Supplementary file:

A new risk model is able to identify patients with a low risk of progression in Systemic Sclerosis.

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Supplementary table S1. Detailed explanation disease progression per organ system

Pulmonary progression	≥ 10% relative decline in forced vital capacity (FVC) with follow-up FVC < 80% predicted or ≥ 5% to < 10% relative decline in FVC and either a ≥ 15% relative decline in diffusing capacity of the lung for carbon monoxide (DLCO) with follow-up DLCO < 80% predicted or increase of the extent of lung involvement (interstitial lung disease (ILD)) as determined by HRCT or new onset ILD as determined by HRCT.
Cardiac progression	Based on a combined definition, which included clinical cardiac involvement [decided in our multidisciplinary team including cardiologist, rheumatologist, pulmonologist and based on the performed physical, standard and addition investigations], decreased left ventricular ejection fraction < 54% (LVEF), arrhythmias (> 2% ventricular extrasystoles, atrial fibrillation), and major cardiac events (including all acute coronary syndromes and pacemaker implantations).
Pulmonary arterial hypertension (PAH)	Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest as assessed by right heart catheterization (RHC), pulmonary capillary wedge pressure ≤ 15 mmHg and a pulmonary vascular resistance > 3 Wood units, was classified as progression. [1]
Gastro-intestinal	Development of gastric antral vascular ectasia (GAVE), or anemia AND weight loss (> 10% in 1 year).
Skin progression	mRSS increased ≥ 5 points and ≥ 25%
Renal progression	Clinical diagnosis of renal crisis is based on the proposed preliminary definition including a combination of including newly developed hypertension, clinically relevant deterioration of renal function with signs of microangiopathy and/ or oligo/anuric acute renal failure. [2]
Myositis progression	Diagnosis of myositis based on muscle complaints and histologic prove of myositis or complaints of

	myositis and an increased creatine kinase not otherwise explained AND muscle weakness.
Detailed explanation disease progression per organ system	

Supplementary Table S2. Predictor variables included in the model.

Variables included in the model	Explanation
Sex	Female/male
Disease duration since first non-Raynaud symptom	Disease specific symptoms other than Raynaud phenomenon, in years.
Autoantibodies	Anti-centromere antibody, anti-topoisomerase antibody, anti-RNApIII antibody, Anti-nuclear antibody
Weight	In kilograms
Weight loss*	> 10% in 1 year
Organ involvement at baseline $	See description in supplementary table S1.
Organ progression previous visits	See description in supplementary table S1.
Skin involvement*	Modified Rodnan Skin Score
Sclerodactyly*	A localized thickening and tightness of the skin of the fingers or toes.
Digital ulcers*	Present when there was visually discernible depth and a loss of continuity of epithelial coverage. Both ischemic and mechanical [3]
Pitting scars*	Pinhole-sized digital concave depressions with hyperkeratosis
Puffy fingers*	Swollen fingers
Telangiectasia*	Small dilated blood vessels that can occur near the surface of the skin or mucous membranes
FVC*	Forced vital capacity
DLCO*	Diffusing capacity for carbon monoxide
Six minute walk test	Walking distance
Calcinosis*	Formation of calcium deposits in any soft tissue
Friction rubs*	Leathery, crepitus feel on palpation during active or passive motion
Contractures*	Joints freezing in permanent (usually flexed) positions
Dyspnea*	Anamnestic
Crepitations on auscultation*	Clicking, rattling, or crackling noises that may be made by one or both lungs of a human with a respiratory disease during inhalation.
Blood pressure*	Systolic and diastolic, in mmHg
Pulse*	Beats per minute
Raynaud VAS score*	Assessment included in the HAQ-DI
Arthritis*	The swelling and tenderness of one or more of your joints
Smoking	Current, ever, never
Reflux*	Current
Dysphagia*	Current
BSE/ESR*	Erythrocyte sedimentation rate
CRP*	C-reactive protein
CK*	Creatinine kinase
Creat*	Creatinine
Hb*	Hemoglobin
Cardiac event*	including all acute coronary syndromes and pacemaker implantations
Medication*	Cyclophosphamide, methotrexate, mycophenolate acid, azathioprine, corticosteroids, hydroxychloroquine, stem cell transplantation

Supplementary Table S2. Variables included in the Machine-Learning-Assisted model. * Included in Delphi model. $ some of the variables included in the organ involvement definitions are also included in the Delphi model; arrhythmias, left ventricular ejection fraction.

