PNEUMOMEDICINA 2022

ILD e sclerosi sistemica: fenotipi clinici e differenze prognostiche, inclusi gli autoanticorpi

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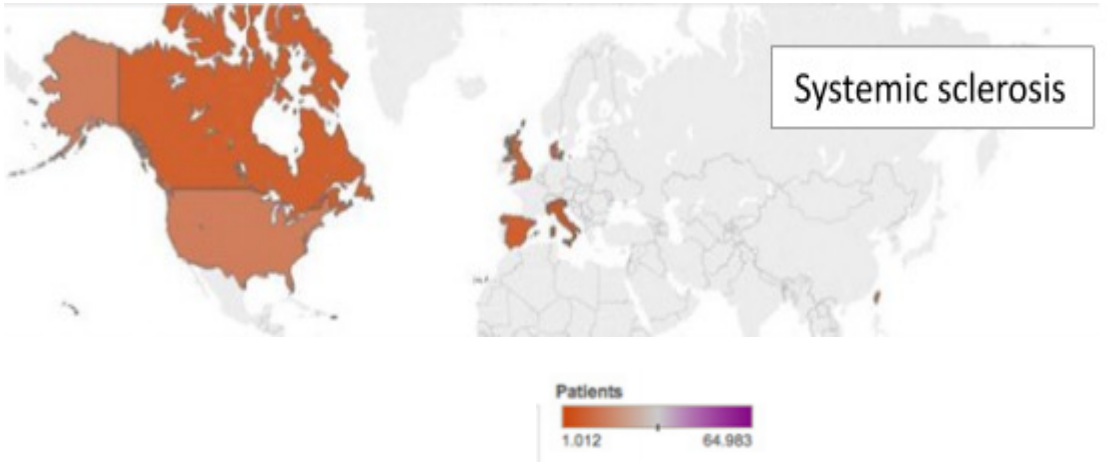
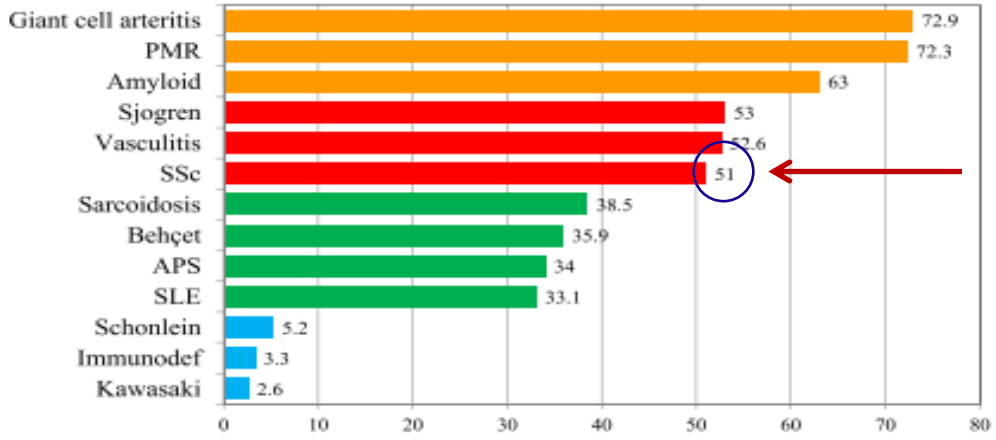
Systemic Sclerosis
Background

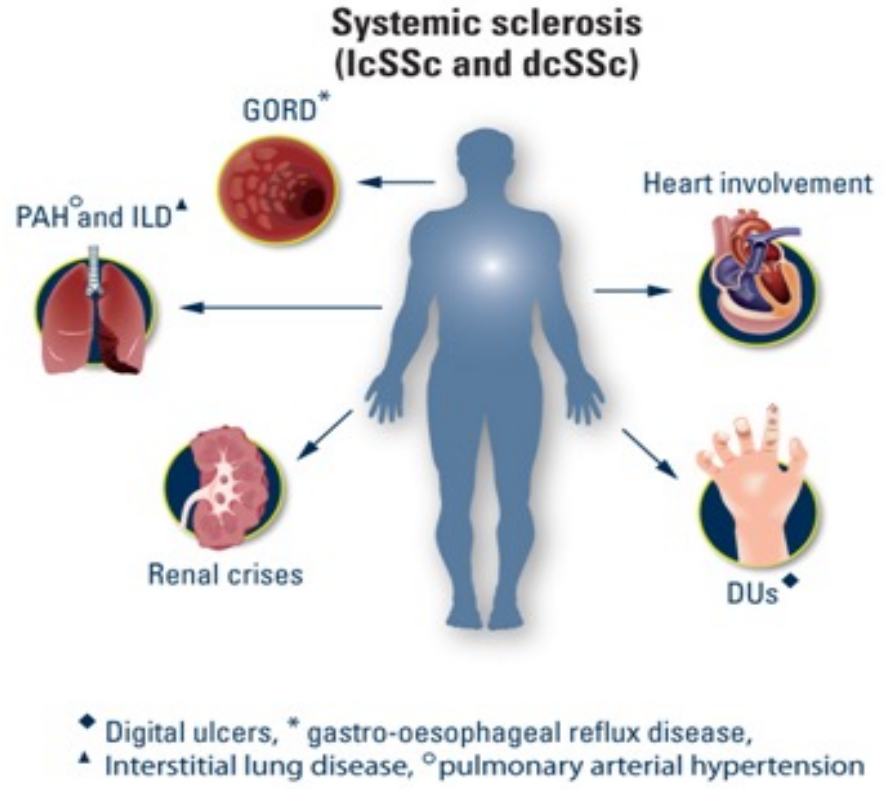
Chronic life-threatening
connective tissue disease
Prevalance: 50-300/1.000.000
Incidence: 2.3-22.8/1.000.000/year





Gabrielli A. Scleroderma. NEJM 2009.
Lo Monaco A, et al. Epidemiology of systemic sclerosis in a district of northern Italy. Clin Exp Rheumatol 2011.
Tyndall AJ et al. Ann Rheum Dis.

Background
Survival data

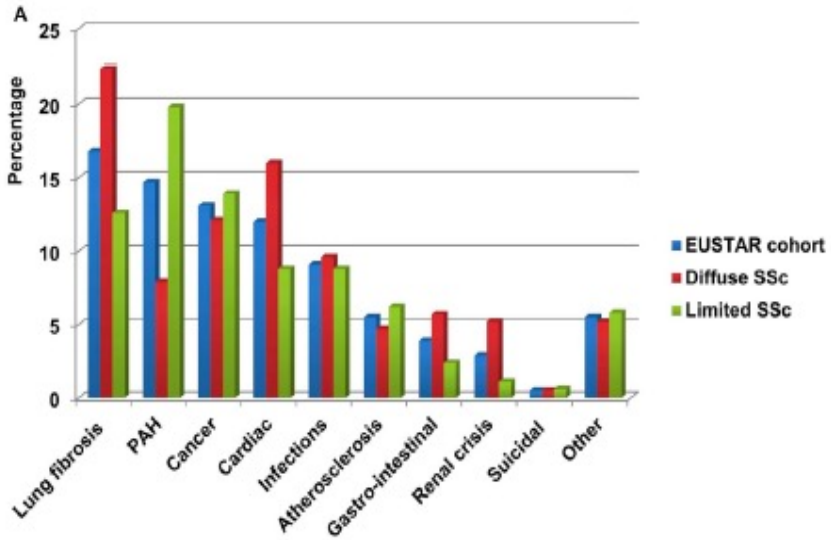


Organ involvement in Systemic sclerosis

Gabrielli A. Scleroderma. NEJM 2009.
Lo Monaco A, et al.. Clin Exp Rheumatol 2011.
Tyndall AJ et al. Ann Rheum Dis 2014.

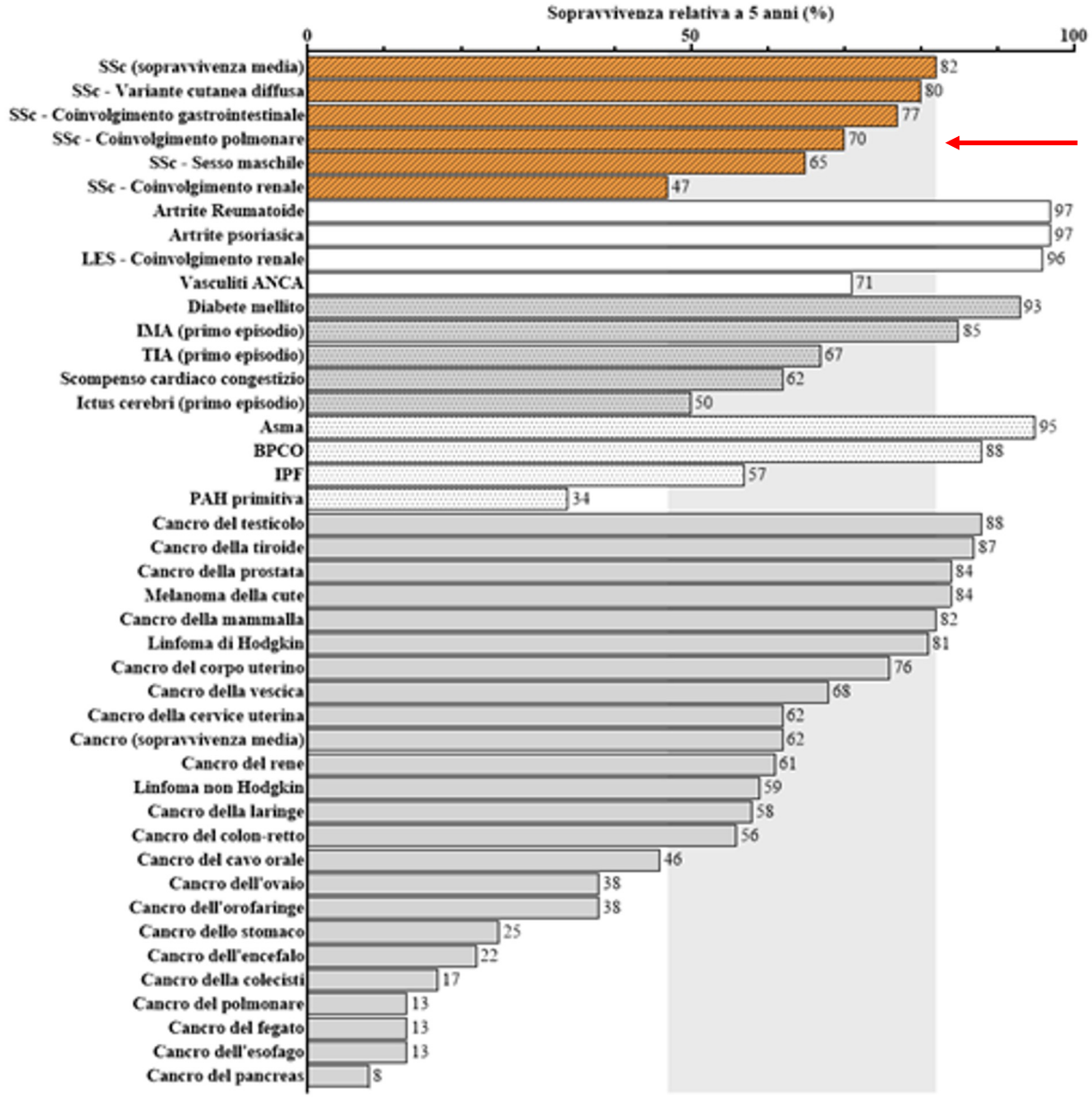
Annual mortality:
68 /1000 person-years of follow-up.
Standardized mortality ratios:
3.5 (1.5-7.2).

The majority of deaths (55%) are directly attributable to SSc



Elhai M, Ann Rheum Dis 2017

Steen VD, Medsger TA. Ann Rheum Dis 2007



- ✓ Although officially labeled **a rare disease**, recent epidemiologic evidence suggests that SSc affects more than **two million patients worldwide**, with approximately 300,000 new cases diagnosed each year

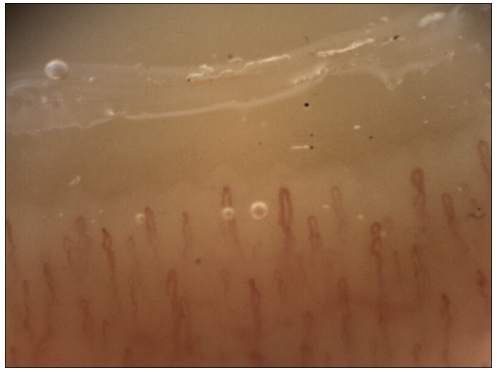
- ✓ **Italy**: about **25.000** persons affected by SSc

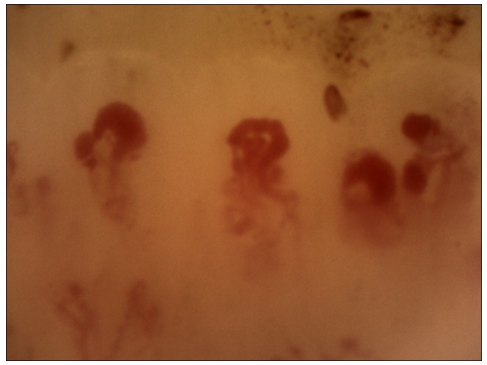
- ✓ **Pulmonary fibrosis** is currently the **leading cause of mortality in SSc,** accounting for approximately a third of deaths;

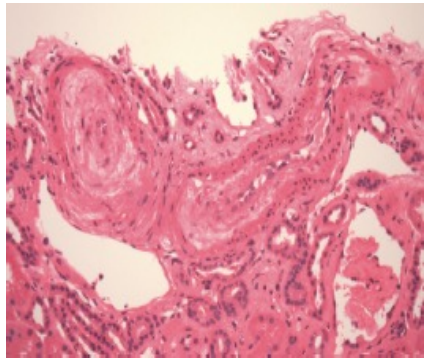
- ✓ **Pulmonary fibrosis** is a major predictor of **poor hospitalization outcomes** in patients with SSc

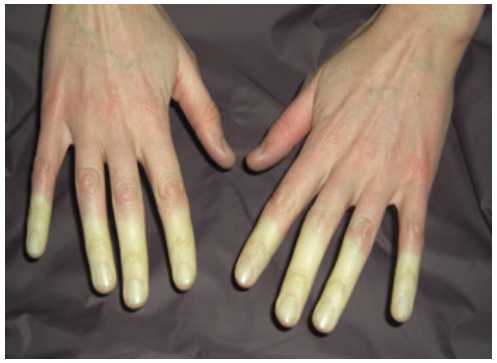
Mayes MD et al. Arthritis Rheum 2003
Toledano E et al. Reumatol Clin 2012
Bata IR et al. Can J Cardiol 2006
Ringbaek T et al. Eur Respir J 2005
De Angelis R et al. Lancet Oncol 2014

