Supplemental material

Formulae connecting predictors, progression score and predicted progression risk

Formula for deriving the progression score from the predictor values:

$$\begin{aligned}\text{Progression score} = {} & 0.6841 * (90 - dlco) * 1_{|dlco \leq 90|} + 0.7866 * mrss \\ & + 4.3045 * (8 - tsnrsym) * 1_{|tsnrsym \leq 8|} + 6.8761 * ata \\ & + 4.7949 * mmf\end{aligned}$$

Note: The expression $1_{[\ldots]}$ is 1 in case the condition [...] in the index is true. Otherwise the expression is 0. E.g. the expression $1_{|dlco \leq 90|}$ is 1 in case of $dlco \leq 90$ and 0 in case of $dlco > 90$.

Formula for deriving the predicted progression risk from the predictor values:

$$\text{Predicted progression risk} = \frac{\exp(1.0784 - 0.0488 * dlco + 0.0561 * mrss - 0.3073 * tsnrsym + 0.4908 * ata + 0.3423 * mmf)}{1 + \exp(1.0784 - 0.0488 * dlco + 0.0561 * mrss - 0.3073 * tsnrsym + 0.4908 * ata + 0.3423 * mmf)}$$

Note: $\exp(x) = e^x$

Formula for deriving the predicted progression risk from the progression score:

$$\text{Predicted progression risk} = \frac{\exp(-5.7748 + \frac{\text{progression score}}{14.0092})}{1 + \exp(-5.7748 + \frac{\text{progression score}}{14.0092})}$$

Note: $\exp(x) = e^x$

Predictor values: *dlco* = diffusing capacity of the lung for carbon monoxide % predicted; *mrss* = modified Rodnan skin score; *tsnrsym* = time since first non-Raynaud symptom (years); *ata* = anti-topoisomerase I antibody status (0 = negative, 1 = positive); *mmf* = mycophenolate use (0 = yes, 1 = no) (all assessed at baseline).

Supplemental table 1 Baseline characteristics of the placebo group of the SENSCIS trial.

	All patients (n=288)	**Patients with absolute decline in FVC % predicted >5% or death over 52 weeks**	
		Yes (n=86)	**No (n=202)**
Age, years, mean (SD)	53.4 (12.6)	54.6 (12.3)	52.9 (12.7)
Female, n (%)	212 (73.6)	59 (68.6)	153 (75.7)
Years since first non-Raynaud symptom, mean (SD)	3.5 (1.8)	3.3 (1.9)	3.6 (1.7)
ATA positive, n (%)	177 (61.5)	57 (66.3)	120 (59.4)
Diffuse cutaneous SSc, n (%)	146 (50.7)	44 (51.2)	102 (50.5)
mRSS, mean (SD)	10.9 (8.8)	12.0 (9.9)	10.4 (8.3)
High-sensitivity CRP, mg/L (log_{10} scale), mean (SD)	6.8 (18.6)	7.9 (28.7)	6.3 (12.2)
FVC % predicted, mean (SD)	72.7 (16.6)	73.6 (16.0)	72.3 (16.9)
DLco % predicted, mean (SD)	53.2 (15.1)	49.7 (14.7)	54.7 (15.0)
Extent of fibrotic ILD on HRCT, %, mean (SD)	35.2 (20.7)	35.9 (21.9)	34.9 (20.3)
Presence of honeycombing on HRCT, n (%)	45 (15.6)	15 (17.4)	30 (14.9)
Presence of ground glass opacities on HRCT, n (%)	246 (85.4)	73 (84.9)	173 (85.6)
Taking mycophenolate, n (%)	140 (48.6)	37 (43.0)	103 (51.0)
History of GERD, n (%)	216 (75.0)	65 (75.6)	151 (74.8)

ATA, anti-topoisomerase I antibody; CRP, C-reactive protein; DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; GERD, gastroeosophageal reflux disease; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; mRSS, modified Rodnan skin score; SSc, systemic sclerosis.

