Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)
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

Epidemiology of SSc-ILD

Overall annual incidence of SSc among adults in the United States:

\[ \approx 20 \text{ per million} \]

Women are more likely to develop SSc (4:1), with an average age at presentation of 45 to 55 years.

All patients with SSc are at risk for developing ILD

It is estimated that >50% of patients with SSc develop associated ILD.

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

ILD has been found in:

- 53% Diffuse cutaneous SSc
- 35% Limited cutaneous SSc

*Based on the EULAR Scleroderma Trials and Research (EUSTAR) group analysis in a cohort of 3656 SSc patients,
Risk of Mortality With SSc-ILD

ILD is the leading cause of SSc-associated mortality, accounting for ≈35% of SSc-related deaths. The mortality risk in patients with SSc-ILD was found to be ≈3 times greater than in patients with SSc alone.

Burden of SSc

- Sleep disturbance
- Difficulty breathing
- Limitations in mobility and hand function
- Pain
- Emotional distress (eg, depression, low self-esteem)
- Fatigue
- GI problems
- Pruritus

Impaired ability to work
Reduced QoL
Disruptions in patients’ social lives

GI, gastrointestinal; QoL, quality of life.
# Distinct ILD Clinical Phenotypes Exist in SSc

<table>
<thead>
<tr>
<th></th>
<th>Rapid progressor</th>
<th>Gradual progressor</th>
<th>Stabilizer</th>
<th>Improver</th>
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<tbody>
<tr>
<td><strong>FVC</strong></td>
<td>Relative decline ≥10%, or decline 5%-9% in association with ≥15% decline in DLO₂ within 1-2 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Relative decline ≥10%, or decline 5%-9% in association with ≥15% decline in DLO₂ within &gt;2 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Relative FVC decline &lt;5%, or FVC increase &lt;5%</td>
<td>Relative FVC improvement &gt;5%&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td><strong>HRCT</strong></td>
<td>Increased extent of reticulations within 1-2 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Increased extent of reticulations over &gt;2 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No change in the extent of reticulations</td>
<td>Decreased extent of reticulations</td>
</tr>
<tr>
<td><strong>Supplemental oxygen</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Initiation within 1-2 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Initiation &gt;2 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No need for supplemental oxygen or no increase in dose from the time of diagnosis</td>
<td>No need for supplemental oxygen or decreased dose from the time of diagnosis</td>
</tr>
<tr>
<td><strong>Lung transplantation or death</strong></td>
<td>Within 5 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;5 years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No need for lung transplantation</td>
<td>No need for lung transplantation</td>
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<sup>a</sup>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).

<sup>b</sup>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.

<sup>c</sup>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.

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

<table>
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<tr>
<th>Demographic characteristics&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Disease-related features&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Pulmonary function tests&lt;sup&gt;1&lt;/sup&gt;</th>
<th>HRCT extent&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Serological profiles&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>• Male sex</td>
<td>• Diffuse cutaneous disease, high mRSS at the time of ILD diagnosis</td>
<td>• Moderate to severe restrictive physiology at the time of ILD diagnosis</td>
<td>• Increased extent of reticulations at the time of ILD diagnosis</td>
<td>• Anti-Scl-70 antibody</td>
</tr>
<tr>
<td>• African American/Native American race</td>
<td>• Increased age</td>
<td>• Shorter disease duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Active smoker</td>
<td>• Diffuse cutaneous disease, high mRSS at the time of ILD diagnosis</td>
<td>• Decline in FVC and DL&lt;sub&gt;co&lt;/sub&gt; over 1-2 years</td>
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</table>

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.

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DL<sub>co</sub>, diffusing capacity of carbon monoxide; mRSS, modified Rodnan skin score.

Pathogenesis of 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)

**Tissue injury**
- Genetic predisposition
- Gastroesophageal reflux
- Oxidative stress
- Environmental stimuli
  - Organic solvents
  - Silica
  - Viruses

**Vascular injury**
- Endothelial cell injury
- Tissue hypoxia
- Ineffective angiogenesis

**Autoimmunity**
- B cell
- Plasma cell
- Auto-ABs
- IL-6

**Inflammation**
- T cells
- Treg
- Th17
- Th2
- IL-4
- IL-5
- IL-13
- CCL18
- TGF-β

**Fibrosis**
- Myofibroblasts express αSMA and produce collagen
- Fibrocytes recruited and resident fibroblasts activated

**SSc-ILD**

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.

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
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.

Clinical Presentation of SSc\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
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<tbody>
<tr>
<td>Skin thickening of the fingers of both hands extending proximally to the metacarpophalangeal joints</td>
<td>9</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal nailfold capillaries</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension or ILD, or both</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>3</td>
</tr>
<tr>
<td>Skin thickening of the fingers (only count highest score)</td>
<td></td>
</tr>
<tr>
<td>Puffy fingers</td>
<td>2</td>
</tr>
<tr>
<td>Sclerodactyly of the fingers</td>
<td>4</td>
</tr>
<tr>
<td>Fingertip lesions (only count highest score)</td>
<td></td>
</tr>
<tr>
<td>Digital tip ulcers</td>
<td>2</td>
</tr>
<tr>
<td>Fingertip pitting scars</td>
<td>3</td>
</tr>
<tr>
<td>Scleroderma-related autoantibodies (eg, anticientromere, antitopoisoerase 1, or anti-RNA polymerase)</td>
<td>3</td>
</tr>
</tbody>
</table>

Patients with a score of \( \geq 9 \) are classified as having SSc.

- As per the EULAR and ACR criteria, SSc includes \textbf{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 \textbf{high sensitivity} (91%) and \textbf{specificity} (92%).

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

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.

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

All patients with SSc should undergo screening for ILD using HRCT

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

Algorithm for Identifying and Assessing SSc-ILD

Screen all patients with SSc for ILD using HRCT

Diagnose ILD using HRCT

Assess ILD severity using multiple methods

Decide whether pharmacological therapy for ILD is required

Assess ILD progression using multiple methods

Continue monitoring for ILD

Positive

Negative

CT, computed tomography; PFT, pulmonary function test.
HRCT Scans Depicting Nonspecific Interstitial Pneumonia

The most common imaging pattern on HRCT is nonspecific interstitial pneumonia (>80% of patients with SSc-ILD)\textsuperscript{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.

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

Pulmonary Function Tests (FVC and DL\textsubscript{co}) Are Supportive Screening and Staging Tools

The PFTs utilized to assess a patient’s clinical status are the FVC and DL\textsubscript{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.
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-ILD²

A reduced FVC is indicative for ILD development in SSc³
  • A decline from baseline of 5% to 10% in FVC and 10% to 15% in DLco 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 disease¹
  • When combined with FVC, HRCT may predict the patient’s risk of mortality

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

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 DLco) 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 DLco 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 DLco 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.

Summary

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

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

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

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.