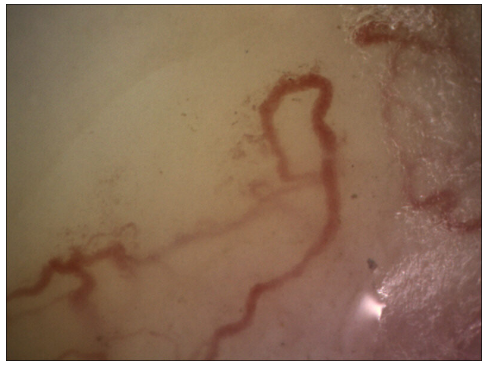
Scleroderma a systemic disease

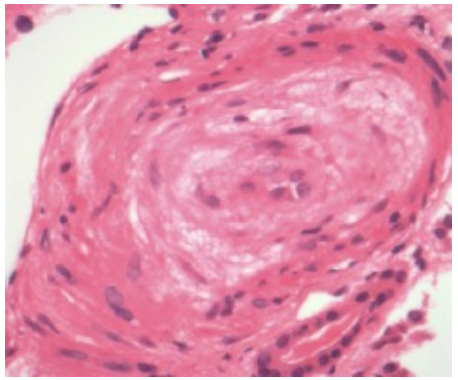


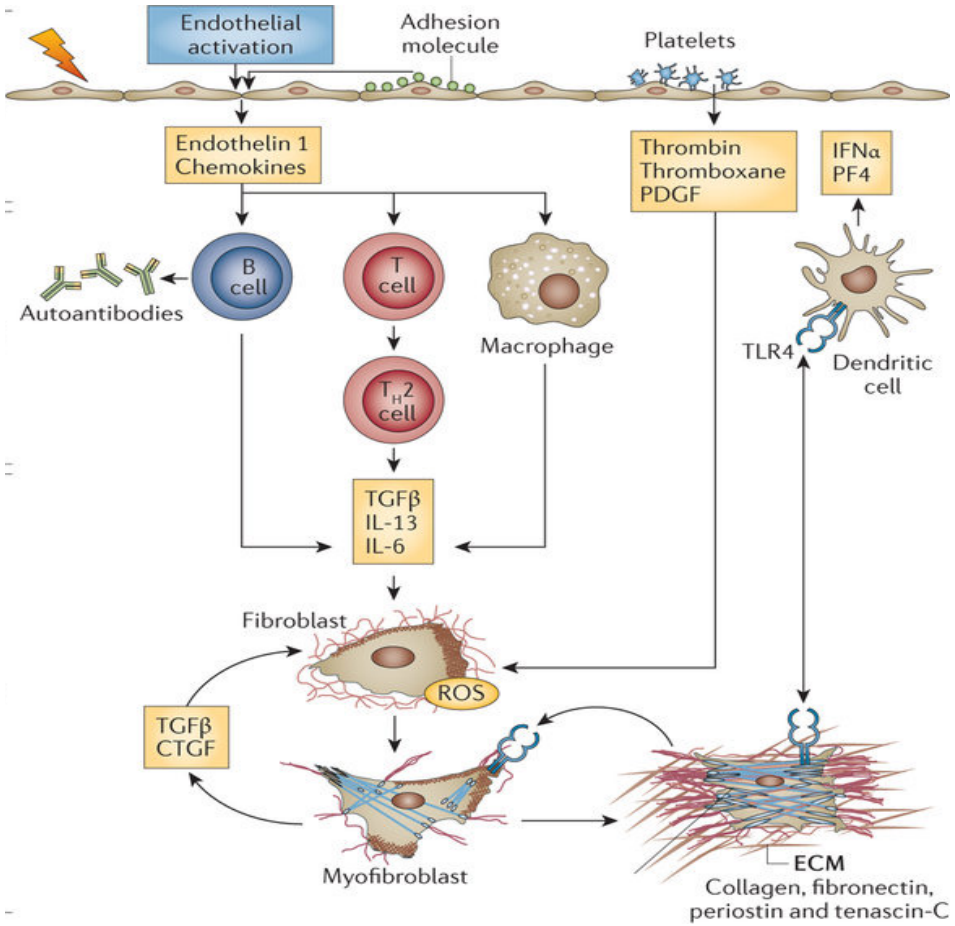








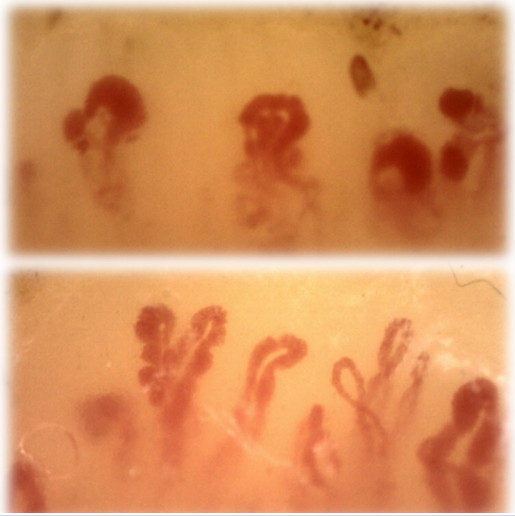




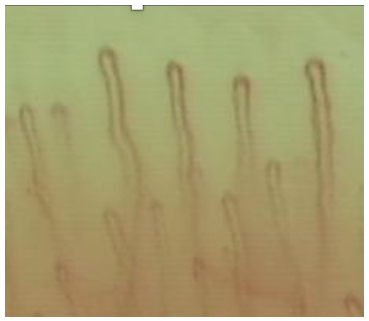
Dhaun, Am J Kidney 2009;54:726-731

Allanore Y.et al. Nat Rev Dis Primers. 2015 Apr 23;1:15002

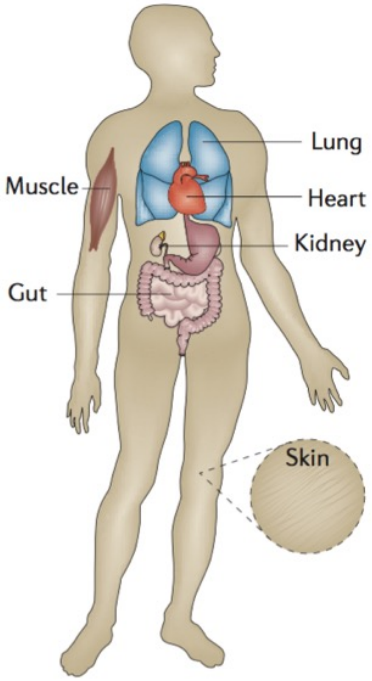
Clinical phenotypes

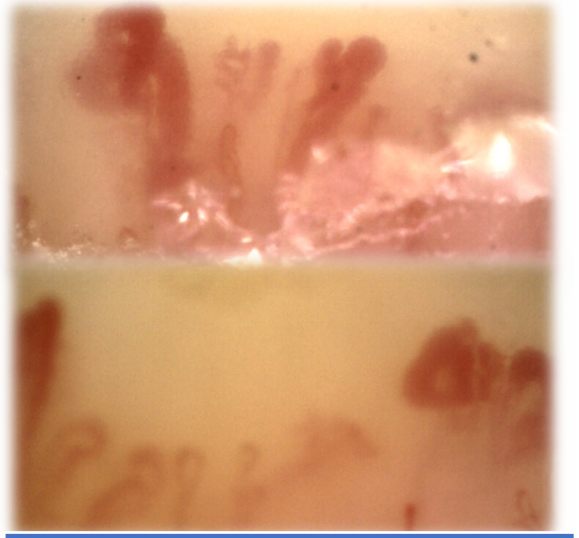


Female
ACA
No digital ulcers
No organ involvement
arthritis



Organ-specific treatment



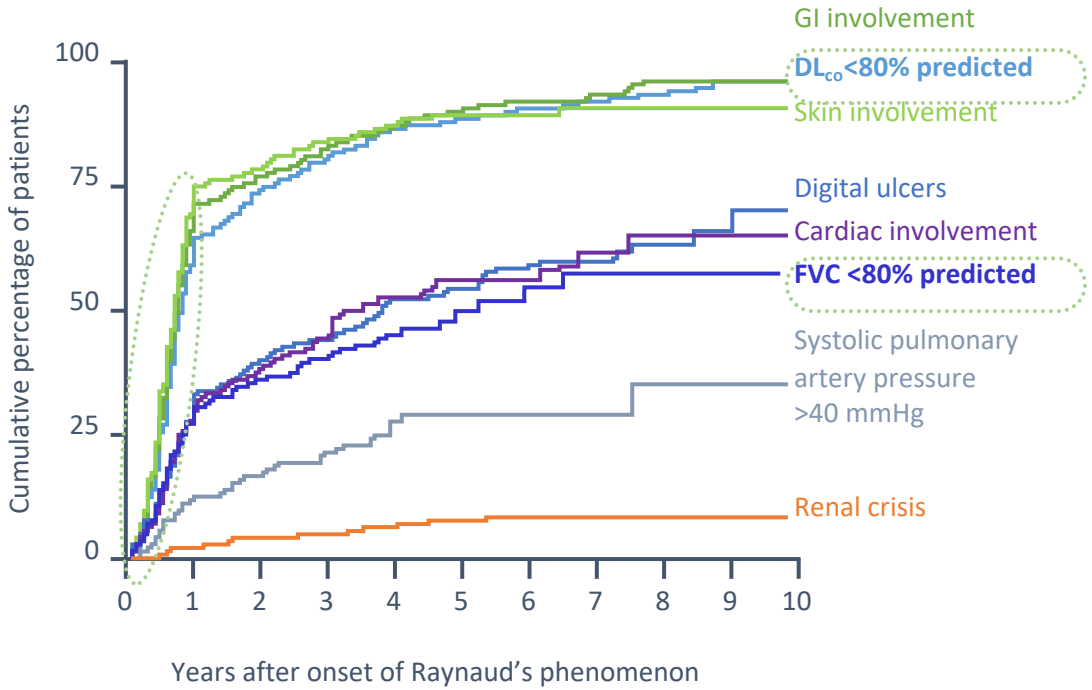


Male
Scl70
Digital ulcers
Lung/GERD/heart
Skin involvement

ILD develops early in the disease course of SSc

Early SSc = patients in the EUSTAR database who had a visit within the first year after RP onset.

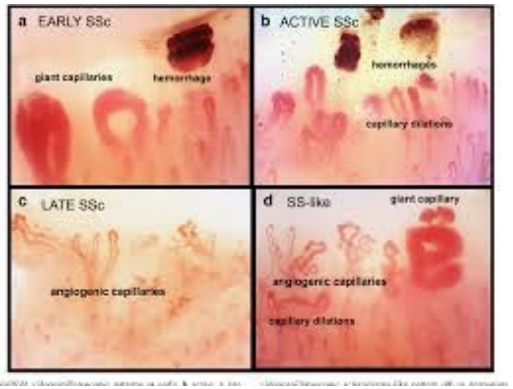
Organ involvement in patients (cumulative percentage) with early SSc[1*]



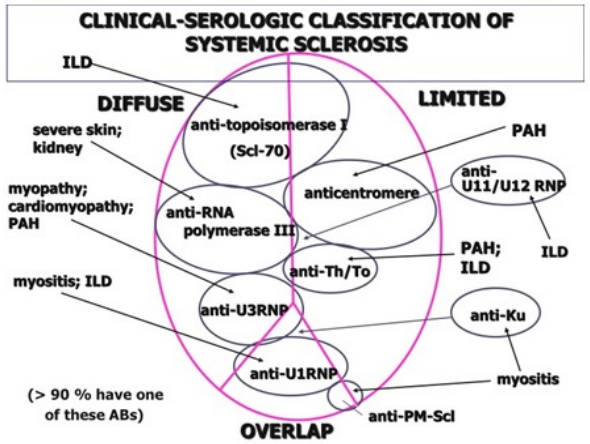
Pulmonary involvement is evident 1 year after presentation of Raynaud's phenomenon

Steen VD *et al. Arthritis Rheum* 1994
Jaeger VK *et al. PLoS One* 2016
Guler SA *et al. Ann Am Thorac Soc* 2018

Early Systemic Sclerosis



The presence of an **abnormal NVC profile specific for SSc**, consisting of enlarged capillaries and capillary loss in patients with isolated RP predicted the future evolution to SSc.



Anti–CENP-B and **anti–topoisomerase I** are known predictors of progression from isolated RP to SSc.

Weiner ES, et al. Arthritis Rheum 1991

	Score
Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints	9
Telangiectasia	2
Abnormal nailfold capillaries	2
Pulmonary arterial hypertension or interstitial lung disease, or both	2
Raynaud's phenomenon	3
Skin thickening of the fingers (only count highest score)	
Puffy fingers	2
Sclerodactyly of the fingers	4
Fingertip lesions (only count highest score)	
Digital tip ulcers	2
Fingertip pitting scars	3
Scleroderma-related autoantibodies (eg, anticentromere, anti-topoisomerase 1, or anti-RNA polymerase 3)	3

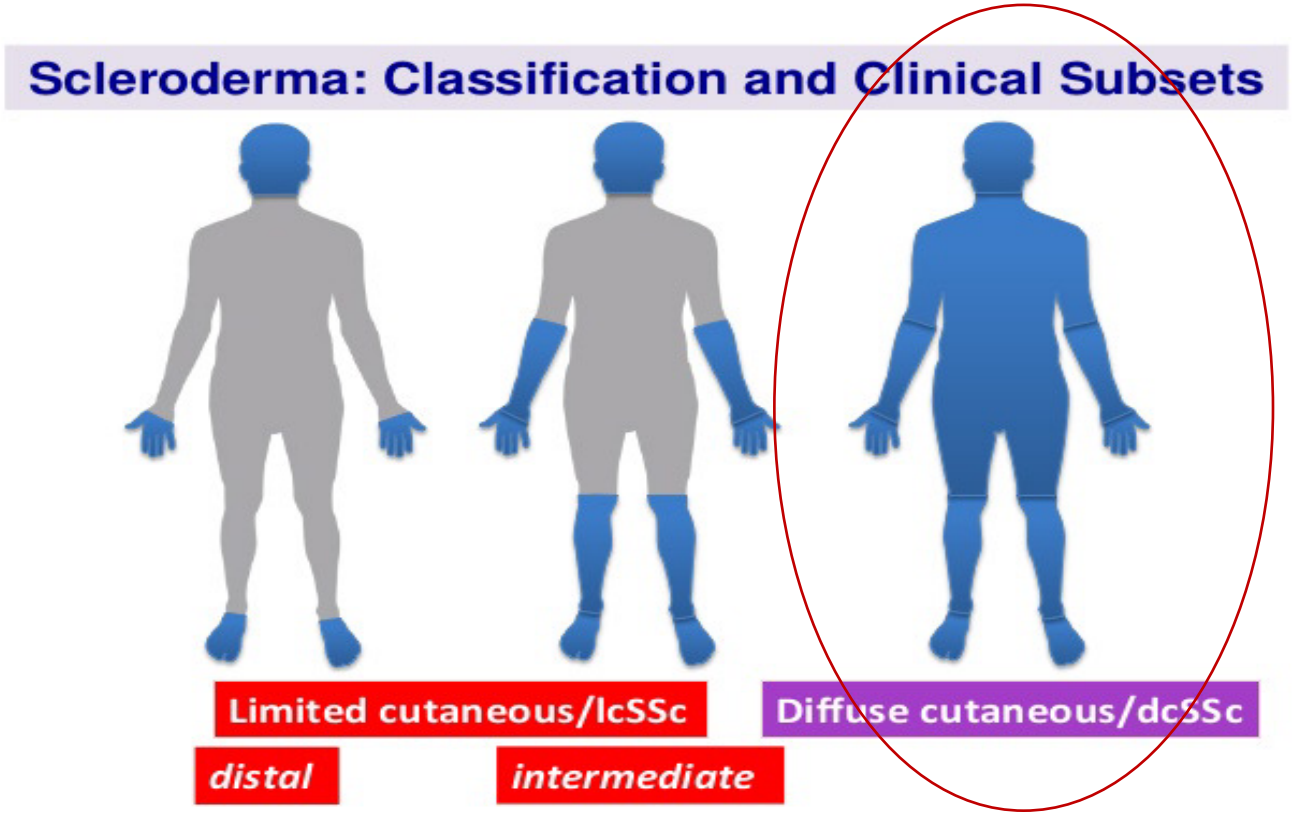
Patients with a total score greater than 9 are classified as having definite systemic sclerosis.

Table 1: **Criteria for the classification of Systemic Sclerosis according to the European League Against Rheumatism and the American College of Rheumatology[2]**

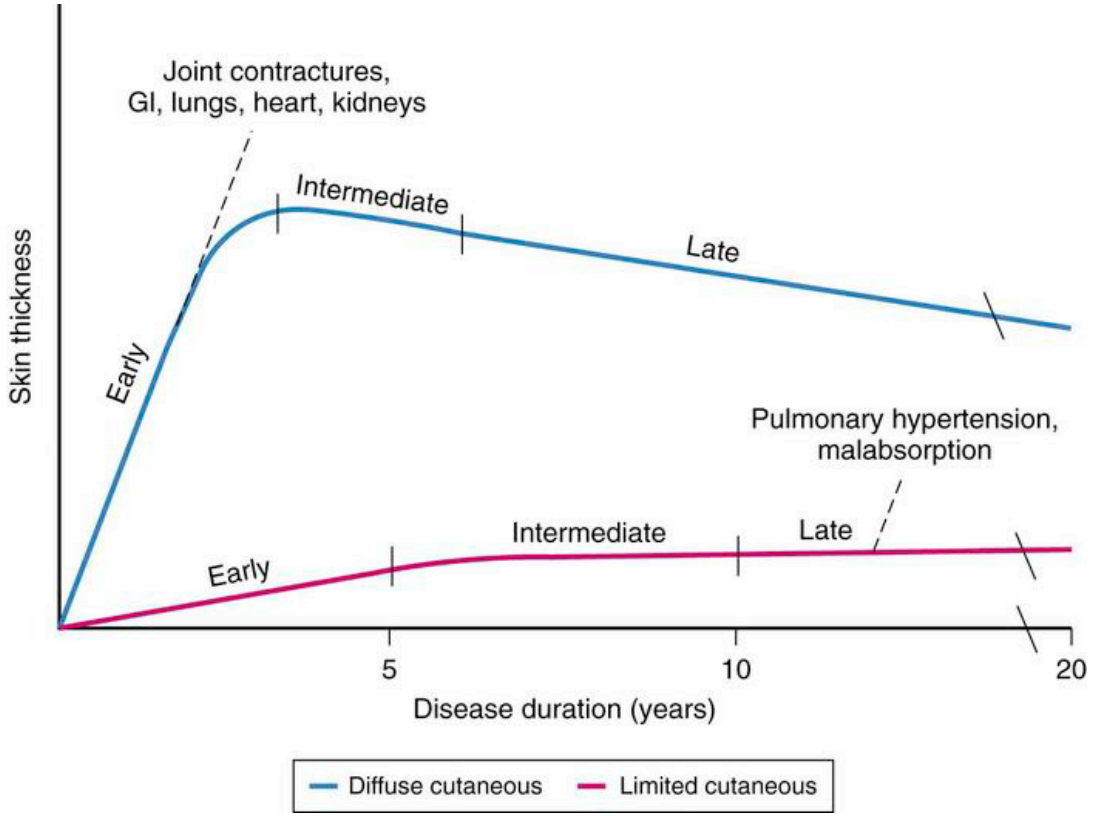
Van der Hoogen, Arthritis Rheum 2013; 65: 2737–47.
Perelas Lancet Respir Med 2020

Systemic Sclerosis

Natural history of skin thickness and organ involvement



Slide courtesy of Francesco Boin, MD



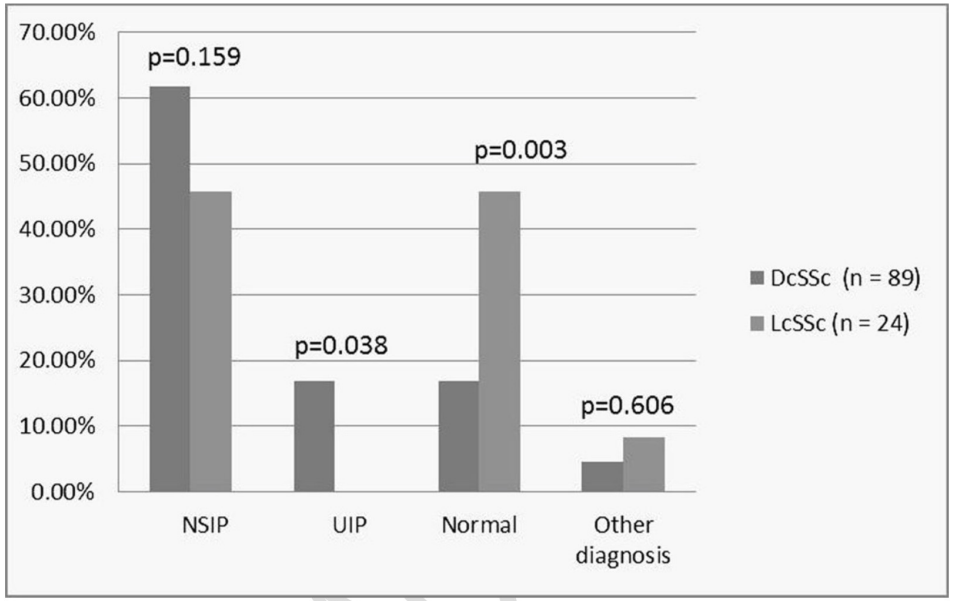
Steen V & Medsger TA. Arhritis & Rheumatism 2000

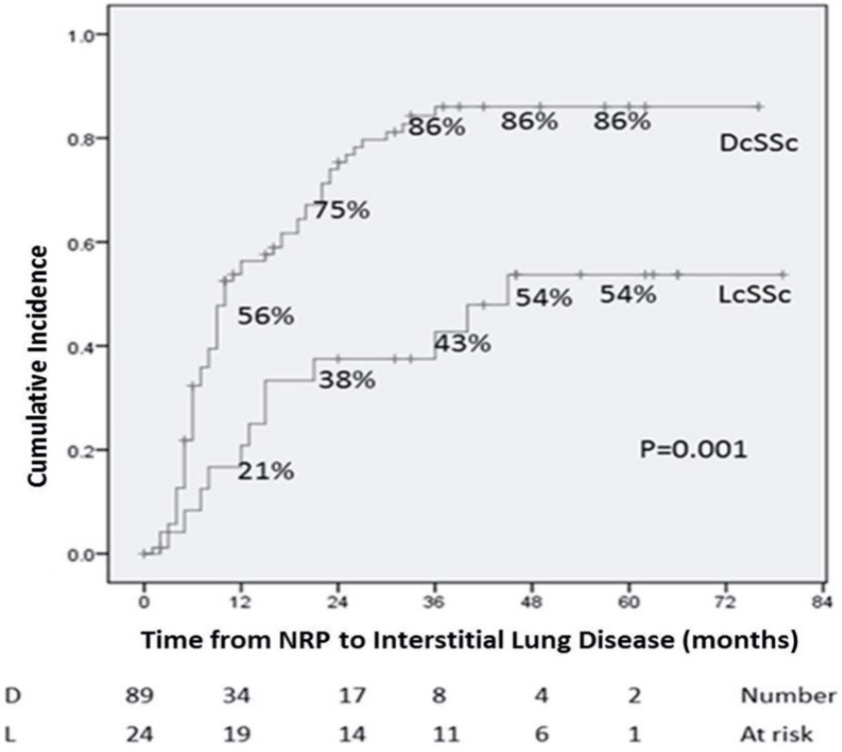
Koenig M, et al. Arthritis Rheum 2000

Diffuse cutaneous disease vs limited

Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: inception cohort study

Suparaporn Wangkaew, Juntima Euathrongchit, Pittaporn Wattanawittawas, Nuntana Kasitanon & Worawit Louthrenoo





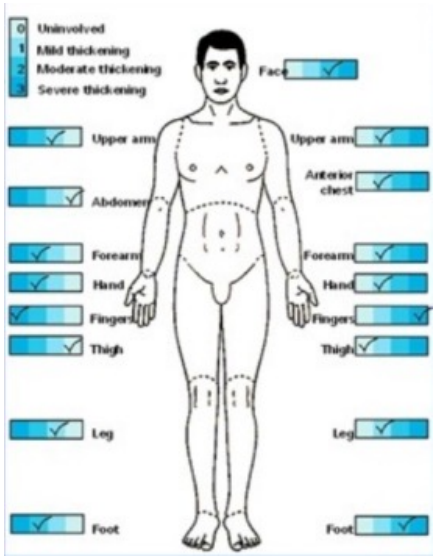
OPEN ACCESS

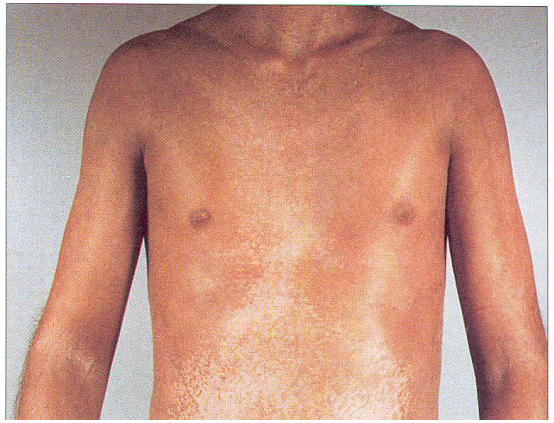
CLINICAL SCIENCE

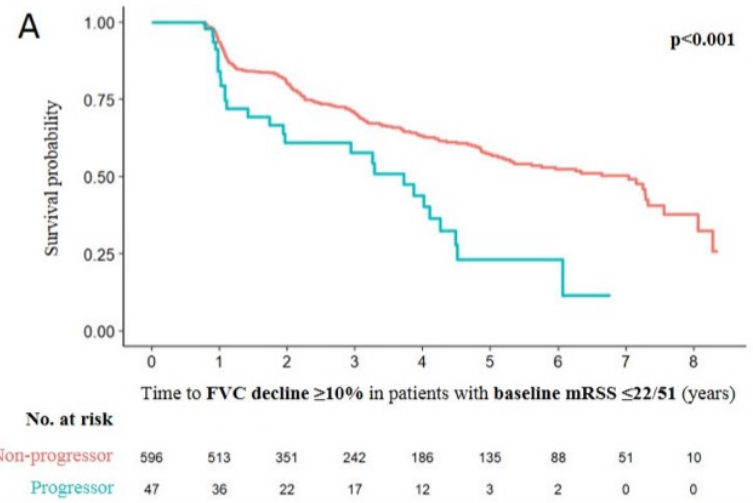
Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort

Wanlong Wu,[1] Suzana Jordan,[1] Nicole Graf,[2] Janethe de Oliveira Pena,[3] John Curram,[4] Yannick Allanore,[5] Marco Matucci-Cerinic,[6] Janet E Pope,[7] Christopher P Denton,[8] Dinesh Khanna,[9] Oliver Distler,[1] EUSTAR Collaborators

Ann Rheum Dis 2019;







In multivariable analyses, skin progression within 1 year was independently associated with FVC decline 10% (HR 1.79, 95% CI 1.20 to 2.65) and all- cause death (HR 2.58, 95% CI 1.31 to 5.09).

