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Bruni, C.; Tofani, L.; Fretheim, H.; Liem, S.I.E.; Velauthapillai, A.; Bjorkekjær, H.; ... ; Distler, O.

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Original Article

Clinical science

A screening tool to detect interstitial lung disease in systemic sclerosis: the ILD-RISC score

Cosimo Bruni [1,2,*], Lorenzo Tofani [3], Håvard Fretheim [4], Sophie I.E. Liem [5], Arthiha Velauthapillai [6], Hilde Bjørkekjær [7], Imon Barua [4], Ilaria Galetti [8,9], Alexandru Garaiman [2], Mike O. Becker [2], Anna-Maria Hoffmann-Vold [2,4], Jeska de Vries-Bouwstra [5], Madelon C. Vonk [6], Jörg H. W. Distler [10,11], Marco Matucci-Cerinic [12], Oliver Distler [2]

[1]Department of Experimental Medicine, University of Florence, Florence, Italy
[2]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland
[3]Department of Statistics, Informatics and Applications, University of Florence, Florence, Italy
[4]Department of Rheumatology, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[5]Department of Rheumatology, Leiden University Medical Center, Leiden, the Netherlands
[6]Department of Rheumatology, Radboud University Medical Center, Nijmegen, Netherlands
[7]Department of Rheumatology, Hospital of Southern Norway, Kristiansand, Norway
[8]GILS, Gruppo Italiano per la Lotta alla Sclerodermia, Milan, Italy
[9]FESCA Federation of European Associations, Saint Maur, Belgium
[10]Clinic for Rheumatology & Hiller Research Center, University Hospital Düsseldorf, Heinrich-Heine University, Düsseldorf, Germany
[11]Department of Internal Medicine 3-Rheumatology and Immunology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU) and University Hospital Erlangen, Erlangen, Germany
[12]Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UniRAR), IRCSS San Raffaele Hospital, Milan, Italy

*Correspondence to: Cosimo Bruni, Department of Rheumatology, University Hospital Zurich, University of Zurich, Rämistrasse 100, Zurich 8006, Switzerland. E-mail: cosimo.bruni@usz.ch

Abstract

Objectives: As a screening tool for the presence of systemic sclerosis-associated interstitial lung disease (SSc-ILD) on high-resolution computed tomography (HRCT) is missing, we aimed to develop the ILD-RISC score, a risk algorithm to guide physicians in ordering HRCTs, with specific focus on follow-up visits.

Methods: The nominal group technique was used to select items for the multivariable logistic regression with backward selection. The ILD-RISC score was developed from baseline visits of the derivation cohort. After identifying a cut-off favoring sensitivity >85% from the ROC curve, it was validated in a separate cross-sectional cohort, and then applied longitudinally in a specific SSc cohort with negative baseline HRCT.

Results: In the derivation cohort (533 patients), 13 variables associated with the presence of SSc-ILD on HRCT were tested. The ILD-RISC score, including FVC%, DLCO/SB%, digital ulcers ever, age and SSc autoantibodies, showed an area under the curve of 79.1% (75.3–83.0%) for the presence of SSc-ILD on HRCT. An ILD-RISC score ≥0.3 had sensitivity 85.6% and specificity 53.6%, as confirmed in the validation cohort (247 patients). Among 819 patients with negative baseline HRCT, 170 developed SSc-ILD: a low ILD-RISC score was detected in almost 50% of the follow-up visits, supporting the sparing of HRCTs.

Conclusion: The ILD-RISC score was developed and validated to predict the presence of SSc-ILD. Thus, the ILD-RISC score may help to decide when to order HRCTs at follow-up, allowing the reduction of costs and radiation exposure, but also at the time of SSc diagnosis when resources are limited.

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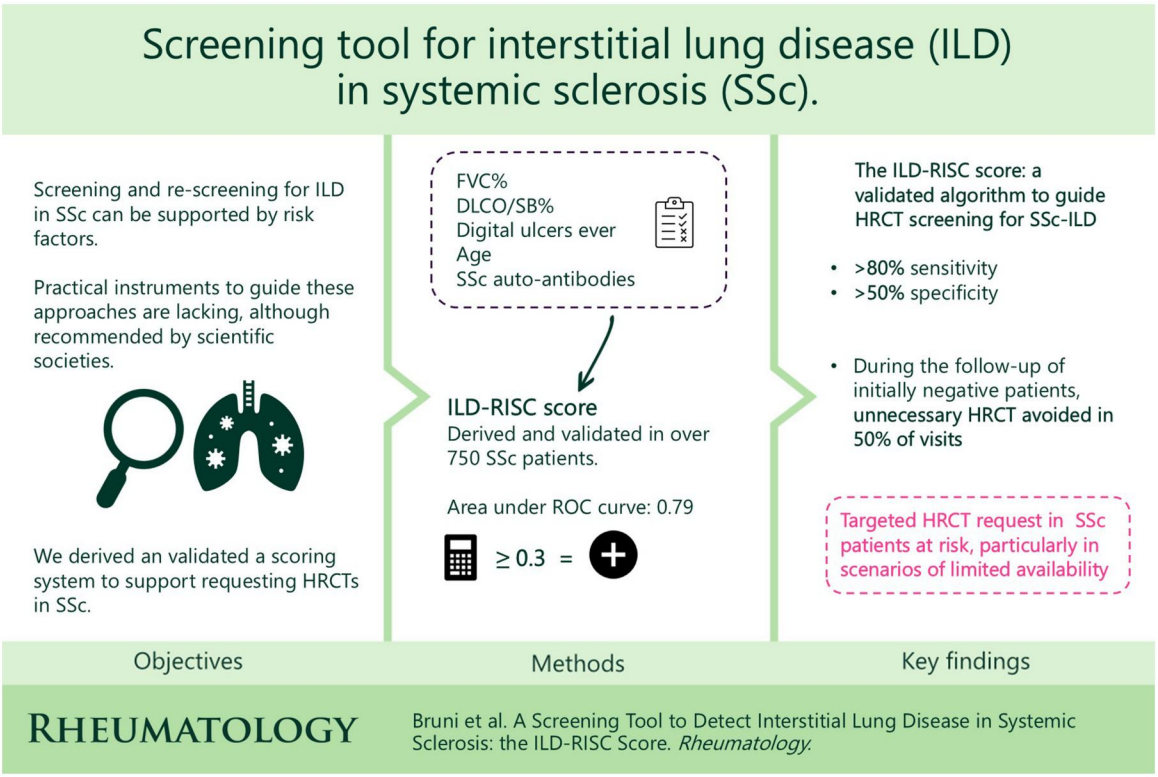
Graphical abstract



