



## Early View

Review

# Assessment of recent evidence for the management of patients with SSc-ILD: A systematic review

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**Assessment of recent evidence for the management of patients with SSc-  
ILD: A systematic review**

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### **Take home message**

This systematic literature review on systemic sclerosis-associated interstitial lung disease summarises the evidence supporting approaches to disease management in clinical practice.

## **Abstract**

This systematic review summarises current evidence to help guide treatment decisions for patients with systemic sclerosis (SSc) associated interstitial lung disease (ILD). A systematic search of the literature (January 2012–April 2018), including grey literature (searched between 1992 and 2011), was conducted using multiple electronic databases. Guidelines, meta-analyses, randomised controlled trials and observational studies reporting on risk stratification, screening, diagnosis, treatment, and management outcomes for patients with SSc-ILD were included. A quality assessment of the included evidence was undertaken.

In total, 2464 publications were identified and 280 included. Multiple independent risk factors for ILD in patients with SSc were identified, including older age, male gender and baseline pulmonary function. High-resolution computed tomography (HRCT) has been used for characterising ILD in patients with SSc, and pulmonary function tests are a key adjunctive component in the diagnostic and monitoring pathway. The clinical value of biomarkers relating to SSc-ILD diagnosis or assessment for disease progression is unknown at present. Immunosuppressive therapy (monotherapy or combined therapy) is the current standard of care for SSc-ILD; long-term evidence for effective and safe treatment of SSc-ILD is limited. Identification of patients at risk for SSc-ILD remains challenging. HRCT and pulmonary function tests are key to diagnosing and monitoring for disease progression. Although immunosuppressive therapy is considered current first-line treatment, it is partly associated with adverse effects and long-term follow-up evidence is limited. Novel therapies and biomarkers should be further explored in well-controlled clinical studies.

**Keywords:** Autoimmune Disease, Interstitial Lung Disease, Pulmonary fibrosis

## **Introduction**

Systemic sclerosis (SSc) is a rare, heterogeneous autoimmune disease characterised by immune-mediated inflammatory processes, vasculopathy and fibrosis, which is clinically manifested by multi-organ involvement [1, 2]. Although the aetiology of SSc is unknown, evidence suggests links between genetic predisposition and environmental factors [3]. Interstitial lung disease (ILD) is a frequent organ manifestation and is a leading cause of morbidity and mortality in patients with SSc [1, 4]. As such, early identification of patients who are at risk of organ disease as well as the subsequent monitoring of these patients are of importance in improving clinical outcomes [5, 6].

The early identification of SSc-ILD is challenging, as symptoms are usually subclinical. Consequently, SSc-ILD is frequently diagnosed during advanced stages of disease. There is a paucity of evidence-based guidelines for the screening and early diagnosis of SSc-ILD, as well as limited scientific information that may be used to guide treatment decisions [7]. Long-term, effective treatment options for SSc-ILD are scarce and current treatment approaches focus on targeting inflammatory pathways with immunosuppressive therapy [8, 9]. In daily clinical practice, treatment initiation is often based on the presence of factors that are related to either expected ongoing lung disease progression or to baseline disease severity.

The objective of this systematic review is to summarise the available scientific literature to help guide decisions for screening, management and monitoring disease progression for patients diagnosed with SSc-ILD. These results formed

the basis for the development of evidence-based consensus statements on the identification and management of SSc-ILD [10].

## **Methods**

### ***Search strategy***

The search strategy methods can be found in the Supplementary Methods.

### ***Outcomes***

Data were collected for the following key outcomes: risk factors for SSc-ILD (comorbidities, biomarkers, polymorphisms); screening (tests for currently undiagnosed disease), diagnosis (tests used to diagnose SSc-ILD) and assessment of disease severity; treatment initiation and options; and disease progression (tests and markers for disease progression).

## **Results**

A total of 2464 citations were retrieved, of which 1894 unique abstracts were identified. Screening of these abstracts led to the inclusion of 708 publications for full-text review, out of which 447 publications were ineligible. In addition, the grey literature search using Google Scholar yielded a total of 360 articles, of which 19 publications were relevant. A total of 280 publications (244 original studies; 36 publications associated with an original study) were considered eligible for inclusion in the review (Figure 1). Most of the evidence is based on observational studies (n=237; 85%); 6 (2.1%) were randomised controlled trials (RCTs).

### ***Quality of the evidence***

The overall risk of bias was low amongst the six included RCTs. Details on the statistical analysis plan and allocation concealment were missing from most of the studies. One open-label RCT was only published as an abstract and not available as a full paper at the time of analysis (Table 1) [11].

The quality of the 235 publications from observational studies was judged to be high for the reporting of primary outcomes (92% of the studies). Ninety-eight percent of these studies included quantitative analyses. There was adequate reporting of treatment exposure in 75% of the studies. However, the quality of publications was judged to be low for reporting and handling of confounding factors and immortal time bias (the period of follow-up time during which the outcome of interest cannot occur), and validation of study primary outcomes, with less than 50% of publications reporting these details. Almost one-third (30%) of the included observational studies were reported as conference abstracts only (Supplementary Table S2).

### **Risk factors**

The evidence was assessed for risk factors that may be associated with the presence, severity and progression of SSc-ILD.

High-quality evidence reported an association between diffuse skin involvement and ILD [12-17]. Moderate-quality evidence suggested that antibody status of anti-centromere (ACA) and anti-topoisomerase I (ATA) are risk factors associated with ILD [13, 14], with ACA being protective for SSc-ILD and ATA increasing the likelihood of the presence of SSc-ILD [13, 18, 19]. Other evidence identified

additional risk factors for the presence of SSc-ILD, including older age, male gender [14, 15] and baseline forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DL<sub>CO</sub>) [20, 21]. High-quality evidence reported that high-resolution computed tomography (HRCT) findings can be used to assess the severity of SSc-ILD at baseline [13, 22, 23]. Baseline C-reactive protein levels correlated with long-term decline in FVC in patients with early SSc [24].

Supplementary Table S3 provides a comprehensive list of other risk factors associated with SSc-ILD.

### **Screening, diagnosis, and assessment of disease severity**

Moderate-quality evidence suggests that pulmonary function tests (including FVC and DL<sub>CO</sub>) in combination with HRCT may be useful in screening for SSc-ILD [20, 25, 26]. No data were reported for the optimal timing for screening.

HRCT was identified as the most common method for diagnosing SSc-ILD (Supplementary Table S3). Moderate-quality evidence identified lung ultrasound as a potential tool to detect the presence of ILD in patients with SSc [27, 28].

Other evidence reported on other tests, including prognostic non-HRCT-based algorithms, serial cardiopulmonary exercise tests, nailfold capillaroscopy, and other less commonly used tests that have been used for detecting ILD in SSc patients (Supplementary Table S3).

In the Scleroderma Lung Study (SLS) 1, the extent of ILD defined by HRCT was a predictor of decline in FVC [29]. Moreover, pulmonary function tests (PFTs)

including FVC and DLco have been used as surrogate measures to assess the presence and severity of SSc-ILD at baseline (moderate-quality evidence) [21, 30]. Moderate-quality evidence found that frequent cough correlated with the presence and severity of SSc-ILD [31].

### **Treatment and options (initiation, escalation, rescue)**

Immunosuppressive drugs (monotherapy and combination) were predominantly used (Supplementary Table S3). No evidence or recommendations were identified for when and how to escalate treatment doses.

There is overall high-quality evidence supporting cyclophosphamide (CYC) [32-34]. The SLS I [33] reported that treatment with CYC improved lung function (FVC% predicted, total lung capacity % predicted) compared with placebo in patients with SSc-ILD at 1 year. Another trial showed a trend for increased efficacy of low-dose prednisolone and intravenous CYC followed by oral azathioprine compared with placebo in an underpowered study [34].

There is also moderate evidence supporting treatment with mycophenolate mofetil (MMF) [35, 36]. The Scleroderma Lung Study II (SLS II) [35] found that treatment with CYC for 1 year or MMF for 2 years both resulted in significant improvements in pre-specified measures of lung function (FVC% predicted), lung imaging, dyspnoea, and skin disease. MMF was more tolerable and less toxic, yet this study failed its primary endpoint of superiority of 2 years' treatment with MMF over 1 year's treatment with CYC, and other RCTs do not exist for MMF. These data support the effectiveness of both treatments for progressive SSc-ILD and the

current preference for MMF because it is more tolerable and associated with fewer adverse effects [35].

Haematopoietic stem cell transplantation should be considered for the treatment of carefully selected patients with rapidly progressing SSc who are at risk of organ failure. Improvements in FVC were seen and sustained at 2-year follow-up [37, 38]; however, the adverse event rate reported in one study was 43% and included two patients (14%) with severe cardiomyopathy, of which one case was fatal (high-quality evidence) [39].

Moderate-quality evidence supports rituximab as a potential therapy in SSc-ILD [30, 40, 41].

Moderate-quality evidence indicates that lung transplantation is a valid treatment for highly selected ILD or pulmonary arterial hypertension patients with SSc [42].

High-quality evidence for the inefficacy of bosentan was identified [43]. References for studies on other therapies can be found in Supplementary Table S3.

Non-pharmacological treatments were not assessed.

### **Disease progression**

PFTs and HRCT were identified as the most common measures to monitor the disease in SSc-ILD patients (Supplementary Table S3).

High-quality evidence identified HRCT as a useful imaging tool to determine the disease pattern in patients with SSc-ILD, correlating with PFTs [20, 26, 44, 45].

High-quality evidence indicates that baseline HRCT can predict survival [46].

High-quality evidence found that disease progression, defined as either FVC decline from baseline  $\geq 10\%$  or FVC decline of 5–9% with a DLco decline of  $\geq 15\%$ , was associated with increased risk of mortality [47]. In a study investigating predictors of mortality in patients in SLS I and II, an FVC decline over 2 years was a superior predictor of mortality compared with baseline FVC [48].

Other evidence identified decline in exercise-induced blood oxygen saturation and arthritis as predictors of ILD progression in patients with SSc who had mild ILD [49].

A correlation between frequent cough and the presence or severity of SSc-ILD has been identified and is recognised as a symptom of disease progression in patients with SSc-ILD [31, 50].

Additional evidence was found for measures associated with disease progression, including exhaled nitric oxide, oesophageal diameter, pulmonary artery/ascending aorta ratio, arthritis and FVC values within the first 3 years following diagnosis (Supplementary Table S3).

### **Circulating biomarkers**

The evidence was assessed for biomarkers that may be diagnostic for the presence or severity of SSc-ILD or prognostic for disease progression. Moderate-quality evidence found that surfactant protein-D serum levels correlated with

markers of ILD severity, lung function and lung fibrosis in patients with SSc-ILD [51-53]. High CC chemokine ligand 18 (CCL18) levels were associated with disease progression and predictive of lower survival rates and deterioration of pulmonary function [54]. However, in a different study, CCL18 levels were only predictive of short-term decline in FVC in patients with early SSc [52]. C-X-C Motif Chemokine Ligand 4 levels were linked to progression of lung fibrosis [55] and Krebs von den Lungen-6 may be a useful biomarker of disease severity in SSc-ILD [56].

A list of other biomarkers identified in the systematic review can be found in Supplementary Table S3.

## **Discussion**

A comprehensive systematic literature review was conducted and provides a broad summary on the SSc-ILD literature landscape regarding screening, diagnosis, management, and disease progression. This review provides the foundation for the evidence-based consensus statements for the identification and management of SSc-ILD [57]. A total of 280 publications (244 original studies; 36 publications associated with an original study) were considered eligible for inclusion in the review. Eighty-five percent of the evidence is based on observational studies.

Screening patients with SSc for lung disease is important for identifying patients with SSc-ILD early. In one study, 30% of patients with SSc-ILD showed progressive disease, defined by PFT decline, which was associated with

decreased survival compared with stable FVC [4]. Progressive ILD is associated with poorer outcomes [4] and therefore regular monitoring of all patients with SSc-ILD is needed to identify those with progression and facilitate treatment decisions [58]. However, of key concern in patients with SSc-ILD are the complex and diverse clinical features that make early identification difficult [59]. The methods with highest-quality evidence identified to screen, diagnose and monitor the disease in SSc-ILD patients were PFTs and HRCT, which are routinely used in clinical practice. HRCT can detect ILD even when PFTs are normal [25], and chest HRCT using limited CT slices can even detect mild SSc-ILD whilst reducing patient exposure to radiation [60]. Several biomarkers, with varying levels of sensitivity and specificity, have also been investigated within clinical studies for the purpose of diagnosis, severity assessment and prediction of progression [18, 19, 51-54, 61-63]. However, the potential application of these biomarkers in the real-world hospital setting is unclear and needs further confirmation with more clinical evidence. The evidence may be indicative of potentially useful markers in the future.

Treatment of SSc-ILD is also challenging because of the clinical complexity and heterogeneity of the disease. Lung function decline has been shown to occur early in the disease course, and early treatment initiation may improve patient outcomes [64]. However, more recent evidence shows that patients may have a slower course of disease progression, demonstrating the importance of monitoring to identify patients at risk of progression [65].

Several different treatment approaches and strategies for SSc-ILD have recently been published [2, 66, 67]. Our SLR showed that immunosuppressive therapies

are the current standard of care in the treatment of SSc-ILD. CYC has been frequently used in the treatment of SSc-ILD, especially as induction therapy. Potential drug toxicity makes it unsuitable for long-term use. IV administration has been shown to be preferable because it is less toxic than oral CYC [68]. MMF is widely suggested as an alternative immunosuppressive therapy for induction and maintenance and has been shown to stabilise lung function, but it actually lacks highest-level evidence, as primary endpoint-positive RCTs are missing. Our findings for CYC concur with recommendations included in the European League Against Rheumatism recommendations for treatment of patients with systemic sclerosis who have lung disease [7]. To date, no randomised placebo-controlled trials investigating rituximab in SSc-ILD have been conducted. Observational and non-controlled studies have shown that rituximab may benefit patients with SSc-ILD by preventing lung function decline and thus be a potential future treatment when further RCTs studies can prove efficacy [40, 41, 69, 70]. Haematopoietic stem cell transplantation is a potential therapy for certain groups of patients with SSc, although adverse events are frequent, including treatment-related mortality [37-39].

Other immunosuppressive treatments are also frequently used in clinical practice, but the evidence base supporting their use is not well described [71]. Thus, the availability of effective treatment options for patients with SSc-ILD remains limited. After our literature search, additional data were published that were used in the development of the evidence-based consensus statements. This included results from the SENSCIS® trial showing that nintedanib is an effective treatment for patients with SSc-ILD [72]. Nintedanib is now approved for the treatment of

patients with SSc-ILD in the US and in Europe [73, 74]. Some important RCTs relating to other therapeutic agents have also been published after the systematic literature review [2]. Data from the Phase II faSScinate and Phase III focuSSced studies investigating tocilizumab as a treatment for early, inflammatory diffuse cutaneous SSc indicate that it has a beneficial effect on ILD disease progression as measured by FVC decline and HRCT, despite the focuSSced study not meeting its primary endpoint (the modified Rodnan skin score) [75-77]. On the basis of these studies, both nintedanib and tocilizumab were considered in the consensus statements [10].

The efficacy of treatments in SSc-ILD have been reviewed in detail elsewhere [2, 66]. Non-pharmacological treatments and management strategies may have a role in supporting patients with SSc-ILD such as supplemental oxygen, pulmonary rehabilitation, physical activity and encouraging smoking cessation [66, 78], but were not evaluated in this systematic review.

This systematic literature review also has some limitations. Full publication of abstracts that were identified could have taken place since the search date in April 2018; this may impact on the current quality assessment of some of the included studies. There are no quality assessments existing that are universally applicable to cover the wide range of prediction, assessment and management covered in this systematic literature review, and thus compromises had to be made. The GRACE Checklist [79] does not have an option for ‘not applicable’ and therefore a lower quality indicator was applied if information was not available, for example from an abstract, which reduced the overall quality of some studies, particularly if they were not published as a full article or if they were not clinical trials. This was

often the case for non-interventional studies. There is also the potential for subjectivity from the Steering Committee in assigning overall quality ratings to the evidence.

A strength of this study was that a comprehensive search of the literature was conducted, using multiple electronic sources and grey literature to identify the current evidence on risk stratification, screening, diagnosis, monitoring, treatment (patterns, pathways, escalation, algorithm), and ongoing management (including criteria for disease progression and biomarkers) outcomes for patients with SSc-ILD. A standardised methodology was used to minimise researcher bias. This review has informed the development of Delphi-based consensus statements for screening, diagnosis, treatment and assessment of disease progression in SSc-ILD, and to develop a management algorithm that will provide a framework for future decision making in SSc-ILD [57].

## **Conclusion**

SSc is a complex disease with diverse manifestations, which makes identification of clinically relevant ILD frequently challenging. Current evidence supports the notion that HRCT is a robust tool to diagnose, determine extent of disease and to identify disease progression of SSc-ILD. More research is required on the optimal quantification method and alternative imaging techniques. Several biomarkers have been investigated, but their relevance in clinical practice needs confirmation. This systematic review has highlighted the lack of high-quality evidence for guidance or recommendations for treatment algorithms and choice of treatments

for patients with SSc-ILD. There is a need for further robust clinical research to evaluate alternative safe and effective treatment options for patients with SSc-ILD.

