Systemic Sclerosis-Associated Interstitial Lung Disease

(SSc-ILD)

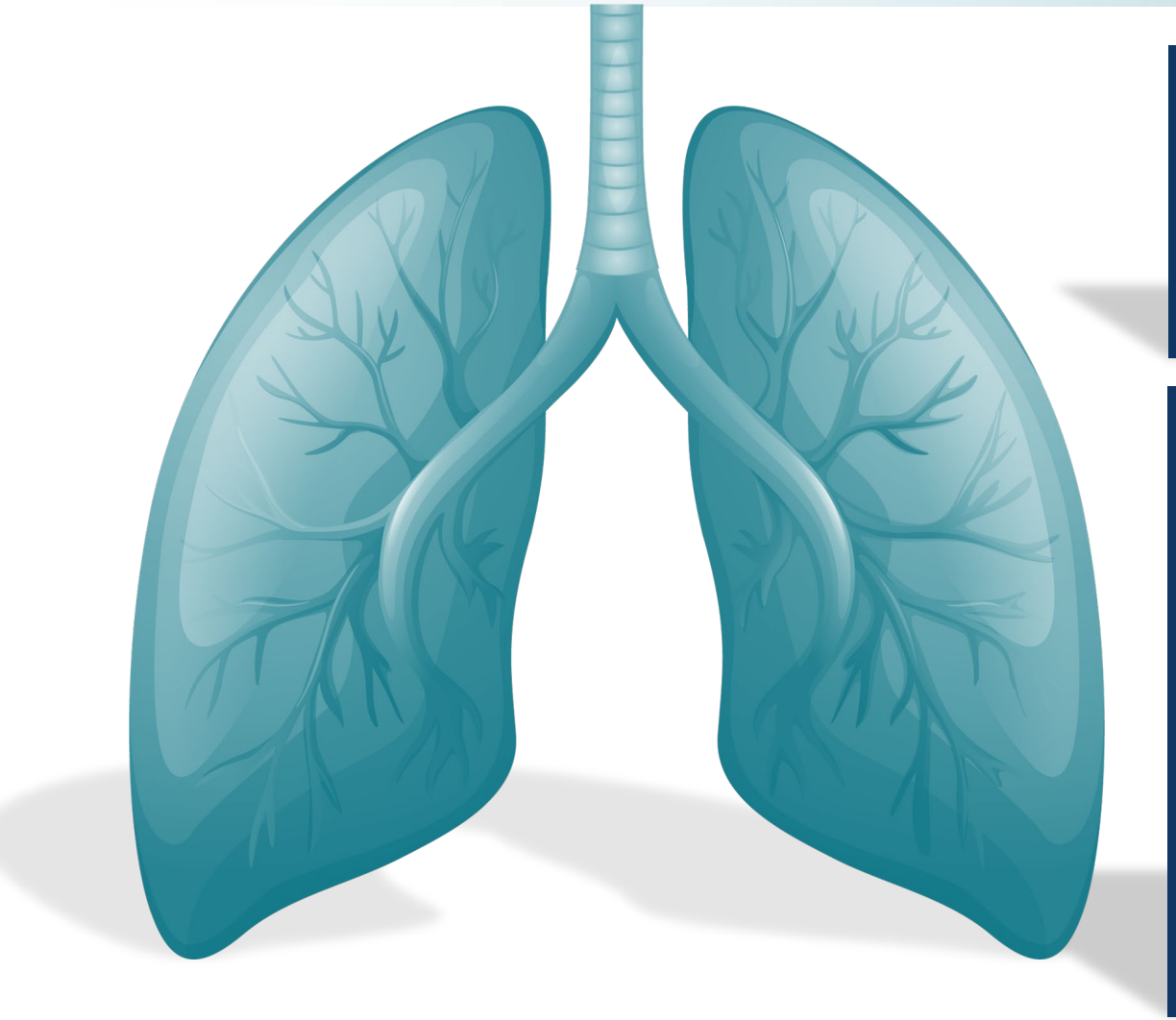
SC-US-68902

Boehringer Ingelheim

Objectives

- Review the epidemiology and burden of SSc-ILD
- Highlight the clinical presentation of SSc-ILD, including the clinical, biological, and radiographic features associated with SSc-ILD progression
- Describe the underlying pathogenesis in SSc-ILD, which is characterized by the interplay between fibrosis, autoimmunity, inflammation, and vascular injury
- Discuss best practices for diagnosing SSc-ILD, including the tools and tests utilized to diagnose SSc-ILD and assess disease severity

Defining SSc-ILD



Definition of SSc-ILD

Chronic lung disease characterized by fibrosis and/or inflammation in the walls of the air sacs of the lungs in patients diagnosed with SSc.[1]

Two components of SSc-ILD

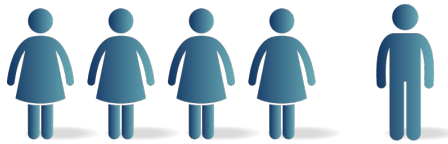
SSc:
Systemic inflammatory autoimmune disorder characterized by vasculopathy, fibrosis of the skin and internal organs, and immunological abnormalities.[2,3]

ILD:
Common manifestation of SSc characterized by inflammation and/or lung fibrosis; often associated with a progressive decline in pulmonary function within the first several years of onset.[3]

1. Lederer D. Scleroderma-associated Interstitial Lung Disease (SSc-ILD). Pulmonary Fibrosis Foundation. https://www.pulmonaryfibrosis.org/docs/default-source/disease-education-brochures/q2-june-2020---pf-series---ssc-ild.pdf?sfvrsn=18a59c8d_8 Accessed September 30, 2020. 2. Suliman S et al. *Respir Med Case Rep*. 2017;22:109-112. 3. Fischer A et al. *Open Access Rheumatol*. 2019;11:283-307.