Supplemental table 2 Baseline characteristics of patients with early and/or inflammatory SSc and/or severe skin fibrosis (<18 months since first non-Raynaud symptom, elevated inflammatory markers [C-reactive protein ≥6 mg/L and/or platelets ≥330 x 10^9/L], or mRSS >18) at baseline in the placebo group of the SENSCIS trial.

	All patients (n=155)	**Patients with absolute decline in FVC % predicted >5% or death over 52 weeks**	
		Yes (n=45)	**No (n=110)**
Age, years, mean (SD)	52.4 (12.8)	53.1 (12.2)	52.1 (13.0)
Female, n (%)	116 (74.8)	29 (64.4)	87 (79.1)
Years since first non-Raynaud symptom, mean (SD)	3.2 (1.9)	2.8 (2.1)	3.4 (1.8)
ATA positive, n (%)	96 (61.9)	31 (68.9)	65 (59.1)
Diffuse cutaneous SSc, n (%)	95 (61.3)	27 (60.0)	68 (61.8)
mRSS, mean (SD)	14.0 (10.0)	16.4 (11.2)	13.0 (9.4)
High-sensitivity CRP, mg/L (log_{10} scale), mean (SD)	10.8 (24.4)	12.9 (38.8)	10.0 (15.4)
FVC % predicted, mean (SD)	70.0 (15.8)	70.1 (15.1)	70.0 (16.1)
DLco % predicted, mean (SD)	51.0 (14.8)	45.7 (13.2)	53.1 (14.9)
Extent of fibrotic ILD on HRCT, %, mean (SD)	37.0 (21.5)	38.6 (24.2)	36.4 (20.4)
Honeycombing on HRCT, n (%)	30 (19.4)	9 (20)	21 (19.1)
Ground glass opacities on HRCT, n (%)	135 (87.1)	41 (91.1)	94 (85.5)

Taking mycophenolate, n (%)	77 (49.7)	20 (44.4)	57 (51.8)
History of GERD, n (%)	120 (77.4)	33 (73.3)	87 (79.1)

ATA, anti-topoisomerase I antibody; CRP, C-reactive protein; DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; GERD, gastroeosophageal reflux disease; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; mRSS, modified Rodnan skin score SSc, systemic sclerosis.

Supplemental table 3 Pearson correlation coefficients among candidate predictors in the placebo group of the SENSCIS trial.

	Age, years	Years since first non-Raynaud symptom	High-sensitivity CRP, mg/L (log_{10} scale)	mRSS	Extent of fibrotic ILD on HRCT, %	FVC % predicted	DLco % predicted	Sex (male = 0; female = 1)	SSc subtype (dcSSc = 0; lcSSc = 1)	ATA status (negative = 0; positive = 1)	Honey-combing on HRCT (no = 0; yes = 1)	Ground glass opacities on HRCT (no = 0; yes = 1)	Taking myco-phenolate (no = 0; yes =1)	History of GERD (no = 0; yes =1)
Age, years	1	-0.071	0.009	-0.283	0.038	0.292	0.011	-0.069	0.194	-0.103	0.078	-0.087	-0.141	-0.056
Years since first non-Raynaud symptom	–	1	0.007	0.197	0.053	-0.060	-0.053	0.060	-0.294	0.033	-0.091	-0.036	0.088	0.057
High-sensitivity CRP, mg/L (log_{10} scale)	–	–	1	0.244	0.061	-0.216	-0.296	-0.091	-0.164	0.045	0.100	0.029	0.023	-0.014
mRSS	–	–	–	1	0.143	-0.175	-0.035	0.077	-0.619	0.092	-0.060	-0.033	0.047	0.064
Extent of fibrotic ILD on HRCT, %	–	–	–	–	1	-0.253	-0.378	0.004	-0.106	0.049	-0.003	0.064	0.025	0.070
FVC % predicted	–	–	–	–	–	1	0.428	0.031	0.110	-0.053	-0.043	0.085	-0.092	-0.050
DLco % predicted	–	–	–	–	–	–	1	0.131	-0.038	-0.009	-0.033	0.096	-0.041	-0.111
Sex (male vs female)	–	–	–	–	–	–	–	1	-0.040	0.109	-0.196	0.031	-0.032	0.036
SSc subtype (dcSSc vs lcSSc)	–	–	–	–	–	–	–	–	1	-0.175	0.115	-0.051	-0.042	-0.088
ATA status (negative vs positive)	–	–	–	–	–	–	–	–	–	1	-0.259	0.095	0.028	-0.045
Honeycombing on HRCT (no	–	–	–	–	–	–	–	–	–	–	1	-0.121	-0.057	-0.042