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**Table 1. Critical appraisal of RCTs using NICE standards\***

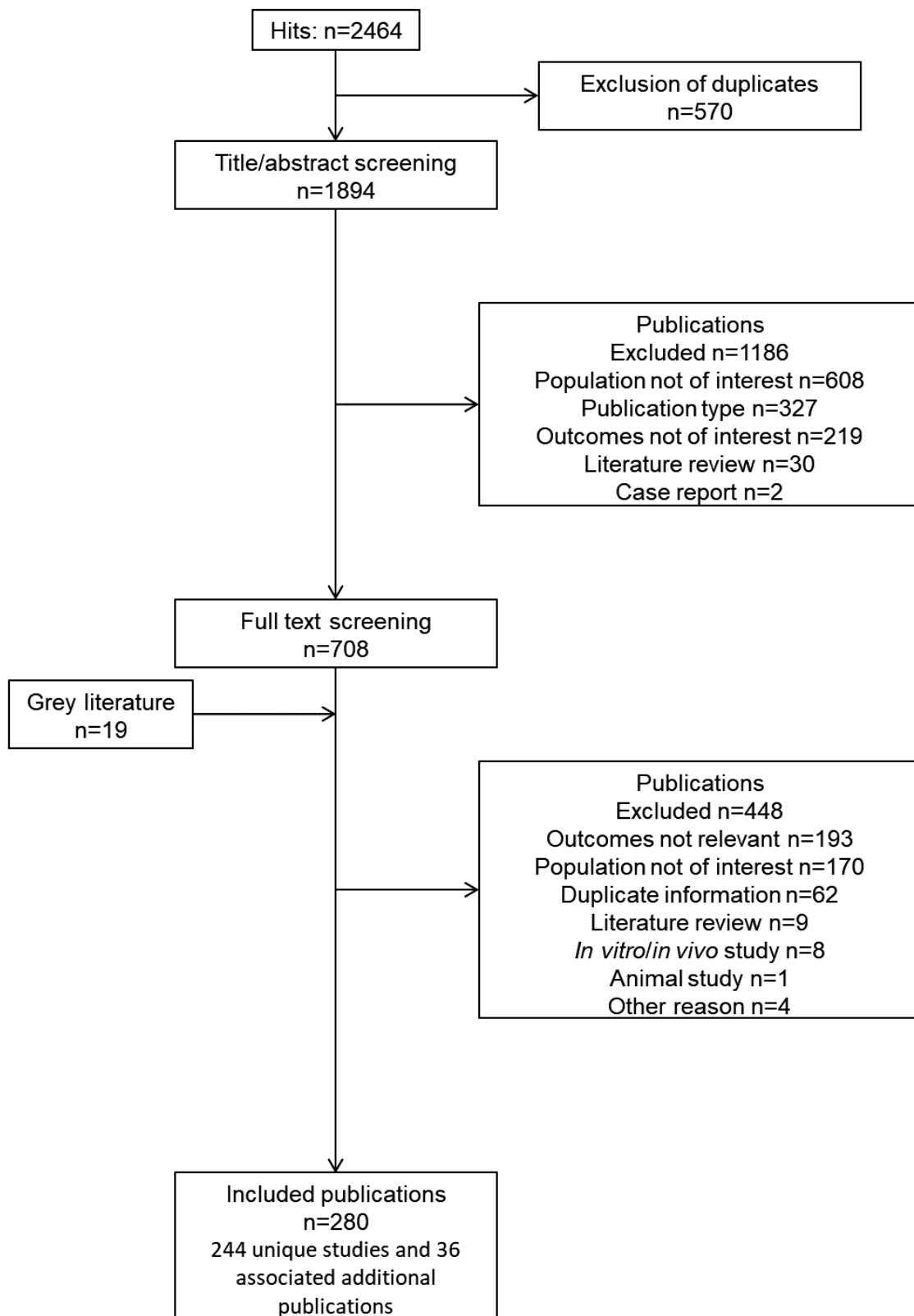
Author	Randomisation	Allocation concealment	Blinding	Follow-up	Selective reporting	Statistical analysis plan
Tashkin 2007 [33]	Yes	Unclear	Yes	No	No	Unclear
Tashkin 2016 [35]	Yes	Unclear	Yes	No	No	Yes
Sircar 2017** [11]	Yes	Unclear	No	Unclear	No	Unclear
Perez Campos 2012 [80]	Yes	Yes	Yes	No	No	Unclear
Seibold 2010 [43]	Unclear	Unclear	Yes	No	No	Unclear

NICE, National Institute for Health and Care Excellence; RCT, randomised controlled trial.

\*Another study was underpowered and therefore not rated at the same evidence level [34]. \*\*Please note that since the date of the literature search, this reference (abstract) has been published in full.

## Figure legend

**Figure 1. Selection process of included publications (PRISMA diagram)**



## SUPPLEMENTARY INFORMATION

**TITLE:** Assessment of recent evidence for the management of patients with SSc-ILD:  
A systematic review

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## **Supplementary Methods**

### ***Eligibility criteria***

Guidelines, consensus statements, meta-analyses, randomised controlled trials (RCTs), observational studies or case series (studies with  $\geq 12$  patients) reporting on risk stratification, screening, diagnosis, monitoring, treatment, ongoing management and outcomes for patients with SSc-ILD were included. Studies reporting on surgery as a comparator, reviews, editorials, letters, commentaries, animal studies, preclinical studies and single case reports were excluded.

### ***Searching the literature***

EMBASE, PubMed, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled trials were searched from January 2012 to April 2018 (Supplementary Table S1 provides details of search strategies).

A grey literature search, including government reports, conference proceedings, theses, and unpublished trials was carried out using Google Scholar (2007–2011; 2002–2006; 1992–2001). The keywords used to identify the relevant articles were ("Systemic Sclerosis" OR Scleroderma) AND ("Interstitial Lung Disease"). The results were captured from the first 20 pages and filtered to retrieve the most frequently cited references for each time period. Searches were limited to the English language.

### ***Study selection***

Titles and abstracts were screened by two independent reviewers; discrepancies were resolved by a third reviewer and the decisions were confirmed by the Steering Committee (AMHV; TMM; OD; AA; EP). Full-text articles were screened by one reviewer and 50% of the results were checked by a second reviewer as per methodology recommended by the National Institute for Health and Care Excellence (NICE) [1], the Centre for Reviews and Dissemination (CRD) [2], and the German Institute for Quality and Efficiency in Healthcare [3].

### ***Quality assessment of individual studies***

The methodological quality of RCTs was assessed using the criteria for NICE and CRD evidence submissions [1, 2]. Appraisal of observational studies was undertaken using the Good Research for Comparative Effectiveness (GRACE) checklist [4] (Supplementary Table S2).

### ***Quality assessment of the overall evidence***

The overall quality of the included evidence was subsequently assessed using a modified approach to Grading of Recommendations Assessment, Development and Evaluation [5] and reported as high to very low quality (Supplementary Table S2). High-quality evidence was defined [5] as where further research is very unlikely to change our confidence in the estimate of effect, as supported by the following evidence: a) several high-quality studies with consistent results or b) in special cases: one large, high-quality multicentre trial. Refer to Supplementary Table S2 for

definitions of moderate-, low- and very-low-quality evidence. The judgements on overall quality were discussed and confirmed by the Steering Committee (AMHV; TMM; OD; AA; EP).

### ***Data extraction and handling***

Data extraction was conducted by one reviewer and quality checking was undertaken on a sample of records by a second reviewer [2]. Discrepancies were resolved by a third reviewer. Data were collated using Excel summary tables and the evidence was summarised narratively.

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Working Group 2007 1 (modified by the EBM Guidelines Editorial Team).

[https://www.essentialevidenceplus.com/product/ebm\\_loe.cfm?show=grade](https://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=grade). Date last

accessed: February 13 2020.

**Table S1- Supplementary Table S1. Search strategies**

- **Search strategy for MEDLINE**

Search #	Search string	# of hits
#1	Search (systemic sclerosis[TIAB] OR systemic scleroses[TIAB] OR SSc [TIAB] OR scleroderma[TIAB] OR "diffuse scleroderma"[TIAB] OR "Diffuse cutaneous systemic sclerosis"[TIAB] OR "Diffuse cutaneous systemic scleroses"[TIAB])	26,701
#2	Search ("Scleroderma, Systemic"[Majr] OR "Scleroderma, Diffuse"[Majr] OR "CREST Syndrome"[Majr])	15,782
#3	Search (#1 OR #2)	27,880
#4	Search ("Lung Diseases, Interstitial"[Majr] OR respirat*[TIAB] OR ILD[TIAB] OR Pneum*[TIAB] OR "interstitial lung disease"[TIAB])	537,320
#5	#3 AND #4	1809
#6	Search (treatment* or therap* or drug* OR pharmacologic* OR prescri* OR medicat* OR pattern* OR regimen* OR sequenc* OR number OR duration OR management OR medicine OR dose escalation OR off label OR "standard of care" OR SoC OR "lines of therapy" OR "line of therapy" OR "first line" OR "second line" OR efficacy OR safety OR algorithm OR diagnos* OR biomarker OR stratif* OR	18,057,256

Search #	Search string	# of hits
	screen* OR monitor* OR “pulmonary function testing” OR PFT OR characteristic* OR progress* OR initiat* OR symptom OR “high resolution computed tomography” OR HRCT OR imaging)	
#7	#5 AND #6	1616
#8	#7 NOT (letter[PT] or comment[PT] or editorial [PT]))	1571
#9	#9 NOT (letter[PT] or comment[PT] or editorial [PT])) Filters: Publication date from 2012 /01/01; Humans; English	496

- **Search strategy for EMBASE**

Search #	Search string	# of hits
#1	Systemic sclerosis:ti,ab OR systemic scleroses:ti,ab OR ssc:ti,ab OR scleroderma:ti,ab OR 'diffuse scleroderma':ti,ab OR 'diffuse cutaneous systemic sclerosis':ti,ab	31,406
#2	'systemic sclerosis'/mj OR 'diffuse scleroderma'/mj OR 'syndrome crest'/mj	18,625
#3	#1 OR #2	36, 655
#4	'interstitial lung disease'/mj OR respirat*:ti,ab OR ild:ti,ab OR 'interstitial lung disease':ti,ab OR pneum*:ti,ab	860,370
#5	#3 AND #4	3373

Search #	Search string	# of hits
#6	treatment* OR therap* OR drug* OR pharmacologic* OR prescri* OR medicat* OR pattern* OR regimen* OR sequenc* OR number OR duration OR management OR medicine OR dose escalation OR off?label OR 'standard of care' OR SoC OR 'lines of therapy' OR 'line of therapy' OR 'first line' OR 'second line' OR efficacy OR safety OR algorithm OR diagnos* OR biomarker OR stratif* OR screen* OR monitor* OR 'pulmonary function testing' OR PFT OR characteristic* OR progress* OR initiat* OR symptom OR 'high resolution computed tomography' OR HRCT OR imaging	25,610,959
#7	#5 AND #6	3244
#8	#7 NOT ([editorial]/lim OR [letter]/lim OR [note]/lim)	3201
#9	#8 AND [2012 -2018 ]/py AND [english]/lim AND [humans]/lim	1828

- **Search strategy for Cochrane Library**

Search #	Search string	# of hits
#1	Systemic sclerosis or systemic scleroses or SSc or scleroderma or "diffuse scleroderma" or "Diffuse cutaneous systemic sclerosis" or "Diffuse cutaneous systemic scleroses"	1199

Search #	Search string	# of hits
#2	MeSH descriptor: [Scleroderma, Systemic] explode all trees	364
#3	#1 OR #2	1199
#4	MeSH descriptor: [Lung Diseases, Interstitial] explode all trees	499
#5	respirat* or ILD or Pneum*	84,463
#6	#4 OR #5	84,635
#7	#3 AND #6	214
#8	treatment* OR therap* OR drug* OR pharmacologic* OR prescri* OR medicat* OR pattern* OR regimen* OR sequenc* OR number OR duration OR management OR medicine OR dose escalation OR off?label OR 'standard of care' OR SoC OR 'lines of therapy' OR 'line of therapy' OR 'first line' OR 'second line' OR efficacy OR safety OR algorithm OR diagnos* OR biomarker OR stratif* OR screen* OR monitor* OR 'pulmonary function testing' OR PFT OR characteristic* OR progress* OR initiat* OR symptom OR 'high resolution computed tomography' OR HRCT OR imaging	1,025,947
#9	#7 AND #8	211
#10	#9 Publication Year from 2012 onwards	140

**Table S2- Supplementary Table S2 Quality assessment**

**Assessment of overall quality of included publications**

Code	Quality of evidence	Definition
A	High	<p>Further research is very unlikely to change our confidence in the estimate of effect, as supported by following evidence:</p> <ul style="list-style-type: none"><li>• Several high-quality studies with consistent results</li><li>• In special cases: one large, high-quality multicentre trial</li></ul>
B	Moderate	<p>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, as supported by following evidence:</p> <ul style="list-style-type: none"><li>• One high-quality study</li><li>• Several studies with some limitations</li></ul>
C	Low	<p>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate, as supported by following evidence:</p> <ul style="list-style-type: none"><li>• One or more studies with severe limitations</li></ul>
D	Very Low	<p>Any estimate of effect is very uncertain, as supported by</p>

Code	Quality of evidence	Definition
		<p>following evidence:</p> <ul style="list-style-type: none"> <li>• Expert opinion</li> <li>• No direct research evidences</li> <li>• One or more studies with very severe limitations</li> </ul>

Modified from GRADE 2007 [1]

GRACE checklist for assessing quality of observational studies

All 11 questions have a Yes/No response.

**Q1:** Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?

**Q2:** Were the primary outcomes adequately recorded for the study purpose (e.g., available in sufficient detail through data source(s))?

**Q3:** Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment (e.g., opinion about whether the patient's condition has improved)?

**Q4:** Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?

**Q5:** Was the primary outcome(s) measured or identified in an equivalent manner between the treatment/ intervention group and the comparison group(s)?

**Q6:** Were important covariates that may be known confounders or effect modifiers available and recorded?

**Q7:** Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?

**Q8:** If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparisons group(s)?

**Q9:** Were important covariates, confounding and effect modifying variables taken into account in the design and/or analysis?

**Q10:** Is the classification of exposed and unexposed person-time free of “immortal time bias”?

**Q11:** Were any meaningful analyses conducted to test key assumptions on which primary results are based?

## GRACE checklist for assessing quality of observational studies

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Abignano 2012 [2]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Adamali 2012 [3]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Adler 2018 [4]	No	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No	Yes
Alder 2014 [5]	No	No	Yes	No							
Alias 2017 [6]	Yes	Yes	Yes	No	No	No	No	No	Yes	No	
Ando 2013 [7]	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No
Aozasa 2012 [8]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Ariani 2014 [9]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Ariani 2015 [10]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Ariani 2015 [11]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Ariani 2017 [12]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes
Ariani 2017 [13]	Yes	No	No	No							
Ashmore 2017 [14]	Yes	Yes	Yes	No	Yes						

Assassi 2013 [15]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Atilla 2016 [16]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Balbir-Gurman 2015 [17]	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No
Baqir 2017 [18]	Yes	Yes	Yes	No	No	No	No	No	Yes	No	
Bavliya 2016 [19]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Benyamine 2018 [20]	Yes	Yes	Yes	No	Yes						
Berezne 2008 [21]	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No
Betteridge 2016 [22]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Betteridge 2016 [22]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Bosello 2017 [23]	No	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Caetano 2016 [24]	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Caetano 2017 [25]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Caramaschi 2007 [26]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Celeste 2013 [27]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Cetintakmak 2016 [28]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No
Cheng 2017 [29]	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes

Chilukuri 2016 [30]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Chinnadurai 2016 [31]	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Chong 2013 [32]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Coiffier 2016 [33]	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No
Daoussis 2012 [34]	Yes	Yes	Yes	No							
Daoussis 2017 [35]	Yes										
De Lauretis 2013 [36]	Yes										
De Luca 2015 [37]	Yes										
De Santis 2012 [38]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	No
Devi 2016 [39]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Dubey 2017 [40]	No	Yes	Yes	No	No	No	Yes	No	No	No	No
Elhaj 2013 [41]	Yes										
Fava 2016 [42]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Fernandez-Codina 2018 [43]	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No
Ferreira 2009 [44]	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No
Fisher 2017 [45]	No	Yes	Yes	No	No	No	Yes	No	No	No	No

