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Mortality Risk Prediction in Scleroderma-Related Interstitial Lung Disease

The SADL Model

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BACKGROUND: Interstitial lung disease (ILD) is an important cause of morbidity and mortality in patients with scleroderma (Scl). Risk prediction and prognostication in patients with Scl-ILD are challenging because of heterogeneity in the disease course.

METHODS: We aimed to develop a clinical mortality risk prediction model for Scl-ILD. Patients with Scl-ILD were identified from two ongoing longitudinal cohorts: 135 patients at the University of California, San Francisco (derivation cohort) and 90 patients at the Mayo Clinic (validation cohort). Using these two separate cohorts, a mortality risk prediction model was developed and validated by testing every potential candidate Cox model, each including three or four variables of a possible 19 clinical predictors, for time to death. Model discrimination was assessed using the C-index.

RESULTS: Three variables were included in the final risk prediction model (SADL): ever smoking history, age, and diffusing capacity of the lung for carbon monoxide (% predicted). This continuous model had similar performance in the derivation (C-index, 0.88) and validation (C-index, 0.84) cohorts. We created a point scoring system using the combined cohort (C-index, 0.82) and used it to identify a classification with low, moderate, and high mortality risk at 3 years.

CONCLUSIONS: The SADL model uses simple, readily accessible clinical variables to predict all-cause mortality in Scl-ILD. CHEST 2017; 152(5):999-1007

KEY WORDS: interstitial lung disease; prognosis; risk prediction; systemic sclerosis

ABBREVIATIONS: ANA = anti-nuclear antibody; DLCO = diffusing capacity of the lung for carbon monoxide; GERD = gastroesophageal reflux disease; HRCT = high-resolution computed tomography; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; PH = pulmonary hypertension; RHC = right heart catheterization; SADL = ever smoking history, age, and diffusing capacity of the lung for carbon monoxide (% predicted); Scl = scleroderma; Scl-ILD = scleroderma-related interstitial lung disease; UIP = usual interstitial pneumonia

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Pulmonary involvement, including pulmonary hypertension (PH) and interstitial lung disease (ILD), is common in scleroderma and is associated with significant morbidity and mortality.[1,2] The prevalence of ILD in scleroderma is high and has been reported to occur in up to 90% of patients.[3] ILD is the most frequent cause of death among patients with scleroderma.[1]

Although many patients with scleroderma-related interstitial lung disease (Scl-ILD) will progress over time,[4] the disease course is heterogeneous.[5-7] This variability in disease evolution makes prognosis a challenging task for clinicians. Previous studies have attempted to identify factors that predict progression and mortality in Scl-ILD,[8-16] but were limited by sample size, lack of validation, and model complexity.[17] Goh et al[11] proposed a staging system for patients with Scl-ILD that combines FVC (% predicted) and extent of ILD on high-resolution CT (HRCT) scanning to classify patients as having either limited or extensive disease. This staging system was found to be predictive of mortality in a single cohort of patients with Scl-ILD.

The goal of this study was to develop and validate a simple-to-use and practical all-cause mortality risk prediction model for patients with Scl-ILD using widely available clinical variables at the time of their initial visit, applying an approach we previously used in idiopathic pulmonary fibrosis (IPF).[18] We demonstrate that 3-year mortality in Scl-ILD can be estimated using the SADL (ever smoking history, age, and diffusing capacity of the lung for carbon monoxide (% predicted)) model in two independent cohorts of patients with Scl-ILD.

Methods

Study Population

We retrospectively identified patients from ongoing longitudinal prospective cohorts at their respective centers. Patients were included in the study if they had received a rheumatologist-confirmed diagnosis of scleroderma[19,20] and had evidence of ILD on HRCT scanning and/or surgical lung biopsy. Patients without ILD on HRCT scanning and/or surgical lung biopsy were excluded (Fig 1). The derivation cohort included 135 patients from the University of California, San Francisco Interstitial Lung Disease Program. The validation cohort included 90 patients from the ILD clinic at the Mayo Clinic (Rochester, MN). Institutional review boards at both centers approved the parent databases (San Francisco Institutional Human Subject Review Committee [#10-01592] and Mayo Clinic Institutional Review Board [#12-009206]), and patients provided written informed consent.