Keywords: systemic sclerosis, interstitial lung disease, screening, re-screening, high-resolution computed tomography.

Rheumatology key messages

- The ILD-RISC score is a feasible, non-invasive tool to predict SSc-ILD presence in HRCT.
- The high sensitivity of the ILD-RISC score is confirmed at baseline and follow-up visits.
- During the follow-up, a low ILD-RISC score allows the skipping of unnecessary HRCTs.

Introduction

In systemic sclerosis (SSc), the gold standard to diagnose interstitial lung disease (ILD) is high-resolution computed tomography (HRCT) [1]. As SSc-ILD impacts on morbidity and mortality [2] and effective treatments have become available [3, 4], it is highly recommended to detect SSc-ILD as early as possible [5].

A recent survey showed wide variability in using HRCT for SSc-ILD screening, both at baseline and follow-up [6]. Reasons not to perform HRCTs may include radiation exposure, availability, patients' disagreement and the expected high number of negative examinations, in particular at follow-up visits, when the prevalence of new-onset ILD is lower [7, 8]. In this context, most physicians order follow-up HRCTs when symptoms occur or pulmonary function tests (PFTs) deteriorate, which are both features of a more advanced disease, missing the goal of early diagnosis [6].

Scientific societies have released guidance for screening of SSc-ILD, which builds upon previous international consensus [5]. The recently presented guideline from the European Respiratory Society (ERS)/European League Against Rheumatisms (EULAR) strongly recommends screening for SSc-ILD with HRCT in all patients at baseline, but details regarding re-screening after a negative baseline are not provided [9]. Conversely, the 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline conditionally recommends screening for ILD in patients with SSc by HRCT only in case of increased risk. This is indicated when features such as male sex, African American ethnicity, diffuse cutaneous subset (dcSSc), anti-topoisomerase I antibodies (ATA), antinuclear antibodies with nucleolar pattern, early disease duration and increased inflammatory biomarkers are present [10]. Once the first screening with HRCT shows negative results, it is recommended to consider yearly screening in high-risk patients, with specific focus on PFTs rather than on HRCT [10].

Unfortunately, none of these risk factors alone can identify the presence of ILD with acceptable sensitivity or in its early stages. This is also the case for PFTs, for which both forced vital capacity (FVC) and diffusion of the lung for carbon oxide

on single breath (DLCO/SB) are neither specific nor sensitive enough to detect SSc-ILD, even when used in combination or when selecting specific cut-offs [11]. Additionally, some risk factors such as antibody profile, ethnicity and sex are fixed and non-modifiable, therefore potentially labelling the patient as 'at risk' for the whole disease course and leading to unnecessary HRCTs if not mitigated by other parameters.

Thus, optimally combining single risk factors for the presence of SSc-ILD would help physicians in the clinical decision-making to order an HRCT, to improve screening and direct HRCTs to those at highest need. This is most important when HRCTs are not readily available. Such a composite risk score would particularly be helpful for follow-up examinations, when the prevalence of new-onset ILD is lower.

Therefore, the aim of our study was to develop and validate a scoring system to identify SSc patients at high risk of presenting ILD on HRCT at baseline visit and then test its performance to detect new-onset ILD in the follow-up of SSc patients.

Methods

The development of the ILD-RISC score followed a multistep approach, inspired by the methodology that was used to develop the DETECT score for pulmonary arterial hypertension (PAH) [12].

Selection of predictors

A broad range of parameters related to ILD was identified from a recent systematic literature review (SLR) [13]. A steering committee including six SSc-ILD experts, two research fellows and a patient research partner participated in a three-round virtual meeting. The suggested variables (Supplementary Table S1) were defined as previously reported [14–16] and discussed following the nominal group technique (NGT), based on the scientific background provided by the above-mentioned SLR, feasibility and personal experience (see Supplementary Data S1).