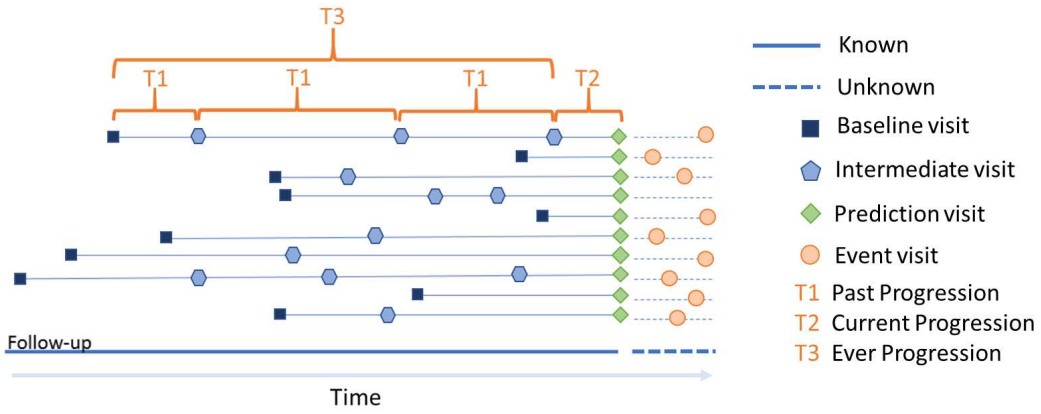

Figure S1, timeline study.

Supplementary table S3. Baseline characteristics of patients included in the Machine-Learning-Assisted model.

Demographics	n=248
Female, n(%)	197 (79)
Age, mean(SD)	53 (14)
Disease duration nonRP, median (IQR)	3.5 (2-9)
Smoking, ever n(%)	117 (47)
Organ involvement	
DcSSc, n(%)	71 (29)
mRSS, median (IQR)	4 (1-6)
DU, n(%)	26 (11)
DLCO% of pred, mean (SD)	55 (22)
FVC% of pred, mean (SD)	82 (33)
ILD on HRCT, n(%)	117 (48)
PAH, n(%)	15 (6)
GAVE, n(%)	4 (2)
Cardiac involvement, n(%)	13 (5)
Myositis, n(%)	4 (2)
Renal crisis, n(%)	8 (3)
Autoantibodies	
Anti-centromere, n(%)	77 (31)
Anti-topoisomerase, n(%)	76 (31)
RNA pol III, n(%)	15 (6)
Medication	
Corticosteroids, n(%)	30 (12)
Methotrexate, n(%)	37 (15)
Mycophenolate mofetil, n(%)	14 (5)
Hydroxychloroquine, n(%)	16 (6)
Cyclophosphamide, n(%)	9 (4)
Azathioprine, n(%)	9 (4)
ASCT, n(%)	4 (2)

Supplementary table S3. Baseline characteristics of patients included in the Machine-Learning-Assisted model.

Supplementary table S4. Stratification baseline characteristics patients ; validation, training set, complete CCISS cohort and included in model

Baseline characteristics	Training set	Validation set	CCISS cohort	Included in model	Excluded in model
Demographics	N=185	N=63	N=598	N=248	N=244
Female, n (%)	148 (80)	49 (78)	478 (80)	197 (79)	192 (79)
Age, mean (SD)	53 (13)	53 (14)	54 (15)	53 (14)	57 (14)
Disease duration nonRP, median (IQR)	3.8 (1.1-9.7)	3.3 (0.9-7.9)	3.5 (1-10)	3.5 (2-9)	2.9 (1-7)
DcSSc, n (%)	52 (28)	21 (33)	131 (22)	71 (29)	47 (19)
ILD on HRCT, n (%)	83 (45)	34 (54)	**139 (24)***	**117 (48)***	**66 (27)***
PAH, n (%)	12 (6)	3 (5)	28 (5)	15 (6)	11 (5)
GAVE, n (%)	3 (2)	1 (2)	9 (2)	4 (2)	5 (2)
Cardiac involvement, n (%)	10 (5)	3 (5)	25 (4)	13 (5)	15 (6)
Myositis, n (%)	3 (2)	1 (2)	14 (3)	4 (2)	4 (2)
Renal crisis, n(%)	6 (3)	2 (3)	17 (3)	8 (3)	6 (3)
Anti-centromere, n (%)	62 (34)	15 (24)	236 (39)	77 (31)	117 (48)
Anti-topoisomerase, n (%)	58 (31)	18 (29)	133 (22)	**40 (16)**	**76 (3)***

Bold indicates significant difference p <0.05. dcSSc=diffuse cutaneous Systemic Sclerosis, ILD= interstitial lung disease, PAH= pulmonary arterial hypertension, GAVE= gastric antral vascular ectasia.

Supplementary table S5. Coefficients included in the final Machine-Learning-Assisted model.

Independent variable	Coefficients
Previous use of cyclophosphamide	0.94
Previous use of corticosteroids	0.43
Previous GI progression	0.34
Cardiac event in medical history	0.31
Pulmonary arterial hypertension	0.30
Start IS treatment	0.21
Previous cardiac progression	0.08
mRSS	0.01
CK	0.0006
DLCO	-0.004

Supplementary table S5. GI=gastro-intestinal, cardiac event= heart infarct, pacemaker implantation, CK= creatine kinase, DLCO=diffusing carbon monoxide, mRSS= modified Rodnan Skin Score, IS=immunosuppressive, intercept: -1.24.

