Clinical significance of interleukin 27 serum concentration in patients with systemic sclerosis: relation to clinical, laboratory and radiological parameters

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Received 20 November 2018
Accepted 20 December 2018

Egyptian Rheumatology & Rehabilitation
2019, 46:101–107

Background
Interleukin 27 (IL27) is a cytokine that belongs to IL12 family and it is mainly produced by antigen presenting cells. IL27 binding to its receptor leads to activation of many intracellular signaling pathways that can exhibit a wide variety of immunomodulatory actions.
Aim of the work
The current study aimed to determine IL27 concentrations in the sera of SSc patients and to assess the relation between these concentrations and the various clinical, laboratory and radiological disease parameters.
Methods
We measured serum IL27 concentrations in 31 SSc patients and 20 controls. The patients were subjected to detailed history and clinical evaluation. In SSc patients, modified Rodnan skin score (MRSS) was used to assess the skin thickness and pulmonary involvement was assessed by high resolution computerized tomography (HRCT) and forced vital capacity (FVC) assessment.
Results
IL27 serum concentrations in diffuse (median, 302.8; 101.6-1034.4 ng/L) and limited (median, 385; 109-826.3 ng/L) subtypes of SSc showed a significant elevation ($P < 0.001$) compared to its concentrations in the controls (median, 104.2; 51-184.2 ng/L). SSc patients with elevated IL27 serum concentrations had significantly lower forced vital capacity (FVC) than those with normal IL27 serum concentrations (p=0.04). Also, serum level of sCD163 significantly correlated with MRSS (r=0.48, p=0.0064) and FVC (r=-0.6, p=0.0005).
Conclusion
Patients with systemic sclerosis have significantly increased serum IL27 concentrations that remarkably associated with significant cutaneous and pulmonary involvement signifying that it could be a beneficial biomarker that reflects disease severity and implies a possible pathogenic role in SSc.

Keywords:
Interleukin 27, pulmonary fibrosis, systemic sclerosis, rodnan skin score

Egypt Rheumatol Rehabil 46:101–107

1110-161X

Introduction

Systemic sclerosis (SSc) is a chronic multisystem complex autoimmune disorder that has the characteristic pathological features of immune dysregulation and microvascular involvement and ends with organ fibrosis [1]. It involves not only the skin but also many visceral organs such as the lungs, the heart, kidneys, and the gastrointestinal tract, with a varying degree of severity. Moreover, the magnitude of visceral involvement is usually reflected by the rate of progression of skin fibrosis [2].

The pathophysiology of SSc remains not fully understood. It is believed that the interaction between the genetic [3] and environmental elements causes an alteration of the immunological response that represents the initial phase of development of SSc [4]. Dysregulation of the adaptive immunity, involving the presence of pathogenic autoreactive T lymphocytes and the autoantibody production by B lymphocytes, was thought to be the only mechanism of immune dysregulation in SSc [5], but recently, there is increased interest about the role of toll-like receptors, a key player of innate immunity, in the pathogenesis of SSc [6].

Interleukin (IL) 27 is a cytokine that belongs to IL12 family and it has a heterodimeric structure [7]. It was thought to be produced only by antigen-presenting

cells, in particular monocytes, dendritic cells, and macrophages, but now it is recognized to be expressed by a wide range of other cells such as keratinocytes and B and T lymphocytes [8,9]. The receptor of IL27 is formed of glycoprotein 130 and IL27Ra subunits [7], and it is distributed on abroad range of cells such as lymphocytes, endothelial cells, macrophages, and mast cells [10]. IL27 binding to its receptor leads to activation of many intracellular signaling pathways that can exhibit a wide variety of immunomodulatory actions according to the nature of stimulated cell [11].

Few studies investigated the role of IL27 in rheumatic autoimmune diseases such as rheumatoid arthritis [12], systemic lupus erythematosus [13], SSC [14], and psoriasis [15], and the exact functional role of IL27 in these disorders is not fully clear. It is found to exhibit a 'functional antagonism' as IL27 can suppress inflammatory reactions through its ability to downregulate the release of IL17 [16] and increase the expression of IL10 [7]. On the contrary, IL27 inhibits the induction and differentiation of regulatory T lymphocyte (Treg) which is known to have a main role in maintenance of self-tolerance [17]. Moreover, it can enhance antibodies production by B lymphocytes [18] and stimulate follicular T helper lymphocytes [10].