vs yes)														
Ground glass opacities on HRCT (no vs yes)	–	–	–	–	–	–	–	–	–	–	–	1	-0.053	0.047
Taking mycophenolate (no vs yes)	–	–	–	–	–	–	–	–	–	–	–	–	1	0.257
History of GERD (no vs yes)	–	–	–	–	–	–	–	–	–	–	–	–	–	1

A coefficient of -1 indicates perfect negative correlation, 1 indicates perfect positive correlation and 0 indicates no correlation. For pairs with one binary and one continuous variable, the Pearson correlation coefficient is also referred to as point-biserial correlation. For pairs with two binary variables, the Pearson correlation coefficient is also referred to as phi coefficient. ATA, anti-topoisomerase I antibody; CRP, C-reactive protein; dcSSc, diffuse cutaneous SSc; DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; GERD, gastroeosophageal reflux disease; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; mRSS, modified Rodnan skin score; SSc, systemic sclerosis.

Supplemental table 4 Pearson correlation coefficients among candidate predictors in patients with early and/or inflammatory SSc and/or severe skin fibrosis (<18 months since first non-Raynaud symptom, elevated inflammatory markers [C-reactive protein ≥6 mg/L and/or platelets ≥330 x 10^9/L], or mRSS >18) at baseline in the placebo group of the SENSCIS trial.