Frauenfelder 2014 [46]	No	Yes	No	Yes	No	No	No	No	No	No	Yes
Fretheim 2017 [47]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Fritzler 2018 [48]	Yes	Yes	Yes	No	Yes						
Fujimoto 2012 [49]	No	Yes	Yes	No	No	No	No	Yes	No	Yes	No
Garthwaite 2017 [50]	No	No	Yes	No	No	No	Yes	No	No	No	No
Gerbino 2008 [51]	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No
Gigante 2016 [52]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Gleason 2017 [53]	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No
Goh 2007 [54]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Goh 2008 [55]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Goh 2014 [56]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Goh 2017 [57]	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Goncalves 2016 [58]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes
Gonzalez-Lopez 2015 [59]	Yes	Yes	Yes	No	Yes						
Guarnieri 2015 [60]	Yes	No	Yes	No							
Guillen-Del Castillo 2014 [61]	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No

Guillen-del Castillo 2017 [62]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Guzelant 2016 [63]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No
Hafez 2018 [64]	Yes	No	Yes								
Harding 2012 [65]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No
Hassanien 2017 [66]	No	Yes	Yes	No	No	No	Yes	No	No	No	No
Hax 2017 [67]	Yes	Yes	Yes	No	Yes						
Hesselstrand 2013 [68]	Yes	No	Yes	No							
Hizal 2015 [69]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Hoa 2016 [70]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Hoffmann-Vold 2016 [71]	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Hoffmann-Vold 2016 [71]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Hoffmann-Vold 2016 [72]	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No
Hoffmann-Vold 2016 [73]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Hoffmann-Vold 2017 [74]	Yes	Yes	Yes	No	Yes						
Huang 2015 [75]	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	No
Hudson 2012 [76]	Yes	No	No	No							

Ichimura 2017 [77]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Iudici 2015 [78]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Ji 2016 [79]	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Jiang 2017 [80]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Kafaja 2018 [81]	No	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes
Karagiannis 2014 [82]	Yes	Yes	Yes	No	No	No	Yes	No	No	No	No
Kennedy 2015 [83]	Yes	No	Yes	No							
Khanna 2015 [84]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Kim 2013 [85]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Kim 2015 [86]	No	Yes	Yes	No							
Kokosi 2015 [87]	No	Yes	Yes	No							
Koneva 2015 [88]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Kowal-Bielecka 2017 [89]	Yes	No	Yes								
Kozij 2017 [90]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Kranenburg 2016 [91]	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Kranenburg 2016 [91]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No

Kumar 2013 [92]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Kundu 2016 [93]	Yes	Yes	Yes	No	Yes	No	Yes	No	No	No	No
Kuwana 2016 [94]	Yes										
Kwon 2015 [95]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Kwon 2016 [96]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	No
Le Gouellec 2017 [97]	Yes	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes
Le-Dong 2017 [98]	No	No	Yes	No	Yes	No	Yes	Yes	No	No	No
Lee 2017 [99]	Yes	Yes	Yes	No	Yes						
Lee 2017 [99]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Lepri 2016 [100]	No	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Liaskos 2017 [101]	No	Yes	Yes	No	No	No	Yes	No	No	No	No
Liu 2012 [102]	Yes	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes
Liu 2013 [103]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Liu 2016 [104]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
López Martínez 2014 [105]	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No
Lucchini 2014 [106]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No

Manetti 2012 [107]	Yes	No	Yes	No							
Mango 2017 [108]	No	Yes	No	Yes	No						
Mani 2015 [109]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Manthram 2015 [110]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Marie 2001 [111]	Yes	No	Yes	No							
Markusse 2017 [112]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Martins 2016 [113]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No
Martis 2018 [114]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Masui 2013 [115]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Mathai 2010 [116]	Yes	Yes	Yes	No	Yes						
Melissaropoulos 2016 [117]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Messina 2016 [118]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Michelfelder 2017 [119]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Mittal 2012 [120]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Miura 2014 [121]	No	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Moazedi-Fuerst 2015 [122]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No

Moore 2012 [123]	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Moore 2013 [124]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Moore 2013 [125]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Moore 2015 [126]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Morrisroe 2014 [127]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Müller 2017 [128]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Nakamura 2018 [129]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	
Nakashita 2016 [130]	No	No	Yes	No	Yes						
Nan 2014 [131]	Yes	No	Yes	No							
Ninaber 2015 [132]	No	No	No	Yes	No	Yes	No	No	Yes	No	Yes
Noviani 2017 [133]	No	Yes	No	Yes							
Odani 2012 [134]	No	Yes	Yes	No	No	No	No	Yes	Yes	No	No
Odani 2013 [135]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Okamoto 2016 [136]	Yes	No	Yes	No							
Olewicz-Gawlik 2014 [137]	Yes	No									
Osborn 2017 [138]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes

Owen 2016 [139]	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No
Padiyar 2017 [140]	Yes	Yes	Yes	No							
Patiwetwitoon 2012 [141]	Yes	No	Yes	No							
Pauling 2018 [142]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Peelen 2017 [143]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Peelen 2017 [144]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Pernot 2012 [145]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Pinal-Fernandez 2014 [146]	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No	No
Pinal-Fernandez 2015 [147]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Pinal-Fernandez 2016 [148]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Pontana 2016 [149]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No
Poormoghim 2014 [150]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Raslan 2016 [151]	No	No	Yes	No	No	Yes	Yes	No	No	No	No
Richardson 2014 [152]	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes
Richardson 2016 [153]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Rolla 2016 [154]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No



Shadly 2013 [171]	No	Yes	Yes	No	No	No	No	No	Yes	Yes	No
Sharif 2012 [172]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Sharma 2016 [173]	Yes	Yes	Yes	Yes	No						
Shenoy 2016 [174]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
Shenoy 2017 [175]	Yes	Yes	Yes	No							
Showalter 2018 [176]	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes
Siegert 2016 [177]	No	Yes	Yes	No	Yes	No	No	Yes	No	No	No
Sosnovskaya 2015 [178]	Yes	No	No	No							
Sousa 2016 [179]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
Steele 2012 [180]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Suliman 2013 [181]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes
Takahashi 2013 [182]	Yes	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No
Takei 2016 [183]	No	No	Yes	No	No	No	No	Yes	No	No	No
Takei 2018 [184]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Takekoshi 2015 [185]	Yes	No	Yes	No							
Taniguchi 2013 [186]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	No



Weigold 2018 [202]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Wilsher 2012 [203]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Winklehner 2012 [204]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No
Winstone 2016 [205]	No	Yes	Yes	No	No	No	Yes	No	No	No	No
Winstone 2016 [206]	No	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes
Winstone 2018 [207]	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes
Wodkowsk 2015 [208]	Yes										
Wu 2016 [209]	No	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes
Wu 2017 [210]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Wu 2017 [211]	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Xiao 2018 [212]	No	Yes	No	No	No						
Yamaguchi 2017 [213]	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Yamakawa 2016 [214]	Yes	Yes	Yes	No	Yes						
Yamakawa 2017 [215]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Yamakawa 2018 [216]	Yes	No	Yes	No							
Yanaba 2013 [217]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No

Yanaba 2013 [218]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No
Yap 2016 [219]	No	Yes	Yes	No	No	No	Yes	No	No	No	No
Yilmaz 2012 [220]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Yilmaz 2014 [221]	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	No
Yilmaz 2014 [221]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No
Zamora 2008 [222]	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No
Zamora 2013 [223]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No
Zanatta 2016 [224]	Yes	Yes	Yes	No	Yes						
Zhang 2013 [225]	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Zhang 2016 [226]	No	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No
Zhang 2018 [227]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
Zhao 2016 [228]	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No
<b>Overall reporting</b>	<b>75.3%</b>	<b>91.9%</b>	<b>98.3%</b>	<b>48.9%</b>	<b>60.4%</b>	<b>50.6%</b>	<b>73.6%</b>	<b>58.7%</b>	<b>36.6%</b>	<b>46.4%</b>	<b>36.6%</b>

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228. Zhao J, Wang K, Ye S. Peripheral CD4 + CXCR4 + T cell proportion is a potential diagnostic biomarker for connective tissue disease associated interstitial lung diseases. *Int J Rheum Dis* 2016; **19**: 40.

**Table S3- Supplementary Table S3 Included publications**

**Risk stratification**

<b>Reference</b>	<b>Risk factor</b>
Aozasa N, Asano Y, Akamata K, Noda S, Masui Y, Tamaki Z, Tada Y, Sugaya M, Kadano T, Sato S. Clinical significance of serum levels of secretory leukocyte protease inhibitor in patients with systemic sclerosis. <i>Mod Rheumatol.</i> 2012;22(4):576-83.	Secretory leukocyte protease inhibitor
DOI: <a href="https://doi.org/10.1007/s10165-011-0553-1">10.1007/s10165-011-0553-1</a>	
Ariani A, Silva M, Bravi E, Saracco M, Parisi S, De Gennaro F, Lumetti F, Idolazzi L, Seletti V, Caramaschi P, Benini C, Bodini FC, Scire CA, Lucchini G, Santilli D, Mozzani F, Imberti D, Arrigoni E, Delsante G, Pellerito R, Fusaro E, Sverzellati N. Operator-independent quantitative chest computed tomography versus standard assessment of interstitial lung disease related to systemic sclerosis: A multi-centric study. <i>Mod Rheumatol.</i> 2015;25(5):724-30.	Quantitative computed tomography
DOI: <a href="https://doi.org/10.3109/14397595.2015.1016200">10.3109/14397595.2015.1016200</a>	
Betteridge ZE, Woodhead F, Lu H, Shaddick G, Bunn CC, Denton CP, Abraham DJ, du Bois RM,	Anti-eukaryotic initiation factor 2B autoantibodies

Reference	Risk factor
Lewis M, Wells AU. Brief Report: Anti-Eukaryotic Initiation Factor 2B Autoantibodies Are Associated With Interstitial Lung Disease in Patients With Systemic Sclerosis. <i>Arthritis Rheumatol.</i> 2016;68(11):2778-83. DOI: <a href="https://doi.org/10.1002/art.39755">10.1002/art.39755</a>	
Caramaschi P, Biasi D, Caimmi C, Vaccari R, Dal Forno I, Pieropan S, Adami S. Adherence to recommendations for cervical and breast cancer screening in systemic sclerosis. <i>Reumatismo.</i> 2015;66(4):264-9. DOI: <a href="https://doi.org/10.4081/reumatismo.2014.794">10.4081/reumatismo.2014.794</a>	Nailfold videocapillaroscopic patterns
De Luca G, Bosello SL, Berardi G, Rucco M, Canestrari G, Correra M, Mirone L, Forni F, Di Mario C, Danza FM. Tumour-associated antigens in systemic sclerosis patients with interstitial lung disease: association with lung involvement and cancer risk. <i>Rheumatology (Oxford).</i> 2015;54(11):1991-9. DOI: <a href="https://doi.org/10.1093/rheumatology/kev204">10.1093/rheumatology/kev204</a>	Diffuse skin involvement, long disease duration and TAAs
Devi S, Tripathy R, Sahoo R, Panda A, Das, B. Plasma TGF-b in systemic sclerosis: patients display lower levels and inversely correlate with	TGF-β

<b>Reference</b>	<b>Risk factor</b>
disease severity. Int J Rheum Dis. 2016;19(Suppl 2):225.  DOI: <a href="https://doi.org/10.1111/1756-185X.12962">10.1111/1756-185X.12962</a>	
Fava A, Cimbro R, Wigley FM, Liu Q-R, Rosen A, Boin F. Frequency of circulating topoisomerase-I-specific CD4 T cells predicts presence and progression of interstitial lung disease in scleroderma. Arthritis Res Ther. 2016;18(1):99.  DOI: <a href="https://doi.org/10.1186/s13075-016-0993-2">10.1186/s13075-016-0993-2</a>	Topoisomerase-I specific CD4 T cells
Goh N, Corte TJ, Moore OA, Rouse H, Hennessy O, Thakkar V, Sahhar J, Roddy J, Youssef P, Gabbay E, Nash P, Zochling J, Stevens W, Proudman S, Nikpour M. Serial change in PFTs is predictive of outcome in systemic sclerosis associated interstitial lung disease. Am J Respir Crit Care Med. 2014;189:[Abstract ID – A1464].  DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A1464">10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A1464</a>	Serial change in PFTs
Gonçalves DR, Fonseca R, Aguiar F, Martins-Rocha T, Bernardes M, Costa L. SAT0221 Determinants Associated with Interstitial Pulmonary Involvement in Patients with Systemic Sclerosis-A Cross-Sectional Study. Ann Rheum Dis.	Digital ulcers, ANAs, topoisomerase I (Scl70) and ACAs, increased age, digital ulcers

<b>Reference</b>	<b>Risk factor</b>
2016;75(Suppl 2):748.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.6115">10.1136/annrheumdis-2016-eular.6115</a>	
Hafez EA, Hamza SH, Morad CS, Alkader AA. Pulmonary manifestations in Egyptian patients with systemic sclerosis. The Egyptian Rheumatologist. 2018;40(1):39-44.  DOI: <a href="https://doi.org/10.1016/j.ejr.2017.06.004">10.1016/j.ejr.2017.06.004</a>	Disease duration and mRSS, pulmonary involvement
Hoffmann-Vold AM, Tennøe AH, Garen T, Midtvedt Ø, Abraityte A, Aaløkken TM, Lund MB, Brunborg C, Aukrust P, Ueland T, Molberg Ø. High Level of Chemokine CCL18 Is Associated With Pulmonary Function Deterioration, Lung Fibrosis Progression, and Reduced Survival in Systemic Sclerosis. Chest. 2016;150(2):299-306.  DOI: <a href="https://doi.org/10.1016/j.chest.2016.03.004">10.1016/j.chest.2016.03.004</a>	Chemokine CCL18
Hudson M, Pope J, Mahler M, Tatibouet S, Steele R, Baron M, Fritzler MJ. Clinical significance of antibodies to Ro52/TRIM21 in systemic sclerosis. Arthritis Res Ther. 2012;14(2):R50.  DOI: <a href="https://doi.org/10.1186/ar3763">10.1186/ar3763</a>	Anti-Ro52/TRIM21 antibodies

Reference	Risk factor
<p>Khanna D, Nagaraja V, Tseng C-H, Abtin F, Suh R, Kim G, Wells G, Furst DE, Clements PJ, Roth MD.</p> <p>Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. <i>Arthritis Res Ther.</i> 2015;17(1):372.</p>	HRCT-defined staging systems
<p>Kowal-Bielecka O, Chwiesko-Minarowska S, Bernatowicz PL, Allanore Y, Radstake T, Matucci-Cerinic M, Broen J, Hesselstrand R, Krasowska D, Riemekasten, G. The arachidonate 5-lipoxygenase activating protein gene polymorphism is associated with the risk of scleroderma-related interstitial lung disease: a multicentre European Scleroderma Trials and Research group (EUSTAR) study. <i>Rheumatology (Oxford).</i> 2017;56(5):844-52.</p>	ALOX5AP gene polymorphism
<p>Kuwana M, Shirai Y, Takeuchi T. Elevated Serum Krebs von den Lungen-6 in Early Disease Predicts Subsequent Deterioration of Pulmonary Function in Patients with Systemic Sclerosis and Interstitial</p>	KL-6

<b>Reference</b>	<b>Risk factor</b>
Lung Disease. J Rheumatol. 2016;43(10):1825-31.	
DOI: <a href="https://doi.org/10.3899/jrheum.160339">10.3899/jrheum.160339</a>	
Kwon HM, Song EY, Lee YJ, Park JK, Lee EY, Song YW, Lee EB. Association of Hla Genes in Systemic Sclerosis with Interstitial Lung Disease. Ann Rheum Dis. 2016;75:668.	HLA alleles
DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.4565">10.1136/annrheumdis-2016-eular.4565</a>	
Manetti M, Guiducci S, Romano E, Bellando-Randone S, Conforti ML, Ibba-Manneschi L, Mtucci-Cerinic M. Increased serum levels and tissue expression of matrix metalloproteinase-12 in patients with systemic sclerosis: correlation with severity of skin and pulmonary fibrosis and vascular damage. Ann Rheum Dis. 2012;71(6):1064-72.	Matrix metalloproteinase-12
DOI: <a href="https://doi.org/10.1136/annrheumdis-2011-200837">10.1136/annrheumdis-2011-200837</a>	
Markusse IM, Meijs J, de Boer B, Bakker J, Schippers HPC, Schouffoer AA, Ajmone Marsan N, Kroft LJM, Ninaber MK, Huizinga TWJ, de Vries-Bouwstra JK. Predicting cardiopulmonary involvement in patients with systemic sclerosis: complementary value of nailfold	Nailfold videocapillaroscopy patterns

