Arthritis Care & Research
Vol. 65, No. 8, August 2013, pp 1375–1380
DOI 10.1002/acr.21968

BRIEF REPORT

Does C-Reactive Protein Predict the Long-Term Progression of Interstitial Lung Disease and Survival in Patients With Early Systemic Sclerosis?

XIAOCHUN LIU,[1] MAUREEN D. MAYES,[1] CLAUDIA PEDROZA,[1] HILDA T. DRAEGER,[2] EMILIO B. GONZALEZ,[3] BROCK E. HARPER,[3] JOHN D. REVEILLE,[1] AND SHERVIN ASSASSI[1]

Objective. **There are no identified clinical markers that reliably predict long-term progression of interstitial lung disease (ILD) in systemic sclerosis (SSc; scleroderma). Elevated C-reactive protein (CRP) levels have been reported in SSc patients. We examined the predictive significance of CRP level for long-term ILD progression in a large early SSc cohort.**
Methods. **First, the CRP levels were compared between baseline samples of 266 SSc patients enrolled in the Genetics Versus Environment in Scleroderma Outcome Study cohort and 97 unaffected matched controls. Subsequently, the correlation between CRP levels and concomitantly obtained markers of disease severity was assessed. Serially obtained % predicted forced vital capacity (FVC) was used to examine the long-term ILD progression. The predictive significance of CRP level was investigated by a joint analysis of longitudinal measurements (serial FVCs up to 13 years) and survival data. This approach allowed inclusion of all 1,016 FVC measurements and accounted for survival dependency.**
Results. **We confirmed that baseline CRP levels were higher in SSc patients than controls. CRP levels were associated with absence of anticentromere antibodies and correlated with the concomitant severity of lung, skin, and joint involvement. More importantly, higher baseline CRP levels were associated with shorter survival ($P < 0.001$) and predicted the long-term decline in FVC independent of potential confounders (age at baseline, sex, ethnicity, disease type, current smoking, body mass index, topoisomerase status, and treatment with immunosuppressive agents) in the multivariable model ($P = 0.006$).**
Conclusion. **Baseline CRP levels are predictive of long-term ILD progression. CRP level might aid clinicians in identifying patients that require more intensive monitoring and treatment.**

Introduction

Systemic sclerosis (SSc; scleroderma) is associated with high mortality and morbidity (1). The primary cause of disease-related mortality in SSc is pulmonary involvement, including both interstitial lung disease (ILD) and pulmonary arterial hypertension (2,3). The course of SSc-related ILD is highly variable (4). Therefore, predictive markers for ILD progression represent a significant advancement, as they would aid clinicians in identifying patients who require more intensive monitoring and treatment. Forced vital capacity (FVC; expressed as percentage of predicted value) is the only validated outcome measure for severity of SSc-related ILD in randomized controlled trials (5). We have previously demonstrated that currently available demographic and clinical characteristics are not able to predict long-term decline in FVC in patients with

Dr. Mayes' work was supported by the NIH/National Institute for Arthritis and Musculoskeletal and Skin Diseases (grant P50-AR-054144) and the NIH/Institute of Allergy and Infectious Diseases (grant U01-AI-09090). Dr. Reveille's work was supported by the NIH (grant T32-AR-052283) and the NIH/Institute of Allergy and Infectious Diseases (grant U01-AI-09090). Dr. Assassi's work was supported by the NIH/National Institute for Arthritis and Musculoskeletal and Skin Diseases (grant K23-AR-061436).

[1]Xiaochun Liu, MD, PhD, Maureen D. Mayes, MD, MPH, Claudia Pedroza, PhD, John D. Reveille, MD, Shervin Assassi, MD, MS: University of Texas Health Science Center, Houston; [2]Hilda T. Draeger, MD: University of Texas Health Science Center at San Antonio; [3]Emilio B. Gonzalez, MD, Brock E. Harper, MD: University of Texas Medical Branch, Galveston.

Dr. Mayes has received speaking fees (less than $10,000) from Actelion and book royalties (less than $10,000) from Oxford University Press.

Address correspondence to Shervin Assassi, MD, MS, University of Texas Health Science Center at Houston, 6431 Fannin, MSB 5.264, Houston, TX 77030. E-mail: shervin.assassi@uth.tmc.edu.