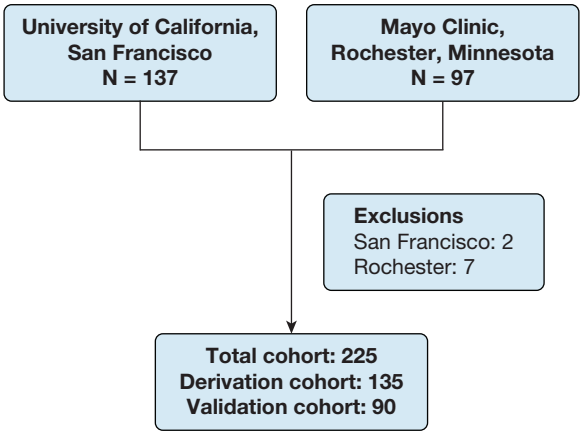

Figure 1 – *Cohort formation. Patients were excluded if they did not have interstitial lung disease on high-resolution CT and/or surgical lung biopsy.*

Clinical Data

Demographic variables including age, sex, body mass index, ever smoking history, ethnicity, and long-term oxygen use were obtained from structured questionnaires at the time of their initial ILD clinic visit and medical chart review. Results of pulmonary function tests performed within 6 months of the ILD visit date were obtained. Scleroderma-specific variables, including comorbid conditions (eg, diffuse skin involvement, Raynaud's disease, gastroesophageal reflux disease [GERD], renal disease), serologic profile (eg, anti-nuclear antibody [ANA], anti-topoisomerase 1 antibody, anti-centromere antibody), and immunosuppressive therapy, were obtained by chart review. Patients were identified as having "signs suggestive of pulmonary hypertension on echocardiogram" if the estimated pulmonary artery systolic pressure was higher than 36 mm Hg.[21]

An expert thoracic radiologist re-reviewed all available HRCT scans performed within 12 months of the initial ILD clinic visit date. The HRCT scan patterns were categorized as definite usual interstitial pneumonia (UIP), possible UIP, or inconsistent with UIP, according to published guidelines.[22] In addition, the total extent of ILD on HRCT scanning was evaluated using previously described methods in the derivation cohort.[11,23] Briefly, the extent of disease was estimated (to the nearest 5%) at five different levels: (1) origin of great vessels, (2) carina, (3) pulmonary venous confluence, (4) halfway between levels 3 and 5, and (5) 1 cm above the right hemidiaphragm. The total extent of disease was calculated as the mean of the five scores. The presence or absence of emphysema was also recorded in the derivation cohort.

Outcome

The primary outcome was mortality. Medical chart review and the US Social Security Death Index were used to determine whether patients had died during the follow-up period. Patients who underwent lung transplantation were censored at the time of transplantation. Cause of death was available for the Mayo Clinic patients.

Statistical Analysis

The mortality risk prediction model was developed and validated using a previously described method.[18] Using the derivation cohort, we estimated every potential candidate Cox model for time to death, each including three or four of a possible 19 clinical predictors, including age, sex, ethnicity, history of smoking, body mass index,

Raynaud's disease, skin involvement, GERD, renal disease, anti-topoisomerase 1 antibody, anti-centromere antibody, FVC (% predicted), DLCO (% predicted), definite UIP on HRCT scanning, extent of ILD on HRCT scanning, presence of emphysema on HRCT scanning, oxygen use, any immunosuppressive therapy, and signs suggestive of pulmonary hypertension on echocardiogram. The models were ranked by the C-index, a measure of discrimination, estimated using 20 repetitions of 10-fold cross-validation,[24] with 95% bootstrap percentile confidence intervals, and the model with the highest cross-validated C-index was chosen. In preliminary analysis, we checked for nonlinearity effects of continuous predictors on mortality risk, as well as for interactions of all other factors with signs suggestive of pulmonary hypertension on echocardiogram. We then used the validation cohort to reassess the C-index of the selected model, also with a 95% bootstrap percentile confidence interval. We assessed calibration in each of the two cohorts, by comparing model-based and nonparametric estimates of mortality at 1, 2, and 3 years.