> Rheumatology (Oxford). 2022 Mar 28;keac188. doi: 10.1093/rheumatology/keac188.
Online ahead of print.

Phenotype of limited cutaneous systemic sclerosis patients with positive anti-topoisomerase I antibodies: data from EUSTAR cohort

Objectives: To characterize patients with positive anti-topoisomerase I (ATA) in the limited cutaneous Systemic Sclerosis (lcSSc).

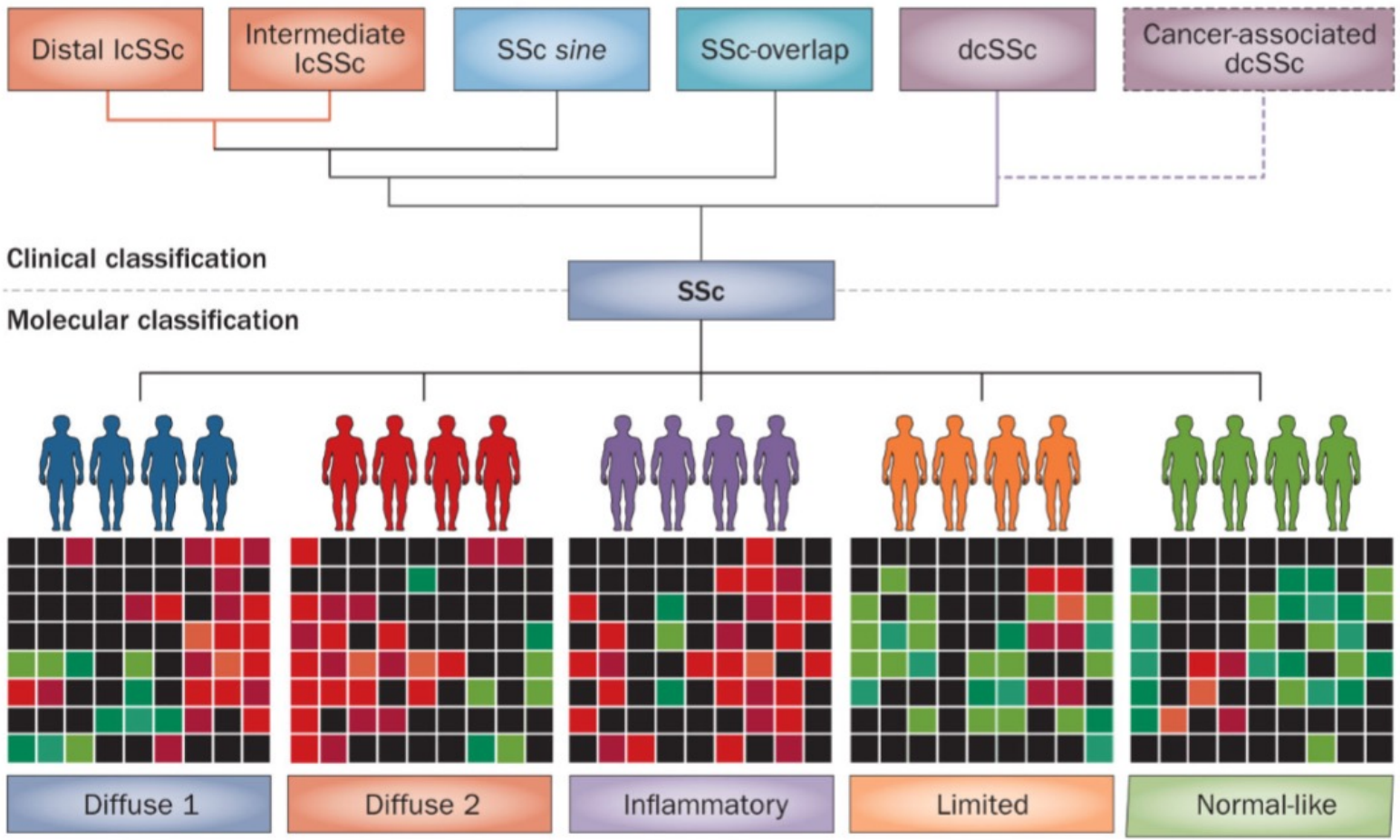
Methods: SSc patients enrolled in the EUSTAR cohort with disease duration ≤3 yrs at database entry were considered. We assessed the risk of major organ involvement in the following groups: 1) ATA-lcSSc vs anticentromere (ACA)-lcSSc and vs antinuclear antibodies without specificity (ANA)-lcSSc; 2) ATA-lcSSc vs ATA-diffuse cutaneous (dc)SSc. Cox regression models with time-dependent covariates were performed with the following outcomes: new-onset interstitial lung disease (ILD), ILD progression (Forced Vital Capacity, FVC decline ≥10% and ≥5% vs values at ILD diagnosis); primary myocardial involvement (PMI); pulmonary hypertension (PH); any organ involvement and all-cause mortality.

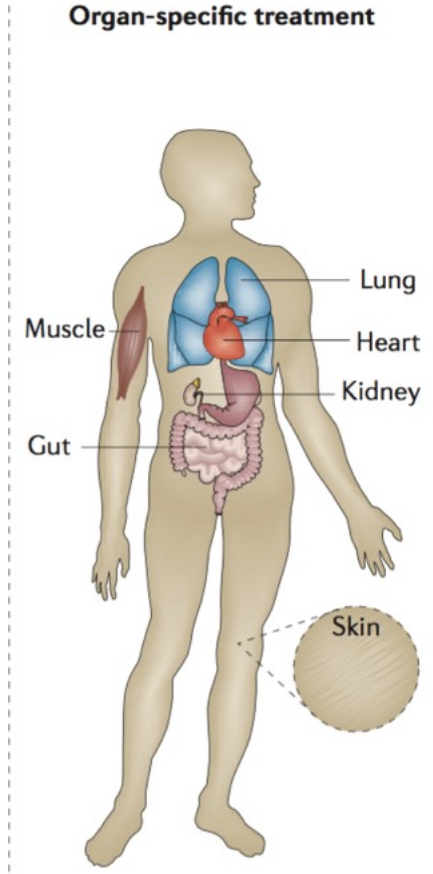
Results: We included 1252 patients (194 ATA-lcSSc, 15.5%), with 7.7 ± 3.5 yrs follow-up. ILD risk was higher in ATA-lcSSc vs ACA- and ANA-lcSSc, and similar to ATA-dcSSc, although with less frequent restrictive lung disease. Risk of FVC decline ≥ 10% (35% of ATA-lcSSc) was lower in ATA-lcSSc than in ATA-dcSSc, whereas FVC decline ≥5% occurs similarly between ATA-lcSSc (58% of patients) and other SSc subsets, including ATA-dcSSc. The risk of PMI was similar in ATA-lcSSc and ANA-lcSSc, lower than in ACA-lcSSc; no difference in PH and mortality risk was observed among lcSSc subsets. Risk of any organ involvement, PMI, PH was lower and the mortality tended to be lower in ATA-lcSSc vs ATA-dcSSc.

Nat Rev Rheumatol. 2014 April ; 10(4): 200–202. doi:10.1038/nrrheum.2014.22.

Systemic sclerosis: beyond limited and diffuse subsets?

John Varga and **Monique Hinchcliff**





Disease duration

Panel 1: **Factors associated with the presence of systemic sclerosis-associated interstitial lung disease**

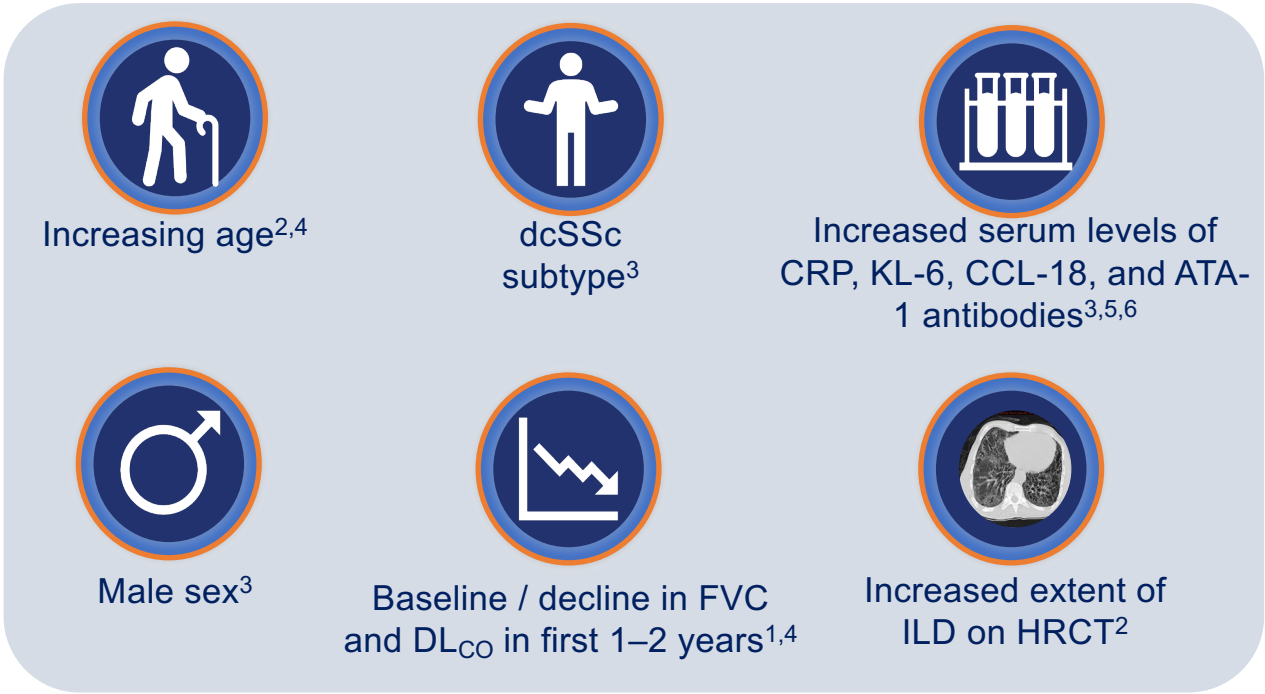
Epidemiology
- African American race
- Male sex
- Genetic polymorphisms

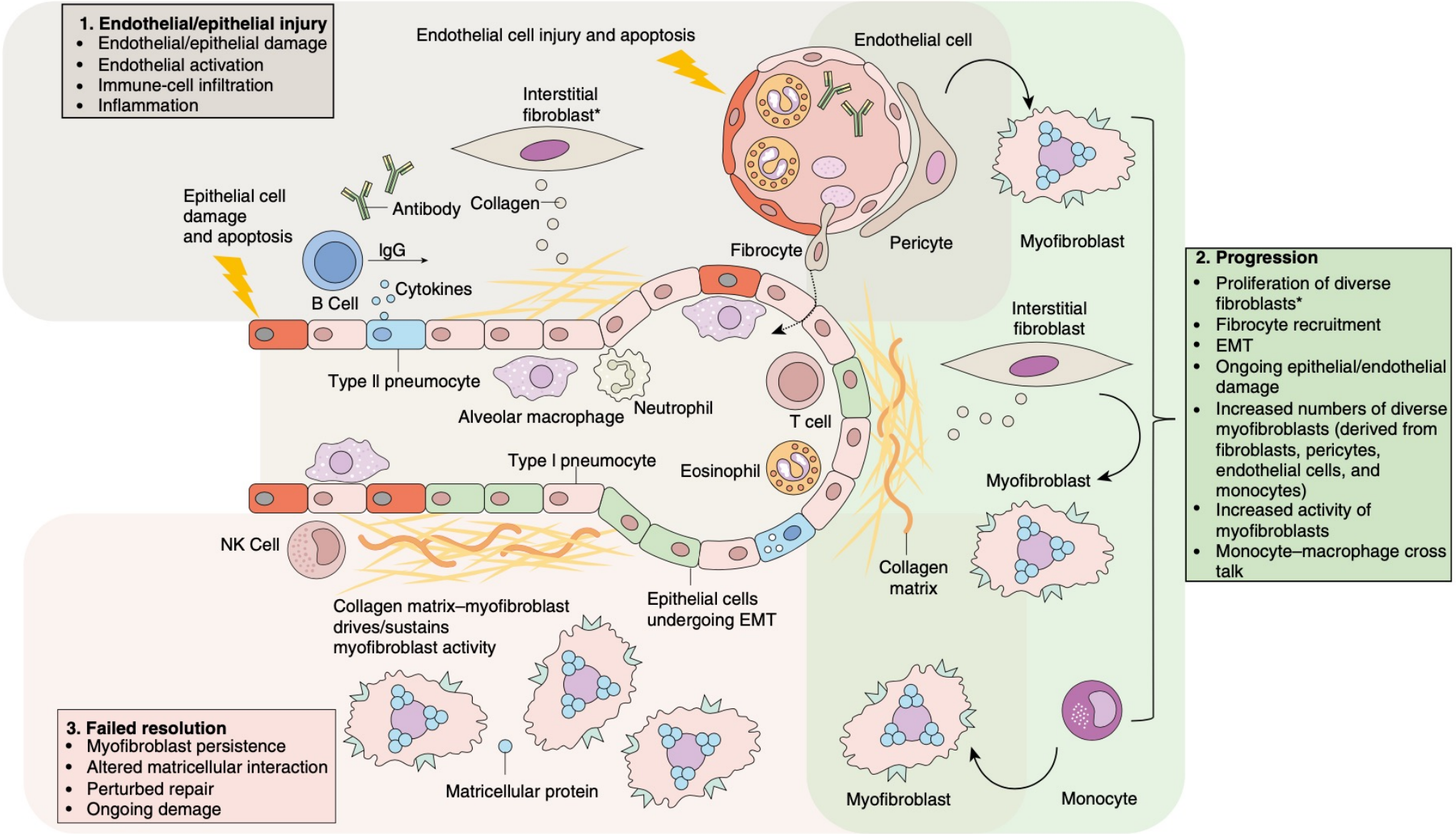
Clinical features
- Diffuse cutaneous scleroderma variant
- Nailfold capillary abnormalities
- Digital ulcers
- Longer disease duration
- Pulmonary hypertension

Autoantibodies
- Anti-topoisomerase I
- Anti-neutrophil cytoplasmic antibody
- Anticardiolipin
- Anti-Ro52
- Anti-NOR90
- Anti-U11/U12
- Anti-Th/To
- Anti-polymyositis-scleroderma

Novel Biomarkers
- Interleukin-6, interleukin-34
- chemokine (C-X-C motif) ligand 4
- chemokine (C-C motif) ligand 18
- Carbohydrate antigen 15·3
- Lysyl oxidase
- Tenascin-C
- Serum amyloid A
- Surfactant protein D
- Chitinase 1
- Krebs von den Lungen-6
- Cartilage oligomeric matrix protein

Risk factors for SSc-ILD




1. Endothelial/epithelial injury
• Endothelial/epithelial damage
• Endothelial activation
• Immune-cell infiltration
• Inflammation
Endothelial cell injury and apoptosis
Endothelial cell
Interstitial fibroblast*
Antibody
Collagen
Epithelial cell damage and apoptosis
IgG
Cytokines
B Cell
Fibrocyte
Pericyte
Myofibroblast
Type II pneumocyte
Alveolar macrophage
Neutrophil
T cell
Interstitial fibroblast
Type I pneumocyte
Eosinophil
Myofibroblast
NK Cell
Collagen matrix
Collagen matrix–myofibroblast drives/sustains myofibroblast activity
Epithelial cells undergoing EMT
2. Progression
• Proliferation of diverse fibroblasts*
• Fibrocyte recruitment
• EMT
• Ongoing epithelial/endothelial damage
• Increased numbers of diverse myofibroblasts (derived from fibroblasts, pericytes, endothelial cells, and monocytes)
• Increased activity of myofibroblasts
• Monocyte–macrophage cross talk
3. Failed resolution
• Myofibroblast persistence
• Altered matricellular interaction
• Perturbed repair
• Ongoing demage
Matricellular protein
Myofibroblast
Monocyte

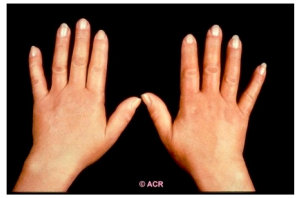
Pneumologist

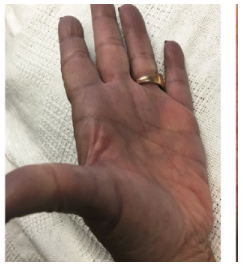
CTD-ILD

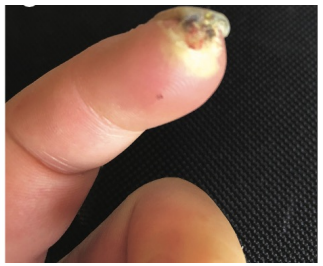
Consider:
Raynaud phaenomenon
Puffy fingers
Digital ulcers
Gastrointestinal involvement
teleangectsia