The current study aimed to determine IL27 concentrations in the sera of patients with SSc and to assess the relation between these concentrations with various clinical, laboratory, and radiological disease parameters.

Participants and methods

Participants

This study was conducted at Rheumatology, Rehabilitation and Physical Medicine Department, Benha University Hospital and Benha Insurance Hospital during the period from February 2016 to July 2018. The study was conducted on two groups: the first group included 31 patients with SSc diagnosed according to the 2013 classification criteria proposed by ACR/EULAR [19], and the second group included 20 apparently healthy volunteers with comparable age and sex who were registered in this study as a control group.

Patients with SSc were separated into two subcategories according to LeRoy *et al.* [20] criteria depending on magnitude of skin involvement: diffuse SSc included 19 patients and limited SSc included 12 patients. Patients having conditions that can affect concentrations of IL27 such as rheumatoid arthritis, multiple sclerosis, other autoimmune disorders, recent infection, and malignancy were excluded.

Detailed medical history was recorded and comprehensive examination was executed with emphasis on skin manifestations, Raynaud phenomenon, musculoskeletal involvement, and manifestations suggestive of involvement of internal organs such as the lung, the heart, gastrointestinal, and the kidney, as demonstrated by Steen *et al.* [21]. Modified Rodnan score (MRS) was used by assessment of the thickness of the skin in 17 anatomical areas [22].

Laboratory and radiological assessment

Venous samples were extracted for measurement of erythrocyte sedimentation rate, C-reactive protein, complete blood count, liver enzymes, and renal function. Moreover, antinuclear antibodies were tested using indirect immunofluorescence kits (IMMCO Diagnostics Inc., New York, USA) whereas antitopoisomerase I (Cusabio, Hubei, China) and anticentromere (My Biosource, San Diego, California, USA) antibodies were measured using the ELISA technique. Calcinosis was assessed using plain radiography of both hands, and high-resolution computed tomography of the lung, forced vital capacity (FVC), and the ratio between forced expiratory volume in first second (FEV_1) and FVC (FEV_1%) were used to assess pulmonary affection. Moreover, pulmonary artery systolic pressure was measured using Doppler echocardiography.

This study was approved by the ethics committee of Faculty of Medicine, Benha University, and all participants signed a written informed consent.

Assessment of IL27 serum concentrations

IL27 concentrations were measured in serum samples obtained from patients with SSc and healthy controls. The serum samples were centrifuged and stored at −40°C till testing. IL27 assay was performed following the manufacturer's instruction using ELISA kits provided by Sunred (Shanghai, China). The range of assay is 6.5–2000 ng/l.

Statistical analyses: the 18th version of the statistical package for the social sciences program (SPSS; SPSS Inc., Chicago, Illinois, USA) was used to statically analyze the data of this study. Mean±SD is the term used to summarize quantitative data, whereas percentages and frequencies were used to describe qualitative data. The Student *t*-test was performed to compare means of two groups with normally distributed data, whereas Fisher's exact test was used

to detect differences in frequencies. The differences of nonparametric data between two groups was detected using Mann–Whitney test. The diagnostic performance of IL27 serum concentrations for FVC of our patients with SSc was examined using the receiver operating characteristic curve (classification variable is considered positive if FVC <80%). Area under the curve, best cut-off point, and its sensitivity and specificity were estimated. The correlations between IL27 levels and various SSc-related variables were evaluated using the test of Pearson's correlation coefficient. *P* value less than 0.05 was accepted to be statistically significant.

