sup>12,16</sup> Our study confirmed that dcSSc is common in patients with high ferritin SSc. Therefore, we concluded that the increase in SF is related to the severity of SSc disease, and patients with high ferritin SSc are more likely to develop organ damage.

From the comparison of SF and laboratory indicators, our study indicated that the levels of GGT, ALT, CK, CK-MB, LD, IgG, IgA, CRP, ESR, and the positive rate of anti-Scl70 antibody in the high ferritin SSc group were significantly higher than those in the normal ferritin

SSc group. The levels of GGT, ALT, CK, CK-MB, LD, IgA, CRP, and ESR were positively correlated with SF. These reveal that the increase of SF may be related to abnormal liver function, myocardial damage, inflammatory state, and production of autoantibodies in patients with SSc.

Glutamine transaminase in normal human serum mainly comes from the liver. This enzyme increases slightly to moderately in acute hepatitis, chronic active hepatitis, and decompensated liver cirrhosis. ALT is mainly stored in hepatocytes and is one of the most sensitive indicators of hepatocyte injury. In patients with high ferritin SSc, we observed that the levels of GGT and ALT were significantly increased and positively correlated with SF, which may reveal the existence of liver function damage in patients with SSc. The SF in the blood circulation was cleared by hepatocytes,<sup>17</sup> and the ability to deal with SF decreased when the liver was injured, resulting in an increase in serum SF. In addition, the increase in SF was caused by the release of SF into the blood because of the degeneration or necrosis of some hepatocytes, and the increase in SF was positively correlated with the degree of hepatocyte damage.<sup>18</sup> Therefore, we believe that the increase in SF in patients with SSc may be related to liver injury.

Serum muscle enzymes mainly include CK, AST, and LD. Among them, CK is the most common and sensitive, which can increase at the early stage of the disease—up to dozens of times the normal level—and is released into blood when the muscle is damaged, representing an vital index to reflect skeletal and muscular lesions of the extremities. What is more, CK-MB is a specific indicator of myocardial injury and can be used to diagnose myocardial infarction without skeletal muscle injury. AST and LD not only reflect skeletal muscle lesions of the extremities but also have a high correlation with myocardial involvement and the occurrence of ILD.<sup>19,20</sup> Our results showed that the levels of CK, CK-MB, and LD in the high ferritin SSc group were significantly higher than those in the normal ferritin SSc group. This is consistent with the clinical manifestations of cardiac involvement in patients with high ferritin levels in our study. Therefore, the increased level of SF in patients with SSc indicates that skeletal muscle lesions of extremities, myocardial involvement, and ILD are more likely to occur.

Erythrocyte sedimentation rate acceleration is common in a variety of infectious or non-infectious inflammations and is also related to the activity of many diseases, such as AID. CRP is an acute-phase reactant and is often used with ESR as a biomarker for predicting morbidity and mortality in patients with SSc.<sup>21</sup> Previous studies have confirmed that the increase of CRP and ESR is related to vascular lesions and fibrosis of SSc. Clinicians usually measure these inflammatory markers to assess the activity of SSc disease, because elevated levels of inflammatory markers are associated with decreased respiratory function and lung damage.<sup>10</sup> Our study found that CRP and ESR were significantly increased in the high ferritin SSc group, and positively correlated with SF levels. Through multiple linear regression analysis, we found that the level of SF was independently correlated with ESR. Therefore, it is suggested that SF can be employed to judge the disease activity and severity of SSc.

Anti-Scl70 is one of the specific antibodies of SSc patients, and its positivity is closely related to diffuse skin lesions, proximal skin

involvement, cardiac involvement, tumor and pulmonary interstitial fibrosis; it is considered an indicator of poor prognosis.<sup>22</sup> Previous studies have shown that anti-Scl70 antibodies may be involved in endothelial damage in SSc,<sup>23</sup> and they are positively correlated with the severity of microvascular lesions.<sup>24</sup> Our results showed that the positive rate of anti-Scl70 in the high ferritin SSc patients was significantly higher than that in the normal ferritin SSc patients. This suggests that the increase in SF is related to the disease severity of SSc patients. Meanwhile, the levels of IgG and IgA antibodies were significantly increased in the high ferritin SSc group. It can be seen that the production of autoantibodies in SSc patients is related to the increase in SF.

There are a few limitations to this study that should be mentioned. Because COVID-19 has led to a significant reduction in patients' follow-up, the SF of SSc patients after treatment cannot be evaluated. The mechanism of SF participating in SSc has not been studied in this study. Therefore, it is necessary to conduct more in-depth research in order to fully understand the clinical characteristics and pathogenesis of SSc patients.

In conclusion, we found that SF was elevated in patients with SSc and that elevated SF was related to abnormal liver function, cardiac involvement, inflammatory status, and production of autoantibodies. Cardiac involvement, ALT, and ESR were independent influencing factors of SF in SSc patients.

#### AUTHOR CONTRIBUTIONS

YJ. and XL. conceptualized the study; YJ. and JW. designed the study; JW. and XL. supervised the study; YL. and WZ. contributed to resources; LS. contributed to materials; MJ. and HZ. collected and/or processed the data; YJ. contributed to analysis and/or interpretation and wrote the article; MJ. contributed to literature search; XL. critically reviewed the study.

#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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