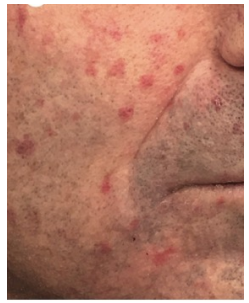
Autoantibodies
Video-capilllroscopy

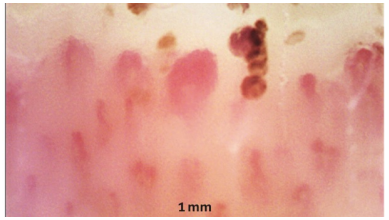
SSc-ILD





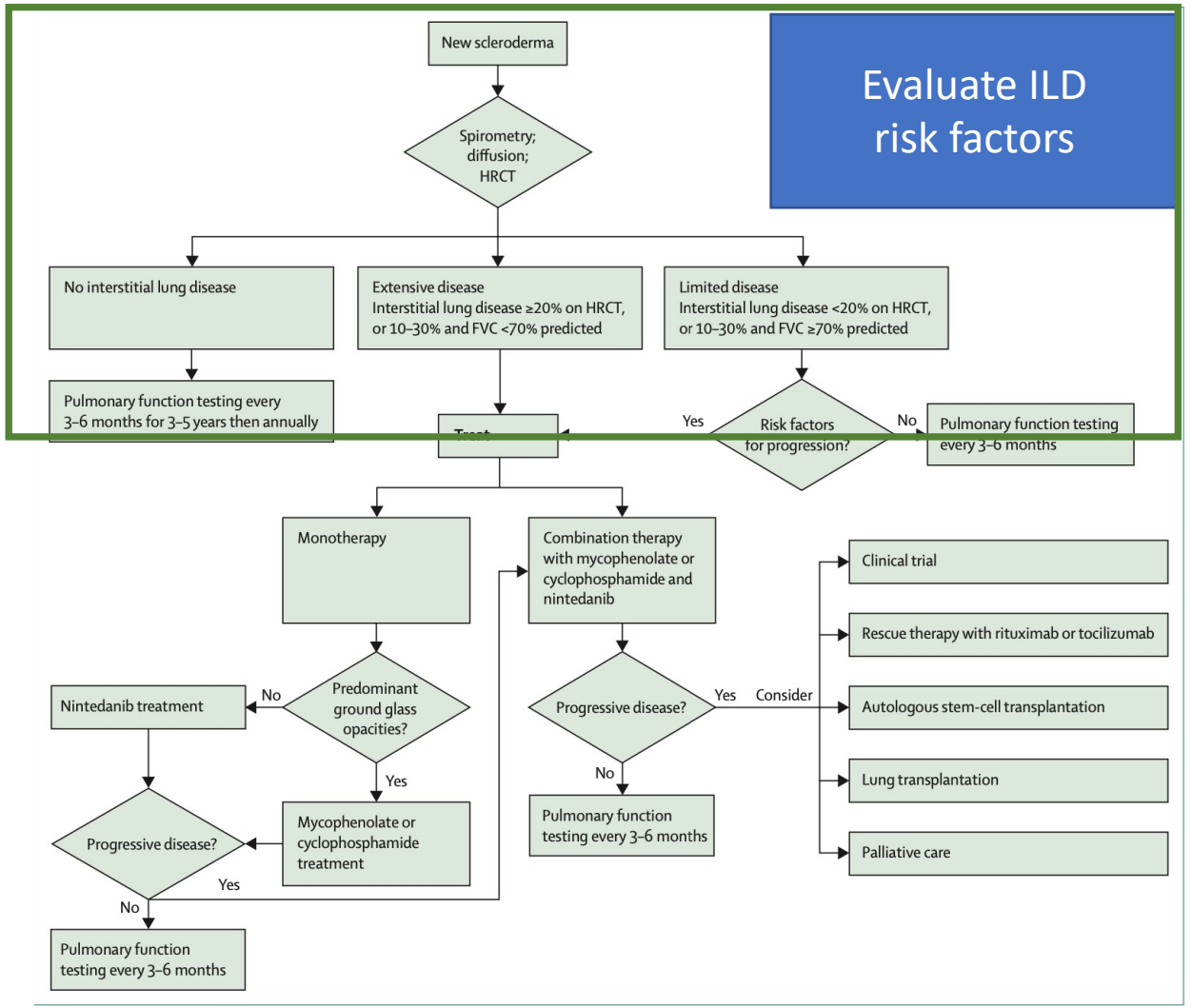




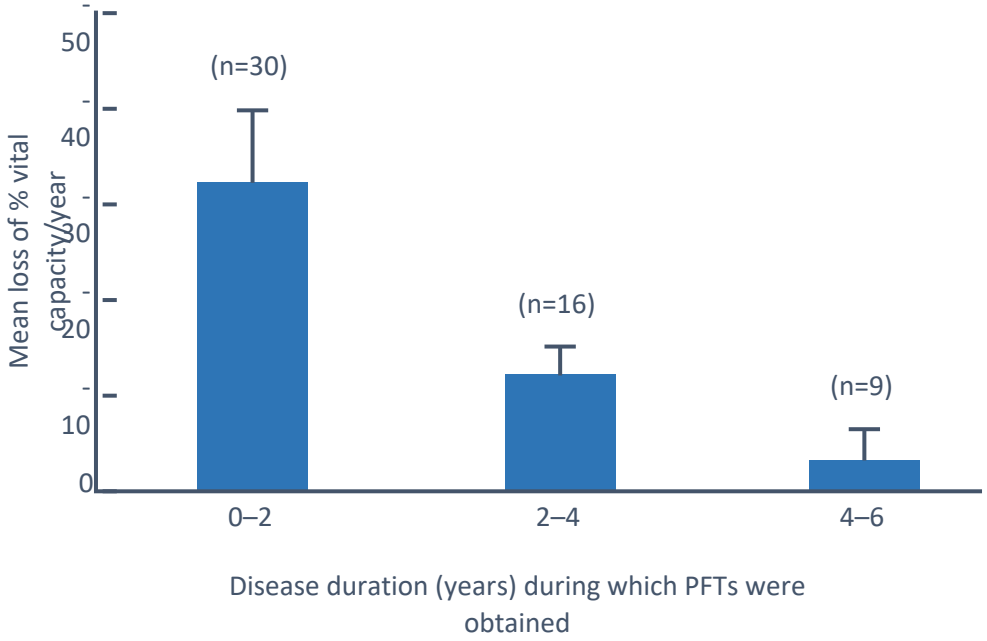


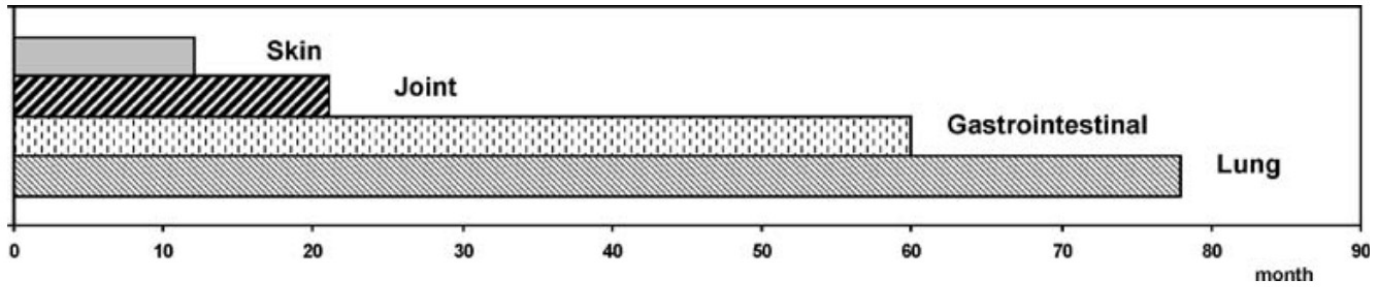
Evaluate ILD progression risk factors

Rheumatologist



There is a high risk of progression of ILD in the first 2 years of SSc





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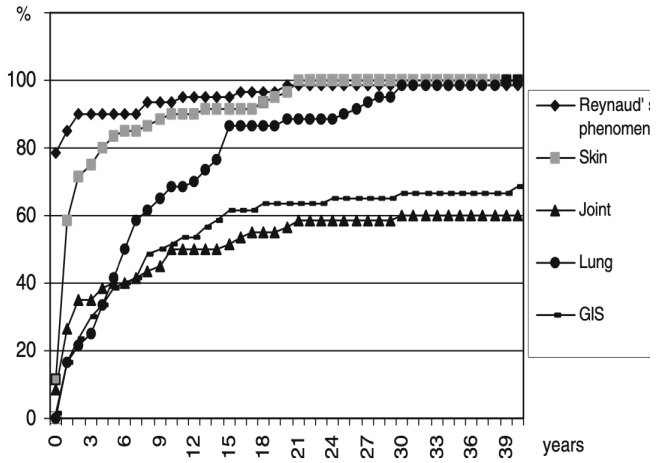

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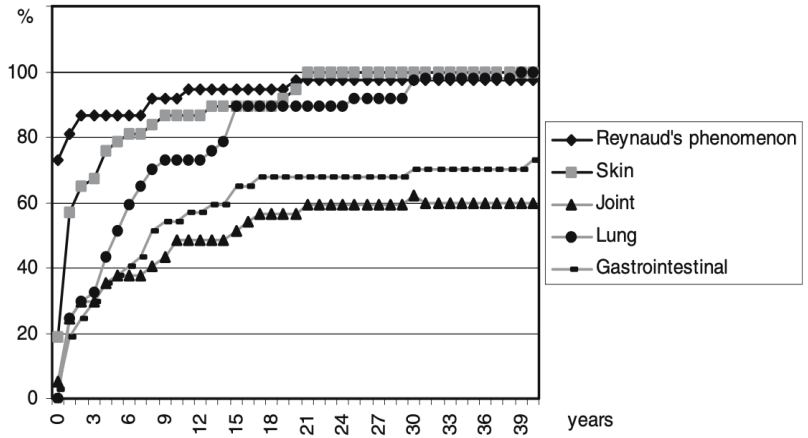
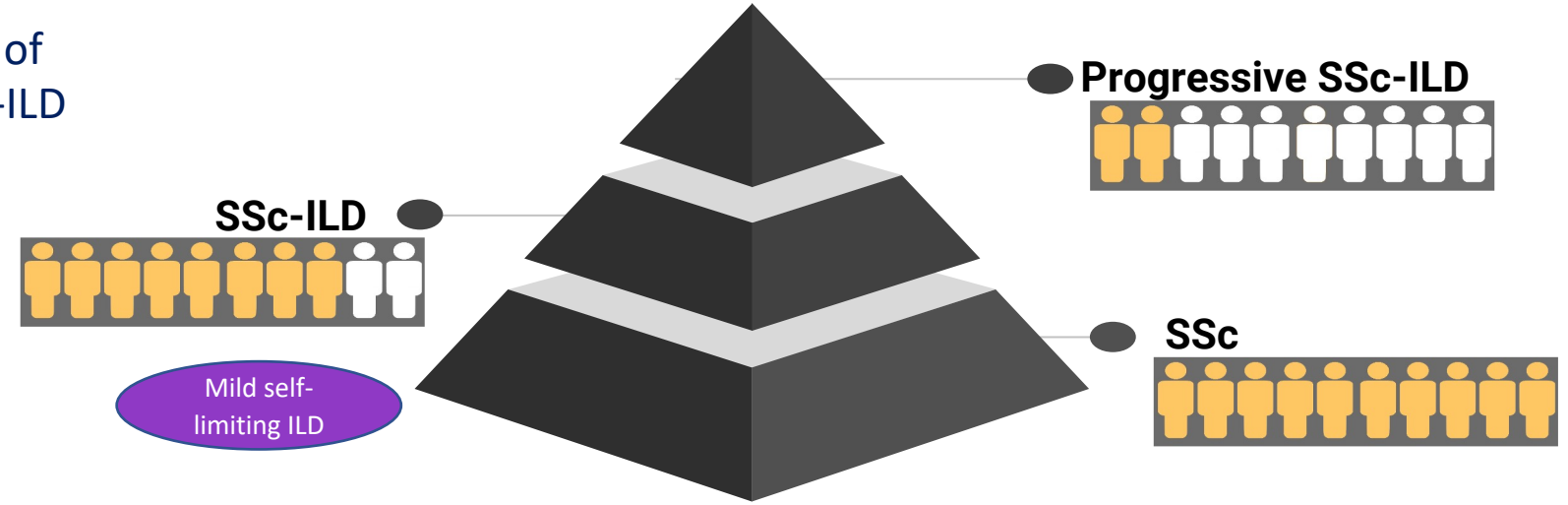


The greatest loss of lung function, indicating progression, occurs in the first 2 years of SSc, highlighting the need for early detection[1]

Steen VD *et al. Arthritis Rheum* 1994, Jaeger VK *et al. PLoS One* 2016 , Guler SA *et al. Ann Am Thorac Soc* 2018

SSc-ILD disease spectrum

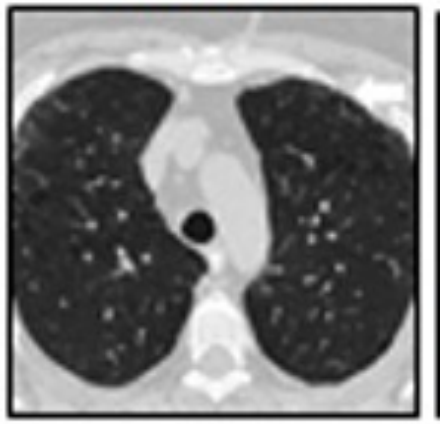
Median survival of patients with SSc-ILD is 5–8 years

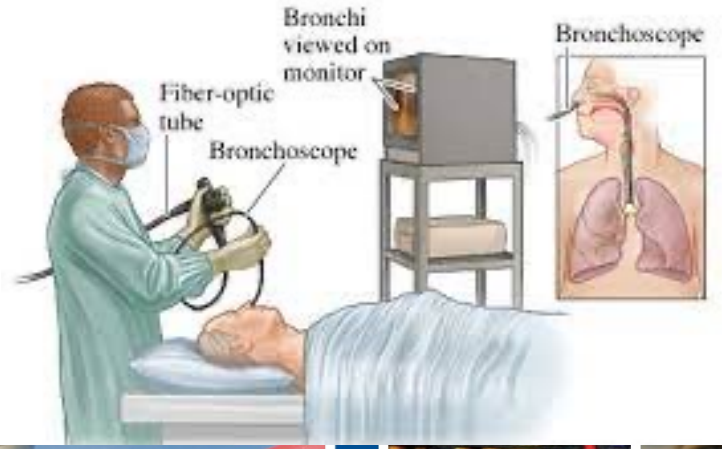


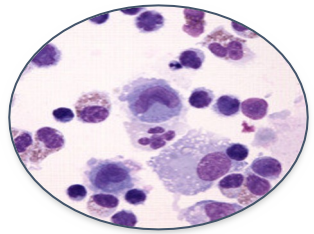
45-50% mild-moderate ILD
13-20% severe ILD

PFR

HRTC







Cell Count (Cytocentrifugation with staining)

Panel 2: Risk factors for systemic sclerosis-associated interstitial lung disease progression

Epidemiology

- Male sex
- Active smoker
- Older age at presentation

Clinical features

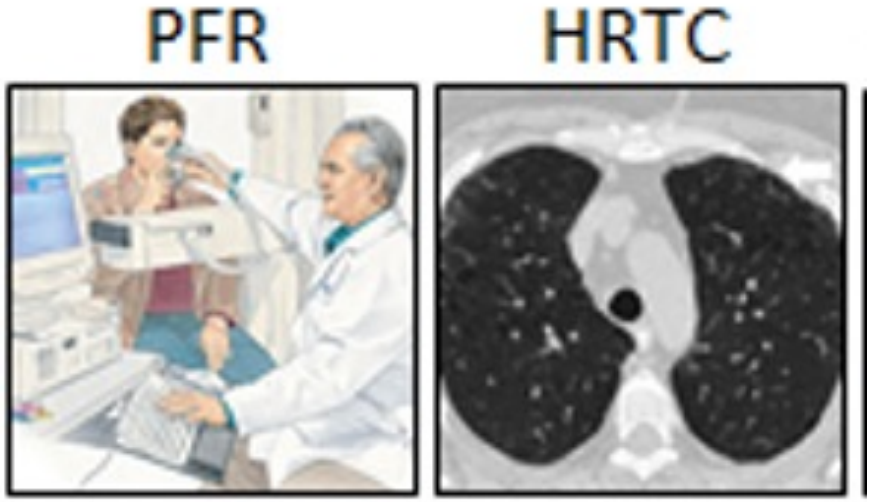
- Digital ulcers
- Arthritis
- Increased oesophageal diameter
- Pulmonary hypertension
- Progressive skin fibrosis
- Renal disease
- Myocardial fibrosis

Physiology and imaging

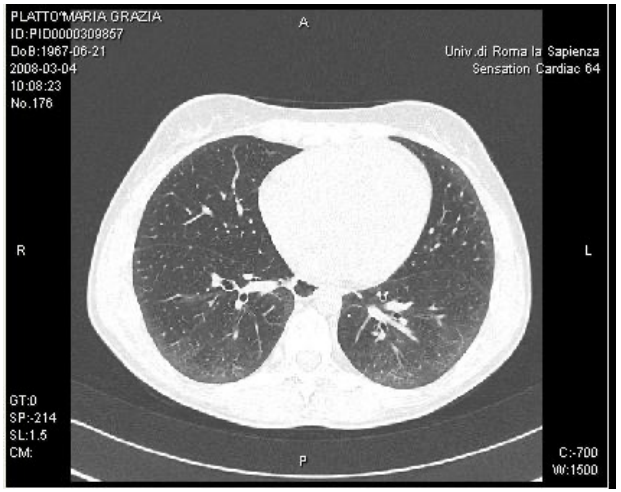
- Forced vital capacity (FVC) decrease of more than 10%
- More than 20% fibrosis on high-resolution CT
- Pulmonary artery-to-aorta ratio of more than 1:1
- FVC decrease of 5–9% with decrease in diffusing capacity for carbon monoxide of more than 15%
- Usual interstitial pneumonia pattern

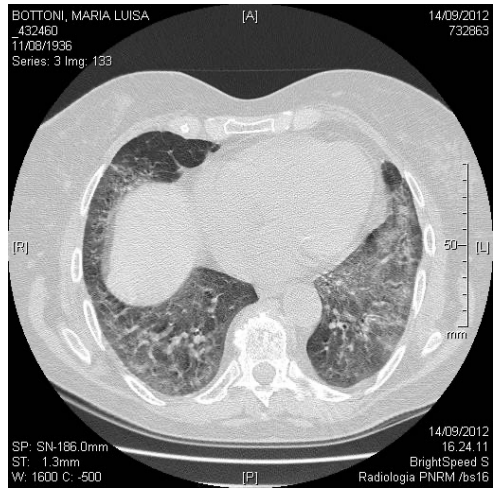
Novel Biomarkers

- Fractional excretion of nitric oxide
- Interleukin 10
- Carbohydrate antigen 15·3
- C-reactive protein
- Monocyte chemoattractant protein 1



HRCT extension

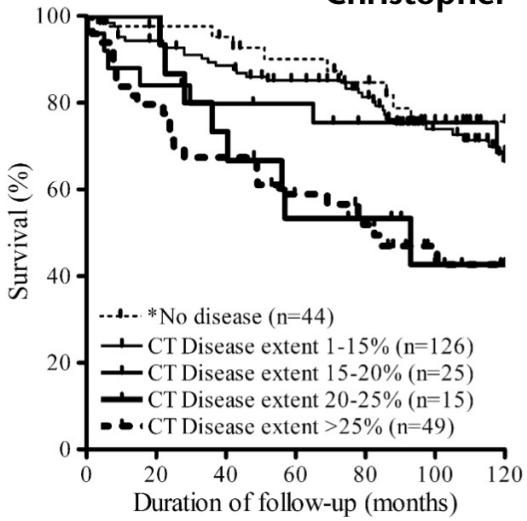


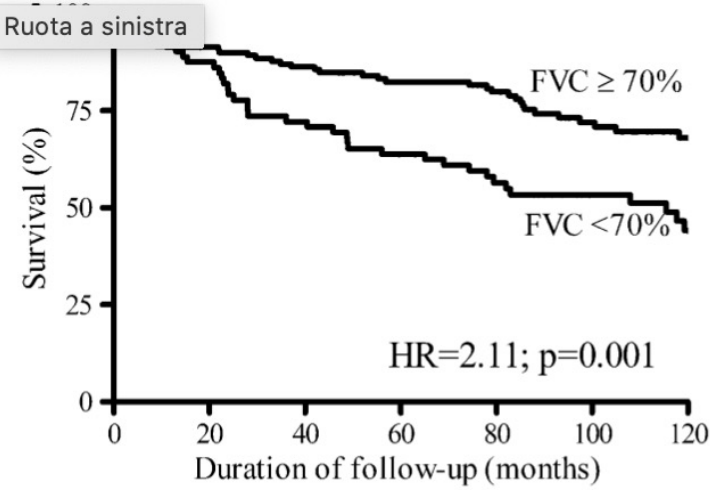


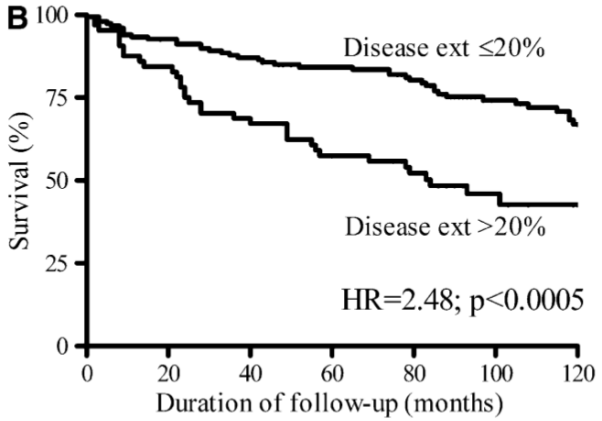
Interstitial Lung Disease in Systemic Sclerosis

