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Combining Clinical and Biological Data to Predict Progressive Pulmonary Fibrosis in Patients With Systemic Sclerosis Despite Immunomodulatory Therapy

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Objective. Progressive pulmonary fibrosis (PPF) is the leading cause of death in systemic sclerosis (SSc). This study aimed to develop a clinical prediction nomogram using clinical and biological data to assess risk of PPF among patients receiving treatment of SSc-related interstitial lung disease (SSc-ILD).

Methods. Patients with SSc-ILD who participated in the Scleroderma Lung Study II (SLS II) were randomized to treatment with either mycophenolate mofetil (MMF) or cyclophosphamide (CYC). Clinical and biological parameters were analyzed using univariable and multivariable logistic regression, and a nomogram was created to assess the risk of PPF and validated by bootstrap resampling.

Results. Among 112 participants with follow-up data, 22 (19.6%) met criteria for PPF between 12 and 24 months. An equal proportion of patients randomized to CYC (n = 11 of 56) and mycophenolate mofetil (n = 11 of 56) developed PPF. The baseline severity of ILD was similar for patients who did, compared to those who did not, experience PPF in terms of their baseline forced vital capacity percent predicted, diffusing capacity for carbon monoxide percent predicted, and quantitative radiological extent of ILD. Predictors in the nomogram included sex, baseline CXCL4 level, and baseline gastrointestinal reflux score. The nomogram demonstrated moderate discrimination in estimating the risk of PPF, with a C-index of 0.72 (95% confidence interval 0.60-0.84).

Conclusion. The SLS II data set provided a unique opportunity to investigate predictors of PPF and develop a nomogram to help clinicians identify patients with SSc-ILD who require closer monitoring while on therapy and potentially an alternative treatment approach. This nomogram warrants external validation in other SSc-ILD cohorts to confirm its predictive power.

INTRODUCTION

Progressive pulmonary fibrosis (PPF) is the leading cause of death in patients with systemic sclerosis (SSc) (1). Although interstitial lung disease (ILD) occurs in the majority of patients with SSc (2), the disease course can vary considerably between patients (3). Recent observational studies have demonstrated that approximately one third of patients with SSc-ILD experience PPF at 1 year (4). However, predicting which patients with SSc-ILD will develop PPF remains a challenge (3).

A number of studies have identified single predictors of SSc-ILD progression (eg, male sex, diffuse cutaneous disease); however, applying the results of these studies to clinical practice is difficult. For example, prior studies have used different definitions of ILD progression (ie, various thresholds of physiological decline). Also, it is unclear how single predictors affect disease course in a given patient who simultaneously possesses other predictors that may increase or decrease the risk of PPF. In addition, the majority of these studies failed to consider the important effects of treatment on ILD course (5–7). Interpreting the results of these

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observational studies, in which patients received various treatments over the course of their follow-up, is not easy.

No valid clinical prediction tools exist for predicting PPF (8) among patients with SSc-ILD who are already receiving an accepted immunomodulating treatment. The purpose of this study was to create a predictive nomogram as a simple intuitive tool to quantify the risk of PPF in patients with SSc-ILD receiving treatment (9). To overcome the limitations inherent with single predictors abstracted from cross-sectional data or retrospective convenience groups, we focused on the rich data set generated during the Scleroderma Lung Study II (SLS II), in which patients received active treatment with either mycophenolate mofetil (MMF) or cyclophosphamide (CYC) (10). The definition of PPF used in this analysis was adapted from the recent guidelines generated by the American Thoracic Society (8). The findings of this research may help clinicians identify patients who require closer monitoring while receiving standard immunomodulating therapy for SSc-ILD.

PATIENTS AND METHODS

Study participants. All participants enrolled in SLS II (ClinicalTrials.gov identifier: NCT00883129) were included in these post hoc analyses (10). SLS II was a National Institutes of Health–sponsored multicenter randomized controlled trail (RCT) that enrolled an ethnically diverse population of both male and female patients with SSc-ILD. Race and ethnicity were determined by patient self-report. The main inclusion criteria included age 18 years or older, disease duration less than or equal to 7 years from the first non–Raynaud's phenomenon symptom of SSc, forced vital capacity percent predicted (FVC%-predicted) value of 40% to 80%, hemoglobin-adjusted single-breath diffusing capacity for carbon monoxide percent predicted (DLCO%-predicted) value of 40% or greater (or 30%-39% if there was no evidence of clinically significant pulmonary hypertension), and evidence of any ground glass opacity on high-resolution computed tomography (HRCT). Key exclusion criteria included clinically significant pulmonary vascular disease, concurrent obstructive lung disease, and smoking within the previous 6 months. The institutional review board of each of the 14 study sites approved this study, and informed consent was obtained by all participants.