Derivation and validation of the ILD-RISC score

A multicentre cohort of SSc patients, classified according to the 2013 ACR/EULAR criteria [17], was created from six European SSc referral centres (University Hospital of Zurich, University of Florence, University of Erlangen, University of Leiden, University of Nijmegen and Oslo University Hospital). All centres have a dedicated SSc database, collect data prospectively and regularly perform HRCT at baseline and follow-up. The study was performed following the principles of the Declaration of Helsinki and under ethical committee approval (KEK-ZH PB_2018-02165); all patients provided written informed consent before participation.

For this study, the multicentre cohort was randomly divided into derivation and validation cohorts, both containing patients of each centre. The outcome of interest was the presence of ILD on HRCT, defined as presence of bilateral, predominantly basal ground-glass or reticular abnormalities, traction bronchiectasis, honeycombing, non-emphysematous cysts or diffuse centrilobular nodularity. For this part of the analysis, we included only the baseline visit. We excluded patients with no available baseline HRCT or missing data in any of the preliminarily selected predictors. The final list of variables derived from stage I was tested in the derivation cohort to create a prediction model (the ILD-RISC score), followed by selection of a cut-off value, and then re-tested in the validation cohort (see the 'Statistical analysis' section).

The longitudinal study

The ILD-RISC score was applied longitudinally to patients who had a baseline HRCT negative for ILD and at least one follow-up visit with HRCT and information on predictors of the final model, to analyse its performance in detecting new onset of ILD.

Testing the model in case of a missing predictor

The performance of the ILD-RISC score was further evaluated in cases in which one of the variables of the final model was missing. This reflects clinical practice in which single parameters are often missing. We selected visits of patients with one missing value in any predictor of the final model and computed the missing value using separate prediction models for each missing variable (see the 'Statistical analysis' section).

Statistical analysis

Handling of missing data was done as listed in Supplementary Data S1. Categorical variables are presented as number (percentage), while continuous variables as mean (SD) or median (IQR), depending on whether data were normally distributed. To prevent multicollinearity, a Pearson's correlation coefficient matrix of the predictors was calculated, considering two predictors as collinear if their coefficient was $>|0.4|$. The required sample size was calculated as follows: with an observed area under the ROC curve (AUC) of 0.80, a null hypothesis of 0.73, a type I error of 0.05 and an ILD prevalence of 50% [1], 500 patients were needed for a power of 90% according to the Hanley–McNeil method for standard error estimation. The derivation and validation cohorts were created by splitting the original cohort into 2/3 and 1/3 cohorts, respectively, using random sampling across all cohorts.

To define the most feasible and smallest set of predictors composing the ILD-RISC score, a multiple logistic regression model with backward selection was used. The *P*-value to be retained in the model was set to 0.1. The odds ratios (ORs) and their 95%CI were reported. The predictive capability was estimated using the AUC and its 95% CI.

To select a cut-off of when to send a patient for HRCT, the steering group decided to aim at a high sensitivity of the ILD-RISC score (>85%). To validate the performance of the selected cut-off, we used the ORs estimations from the derivation cohort to calculate the predicted probability of ILD on HRCT in the validation cohort and then predict ILD on HRCT applying the cut-off, again reporting specificity, sensitivity, positive and negative predictive values (PPV, NPV) and their 95%CI were reported. Calibration plots were plotted to evaluate the goodness of fitting of the model.

Finally, different prediction models (logistic, multiple or linear regression) were used to impute a missing predictor. Using the missing parameter as the dependent variable and the other predictors as independent variables, the derivation cohort was used to estimate the OR coefficients and impute the missing data. Once the missing values were replaced, the predicted probability of ILD on HRCT (calculated using derivation ORs estimation) was calculated and the cut-off applied. The sensitivity, specificity, PPV, NPV of the cut-off and its 95%CI were reported. Results are overall reported according to the "Transparent Reporting of a multivariable

prediction model for Individual Prognosis Or Diagnosis (TRIPOD)" guidelines.

Results

Selection of variables

The steps of the variables' selection process are presented in Supplementary Table S1. The initial list from the literature review included 94 variables; three were added to the dataset upon discussion in the NGT group, who decided to vote on 44/97 variables based on face validity, usefulness and expert opinion. Following three rounds of voting and discussion (Supplementary Data S1), the final selection included 13 variables, for which the NGT group agreed unanimously. These were: age, sex, disease duration since the first non-Raynaud's sign/symptom, cigarette smoking ever, presence of esophageal symptoms, dyspnea stage by NYHA functional class, dcSSc, digital ulcers (DU) ever, joint synovitis ever, SSc antibody positivity, increased inflammatory markers, DLCO/SB% and FVC%.

Derivation and validation of the ILD-RISC score

Merging the dataset of the six centres resulted in 3254 patients included in the respective local registries for over 15 years. Among them, 77.6% were female with a mean age of 56 years and a median disease duration of 5 years. At baseline, 304 (9.3%) had not received a screening chest HRCT and were therefore excluded from the analysis. Of the remaining 2950 SSc patients, ILD was detected at baseline visit in 42.7% of patients. At least one follow-up HRCT was available in 1881 (63.7%) cases, more frequently for patients with ILD than in those without ILD at baseline ($n = 962/1256$, 76.6% *vs* $n = 919/1694$, 54.3%).