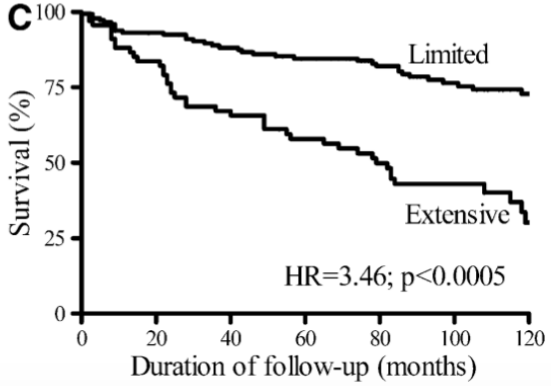
A Simple Staging System

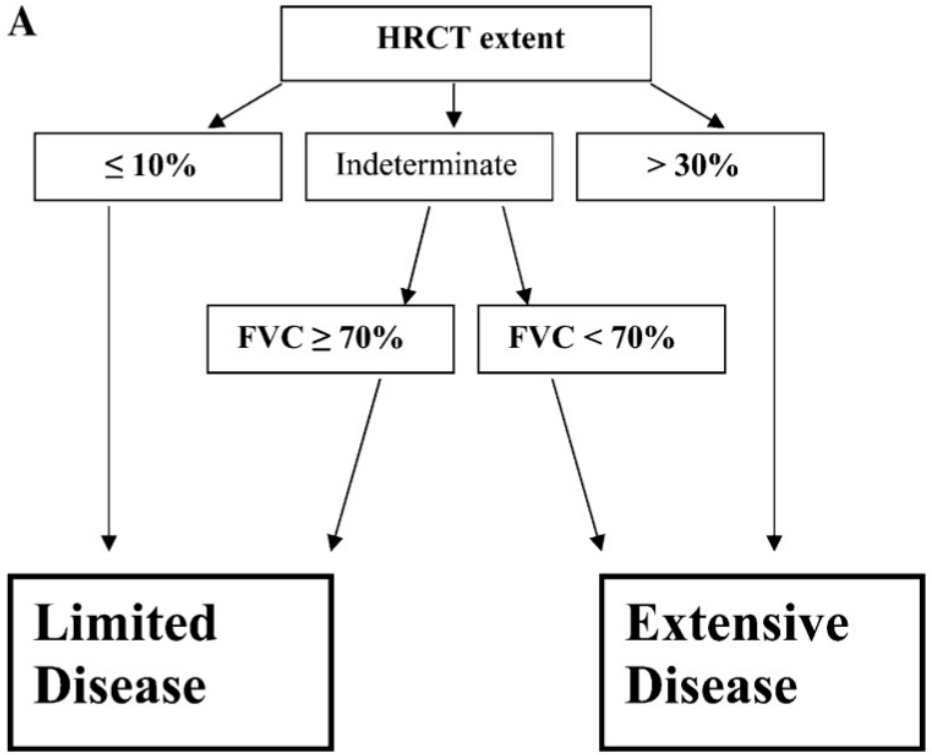
Nicole S. L. Goh[1], Sujal R. Desai[2], Srihari Veeraraghavan[1], David M. Hansell[1], Susan J. Copley[3], Toby M. Maher[1], Tamera J. Corte[1], Clare R. Sander[1], Jonathan Ratoff[1], Anand Devaraj[1], Gracijela Bozovic[1], Christopher P. Denton[4], Carol M. Black[4], Roland M. du Bois[1], and Athol U. Wells[1]











Predictors of progression in systemic sclerosis patients with interstitial lung disease

Eur Respir J 2020; 55: 1902026

@ERSpublications
Lung function tests and chest imaging help predict who has SSc-associated ILD and whether it will progress. In the absence of standardised methods for doctors, we recommend a strategy that combines both lung function tests and chest imaging. http://bit.ly/2uK9ZD2

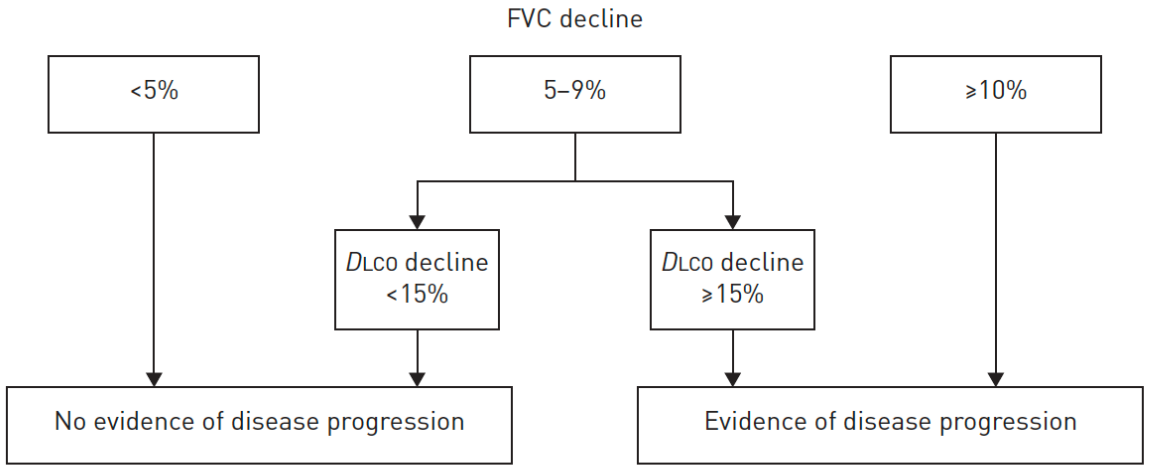
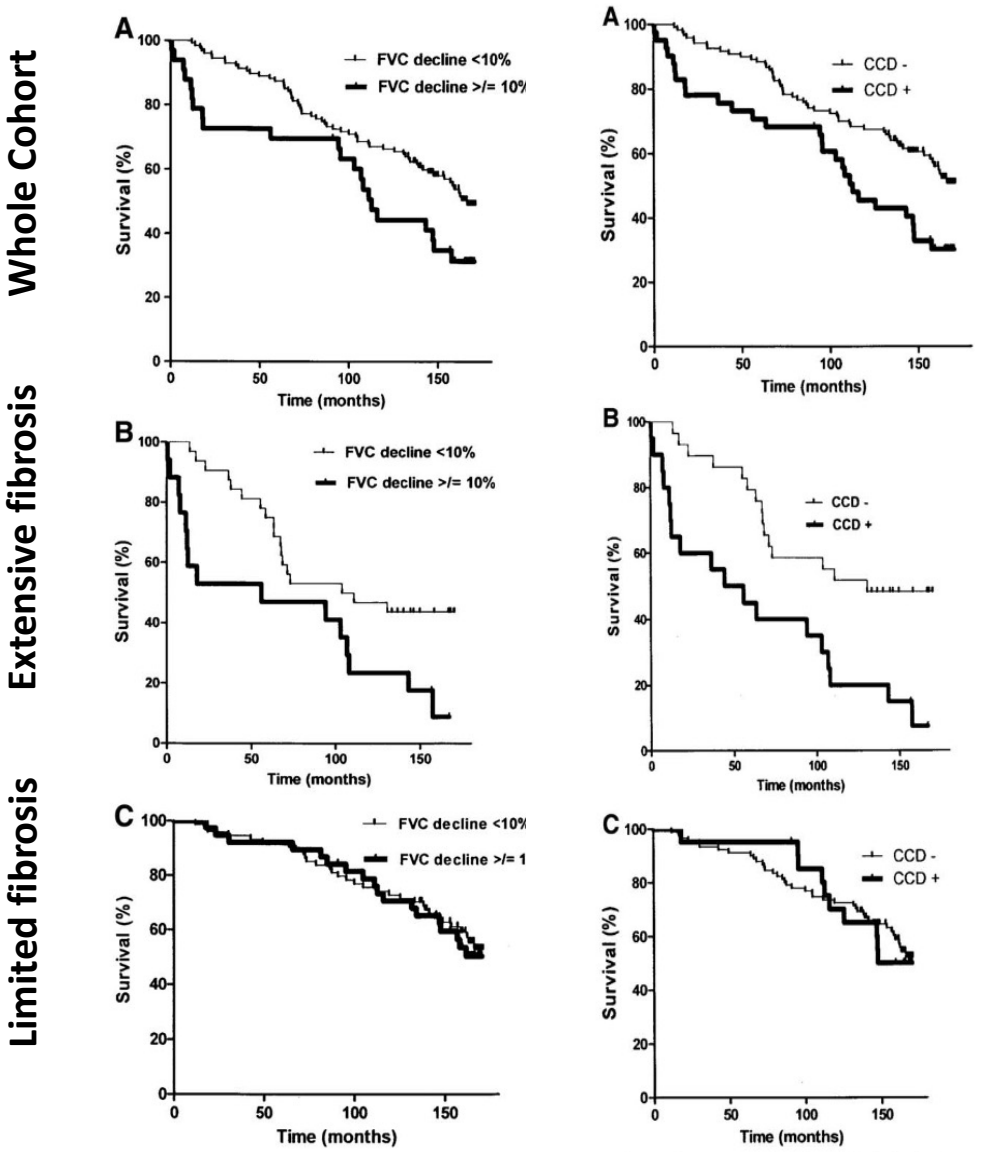


FIGURE 3 Proposed definition of disease progression. FVC: forced vital capacity; D_{LCO}: diffusing capacity of the lungs for carbon monoxide.

CCD: composite categorical decline



Goh NS, et al. Arthritis Rheumatol. 2017;69:1670–8.

SSc-ILD: FVC decline and mortality

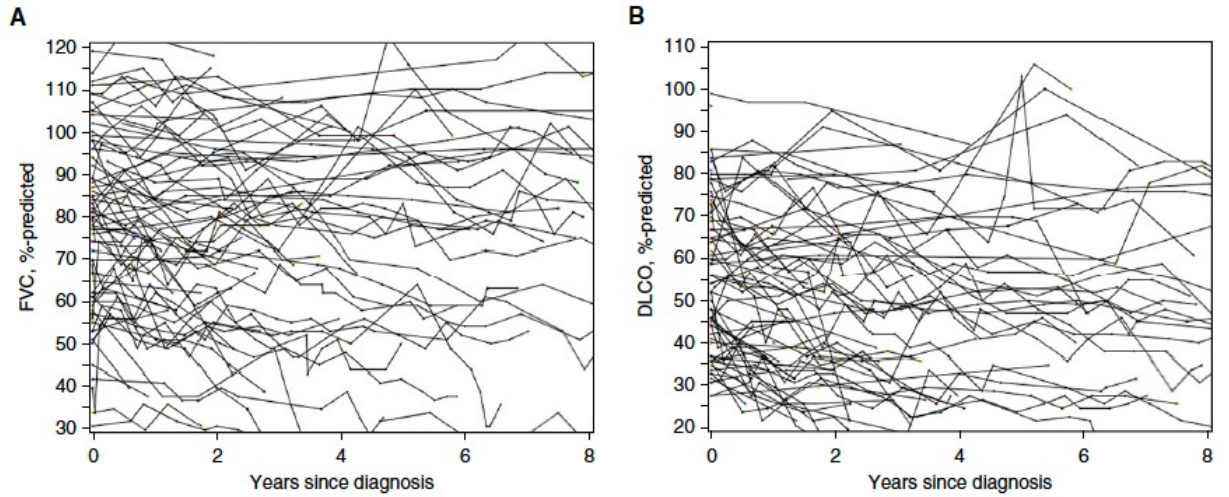
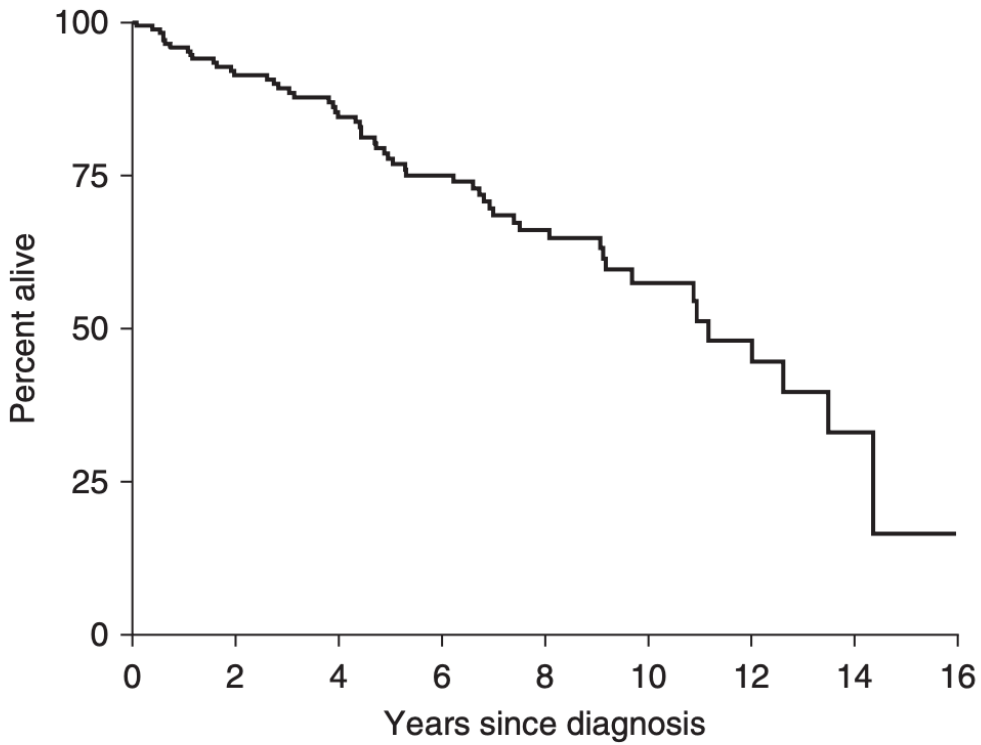


Figure 2. Connected plots with (*A*) FVC % predicted and (*B*) D_{LCO} % predicted trajectory for 80 randomly selected study participants. D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity.



171 patients retrospective enrolled with SSc-ILD:

1. Long term survival (>8 yy)
2. Medium term survival (4-8 YY)
3. Short term survival <4 yy

Guler SA, et al. Ann Am Thorac Soc 2018 Dec;15(12):1427-1433

SSc-ILD: FVC decline and mortality

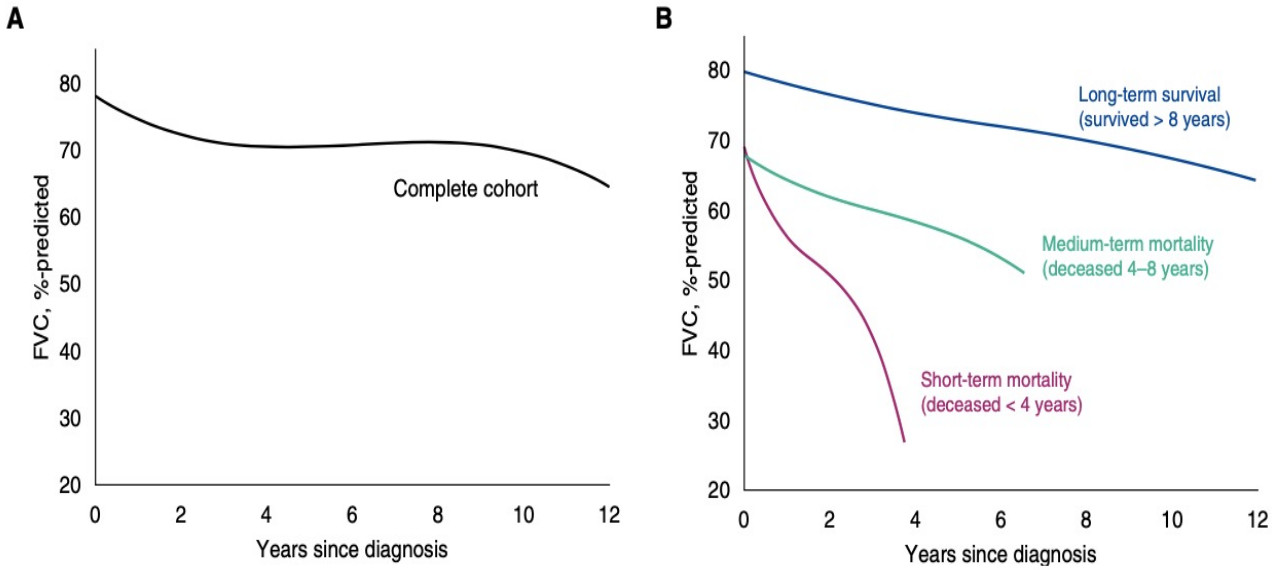


Figure 3. Progression of FVC (% predicted) in 171 patients with SSc-ILD: (*A*) Complete cohort and (*B*) categorized by prognostic groups. FVC = forced vital capacity; SSc-ILD = systemic sclerosis–associated interstitial lung disease.

Table 3. Annual decline in FVC and diffusing capacity of the lung for carbon monoxide by prognostic group

Survival Group	FVC (% Predicted)			
	Unadjusted Analysis		Adjusted Analysis*	
	Decline/Year	95% CI	Decline/Year	95% CI
Deceased within <4 yr	−4.42	−8.34 to −0.49	−4.10	−7.92 to −0.28
Deceased within 4–8 yr	−2.15	−3.32 to −0.99	−2.14	−3.31 to −0.97
Survived >8 yr	−0.93	−1.45 to −0.41	−0.94	−1.46 to −0.42
Group difference:	*P* value = 0.006		*P* value = 0.003	

Survival Group	D_{LCO} (% Predicted)			
	Unadjusted Analysis		Adjusted Analysis*	
	Decline/Year	95% CI	Decline/Year	95% CI
Deceased within <4 yr	−5.60	−9.91 to −1.29	−5.28	−9.58 to −0.99
Deceased within 4–8 yr	−3.16	−4.37 to −1.94	−3.13	−4.35 to −1.92
Survived >8 yr	−1.32	−2.02 to −0.63	−1.32	−2.01 to −0.63
Group difference:	*P* value < 0.001		*P* value < 0.001	

Definition of abbreviations: CI = confidence interval; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity.
*Adjusted for age, sex, and pack-years.

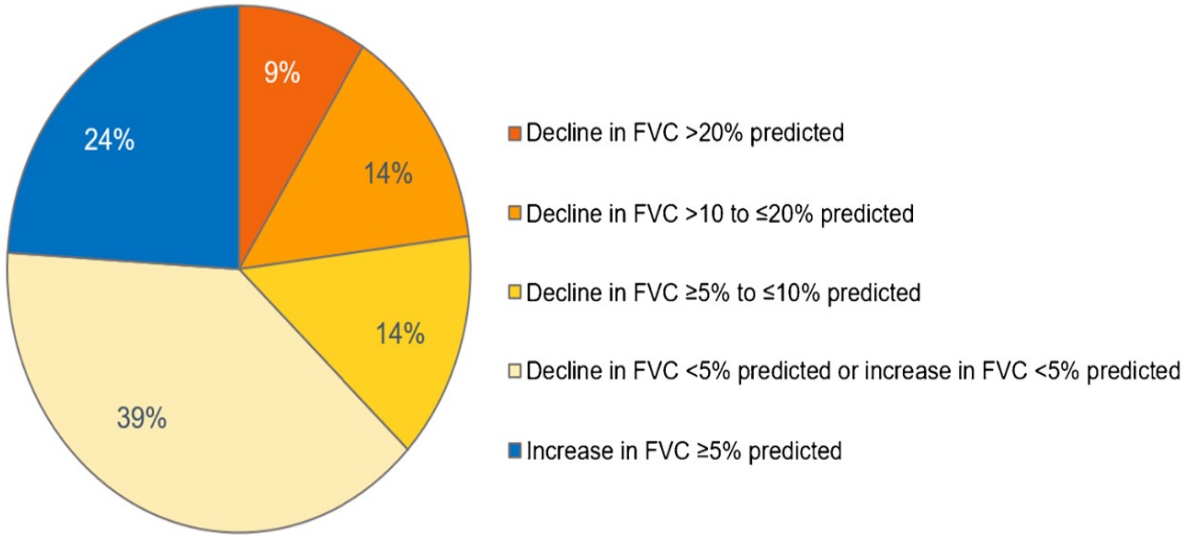
Adults with SSc-ILD have distinct patterns of physiological progression that remain relatively consistent during long-term follow-up;

Recent change in FVC cannot be used to predict future change in FVC within shorter follow-up intervals.