SLS II study design. In SLS II, 142 patients were randomized to receive MMF for 24 months or oral CYC for 12 months followed by 12 months of placebo. The primary end point, FVC %-predicted, was measured every 3 months during the 24-month study period. HRCT thoracic imaging was obtained at baseline and at 24 months. To calculate the change in the extent of quantitative ILD (QILD) over the course of the study, a computer-aided design scoring system was used (see Supplementary Material) (11). The reflux domain of the University of California, Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0) was used to assess patient-reported symptoms of esophageal dysfunction (see Supplementary Material) (12). The Mahler baseline dyspnea index was used to assess patient-reported dyspnea (13). To assess changes in dyspnea, the transitional dyspnea index (TDI) (14) was administered every 6 months.

Definition of PPF. The definition of PPF in the present study was based on the aforementioned guideline (9). Patients meeting at least two of the following were classified as having PPF: 1) worsening respiratory symptoms, 2) absolute decline in FVC%-predicted greater than or equal to 5% and/or absolute decline in DLCO%-predicted corrected for hemoglobin greater than or equal to 10%, and 3) radiological evidence of disease progression. Worsening respiratory symptoms was defined as a decrease in the TDI score of greater than or equal to 1.5, based on the mean minimally important difference for TDI worsening in SSc-ILD (15). Radiological evidence of disease progression was defined as an increase in the whole lung QILD score of greater than or equal to 2%. The 2% threshold for the QILD change has been defined as the upper limit of error for repetitive measurement within the same person (16). Also, an increase in the whole lung QILD score of greater than or equal to 2% predicted long-term mortality in both SLS I and SLS II (14).

Because SLS II was a 24-month study wherein the peak response to therapy occurred at 21 months, we evaluated for the presence of PPF not only at 12 months, that is, the timeline proposed in the 2022 guideline (9), but also at 18 and 24 months. This approach enabled us to assess the complete response to treatment as well as to include the radiological component of the criteria because HRCT was only performed at 24 months. Patients were classified as having PPF if they fulfilled PPF criteria at 12, 18, or 24 months. Patients needed to fulfill both the symptom and physiological criteria at 12 and 18 months to be classified as having PPF. At 24 months, patients could fulfill any two of the three criteria.

Biomarker assessment. A select group of serum and plasma biomarkers of inflammation and fibrosis measured at baseline were evaluated based on their association with SSc-ILD outcomes in prior studies, including C-reactive protein (17), interleukin 6 (18), monocyte count (19), neutrophil count and neutrophil to lymphocyte ratio (20), CCL18 (21), Krebs von den Lungen 6 (22), and CXCL4 (23). At baseline, plasma samples were collected in EDTA tubes and immediately processed on-site on the day of collection, stored at −70°C, and shipped on dry ice to the central repository at the University of Texas Health Science Center at Houston. Technicians performing the assays were blinded to the clinical diagnosis and outcome data. Please see the Supplementary Material for further details on the assessment of these biomarkers.

Statistical analysis. *Baseline characteristics.* Summary statistics were generated for baseline characteristics. Group comparisons were performed using two-sample Student's *t*-tests for continuous variables and chi-square tests or Fischer's exact tests for categorical variables.

Primary outcome: PPF. The primary outcome was meeting criteria for PPF at 12, 18, or 24 months. Univariable logistic regression was performed to evaluate the relationship between variables previously shown to be associated with ILD progression (Supplementary Table 1). A logistic regression analysis was performed because the primary outcome of interest was whether someone developed PPF (yes or no) at 12, 18, or 24 months. A Cox proportional hazards regression analysis was not performed because the event components were measured at different time intervals (ie, the assumption that the hazards were proportional was not met), and we were more interested in the occurrence of PPF versus the time to PPF.

An a priori variable selection process was performed to create the multivariable model. Any variables having a significant univariable test at a *P* value of less than 0.1 were included in the multivariable logistic regression analysis. To assess the internal validity and quantify the optimism of the predictive model, bootstrap analyses were performed. Specifically, 2000 sample data sets were generated from the data with replacement, and the average model coefficients were estimated. The adjusted bootstrap percentile method was used to calculate 95% confidence intervals (CIs) for the estimates. Additionally, the model optimism was assessed using Harrell's bias correction of the concordance. A nomogram was generated to graphically represent the probability of PPF based on the multivariable regression model. Various studies have demonstrated that nomograms represent more accurate and discriminatory tools for predicting outcomes compared with risk grouping, look-up tables, classification and regression tree analysis, and artificial neural networks (24). Statistical effect plots for the multivariable regression model were created to demonstrate the effect of selected regressor variables on the outcome while holding other regressors at their mean value.