Next, we derived a point score system based on the original model, using data from the combined cohorts. Specifically, we refit the Cox model for time to death after categorization of the two continuous predictors (age and DLCO [% predicted]) at clinically meaningful cut points. Each of the resulting categories was assigned one to four points by rescaling and rounding the resulting regression coefficients. A classification system was developed by grouping the point score results into three clinically meaningful categories: low, moderate, and high risk. The discrimination and calibration of this final model were assessed by cross-validation in the combined cohort. Finally, we compared our model performance with that of the staging system proposed by Goh et al[11] in the derivation cohort. Briefly, the grading system proposed by Goh et al[11] includes grading HRCT scans according to the extent of lung disease (< 20%, limited; > 20%, extensive) and among those that were indeterminate, limited or extensive disease was defined by an FVC threshold of 70% predicted. STATA version 14 (Stata Corp) was used for all the statistical analyses.

Results

Patient Characteristics

Table 1 shows the baseline characteristics of all patients and of those in each cohort. As a group, the patients were predominantly white women with a mean age of 55.5 ± 12.3 years. A history of current or past smoking was reported in 42% of patients. Of those patients evaluated for Raynaud's disease, most had Raynaud's disease (95%) and diffuse skin involvement (82%), and of those for whom serologic data were available, all had a positive ANA result. Thirty-seven percent of patients had signs suggestive of pulmonary hypertension on echocardiogram. However, only 21 patients (9%) were receiving vasodilator therapies for pulmonary hypertension at their baseline visit (Table 2). The mean FVC (% predicted) was 71 and the mean DLCO (% predicted) was 50. Surgical lung biopsy was rarely performed in this population (9%).

Patients in the derivation and validation cohorts exhibited some differences at baseline (Table 1). Patients in the validation cohort were more likely to be white and to have a history of Raynaud's disease and GERD. A definite UIP pattern on HRCT scanning was more common in the validation cohort (15%) than in the derivation cohort (5%; $P = .02$). In addition, the proportion of patients receiving oxygen and immunosuppressive treatment at baseline differed between study cohorts (Table 2). Patients in the validation cohort were more likely to have been receiving immunosuppressive therapy (70%) at the time of their initial ILD clinic visit compared with the derivation cohort (41%; $P < .001$). Additional baseline characteristics are presented in e-Table 1 of the online supplement.

During the follow-up period, 56 patients died: 27 in the derivation cohort and 29 in the validation cohort. Five patients in the derivation cohort underwent lung transplantation; none occurred in the validation cohort. The median (range) follow-up time was 3.15 (0.07-15.16) and 4.64 (0.1-12.31) years in the derivation and validation cohorts, respectively. We were not able to identify the cause of death for patients in the derivation cohort. The majority of the deaths (70%) in the validation cohort were attributable to respiratory causes.

SADL Model Derivation and Validation

The model screening process identified a three-variable continuous model including history of ever smoking, age, and DLCO (% predicted) (SADL). The cross-validated C-index for the selected continuous model was 0.88 (95% CI, 0.78-0.95) in the derivation cohort and 0.84 (95% CI, 0.75-0.91) in the validation cohort. Table 3 shows the calibration of this continuous model in the derivation and validation cohorts for 1-, 2-, and 3-year mortality.