<b>Reference</b>	<b>Risk factor</b>
videocapillaroscopy patterns and disease-specific autoantibodies. <i>Rheumatology</i> (Oxford). 2017;56(7):1081-8.	
DOI: <a href="https://doi.org/10.1093/rheumatology/kew402">10.1093/rheumatology/kew402</a>	
Martins Rocha T, Fonseca R, Rosa-Gonçalves D, Aguiar F, Meirinhos T, Bernardes M, Bernado A, Costa L. Anti-Ssa/ro Antibodies in A Cohort of Systemic Sclerosis Patients: The Association with Interstitial Lung Disease. <i>Ann Rheum Dis.</i> 2016;75:1125.	Anti-SSA/Ro
DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.2573">10.1136/annrheumdis-2016-eular.2573</a>	
Moore OA, Goh N, Corte T, Rouse H, Hennessy O, Thakkar V, Byron J, Sahhar J, Roddy J, Gabbay E, Youssef P, Nash P, Zochling J, Proudman SM, Stevens W, Nikpour M. Extent of disease on high-resolution computed tomography lung is a predictor of decline and mortality in systemic sclerosis-related interstitial lung disease. <i>Rheumatology</i> (Oxford). 2013;52(1):155-60.	Extent of disease on HRCT
DOI: <a href="https://doi.org/10.1093/rheumatology/kes289">10.1093/rheumatology/kes289</a>	
Moore OA, Proudman SM, Goh N, Corte TJ, Rouse H, Hennessy O, Morrisroe K, Thakkar V, Sahhar J, Roddy J, Youssef P, Gabbay E, Nash P, Zochling	Change in PFT

Reference	Risk factor
J, Stevens W, Nikpour M. Quantifying change in pulmonary function as a prognostic marker in systemic sclerosis-related interstitial lung disease. Clin Exp Rheumatol. 2015;33(4 Suppl 91):S111-6.	
Morrisroe KB, Stevens W, Nandurkar H, Prior D, Thakkar V, Roddy J, Zochling J, Sahhar J, Tymms K, Sturgess A, Major G, Kermeen F, Hill C, Walker J, Nash P, Gabbay E, Youssef P, Proudman SM, Nikpour M. The association of antiphospholipid antibodies with cardiopulmonary manifestations of systemic sclerosis. Clin Exp Rheumatol. 2014;32(6 Suppl 86):S-133-7.	Antiphospholipid antibodies
Odani T, Yasuda S, Ota Y, Fujieda Y, Kon Y, Horita T, Kawaguchi Y, Atsumi T, Yamanaka H, Koike T. Up-regulated expression of HLA-DRB5 transcripts and high frequency of the HLA-DRB5*01:05 allele in scleroderma patients with interstitial lung disease. Rheumatology (Oxford). 2012;51(10):1765-74.	HLA-DRB5 and HLA-DRB5*01:05 allele
DOI: <a href="https://doi.org/10.1093/rheumatology/kes149">10.1093/rheumatology/kes149</a>	

<b>Reference</b>	<b>Risk factor</b>
Okamoto M, Fujimoto K, Sadohara J, Furuya K, Kaieda S, Miyamura T, Suematsu E, Kitasato Y, Kawayama T, Ida H, Ichiki M, Hoshino T. A retrospective cohort study of outcome in systemic sclerosis-associated interstitial lung disease. <i>Respir Investig.</i> 2016;54(6):445-53. DOI: <a href="https://doi.org/10.1016/j.resinv.2016.05.004">10.1016/j.resinv.2016.05.004</a>	HRCT pattern and acute exacerbation
Richardson C, Agrawal R, Lee J, Almagor O, Varga J, Chang RW, Hinchcliff ME. A Dilated Esophagus Is an Independent Risk Factor for Interstitial Lung Disease in SSc. <i>Arthritis Rheumatol.</i> 2014;66:S319. DOI: <a href="https://doi.org/10.1002/art.38914">10.1002/art.38914</a>	Oesophageal diameter
Ryerson CJ, O'Connor D, Dunne JV, Schooley F, Hague CJ, Murphy D, Leipsic J, Wilcox PG. Predicting Mortality in Systemic Sclerosis-Associated Interstitial Lung Disease Using Risk Prediction Models Derived From Idiopathic Pulmonary Fibrosis. <i>Chest.</i> 2015;148(5):1268-75. DOI: <a href="https://doi.org/10.1378/chest.15-0003">10.1378/chest.15-0003</a>	Risk prediction models – the Composite Physiologic Index, the Interstitial Lung Disease-Gender, Age, Physiology Index, the du Bois index, and the modified du Bois index
Salazar GA, Kuwana M, Wu M, Estrada-Y-Martin RM, Ying J, Charles J, Mayes MD, Assassi S. KL-6	KL-6

Reference	Risk factor
But Not CCL-18 Is a Predictor of Early Progression in Systemic Sclerosis-related Interstitial Lung Disease. <i>J Rheumatol.</i> 2018;45(8):1153-8. DOI: <a href="https://doi.org/10.3899/jrheum.170518">10.3899/jrheum.170518</a>	
Sanchez-Cano D, Ortego Centeno N, Cruces Moreno MT, Sáez Comet L, Freire M, Parra Todlí JA, Rodríguez Caballeira M, Simeón Aznar C. AB0624 Interstitial lung disease in scleroderma: severity associated factors. <i>Objectives. Ann Rheum Dis.</i> 2017;76:1270. DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.2545">10.1136/annrheumdis-2017-eular.2545</a>	Pulmonary function and autoantibody testing
Sánchez-Cano D, Ortego-Centeno N, Callejas J, Plá, V F, Ríos-Fernández R, Tolosa-Vilella C, Espinosa-Garriga G, Colunga-Argüelles D, Egurbide-Arberas MV, Rubio-Rivas M. Interstitial lung disease in systemic sclerosis: data from the spanish scleroderma study group. <i>Rheumatol Int.</i> 2018;38(3):363-74. DOI: <a href="https://doi.org/10.1007/s00296-017-3916-x">10.1007/s00296-017-3916-x</a>	ATA positivity, an active nailfold capillaroscopy pattern, age at symptoms onset, and time lapse between symptoms onset and ILD diagnosis
Sawicka K, Michalska-Jakubus M, Kowal M, Potembska E, Krasowska D. Resistin: a possible biomarker of organ involvement in systemic sclerosis patients? <i>Clin Exp Rheumatol.</i>	Resistin

<b>Reference</b>	<b>Risk factor</b>
2017;35(4):144-50.	
Sharif R, Mayes MD, Tan FK, Gorlova OY, Hummers LK, Shah AA, Furst DE, Khanna D, Martin J, Bossini-Castillo L. IRF5 polymorphism predicts prognosis in patients with systemic sclerosis. Ann Rheum Dis 2012;71(7):1197-202.	IRF5 rs4728142
DOI: <a href="https://doi.org/10.1136/annrheumdis-2011-200901">10.1136/annrheumdis-2011-200901</a>	
Suliman YA, Huscher D, Nguyen-Kim TDL, Maurer B, Jordan S, Treder U, Speich R, Frauenfelder T, Distler O. High rate of false negatives in the early detection of interstitial lung disease associated with systemic sclerosis by pulmonary function tests. Ann Rheum Dis. 2013;72(Suppl 3):A500-1.	Stomach symptoms, pulmonary artery pressure on echocardiography and ACA
DOI: <a href="https://doi.org/10.1136/annrheumdis-2013-eular.1504">10.1136/annrheumdis-2013-eular.1504</a>	
Tashkin D, Volkmann E, Khanna D, Roth M, Theodore A, Wang B, Tseng C-H, Elashoff R. Frequent Cough in Scleroderma-Related Interstitial Lung Disease (SSc-ILD): Characteristics and Response to Potentially Disease-Modifying Therapy in a Randomized Controlled Trial (RCT) (Scleroderma Lung Study II). Chest.	Frequent cough
2016;150(4):473A.	

Reference	Risk factor
DOI: <a href="https://doi.org/10.1016/j.chest.2016.08.487">10.1016/j.chest.2016.08.487</a>	
Tashkin DP, Volkmann ER, Tseng C-H, Roth MD, Khanna D, Furst DE, Clements PJ, Theodore A, Kafaja S, Kim GH. Improved cough and cough-specific quality of life in patients treated for scleroderma-related interstitial lung disease: results of Scleroderma Lung Study II. Chest.	Frequent cough
2017;151(4):813-20.	
DOI: <a href="https://doi.org/10.1016/j.chest.2016.11.052">10.1016/j.chest.2016.11.052</a>	
Tomiyama F, Watanabe R, Ishii T, Kamogawa Y, Fujita Y, Shirota Y, Sugimura K, Fujii H, Harigae, H.	Acute exacerbation
High Prevalence of Acute Exacerbation of Interstitial Lung Disease in Japanese Patients with Systemic Sclerosis. Tohoku J Exp Med.	
2016;239(4):297-305.	
DOI: <a href="https://doi.org/10.1620/tjem.239.297">10.1620/tjem.239.297</a>	
Volkmann ER, Khanna D, Tseng C-H, Elashoff R, Wang B, Roth M, Clements PJ, Furst DE, Theodore A, Tashkin DP. Improvement in Cough and Cough-Related Quality of Life in Participants Undergoing Treatment for Systemic Sclerosis-Related Interstitial Lung Disease. Arthritis Rheumatol.	Frequent cough
2016;68 (suppl 10): 3249.	

Reference	Risk factor
DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	
Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N, Louthrenoo W. Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: Inception cohort study. <i>Mod Rheumatol</i> . 2016;26(4):588-93.	ATAs, and absence of ACAs
DOI: <a href="https://doi.org/10.3109/14397595.2015.1115455">10.3109/14397595.2015.1115455</a>	
Weigold F, Günther J, Pfeiffenberger M, Cabral-Marques O, Siegert E, Dragun D, Philippe A, Regensburger A-K, Recke A, Yu X. Antibodies against chemokine receptors CXCR3 and CXCR4 predict progressive deterioration of lung function in patients with systemic sclerosis. <i>Arthritis Res Ther</i> . 2018;20(1):52.	CXCR3 and CXCR4
DOI: <a href="https://doi.org/10.1186/s13075-018-1545-8">10.1186/s13075-018-1545-8</a>	
Winstone TA, Hague CJ, Soon J, Sulaiman N, Murphy D, Leipsic J, Dunne JV, Wilcox PG, Ryerson CJ. Oesophageal diameter is associated with severity but not progression of systemic sclerosis-associated interstitial lung disease. <i>Respirology</i> . 2018;23(10):921-6.	Oesophageal diameter
DOI: <a href="https://doi.org/10.1111/resp.13309">10.1111/resp.13309</a>	

Reference	Risk factor
<p>Wu W, Jordan S, Becker MO, Dobrota R, Maurer B, Fretheim H, Ye S, Siegert E, Allanore Y, Hoffmann-Vold AM, Distler O. Prediction of progression of interstitial lung disease in patients with systemic sclerosis: the SPAR model. Ann Rheum Dis. 2018;77(9):1326-32.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2018-213201">10.1136/annrheumdis-2018-213201</a></p>	SpO <sub>2</sub> and arthritis ever
<p>Yilmaz N, Can M, Kocakaya D, Karakurt S, Yavuz S. Two-year experience with mycophenolate mofetil in patients with scleroderma lung disease: a case series. Int J Rheum Dis. 2014;17(8):923-8.</p> <p>DOI: <a href="https://doi.org/10.1111/1756-185X.12399">10.1111/1756-185X.12399</a></p>	Caveolin-1
<p>Zhang X, Bonner A, Baron M, Hudson M, Pope JE. Association of gastroesophageal factors and progression of interstitial lung disease in the canadian scleroderma research group (CSRG); a large, multi-center database. Ann Rheum Dis. 2013;71:395.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2012-eular.2698">10.1136/annrheumdis-2012-eular.2698</a></p>	Gastroesophageal dysmotility, post-oesophageal dilatation, dysphagia and waking up choking
	ACA anti-centromere antibody; ALOX5AP arachidonate 5-lipoxygenase activating protein; ANA antinuclear antibody; ATA anti-topoisomerase I antibody; CCL18 C-C motif chemokine ligand 18; CXCR C-X-C motif chemokine receptor; HLA human leukocyte antigen; HLA-DRB5 major histocompatibility complex, class II, DR beta

5; HRCT high-resolution computed tomography; ILD interstitial lung disease; IRF5 Interferon Regulatory Factor 5; KL-6 Krebs von den Lungen 6; mRSS modified Rodnan skin score; PFT pulmonary function test; SpO<sub>2</sub> oxygen saturation; TAA tumour-associated antigen; TGF- $\beta$  transforming growth factor-beta; TRIM21 tripartite motif containing 21.

### **Screening and diagnosis**

<b>Reference</b>	<b>Screening technique evaluated</b>
Ariani A, Aiello M, Silva M, Alfieri V, Bonati E, Lumetti F, Delsante G, Sverzellati N, Chetta A. Quantitative CT indexes are significantly associated with exercise oxygen desaturation in interstitial lung disease related to systemic sclerosis. Clin Respir J. 2017;11(6):983-9.  DOI: <a href="https://doi.org/10.1111/crj.12451">10.1111/crj.12451</a>	Quantitative CT index to measure significant oxygen desaturation
Ariani A, Bravi E, Saracco M, Parisi S, De Gennaro F, Idolazzi L, Silva M, Lumetti F, Benini C, Arrigoni E, Santilli D, Fusaro E, Pellerito R, Delsante G, Bodini FC, Sverzellati N. Comparison of Interstitial Lung Disease CT Indexes and Pulmonary Function Values in	Quantitative CT parameters

Reference	Screening technique evaluated
<p>Systemic Sclerosis Patients: A Multicenter Study. Ann Rheum Dis. 2014;73(Suppl 2):97.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2014-eular.3048">10.1136/annrheumdis-2014-eular.3048</a></p>	
<p>Ariani A, Ronconi M, Matucci-Cerinic M, Quantitative CT Furst DE. AB0931 Quantitative CT in IId-Ssc: Feasibility of An Operator Independent Method Based on Free Open Source Dicom Viewer. Ann Rheum Dis. 2016;75(Suppl 2):1219.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.5682">10.1136/annrheumdis-2016-eular.5682</a></p>	
<p>Ariani A, Silva M, Bravi E, Saracco M, QCTI Parisi S, De Gennaro F, Lumetti F, Idolazzi L, Seletti V, Caramaschi P, Benini C, Bodini FC, Scire CA, Lucchini G, Santilli D, Mozzani F, Imberti D, Arrigoni E, Delsante G, Pellerito R, Fusaro E, Sverzellati N. Operator-independent quantitative chest computed tomography versus standard assessment of interstitial lung disease</p>	

Reference	Screening technique evaluated
<p>related to systemic sclerosis: A multi-centric study. Mod Rheumatol. 2015;25(5):724-30.</p>	
<p>DOI: <a href="https://doi.org/10.3109/14397595.2015.1016200">10.3109/14397595.2015.1016200</a></p> <p>Ariani A, Silva M, Parisi S, Saracco M, Bravi E, De Gennaro F, Benini C, Caramaschi P, Lumetti F, Seletti V. FRI0443 Can Quantitative Chest CT Predict Interstitial Lung Disease Worsening in Systemic Sclerosis? Results from a Multi-Centre Prospective Cohort Study. Ann Rheum Dis. 2015;74(Suppl 2):587-8.</p>	QCTI
<p>Bernstein EJ, Peterson ER, Sell JL, D'Ovidio F, Arcasoy SM, Bathon JM, Lederer DJ. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. Arthritis Rheumatol. 2015;67(5):1314-22.</p>	HRCT

<b>Reference</b>	<b>Screening technique evaluated</b>
Bosello S, Occhipinti ME, Canestrari G, De Lorenzis E, Parisi F, Natalello G, Leuconeo G, Larici AR, De Waure C, Ferraccioli G. Quantitative CT Evaluation in Diffuse Interstitial Lung Involvement in Systemic Sclerosis: Usefulness of Lung Texture Analysis to Predict the Functional Change over Time. Arthritis Rheumatol. 2017;69(Suppl 10): [Abstract ID – 742].	CALIPER (an automated system that integrates PFT and HRCT data)
DOI: <a href="https://doi.org/10.1002/art.40321">10.1002/art.40321</a>	
Çetinçakmak MG, Göya C, Hamidi C, Tekbaş G, Abakay Ö, Batmaz I, Hattapoğlu S, Yavuz A, Bilici A. Quantitative volumetric assessment of pulmonary involvement in patients with systemic sclerosis. Quant Imaging Med Surg. 2016;6(1):50-6.	Percentage of lower lobe volume was calculated using HRCT
DOI: <a href="https://doi.org/10.3978/j.issn.2223-4292.2016.02.03">10.3978/j.issn.2223-4292.2016.02.03</a>	
Chong D, Kim HJ, Goldin J, Abtin F, Brown M. Computer-aided classification of interstitial lung diseases in high-	HRCT using 3D multiscale texture features

Reference	Screening technique evaluated
<p>resolution computed tomography using 3D multiscale texture features. Am J Respir Crit Care Med. 2013;187:[Abstract ID – A1076].</p>	
<p>DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2013.187.1_MeetingAbstrac_ts.A1076">10.1164/ajrccm-conference.2013.187.1_MeetingAbstrac_ts.A1076</a></p>	
<p>Coiffier G, Lescoat A, Droitcourt C, Cazalets C, Albert JD, Jégo P, Perdriger A. Ultrasonographic features of the hands in patients with systemic sclerosis reflect visceral manifestations of the disease. Ann Rheum Dis. 2016;75(Suppl 2):742-3.</p>	Ultrasonography of the hands
<p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.4902">10.1136/annrheumdis-2016-eular.4902</a></p>	
<p>Fisher CJ, Namas R, Young A, Wilhalme H, Homer K, Schiopu E, Flaherty K, Khanna D. Reliability and validity of the PROMIS-29 in systemic sclerosis associated interstitial lung disease. J Investig Med. 2017;65:872.</p>	PROMIS-29