Table 1. Baseline characteristics of participants who experienced PPF (n = 22) and those who did not (n = 90) in SLS II

Variable	n	No PPF (n = 90)	Yes PPF (n = 22)	*P* value[a]
Treatment arm	112			1.000
MMF		45 (80.4%)	11 (19.6%)	
CYC		45 (80.4%)	11 (19.6%)	
Age, mean (SD) y	112	51.8 (9.34)	51.5 (9.90)	0.906
Female, no. (% of all female patients)	112	70 (85.4)	12 (14.6)	0.0274
Male, no. (% of all male patients)	112	20 (66.7)	10 (33.3)	
African American, no. (% of all African American patients)	112	19 (76.0)	6 (24.0)	0.534
Not African American, no. (% of all non–African American patients)	112	71 (81.6)	16 (18.4)	
Disease duration, mean (SD) y	110	2.66 (1.70)	3.03 (2.01)	0.385
Disease duration, median (IQR) y	112	2.12 (1.28-4.04)	2.81 (1.22-4.46)	
Diffuse cutaneous sclerosis, no. (% of all participants with diffuse cutaneous sclerosis)	112	53 (80.3)	13 (19.7)	0.986
Limited cutaneous sclerosis, no. (% of all participants with limited cutaneous sclerosis)	112	37 (80.4)	9 (19.6)	
mRSS, mean (SD)	112	14.5 (9.75)	14.6 (10.85)	0.951
FVC%-predicted, mean (SD)	112	67.21 (8.98)	65.31 (9.76)	0.384
DLCO%-predicted, mean (SD)	112	54.62 (12.60)	56.47 (15.62)	0.558
QILD-WL score, mean (SD)	108	28.34 (14.33)	26.51 (9.37)	0.588
QILD-WL score >20%, no. (% of all participants with QILD-WL score >20%)	108	31 (83.8)	6 (16.2)	0.796
QILD-WL score ≤20%, no. (% of all participants with QILD-WL score ≤20%)	108	57 (80.3)	14 (19.7)	
GIT 2.0 reflux score, mean (SD)	109	0.55 (0.50)	0.80 (0.69)	0.0542
BDI score, mean (SD)	107	7.60 (2.11)	6.70 (2.52)	0.098
Scl-70 antibody presence, no. (% of all participants with Scl-70 antibody)	106	44 (84.6)	8 (15.4)	0.181
Scl-70 antibody absence, no. (% of all participants without Scl-70 antibody)		40 (74.1)	14 (25.9)	
CRP (log2), mean (SD)	106	2.22 (1.84)	2.61 (1.85)	0.379
IL-6 (log2), mean (SD)	105	1.88 (1.16)	1.93 (1.27)	0.857
Monocyte count (log2), mean SD	108	0.48 (0.21)	0.53 (0.28)	0.371
Neutrophil count (log2), mean (SD)	108	2.31 (0.56)	2.50 (0.52)	0.160
Neutrophil to lymphocyte ratio (log2), mean (SD)	108	1.64 (0.81)	1.78 (0.88)	0.501
KL-6 (log2), mean (SD)	104	10.37 (0.98)	10.58 (0.73)	0.369
CCL18 (log2), mean (SD)	106	7.29 (0.88)	7.06 (0.95)	0.275
CXCL4 (log2), mean (SD)	107	11.22 (1.02)	10.76 (1.27)	0.073

Abbreviations: BDI, baseline dyspnea index; CRP, C-reactive protein; CYC, cyclophosphamide; DLCO%-predicted, diffusing capacity for carbon monoxide percent predicted; FVC%-predicted, forced vital capacity percent predicted; GIT 2.0, University of California, Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0; IL-6, interleukin 6; IQR, interquartile range; KL-6, Krebs von den Lungen 6; MMF, mycophenolate mofetil; mRSS, modified Rodnan skin score; PPF, progressive pulmonary fibrosis; QILD-WL, quantitative interstitial lung disease- whole lung; SLS II, Scleroderma Lung Study II.

[a]*P* values were obtained through Student's *t*-test for continuous variables and the chi-square test or Fischer's exact test for categorical variables.