Submitted for publication September 22, 2012; accepted in revised form January 18, 2013.

Significance & Innovations

- C-reactive protein (CRP) level predicts long-term progression of interstitial lung disease in patients with systemic sclerosis.
- Higher CRP levels are also predictive of shorter survival.
- CRP might aid clinicians in identifying patients that require more intensive monitoring and treatment.

early SSc. Only anti–topoisomerase I (anti–topo I) antibody was able to predict short-term progression of ILD, although it failed to predict long-term disease progression (4). In another study, fibrosis scores on high-resolution computed tomography (HRCT) of the chest were predictive of FVC course over a 1-year period (6). However, there are currently no clinically utilized long-term predictors of ILD progression in SSc patients.

C-reactive protein (CRP) is an acute-phase reactant that has been utilized as a marker of infection and inflammation. CRP is elevated in patients with SSc (7,8) and is associated with poor survival (7,9). In a recent large Canadian study, CRP was elevated in 25% of patients and was associated with diffuse disease type, shorter disease duration, and more severe skin and pulmonary involvement at the cross-sectional level (7). The predictive implication of CRP levels for long-term ILD progression has not been investigated in the previous studies.

This study examined the predictive significance of CRP for progression of ILD (based on longitudinally obtained serial FVC) and survival in a large early SSc cohort. We also examined the correlates of CRP at the cross-sectional level in this cohort.

Patients and methods

Study participants. All patients with SSc met the 1980 American College of Rheumatology preliminary criteria for the classification of SSc (10) or had 3 of 5 CREST syndrome features (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia, with presence of sclerodactyly being mandatory).

Patients were recruited from the prospective Genetics Versus Environment in Scleroderma Outcome Study (GENISOS; n = 266) (4). The unaffected control subjects had no history of autoimmune diseases and were matched by age, sex, and ethnicity to patients with SSc (n = 97). All study subjects provided written informed consent and the study was approved by the institutional review boards of all participating centers.

Plasma CRP measurements. Plasma was collected using EDTA blood collection tubes and stored at −80°C until analysis. Plasma samples had not undergone more than 2 thaw–freeze cycles before CRP level determination. CRP levels were determined by enzyme-linked immunosorbent assay (ELISA) using electrochemiluminescent multiplex assays (Meso Scale Discovery) (11). Each sample was examined in duplicate.

Clinical outcome measures. The disease duration was calculated using 2 different starting points: 1) the onset of disease from the first non–Raynaud's phenomenon symptom, and 2) the onset of disease from the first symptom attributable to SSc (Raynaud's phenomenon or non–Raynaud's phenomenon). Presence of autoantibodies, including anti–RNA polymerase III antibodies (anti-RNAP III), anti–U1 RNP antibodies, anticentromere antibodies (ACAs), and anti–topo I, was investigated in all SSc serum samples at the laboratories of the Division of Rheumatology at the University of Texas, Houston. Briefly, antinuclear antibodies and ACAs were detected by indirect immunofluorescence using HEp-2 cell substrates (antibodies). Anti–topo I and RNP antibodies were determined by passive immunodiffusion against calf thymus extract (Inova Diagnostics). Anti-RNAP III testing was performed by ELISA (MBL).

The Medsger Severity Index (MSI), including skin, muscle, gastrointestinal tract, lung, heart, and kidney components, was captured prospectively and utilized for the assessment of clinical severity (12). Furthermore, the concomitantly collected % predicted FVC, diffusing capacity in liters of carbon monoxide (DLCO), modified Rodnan Skin Score (mRSS), and creatine kinase (CK) were used as additional surrogates for severity of ILD, skin, and muscle involvement, respectively. Medication information was also collected prospectively. Patients on immunosuppressive agents at the time of blood draw (exception: prednisone equivalent dosage ≤5 mg/day or hydroxychloroquine) were categorized as treated with immunosuppressive agents.

Pulmonary function test. Pulmonary function tests (PFTs) were performed at the initial visit and annually thereafter. Serially obtained FVC, expressed as the percentage of predicted FVC, was utilized as the outcome measure for the severity of SSc-related ILD. Predicted FVC values were calculated according to the patient's age, height, weight, sex, and ethnicity using consistent reference values. Furthermore, all PFT data were reviewed by a pulmonologist and data were excluded if the American Thoracic Society/European Respiratory Society criteria for pulmonary function testing were not fulfilled.