Results

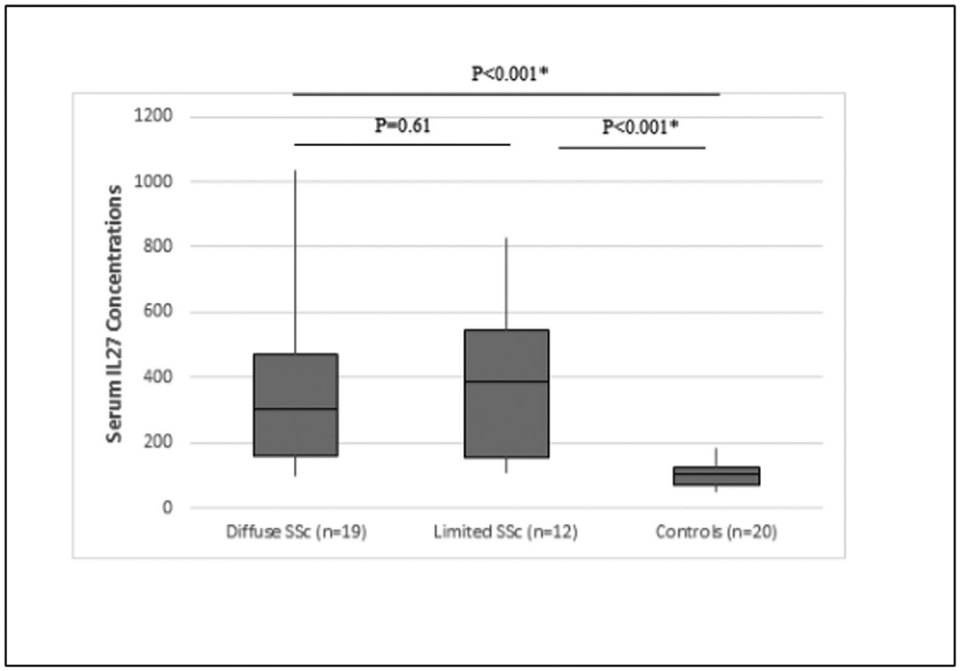
The mean age of patients with SSc was 33.13±9.5 years (range: 18–54 years) and was comparable with that of the healthy control 36.1±8.33 (range: 20–51 years). The sex of our patients with SSc (female 27 : male 4) was also matched with that of the control (female 17 : male 3). Moreover, there was no significant difference (P=0.14) in the mean of disease duration between patients with SSc with diffuse (3.26±1.99 years) and limited (4.67±2.9) subtypes.

IL27 concentrations in the serum of patients with SSc (median: 319.6; range: 101.6–1034.4 ng/l) were significantly higher (P<0.001) than its concentrations in the controls (median: 104.2; 51–184.2 ng/l). Moreover, serum concentrations of IL27 in diffuse (median: 302.8; 101.6–1034.4 ng/l) and limited (median: 385; 109–826.3 ng/l) subtypes of SSc showed a significant elevation (P<0.001) compared with its concentrations in the controls (Fig. 1). No significant difference was found in the median of IL27 serum concentrations between patients with diffuse SSc and those with limited SSc (P=0.61).

Nineteen (61.29%) patients with SSc had elevated IL27 concentrations in the serum, considered if more than the mean plus 2 SD of its concentration in the serum of healthy controls (176.24 ng/l), whereas 12 (28.71%) patients had normal serum IL27 concentrations. Patients with SSc who had elevated serum concentrations of IL27 had a significant increase in MRS (20.16±6.53) compared with those with normal IL27 serum concentrations (14.08±7.09) (P=0.02). Moreover, FVC was significantly lower (P=0.04) in patients with SSc with elevated IL27 serum concentrations (84.53±9.37) compared with those with normal serum concentrations of IL27 (93.42±14.05). There was no significant difference between patients with SSc with elevated and normal IL27 serum concentrations regarding disease duration, demographic, clinical, laboratory, or radiological data (Table 1**).**

Seventeen (54.84%) of our patients with SSC were receiving treatment at the time of their inclusion in the study, with 16 (51.61%) patients receiving

Figure 1



Distribution of interleukin 27 serum concentrations among patients with diffuse and limited SSc and healthy controls. SSc, systemic sclerosis. *Significant at P<0.05.