Table 2. Frequency of participants who met individual and combined criteria for PPF at 12, 18, and/or 24 months (n = 112)

	12 months	18 months	24 months
Individual criterion			
Symptoms	8	1	6
Physiological	10	5	13
Radiographic	NA	NA	12
Combined criteria[a]			
Symptoms and physiological	7	0	3
Physiological and radiographic	NA	NA	9
Symptoms and radiographic	NA	NA	2
Symptoms, physiological, and radiographic	NA	NA	1

Note: High-resolution computed tomography thoracic imaging was obtained at baseline and 24 months.
Abbreviations: NA, not available; PPF, progressive pulmonary fibrosis.
[a]Based on the first time a patient met PPF criteria. Patients who met PPF criteria at 12 months (n = 7) were not included in the 18- and 24-month assessments to avoid the same patient being counted twice in the multivariable model.

All tests were two-sided and performed using SAS 9.4 (SAS Institute).

RESULTS

Participant characteristics. Among all SLS II (N = 142) participants, 112 (78.9%) had nonmissing data for at least two of the three criteria for PPF at 12, 18, or 24 months (Table 1); 97 participants had a follow-up HRCT scan at 24 months. The baseline disease features and demographic characteristics of the SLS II participants who had follow-up PPF criteria data closely reflected those of the overall study population (Supplementary Table 2) (10).

PPF. In SLS II, 22 of 112 (19.6%) participants met PPF criteria from 12 to 24 months, with 11 of 56 (19.6%) randomized to CYC and 11 of 56 (19.6%) randomized to MMF. Baseline characteristics were similar for participants who met PPF criteria and those who did not, with the following exception: a greater proportion of male participants than female participants met PPF criteria (33.3% vs. 14.6%; P = 0.0274). Participants who met PPF criteria also had lower CXCL4 levels (P = 0.073) and higher (worse) reflux scores at baseline (P = 0.0542) (Table 1, Supplementary Figure 1).

Among the 22 study participants who fulfilled PPF criteria, 10 met the symptoms and physiological criteria, nine met the physiological and radiological criteria, two met the symptoms and radiological criteria, and one met all three criteria (ie, symptoms, physiological, and radiological) (Table 2).

Table 3. Multivariable logistic regression model for predicting PPF in SLS II (n = 112)

Variable	Odds Ratio	95% CI	*P* value
Sex (male vs. female)	3.54	1.23-10.21	0.0194
CXCL4 level	0.59	0.38-0.92	0.0220
Reflux score	2.34	0.95-5.78	0.0652

Abbreviations: CI, confidence interval; PPF, progressive pulmonary fibrosis; SLS II, Scleroderma Lung Study II.

More participants who met PPF criteria prematurely discontinued treatment (11 of 22 [50%]) compared with participants who did not meet PPF criteria (15 of 90 [16.7%]). The most common reason for discontinuation in both groups was an adverse event or intercurrent illness (Supplementary Table 3). Among the 11 participants who prematurely discontinued treatment in the PPF group, the median duration of study treatment was 10 (interquartile range 7-14.25) months; seven participants were randomized to CYC, and four were randomized to MMF. Six of these 11 patients started on alternate SSc-ILD therapy before the end of the 24-month study period (three on CYC and three on MMF). All but 2 of the 11 participants who prematurely

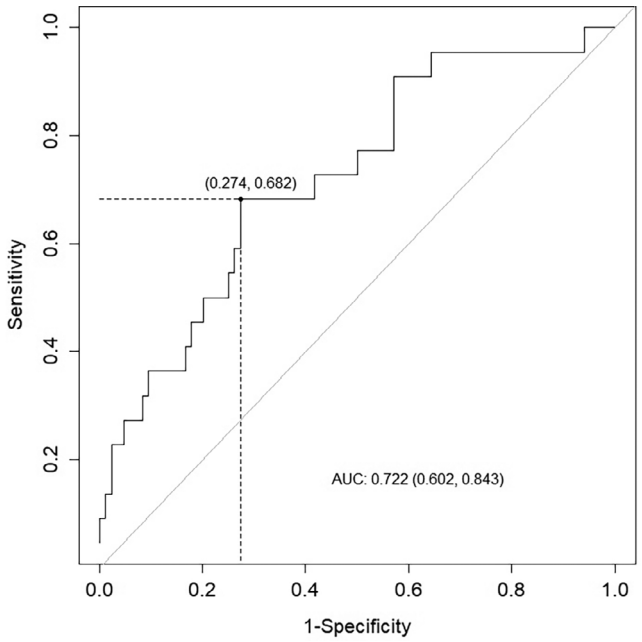

Figure 1. Area under the receiver operating characteristic curve (AUC) for the multivariable logistic regression model. Based on the Youden index analysis, the sensitivity and specificity were 68% and 72%, respectively.

discontinued treatment returned for their 24-month study visit. The two participants who did not return for the final study visit had died.