Epidemiology of SSc-ILD

Women are more likely to **develop SSc (4:1),**



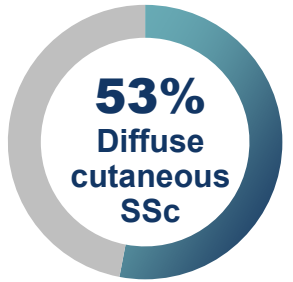
with an average age at presentation **of 45 to 55 years[1]**

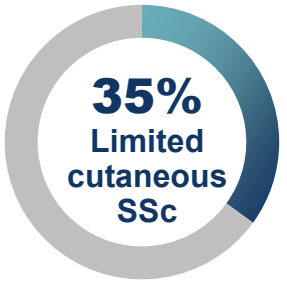
All patients with SSc are at risk for developing ILD

It is estimated that **>50%** of patients with SSc develop associated ILD[2]

70% to 90% of patients with SSc who develop ILD will develop ILD within the **first 3 years** of SSc diagnosis[3]

ILD has been found in[4,a]:





[a]Based on the EULAR Scleroderma Trials and Research (EUSTAR) group analysis in a cohort of 3656 SSc patients,

1. Mirsaeidi M et al. *Front Med (Lausanne)*. 2019;6:1-10. 2. Fischer A et al. *Autoimmun Rev*. 2017;16(11):1147-1154. 3. Fischer A et al. *Open Access Rheumatol*. 2019;11:283-307.
4. Walker UA et al. *Ann Rheum Dis*. 2007;66:754-763.

Risk of Mortality With SSc-ILD

ILD is the leading cause
of **SSc-associated mortality**, accounting for
≈35% of SSc-related deaths[1-3]

The mortality risk in patients with SSc-ILD
was found to be
≈3 times greater
than in patients with SSc alone[1]

1. Fischer A et al. *Open Access Rheumatol*. 2019;11:283-307. 2. Cottin V Brown KK. *Respir Res*. 2019;20(1):13. 3.Tyndall AJ et al. *Ann Rheum Dis*. 2010;69(10):1809-1815 .

Burden of SSc

Sleep disturbance

Emotional distress
(eg, depression, low self-esteem)

Difficulty breathing

Fatigue

Limitations in mobility and hand function

GI problems

Pain

Pruritus

Impaired ability to work

Reduced QoL

Disruptions in patients' social lives

GI, gastrointestinal; QoL, quality of life.

Fischer A et al. *Autoimmun Rev*. 2017;16(11):1147-1154.

Distinct ILD Clinical Phenotypes Exist in SSc

	Rapid progressor	Gradual progressor	Stabilizer	Improver
FVC	Relative decline ≥10%, or decline 5%-9% in association with ≥15% decline in DL_{CO} within 1-2 years[a]	Relative decline ≥10%, or decline 5%-9% in association with ≥15% decline in DL_{CO} within >2 years[a]	Relative FVC decline <5%, or FVC increase <5%	Relative FVC improvement >5%[b]
HRCT	Increased extent of reticulations within 1-2 years[a]	Increased extent of reticulations over >2 years[a]	No change in the extent of reticulations	Decreased extent of reticulations
Supplemental oxygen[c]	Initiation within 1-2 years[a]	Initiation >2 years[a]	No need for supplemental oxygen or no increase in dose from the time of diagnosis	No need for supplemental oxygen or decreased dose from the time of diagnosis
Lung transplantation or death	Within 5 years[a]	>5 years[a]	No need for lung transplantation	No need for lung transplantation

[a]These time periods are based on the time from the diagnosis of ILD; however, disease duration is often defined in different ways across studies (eg, time of the SSc diagnosis from an SSc expert, the time from the onset of the first non-Raynaud's symptom of SSc).
[b]The MCID for improvement in FVC% based on SLS I and II data were 3.0% to 5.3% at the cohort level. For an individual patient, however, using 5% as the threshold for improvement is a likely more conservative and reliable approach given the wide variation in FVC measurements.
[c]Initiated for progression of ILD and not for other causes, such as progression of PH.
FVC, forced vital capacity; HRCT, high-resolution computed tomography; MCID, minimal clinically important difference; PH, pulmonary hypertension; SLS, Scleroderma Lung Study.
Volkmann ER. *J Scleroderma Relat Disord.* 2020;5(2 suppl):31-40.

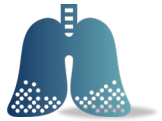
Rapid SSc-ILD Progression Is Associated With Various Clinical, Biological, and Radiographical Features

Demographic characteristics[1,2]

- Male sex
- African American/ Native American race
- Increased age
- Active smoker

Disease-related features[1]

- Diffuse cutaneous disease, high mRSS at the time of ILD diagnosis
- Shorter disease duration



Pulmonary function tests[1]

- Moderate to severe restrictive physiology at the time of ILD diagnosis
- Decline in FVC and DL_{co} over 1-2 years

HRCT extent[1]

- Increased extent of reticulations at the time of ILD diagnosis

Serological profiles[1]

- Anti-Scl-70 antibody

Each of these factors can independently predict the progression of ILD in SSc, and the risk of progression can increase as the number of factors increases.

DL_{co}, diffusing capacity of carbon monoxide; mRSS, modified Rodnan skin score.