Next, a point score system was developed by assigning values to subcategories within each of the three variables of the continuous SADL model, using both cohorts. On the basis of the SADL point score model, patients in the combined cohort with scores of 0 to 3, 4 or 5, and 6 or 7 points were classified as low, moderate, and high risk, respectively (Table 4). The distribution of patients within each risk category is presented in Table 5, and the results of the multivariable survival analysis using the point score SADL model are shown in Table 6. The C-index of the point score SADL model was 0.82 (95% CI, 0.77-0.87), and its calibration was satisfactory (Table 7). The C-index of the point score SADL model was similar in the individual cohorts: derivation cohort (C-index, 80.20;

TABLE 1] Patient Characteristics

Characteristic	All (N = 225)	Derivation Cohort (n = 135)	Validation Cohort (n = 90)	*P* Value
Age, y (SD)	55.5 (12.3)	54.4 (12.8)	57.1 (11.2)	.10
Female, No./total (%)	163/225 (72)	101/135 (75)	62/90 (69)	.33
White, No./total (%)	170/225 (76)	87/135 (64)	83/90 (92)	< .001
Asian, No./total (%)	21/225 (9)	18/135 (13)	3/90 (3)	.01
Black or African American, No./total (%)	14/225 (6)	10/135 (7)	4/90 (4)	.35
Hispanic or Latino, No./total (%)	12/225 (5)	12/135 (9)	…	…
Native American, No./total (%)	4/225 (2)	4/135 (3)	…	…
Pacific Islander, No./total (%)	4/225 (2)	4/135 (3)	…	…
Ever smoker, No./total (%)	94/225 (42)	52/135 (39)	42/90 (47)	.23
Raynaud's, No./total (%)[a]	168/176 (95)	85/93 (91)	83/83 (100)	.01
Diffuse skin involvement, No./total (%)[a]	142/173 (82)	64/83 (77)	78/90 (87)	.09
Renal disease, No./total (%)[a]	9/185 (5)	4/95 (4)	5/90 (6)	.67
GERD, No./total (%)[a]	133/194 (69)	64/104 (62)	69/90 (77)	.02
Signs suggestive of pulmonary hypertension on echocardiogram, No./total (%)[a,b]	72/194 (37)	40/104 (38)	32/90 (36)	.68
Anti-nuclear antibody, No./total (%)[a]	167/167 (100)	87/87 (100)	80/80 (100)	…
Anti-topoisomerase I antibody, No./total (%)[a]	59/145 (41)	34/73 (47)	25/75 (35)	.15
Anti-centromere antibody, No./total (%)[a]	20/102 (20)	9/41 (22)	11/61 (18)	.63
FVC				.50
Percent predicted (SD)	71.0 (19.7)	71.9 (22.6)	69.9 (15.2)	
No./total[a]	194/225	110/135	84/90	
D_{LCO}				.57
Percent predicted (SD)	50.0 (18.6)	50.7 (20.4)	49.2 (12.2)	
No./total[a]	191/225	107/135	84/90	
HRCT, No./total (%)[c]	155/225 (69)	89/135 (66)	66/90 (73)	.24
Definite UIP, No./total (%)[a]	14/155 (9)	4/89 (5)	10/66 (15)	.02
Possible UIP, No./total (%)[a]	23/155 (15)	10/89 (11)	13/66 (20)	.14
Inconsistent with UIP, No./total (%)[a]	118/155 (76)	75/89 (84)	43/66 (65)	.01
Extent of disease, median % (IQR)[a]	…	14.9 (4-23)	…	…
Presence of emphysema, No./total (%)[a]	…	6/89 (6.7)	…	…
Surgical lung biopsy, No./total (%)	20/225 (9)	11/135 (8)	9/90 (10)	.60
UIP pattern, No./total (%)	5/20 (25)	2/11 (18)	3/9 (33)	.44
NSIP pattern, No./total (%)	6/20 (30)	4/11 (36)	2/9 (22)	.50
Others, No./total (%)	9/20 (55)	5/11 (45)	4/9 (44)	.96
Staging system, No./total (%)[d]				
Limited disease[a]	…	59/89 (66)	…	…
Extensive disease[a]	…	30/89 (34)	…	…

D_{LCO} = diffusing capacity of the lung for carbon monoxide; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; NSIP = nonspecific interstitial pneumonia; UIP = usual interstitial pneumonia.

[a]These variables have missing data as indicated by the denominator reporting the total number of observations.