Prediction model. In the univariable analysis (Supplementary Table 4), the following variables met the inclusion criterion for the multivariable model: male sex (odds ratio [OR] 2.92 [95% CI 1.10-7.73]; $P = 0.032$), CXCL4 level (OR 0.70 [95% CI 0.46-1.05]; $P = 0.083$), and reflux score (OR 2.15 [95% CI 0.96-4.79]; $P = 0.063$). Baseline FVC%-predicted, DLCO %-predicted, modified Rodnan skin score, disease duration, QILD scores for the whole lung, anti-Scl-70 antibody presence, and other inflammatory marker levels were not significantly associated with PPF in this univariable analysis (Supplementary Table 4).

When the aforementioned variables were combined into the multivariable model (Table 3), the area under the receiver operating characteristic curve (ROC) was 0.72 (95% CI 0.60-0.84) in the Youden index analysis, and the sensitivity and specificity were 68% and 72%, respectively (Figure 1). The optimism-corrected area under the ROC was 0.69. The bootstrapped mean coefficients were higher than the original coefficients (Supplementary Table 5).

In the nomogram constructed from this analysis (Figure 2), the effect of each variable on the outcome is represented in the format of axes. Risk points are calculated according to the predictive importance of the variable of interest (24). Male sex, higher reflux score, and lower CXCL4 level were associated with an increased risk of PPF. Effect plots (Figure 3) demonstrate the effect of selected regressor variables on the outcome while holding other regressors (eg, reflux score, CXCL4 level) at their mean value.

Because CXCL4 measurement is not routinely performed in clinical practice, we created a multivariable model composed only of male sex and reflux score in an exploratory analysis (Supplementary Table 6). The area under the ROC for this model was 0.67 (95% CI 0.54-0.80).

DISCUSSION

Over the last decade, RCTs have demonstrated the efficacy of four new therapeutic agents for SSc-ILD: MMF, nintedanib, rituximab, and tocilizumab (10,25–28). Although the expansion