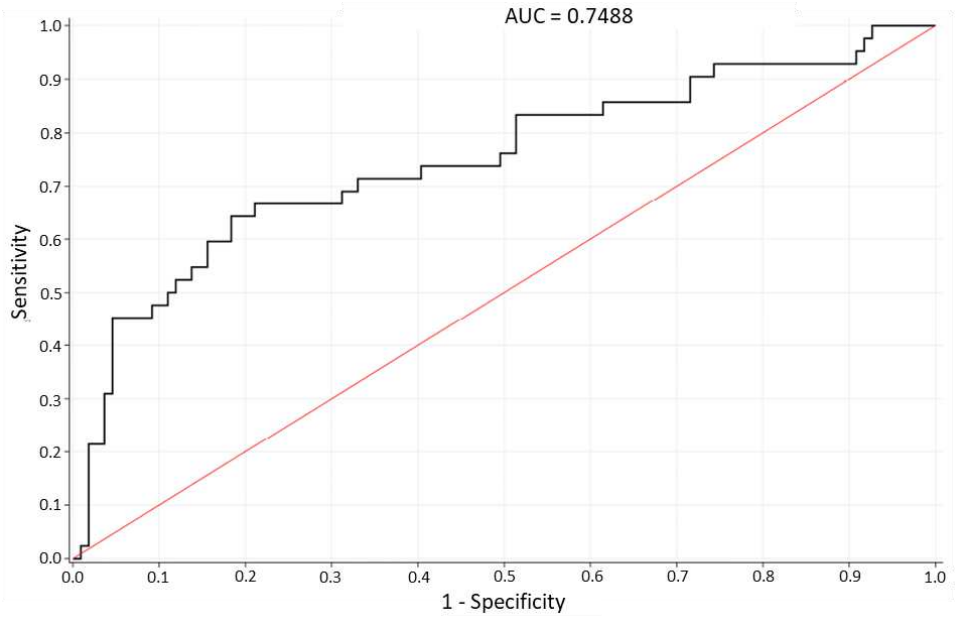
	Age, years	Years since first non-Raynaud symptom	High-sensitivity CRP, mg/L (log_{10} scale)	mRSS	Extent of fibrotic ILD on HRCT, %	FVC % predicted	DLco % predicted	Sex (male = 0; female = 1)	SSc subtype (dcSSc = 0; lcSSc = 1)	ATA status (negative = 0; positive = 1)	Honey-combing on HRCT (no = 0; yes = 1)	Ground glass opacities on HRCT (no = 0; yes = 1)	Taking myco-phenolate (no = 0; yes =1)	History of GERD (no = 0; yes =1)
Age, years	1	-0.090	0.100	-0.318	-0.016	0.319	0.016	-0.100	0.171	-0.151	0.073	-0.030	-0.194	-0.053
Years since first non-Raynaud symptom)	–	1	0.055	0.295	0.118	-0.101	-0.180	0.086	-0.342	-0.031	-0.052	-0.119	0.123	0.081
High-sensitivity CRP, mg/L (log_{10} scale)	–	–	1	0.063	-0.018	-0.157	-0.238	-0.247	-0.023	-0.068	0.120	0.060	0.076	-0.047
mRSS	–	–	–	1	0.178	-0.149	-0.001	0.109	-0.632	0.076	-0.138	-0.106	0.073	0.119
Extent of fibrotic ILD on HRCT, %	–	–	–	–	1	-0.200	-0.376	0.065	-0.202	0.084	-0.005	0.062	0.002	0.177
FVC % predicted	–	–	–	–	–	1	0.440	-0.033	0.014	-0.020	-0.062	0.157	-0.106	-0.072
DLco % predicted	–	–	–	–	–	–	1	0.151	-0.069	-0.063	-0.060	0.115	-0.047	-0.199
Sex (male vs female)	–	–	–	–	–	–	–	1	-0.089	0.097	-0.285	-0.027	0.041	0.078
SSc subtype (dcSSc vs lcSSc)	–	–	–	–	–	–	–	–	1	-0.114	0.180	0.086	-0.101	-0.078

ATA status (negative vs positive)	–	–	–	–	–	–	–	–	–	1	-0.263	0.133	0.088	-0.010
Honeycombing on HRCT (no vs yes)	–	–	–	–	–	–	–	–	–	–	1	-0.073	-0.017	-0.120
Ground glass opacities on HRCT (no vs yes)	–	–	–	–	–	–	–	–	–	–	–	1	-0.048	-0.006
Taking mycophenolate (no vs yes)	–	–	–	–	–	–	–	–	–	–	–	–	1	0.290
History of GERD (no vs yes)	–	–	–	–	–	–	–	–	–	–	–	–	–	1