The derivation and validation cohorts, retrieved by random distribution from the whole cohort, were overall well-balanced (Table 1). After applying the inclusion criteria to the derivation cohort, 533/2181 patients formed the derivation set. The most frequent reasons for exclusion were missing data on NYHA functional class, smoking history and increased inflammatory markers.

The initial derivation model applying the 13 selected variables showed an AUC of 0.802 (CI 95% 0.764–0.839). The backward selection process (Supplementary Table S2) simplified the model to five variables: age, SSc antibody positivity, DLCO/SB%, FVC% and DU ever (Tables 2 and 3), with an AUC of 0.791 (95%CI 0.752—0.830, $P < 0.001$, Fig. 1). The model showed an optimal calibration (Fig. 2A) and the ILD-RISC score separated presence *vs* absence of ILD on HRCT well (Fig. 3A).

Next, the optimal cut-off of the ILD-RISC score was selected. Applying a sensitivity of at least 85%, the ROC curve analysis of different ILD-RISC scores identified the target cut-off at 0.30. An ILD-RISC score ≥ 0.30 showed a sensitivity of 85.6%, specificity of 53.6%, PPV of 58.2% and NPV of 83.2% for presence of ILD on HRCT.

The validation cohort included 247/1103 patients, with similar reasons for exclusion to the derivation cohort. Patients in the validation cohort showed higher prevalence of smoking ever, ATA, ILD and immunosuppression, but lower presence of esophageal symptoms and ACA. The ILD-RISC score confirmed its performance in the validation cohort: the AUC to identify the presence of ILD was 0.768 (95%CI 0.710–0.827, $P < 0.001$, Fig. 1B). The good calibration (Fig. 2B) and the ability to separate presence *vs* absence of ILD on HRCT (Fig. 3B) were confirmed. Similar to the derivation cohort, an ILD-RISC score ≥ 0.30 predicted the presence of ILD with sensitivity of 85.7%, specificity of 49.2%, PPV of 61.1% and NPV of 78.8%.

The longitudinal study

Among the 919 patients with negative HRCT at baseline, 819 also had the variables required for the calculation of the ILD-RISC score at baseline and follow-up. A total of 1988 visits were included in the analysis, along a mean follow-up of 3.8 ± 3.0 years. In comparison to the derivation and validation cohorts, the longitudinal cohort had more female patients, limited cutaneous disease and ACA, while lower prevalence of vascular manifestations and ATA (Table 1). A total of 170 (20.8%) cases were detected with ILD on HRCT during follow-up, on average after 2.6 years. The serial application of the ILD-RISC score during the follow-up visits confirmed the performance of an ILD-RISC score ≥ 0.30 in predicting the presence of ILD, with sensitivity 80.4%, specificity 50.5%, PPV 13.9% and NPV 96.3%. From a different perspective, the ILD-RISC score correctly identified 914/1809 visits in which the HRCT was negative, showing that a score below the cut-off would avoid 50.5% of unnecessary HRCTs during the follow-up.

Testing the model in case of a missing predictor

The baseline visits of 1230 patients had one missing variable needed to calculate the ILD-RISC score: SSc antibody positivity for at least one antibody was missing in 44.3%, FVC% in 23.5%, DU ever in 20.3% and DLCO/SB% in 11.9% of the patients. No patient had missing values for age.

This cohort showed a higher prevalence of male patients, ATA, dcSSc and vascular complications in comparison to the derivation and validation cohorts (Supplementary Table S3). Imputation of missing values was performed using five regression models created from the derivation cohort to predict age, SSc antibody positivity, DU ever, FVC% and DLCO/SB%, respectively (Supplementary Tables S4–8). After imputation of the missing values, the performance of the ILD-RISC score was similar to the derivation and validation cohorts. Specifically, an ILD-RISC score ≥ 0.30 showed sensitivity 80.5%, specificity 45.9%, PPV of 56.1% and NPV of 73.3% for the presence of ILD on HRCT. Similarly, the ILD-RISC score could allow to skip 304/662 negative HRCTs, also in case of one missing parameter.

Comparing the ILD-RISC with other screening approaches

Simulating the ACR/CHEST baseline screening approach in our derivation cohort, the presence of at least one risk factor (male sex, African American ethnicity, dcSSc, ATA, antinuclear antibodies with nucleolar pattern, early disease duration or increased inflammatory biomarkers) was positive in 419/533 patients (78.6%), leading to the detection of 191/229 ILD cases. This translates into an 83.4% sensitivity but 25% specificity. Overall, this is worse than the performance of the ILD-RISC in the same patients. An ILD-RISC score ≥ 0.3 would suggest HRCT in 337/553 (60.9%) patients to capture 196/229 ILD cases, carrying comparable sensitivity but a specificity twice as high.