<b>Reference</b>	<b>Screening technique evaluated</b>
Frauenfelder T, Winklehner A, Nguyen TD, Dobrota R, Baumueller S, Maurer B, Distler O. Screening for interstitial lung disease in systemic sclerosis: performance of high-resolution CT with limited number of slices: a prospective study. Ann Rheum Dis. 2014;73(12):2069-73.	9-slice HRCT protocol
DOI: <a href="https://doi.org/10.1136/annrheumdis-2014-205637">10.1136/annrheumdis-2014-205637</a>	
Gigante A, Fanelli FR, Lucci S, Barilaro GQS, Barbano B, Giovannetti A, Amoroso A, Rosato E. Lung ultrasound in systemic sclerosis: correlation with high-resolution computed tomography, pulmonary function tests and clinical variables of disease. Intern Emerg Med. 2016;11(2):213-7.	Lung ultrasound
DOI: <a href="https://doi.org/10.1007/s11739-015-1329-y">10.1007/s11739-015-1329-y</a>	
Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, Corte TJ, Sander CR, Ratoff J, Devaraj	Staging algorithm integrating PFTs and HRCT

Reference	Screening technique evaluated
<p>A, Bozovic G, Denton CP, Black CM, du Bois RM, Wells AU. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med. 2008;177(11):1248-54.</p>	
DOI: <a href="https://doi.org/10.1164/rccm.200706-877OC">10.1164/rccm.200706-877OC</a>	HRCT
<p>Goldin JG, Lynch DA, Strollo DC, Suh RD, Schraufnagel DE, Clements PJ, Elashoff RM, Furst DE, Vasunilashorn S, McNitt-Gray MF, Brown MS, Roth MD, Tashkin DP; Scleroderma Lung Study Research Group. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. Chest. 2008;134(2):358-67.</p>	
DOI: <a href="https://doi.org/10.1378/chest.07-2444">10.1378/chest.07-2444</a>	Increasing age, presence of ACA
<p>Gonçalves DR, Fonseca R, Aguiar F, Martins-Rocha T, Bernardes M, Costa L. SAT0221 Determinants Associated with Interstitial Pulmonary Involvement in Patients with Systemic Sclerosis-A Cross-Sectional Study. Ann Rheum Dis.</p>	

Reference	Screening technique evaluated
2016;75(Suppl 2):748.	
DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.6115">10.1136/annrheumdis-2016-eular.6115</a>	
Guarnieri G, Zanatta E, Mason P, Scarpa MC, Pigatto E, Maestrelli P, Cozzi F. Determinants of impairment in lung diffusing capacity in patients with systemic sclerosis. Clin Exp Rheumatol. 2015;33(4 Suppl 91):S80-6.	DL <sub>CO</sub> ; diffusing capacity of the lung for nitric oxide
Guillen-Del Castillo A, Sanchez- Vidaurre S, Simeon-Aznar CP, Cruz MJ, Fonollosa-Pla V, Munoz X. Prognostic Role of Exhaled Breath Condensate pH and Fraction Exhaled Nitric Oxide in Systemic Sclerosis Related Interstitial Lung Disease. Arch Bronconeumol. 2017;53(3):120-7. DOI: <a href="https://doi.org/10.1016/j.arbres.2016.09.014">10.1016/j.arbres.2016.09.014</a>	Exhaled breath and exhaled breath condensate
Hassanien M, Rashad S, Aljohee A. An ultrasound assessment of the hand and wrist in egyptian patients with systemic sclerosis. Ann Rheum Dis 2017;76(Suppl 2):1281.	Ultrasound

Reference	Screening technique evaluated
DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.1101">10.1136/annrheumdis-2017-eular.1101</a>	
<p>Hax V, Bredemeier M, Didonet Moro AL, Pavan TR, Vieira MV, Pitrez EH, de Silva Chakr RM, Xavier RM. Clinical algorithms for the diagnosis and prognosis of interstitial lung disease in systemic sclerosis. <i>Semin Arthritis Rheum.</i> 2017;47(2):228-34.</p>	<p>Clinical algorithms, combining lung auscultation, chest radiography and FVC % predicted for the diagnosis of different extents of ILD on HRCT</p>
DOI: <a href="https://doi.org/10.1016/j.semarthrit.2017.03.019">10.1016/j.semarthrit.2017.03.019</a>	
<p>Huang H, Fava A, Guhr T, Cimbro R, Rosen A, Boin F, Ellis H. A methodology for exploring biomarker--phenotype associations: application to flow cytometry data and systemic sclerosis clinical manifestations. <i>BMC Bioinformatics.</i> 2015;16:293.</p>	<p>Conditional Random Forests and Gene Set Enrichment Analysis</p>
DOI: <a href="https://doi.org/10.1186/s12859-015-0722-x">10.1186/s12859-015-0722-x</a>	

Reference	Screening technique evaluated
<p>Ji L, Zhang X, Zhang Z. The value of nailfold videocapillaroscopy in connective tissue disease related lung fibrosis. <i>Int J Rheum Dis.</i> 2016;19(Suppl 2):220.</p>	Nailfold videocapillaroscopy
<p>Kafaja S, Clements PJ, Wilhalme H, Tseng C-H, Furst DE, Kim GH, Goldin J, Volkmann ER, Roth MD, Tashkin DP. Reliability and Minimal Clinically Important Differences of FVC. Results from the Scleroderma Lung Studies (SLS-I and SLS-II). <i>Am J Respir Crit Care Med.</i> 2018;197(5):644-52.</p>	FVC% predicted

DOI: [10.1111/1756-185X.12962](https://doi.org/10.1111/1756-185X.12962)

DOI: [10.1164/rccm.201709-1845OC](https://doi.org/10.1164/rccm.201709-1845OC)

<b>Reference</b>	<b>Screening technique evaluated</b>
<p>Khanna D, Nagaraja V, Tseng C-H, Abtin F, Suh R, Kim G, Wells A, Furst DE, Clements PJ, Roth MD. Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials. <i>Arthritis Res Ther.</i> 2015;17(1):372.</p>	HRCT
<p>Kim HJ, Tashkin DP, Gjertson DW, Brown MS, Kleerup E, Chong S, Belperio JA, Roth MD, Abtin F, Elashoff R, Tseng CH, Khanna D, Goldin JG. Transitions to different patterns of interstitial lung disease in scleroderma with and without treatment. <i>Ann Rheum Dis.</i> 2016;75(7):1367-71.</p>	Quantitative changes in HRCT

<b>Reference</b>	<b>Screening technique evaluated</b>
<p>Kim HJ, Tashkin DP, Gjertson DW, Brown MS, Kleerup E, Chong S, Belperio JA, Roth MD, Abtin F, Elashoff R, Tseng CH, Khanna D, Goldin JG. Transitions to different patterns of interstitial lung disease in scleroderma with and without treatment. Ann Rheum Dis. 2016;75(7):1367-71.</p>	Quantitative assessments of reticulations from CT and QLF
<p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2015-208929">10.1136/annrheumdis-2015-208929</a></p> <p>Kim HJG, Tashkin DP, Brown MS, Kleerup EC, Goldin JG. Systemic sclerosis interstitial lung disease evaluation: comparison between two quantitative computed tomography for the change assessments. Am J Respir Crit Care Med. 2015;191: [Abstract ID – A1161].</p>	Markov-Chain Transition Matrix ILD transitional index
<p>DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2015.191.1_MeetingAbstrac_ts.A1161">10.1164/ajrccm-conference.2015.191.1_MeetingAbstrac_ts.A1161</a></p> <p>Krasowska D, Rudnicka L, Dańczak-Pazdrowska A, Chodorowska G,</p>	HRCT and PFTs

Reference	Screening technique evaluated
<p>Woźniacka A, Lis-Święty A, Czuwara J, Maj J, Majewski S, Sysa-Jędrzejowska A. Systemic sclerosis-diagnostic and therapeutic recommendations of the Polish Dermatological Society. Part 1: diagnosis and monitoring. Przegl Dermatol. 2017;104(5):483-98.</p>	
<p>DOI: <a href="https://doi.org/10.5114/dr.2017.71214">10.5114/dr.2017.71214</a></p> <p>Le Gouellec N, Duhamel A, Perez T, Hachulla A-L, Sobanski V, Faivre J-B, Morell-Dubois S, Lambert M, Hatron P-Y, Hachulla E. Predictors of lung function test severity and outcome in systemic sclerosis-associated interstitial lung disease. PloS One. 2017;12(8):e0181692.</p>	FVC; DL <sub>CO</sub>
<p>Le-Dong NN, Hua-Huy T, Nguyen Ngoc H, Martinot JB, Dinh Xuan AT. Detection of interstitial lung disease in systemic sclerosis using a machine learning approach based on pulmonary</p>	Machine-learning algorithms to evaluate PFTs

Reference	Screening technique evaluated
function tests. Am J Respir Crit Care Med. 2017;195:[Abstract ID – A2531].	
DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2017.195.1_MeetingAbstrac_ts.A2531">10.1164/ajrccm-conference.2017.195.1_MeetingAbstrac_ts.A2531</a>	
Liu Y. The role research of nailfold microcirculation in systemic sclerosis with interstitial lung disease. Int J Rheum Dis. 2016;19(Suppl 2):230.	Nailfold microcirculation
DOI: <a href="https://doi.org/10.1111/1756-185X.12962">10.1111/1756-185X.12962</a>	
Lopez Martinez R, Hassan R, Lubertino L, Cosentino V, Barth M, Saenz C, Binda M, Montoya S, Kerzberg E. Lung ultrasound for detecting interstitial lung disease in patients with systemic sclerosis. Clin Exp Rheumatol. 2014;32(2 suppl 81):S29.	Lung ultrasound

Reference	Screening technique evaluated
<p>Lucchini GS, N: Silva, M: Delsante, G: Ariani, A. Correlations between Quantitative Nailfold Videocapillaroscopy and Radiological Assessment of Interstitial Lung Disease Extent in Systemic Sclerosis: A Pilot Study. Ann Rheum Dis. 2014;73(Suppl 2):1119.</p>	Nailfold videocapillaroscopy
<p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2014-eular.5457">10.1136/annrheumdis-2014-eular.5457</a></p> <p>Mangat P, Conron M, Gabbay E, Proudman SM, Pulmonary Interstitial Vascular Organisational Taskforce. Scleroderma lung disease, variation in screening, diagnosis and treatment practices between rheumatologists and respiratory physicians. Intern Med J. 2010;40(7):494-502.</p>	<p>Self-reported screening, diagnosis and treatment practices of rheumatologists and respiratory physicians for SSc-ILD</p>
<p>DOI: <a href="https://doi.org/10.1111/j.1445-5994.2009.01990.x">10.1111/j.1445-5994.2009.01990.x</a></p> <p>Manthram V, Kumar U, Seith Bhalla A, Kumar R, Mohan A, Mathur S, Srinivas V, Ranjan P, Khanpur S. Utility of</p>	18FDG-PET CT and HRCT chest

Reference	Screening technique evaluated
<p>PET/CT/HRCT chest in the assessment of activity of interstitial lung diseases (ILD) in patients with systemic sclerosis (SSC). Int J Rheum Dis. 2015;18(Suppl 1): APL15-0129.</p>	
DOI: <a href="https://doi.org/10.1111/1756-185X.12730">10.1111/1756-185X.12730</a>	
<p>Markusse IM, Meijis J, de Boer B, Bakker J, Schippers HPC, Schouffoer AA, Ajimone MN, Kroft LJM, Ninaber MK, Huizinga TWJ, de Vries-Bouwstra, JK. Predicting cardiopulmonary involvement in patients with systemic sclerosis: complementary value of nailfold videocapillaroscopy patterns and disease-specific autoantibodies. Rheumatology (Oxford). 2017;56(7):1081-8.</p>	Nailfold videocapillaroscopy patterns
DOI: <a href="https://doi.org/10.1093/rheumatology/kew402">10.1093/rheumatology/kew402</a>	

<b>Reference</b>	<b>Screening technique evaluated</b>
Martis N, Queyrel-Moranne V, Launay D, Neviere R, Fuzibet J-G, Marquette C-H, Leroy S. Limited Exercise Capacity in Patients with Systemic Sclerosis: Identifying Contributing Factors with Cardiopulmonary Exercise Testing. <i>J Rheumatol.</i> 2018;45(1):95-102.  DOI: <a href="https://doi.org/10.3899/jrheum.161349">10.3899/jrheum.161349</a>	Cardiopulmonary exercise testing
Michelfelder M, Becker M, Riedlinger A, Siegert E, Drömann D, Yu X, Petersen F, Riemarkasten G. Interstitial lung disease increases mortality in systemic sclerosis patients with pulmonary arterial hypertension without affecting hemodynamics and exercise capacity. <i>Clin Rheumatol.</i> 2017;36(2):381-90.  DOI: <a href="https://doi.org/10.1007/s10067-016-3504-6">10.1007/s10067-016-3504-6</a>	TLC, FVC, FEV <sub>1</sub> , DL <sub>CO</sub> and HRCT
Mittal S, Kumar U, Guleria R, Seith BHalla A, Mohan A, Mathur S, Sreenivas V. HRCT chest score and bronchoalveolar lavage fluid cytology in assessment of disease activity of	Correlation between HRCT, PFT and 6MWT

Reference	Screening technique evaluated
systemic sclerosis associated interstitial lung disease. Indian J Rheumatol. 2012;7:S5.	
Moazedi-Fuerst FC, Kielhauser S, Brickmann K, Tripolt N, Meilinger M, Lufti A, Graninger W. Sonographic assessment of interstitial lung disease in patients with rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus. Clin Exp Rheumatol. 2015;33(4 Suppl 91):S87-91.	Transthoracic ultrasound
Moazedi-Fuerst FC, Zechner PM, Tripolt NJ, Kielhauser SM, Brickmann K, Scheidl S, Lufti A, Graninger WG. Pulmonary echography in systemic sclerosis. Clin Rheumatol. 2012;31(11):1621-5.	Transthoracic lung ultrasound
DOI: <a href="https://doi.org/10.1007/s10067-012-2055-8">10.1007/s10067-012-2055-8</a>	
Müller CDS, Warszawiak D, Paiva EDS, Escuissato DL. Pulmonary magnetic resonance imaging is similar to chest tomography in detecting inflammation in patients with systemic sclerosis. Re	Comparison of lung MRI to CT in assessing SSc-ILD

<b>Reference</b>	<b>Screening technique evaluated</b>
Bras Reumatol. 2017;57(5):419-24.  DOI: <a href="https://doi.org/10.1016/j.rbre.2017.02.001">10.1016/j.rbre.2017.02.001</a>	
Ninaber MK, Stolk J, Smit J, Le Roy EJ, Kroft LJM, Bakker ME, de Vries Bouwstra JK, Schouffoer AA, Staring M, Stoel BC. Lung structure and function relation in systemic sclerosis: application of lung densitometry. Eur J Radiol. 2015;84(5):975-9.  DOI: <a href="https://doi.org/10.1016/j.ejrad.2015.01.012">10.1016/j.ejrad.2015.01.012</a>	Quantitative CT densitometry using the percentile density method (Perc85)
Osborn T, Zhang X, Kalra S, Zhou B, Bartholmai BJ. A Non-Invasive Ultrasound Surface Wave Elastography Technique for Assessing Interstitial Lung Disease. Arthritis Rheumatol. 2017;69(Suppl 1):[Abstract ID – 1876].  DOI: <a href="https://doi.org/10.1002/art.40321">10.1002/art.40321</a>	Lung ultrasound surface wave elastography
Patiwetwitoon S, Wangkaew S, Euathrongchit J, Kasitanon N, Louthrenoo W. High-resolution computed tomographic findings in systemic sclerosis-associated interstitial lung disease: comparison between	HRCT and its correlation with disease duration, function classification, SpO <sub>2</sub> , the widest coronal oesophageal diameter, the maximum diameter of the main pulmonary artery and the main pulmonary artery/ascending aortic

Reference	Screening technique evaluated
diffuse and limited systemic sclerosis. J Clin Rheumatol. 2012;18(5):229-33.	diameter ratio
DOI: <a href="https://doi.org/10.1097/RHU.0b013e318261176f">10.1097/RHU.0b013e318261176f</a>	
Peelen D, Zwezerijnen B, Nossent E, Meijboom L, Hoekstra O, van der Laken C, Voskuyl AE. The Use of Positron Emission Tomography (PET)-Scan for the Quantitative Assessment of Interstitial Lung Disease in Systemic Sclerosis. Arthritis Rheumatol. 2017;69(Suppl 10):[Abstract ID – 257].	PET
DOI: <a href="https://doi.org/10.1002/art.40321">10.1002/art.40321</a>	
Peelen DM, Zwezerijnen B, Nossent EJ, Meijboom LJ, Hoekstra OS, van der Laken C, Voskuyl AE. The potential value of positron emission tomography (PET)-scan in systemic sclerosis for the quantitative assessment of interstitial lung disease. Ann Rheum Dis. 2017;76(Suppl 2):732.	18F-FDG PET – scan
DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.3677">10.1136/annrheumdis-2017-eular.3677</a>	