Survival data collection. The vital status of each patient was obtained through medical records and queries, obtained from the National Death Index at the Centers for Disease Control and Prevention, and the Social Security Death Index.

Statistical analysis. The CRP levels were log-transformed for the analysis. We first compared the CRP levels between 266 SSc patients enrolled in the GENISOS cohort and 97 unaffected controls using Student's *t*-test. The associations of plasma CRP levels with the clinical manifestations of SSc were investigated by univariable linear regression and by Pearson's correlation in all patients, as

Table 1. Study subject characteristics at enrollment*

Characteristic	GENISOS cohort (n = 266)	Control subjects (n = 97)
Women	221 (83)	78 (80)
Age at first study visit, mean ± SD years	48.6 ± 13.5	48 ± 12.7
Ethnicity		
White	125 (47)	48 (49)
African American	54 (20)	17 (18)
Latino	77 (29)	27 (29)
Diffuse cutaneous involvement	156 (59)	
Disease duration 1, mean ± SD years†	2.5 ± 1.6	
Disease duration 2, mean ± SD years‡	4.5 ± 5.4	
Anticentromere antibody	32 (12)	
Anti–topoisomerase I antibody	49 (18)	
Anti–RNA polymerase III antibody	61 (23)	
Anti–U1 RNP antibody	30 (11)	
Treatment with immunosuppressive agents	82 (32)	

* Values are the number (percentage) unless indicated otherwise. GENISOS = Genetics Versus Environment in Scleroderma Outcome Study.
† Calculated from the onset of the first non–Raynaud's phenomenon symptom.
‡ Calculated from the onset of the first symptom attributable to systemic sclerosis, including Raynaud's phenomenon.

well as the subgroup of patients that were not on immunosuppressive agents at the baseline visit. Multivariable linear regression models were also constructed to adjust for potential demographic confounders, namely, age at the baseline visit, sex, and body mass index (BMI; kg/m^2). First, the association of disease subtypes (independent variable) with CRP levels (outcome variable) was examined after adjustment for potential confounding demographic variables. Subsequently, the correlation of CRP levels (independent variable) with disease severity (outcome variable) was examined after adjustment for potential demographic confounders. Two-sided *P* values less than 0.05 were considered significant. The analyses were performed using the STATA/SE 11.2 statistical program (StataCorp).

A joint analysis of longitudinal measurements (sequentially obtained % predicted FVC) and survival data was also conducted in order to investigate the predictive significance of the baseline CRP levels (as continuous variable) for the long-term change in FVC. This analysis allows inclusion of all FVC measurements and better reflects the slope of decline in FVC than other approaches, such as annualized rate of decline and time to respiratory failure. This analysis also adjusts for baseline differences in FVC (random intercept). Furthermore, it accounts for the association between FVC and survival, and it reduces the bias resulting from the fact that patients with more rapid decline in FVC are more likely to die (4). The longitudinal component consisted of a linear model with random effects. Predictors in the linear model included baseline plasma CRP levels and followup time. The ultimate goal of this analysis was to investigate whether baseline CRP level has predictive significance for the rate of decline in FVC over time (i.e., to identify patients with steeper decline in FVC on the subsequent visits). This was investigated by the interaction term between the protein levels and followup time in the longitudinal component (13). Secondary models also included age, ethnicity, sex, BMI, disease type, current smoking, topoisomerase status, and treatment with immunosuppressive agents as predictors in the linear model. The survival component fitted a parametric Weibull model with CRP as predictors. The starting point of the survival analysis was time of enrollment.