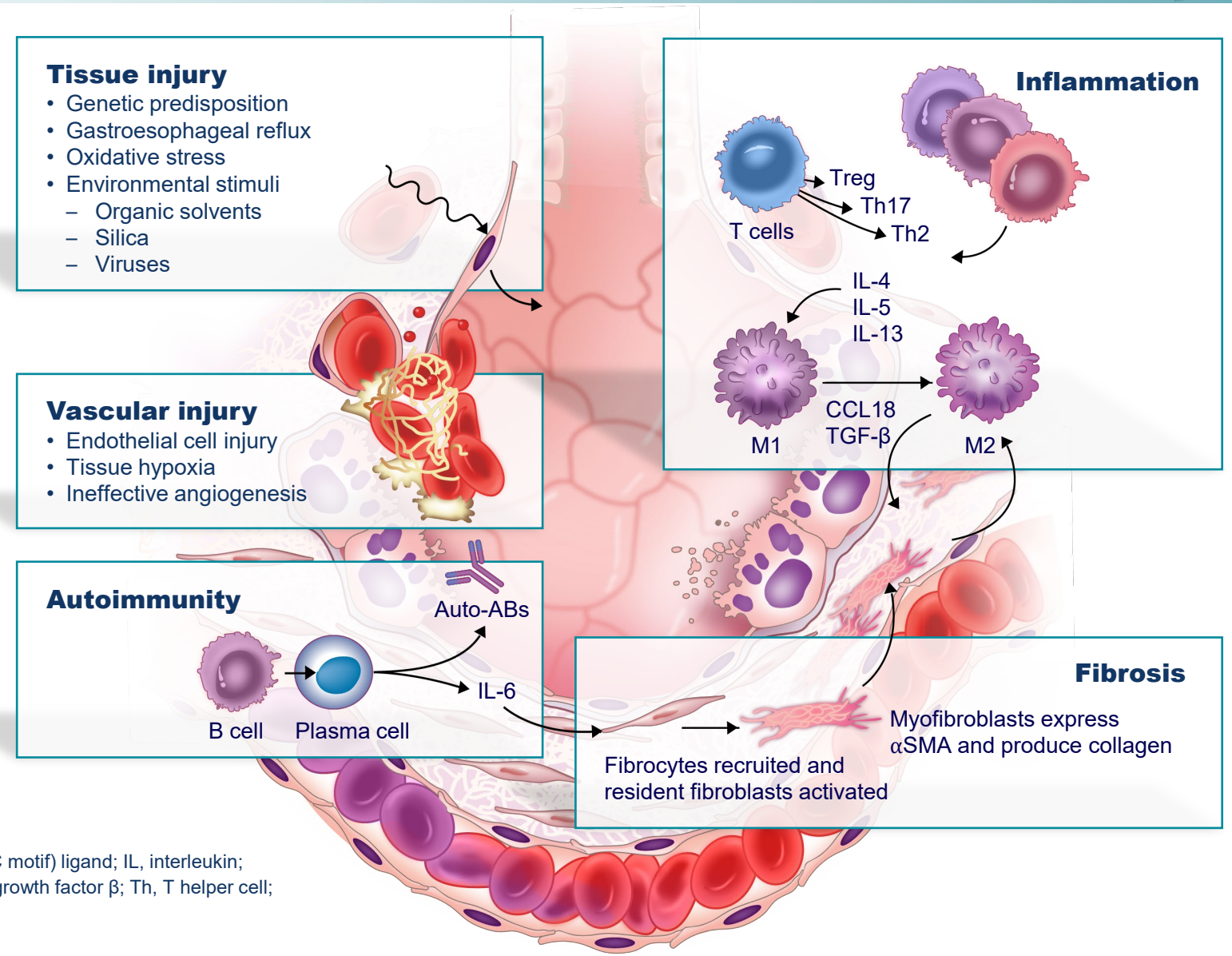
1. Volkmann ER. *J Scleroderma Relat Disord.* 2020;5(2 suppl):31-40. 2. Hoffmann-Vold A et al. *Lancet Rheumatol*. 2020;2:e71-e83.

Pathogenesis of SSc-ILD

SSc-ILD

Clinically heterogeneous disease that involves the interplay between fibrosis, autoimmunity, inflammation, and vascular injury:

- Initially, an injury to the alveolar epithelium or vasculature, or both, is typically followed by immune system activation
- This then paves the way for fibroblast recruitment and activation, which replaces the natural pulmonary architecture with scarring (ie, fibrosis)



ABs, antibodies; αSMA, α-smooth muscle actin; CCL, CCL, chemokine (C-C motif) ligand; IL, interleukin; M1, M1-type macrophage; M2, M2-type macrophage; TGF-β, transforming growth factor β; Th, T helper cell; Treg, regulatory T cells.

Perelas A et al. *Lancet Respir Med.* 2020;8(3):304-320.

3 Phases Characterize the Pathogenesis of SSc-ILD

Early Phase
(Characterized by susceptibility and triggering)

- **Environmental factors likely influence or trigger the disease in a susceptible individual,** as well as mimic other triggers that modulate progression
- **Susceptibility to tissue damage** and a predilection for fibrotic scarring in response to recurrent or persistent lung injury is relevant to ILD
- **Early inflammation** is a key finding in the lungs of patients who are susceptible to developing ILD

Established Phase
(Characterized by progression and failed resolution)

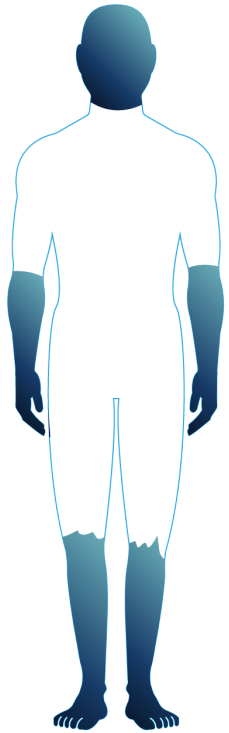
- **Progression from early inflammation** toward a fibrotic phenotype is recognized during this phase
- **The main factors that contribute** to this process include ongoing inflammation and the interplay between the innate and adaptive immune systems; fibroblasts that lead to an increased matrix deposition
- **This phase typically predicts** whether patients will progress to more extensive disease (some cases remain stable)