[b]Pulmonary hypertension was defined by an estimated pulmonary artery systolic pressure higher than 36 mm Hg on echocardiogram.[21]

[c]According to the published guidelines.[22]

[d]Using the staging system proposed by Goh et al.[11]

TABLE 2] Treatment Data

Characteristic	All (N = 225)	Derivation Cohort (n = 135)	Validation Cohort (n = 90)	*P* Value
Long-term oxygen therapy, No./total (%)[a]	26/194 (13)	4/104 (4)	22/90 (24)	< .001
Immunosuppressive therapy, No./total (%)[a]	106/196 (47)	43/106 (41)	63/90 (70)	< .001
Prednisone[a]	73/196 (37)	32/106 (30)	41/90 (46)	.03
Cytoxan[a]	17/195 (9)	5/105 (5)	12/90 (13)	.03
Mycophenolate mofetil[a]	54/195 (28)	24/105 (23)	30/90 (33)	.10
Vasodilator therapies, No./total (%)[a]	21/225 (9)	8/105 (8)	13/90 (14)	.13

[a]These variables have missing data as indicated by the denominator reporting the total number of observations.

95% CI, 71.76-88.29) and validation cohort (C-index, 82.92; 95% CI, 75.69-90.16). Figure 2 shows the cumulative mortality difference within the combined cohort when categorized by the three risk groups. We performed a sensitivity analysis excluding nonrespiratory deaths from the validation cohort. The performance of the SADL model was not affected by the exclusion of these patients (C-index, 0.84; 95% CI, 0.74-0.92) and provided satisfactory calibration. An additional sensitivity analysis was performed to evaluate the SADL model excluding patients with signs suggestive of PH on echocardiography. Again, the performance of the model was similar to the combined cohort (data not shown).

Finally, we applied the staging system proposed by Goh et al[11] to our derivation cohort to compare its performance with that of the SADL model in predicting mortality in patients with Scl-ILD. Although the calibration of this staging system was satisfactory in our cohort (e-Table 2 and e-Fig 1), the discrimination of the Goh et al[11] staging system was significantly lower (C-index, 0.62; 95% CI, 0.50-0.74) than the SADL model.

Discussion

The SADL model is an easy-to-use mortality risk prediction classification system designed for patients with Scl-ILD. It is based on two clinical variables (age and ever smoking history) and one physiological variable (Dlco [% predicted]), which are commonly used and easy to obtain in clinical practice at the initial clinic visit. Model discrimination for all-cause mortality is good and calibration is acceptable, both in the derivation and validation cohorts, and as a continuous model and a point-scoring system. This risk classification system could be applied at the initial visit of a patient with Scl-ILD in an ILD clinic to help discuss prognosis and to guide management decisions.

Unlike risk prediction for IPF, FVC (% predicted) was not included in the top-scoring candidate models, all of which included Dlco (% predicted) instead. These results are not surprising as Dlco has been shown to be a significant predictor of mortality in several prior studies of Scl-ILD.[9,11,13] For example, a recent substudy[25] from the Scleroderma Lung Study 1[26] demonstrated that Dlco (% predicted) was the best predictor of both extent of lung fibrosis and total interstitial lung disease in patients with Scl-ILD. Baseline Dlco (% predicted) was also highly predictive of mortality and as predictive of HRCT disease extent in another model of mortality in Scl-ILD.[11] In our model, replacing Dlco (% predicted) with FVC (% predicted) in the model dropped the C-statistic from 0.88 to 0.79. The Dlco, in addition to capturing the extent of ILD in scleroderma, is likely capturing the impact of pulmonary vascular disease in this patient population. Of note, echocardiographic signs suggestive

TABLE 3] Continuous Model Performance in Derivation and Validation Cohorts

	C-Index (95% CI) for Derivation Cohort: 0.88 (0.78-0.95)		C-Index (95% CI) for Validation Cohort: 0.84 (0.75-0.91)	
Mortality	Predicted	Observed (95% CI)	Predicted	Observed (95% CI)
1 y, %	2.9	3.0 (1-9.1)	6.1	4.9 (1.9-12.6)
2 y, %	6.4	6.5 (3-14)	11.8	16.6 (9.7-27.5)
3 y, %	14.0	13.3 (7.6-23)	21.1	28.6 (19.1-41.3)