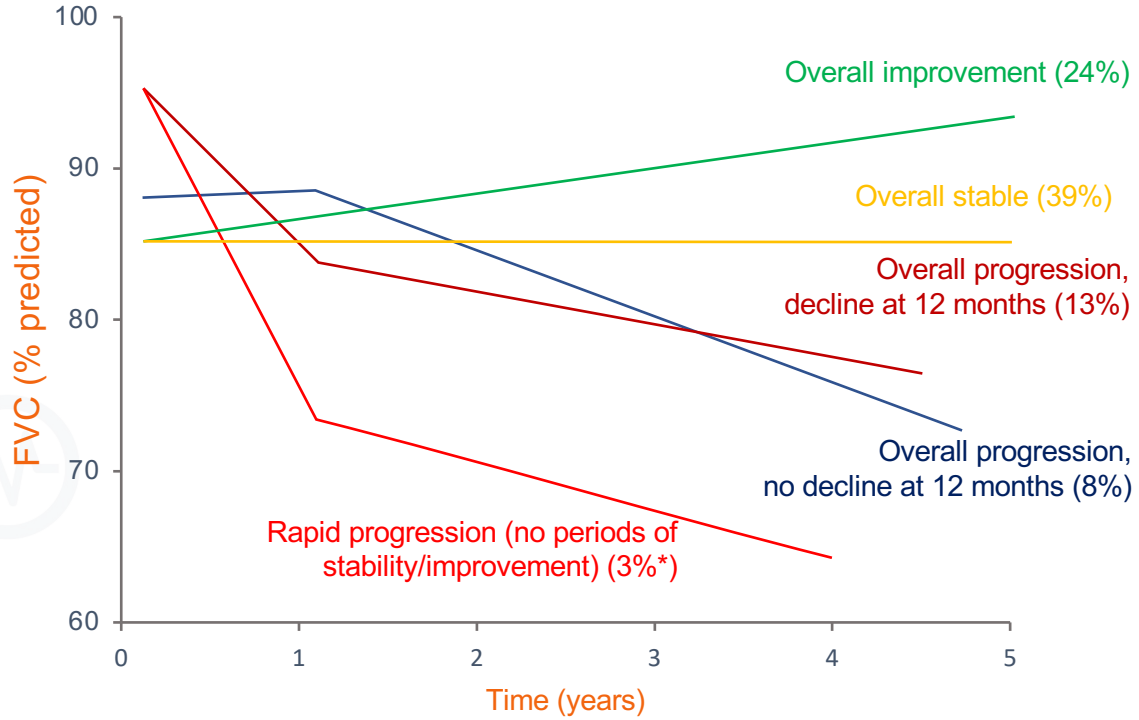
Guler SA, et al. Ann Am Thorac Soc 2018 Dec;15(12):1427-1433

Heterogeneous disease course of SSc-ILD

Change in FVC in 535 patients with SSc-ILD from the EUSTAR database over 5 years

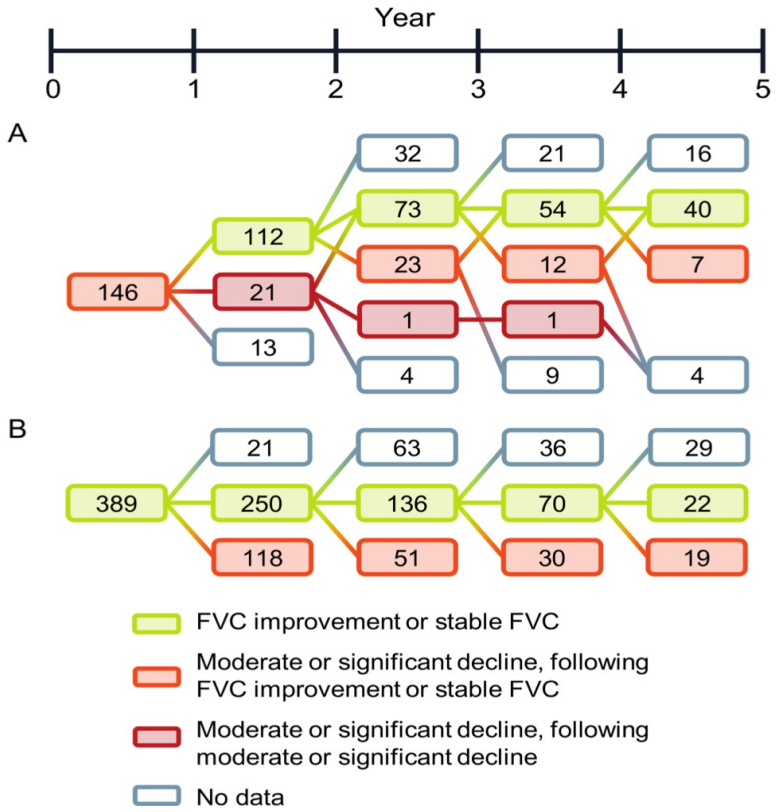


Due to the heterogeneous disease progression of SSc-ILD, **identifying who and when to treat is challenging**



Hoffmann-Vold A-M *et al. Ann Rheum Dis* 2020;; Distler O *et al. Eur Resp J* 2020;55:1902026;

Heterogeneous disease course of SSc-ILD



- Progressive periods rarely appeared in consecutive 12-month periods, and progressive periods were mostly followed by stable periods.
- Stable periods were followed by a progressive period in about 30% of cases

In multivariable linear mixed-effect models:

- male sex,
- presence of reflux/dysphagia symptoms
- high baseline mRSS as the strongest predictors

with significant interaction effects between time and these variables.

Immunosuppressive treatment was not predictive for FVC decline over time.

PRIMARY DILEMMA FOR CLINICIANS

To introduce treatment when the disease is progressive, but avoid side effects from unnecessary treatment when SSc-ILD is initrisically stable

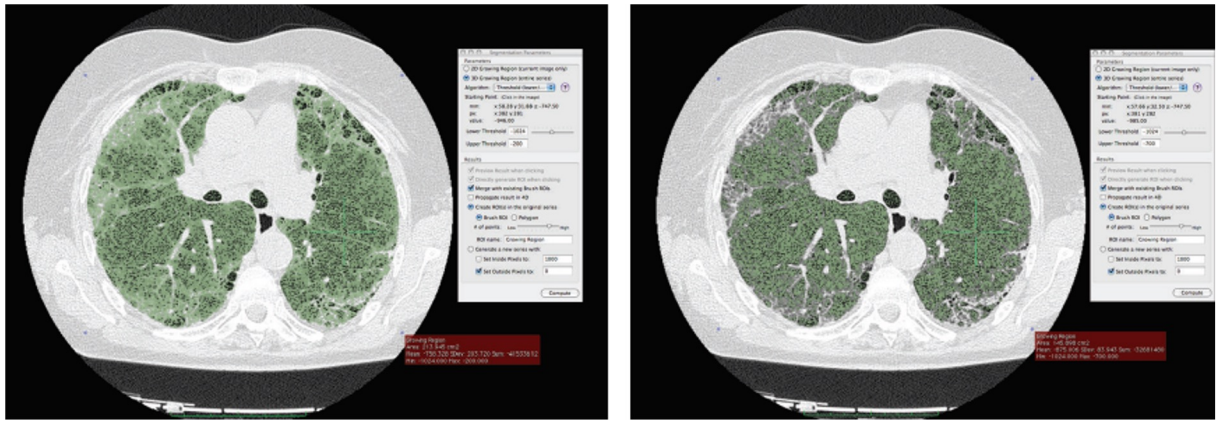
Hoffmann-Vold A-M *et al. Ann Rheum Dis* 2020;; Distler O *et al. Eur Resp J* 2020;55:1902026;

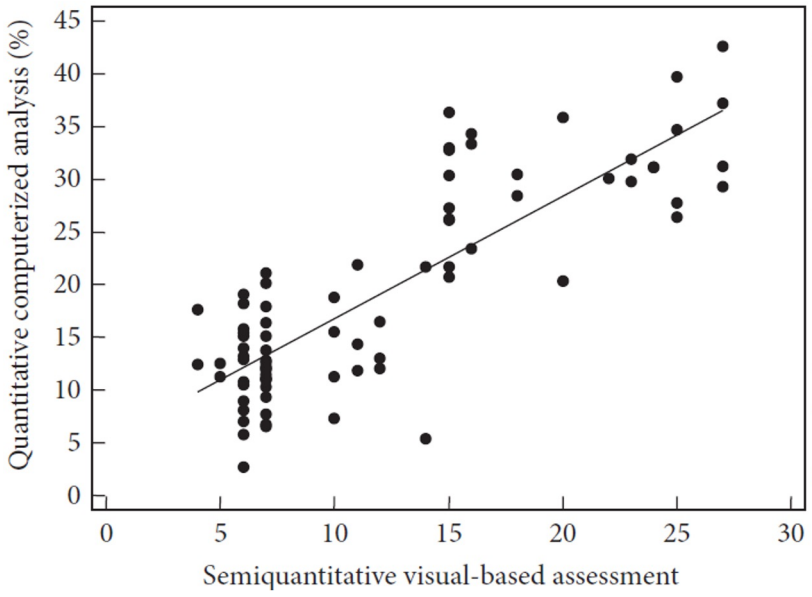
BioMed Research International

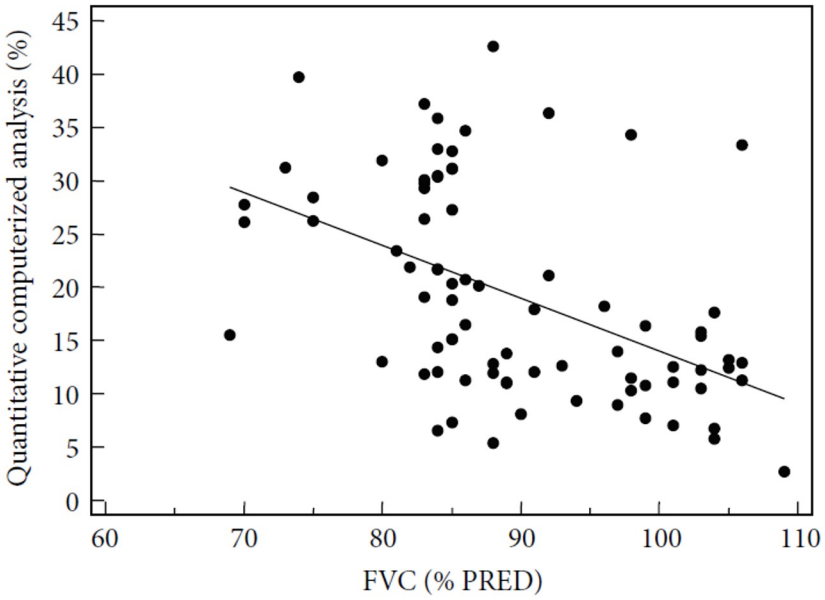
Research Article

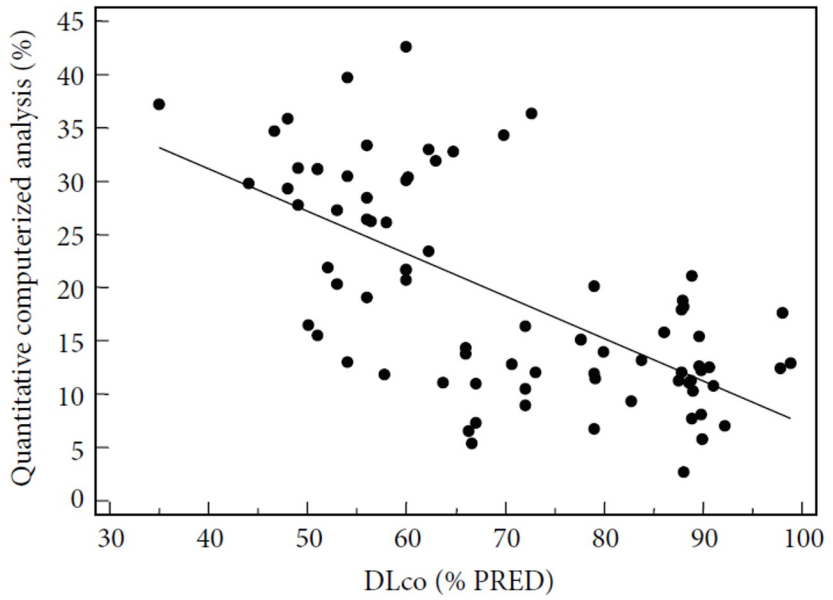
Computer-Aided Quantification of Interstitial Lung Disease from High Resolution Computed Tomography Images in Systemic Sclerosis: Correlation with Visual Reader-Based Score and Physiologic Tests

Fausto Salaffi,[1] Marina Carotti,[2] Silvia Bosello,[3] Alessandro Ciapetti,[1] Marwin Gutierrez,[1] Elisabetta Bichisecchi,[2] Gianmarco Giuseppetti,[2] and Gianfranco Ferraccioli[3]









OSIRIX: open source Digital imaging software

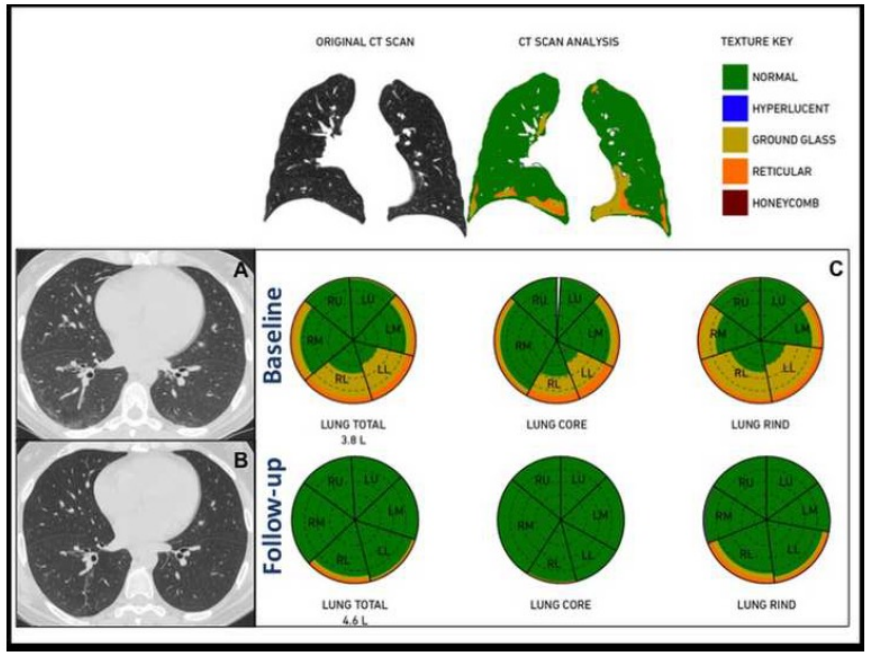
PLOS ONE

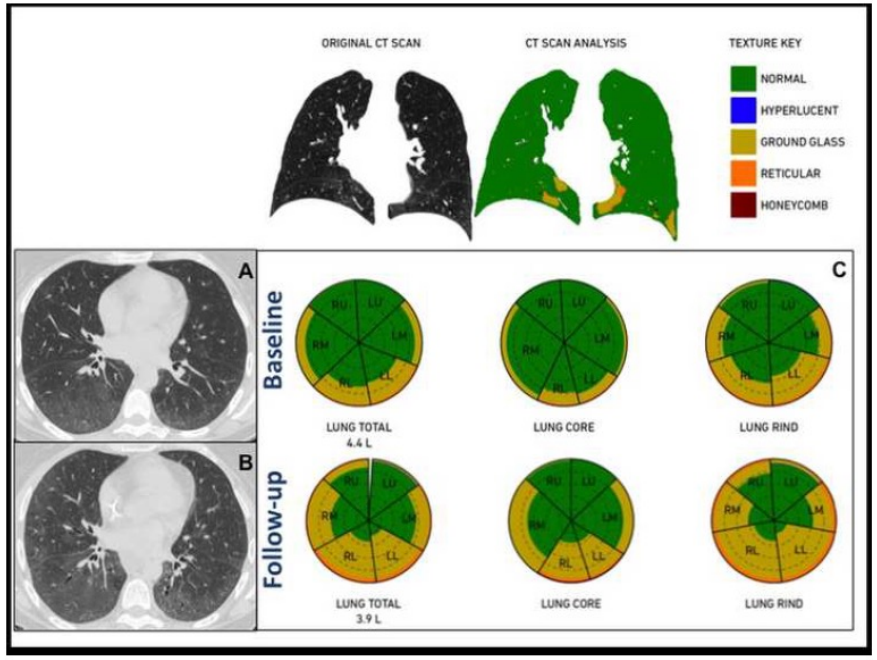
RESEARCH ARTICLE

Quantitative and semi-quantitative computed tomography analysis of interstitial lung disease associated with systemic sclerosis: A longitudinal evaluation of pulmonary parenchyma and vessels

Mariaelena Occhipinti[1]*, Silvia Bosello[2], Leuconoe Grazia Sisti[3], Giuseppe Cicchetti[4], Chiara de Waure[5], Tommaso Pirronti[4], Gianfranco Ferraccioli[2], Elisa Gremese[2], Anna Rita Larici[4]

- Quantitative evaluation had a weak-to-good concordance with semiQA
- Quantitative evaluation correlated better than semiQA with functional parameters.
- Changes in QA patterns during treatment were not accurate in predicting disease progression as assessed by functional parameters.





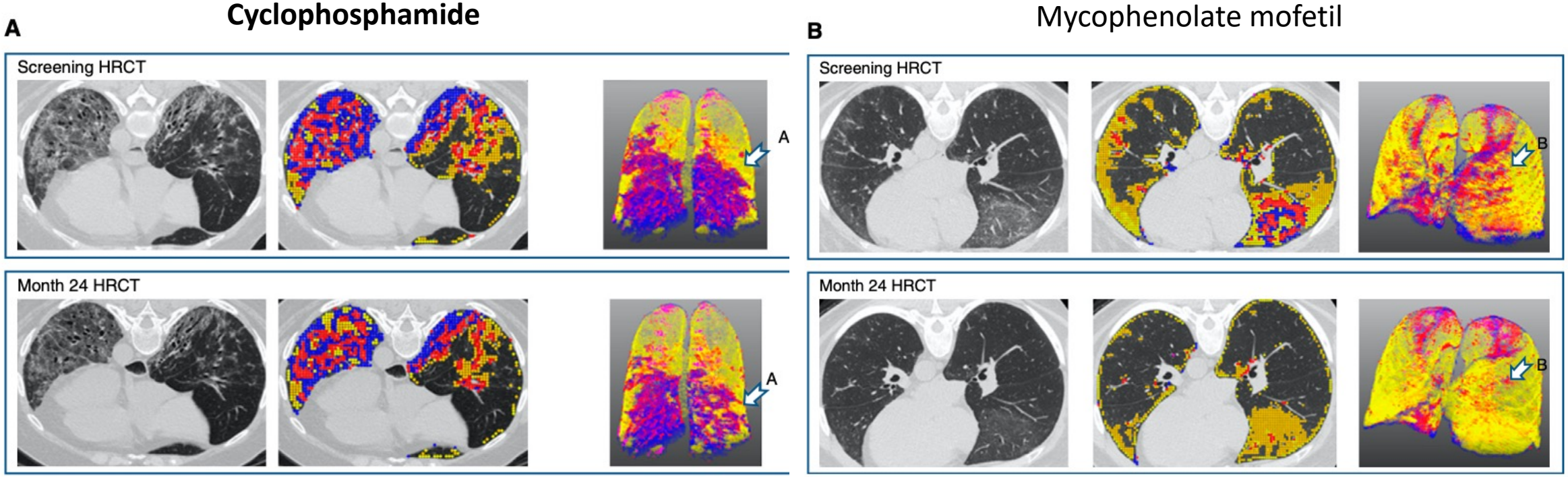
Imbio LTA, based on CALIPER software **TEXTURE ANALYSYS** based on anatomo-pathological validation

Longitudinal Changes in Quantitative Interstitial Lung Disease on Computed Tomography after Immunosuppression in the Scleroderma Lung Study II

Jonathan G. Goldin[1], Grace Hyun J. Kim[1,2], Chi-Hong Tseng[3], Elizabeth Volkmann[4], Daniel Furst[4], Philip Clements[4], Matt Brown[1], Michael Roth[5], Dinesh Khanna[6], and Donald P. Tashkin[5]