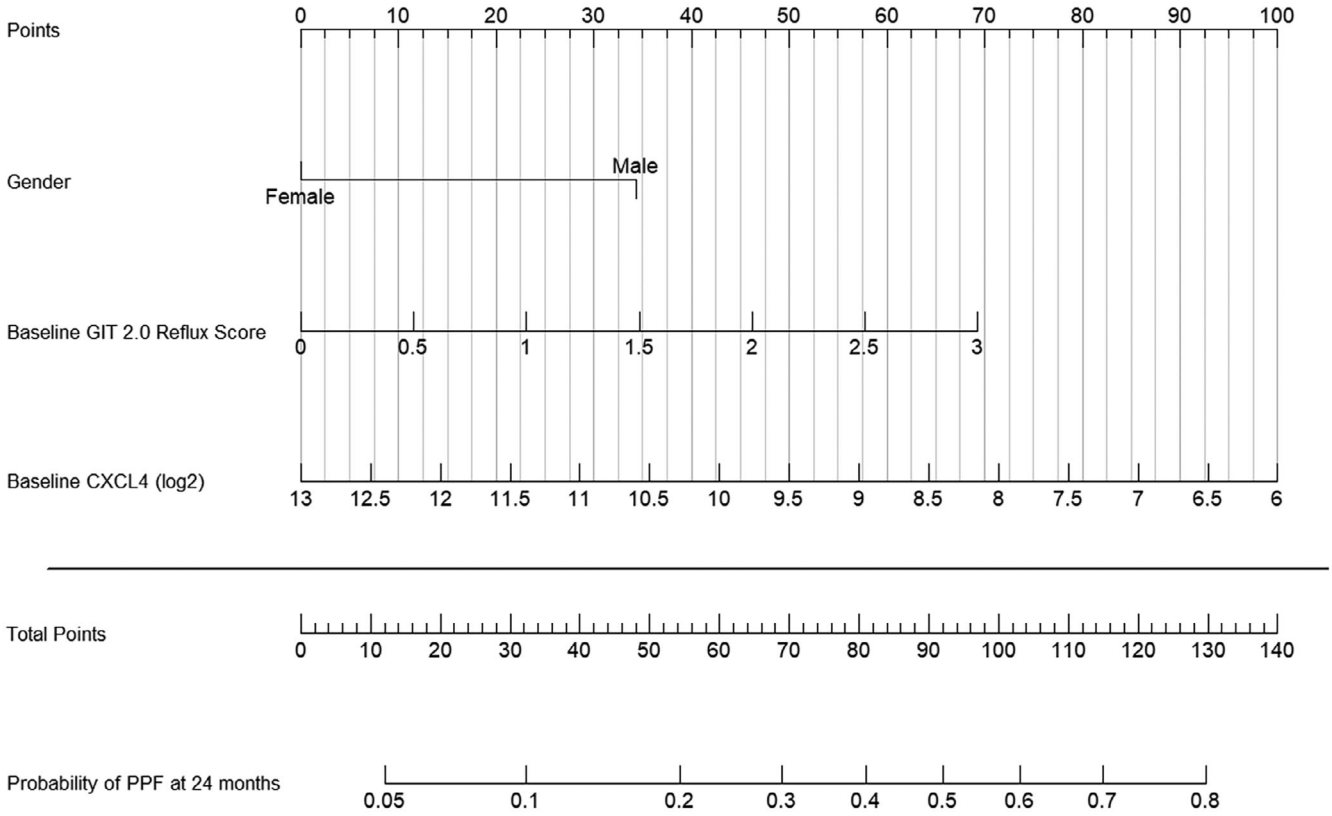

Figure 2. Progressive pulmonary fibrosis (PPF) risk nomogram. Each predictor is assigned a score on each axis based on the points that appear on the first (most superior) horizontal axis. The sum of all points for each single predictor is computed and denoted as the total score. The probability of PPF is ascertained by matching the total points to the probability of PPF (most inferior horizontal axis). For example, a male patient (35 points) with a baseline University of California, Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0) reflux score of 1.5 (35 points) and a baseline log2 CXCL4 level of 9.5 (50 points) would have a total score of 120, which indicates a probability of PPF of greater than 70%.

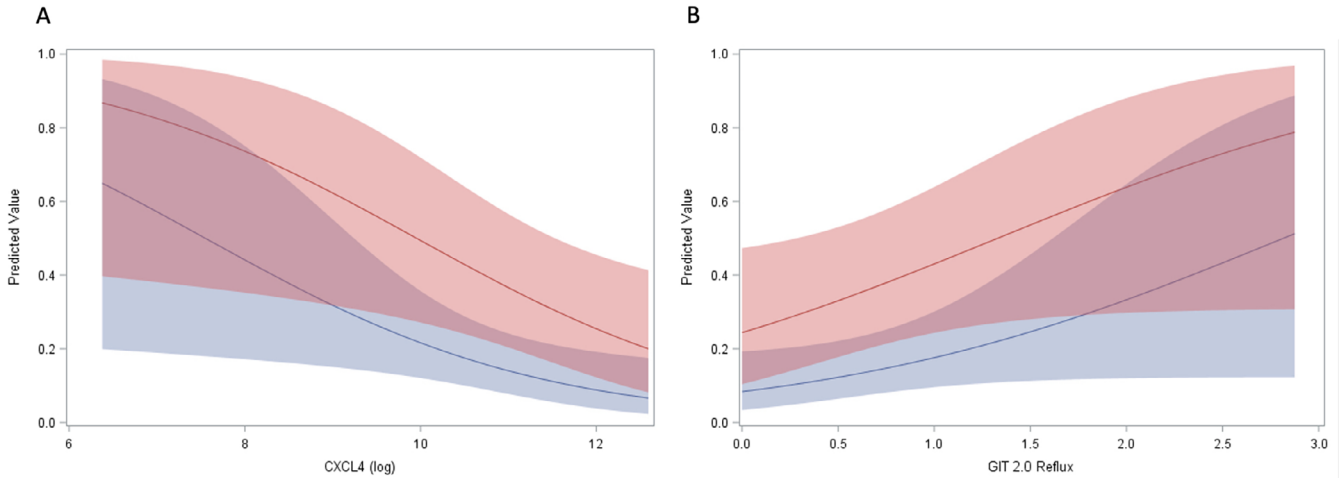

Figure 3. Effect plots demonstrate the effect of selected regressor variables on the outcome while holding other regressors at their mean value. **A,** Reflux score is held at the mean value (0.61) to visualize how sex affects the predictive ability of CXCL4 level on the outcome. **B,** CXCL4 level is held at the mean value (11.12) to visualize how sex affects the predictive ability of reflux score on the outcome. The shaded areas represent the 95% confidence interval. GIT 2.0, University of California, Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0.

of the treatment armamentarium represents a major advance for this rare disease, it also brings forth an opportunity to understand how to personalize the care of patients with SSc-ILD. The present study endeavored to determine whether a combination of patient factors could predict the likelihood of PPF in the approximately 20% of patients with SSc-ILD who met criteria for PPF despite a course of treatment with MMF or CYC. This study suggests that an evaluation of reflux severity, a biomarker level (CXCL4), and self-reported sex may predict PPF with good accuracy. If validated in future studies, such an approach could identify patients with SSc-ILD who would benefit from closer monitoring of their response to the initial treatment approach to help identify those who might benefit from alternative therapy (eg, biologic therapy or combination therapy).