TABLE 4] SADL Model and Staging System

	Predictor		Points
S	Ever smoking history		
	No		0
	Yes		1
A	Age, y		
	< 55		0
	55-70		1
	> 70		2
DL	D_{LCO} (% predicted)		
	> 60%		0
	40-60%		3
	< 40%		4
Total possible points:			7
	Risk Category		
	Low	Moderate	High
Points	0-3	4-5	6-7

SADL = ever smoking history, age, and diffusing capacity of the lung for carbon monoxide (% predicted). See Table 1 legend for expansion of other abbreviation.

of pulmonary hypertension were not included in the final model. This may be due to the poor sensitivity and specificity of echocardiographic screening for pulmonary hypertension when compared with right heart catheterization (RHC) in patients with ILD.[27,28] Additional studies should investigate the role of RHC-diagnosed pulmonary hypertension in this model.

The inclusion of smoking history in the model was somewhat unexpected. Smoking has been previously shown to be associated with worse vascular and gastrointestinal outcomes in patients with scleroderma,[29] and the prevalence of smoking history among the patients with scleroderma is similar to what has been previously reported in the literature.[29,30] In patients with other forms of ILD, specifically IPF, smoking history has also been associated with worse survival time.[31] One potential explanation for this finding could be the coexistence of emphysema (ie, combined pulmonary fibrosis and emphysema).[32] Interestingly, the presence of emphysema in this cohort was low (6.7%), suggesting additional mechanisms for worse outcomes among patients with Scl-ILD who have a history of smoking. We did not find an association between the number of pack-years and mortality in these two cohorts, but it is worth further investigation, as this is the only modifiable factor in the model.

Mortality risk prediction models have previously been proposed for patients with Scl-ILD. A systematic review highlighted the current limitations of the prior studies, including methodologic quality and lack of validation.[17] As previously mentioned, one Scl-ILD-tailored staging system (Goh et al[11]) uses FVC (% predicted) and the extent of disease on HRCT to categorize patients as having either limited or extensive disease. This staging system provided prognostic separation between groups in two different cohorts of patients with Scl-ILD,[11,33] but is limited by the need to interpret disease extent on HRCT imaging. The application of this staging system in our derivation cohort demonstrated significantly lower discrimination compared with the SADL model, although its calibration was satisfactory.

IPF risk prediction models have been applied to a cohort of patients with Scl-ILD.[34] The modified du Bois index[35] had the best combination of discrimination and calibration in predicting mortality at 1 year. This index is calculated on the basis of age, history of respiratory hospitalization in the last 24 weeks, FVC, change in FVC in 24 weeks, distance walked in a 6-min walk test, and change in distance walked in a 6-min walk test. Although the modified du Bois index appeared to predict mortality of patients with Scl-ILD at 1 year, it requires longitudinal assessments, has not been validated, and has not been shown to predict mortality beyond 1 year.

Well-thought-out mortality risk prediction models can be useful tools in clinical practice as well as in the

TABLE 5] Distribution of Patients by SADL Score and Risk Category

	Risk Category Based on SADL Score		
	Low Risk	Moderate Risk	High Risk
Points	0-3	4-5	6-7
Distribution in combined cohort, %	48	31	21
Distribution in derivation cohort, %	42	35	23
Distribution in validation cohort, %	56	24	20

See Table 4 legend for expansion of abbreviation.

TABLE 6] Multivariate Survival Analysis Using SADL Point Score

Point Score Variable	Hazard Ratio (95% CI)	*P* Value
Ever smoking history	2.58 (1.32-5.02)	.005
Age, y		
55-70	2.24 (1.00-5.03)	.05
> 70	7.48 (3.03-18.5)	< .001
DLCO (% predicted)		
40%-60%	18.3 (2.24-150)	.007
< 40%	40.9 (4.97-337)	.001

See Table 1 and 4 legends for expansion of abbreviations.