Late Phase
(Characterized by severe fibrosis in a subset of patients)

- **The extent of disease and damage** associated with disease progression can result in altered lung structure

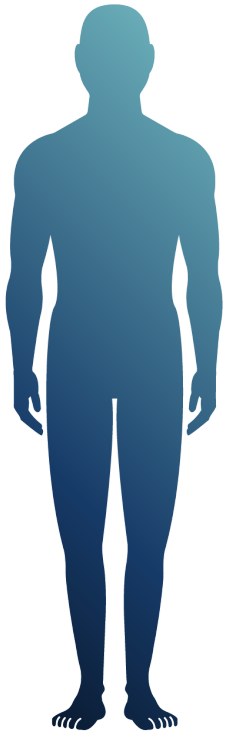
Nihtyanova SI, Denton CP. *J Scleroderma Relat Disord*. 2020;5(2 suppl):6-16.

SSc Is Divided Into 3 Subsets Based on the Extent of Skin Involvement



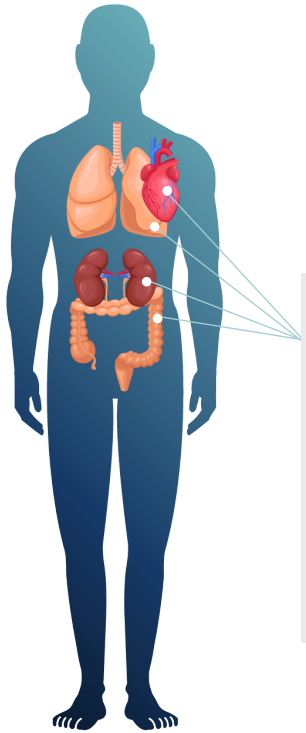
Limited cutaneous scleroderma

Skin changes distal to the elbows and knees but can involve the face and neck



Diffuse cutaneous scleroderma

Skin involvement extends proximally to the elbows and knees



SSc sine scleroderma

Absence of skin thickening

but internal organ involvement and serological abnormalities

ILD can occur in all 3 subsets.

Perelas A et al. *Lancet Respir Med*. 2020;8(3):304-320.

Clinical Presentation of SSc[1,2]

	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 ILD, 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, antitopoisomerase 1, or anti-RNA polymerase)	**3**

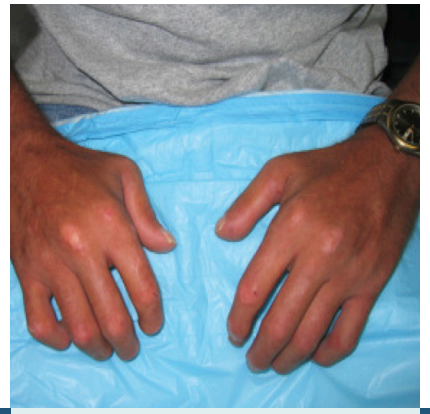
Patients with a **score of ≥9** are classified as having SSc.

- As per the EULAR and ACR criteria, SSc includes **immunological, fibrotic, and vascular features**
- **The point system** is applied by adding the scores for characteristics that are present in the patient
- These criteria yield **high sensitivity** (91%) and **specificity** (92%)

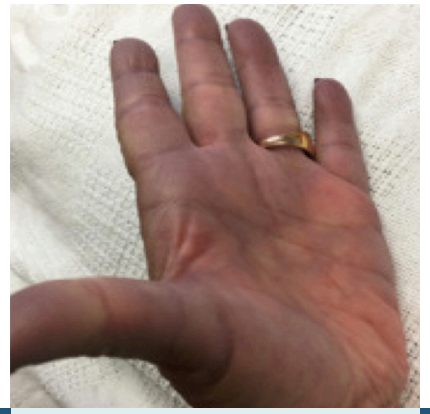
ACR, American College of Rheumatology; EULAR, European League Against Rheumatism.

1. van den Hoogen F et al. *Arthritis Rheum*. 2013;65(11): 2737-2747. 2. Perelas A et al. *Lancet Respir Med*. 2020;8(3):304-320.

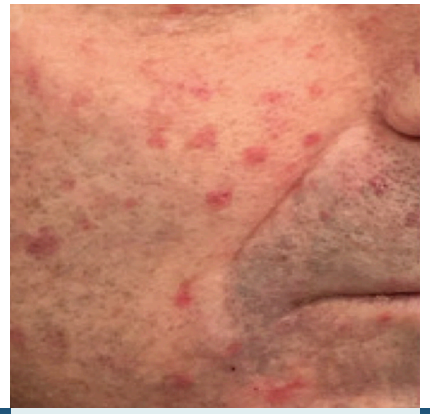
Clinical Presentation of SSc (cont'd)



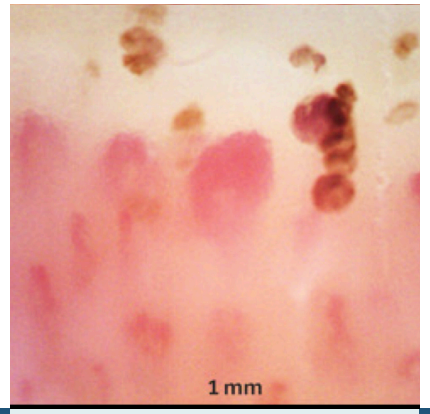
Sclerodactyly: Thickening of the skin on the fingers with associated with flexion contractures