Table 1 Clinical, laboratory, and radiological characteristics of patients with systemic sclerosis with elevated and normal interleukin 27 serum concentrations

	Patients with elevated IL27 levels (*n*=19)	Patients with normal IL27 levels (*n*=12)	*P* value
Continuous variables (mean±SD)			
Age (years)	33.95±10.67	31.75±6.99	0.53
Disease duration (years)	3.37±2.65	4.5±1.98	0.21
MRS	20.16±6.53	14.08±7.09	0.02*
PASP (mmHg)	41.58±22.04	39.58±19.05	0.79
FVC %	84.53±9.37	93.42±14.05	0.04*
FEV_1/FVC	83.21±4.57	81.42±5.88	0.35
ESR (mm/first hr)	46.26±17.73	35.33±11.41	0.068
CRP (mg/dl)	27.63±20.77	19.58±14.34	0.25
Categorical variables [*n* (%)]			
Type (diffuse : limited)	11 : 8	8 : 4	
Raynaud's phenomenon	19 (100)	12 (100)	–
Digital pitting scars	7 (36.84)	4 (33.33)	0.85
Calcinosis	4 (21.05)	2 (16.67)	0.87
Diffuse pigmentation	6 (31.57)	4 (33.33)	0.77
Pulmonary fibrosis on HRCT	8 (42.1)	4 (33.33)	0.91
FVC <80%	7 (36.84)	3 (25)	0.77
Pulmonary hypertension (>30 mmHg)	9 (47.37)	5 (41.67)	0.73
Arthritis	1(5.26)	0(0)	–
Renal	2 (10.52)	1 (8.33)	0.67
Heart	1 (5.26)	1 (8.33)	0.68
Antitopoisomerase I antibody	6 (31.57)	4 (33.33)	0.77
Anticentromere antibody	5 (26.32)	3 (25)	0.73
Treatment [*n* (%)]			
Corticosteroids	9 (47.37)	7 (58.33)	0.82
Immunosuppressive medications	10 (52.63)	7 (58.33)	0.95

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL, interleukin; MRS, modified Rodnan score; PASP, pulmonary artery systolic pressure. *$P<0.05$, significant.

corticosteroids, eight (25.8%) patients receiving cyclophosphamide, seven (22.58%) patients receiving azathioprine, and two (6.45%) patients receiving mycophenolate mofetil, whereas 14 (45.16%) patients with SSc were recently diagnosed and did not receive corticosteroids or immunosuppressive drugs at the time of their enrollment in the study. IL27 serum concentration of patients with SSc who were treated with corticosteroids and immunosuppressive medications (317.41±209.91 ng/l) was lower than its concentration in those who did not receive treatment (421.05± 288.28 ng/l), but this difference was not statically significant (P=0.26).

Patients with SSC with pulmonary fibrosis (PF), as evaluated with high-resolution computed tomography, had significantly higher (P=0.023) serum IL27 concentrations (median: 405.8; 101.6–1034.4 ng/l) than those who did not have PF (median: 169.1; 103.4–826.3 ng/l) (Fig. 2).

The receiver operating characteristic curve between serum concentrations of IL27 and FVC revealed area under the curve of 0.755 and the cut off for the decrease of FVC less than 80% was 534 ng/l with sensitivity of 60% and specificity of 90.84% (Fig. 3).

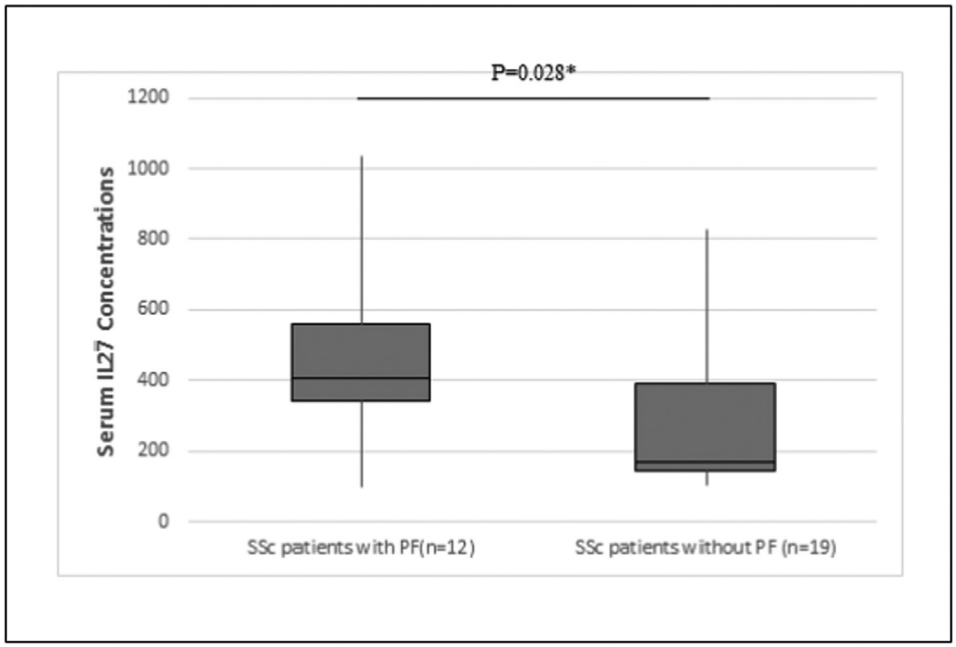
Serum IL27 concentrations had a significant positive correlation with MRSS (r=0.48, P=0.0064) whereas it revealed a significant negative correlation with FVC (r=-0.6, P=0.0005) (Table 2). IL27 did not show any significant correlation with other clinical and laboratory parameters of our patients with SSc.