Results

Comparison of CRP levels in SSc patients and unaffected controls. The CRP levels were determined in all baseline plasma samples of patients enrolled in the GENISOS cohort (n = 266) and their age-, sex-, and ethnicity-matched controls (n = 97). The demographic and clinical characteristics of the patients and control subjects at enrollment are shown in Table 1. In the patient cohort at the baseline visit, 82 (32%) were treated with immunosuppressive agents. Specifically, azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide were administered to 7 (3%), 25 (9%), 3 (1%), and 8 (3%) patients, respectively. Furthermore, 57 patients (21%) were treated with prednisone (>5 mg/day dosages), and the mean ± SD daily prednisone equivalent dose was 15.8 ± 10.4 mg in this group of patients. Based on a composite outcome of increased interstitial markings on chest radiography, rales on physical exam, or an FVC of ≤70%, shown to correlate with SSc-related ILD on HRCT of the chest (14), 44.4% of patients already had ILD at the baseline visit. The mean ± SD FVC in the patients with ILD was 68 ± 20 liters. Patients with SSc had higher circulating levels of CRP (P = 0.027) than the unaffected controls. Dichotomizing the CRP values based on the 90th percentile value among unaffected controls revealed that 22.4% of patients had a high CRP value. Supplementary Figure 1 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21968/abstract) shows the distribution of CRP measurements in patients and controls.

Table 2. Association of disease subtypes with plasma CRP levels*

	P_u†	Mean difference (95% CI)	P_m‡	Mean difference (95% CI)	P_u§	Mean difference (95% CI)
Disease duration 1¶	0.303	0.07 (−0.06, 0.19)	0.625	0.04 (−0.12, 0.20)	0.348	0.07 (−0.08, 0.22)
Disease duration 2#	0.809	0.005 (−0.03, 0.04)	0.854	−0.05 (−0.55, 0.46)	0.911	0.003 (−0.05, 0.06)
Disease type**	0.075	−0.37 (−0.77, 0.04)	0.040	−0.05 (−0.10, −0.002)	0.052	−0.48 (−0.96, 0.005)
Age at baseline, years	0.015	0.02 (0.004, 0.03)	0.047	0.015 (0.0002, 0.03)	0.026	0.02 (0.002, 0.04)
Anticentromere antibody	0.137	−0.46 (−1.06, 0.15)	0.043	−0.033 (−0.07, −0.001)	0.042	−0.65 (−1.27, −0.02)
Anti–topoisomerase I antibody	0.291	0.30 (−0.25, 0.84)	0.409	0.02 (−0.02, 0.05)	0.521	0.22 (−0.45, 0.88)
Anti–RNA polymerase III antibody	0.071	0.44 (−0.04, 0.92)	0.120	0.03 (−0.009, 0.08)	0.030	0.66 (0.06, 1.27)
Anti–U1 RNP antibody	0.962	0.02 (−0.63, 0.66)	0.538	0.009 (−0.02, 0.04)	0.478	0.31 (−0.55, 1.17)

* CRP = C-reactive protein; 95% CI = 95% confidence interval.
† *P* value from univariable model.
‡ *P* value from multivariable model after adjustment for age at enrollment, sex, ethnicity, and body mass index.
§ *P* value from univariable model when patients on immunosuppressive agents were excluded.
¶ Disease duration calculated from the onset of the first non–Raynaud's phenomenon symptom.
# Disease duration calculated from the onset of the first systemic sclerosis symptom, including Raynaud's phenomenon.
** Based on the extent of skin disease (limited versus diffuse).

Association of disease subtypes with plasma CRP levels. Table 2 shows the univariable and multivariable associations of disease subtypes with plasma CRP levels in 266 SSc patients enrolled in the GENISOS cohort. After adjustment for confounders (age at enrollment, sex, ethnicity, and BMI) in the multivariable model, higher CRP levels were associated with more diffuse cutaneous involvement ($P = 0.040$) and older age at baseline ($P = 0.026$). Higher CRP levels were also associated with absence of ACAs ($P = 0.043$). Disease duration calculated according to both methods did not correlate with plasma CRP levels. Furthermore, the other SSc-related antibodies did not correlate with plasma CRP levels. The exclusion of patients who were treated with immunosuppressive agents at the time of blood draw did not change the above observed associations. However, the presence of anti-RNAP III was associated with higher CRP levels in this subgroup analysis.

Correlation of plasma CRP levels with disease severity. Table 3 shows the univariable and multivariable associations of plasma CRP levels with disease severity in SSc patients. After adjustment for age at enrollment, sex, ethnicity, and BMI, high plasma CRP levels correlated with higher mRSS ($P = 0.018$), lower FVC ($P = 0.001$) and DLco ($P = 0.002$), and higher MSI skin ($P = 0.018$), lung ($P = 0.003$), and joint component scores ($P = 0.001$). After exclusion of patients on immunosuppressive agents, all above correlations remained significant (Table 2).