<b>Reference</b>	<b>Screening technique evaluated</b>
Pernot J, Puzenat E, Magy-Bertrand N, Manzoni P, Gondouin A, Bourdin H, Simon-Rigaud ML, Regnard J, Degano B. Detection of interstitial lung disease in systemic sclerosis through partitioning of lung transfer for carbon monoxide. <i>Respiration.</i> 2012;84(6):461-8. DOI: <a href="https://doi.org/10.1159/000335473">10.1159/000335473</a>	Membrane conductance for carbon monoxide and alveolar capillary blood volume
Pinal-Fernandez I, Pallisa-Nuñez E, Selva-O'Callaghan A, Castella-Fierro E, Simeon-Aznar CP, Fonollosa-Pla V, Vilardell-Tarres M. Pleural irregularity, a new ultrasound sign for the study of interstitial lung disease in systemic sclerosis and antisynthetase syndrome. <i>Clin Exp Rheumatol.</i> 2015;33(4 Suppl 91):S136-41.	Pleural irregularity using ultrasound
Pinal-Fernandez I, Pineda-Sanchez V, Nunez E, Simeon-Aznar CP, O'Callaghan A. Comparison of fast 1.5T chest MRI with HRCT scan in the assessment of interstitial lung disease	Fast 1.5t chest MRI; HRCT scan

Reference	Screening technique evaluated
extension secondary to systemic sclerosis. Ann Rheum Dis. 2014;73(Suppl 2):[Abstract ID – SAT0315].	
DOI: <a href="https://doi.org/10.1136/annrheumdis-2014-eular.1587">10.1136/annrheumdis-2014-eular.1587</a>	
Pinal-Fernandez I, Pineda-Sanchez V, MRI Pallisa-Nunez E, Simeon-Aznar CP, Selva-O'Callaghan A, Fonollosa-Pla V, Vilardell-Tarres M. Fast 1.5 T chest MRI for the assessment of interstitial lung disease extent secondary to systemic sclerosis. Clin Rheumatol. 2016;35(9):2339-45.	
DOI: <a href="https://doi.org/10.1007/s10067-016-3267-0">10.1007/s10067-016-3267-0</a>	
Pontana F, Billard AS, Duhamel A, Schmidt B, Faivre JB, Hachulla E, Matran R, Remy J, Remy-Jardin M. Effect of Iterative Reconstruction on the Detection of Systemic Sclerosis-related Interstitial Lung Disease: Clinical Experience in 55 Patients. Radiology. 2016;279(1):297-305.	CT-second-generation iterative reconstruction (reduced-dose images with SAFIRE)

Reference	Screening technique evaluated
DOI: <a href="https://doi.org/10.1148/radiol.2015150849">10.1148/radiol.2015150849</a>	
Raslan A, Stermer C, Hsu V. The clinical relevance of common ANA patterns in systemic sclerosis. <i>Arthritis Rheumatol.</i> 2016;68(Suppl 10):3895-7.	ANA patterns
DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	
Richardson C, Agrawal R, Lee J, Almagor O, Nelson R, Varga J, Cuttica MJ, D'Amico Dematte J, Chang RW, Hinchcliff ME. Esophageal dilatation and interstitial lung disease in systemic sclerosis: a cross-sectional study. <i>Semin Arthritis Rheum.</i> 2016;46(1):109-14.	Widest oesophageal diameter on HRCT
DOI: <a href="https://doi.org/10.1016/j.semarthrit.2016.02.004">10.1016/j.semarthrit.2016.02.004</a>	
Richardson C, Agrawal R, Lee J, Almagor O, Varga J, Chang RW, Hinchcliff ME. A Dilated Esophagus Is an Independent Risk Factor for Interstitial Lung Disease in SSc. <i>Arthritis Rheumatol.</i> 2014;66(Suppl 10):S319.	Oesophageal diameter
DOI: <a href="https://doi.org/10.1002/art.38914">10.1002/art.38914</a>	

<b>Reference</b>	<b>Screening technique evaluated</b>
Roth MD, Kim HJG, Tseng C-H, Kiertscher SM, Keane MP, Tashkin DP, Elashoff RM, Goldin JG. Biologic And Physiologic Correlates Of The Quantitative Lung Fibrosis CT Score In Scleroderma-Related Interstitial Lung Disease. Am J Respir Crit Care Med. 2013;187:[Abstract ID – A1079].  DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A1079">10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A1079</a>	Correlation between QLF CT score and polymorphonuclear neutrophils, eosinophils, lymphocytes, cytokines and chemokines concentrations, PFTs and mRSS
Rotondo C, Chialà A, Nivuori M, Coladonato L, Giannini M, Anelli MG, Righetti G, Scioscia C, Fiorentini C, Lopalco G. Chest Ultrasound Signs of Interstitial Lung Disease in Systemic Sclerosis Patients: A Comparison between High Resolution Chest Computed Tomography Findings. Ann Rheum Dis. 2016;75(Suppl 2):747.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.4641">10.1136/annrheumdis-2016-eular.4641</a>	Correlation of the lung ultrasound and HRCT in assessing SSc-ILD

<b>Reference</b>	<b>Screening technique evaluated</b>
<p>Rotondo C, Praino E, Lanciano E, Fornaro M, Lopalco G, Nivuori MG, Iannone F, Lapadula G. Residual volume: A candidate as early marker of interstitial lung disease in systemic sclerosis patients? Clin Exp Rheumatol. 2014;32(2):S83.</p>	Residual volume
<p>Salaffi F, Carotti M, Di Donato E, Di Carlo M, Ceccarelli L, Giuseppetti G. Computer-aided tomographic analysis of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Correlation with pulmonary physiologic tests and patient-centred measures of perceived dyspnea and functional disability. PLoS One. 2016;11(3):e0149240.</p>	QLF score based on a CaM system and the correlation between PFTs, patient- centred measures of dyspnoea and functional disability, CaM and visual reader-based (CoVR) methods
<p>DOI: <a href="https://doi.org/10.1371/journal.pone.0149240">10.1371/journal.pone.0149240</a></p> <p>Sanchez-Cano D, Ortego Centeno N, Cruces Moreno MT, Sáez Comet L, Freire M, Parra Todlí JA, Rodríguez Caballeira M, Simeón Aznar C. AB0624 Interstitial lung disease in scleroderma:</p>	ATA positivity; FVC<50%

Reference	Screening technique evaluated
severity associated factors. Ann Rheum Dis. 2017;76(Suppl 2):1270.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.2545">10.1136/annrheumdis-2017-eular.2545</a>	
Sanges S, Giovannelli J, Sobanski V, Morell-Dubois S, Maillard H, Lambert M, Podevin C, Lamblin N, De Groote P, Bervar J-F. Factors associated with the 6-minute walk distance in patients with systemic sclerosis. Arthritis Res Ther. 2017;19(1):279.	6-minute walk distance
DOI: <a href="https://doi.org/10.1186/s13075-017-1489-4">10.1186/s13075-017-1489-4</a>	
Showalter K, Hoffmann A, Rouleau G, Aaby D, Lee J, Richardson C, Dematte J, Agrawal R, Chang RW, Hinchcliff M. Performance of Forced Vital Capacity and Lung Diffusion Cutpoints for Associated Radiographic Interstitial Lung Disease in Systemic Sclerosis. J Rheumatol. 2018;45(11):1572-6.	FVC and DL <sub>CO</sub> thresholds for SSc-ILD on HRCT scans
DOI: <a href="https://doi.org/10.3899/jrheum.171362">10.3899/jrheum.171362</a>	

<b>Reference</b>	<b>Screening technique evaluated</b>
<p>Song G, Bae SC, Lee YH. Diagnostic accuracy of lung ultrasound for interstitial lung disease in patients with connective tissue diseases: a meta-analysis. <i>Clin Exp Rheumatol.</i> 2016;34(1):11-16.</p>	Lung ultrasound
<p>Steele R, Hudson M, Lo E, Baron M. Clinical decision rule to predict the presence of interstitial lung disease in systemic sclerosis. <i>Arthritis Care Res.</i> 2012;64(4):519-24.</p>	Clinical decision rule based on lung auscultation, chest radiography, and % predicted FVC
<p>DOI: <a href="https://doi.org/10.1002/acr.21583">10.1002/acr.21583</a></p> <p>Suliman YA, Huscher D, Nguyen-Kim TDL, Maurer B, Jordan S, Treder U, Speich R, Frauenfelder T, Disler O. High rate of false negatives in the early detection of interstitial lung disease associated with systemic sclerosis by pulmonary function tests. <i>Ann Rheum Dis</i> 2013;72(Suppl 3):A500-1.</p>	PFTs
<p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2013-eular.1504">10.1136/annrheumdis-2013-eular.1504</a></p>	

<b>Reference</b>	<b>Screening technique evaluated</b>
Tardella M, Di Carlo M, Carotti M, Filippucci E, Grassi W, Salaffi F.  Ultrasound b-lines in the evaluation of interstitial lung disease in patients with systemic sclerosis: cut-off point definition for the presence of pulmonary fibrosis. Ann Rheum Dis 2017;76(Suppl 2):1281.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.6828">10.1136/annrheumdis-2017-eular.6828</a>	Ultrasound
Tashkin D, Volkmann E, Khanna D, Roth M, Theodore A, Wang B, Tseng C- H, Elashoff R. Frequent Cough in Scleroderma-Related Interstitial Lung Disease (SSc-ILD): Characteristics and Response to Potentially Disease- Modifying Therapy in a Randomized Controlled Trial (RCT) (Scleroderma Lung Study II). Chest. 2016;150(4):473A.  DOI: <a href="https://doi.org/10.1016/j.chest.2016.08.487">10.1016/j.chest.2016.08.487</a>	QLF and QILD
Teixeira LC, Cordeiro I, Sousa S, Duarte AC, da Silva JC, Cordeiro A,	Nailfold capillaroscopy

Reference	Screening technique evaluated
<p>Santos MJ. Nailfold Capillaroscopy Findings in Scleroderma Patients- Prognostic Implications. Ann Rheum Dis. 2016;75(Suppl 2):754.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.6109">10.1136/annrheumdis-2016-eular.6109</a></p>	
<p>Walkoff L, White DB, Chung JH, Asante HRCT D, Cox CW. The Four Corners Sign: A Specific Imaging Feature in Differentiating Systemic Sclerosis-related Interstitial Lung Disease From Idiopathic Pulmonary Fibrosis. J Thorac Imaging. 2018;33(3):197-203.</p>	
DOI: <a href="https://doi.org/10.1097/RTI.0000000000000319">10.1097/RTI.0000000000000319</a>	
<p>Wang Z, Zhang X, Ma L. Electromyography Electromyography in newly-diagnosed systemic connective tissue disease-associated interstitial lung disease. Chest. 2016;149(4):[Abstract ID – A207].</p>	
DOI: <a href="https://doi.org/10.1016/j.chest.2016.02.214">10.1016/j.chest.2016.02.214</a>	
<p>Wangkaew S, Euathrongchit J, HRCT Patiwetwitoon S, Prasertwitayakij N,</p>	

<b>Reference</b>	<b>Screening technique evaluated</b>
Kasitanon N, Louthrenoo W. The relevance of high-resolution computed tomographic findings and pulmonary arterial hypertension in systemic sclerosis-associated interstitial lung disease. <i>J Med Assoc Thai.</i> 2014;97(8):878-85.	
Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N. Correlation of delta high-resolution computed tomography (HRCT) score with delta clinical variables in early systemic sclerosis (SSc) patients. <i>Quant Imaging Med Surg.</i> 2016;6(4):381-90.	Correlation of change in HRCT score with change in clinical variables
Wilsher M, Good N, Hopkins R, Young P, Milne D, Gibson A, Suppiah R, Ly J, Doughty R, Dalbeth N. The six-minute walk test using forehead oximetry is reliable in the assessment of scleroderma lung disease. <i>Respirology.</i> 2012;17(4):647-52.	6MWT

Reference	Screening technique evaluated
DOI: <a href="https://doi.org/10.1111/j.1440-1843.2012.02133.x">10.1111/j.1440-1843.2012.02133.x</a>	
Winklehner A, Berger N, Maurer B, Distler O, Alkadhi H, Frauenfelder T. Screening for interstitial lung disease in systemic sclerosis: the diagnostic accuracy of HRCT image series with high increment and reduced number of slices. Ann Rheum Dis. 2012;71(4):549-52.	HRCT image series
DOI: <a href="https://doi.org/10.1136/annrheumdis-2011-200564">10.1136/annrheumdis-2011-200564</a>	
Yamakawa H, Hagiwara E, Kitamura H, Yamanaka Y, Ikeda S, Sekine A, Kitamura H, Baba T, Iso S, Okudela K, Kuwano K, Ogura T. Clinical Features of Idiopathic Interstitial Pneumonia with Systemic Sclerosis-Related Autoantibody in Comparison with Interstitial Pneumonia with Systemic Sclerosis. PLoS One. 2016;11(8):e0161908.	HRCT and surgical lung biopsy
DOI: <a href="https://doi.org/10.1371/journal.pone.0161908">10.1371/journal.pone.0161908</a>	

<b>Reference</b>	<b>Screening technique evaluated</b>
<p>Yamakawa H, Takemura T, Iwasawa T, Yamanaka Y, Ikeda S, Sekine A, Kitamura H, Baba T, Iso S, Okudela K, Kuwano K, Ogura T. Emphysematous change with scleroderma-associated interstitial lung disease: the potential contribution of vasculopathy? BMC Pulm Med. 2018;18(1):25.</p> <p>DOI: <a href="https://doi.org/10.1186/s12890-018-0591-y">10.1186/s12890-018-0591-y</a></p>	HRCT
<p>Yap V, Zantah M, Athwal P, Kaloudis E, Datta D, Foley R. Correlation of PFT Parameters With HRCT-Fibrosis Score in Scleroderma Patients. Chest. 2016;150(4):476A.</p> <p>DOI: <a href="https://doi.org/10.1016/j.chest.2016.08.490">10.1016/j.chest.2016.08.490</a></p>	Correlation between PFT parameters with the extent of ILD measured by a fibrosis score on HRCT
<p>Yilmaz N, Abul Y, Bicakcigil M, Golabi P, Celikel C, Karakurt S, Yavuz S. Induced sputum as a method for detection of systemic sclerosis-related interstitial lung disease. Rheumatol Int. 2012;32(7):1921-5.</p> <p>DOI: <a href="https://doi.org/10.1007/s00296-011-1872-4">10.1007/s00296-011-1872-4</a></p>	Induced sputum

<b>Reference</b>	<b>Screening technique evaluated</b>
Zamora FD, Kim HJ, Wang Q. Prevalence of pulmonary function test abnormalities and their correlation to high resolution computer tomography in a large scleroderma population. Am J Respir Crit Care Med. 2013;187:[Abstract ID – A2920].	Correlation between PFT measurements and HRCT abnormalities
DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2013.187.1_MeetingAbstrac_ts.A2920">10.1164/ajrccm-conference.2013.187.1_MeetingAbstrac_ts.A2920</a>	
Zanatta E, Martini A, Biasiolo A, Pigatto E, Bourji K, Favaro M, Punzi L, Pontisso P, Cozzi F. SCCA-IGM is up-regulated in scleroderma patients with reduced DLCO: A new biomarker of pulmonary involvement? Ann Rheum Dis. 2016;75(Suppl 2):522.	Squamous cell carcinoma antigen
DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.4283">10.1136/annrheumdis-2016-eular.4283</a>	
Zhang G, Liu Q, Zhao Z, Lin H, Wu C. Correlation between Imaging Features of High-resolution Computed Tomography and Histopathology of	Correlation between HRCT and histopathological patterns of CTD-ILDs

Reference	Screening technique evaluated
<p>Connective Tissue Diseases associated Interstitial Lung Disease in Chinese Population: Avoid Lung Biopsy in Those Patients? Int J Radiol Med Imag. 2016;3:118.</p>	
DOI: <a href="https://doi.org/10.15344/2456-446X/2017/118">10.15344/2456-446X/2017/118</a>	
<p>Zhang X, Zhou B, Kalra S, Bartholmai B, Greenleaf J, Osborn T. An Ultrasound Surface Wave Technique for Assessing Skin and Lung Diseases. Ultrasound Med Biol. 2018;44(2):321- 31.</p>	Ultrasound surface wave elastography
DOI: <a href="https://doi.org/10.1016/j.ultrasmedbio.2017.10.01">10.1016/j.ultrasmedbio.2017.10.01</a>	
<p>0</p> <p>Zhao J, Wang K, Ye S. Peripheral CD4 + CXCR4 + T cell proportion is a potential diagnostic biomarker for connective tissue disease associated interstitial lung diseases. Int J Rheum Dis. 2016;19(Suppl 2):40.</p>	CD4 and CXCR4 and T-cell proportion
DOI: <a href="https://doi.org/10.1111/1756-185X.12962">10.1111/1756-185X.12962</a>	
6MWT 6-minute walk test; ACA anti-centromere antibody; ANA antinuclear antibody; ATA anti-topoisomerase I antibody; CaM computer-aided diagnosis;	

CD4 cluster of differentiation 4; CoVR conventional visual based reader score; CT computed tomography; CTD connective tissue disease; CXCR4 C-X-C motif chemokine receptor 4; DL<sub>CO</sub> diffusing capacity of the lungs for carbon monoxide; FDG fluorodeoxyglucose; FEV<sub>1</sub> forced expiratory volume in 1 second; FVC forced vital capacity; HRCT high-resolution computed tomography; ILD interstitial lung disease; MRI magnetic resonance imaging; mRSS modified Rodnan skin score; PET position emission tomography; PROMIS patient reported outcome measures information system; PFT pulmonary function test; QCTI CT quantitative indexes; QLF quantitative lung fibrosis; QILD, quantitative ILD; SAFIRE sinogram-affirmed iterative reconstruction; SpO<sub>2</sub> oxygen saturation; SSc systemic sclerosis; SSc-ILD systemic sclerosis-associated ILD; TLC total lung capacity.