Discussion

There is a strong evidence of early activation of the immune cells as an essential component of the pathophysiology of SSc [23]. Infiltration of the skin by immune cells, mainly T helper (Th) type 2 lymphocytes and macrophages, is considered the initial event in SSc course that is followed later by fibrosis of the skin [24].

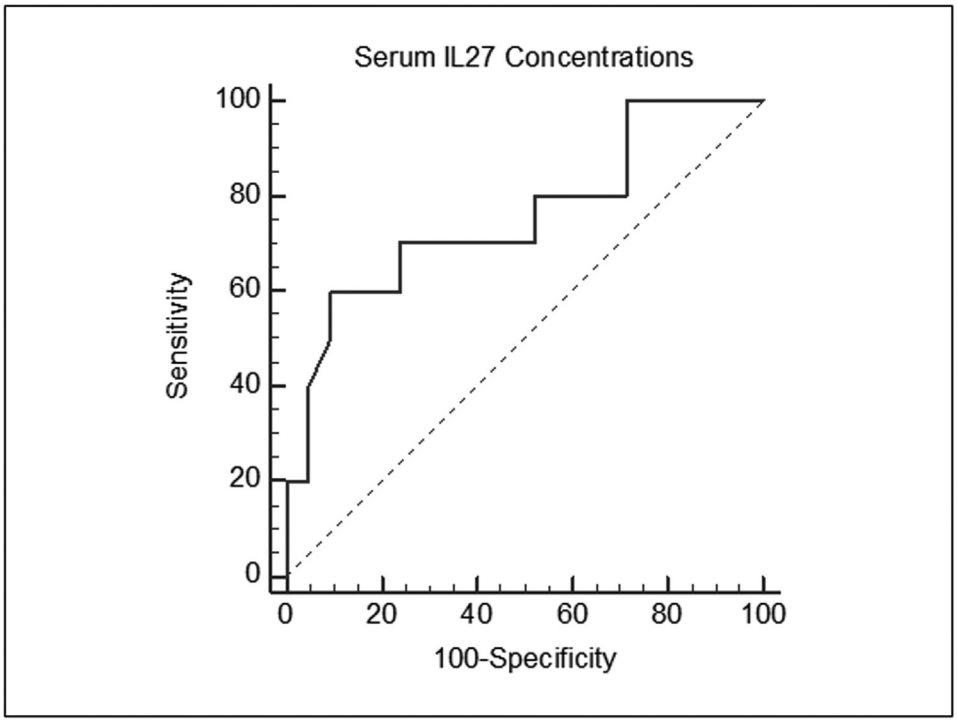
Fibrosis can be induced by Th2 lymphocytes through numerous mechanisms. In addition to its ability to activate fibroblasts by direct contact process [23], Th2 lymphocytes also secretes several cytokines that have a

Figure 2



Distribution of interleukin 27 serum concentrations among patients with SSc with and without pulmonary fibrosis. PF, pulmonary fibrosis; SSc, systemic sclerosis. *Significant at $P<0.05$.

Figure 3



Receiver operating characteristic curve evaluating the validity of the serum interleukin 27 concentrations in prediction of forced vital capacity in patients with systemic sclerosis. Area under the curve was 0.755, 95% confidence interval.

profibrotic activity, such as IL4 [25] and IL13 [26], which are known to upregulate secretion of transforming growth factor-β, a key mediator of fibrosis in SSC, by the macrophages.