Looking at the longitudinal cohort, 578/819 (70.7%) patients showed at least one ACR/CHEST risk factor over time. If each of these patients was re-screened during the follow-up, 1139 CTs would be performed over 1881 visits to detect 121/170 new-onset ILDs, determining 70.7% sensitivity and 40.5%

Table 1. Description of the study populations: derivation, validation and longitudinal cohorts

	Derivation cohort				Validation cohort				Longitudinal cohort	
	Whole group $n = 2151$		Selected sample $n = 533$		Whole group $n = 1103$		Selected sample $n = 247$		Whole group—baseline $n = 819$	
	Distribution	Missing (%)	Distribution	Missing (%)	Distribution	Missing (%)	Distribution	Missing (%)	Distribution	Missing (%)
Age, years, mean ± SD	55.8 ± 13.9	1.5	55.9 ± 13.8	0	56.3 ± 13.3	1.3	55.6 ± 13.6	0	54 ± 13.4	0
Female sex, *n* (%)	1656 (76.9)	0	417 (78.2)	0	870 (78.9)	0	187 (75.7)	0	677 (82.7)	0
Disease duration, years, median (IQR)	4 (1–10)	13.5	4 (1–11)	0	4 (1–9)	14.8	5 (2–10)	0	4 (1–8)	11.9
Cigarette smoking ever, *n* (%)	664 (42.2)	26.8	225 (42.2)	0	371 (46.4)	27.5	123 (49.8)	0	344 (46.6)	9.9
Esophageal symptoms, present, *n* (%)	1090 (55.6)	8.9	332 (62.3)	0	568 (57.7)	10.8	139 (56.3)	0	431 (54.5)	3.4
Dyspnea Stage (NYHA functional class), *n* (%)										
I	772 (60.1)	41.8	317 (59.5)	0	339 (58.9)	47.7	140 (56.7)	0	360 (69.1)	36.4
II	372 (30.9)		176 (33.0)		180 (31.3)		85 (34.4)		137 (26.3)	
III	86 (7.2)		34 (6.5)		48 (8.3)		21 (8.5)		23 (4.4)	
IV	22 (1.8)		6 (1.1)		9 (1.5)		1 (0.4)		1 (0.1)	
Diffuse cutaneous subset, *n* (%)	517 (27.8)	13.5	140 (26.3)	0	241 (25.0)	11.6	68 (28.7)	0	140 (19.9)	12.1
mRSS, median (IQR)	4 (1–9)	16.4	5 (2–10)	8.1	5 (1–10)	15.8	5 (1–11)	7.7	3 (0–7)	8.1
Digital ulcers, ever, *n* (%)	588 (29.1)	9.5	184 (34.5)	0	284 (28.9)	9.9	91 (36.8)	0	215 (26.5)	0
Joint synotivits, ever, *n* (%)	246 (12.5)	8.6	78 (14.6)	0	131 (13.2)	8.9	31 (12.6)	0	120 (14.8)	1
SSc antibody positivity, *n* (%)										
ACA	809 (43.6)	13.7	240 (45.0)	0	393 (41.3)	13.7	89 (36.0)	0	477 (58.2)	0
ATA	451 (24.3)		121 (22.7)		232 (24.4)		72 (29.2)		127 (15.5)	
ARA	101 (5.4)		38 (7.3)		45 (4.8)		16 (6.5)		59 (6.8)	
PM/Scl	60 (3.2)		23 (4.3)		27 (2.8)		8 (3.2)		17 (2.1)	
None or other	434 (23.4)		110 (20.6)		255 (26.7)		62 (25.1)		142 (17.3)	
Increased inflammatory markers, present, *n* (%)	505 (29.4)	15.4	155 (29.1)	0	241 (28.2)	22.5	71 (28.7)	0	174 (22.7)	6.5
Pulmonary arterial hypertension, *n* (%)	121 (9.2)	38.9	34 (8.9)	28.3	61 (9.1)	38.9	15 (8.3)	26.8	27 (4.8)	30.1
Scleroderma renal crisis, *n* (%)	55 (2.8)	8.5	15 (2.8)	0.4	17 (1.7)	10.7	5 (2.1)	1.6	15 (1.9)	3.2
Interstitial lung disease on HRCT, *n* (%)	823 (42.4)	9.4	229 (43.0)	0	433 (43.4)	9.2	119 (48.2)	0	0	0
FVC%, mean ± SD	96 ± 21	16.9	95 ± 20	0	96 ± 21	17.7	96 ± 19	0	102 ± 18	0
DLCO/SB%, mean ± SD	68 ± 20	13.2	71 ± 21	0	68 ± 20	13.2	69 ± 20	0	75 ± 18	0
Ongoing Immunosuppressive medication, *n* (%)	356 (21.8)	24.2	139 (28.2)	9.2	187 (23.1)	26.6	86 (38.1)	8.5	119 (15.5)	6.2

ACA: anti-centromere antibodies; ARA: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase I antibodies; DLCO/SB%: diffusion of the lung for carbon oxide on single breath; FVC: forced vital capacity; HRCT: high-resolution computed tomography; IQR: interquartile range; mRSS: modified Rodnan's skin score; NYHA: New York Heart Association; SD: standard deviation.

specificity. Conversely, using an ILD-RISC ≥0.3 as a screening tool to request HRCT in the same population, 495/819 (60.4%) patients would be screened at least once over time, for a total of 1036 CTs to detect 137/170 ILD patients. Again, ILD-RISC score performs overall better than the approach suggested by the ACR/CHEST guideline, in terms of fewer patients scanned, fewer CTs performed, more positive cases detected and more negative HRCTs avoided.