Prior studies have attempted to elucidate the most important factors for predicting progression of ILD in SSc. Although some factors (eg, sex) have been consistently found to predict outcomes for SSc-ILD (4,29), other factors have yielded inconsistent predictive potential, for example, African American race (30,31) and CCL18 level (32,33). Applying varying definitions of ILD progression may have hampered progress in this area. For example, studies have used different thresholds of physiological decline to define ILD progression (eg, absolute or relative FVC%-predicted decline greater than 5% or greater than 10%, sometimes combined with a decline in DLCO%-predicted). Although physiological decline has been associated with mortality in SSc-ILD (34,35), RCTs have demonstrated that physiological changes correlate poorly with patient-reported outcomes in SSc-ILD (25,36). Furthermore, in SSc, other factors independent of the parenchymal lung disease may affect FVC%-predicted measurement (eg, cutaneous sclerosis of the chest, respiratory muscle weakness).

The recently published definition of PPF (9) not only includes physiological criteria but also considers a patient's perception of their shortness of breath, along with radiological changes. In the present study, we adapted this approach and demonstrated that approximately 20% of patients in SLS II experienced PPF between 12 and 24 months. Consistent with our prior studies that found no significant differences in physiological, radiological, or patient-reported outcomes between patients randomized to MMF and those randomized to CYC (10,37,38), a similar proportion of patients in both treatment arms experienced PPF. These findings suggest that despite receiving relatively early introduction of MMF or CYC (the mean disease duration was less than 3 years), a subgroup of patients with SSc-ILD will nonetheless experience PPF in the ensuing 1 to 2 years.

Interestingly, the baseline characteristics of the patients who did, compared with those who did not, experience PPF were similar in terms of their baseline FVC%-predicted, DLCO%-predicted, and radiological extent of ILD. Although these measurements are often used to predict prognosis in SSc-ILD (6,39), their ability to predict ILD progression in the setting of disease-modifying antirheumatic treatment is not well established. The present findings demonstrate that the physiological and radiological burden may not represent the most important factors to consider when identifying patients at greatest risk for developing PPF when initiating treatment. The results of the current analysis suggest that other factors should be taken into consideration, such as the patient's sex, self-reported reflux symptoms, and plasma markers of inflammation and fibrosis.

The finding that sex played a significant role in predicting PPF in the present cohort is consistent with those of prior studies (4,29). These studies have demonstrated that male patients are more likely to experience SSc-ILD progression, both with and without treatment, than female patients (40). In the present analysis, the odds of developing PPF despite initial treatment with MMF

or CYC was 3.5 times higher in male patients than female patients. Although the number of male patients with SSc-ILD is relatively small compared with female patients presenting with SSc-ILD, these findings have important clinical implications for the approach to treatment in male patients with SSc. Although our understanding of the biological underpinnings of sex differences in SSc-ILD is still evolving, a recent proteomic evaluation of bronchoalveolar lavage fluid of patients with SSc-ILD demonstrated that male patients with SSc-ILD have increased levels or presence of profibrotic mediators, whereas female patients with SSc-ILD have increased levels or presence of proinflammatory mediators (40). Additional research is needed to understand whether male patients might benefit more from an alternative treatment strategy.

Severity of reflux symptoms at baseline was also associated with PPF in this cohort. Accumulating evidence supports a relationship between gastroesophageal reflux, microaspiration, and ILD (41). In idiopathic pulmonary fibrosis, for example, treatment of gastroesophageal reflux may slow the progression of ILD (42). In SSc, absent contractility of the esophagus is associated with more severe restriction on pulmonary function testing (43). The reflux domain of the GIT 2.0 is a valid and relatively short questionnaire that discriminates between patients with and without objective evidence of upper gastrointestinal tract involvement (44). During SLS II, there were no significant changes in reflux scores from baseline to 24 months in either treatment arm (38). Most patients (~80%) in SLS II were taking a proton pump inhibitor at baseline. These results suggest that the initial evaluation of reflux symptoms in SSc-ILD may help risk stratify patients. Additional research is needed to determine how to optimize the management of reflux disease, with the hope that such treatment might reduce the risk of PPF.