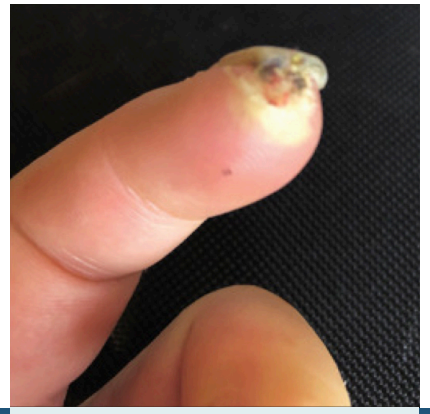
Raynaud's phenomenon: Vasospasm of the fingers, resulting in cyanotic discoloration



Telangiectasias: Dilated blood vessels near the surface of the skin (common on face and palms)



Abnormal nailfold capillaroscopy: Active pattern revealing dilated capillaries as well as areas of dropout



Ulcer on the digits

Perelas A et al. *Lancet Respir Med*. 2020;8(3):304-320.

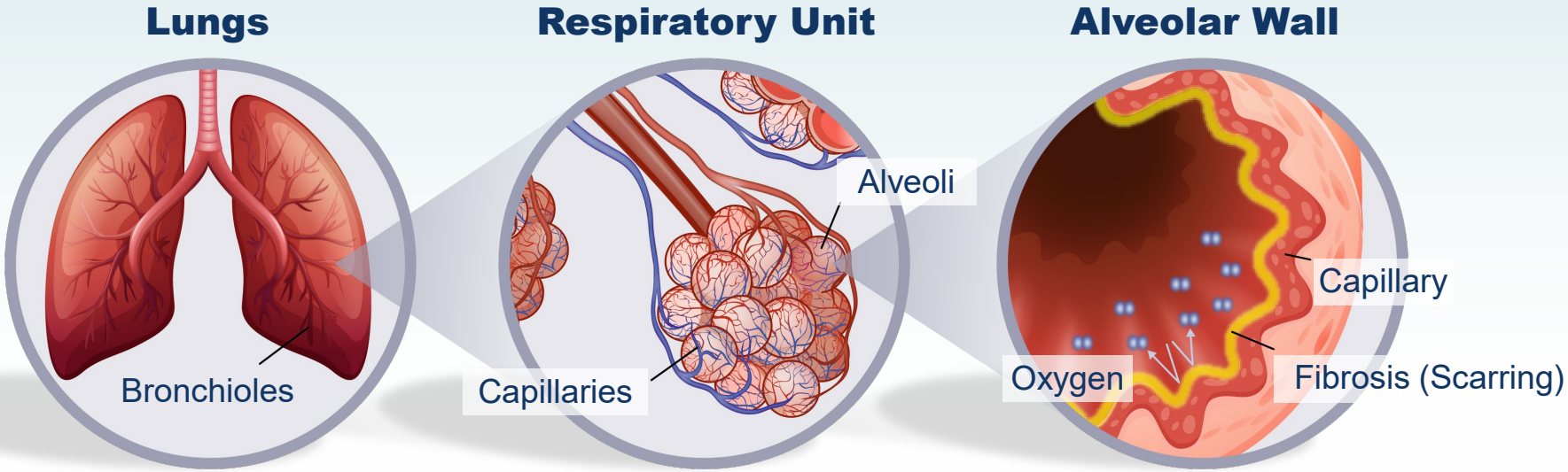
Symptoms of SSc-ILD

Symptoms are often absent or nonspecific for patients with early SSc-ILD, but they may include:

Nonproductive cough
Interstitial changes in the lung usually produce dry cough

Dyspnea on exertion and fatigue, which may worsen with progressive lung scarring

In ILD, lung inflammation and fibrosis thickens the interstitium, restricting the lungs from filling to their normal capacity, thus preventing oxygen from passing freely into the bloodstream