Predictive significance of baseline CRP levels for long-term change in FVC and survival. Using a joint analysis of longitudinal measurements (sequentially obtained FVCs) and survival data, we investigated the predictive significance of baseline CRP levels for long-term change in FVC accounting for mortality. The mean time-in-study was 4.36 years (up to 13.1 years). The longitudinal FVC analysis was based on 1,016 FVC measurements belonging to 248 patients that fulfilled the American Thoracic Society/European Respiratory Society criteria. A line plot showing the longitudinal progression of FVC in the GENISOS cohort is shown in Supplementary Figure 2 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.21968/abstract).

In the survival component of the analysis, 86 patients (32.3%) had died at the time of our death search query. Baseline CRP levels correlated with higher mortality (hazard ratio 1.51, 95% confidence level [95% CI] 1.09, 2.08; $P < 0.001$) and predicted the long-term decline in % predicted FVC ($\beta = -0.35$, 95% CI −0.61, −0.09; $P = 0.006$). The predictive significance of CRP for ILD progression was independent of potential confounders (age at baseline, sex, ethnicity, BMI, and treatment with immunosuppressive agents) in the multivariable model ($\beta = -0.36$, 95% CI −0.62, −0.1; $P = 0.006$). The CRP level also remained a significant predictor of ILD progression ($\beta =$

Table 3. Correlation of plasma CRP levels with disease severity*

	R	P_u†	P_m‡	P_u§
FVC	−0.25	0.001	0.001	< 0.001
DLco	−0.25	0.001	0.002	0.001
CK	−0.06	0.423	0.700	0.226
mRSS	0.16	0.023	0.018	0.010
Skin	0.16	0.021	0.018	0.033
Muscle	0.09	0.222	0.207	0.640
Joint	0.24	0.001	0.001	0.002
GI	0.02	0.798	0.904	0.799
Lung	0.21	0.003	0.003	0.004
Heart	0.03	0.718	0.616	0.431
Kidney	0.07	0.334	0.380	0.685

* Components of the Medsger Severity Index. CRP = C-reactive protein; FVC = percent predicted forced vital capacity; DLco = % predicted diffusing capacity for carbon monoxide; CK = creatine kinase; mRSS = modified Rodnan Skin Score; GI = gastrointestinal.
† *P* value from univariable model.
‡ *P* value from multivariable model after adjustment for age at enrollment, sex, ethnicity, and body mass index.
§ *P* value from univariable model when patients on immunosuppressive agents were excluded.

−0.35, 95% CI −0.60, −0.1; $P = 0.006$) even after the multivariable model was extended by disease type (limited versus diffuse), current smoking, and topo I positivity status. Contrary to ILD, baseline CRP levels did not predict a long-term increase in mRSS ($P = 0.588$).

Discussion

In the present study, we demonstrate for the first time that baseline CRP levels predicted long-term ILD progression independent of potential confounders in a large, well-characterized prospective cohort of patients with early SSc. This finding can have important clinical implications, as a previous longitudinal study in the same cohort investigating a comprehensive list of demographic and clinical factors was not able to identify any predictors of long-term ILD progression (4).

This study confirmed the findings of a large Canadian study (7) reporting that elevated baseline CRP levels were associated with the concomitant diffuse cutaneous involvement and severity of skin and lung involvement. Of interest, both studies did not observe a correlation of CRP with CK levels (7). Contrary to the previous study, CRP level was not associated with disease duration in the present study. However, the disease duration varied in a smaller range, as disease duration ≤5 years was an inclusion criterion in the GENISOS cohort, whereas the Canadian cohort did not restrict enrollment based on the disease duration. Furthermore, the present study confirmed the previously reported association of elevated CRP level with mortality (7,9).

CRP level is a general marker of inflammation. It is a part of the innate immune response to systemic inflammation downstream to interleukin-6 (IL-6) and IL-1β (15). In a previous study, IL-6 level showed moderate correlation with high-sensitivity CRP level ($r = 0.69$, $r^2 = 0.48$), indicating that 48% of variation in CRP levels can be explained by IL-6 (16). Future studies need to examine whether IL-6 or other inflammatory cytokines have added predictive significance beyond CRP level for ILD progression.