Discussion

The ILD-RISC score was developed and validated as the first multi-parametric, consensus-based, data-driven algorithm to predict the presence of ILD on HRCT in SSc. In addition to its high sensitivity in identifying patients who should undergo HRCT at baseline, the ILD-RISC score performed well during follow-up to decide when to repeat HRCTs in baseline ILD-negative patients. In fact, it may avoid >50% of unnecessary CTs during follow-up, when a low score is calculated.

The use of composite scores for screening purposes in SSc

Composite scores for early detection of organ manifestations of SSc have been successfully developed [18]. For example, the DETECT score has established a standardized approach for PAH screening [12] and is now included in international

Table 2. Variables included in the final ILD-RISC model

Parameter	OR	95% CI	*P* value
Age	1.026	1.010–1.042	0.001
Digital ulcers, ever	2.058	1.347–3.145	<0.001
DLCO/SB%	0.971	0.960–0.982	<0.001
FVC%	0.990	0.979–1.002	0.091
SSc ATB_ None or other	1.000		
SSc ATB_ ACA	0.334	0.198–0.563	<0.001
SSc ATB_ ATA	2.379	1.326–4.267	0.004
SSc ATB_ ARA	1.407	0.636–3.113	0.399
SSc ATB_ Pm/Scl	2.556	0.916–7.135	0.073

ACA: anti-centromere antibodies; ARA: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase I antibodies; DLCO/SB%: diffusion of the lung for carbon oxide on single breath; FVC: forced vital capacity; SSc: systemic sclerosis; ATB: antibody positivity.

Table 3. Formulas to calculate the ILD-RISC score

SSc antibody positivity	ILD RISC score
ACA	$1-\left(\frac{1}{(1+e^{1.2027-1.0975+0.0253*Age+0,7217*DU-0.0294*DLCO\|SB\%-0.0098*FVC\%)}}\right)$
ATA	$1-\left(\frac{1}{(1+e^{1.2027+0.8666+0.0253*Age+0,7217*DU-0.0294*DLCO\|SB\%-0.0098*FVC\%)}}\right)$
ARA	$1-\left(\frac{1}{(1+e^{1.2027+0.3417+0.0253*Age+0,7217*DU-0.0294*DLCO\|SB\%-0.0098*FVC\%)}}\right)$
PM/Scl	$1-\left(\frac{1}{(1+e^{1.2027+0.9385+0.0253*Age+0,7217*DU-0.0294*DLCO\|SB\%-0.0098*FVC\%)}}\right)$
None of the above	$1-\left(\frac{1}{(1+e^{1.2027+0.0253*Age+0,7217*DU-0.0294*DLCO\|SB\%-0.0098*FVC\%)}}\right)$

A different formula is required according to the antibody positivity subset. While age, FVC% and DLCO/SB% are counted as continues values, digital ulcers ever is a categorical variable (if yes DU = 1, if no DU = 0).
ACA: anti-centromere antibodies; ARA: anti-RNA polymerase III antibodies; ATA: anti-topoisomerase I antibodies; DLCO/SB%: diffusion of the lung for carbon oxide on single breath; DU: digital ulcers, ever; FVC: forced vital capacity; SSc: systemic sclerosis; ATB: antibody positivity.

guidelines [19]. Given the prevalence of baseline ILD of around 40% already at baseline, screening all SSc patients at baseline is well justified. Thus, screening for ILD of all SSc patients at baseline by HRCT is recommended by the ERS/EULAR guideline, and we strongly agree with this statement. Our newly developed ILD-RISC score is not thought to replace this recommendation [5, 9]. However, financial, geographical and institutional difficulties might limit the access to HRCTs for all SSc patients. In these cases, the ACR/CHEST screening approach could be applied [10]. It recommends screening by HRCT in patients with increased risk for ILD, such as male patients, diffuse cutaneous subset, increased inflammatory biomarkers, ATA positivity and early disease duration, therefore requiring a pre-selection of patients at high risk [10]. Still, there is no clear guidance on how to interpret these risk factors (i.e. how many are needed and how to handle the fixed, non-modifiable features). In this context, the ILD-RISC score could be helpful as a data-driven approach to support the use of HRCT [6, 10].

The scenario for ILD screening changes profoundly during longitudinal follow-up, as the incidence of newly detected ILD is much lower and continuous screening of all SSc patients with HRCT is more difficult to justify. In this case, the ERS/EULAR guideline do not provide guidance for re-screening, while the ACR/CHEST guideline recommends a similar approach to the baseline visit, based on the presence of risk factors but acknowledging that their absence does not preclude screening. These are exactly the circumstances in which the ILD-RISC score might help in selecting patients independent from HRCT availability and provides an evidence-based tool to support physicians from any centre in the decision-making regarding re-screening, when initially ILD negative patients should be sent for a new HRCT. Simultaneously, it may allow omitting unnecessary HRCTs, promoting a reduction of expenses/burden for healthcare providers and avoiding unnecessary radiation exposure for patients.