### **Treatment patterns**

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Abignano G, Del Galdo F, Emery P, Buch M. Extended course cyclophosphamide and methylprednisolone pulse therapy can stabilize initially refractory interstitial lung disease in patients with SSc: a single-centre experience. <i>Rheumatology (Oxford)</i> . 2012;51(Suppl 2):ii114.	Cyclophosphamide and methylprednisolone (N=45)	NA
DOI: <a href="https://doi.org/10.1093/rheumatology/ker475">10.1093/rheumatology/ker475</a>		
Adler S, Huscher D, Allanore Y, Czirjak L, Del Galdo F, Denton CP, Distler O, Frerix	Immunosuppressant (n=3272)	NA

Reference	Intervention	Comparison
M, Matucci-Cerinic M, Mueller-Ladner U. Use of immunosuppressants in SSc patients with interstitial lung disease - results of the DeSScipher project of the EUSTAR Group. Clin Exp Rheumatol. 2014;32(2):S85-6.		
Adler S, Huscher D, Siegert E, Allanore Y, Czirjak L, DelGaldo F, Denton CP, Distler O, Frerix M, Matucci-Cerinic M, Mueller-Ladner U, Tarner IH, Valentini G, Walker UA, Villiger PM, Riemekasten G. Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung function: results of the EUSTAR group. Arthritis Res Ther. 2018;20(1):17.	Immunosuppressive therapy	NA
	(N=2681)	
DOI: <a href="https://doi.org/10.1186/s13075-018-1517-z">10.1186/s13075-018-1517-z</a>		
Alias B, Lawrence A, Nalianda K, Sreenath S. Maintenance therapy reduces mortality in scleroderma interstitial lung disease: Long term follow up of an observational study. Indian J Rheumatol.	AZA, MMF or methotrexate (N=46)	NA
2017;12(5):S85-6.		

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Ando K, Motojima S, Doi T, Nagaoka T, Kaneko N, Aoshima M, Takahashi K. Effect of glucocorticoid monotherapy on pulmonary function and survival in Japanese patients with scleroderma-related interstitial lung disease. Respir Investig. 2013;51(2):69-75.  DOI: <a href="https://doi.org/10.1016/j.resinv.2012.12.002">10.1016/j.resinv.2012.12.002</a>	Treatment group: glucocorticoid monotherapy (n=14) or immunosuppressive agents (n=7)	Non-treatment group (N=50)
Balbir-Gurman A, Yigla M, Guralnik L, Hardak E, Solomonov A, Rozin AP, Toledano K, Dagan A, Bishara R, Markovits D, Nahir MA, Braun-Moscovici, Y. Long-term follow-up of patients with scleroderma interstitial lung disease treated with intravenous cyclophosphamide pulse therapy: a single-center experience. Isr Med Assoc J. 2015;17(3):150-6.	Intravenous cyclophosphamid e (N=26)	NA
Baqir M, Makol A, Osborn TG, Bartholmai BJ, Ryu JH. Mycophenolate mofetil for scleroderma-related interstitial lung disease: A real world experience. PloS One. 2017;12(5):e0177107.	MMF (N=46)	NA

Reference	Intervention	Comparison
DOI: <a href="https://doi.org/10.1371/journal.pone.0177107">10.1371/journal.pone.0177107</a>		
Barnes H, Holland AE, Westall GP, Goh NS, Glaspole IN. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. Cochrane Database Syst Rev. 2018;1:CD010908.	Cyclophosphamide vs placebo (N=195)	Cyclophosphamid e vs MMF (N=300)
DOI: <a href="https://doi.org/10.1002/14651858.CD010908.pub2">10.1002/14651858.CD010908.pub2</a>		
Bavliya MK, Shenoy P. Cyclophosphamide vs mycophenolate mofetil in scleroderma interstitial lung disease (SSC-ILD) as induction therapy: A single center, retrospective analysis. Ann Rheum Dis 2016;75(Suppl 2):1115.	Cyclophosphamide (N=23) and MMF (N=44)	NA
DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.1069">10.1136/annrheumdis-2016-eular.1069</a>		
Berezne A, Ranque B, Valeyre D, Brauner M, Allanore Y, Launay D, Le Guern V, Kahn, J-E, Couderc L-J, Constans J. Therapeutic strategy combining intravenous cyclophosphamide followed by oral azathioprine to treat worsening interstitial lung disease associated with systemic sclerosis: a retrospective	Intravenous cyclophosphamid e followed by oral AZA (N=27)	NA

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
multicenter open-label study. J Rheumatol. 2008;35(6):1064-72.		
Daoussis D, Liossis SC, Tsamandas AC, Kalogeropoulou C, Paliogianni F, Sirinian C, Yiannopoulos G, Andonopoulos AP. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clin Exp Rheumatol. 2012;30(2):S17-22.	RTX (N=8)	NA
Daoussis D, Melissaropoulos K, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, Georgiou,P, Andonopoulos AP, Drosos AA, Sakkas L, Liossis SN. A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum. 2017;46(5):625-31.	RTX (N=33)	Control (N=18)
DOI: <a href="https://doi.org/10.1016/j.semarthrit.2016.10.003">10.1016/j.semarthrit.2016.10.003</a>		
Fernandez-Codina A, Berastegui C, Pinal- Fernandez I, Silveira MG, Lopez-	Lung transplantation	NA

Reference	Intervention	Comparison
Meseguer M, Monforte V, Guillen-Del Castillo A, Simeon-Aznar CP, Fonollosa-Pla V, Sole J, Bravo-Masgoret C, Roman-Broto A. Lung transplantation in systemic sclerosis: A single center cohort study. Joint Bone Spine. 2018;85(1):79-84.  DOI: <a href="https://doi.org/10.1016/j.jbspin.2017.03.012">10.1016/j.jbspin.2017.03.012</a>	(N=15)	
Fraticelli P, Gabrielli B, Pomponio G, Valentini G, Bosello S, Riboldi P, Gerosa M, Faggioli P, Giacomelli R, Del Papa N, Gerli R, Lunardi C, Bombardieri S, Malorni W, Corvetta A, Moroncini G, Gabrielli A. Low-dose oral imatinib in the treatment of systemic sclerosis interstitial lung disease unresponsive to cyclophosphamide: a phase II pilot study. Arthritis Res Ther. 2014;16(4):R144.  DOI: <a href="https://doi.org/10.1186/ar4606">10.1186/ar4606</a>	Imatinib (N=30)	NA
Fretheim H, Midtved Ø, Volkmann E, Garen T, Lund MB, Aaløkken T, Molberg Ø, Hoffmann-Vold AM. Mycophenolate mofetil versus cyclophosphamide in scleroderma-related interstitial lung	MMF (N=14)	Cyclophosphamide (N=21)

Reference	Intervention	Comparison
disease in a real life scenario. Ann Rheum Dis. 2017;76(Suppl 2):106.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.4819">10.1136/annrheumdis-2017-eular.4819</a>		
Fujimoto Y, Ando K, Motojima S, Nagaoka T, Ohkuni Y, Kaneko N, Aoshima M, Seyama K, Takahishi K. The Treatment Effect For The Pulmonary Function And Long Term Survival In Scleroderma Related Interstitial Lung Disease. Am J Respir Crit Care Med. 2012;185:[Abstract ID – A6618].	Treatment group (N=21)	Non-treatment group (N=50)
Gerbino AJ, Goss CH, Molitor JA. Effect of mycophenolate mofetil on pulmonary function in scleroderma-associated interstitial lung disease. Chest. 2008;133(2):455-60.	MMF (N=13)	NA
Goldin J, School G, Kim GHJ, Kleerup E, Kim GHJ, Clements P, Brown M, Roth M,	MMF	Cyclophosphamid e

Reference	Intervention	Comparison
Tashkin D. Quantitative CT as an Outcome Measure in the Scleroderma Lung Study II. QJM. 2016;109(Suppl 1):S26.  DOI: <a href="https://doi.org/10.1093/qjmed/hcw119.018">10.1093/qjmed/hcw119.018</a>		
Goldin JG, Kim GHJ, Kleerup E, Elashoff R, Lu P, Clements P, Roth MD, Tashkin DP. Association Of Changes In Quantitative CT With Outcome Measures In The Scleroderma Lung Study II. Am J Respir Crit Care Med. 2017. 195:[Abstract ID – A7416].  DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A7416">10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A7416</a>	MMF(N=50)	Cyclophosphamide (N=47)
Guzelant G, Melikoglu M, Musellim B, Yilmaz DD, Fresko I, Seyahi E, Hatemi G, Ugurlu S, Hamuryudan V. Rituximab in systemic sclerosis-interstitial lung disease, a case series of 18 patients. Ann Rheum Dis. 2017;76(Suppl 2):1274.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.4908">10.1136/annrheumdis-2017-eular.4908</a>	RTX (Group 1; naïve patients) (N=4)	RTX (Group 2; patients with previous immunosuppress ant) (N=14)

Reference	Intervention	Comparison
Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, Roberts C, Desai S, Herrick AL, McHugh N, Foley NM, Pearson SB, Emery P, Veale DJ, Denton C, Wells AU, Black CM, du Bois RM. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma.	Intravenous cyclophosphamid e followed by AZA (N=22)	Placebo (N=23)
Arthritis Rheum. 2006;54(12):3962-70.		
DOI: <a href="https://doi.org/10.1002/art.22204">10.1002/art.22204</a>		
Ichimura Y, Kawaguchi Y, Takagi K, Tochimoto A, Higuchi T, Katsumata Y, Yamanaka H. Effectiveness and safety of tacrolimus following intravenous cyclophosphamide pulse therapy as the treatment of systemic sclerosis-associated interstitial lung disease. Arthritis Rheumatol. 2017;69(Suppl 10):[Abstract ID – 1684].	Tacrolimus (N=10)	Intravenous cyclophosphamid e (N=10)
DOI: <a href="https://doi.org/10.1002/art.40321">10.1002/art.40321</a>		

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Iudici M, Cuomo G, Vettori S, Bocchino M, Sanduzzi Zamparelli A, Cappabianca S, Valentini G. Low-dose pulse cyclophosphamide in interstitial lung disease associated with systemic sclerosis (SSc-ILD): efficacy of maintenance immunosuppression in responders and non-responders. Semin Arthritis Rheum. 2015;44(4):437-44.  DOI: <a href="https://doi.org/10.1016/j.semarthrit.2014.09.003">10.1016/j.semarthrit.2014.09.003</a>	Cyclophosphamide induction followed by AZA (N=24)	Cyclophosphamide induction followed by MMF (N=12)
Khanna D, Albera C, Fischer A, Khalidi N, Raghu G, Chung L, Chen D, Schiopu E, Tagliaferri M, Seibold JR. An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. J Rheumatol. 2016;43(9):1672-9.  DOI: <a href="https://doi.org/10.3899/jrheum.151322">10.3899/jrheum.151322</a>	Pirfenidone (N=63)	NA
Khanna D, Albera C, Fischer A, Khalidi N, Raghu G, Chung L, Chen D, Schiopu E, Gorina E, Tagliaferri M, Seibold JR. Safety and tolerability of pirfenidone in patients	Pirfenidone (N=63)	NA

Reference	Intervention	Comparison
<p>with systemic sclerosis-associated interstitial lung disease-The LOTUSS study. Am J Respir Crit Care Med. 2015;191:[Abstract ID – A1175].</p> <p>DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A1175">10.1164/ajrccm-conference.2015.191.1_MeetingAbstracts.A1175</a></p>		
<p>Khanna D, Roth M, Clements P, Furst D, Tseng CH, Elashoff R, Volkmann E, Kafaja S, Goldin J, Tashkin D.</p> <p>Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease: Scleroderma Lung Study II. Ann Rheum Dis. 2016;75(Suppl 2):531.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.2126">10.1136/annrheumdis-2016-eular.2126</a></p>	MMF (N=63)	Cyclophosphamid e (N=63)
<p>Khanna D, Saggar R, Mayes MD, Abtin F, Clements PJ, Maranian P, Assassi S, Saggar R, Singh R, Furst DE. A one-year, phase I/IIa, open-label pilot trial of imatinib mesylate in the treatment of systemic sclerosis–associated active interstitial lung</p>	Imatinib (N=20)	NA

Reference	Intervention	Comparison
disease. <i>Arthritis Rheum.</i> 2011;63(11):3540-6.  DOI: <a href="https://doi.org/10.1002/art.30548">10.1002/art.30548</a>		
Khanna D, Tashkin D, Furst D, Tseng CH, Wilhalme H, Roth M, Kafaja S, Volkmann E, Elashoff R, Clements P. Efficacy of mycophenolate mofetil (MMF) versus oral cyclophosphamide (CYC) on skin thickness in the scleroderma lung study II. <i>Ann Rheum Dis.</i> 2016;75(Suppl 2):525.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.2123">10.1136/annrheumdis-2016-eular.2123</a>	MMF (N=69) Cyclophosphamide (N=73)	
Kokosi M, Saunders P, Karagiannis K, Chua F, Maher TM, Renzoni EA, Wells AU. Rituximab as rescue therapy in advanced progressive systemic sclerosis associated interstitial lung disease. <i>Thorax.</i> 2015;70(Suppl 3):[Abstract ID – A92].  DOI: <a href="https://doi.org/10.1136/thoraxjnl-2015-207770.170">10.1136/thoraxjnl-2015-207770.170</a>	RTX (N=18)	NA
Koneva O, Desinova O, Ovsyannikova O, Starovoytova M, Glukchova S, Ananieva LP. FRI0484 Impact of Anti-B-Cell	RTX (N=54)	NA

Reference	Intervention	Comparison
<p>Therapy with Rituximab on Pulmonary Function of the Patients with Systemic Sclerosis and Interstitial Lung Disease.</p> <p>Ann Rheum Dis. 2015;74(Suppl 2):603.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2015-eular.4154">10.1136/annrheumdis-2015-eular.4154</a></p>		
<p>Kundu S, Paul S, Hariprasath K, Agarwal R, Ghosh S, Biswas D. Effect of Sequential Intravenous Pulse Cyclophosphamide-Azathioprine in Systemic Sclerosis-Interstitial Lung Disease: An Open-Label Study. Indian J Chest Dis Allied Sci. 2016;58(1):7-10.</p>	<p>Sequential intravenous pulse cyclophosphamid e-AZA (N=9)</p>	NA
<p>Lepri G, Avouac J, Airo P, Anguita Santos F, Bellando-Randone S, Blagojevic J, Garcia Hernandez F, Gonzalez Nieto JA, Guiducci S, Jordan S, Limaye V, Maurer B, Selva-O'Callaghan A, Riccieri V, Distler O, Matucci-Cerinic M, Allanore Y. Effects of rituximab in connective tissue disorders related interstitial lung disease. Clin Exp Rheumatol. 2016;34:181-5.</p>	RTX (N=23)	NA

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Mani M, Sriram S, Saranya S, Saravanan M, Euphrasia L, Sankaralingam R. Rituximab in systemic sclerosis with ILD- two year outcome from a tertiary care hospital in South India. <i>Int J Rheum Dis.</i> 2015;18(Suppl 1):114.  DOI: <a href="https://doi.org/10.1111/1756-185X.12730">10.1111/1756-185X.12730</a>	RTX followed by AZA (N=22)	Cyclophosphamid e as monthly pulses for 6 months followed by quarterly for 6 doses (n=40)
Martyanov V, Kim GJ, Hayes W, Du S, Ganguly BJ, Sy O, Lee SK, Bogatkevich GS, Schieven GL, Schiopu E, Marangoni RG, Goldin J, Whitfield ML, Varga J. Novel lung imaging biomarkers and skin gene expression subsetting in dasatinib treatment of systemic sclerosis-associated interstitial lung disease. <i>PLoS One.</i> 2017;12(11):e0187580.  DOI: <a href="https://doi.org/10.1371/journal.pone.0187580">10.1371/journal.pone.0187580</a>	Dasatinib (N=31)	NA
Melissaropoulos K, Daoussis D, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, Georgiou P, Andonopoulos AP, Drosos AA, Sakkas L, Liossis SN. B cell depletion therapy in systemic sclerosis associated interstitial	RTX (N=33)  (N=18)	Standard treatment (AZA, methotrexate and mycophenolate)