Cyclophosphamide

Mycophenolate mofetil



FVC 67% to FVC 79%

FVC 69% to FVC 81%

Monitoring SSc-ILD: risk factors

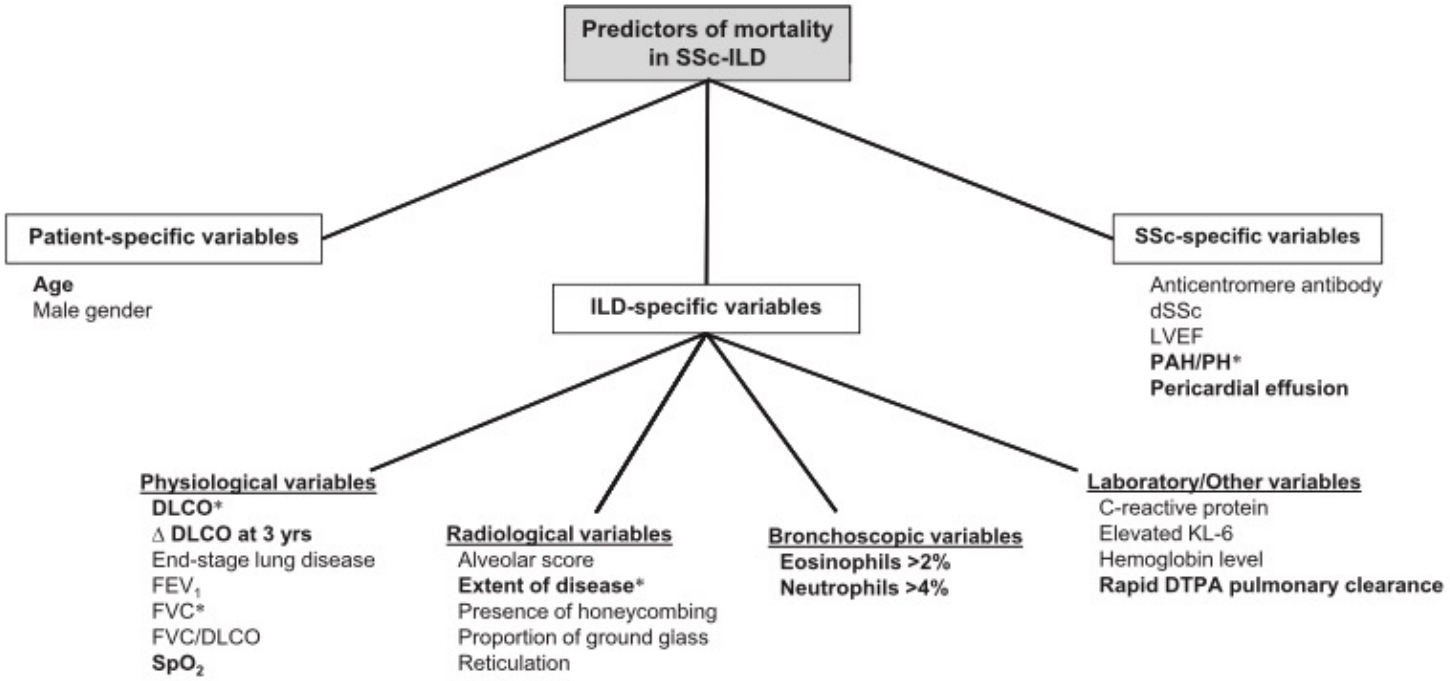


Figure 2 – *Statistically significant predictors of mortality in SSc-ILD. Variables listed in bold were associated with mortality on both bivariate and multivariate analysis. *Statistically significant predictors of mortality that were identified in multiple studies. DLCO = diffusing capacity of the lung for carbon monoxide; dSSc = diffuse SSc; DTPA = diethylene thiamine pentacetate clearance; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; SpO_2 = oxygen saturation. See Figure 1 legend for expansion of other abbreviations.*

Winstone TA, et al. Chest 2014 Aug;146(2):422-436. Review

RESEARCH ARTICLE

Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis

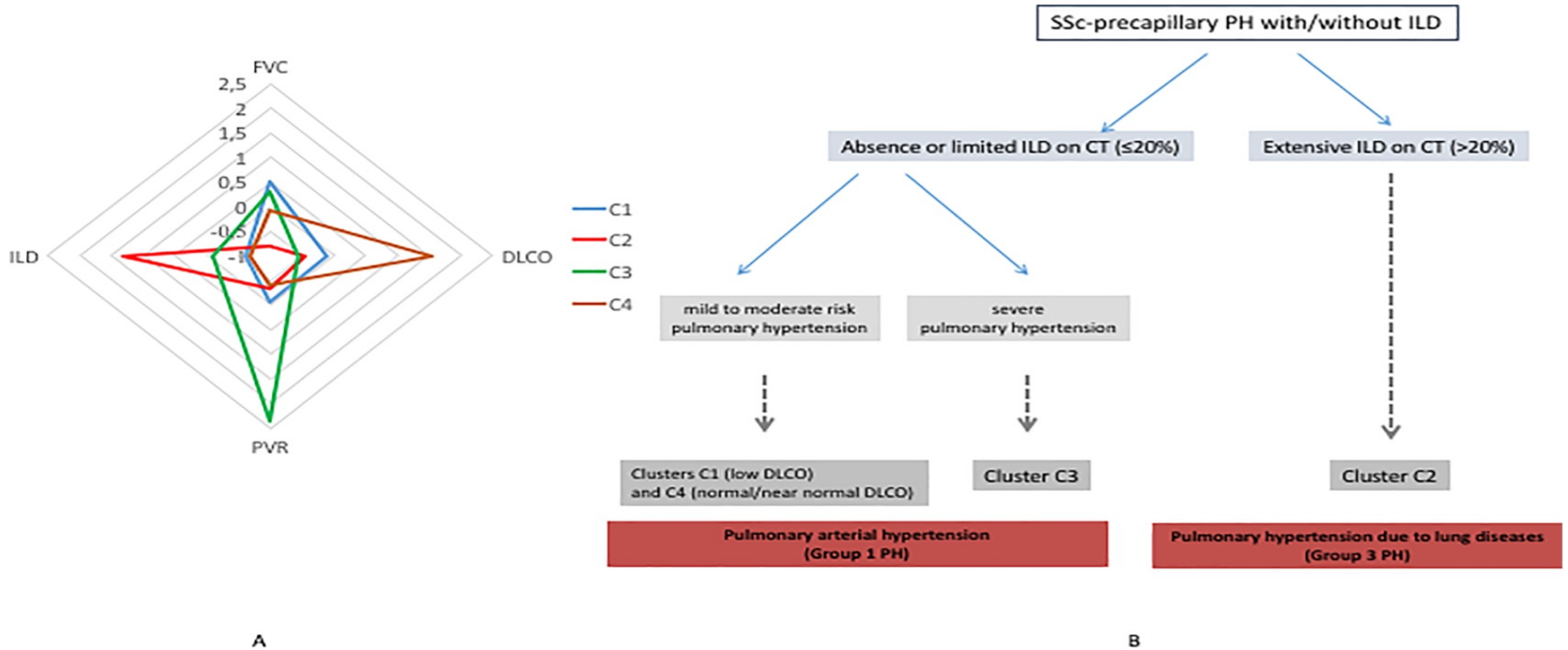
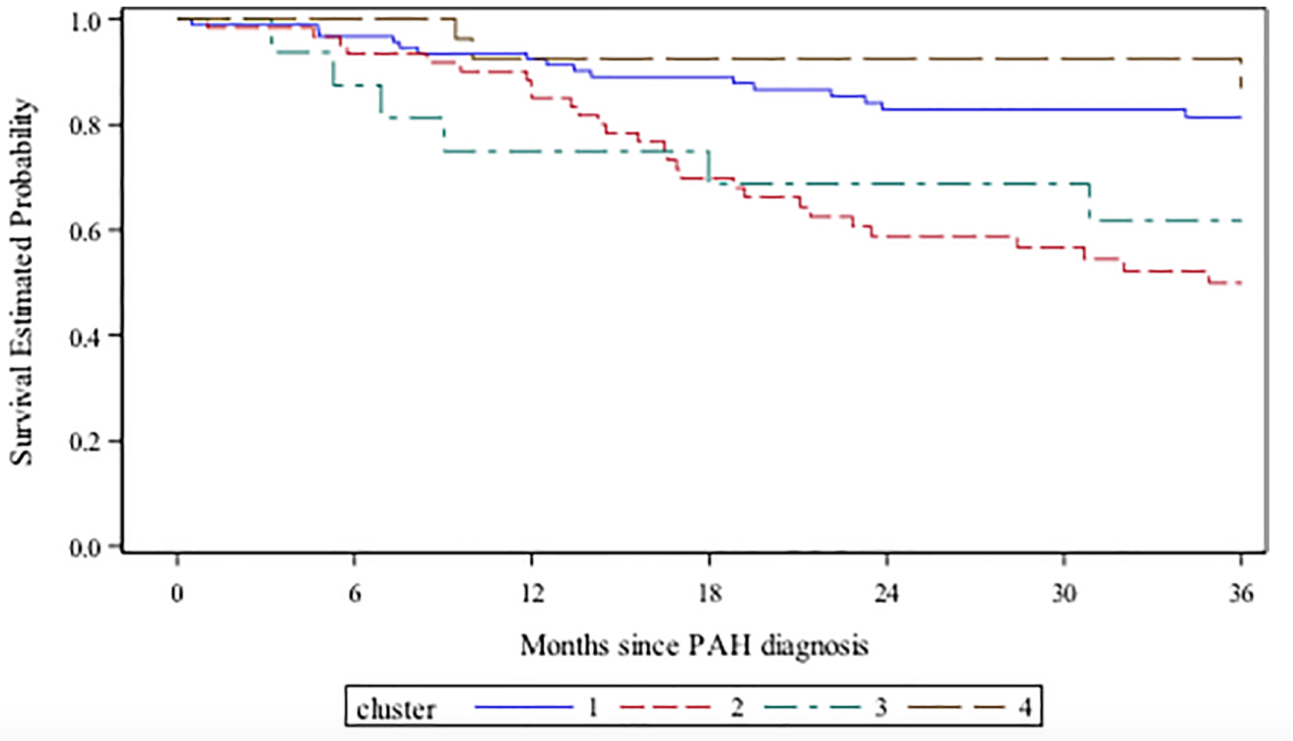


Fig 3. A. Radar plot of the four clusters according to clinical characteristics, presence and severity of interstitial lung disease and severity of hemodynamics. B. Algorithm of classification in the four clusters C1, C2, C3 and C4.

RESEARCH ARTICLE

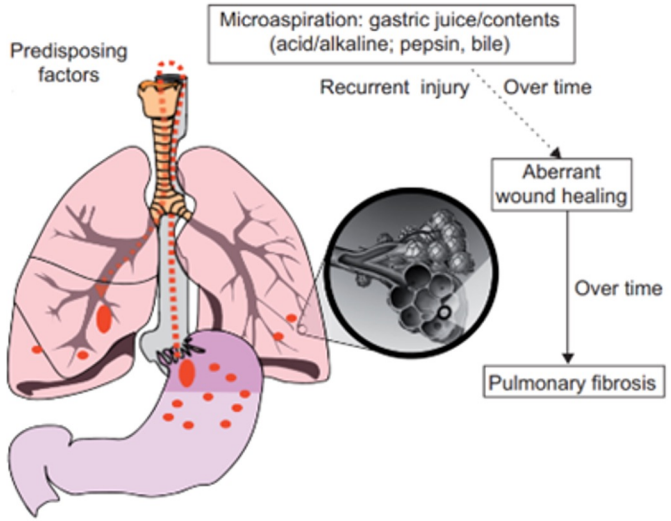
Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis



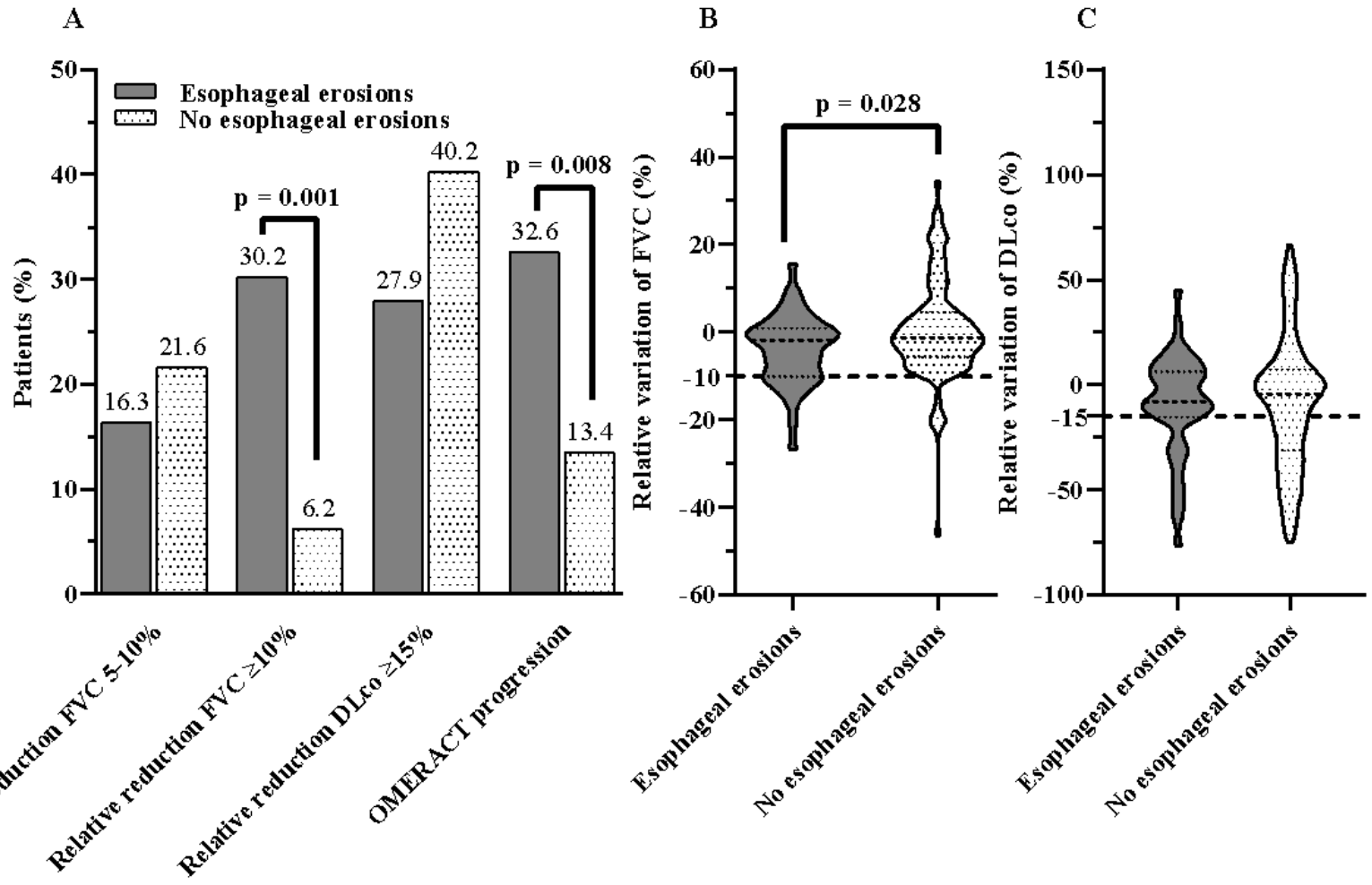
1. The presence of an extensive ILD, whatever the hemodynamics, is associated with a very severe outcome

2. The presence of a limited ILD (often seen as a potent cofounder the classification of PH in tne context of SSc) has to be considered in the same group of patients with no ILD, where the severity of hemodynamics drives the prognosis.

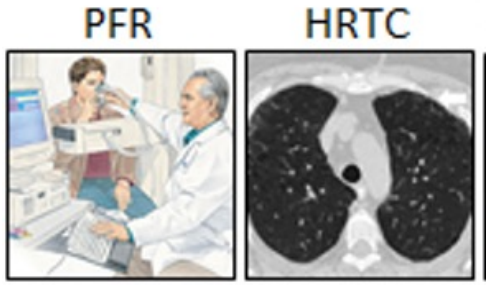
ESOPHAGEAL EROSIONS PREDICT FUNCTIONAL PROGRESSION OF LUNG DISEASE IN PATIENTS WITH SYSTEMIC SCLEROSIS



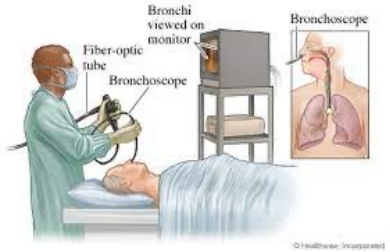
Scleroderma patients with erosive esophagitis present a greater risk of deterioration of lung function related to interstitial lung disease

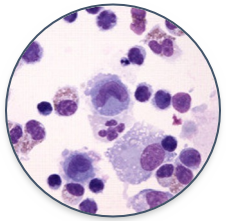


De Lorenzis, on going, Houghton LA et al. Nat Rev Gastroenterol Hepatol 2020



The role of BALF





Alveolitis was present in **38.1%** of the patients who had ground glass on HRCT and then underwent BAL.

Table 5: Diagnostic accuracy of the predictors of alveolitis

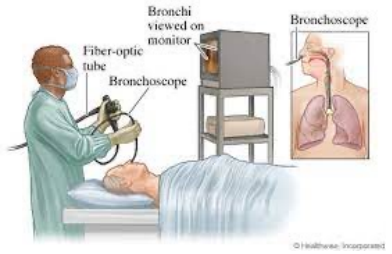
	AUC (95% CI)	p	Cut-off value	Se(%)	Sp (%)
FVC	0.145 (-0.003 – 0.292)	0.000	80.5	77.8	100.0
DLCO	0.199 (0.058 – 0.340)	0.001	50.0	72.2	70.8
IL-6	0.694 (0.524 – 0.864)	0.045	0.75	80.0	60.9
Skin score	0.650 (0.473 – 0.826)	0.109	14.5	58.8	78.3
Alveolar score on HRCT	0.742 (0.591 – 0.893)	0.008	6.5	66.7	75.0

AUC: area under curve ROC; FVC: forced vital capacity; DLCO: diffusing capacity for carbon monoxide; HRCT: high resolution computed tomography.

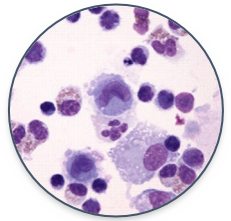
A diffuse skin involvement and a restrictive pattern on PFTs together with ground glass on HRCT were judged possible markers of alveolitis

BAL would be necessary to **detect any infections** of the lower respiratory tract that may cause further deterioration in lung function.

De Santis and Bosello, Respiratory Research 2005, 6:96



BALF and ILD progression



<u>3-years - ILD progression was associated with:</u>

- ✓ honeycombing on HRCT,
- ✓ Neutrophils,
- ✓ eosinophils,
- ✓ an inverted CD4/CD8 lymphocytes ratio
- ✓ higher CD19 percentage count
- ✓ a positive BALF microbiological culture.

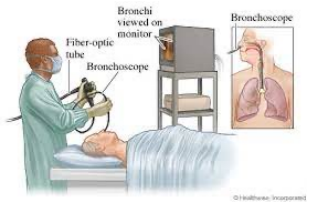
The diffuse disease was the only independent risk factor of overall mortality.

The extent of honeycombing on HRCT was the only independent risk factor of lung disease-related mortality.