The ILD-RISC score has validity, it is feasible and easy to apply

The ILD-RISC score combines well-known risk factors for SSc-ILD. Despite being well-established to quantify the functional impairment in ILDs [20], PFTs showed low sensitivity and specificity as a single screening tool for the presence of ILD in multiple studies [11, 21]. The current study added to the existing knowledge by showing that the predictive performance is improved when combined with other parameters [11, 21]. In addition, the ILD-RISC study confirmed the association of SSc-specific autoantibodies with ILD [22–24]. Moreover, DU at any time before the visit were associated with increased risk of ILD, in line with previous data indicating peripheral vascular involvement as a red flag for a more aggressive disease phenotype [25, 26]. Similarly, age has been associated with higher prevalence of cardiopulmonary complications in SSc [27].

In addition to their validity, these parameters are clinically feasible, which makes it applicable also in non-SSc referral centres. This might enable smaller centres with fewer resources to improve patients' management, lowering the inequity for all patients as well, by supporting the request for HRCTs in situations of limited accessibility. To further support such circumstances and to reflect real-life clinical practice, we showed the ILD-RISC score calculation to work also when one of the necessary parameters is missing. For easy application, a ready-to-use calculator has been made available as Supplementary Data S2.

Patient involvement

Different from most previous screening tools, a patient research partner was a member of the steering committee, allowing to foresee a positive acceptance of SSc patients for using the ILD-RISC score, given the non-invasive nature, the possibility of its use also when one parameter is missing and the consequent reduction of unnecessary HRCTs. Additionally, the possibility of an early diagnosis of organ involvement may lead over time to a better prognosis and better-preserved quality of life.

Study limitations

Despite the methodological strengths, our study also has some limitations. First, the high number of missing data resulted in a reduction of our study population, which might have determined a certain selection bias, despite easily reaching the required sample size and being broadly representative. The relatively low specificity of the ILD-RISC score represents a second limitation, which determines a high number of false-positive cases [12]. However, the major concern for a false-positive ILD-RISC score would be the unnecessary exposure to ionizing radiation, which can be partially overcome

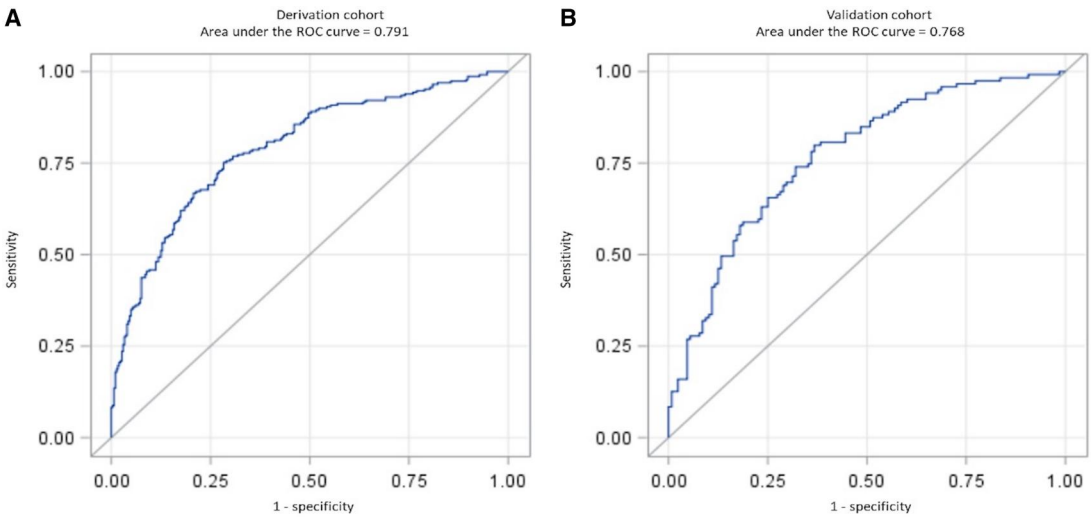


Figure 1. ROC curve of the ILD-RISC score to predict presence of ILD on HRCT in the derivation (**A**) and validation (**B**) cohorts