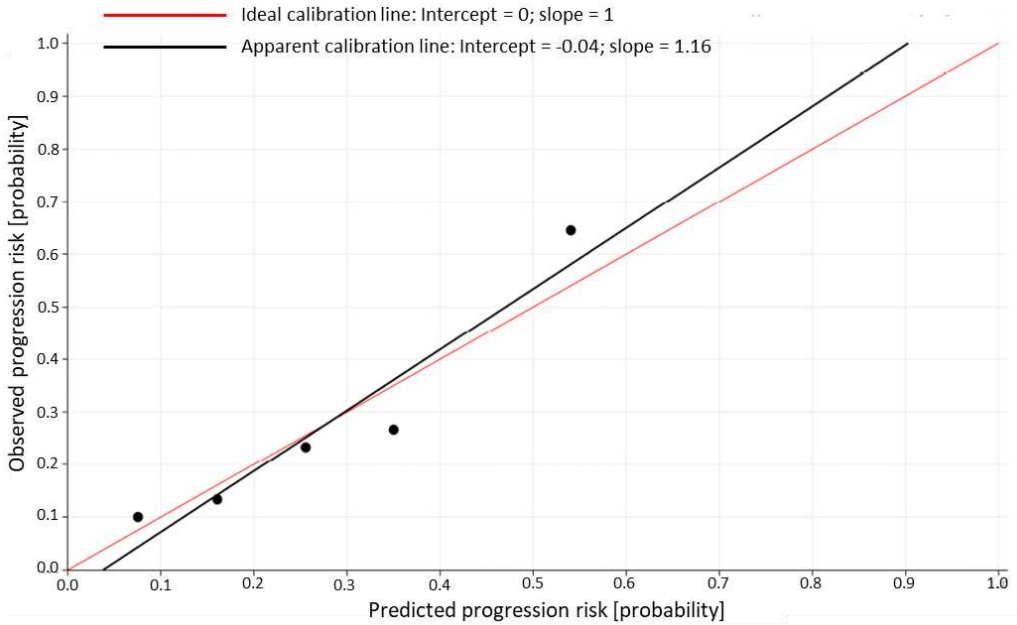
A coefficient of -1 indicates perfect negative correlation, 1 indicates perfect positive correlation and 0 indicates no correlation. For pairs with one binary and one continuous variable, the Pearson correlation coefficient is also referred to as point-biserial correlation. For pairs with two binary variables, the Pearson correlation coefficient is also referred to as phi coefficient. ATA, anti-topoisomerase I antibody; CRP, C-reactive protein; dcSSc, diffuse cutaneous SSc; DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; GERD, gastroeosophageal reflux disease; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; mRSS, modified Rodnan skin score; SSc, systemic sclerosis.

Supplemental figure 1 Predictive performance of the multivariable prediction model for progression of SSc-ILD over 52 weeks in patients with early and/or inflammatory SSc and/or severe skin fibrosis (<18 months since first non-Raynaud symptom, elevated inflammatory markers [C-reactive protein ≥6 mg/L and/or platelets ≥330 x 10^9/L], or mRSS >18) at baseline in the placebo group of the SENSCIS trial.

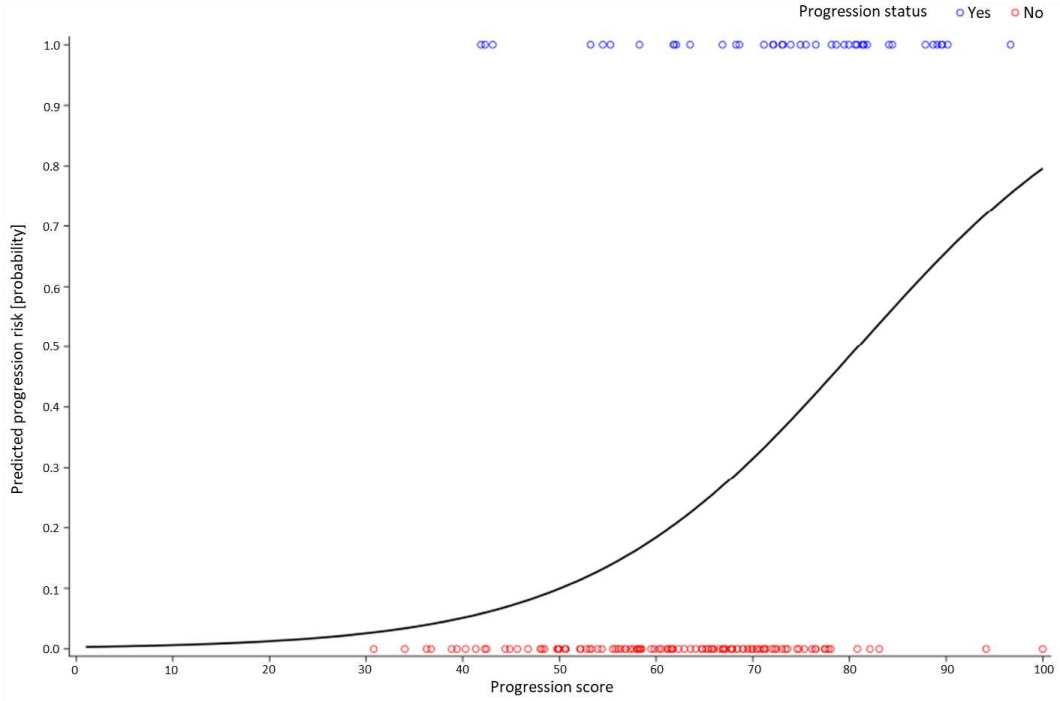
A. Discrimination (ROC curve)