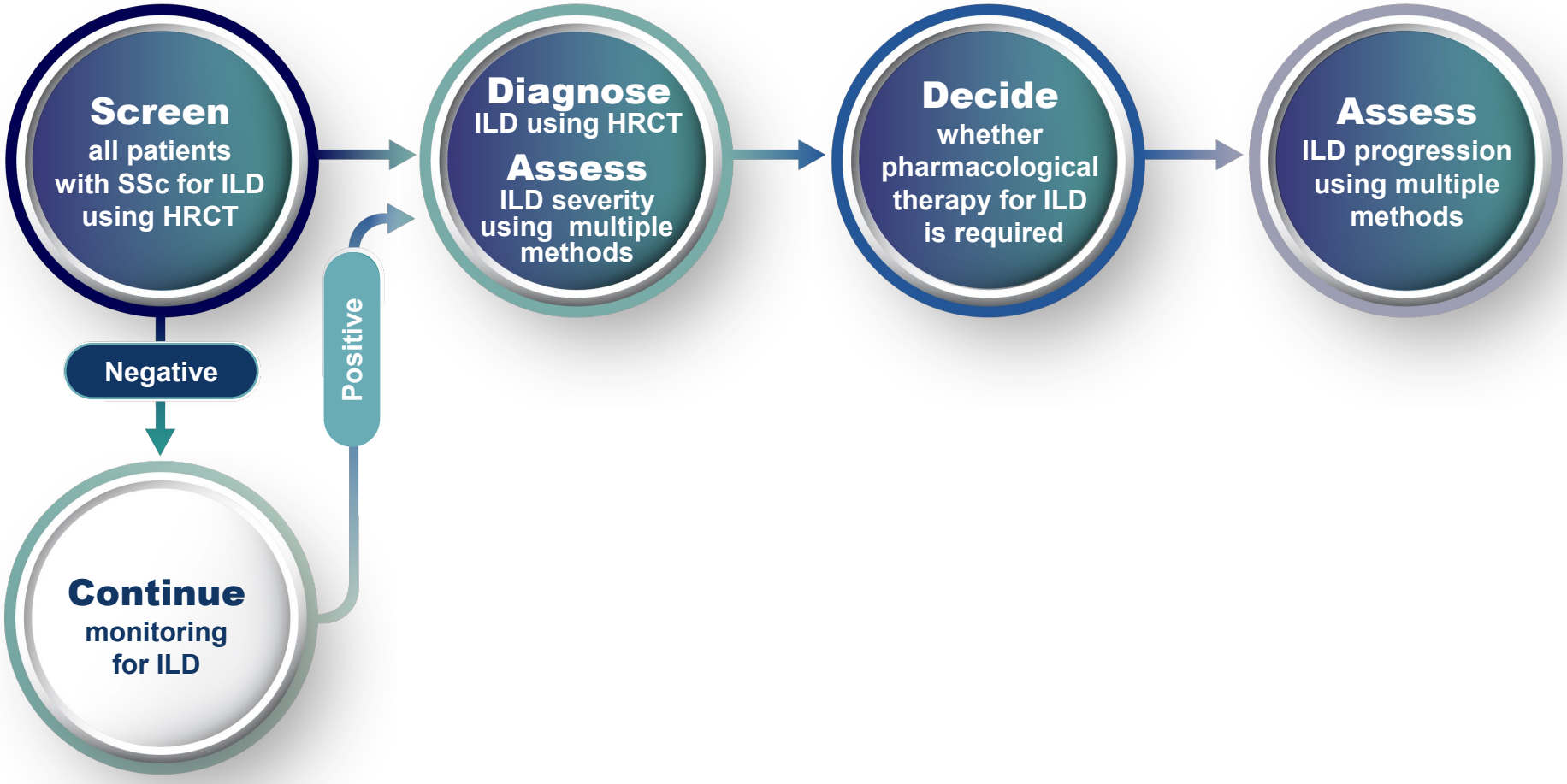
Perelas A et al. *Lancet Respir Med*. 2020;8(3):304-320.

HRCT: Primary Tool for Diagnosing and Assessing Severity of SSc-ILD

All patients with SSc should undergo screening for ILD using HRCT[1]

- More sensitive than conventional chest CT or PFTs and allows detection of mild abnormalities[2]
- Can also predict the development of fibrosis, ILD progression, and decline in pulmonary function[2]
- Frequency of screening and use of HRCT should be guided by risk of ILD, in combination with lung function and symptoms[1]

Algorithm for Identifying and Assessing SSc-ILD[1]



CT, computed tomography; PFT, pulmonary function test.

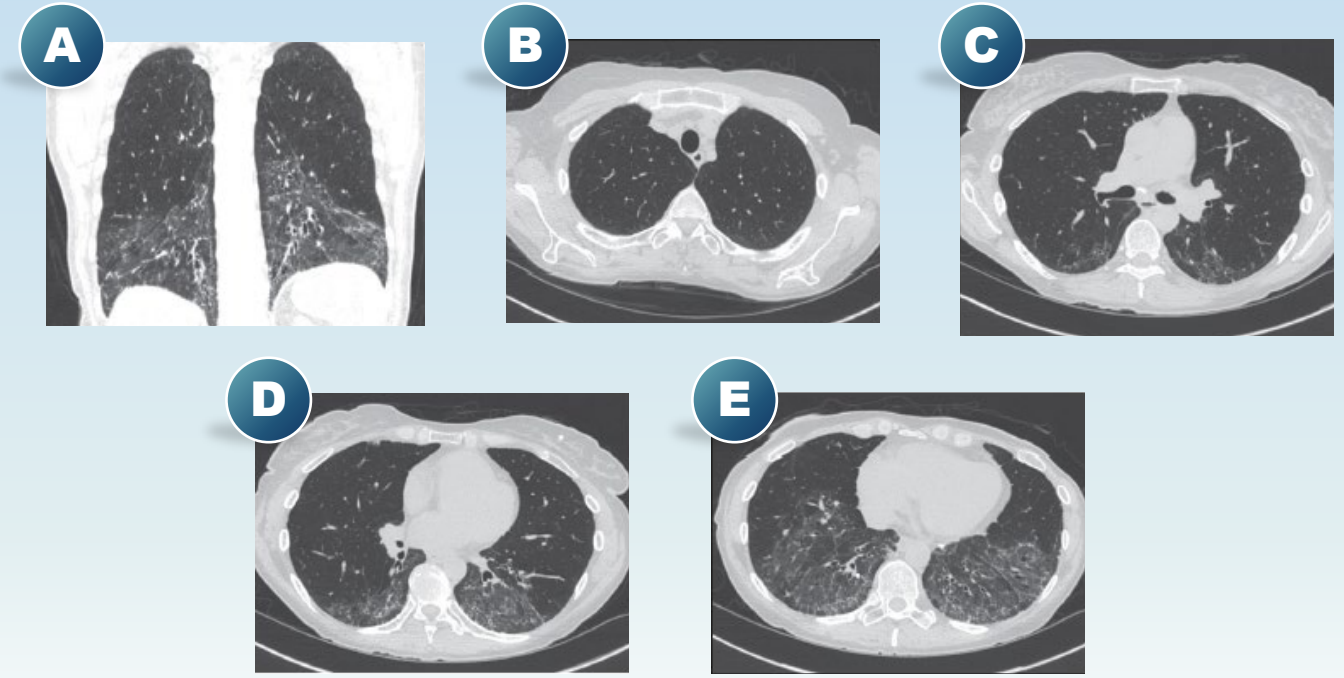
1. Hoffmann-Vold A et al. *Lancet Rheumatol*. 2020;2:e71-e83. 2. Fischer A et al. *Open Access Rheumatol*. 2019;11:283-307.