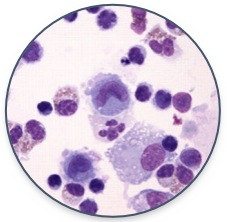
Table 3. Microbial agents recovered from the lower respiratory tract

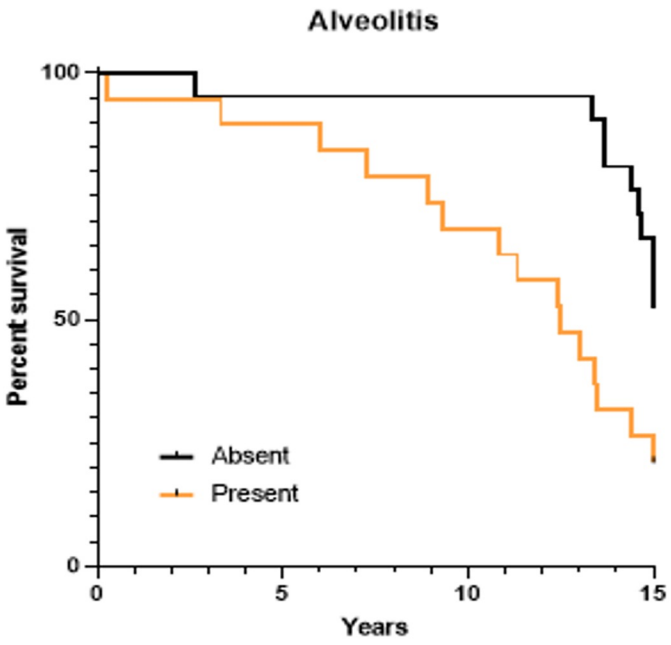
Single microbial agent:	16 (80.0%)
Haemophilus influenzae	4 (25.0%)
Staphylococcus aureus	4 (25.0%)
Candida albicans	4 (25.0%)
Streptococcus pneumoniae	2 (12.5%)
Enterococcus faecalis	1 (6.3%)
Fusarium oxisporium	1 (6.3%)
Mixed flora:	4 (20.0%)
Candida albicans and Heamophilus influenzae	1 (25.0%)
Candida albicans and Staphylococcus aureus	1 (25.0%)
Streptococcus constellatus and Aspergillus terreus	1 (25.0%)
Stenotrophomonas maltophilia and Aspergillus fumigatus and Candida albicans	1 (25.0%)

De Santis, The Clinical Respiratory Journal (2012)

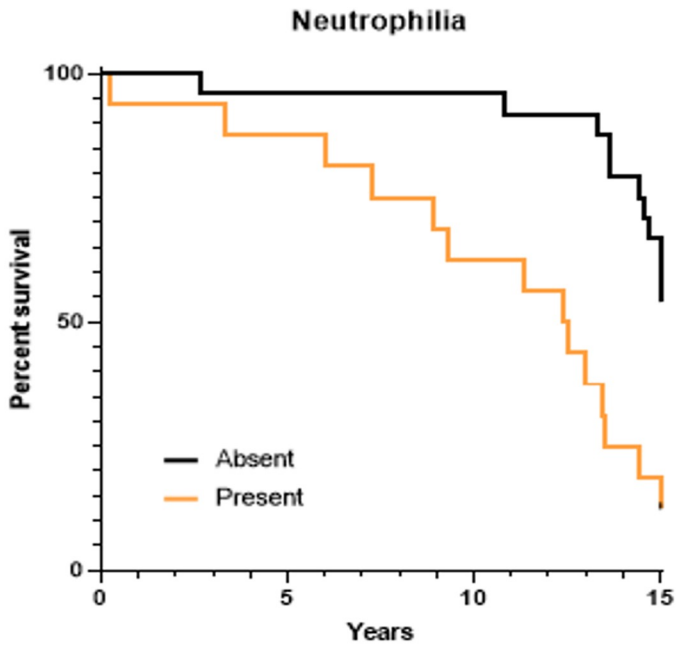


BALF cells and 15-year survival

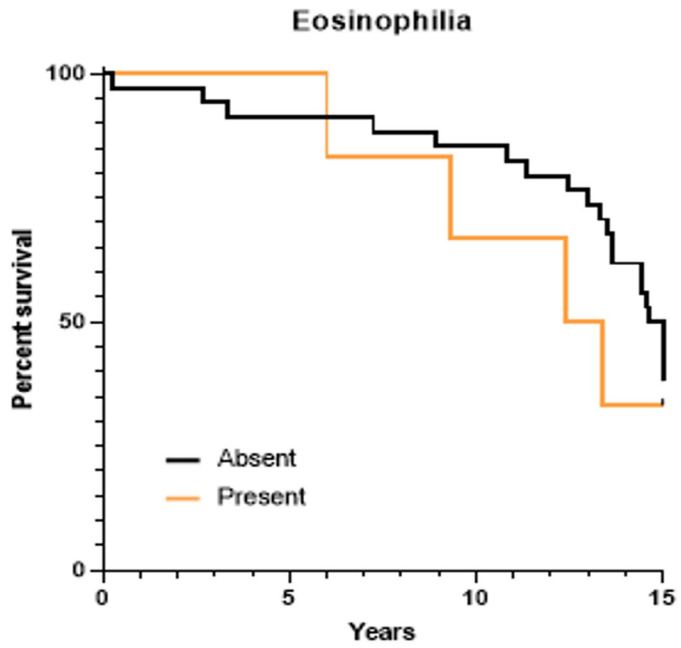




LR X^2=6.962, p=0.008

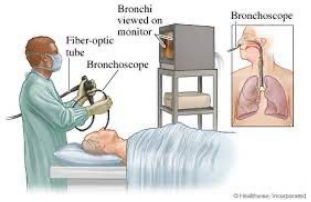


LR X^2=11.274, p=0.001

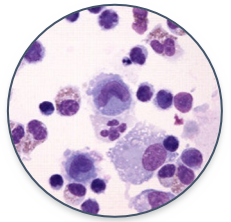


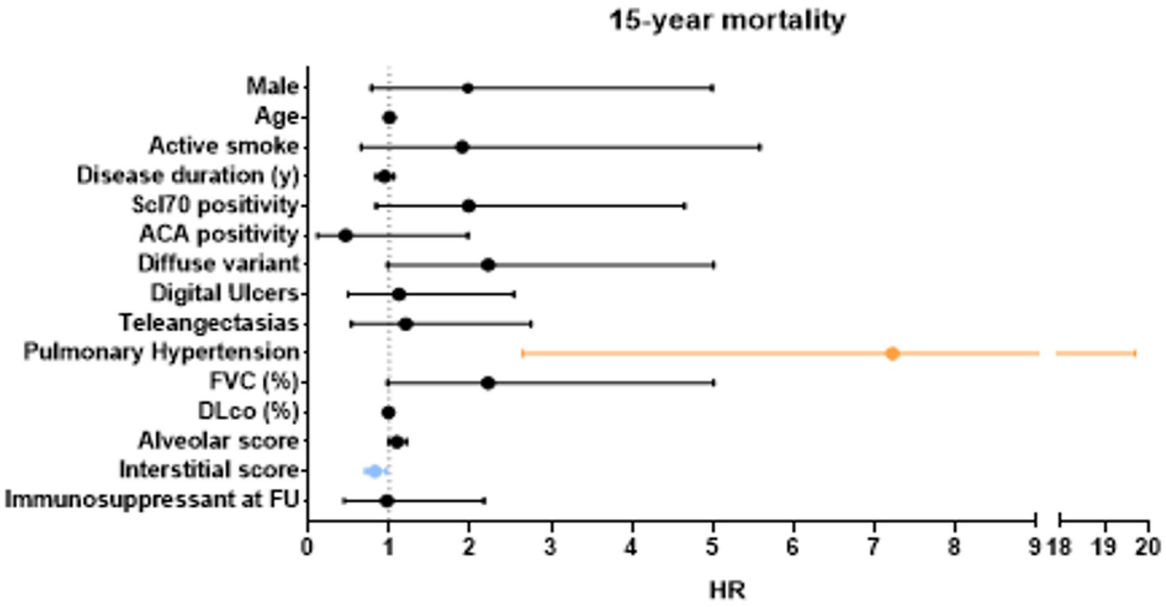
LR X^2=0.631, p=0.427

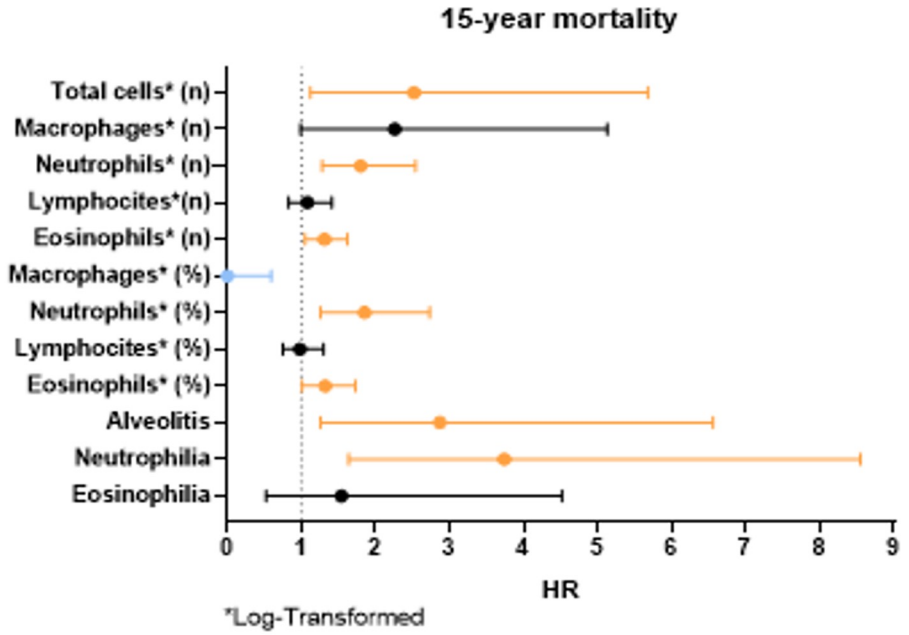
De Lorenzis, on going



BALF abnormalities and 15-year survival

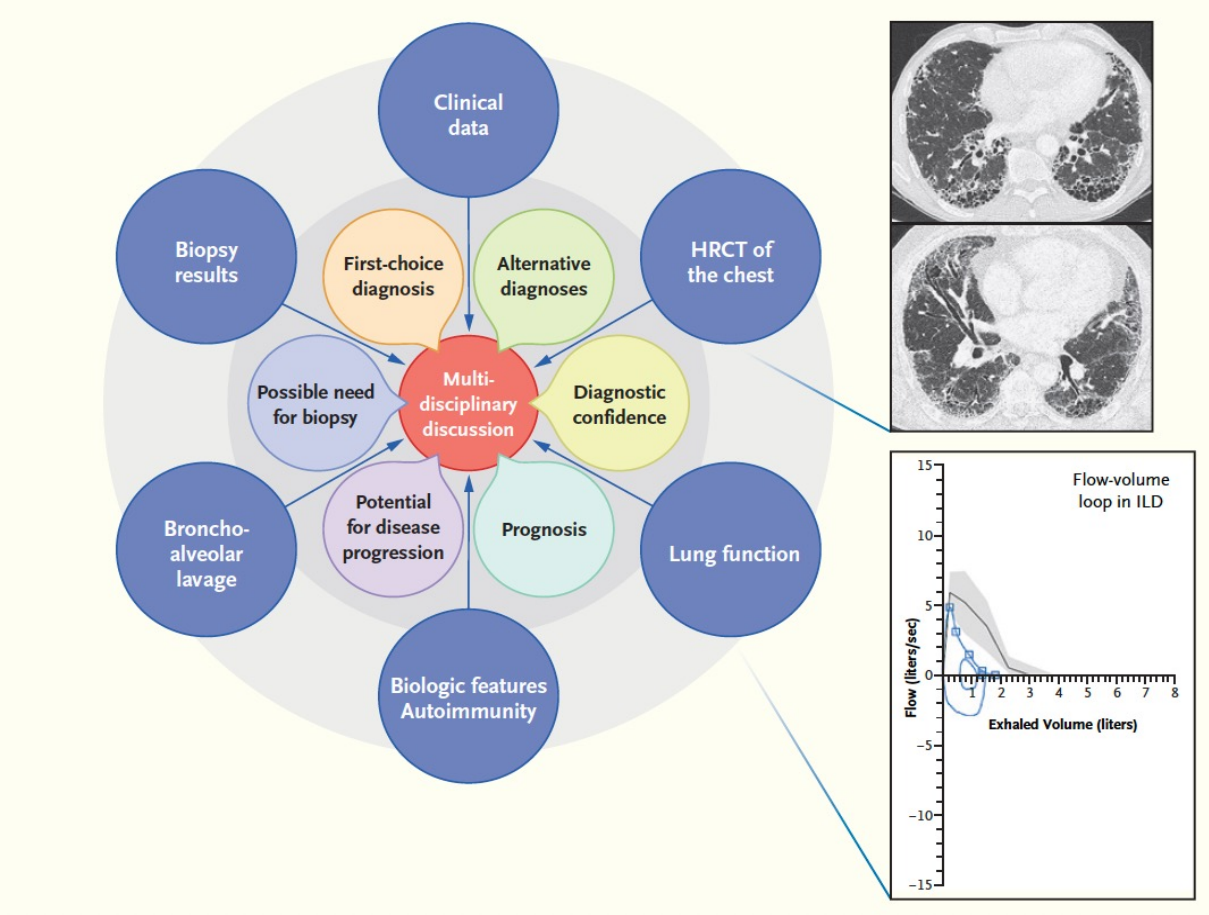






De Lorenzis, on going

Multidisciplinary approach and/or combination scores



Multidisciplinary team (MDT) discussion is the gold standard in the management of SSC-ILD

Combination of:

- **Biomarkers of the disease**
- **HRCT extension analysys**
- **Pulmonary function test**
- **BALF biomarkers**

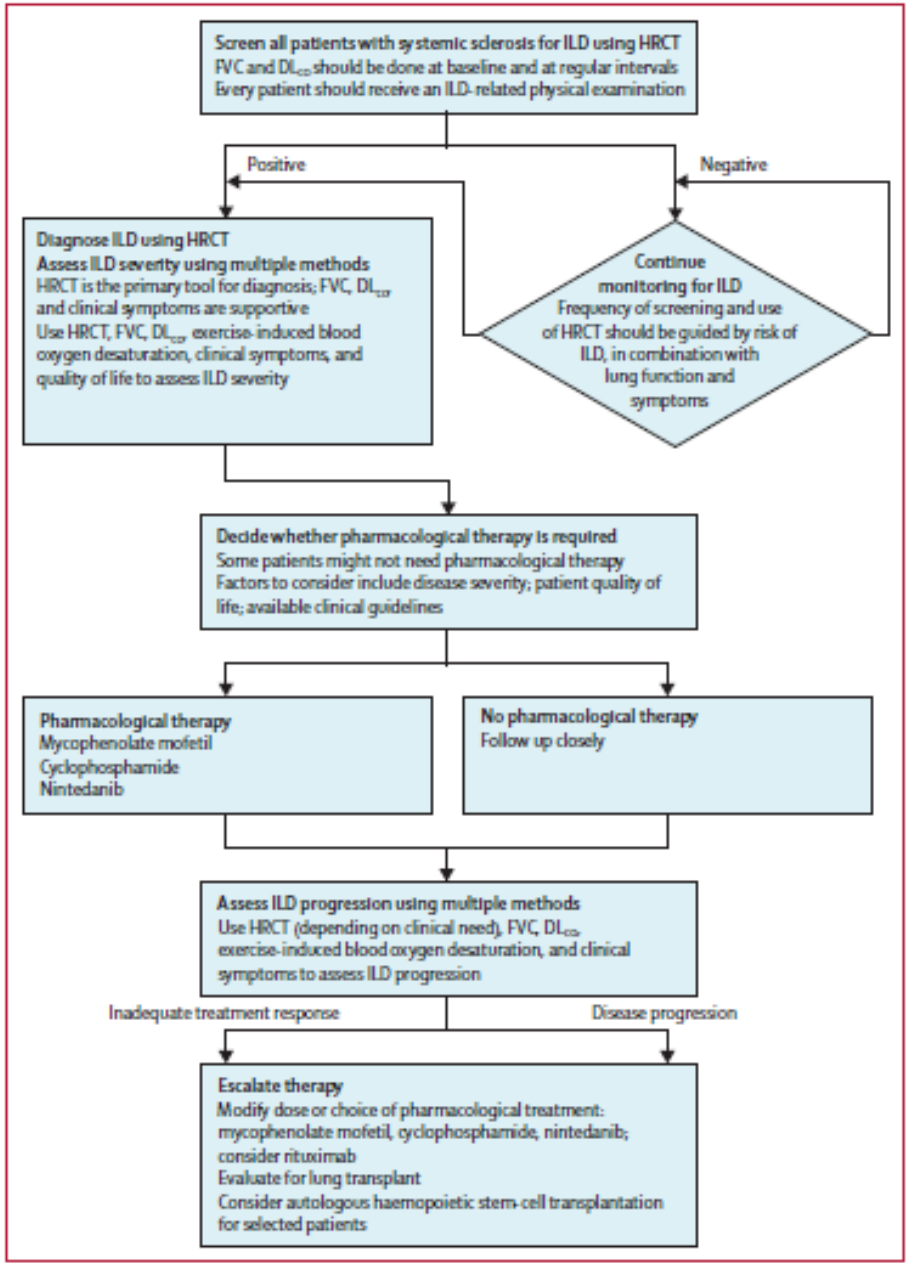
Lancet Rheumatology
2020

The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements

Anna-Maria Hoffmann-Vold, Toby M Maher*, Edward E Philpot, Ali Ashrafzadeh, Rafic Barake, Simone Barsotti, Cosimo Bruni, Paolo Carducci, Patricia E Carreira, Ivan Castellví, Francesco Del Galdo, Jörg H W Distler, Ivan Foeldvari, Paolo Fraticelli, Peter M George, Bridget Griffiths, Alfredo Guillén-Del-Castillo, Abdul Monem Hamid, Rudolf Horváth, Michael Hughes, Michael Kreuter, Florentine Moazedi-Fuerst, Jacek Olas, Suman Paul, Cinzia Rotondo, Manuel Rubio-Rivas, Andrei Seferian, Michal Tomčík, Yurdagül Uzunhan, Ulrich A Walker, Ewa Więsik-Szewczyk, Oliver Distler*

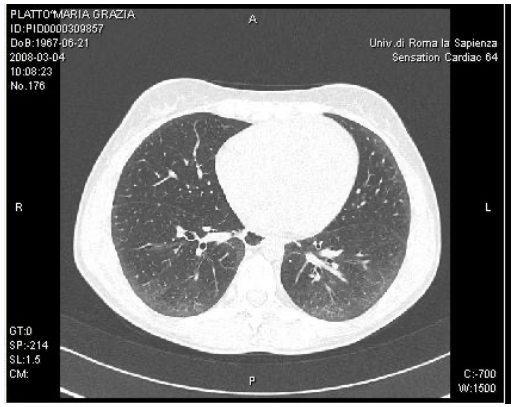
SIX DOMAINS:

1. Risk factors
2. Screening
3. Diagnosis and severity assessment
4. Treatment initiation and options
5. Disease progression
6. Treatment escalation



MANAGEMENT of SSc-ILD

(based on the extent of lung changes on HRTC and FVC values)



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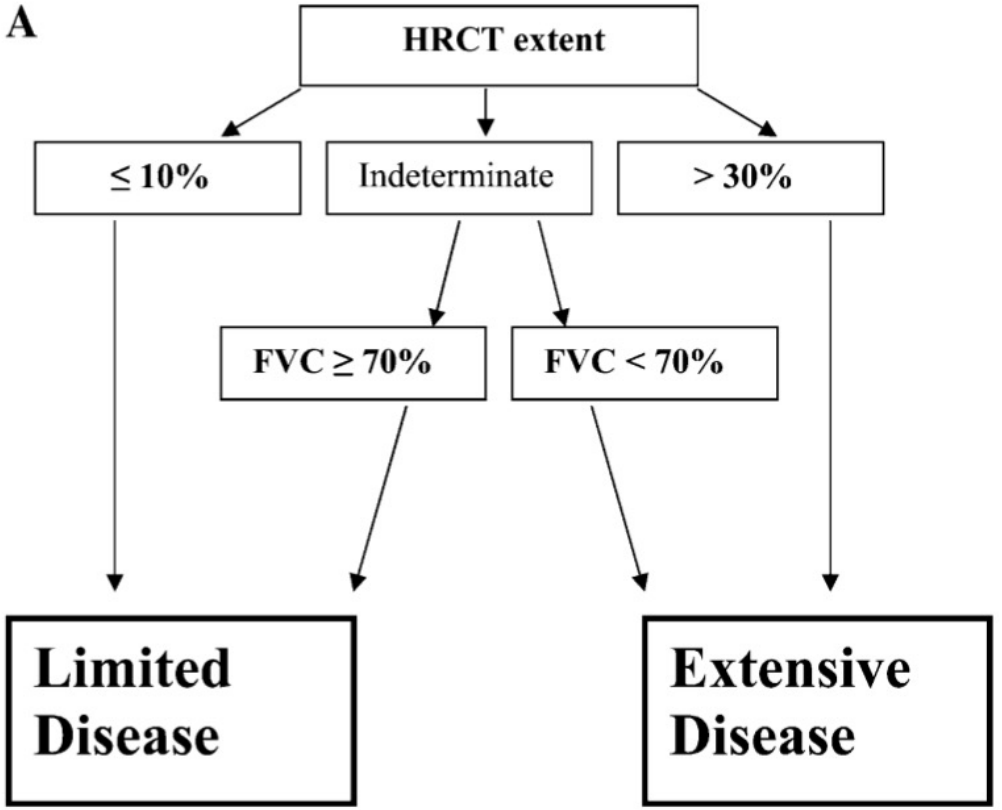

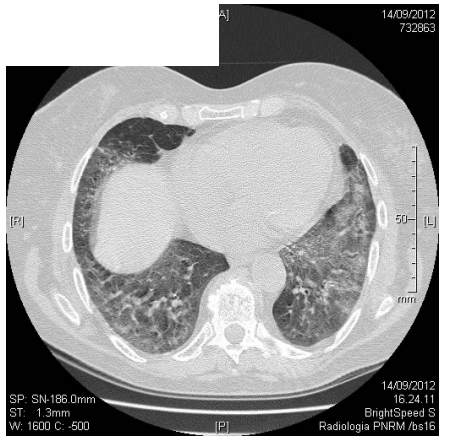

Goh NS et al. Am J Respir Crit Care Med 2008;
Moore OA et al. Rheumatol 2013;
Sanchez-Cano D et al Rheumatol Int 2018;
Chowaniec M et al. Reumaologia 2018.

Conclusions

- SSc-ILD has a variable clinical course with an early mortality
- Monitor both the FVC and the DLCO in the longer term, regardless of whether the disease has stabilized in the shorter term
- Monitor more than one single variable in clinical practice
- immense efforts have to cluster SSc patient also including stimulating biomarkers to tailor patient treatment.