IL27 is an interesting mediator as it has multiple effects on the immune system. It enhances Th1 lymphocytes differentiation whereas downregulates the development of Th2, Treg, and Th17 lymphocytes through its effect on

Table 2 Correlations between interleukin 27 serum concentration and systemic sclerosis disease parameters

SSc parameters	IL27 serum concentration	
	r	*P*
Age (years)	0.08	0.67
Duration of illness (years)	−0.23	0.21
PASP (mmHg)	0.24	0.2
Forced vital capacity	−0.6	0.0005*
MRS	0.48	0.0064*
ESR (mm/first hr)	0.19	0.3
CRP	0.18	0.32

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IL, interleukin; MRSS, modified Rodnan score; PASP, pulmonary artery systolic pressure; SSc, systemic sclerosis.
*$P<0.05$, significant.

the signaling pathways [10]. Moreover, it exhibits opposite functions on modulation of the inflammatory response as it has both proinflammatory and anti-inflammatory roles [27], and which effect prevails in SSc is still unclear.

We found patients with SSc to have a significant elevation ($P<0.001$) in IL27 serum concentrations compared with its concentrations in the serum of controls, and this increase was also observed in both the diffuse and limited subtypes. Moreover, we found IL27 to be associated with more severe skin involvement as it correlates positively ($r=0.48$, $P=0.0064$) with skin thickness scores, which were significantly higher ($P=0.02$) in patients with SSc who had elevated serum concentrations of IL27. These results were consistent with the findings of Yoshizaki *et al.* [14] who found elevated expression of IL27 in the serum as well as the skin of patients with SSc. In addition, receptors of IL27 were highly expressed in the fibroblasts of patients with SSc compared with those of the controls and a positive correlation was established between MRS and IL27.

Pflanz *et al.* [28] found activated fibroblasts to have increased expression of IL27R, and the binding of IL27 to its receptors enhances more activation of fibroblasts with increased collagen synthesis.

Our patients with SSc, who had PF, had a significant elevation ($P=0.023$) in their serum concentrations of IL27 compared with those without PF. Moreover, FVC was significantly lower ($P=0.04$) in patients with SSc with elevated IL27 serum concentration than those with normal concentrations, and a significant negative correlation ($r=-0.6$, $P=0.0005$) was found between serum concentrations of IL27 and FVC in our patients with SSc. Yoshizaki *et al.* [14] established the association of IL27 and PF in their patients with SSc, as they found a negative correlation between serum IL27 and FVC and carbon monoxide diffusion capacity.It is postulated that IL27 constitutes a bridge between innate and acquired immune systems [10], as Kopiński *et al.* [29] found a positive correlation between IL27 concentrations and CD4+ and total lymphocytic count in the fluid of bronchoalveolar lavage obtained from 12 patients with idiopathic PF, and they suggested that IL27 may be produced locally by CD4+ and CD8+ cells. Nevertheless, Su *et al.* [30] revealed that IL27 stimulates innate immunity through the expanded expression of toll-like receptor 4 in pulmonary fibroblasts leading to increased secretion of lipopolysaccharide-induced cytokines such as IL6 and IL8.

We could not find a significant relation between disease duration and IL27 concentrations in our patients with SSc. In contrast, Yoshizaki *et al.* [14] found IL27 to be higher in the early phase of SSc and suggested a possible role in the pathogenesis of early SSc. This can be attributed to the difference in sample size and disease duration between the two studies. Moreover, we did not follow-up our patients with SSc to examine the precise effect of duration of SSc on LI27 concentrations.

Although many studies investigated the role of IL27 in PF in various conditions with pulmonary involvement [14,29,31], only one previous study evaluated the potential role of IL27 in SSc [14]. Limitations of our study were the relative small sample size of our patients with SSc, and some of our patients were already treated at the time of study. Moreover, we did not follow-up our patients over sufficient period of time to investigate the role of IL27 in the progression of SSc.

In conclusion, patients with SSc have significantly increased serum IL27 concentrations that are remarkably associated with significant cutaneous and pulmonary involvement, signifying that it could be a beneficial biomarker that reflects disease severity and implies a possible pathogenic role in SSc.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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