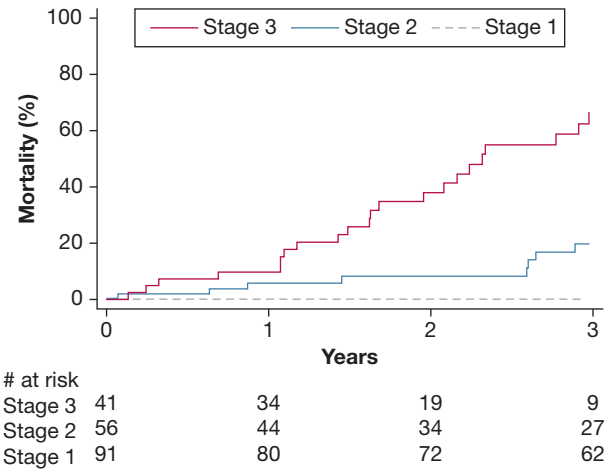

Figure 2 – *Cumulative mortality in the combined cohort by risk category. Red line, high-risk patients; blue line, moderate-risk patients; dashed gray line, low-risk patients.*

research setting. Identification of those at differential risk for disease progression can help guide treatment and management decisions, as well as inform the counseling and education of patients and their caregivers. From a research standpoint, risk prediction models can be useful for selecting high-risk clinical trial populations. By using advanced statistical methodology to develop and validate a risk prediction model, with an unbiased approach to candidate variable selection, we have identified a group of three variables that can predict mortality in Scl-ILD. The SADL model uses simple variables readily available to clinicians caring for patients with Scl-ILD, thereby facilitating its use. This same statistical method has proven useful in the field of IPF.[18,36,37]

TABLE 7] Point Score Model Performance in Combined Cohort

	C-Index (95% CI) for Combined Cohort: 0.82 (0.77-0.87)	
	Predicted	Observed (95% CI)
1-y mortality, %		
Low risk	0.5	0 (0-5.6)[a]
Moderate risk	3.8	4.7 (1.8-12.1)
High risk	12.8	11.1 (3.7-30.6)
2-y mortality, %		
Low risk	1.6	0 (0-6.1)[a]
Moderate risk	11.3	10.5 (5.3-20)
High risk	34.0	40.4 (24-62.3)
3-y mortality, %		
Low risk	3.2	0 (0-7.0)[a]
Moderate risk	22.2	22.8 (14.3-35.3)
High risk	56.9	63.3 (44.3-82.1)

[a]When no events have occurred, Greenwood confidence intervals for the Kaplan-Meier incidence proportion are undefined. We substituted exact binomial confidence intervals for this proportion, with zero events, and the number at risk at the end of the year as the denominator.

There are limitations to this study. First, both cohorts of patients originated from academic centers using a retrospective design. Patients with Scl-ILD seen in both of these clinics may differ from the general population of people with Scl-ILD and could limit the generalizability of this model. Second, although data were obtained primarily from ongoing prospective longitudinal ILD cohorts, missing data could bias this analysis. The SADL model should not be applied to patients who are unable to perform the DLCO maneuver, as it has not been tested in this population. Third, the majority of the enrolled patients were white. The impact of race/ethnicity on mortality in the Scl-ILD population needs further investigation. Furthermore, all the patients in our cohort had positive ANA results. A small proportion of patients with scleroderma have negative ANA results (5%-10%[38-40]), and the SADL model would need to be tested in this subset of patients before it could be applied to this population. Finally, the SADL model was derived to predict all-cause mortality in patients with Scl-ILD; it is not specific for ILD-related mortality. Since the patients in our cohort did not systematically undergo RHC, our estimation of PH is prone to bias and the observed mortality could be attributed to any cause.

In conclusion, the SADL model successfully predicts mortality using ever smoking history, age, and DLCO (% predicted). Future studies should evaluate the impact of incorporating biomarkers as well as longitudinal measures on risk prediction in Scl-ILD.

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Additional information: The e-Figure and e-Tables can be found in the Supplemental Materials section of the online article.

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