Data S1. Cause of Death

One patients died due to progressive PAH, four patients with progressive ILD died due to respiratory failure and one patients died after stem cell transplantation. Of two patients who do not have a registration of the cause of death, one patients was referred to another hospital in the Netherlands and one patient moved to Thailand and died there. The other patients died of malignancies (n=2 lung cancer, and n=1 acute myeloid leukemia). The two unknown deaths, showed progression in other organ systems which means that for our analyses it would not have changed the results. Of the three patients who died of malignancies two patients did not show progression on other organ systems according to the definitions we used.

Supplementary table S6. Coefficient of predictors in the Delphi model

Independent variables	Coefficients
Smoking	4.60
Digital Ulcers	-5.52
Telangiectasia	6.88
Arrhythmias	-6.18
Cardiac event in the past	5.39
Creatine kinase	0.016
Previous use of corticosteroids	6.66
Ever use of mycophenolate acid	5.98
Previous use of iloprost	15.1
Previous use of bosentan	-18.0
Calcinosis	-4.72
Synovitis	-5.27
Contractures	3.74
Friction Rubs	4.98
mRSS change over one year	-3.98

Supplementary table S6. Independent variables in the Delphi model consisted of 51 variables from the consensus guidelines. In this table the variables which were significant in this model are displayed, intercept β -7.02.

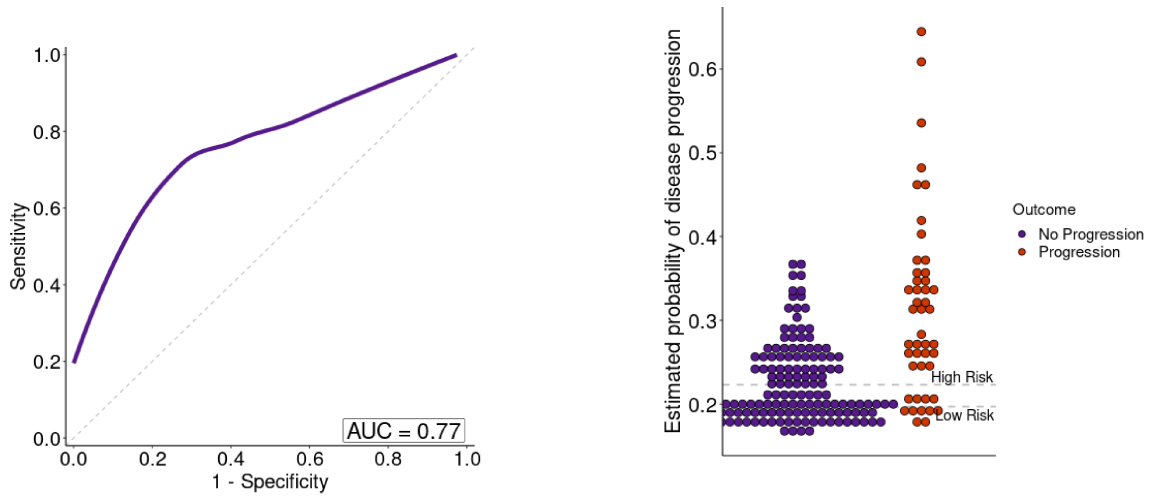

Figure S2. AUC-ROC curve and probability plots of the training set (n=189)

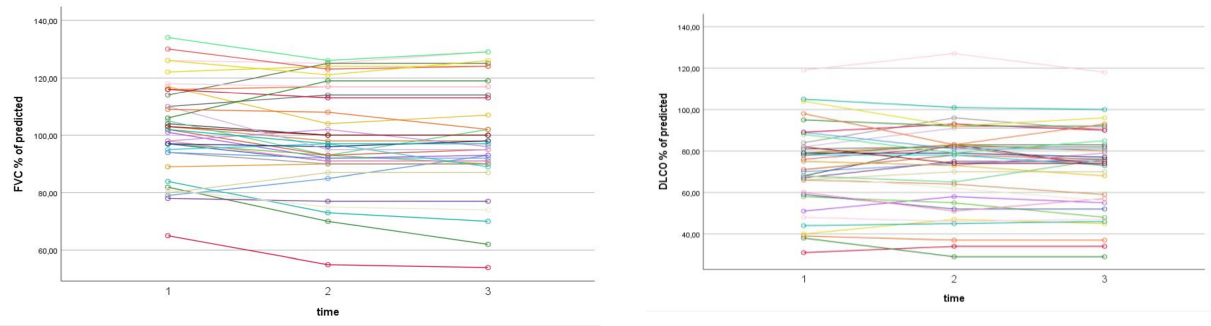

Figure S3. Spaghetti plots of excluded patients due to missing data (n=92) and the change in FVC/DLCO between the first three visits. 89% remained stable, 7% decrease of > 10% in FVC and 4% decrease of > 15% in DLCO.

1. Galie, N., et al., *2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT).* Eur Respir J, 2015. **46**: p. 903-75.
2. Butler, E.A., et al., *Generation of a Core Set of Items to Develop Classification Criteria for Scleroderma Renal Crisis Using Consensus Methodology.* Arthritis Rheumatol, 2019. **71**: p. 964-971.
3. Hughes, M., et al., *Raynaud phenomenon and digital ulcers in systemic sclerosis.* Nature Reviews Rheumatology, 2020. **16**: p. 208-221.