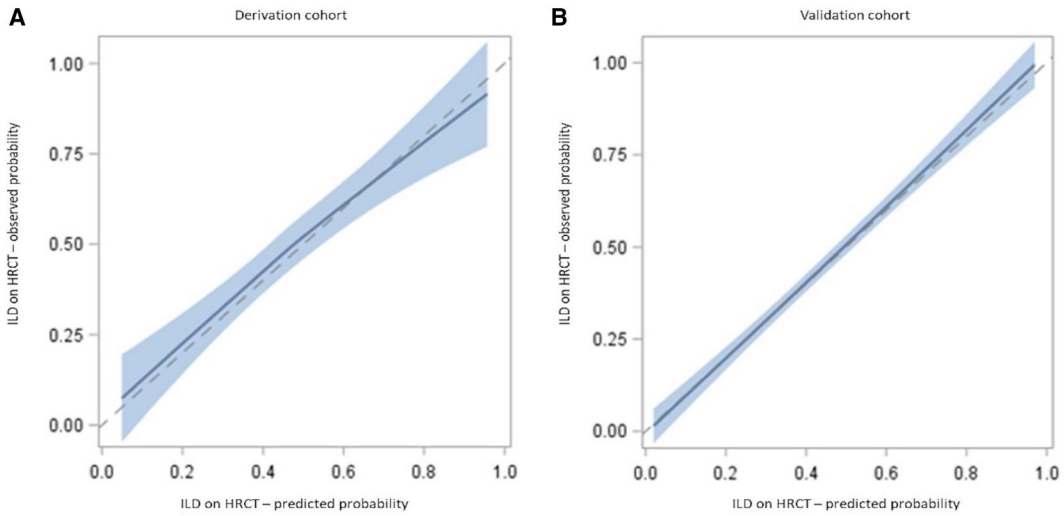


Figure 2. Calibration plots of the ILD-RISC score in the derivation (**A**) and validation (**B**) cohorts. The dashed lines represent the optimal interpolation between predicted and observed probability. The dark blue lines represent the interpolation in the studied cohorts, with their 95% confidence interval in light blue

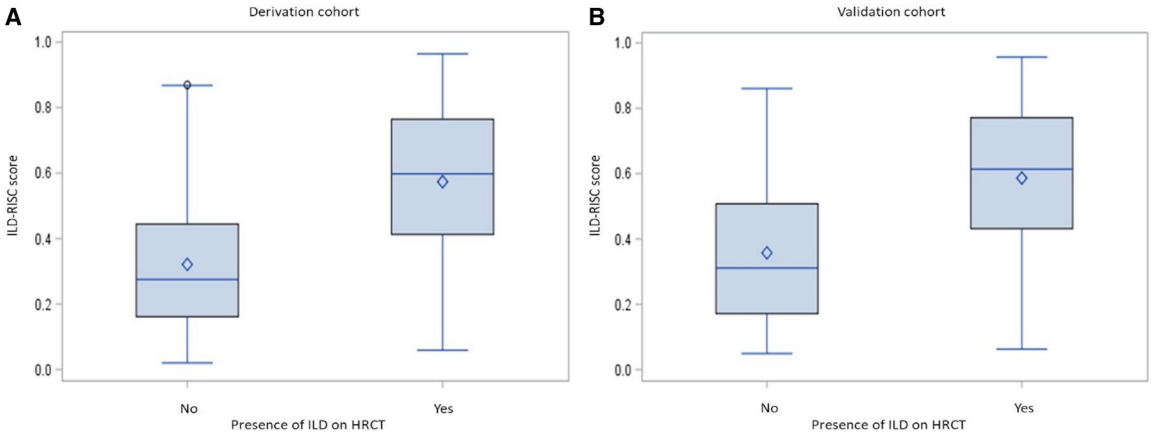


Figure 3. Distribution of the ILD-RISC score between patients with and without ILD on HRCT, in the derivation (**A**) and validation (**B**) cohorts

through HRCT protocols with a reduced number of slices, low-radiation regimens or more advanced technology [28, 29]. Another potential limitation is the small number of patients with PAH and with non-Caucasian ethnicity. As both factors could determine a higher rate of false-positive ILD-RISC tests, impacting both on DLCO/SB% values or

more severe PFTs impairment overall [30], further studies will have to analyze the performance of the ILD-RISC score in these populations. Finally, we acknowledge that certain autoantibody detection methods may yield false-positive or false-negative results, potentially biasing the ILD-RISC score results. However, in our study we intentionally did not restrict the analysis to a single testing method, reflecting both the change in techniques at our institution over decades and the real-world clinical practice, where a variety of diagnostic assays are commonly used, and to ensure that our findings are both reproducible and generalizable across different laboratory settings. Additionally, patients with double positivity of SSc antibodies were excluded from this analysis, therefore limiting the generalizability of the ILD-RISC score application to this specific sub-cohort of SSc patients. However, the number of double positive cases in our cohort was extremely small, consistent with a previous report [31].

In summary, the ILD-RISC score is a unique, non-invasive and feasible screening tool, specifically developed for SSc-ILD. We are in strong agreement with the ERS/EULAR guidelines that a screening HRCT should be performed in all SSc patients at baseline [9]. However, if HRCT is not readily available and resources are limited, the ILD-RISC helps to identify SSc patients at risk according to the ACR/CHEST guideline. Even more importantly, our data strongly suggest that the ILD-RISC score avoids unnecessary HRCTs for initially ILD-negative patients during follow-up and provides data-driven support for the performance of re-screening. This might allow the future development of evidence-based recommendations for the re-screening of SSc-ILD following a negative baseline HRCT, supporting prompt diagnosis and early intervention.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Anonymized data might be available from OD at the Department of Rheumatology, University Hospital Zurich, University of Zurich, Switzerland on reasonable request.

Contribution statement

Criterion 1: (i) Substantial contributions to study conception and design: C.B., L.T., O.D. (ii) Substantial contributions to acquisition of data: H.F., S.I.E.L., A.V., H.B., I.B., A.G., A.-M.H.-V., C.B., O.D., M.C.V., J.D.V.-B., J.H.W.D. (iii) Substantial contributions to analysis and interpretation of data: All authors. Criterion 2: Drafting the article or revising it critically for important intellectual content: all authors. Criterion 3: Final approval of the version of the article to be published: all authors.

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Patients and public involvement (PPI): A patient research partner (I.G.) was involved in the design and conduct of our research.

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