HRCT Scans Depicting Nonspecific Interstitial Pneumonia

The most common imaging pattern on HRCT is nonspecific interstitial pneumonia (>80% of patients with SSc-ILD)[1,2]

Characterized by:

- Peripheral ground-glass opacities with an apical to basal gradient, frequently accompanied by subpleural sparing
- Fibrotic, nonspecific interstitial pneumonia is characterized by the presence of reticulation, traction bronchiectasis, and bronchiolectasis in a similar distribution
- Lack of honeycombing



HRCT from coronal **(A)** and sagittal **(B–E)** views showing fibrotic, nonspecific interstitial pneumonia with ground-glass opacities, reticulations, and traction bronchiectasis with a peripheral distribution, apicobasal gradient, and subpleural sparing.

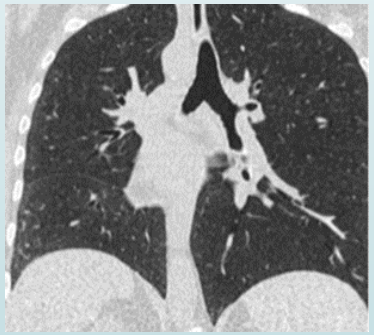
1. Perelas A et al. *Lancet Respir Med*. 2020;8(3):304-320. 2. Khanna D et al. *Am J Respir Crit Care Med*. 2020;201(6):650-660.

HRCT Scans Depicting the Different Extent of Lung Involvement in SSc-ILD

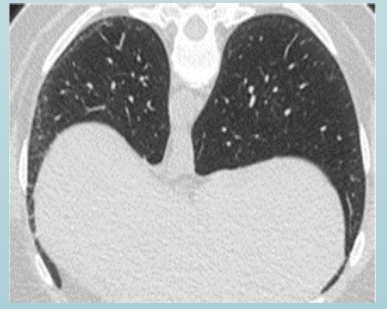
HRCT Can Assess the Extent of SSc-ILD

- The high sensitivity of HRCT can help identify mild interstitial abnormalities associated with SSc-ILD
- This can help prompt heightened surveillance for signs of disease progression

Patient with mild disease

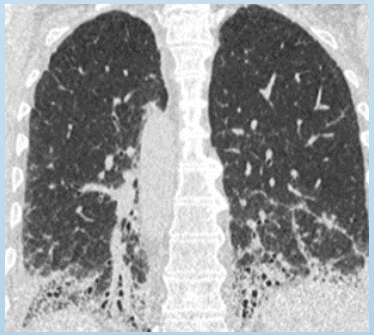


Coronal view

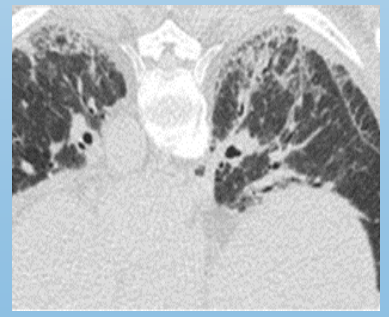


Axial view

Patient with severe disease



Coronal view



Axial view

Fischer A et al. *Open Access Rheumatol*. 2019;11:283-307.

Pulmonary Function Tests (FVC and DL_{co}) Are Supportive Screening and Staging Tools

The PFTs utilized to assess a patient's clinical status are the **FVC** and **DL_{co},** which should provide baseline considerations for clinicians

Although the primary tool for assessing severity in these patients is HRCT, **PFTs are also important in supporting the diagnosis and assessing severity**

Screening with **PFTs** should be **repeated regularly** in all patients with SSc

Hoffmann-Vold A et al. *Lancet Rheumatol*. 2020;2:e71-e83.

Proposed System of Staging the Extent of Fibrosis in SSc-ILD

In cases where the patient's disease extent remains indeterminate on HRCT imaging, FVC is used to classify the disease as limited or extensive disease.[1]