This study also evaluated the relationship between serum and plasma biomarkers of inflammation and fibrosis and risk of PPF. To minimize the likelihood of type 1 error, our analysis included a focused list of biomarkers associated with ILD progression. The multifunctional CXCL4 was significantly associated with PPF development. CXCL4 promotes inflammation and angiogenesis (45), and emerging research suggests that it may play a direct role in initiating fibrosis through myofibroblast precursor cells (46). In patients with SSc, CXCL4 levels are increased compared with controls and correlate with severity of skin and lung fibrosis (23).

The present study demonstrated that higher CXCL4 levels were associated with a reduced risk of PPF after initial treatment with MMF or CYC, suggesting that patients with this immune signature may respond better to upfront treatment with antiinflammatory agents. Higher CXCL4 levels may reflect an ongoing inflammatory process portending an improved response to MMF or CYC. This hypothesis is supported by our prior study, which demonstrated that patients with SSc-ILD who had the greatest decline in CXCL4 levels from baseline to 12 months after treatment with MMF or CYC had an improved course of their FVC%-predicted from 12 to 24 months (47). Although an earlier study demonstrated that high baseline CXCL4 was associated with an increased decline in DLCO%-predicted in a small group of patients with SSc, that prior study did not evaluate the effects of treatment on the course of DLCO%-predicted, nor did it evaluate the relationship between baseline CXCL4 levels and decline in FVC%-predicted or changes in radiological extent of ILD (21). Future studies are needed to determine whether levels of CXCL4 can predict PPF in patients receiving other SSc-ILD therapies.

This study has limitations. First, we had planned to test the nomogram in a clinical trial cohort with similar entry criteria, but neither the SLS I nor the SENSCIS trial measured reflux severity at baseline. Although the results of the internal validation analyses were encouraging, without a validation cohort, we consider the present findings to be hypothesis generating. Second, these findings may not be directly generalizable to patients who were not preselected for specific criteria and enrolled in a clinical trial. Third, while employing the three key tenets for defining PPF (9), we adapted this approach to evaluate for the presence of PPF over the course of 12 to 24 months. Treatment with MMF and CYC has a sigmoidal response curve with an initial period of progressive decline in lung function, likely due to a delayed onset of action of these medications, followed by progressive improvement and a plateau in the response by 18 to 21 months of therapy (10). As such, we relied on these later outcome points to identify those participants who developed PPF despite treatment. Integrating the established features of the clinical response curve into the analysis and prediction is a novel concept that may need to be adapted to the nature of the therapeutic agent being evaluated. Furthermore, some participants had missing PPF data at follow-up time points, particularly for the TDI (Supplementary Table 7), and this may have affected the study results.

Other limitations included the fact that platelet-poor plasma was not available in the current study or in the study by Van Bon and colleagues (23), and because CXCL4 is abundant in platelets, use of platelet-poor plasma may lead to more accurate CXCL4 measurements (48). Moreover, the measurement of CXCL4 levels is not routinely done in clinical practice. Although the accuracy of the prediction model slightly diminished when CXCL4 was removed from the multivariable model, the area under the ROC was 0.67, suggesting reasonable accuracy for predicting PPF with sex and reflux score alone. In addition, a limited number of patients possessed the anticentromere antibody or the anti-RNA polymerase III antibody, so we were unable to determine whether the presence of these antibodies was associated with PPF. Finally, the HRCT assessment was only done at 24 months. However, this approach likely reflects a real-world experience in which HRCT assessment is performed less often than symptom and physiological assessment.

Strengths of this study include the prospective approach with defined entry criteria and uniform serial assessment of PPF

criteria, minimizing the risk of systematic bias. Established disease-specific questionnaires were used to measure and report clinical symptoms. Moreover, spirometry results were overread for quality assurance at a pulmonary function reading center, and HRCT interpretation was conducted using quantitative image analysis on data generated from imaging equipment that was individually validated and standardized. In addition, all patients received a standard treatment approach with either MMF or CYC. Another strength was that the primary outcome (PPF) included a patient-reported outcome, a measure that directly assesses treatment outcomes in terms that are meaningful to the patient. Finally, SLS II was conducted at 14 centers, increasing the likelihood that these findings are generalizable to other cohorts.

In summary, a combination of variables predicted the likelihood of PPF following initial treatment with MMF or CYC in patients with SSc-ILD with moderate discrimination. If validated in future studies, this nomogram or further iterations of it could be applied in clinical practice to identify patients with SSc-ILD who require careful monitoring during therapy or perhaps to enrich future clinical trials for patients with a greater likelihood of experiencing PPF despite background therapy with MMF. Future studies are needed to identify a combination of factors that predict PPF among patients receiving other therapies for SSc-ILD (eg, nintedanib, tocilizumab, rituximab).

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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 published. Drs. Volkmann, Tashkin and Roth 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.

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