The present study has several strengths. The GENISOS cohort is a well-characterized, multiethnic cohort. It is an early SSc cohort with mean disease duration of 2.5 years at enrollment, reducing problems arising from survival bias. Furthermore, the utilized advanced analytic methods allowed the joint analysis of the longitudinal outcome (all serially obtained FVCs) and the survival status. This joint model accounts for the fact that patients with a rapid decline in FVC have a higher mortality (4). This approach also allows inclusion of all FVC measurements in an individual patient, reflecting better the slope of decline in FVC than other methods that analyze only the first and last measurements.

The present study has some limitations. The GENISOS cohort contains a relatively high proportion of patients with diffuse disease, which can be explained in part by the fact that it is based in 3 tertiary care centers. Furthermore, the added predictive significance of HRCT fibrosis score could not be investigated because this information was not available in the GENISOS cohort. Furthermore, we examined the overall mortality because reliable data on causes of death were not available in our sample. We were also unable to perform well-powered subgroup analysis in SSc patients with certain disease manifestation (e.g., arthritis) due to limitations in sample size.

In summary, the present study demonstrates that CRP level can predict long-term SSc-ILD progression in addition to survival. These results indicate that CRP level can be used as a predictive biomarker to identify the subgroup of SSc patients that would benefit from more intensive monitoring and treatment.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Assassi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Liu, Mayes, Draeger, Assassi.
Acquisition of data. Liu, Mayes, Draeger, Gonzalez, Harper, Reveille, Assassi.
Analysis and interpretation of data. Liu, Mayes, Pedroza, Harper, Reveille, Assassi.

REFERENCES

1. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2012;51:1017–26.
2. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994; 37:1283–9.
3. Tyndall AJ, Bannert B, Vonk M, Airo P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis 2010;69:1809–15.
4. Assassi S, Sharif R, Lasky RE, McNearney TA, Estrada YM, Draeger HT, et al. Predictors of interstitial lung disease in early systemic sclerosis: a prospective longitudinal study of the GENISOS cohort. Arthritis Res Ther 2010;12:R166.
5. Furst D, Khanna D, Matucci-Cerinic M, Clements P, Steen V, Pope J, et al. Systemic sclerosis: continuing progress in developing clinical measures of response. J Rheumatol 2007;34: 1194–200.
6. Khanna D, Tseng CH, Farmani N, Steen V, Furst DE, Clements PJ, et al. Clinical course of lung physiology in patients with scleroderma and interstitial lung disease: analysis of the Scleroderma Lung Study Placebo Group. Arthritis Rheum 2011;63:3078–85.
7. Muangchan C, Harding S, Khimdas S, Bonner A, Canadian Scleroderma Research Group, Baron M, et al. Association of C-reactive protein with high disease activity in systemic sclerosis: results from the Canadian Scleroderma Research Group. Arthritis Care Res (Hoboken) 2012;64:1405–14.
8. Ohtsuka T. Relation between elevated high-sensitivity C-reactive protein and anti-mitochondria antibody in patients with systemic sclerosis. J Dermatol 2008;35:70–5.
9. Nagy Z, Czirjak L. Increased levels of amino terminal propeptide of type III procollagen are an unfavourable predictor of survival in systemic sclerosis. Clin Exp Rheumatol 2005;23: 165–72.
10. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
11. Gourh P, Arnett FC, Assassi S, Tan FK, Huang M, Diekman L, et al. Plasma cytokine profiles in systemic sclerosis: associations with autoantibody subsets and clinical manifestations. Arthritis Res Ther 2009;11:R147.

12. Medsger TA Jr, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol 1999;26:2159–67.
13. Rizopoulos D. An R package for the joint modelling of longitudinal and time-to-event data. J Stat Soft 2010;35:1–33.
14. Steele R, Hudson M, Lo E, Baron M, Canadian Scleroderma Research Group. Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. Arthritis Care Res (Hoboken) 2012;64:519–24.
15. Mortensen RF. C-reactive protein, inflammation, and innate immunity. Immunol Res 2001;24:163–76.
16. Ohtsuka T. Serum interleukin-6 level is reflected in elevated high-sensitivity C-reactive protein level in patients with systemic sclerosis. J Dermatol 2010;37:801–6.