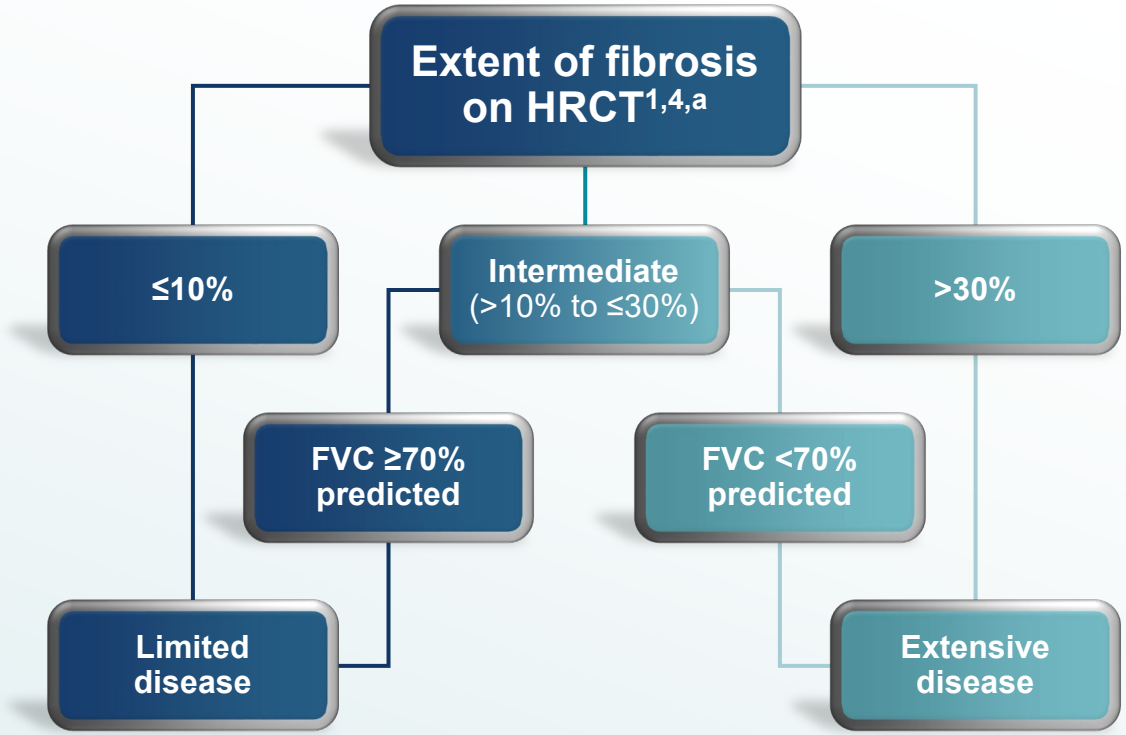
A definite usual interstitial pneumonia pattern–without ground-glass opacities but with honeycombing–is present in **<10%** of patients with SSc-ILD[2]

A reduced FVC is indicative for **ILD development** in SSc[3]

- A decline from baseline of 5% to 10% in FVC and 10% to 15% in DL_{CO} in a patient with SSc-ILD should be further evaluated as a sign of disease progression

The extent of fibrosis seen on the HRCT of the lungs, plus FVC % predicted in patients with **10% to 30% fibrosis on HRCT,** can help to determine whether patients with SSc-ILD have limited or extensive disease[1]

- When combined with FVC, HRCT may predict the patient's risk of mortality



[a]**Note: Proposed system of staging the extent of fibrosis; this has not been endorsed by any regulatory or professional society.**

1. Cottin V, Brown KK. *Respir Res*. 2019;20(1):13. 2. Perelas A et al. *Lancet Respir Med*. 2020;8(3):304-320. 3. Fischer A et al. *Open Access Rheumatol*. 2019;11:283-307. 4. Goh NS et al. *Am J Respir Crit Care Med*. 2008;177(11):1248-1254.

Summary of Tools and Tests Utilized to Diagnose SSc-ILD and Assess Disease Severity

Patients who should be screened and associated methods and frequencies

Symptoms

- Respiratory symptoms such as frequent cough or dyspnea might suggest the presence of ILD in patients with SSc

Tools

- All patients with SSc should be screened for ILD
- Lung function testing (FVC and DL_{co}) should be done in patients with SSc to provide a baseline parameter and should be repeated regularly as screening in all patients with SSc
- Every patient should undergo chest auscultation
- All patients with SSc should be screened at baseline with HRCT
- Frequency of screening and the use of HRCT should be guided by likelihood of developing ILD combined with symptoms and lung function

Diagnostic tools to identify the presence of ILD in SSc

- The primary tool to diagnose ILD in patients with SSc is HRCT
- FVC and DL_{co} are supporting tools for diagnosing and assessing degree of ILD in patients with SSc
- Assessment of clinical symptoms is a supporting tool for diagnosing ILD in patients with SSc
- Assessment for supplemental oxygen need

Tools to diagnose the severity of disease

Diagnostic tools for severity – Use more than 1 tool

- HRCT pattern and extent
- Lung function
  - Percentage predicted FVC value
  - Disease severity can be assessed using FVC value change from baseline
  - Percentage predicted DL_{co} value

Symptoms to consider severity

- Dyspnea (6-min walk test)
- QoL
- Cough

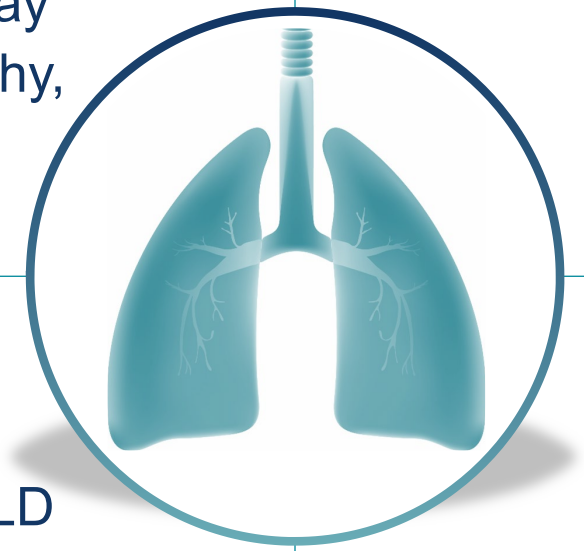
Note: Proposed algorithm for diagnosing the severity of disease; this has not been endorsed by any regulatory or professional science body.

Hoffmann-Vold A et al. *Lancet Rheumatol*. 2020;2:e71-e83.

Summary

SSc-ILD is a clinically heterogeneous disease
characterized by a complex interplay between autoimmunity, vasculopathy, and fibrosis, yielding a significant burden on patients

The clinical presentations of SSc-ILD
are distinct, and should be recognized and monitored appropriately



Various clinical, biological, and radiographic features
can drive the progression of SSc-ILD

HRCT is the primary tool
for diagnosing and assessing degree of disease severity, with nonspecific interstitial pneumonia being the most common imaging pattern on HRCT