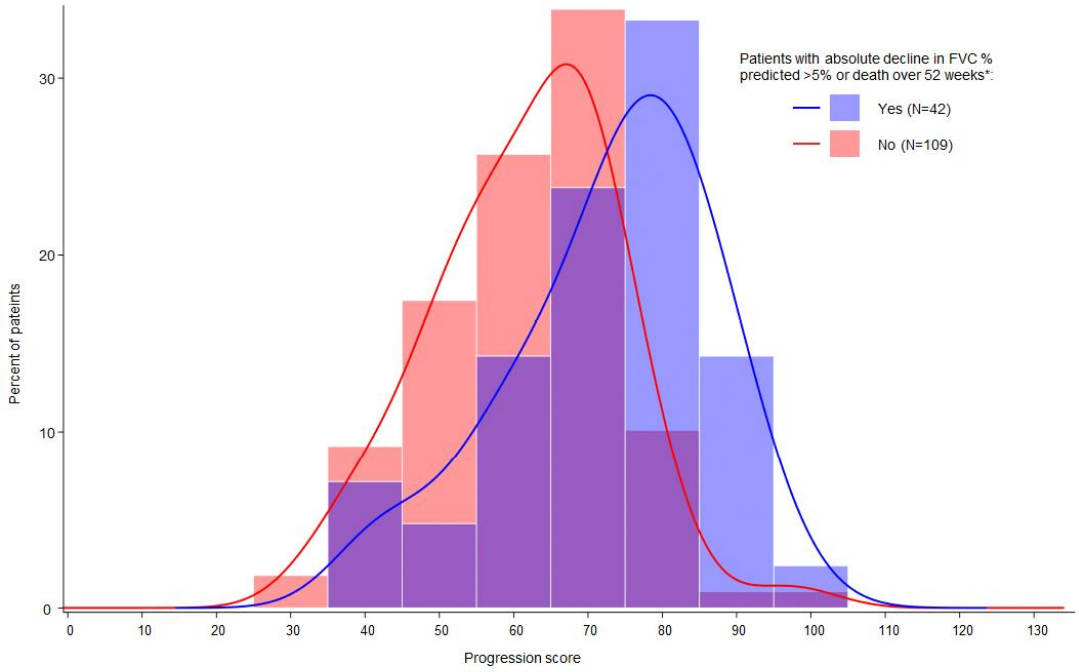
B. Calibration



Supplemental figure 2 Relationship between the progression score and the predicted risk of SSc-ILD progression derived from the multivariable model in patients with early and/or inflammatory SSc and/or severe skin fibrosis at baseline in the placebo group of the SENSCIS trial.



Supplemental figure 3 Distribution of progression score in progressors and non-progressors in patients with early and/or inflammatory SSc and/or severe skin fibrosis at baseline in the placebo group of the SENSCIS trial.



*Of 155 patients with early and/or inflammatory SSc and/or severe skin fibrosis at baseline, a progression score could not be calculated for 4 patients who had a missing value for ≥1 predictor.