Reference	Intervention	Comparison
<p>lung disease. A multicenter, open label, comparative study with a follow up of 94 patient-years. Ann Rheum Dis. 2016;75(Suppl 2):749.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.5233">10.1136/annrheumdis-2016-eular.5233</a></p>		
<p>Miura Y, Saito T, Fujita K, Tsunoda Y, Tanaka T, Takoi H, Yatagai Y, Rin S, Sekine A, Hayashihara K, Nei T, Azuma A. Clinical experience with pirfenidone in five patients with scleroderma-related interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31(3):235-8.</p>	Pirfenidone (N=5)	NA
<p>Nakamura H, Odani T, Yasuda S, Noguchi A, Fujieda Y, Kato M, Oku K, Bohgaki T, Sugita J, Endo T, Teshima T, Atsumi T. Autologous haematopoietic stem cell transplantation for Japanese patients with systemic sclerosis: Long-term follow-up on a phase II trial and treatment-related fatal cardiomyopathy. Mod Rheumatol. 2018;28(5):879-84.</p> <p>DOI: <a href="https://doi.org/10.1080/14397595.2017.1416920">10.1080/14397595.2017.1416920</a></p>	Haematopoietic stem cell transplantation (N=14)	NA

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Nannini C, West CP, Erwin PJ, Matteson EL. Effects of cyclophosphamide on pulmonary function in patients with scleroderma and interstitial lung disease: a systematic review and meta-analysis of randomized controlled trials and observational prospective cohort studies. Arthritis Res Ther. 2008;10(5):R124. DOI: <a href="https://doi.org/10.1186/ar2534">10.1186/ar2534</a>	Cyclophosphamide (the study is a systematic review and meta-analysis of randomised controlled trials and observational prospective cohort studies)	NA (the study is a systematic review and meta-analysis of randomised controlled trials and observational prospective cohort studies)
Odani T, Yasuda S, Kono M, Kurita T, Fujieda Y, Kon Y, Horita T, Kawaguchi Y, Atsumi T, Yamanaka H, Koike, T. Effectiveness of autologous hematopoietic stem cell transplantation for interstitial lung diseases in patients with systemic sclerosis. Ann Rheum Dis. 2013;71(Suppl 3):241. DOI: <a href="https://doi.org/10.1136/annrheumdis-2012-eular.2221">10.1136/annrheumdis-2012-eular.2221</a>	Haematopoietic stem cell transplantation (N=10)	Conventional therapy (N=30)
Onat AM, Zengin O, Aksoy S, Onder ME, Saciniti KG, Kisacrik B. Efficacy of RTX (N=39)	RTX (N=39)	NA

Reference	Intervention	Comparison
Rituximab in Systemic Sclerosis with Interstitial Lung Disease. Arthritis Rheumatol. 2016;68 (suppl 10): [Abstract ID – A2894]. DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>		
Owen CE, Ngian GS, Elford K, Moore OA, Stevens W, Nikpour M, Rabusa C, Proudman SM, Roddy J, Zochling J, Hill CL, Sturgess A, Tymms K, Youssef P, Sahhar J. Mycophenolate mofetil is an effective and safe option for the management of systemic sclerosis-associated interstitial lung disease: Results from the Australian Scleroderma Cohort Study. Clin Exp Rheumatol. 2016;34:170-6.	MMF (N=22)	AZA (N=49)
Padiyar S, Janardana R, Chebbi P, Danda D. Long term outcomes of mycophenolate in interstitial lung disease associated with scleroderma. Indian J Rheumatol. 2017;12(5):S87-8.	MMF (N=101)	NA
Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM,	High-dose prednisone +	Low-dose prednisone +

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. J Rheumatol. 2002;29(2):298- 304.	intravenous pulse cyclophosphamid e (N=10)	intravenous pulse cyclophosphamid e (N=10)
Parida J, Nath A, Z. N, Agarwal V. A double blind randomized control trial of oral tadalafil in interstitial lung disease of scleroderma. Arthritis Rheumatol. 2014;66(Suppl 10):S739.	Tadalafil (N=17)	Placebo (N=13)
DOI: <a href="https://doi.org/10.1002/art.38914">10.1002/art.38914</a>		
Perez Campos D, Estevez Del Toro M, Pena Casanovas A, Gonzalez Rojas PP, Morales Sanchez L, Gutierrez Rojas AR. Are high doses of prednisone necessary for treatment of interstitial lung disease in systemic sclerosis? Reumatol Clin. 2012;8(2):58-62.	Cyclophosphami de monthly for 6 months followed by twice monthly for the next 6 months with oral prednisone (1 mg × kg × day) for 4 weeks followed by 5 mg every 2 weeks up to 10	Cyclophosphamid e + oral prednisone 10 mg daily (N=10)
DOI: <a href="https://doi.org/10.1016/j.reuma.2011.11.006">10.1016/j.reuma.2011.11.006</a>		

Reference	Intervention	Comparison
	mg (N=13)	
Poormoghim H, Rezaei N, Sheidaie Z, Almasi AR, Moradi-Lakeh M, Almasi S, Andalib E. Systemic sclerosis: comparison of efficacy of oral cyclophosphamide and azathioprine on skin score and pulmonary involvement-a retrospective study.  Rheumatol Int. 2014;34(12):1691-9.	AZA (N=15)	Cyclophosphamid e (N=21)
DOI: <a href="https://doi.org/10.1007/s00296-014-3026-y">10.1007/s00296-014-3026-y</a>		
Saigusa R, Asano Y, Nakamura K, Yamashita T, Ichimura Y, Takahashi T, Toyama T, Taniguchi T, Yoshizaki A, Miyazaki M, Tamaki Z, Sato S. Plasma plasmin- $\alpha$ 2-plasmin inhibitor complex levels may predict the effect of cyclophosphamide for systemic sclerosis- related interstitial lung disease. Mod  Rheumatol. 2017;27(4):618-22.	Intravenous cyclophosphamid e pulse (N=23)	NA
DOI: <a href="https://doi.org/10.1080/14397595.2016.1226472">10.1080/14397595.2016.1226472</a>		
Sari A, Guven D, Armagan B, Erden A, Kalyoncu U, Karadag O, Apras Bilgen S, Ertenli I, Kiraz S, Akdogan A. Rituximab Experience in Patients With Long-standing	RTX (N=14)	NA

Reference	Intervention	Comparison
<p>Systemic Sclerosis-Associated Interstitial Lung Disease: A Series of 14 Patients. J Clin Rheumatol. 2017;23(8):411-15.</p> <p>DOI: <a href="https://doi.org/10.1097/RHU.0000000000000584">10.1097/RHU.0000000000000584</a></p>		
Sari A, Guven D, Armagan B, Kilic A, Erden A, Akdogan A. Rituximab experience in patients with longstanding systemic sclerosis-associated interstitial lung disease: A series of 14 patients. Ann Rheum Dis. 2017;76(Suppl 2):1262-3.	RTX (N=14)	NA
<p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.5501">10.1136/annrheumdis-2017-eular.5501</a></p>		
<p>Saunders P, Sharma S, Kokosi M, Chua F, Renzoni EA, Wells AU, Maher TM. Intravenous cyclophosphamide as a treatment for severe interstitial lung disease. Am J Respir Crit Care Med. 2017;195:[Abstract ID – A1544].</p> <p>DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A1544">10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A1544</a></p>	Intravenous cyclophosphamid e (N=307)	NA
Seibold JR, Denton CP, Furst DE, Guillevin L, Rubin LJ, Wells AU, Matucci-	Bosentan (N=77)	Placebo (N=86)

Reference	Intervention	Comparison
Cericic M, Riemakasten G, Emery P, Chadha-Boreham H. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. Arthritis Rheum. 2010;62(7):2101-8.  DOI: <a href="https://doi.org/10.1002/art.27466">10.1002/art.27466</a>		
Sharma S, Naidu S, Dhir V, Singh S. Outcomes of scleroderma related ILD; does Indian scleroderma respond differently? Int J Rheum Dis. 2016;19(Suppl 2):224.  DOI: <a href="https://doi.org/10.1111/1756-185X.12962">10.1111/1756-185X.12962</a>	Cyclophosphamide (N=37)	NA
Shenoy P, Alias B, Nalianda K, Ahmed S, Sreenath S. Role of maintenance therapy after induction in patients with scleroderma ILD: results of 5 years observational study. Int J Rheum Dis. 2017;20(Suppl. 1):[Abstract ID – ABS345].  DOI: <a href="https://doi.org/10.1111/1756-185X.13178">10.1111/1756-185X.13178</a>	Induction – cyclophosphamide or MMF; maintenance – AZA, MMF, RTX or methotrexate (N=45)	NA
Shenoy PD, Bivaliya M, Sashidharan S, Nalianda K, Sreenath S. Cyclophosphamide versus mycophenolate	Cyclophosphamide (N=23)	MMF (N=34)

Reference	Intervention	Comparison
mofetil in scleroderma interstitial lung disease (SSc-ILD) as induction therapy: a single-centre, retrospective analysis.  Arthritis Res Ther. 2016;18(1):123.  DOI: <a href="https://doi.org/10.1186/s13075-016-1015-0">10.1186/s13075-016-1015-0</a>		
Sircar G, Goswami RP, Rath D, Naskar A, RTX (N=30)  Sit H, Haldar S, Sinhamahapatra P,  Ghosh A, Ghosh P. A randomized controlled, open label trial of cyclophosphamide versus rituximab in diffuse systemic sclerosis. Indian J Rheumatol. 2017;12(5):S14.		Cyclophosphamid e (N=30)
Takei H, Yasuoka H, Yamaoka K,  Takeuchi T. Are Patients with Extended Interstitial Lung Disease Better Target for The Treatment in SSC? Ann Rheum Dis. 2016;75(Suppl 2):537-8.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.3825">10.1136/annrheumdis-2016-eular.3825</a>	Cyclophosphami de (N=16)	NA
Tashkin D, Roth M, Furst D, Clements P, MMF (N=69)  Khanna D, Volkmann E. Scleroderma Lung Study II: comparison of Therapy with Mycophenolate Mofetil Versus Oral		Cyclophosphamid e (N=73)

Reference	Intervention	Comparison
<p>Cyclophosphamide in Patients with Symptomatic Scleroderma Interstitial Lung Disease. Am J Respir Crit Care Med. 2016. 193:[Abstract ID – A6432].</p> <p>DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A6432">doi/abs/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A6432</a></p>		
<p>Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, Goldin J, Arriola E, Strange C, Bolster, MB, Seibold JR, Riley DJ, Hsu VM, Varga J, Schraufnagel D, Theodore A, Simms R, Wise R, Wigley F, White B, Steen V, Read C, Mayes M, Parsley E, Mubarak K, Connolly MK, Golden J, Olman M, Fessler B, Rothfield N, Metersky M, Khanna D, Li N, Li G. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med. 2007;176(10):1026-34.</p> <p>DOI: <a href="https://doi.org/10.1164/rccm.200702-326OC">10.1164/rccm.200702-326OC</a></p>	<p>Cyclophosphamide</p>	<p>Placebo (N=79)</p>

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, <i>et al.</i> Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708-19.  DOI: <a href="https://doi.org/10.1016/S2213-2600(16)30152-7">10.1016/S2213-2600(16)30152-7</a>	MMF (N=69)	Cyclophosphamide (N=73)
Tashkin DP, Volkmann E, Roth MD, Li N, Khanna D, Furst D, Elashoff R. Mycophenolate versus placebo for the treatment of systemic sclerosis-related interstitial lung disease. Am J Respir Crit Care Med. 2017;195:[Abstract ID – A1553].  DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A1553">10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A1553</a>	MMF (N=69)	Placebo (N=79)
Theodore AC, Tseng C-H, Li N, Elashoff RM, Tashkin DP. Correlation of cough with disease activity and treatment with cyclophosphamide in scleroderma interstitial lung disease: findings from the	Cyclophosphamide	Placebo

Reference	Intervention	Comparison
Scleroderma Lung Study. Chest. 2012;142(3):614-21.  DOI: <a href="https://doi.org/10.1378/chest.11-0801">10.1378/chest.11-0801</a>		
Tiev KP, Riviere S, Hua-Huy T, Cabane J, Dinh-Xuan AT. Exhaled NO predicts cyclophosphamide response in scleroderma-related lung disease. Nitric Oxide. 2014;40:17-21.  DOI: <a href="https://doi.org/10.1016/j.niox.2014.04.011">10.1016/j.niox.2014.04.011</a>	Intravenous cyclophosphamid e (N=19)	NA
Troy L, Keir G, Jo H, Lau E, Taylor N, Webster S, Torzillo P, Corte P, Corte TJ. Rituximab may be an effective rescue therapy in connective-tissue disease-associated interstitial lung disease. Respirology. 2016;21(Suppl 3):68.  DOI: <a href="https://doi.org/10.1111/resp.12939_14">10.1111/resp.12939_14</a>	RTX (N=11)	NA
Tzouvelekis A, Galanopoulos N, Bouros E, Kolios G, Zacharis G, Ntolios P, Koulelidis A, Oikonomou A, Bouros D. Effect and safety of mycophenolate mofetil or sodium in systemic sclerosis-associated interstitial lung disease: a meta-analysis. Pulm Med.  DOI: <a href="https://doi.org/10.1111/pulm.12939">10.1111/pulm.12939</a>	MMF (N=69)	NA

Reference	Intervention	Comparison
2012;2012:143637.  DOI: <a href="https://doi.org/10.1155/2012/143637">10.1155/2012/143637</a>		
Volkmann ER, Khanna D, Tseng C-H, Elashoff R, Wang B, Roth M, Clements PJ, Furst DE, Theodore A, Tashkin DP.  Improvement in Cough and Cough- Related Quality of Life in Participants Undergoing Treatment for Systemic Sclerosis-Related Interstitial Lung Disease. Arthritis Rheumatol. 2016;68 (suppl 10): [Abstract ID – 3249].  DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	MMF (N=65)	Cyclophosphamid e (N=72)
Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, Kim G, Goldin J, Clements PJ, Furst DE, Elashoff RM. Treatment with cyclophosphamide for systemic sclerosis- related interstitial lung disease does not improve survival after 12 years. Ann Rheum Dis. 2017;76(Suppl 2):104.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2017-eular.2488">10.1136/annrheumdis-2017-eular.2488</a>	Cyclophosphami de (N=79)	Placebo (N=79)

<b>Reference</b>	<b>Intervention</b>	<b>Comparison</b>
<p>Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, Kim G, Goldin J, Clements PJ, Furst DE, Elashoff RM. Mycophenolate Mofetil Versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease An Analysis of Scleroderma Lung Studies I and II. <i>Arthritis Rheumatol.</i> 2017;69(7):1451-60.</p> <p>DOI: <a href="https://doi.org/10.1002/art.40114">10.1002/art.40114</a></p>	MMF (N=69)	Placebo (N=79)
<p>Volkmann ER, Tashkin DP, Sim M, Khanna D, Roth M, et al. Treatment with cyclophosphamide for systemic sclerosis-interstitial lung disease does not lead to a sustained improvement in lung function in two independent cohorts. <i>Arthritis Rheumatol.</i> 2017;69(Suppl 10):[Abstract ID – 749].</p> <p>DOI: <a href="https://doi.org/10.1002/art.40321">10.1002/art.40321</a></p>	Cyclophosphamide – SLS I (N=79)	Cyclophosphamide – SLS II (N=73)
<p>Volkmann ET, D: Fischer, A: Hoffmann-Vold, A-M: Tseng, C-H: LeClair, H: Khanna, D: Clements, P: Roth, M: Elashoff, R. Predictors of Survival in</p>	MMF (N=65)	Cyclophosphamide (N=72)

Reference	Intervention	Comparison
<p>Patients with Systemic Sclerosis-Related Interstitial Lung Disease Enrolled in The Scleroderma Lung Study II. Ann Rheum Dis. 2016;75(Suppl 2):534.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.2999">10.1136/annrheumdis-2016-eular.2999</a></p>		
<p>Xiao H, Zhang G, Liao X, Li X, Zhang J, Lin H, Chen Z, Zhang X. Anti-fibrotic effects of pirfenidone by interference with the hedgehog signalling pathway in patients with systemic sclerosis-associated interstitial lung disease. Int J Rheum Dis. 2018;21(2):477-86.</p> <p>DOI: <a href="https://doi.org/10.1111/1756-185X.13247">10.1111/1756-185X.13247</a></p>	Pirfenidone (N=25)	Control (N=10)
<p>Yilmaz N, Can M, Kocakaya D, Karakurt S, Yavuz S. Two-year experience with mycophenolate mofetil in patients with scleroderma lung disease: a case series. Int J Rheum Dis. 2014;17(8):923-8.</p> <p>DOI: <a href="https://doi.org/10.1111/1756-185X.12399">10.1111/1756-185X.12399</a></p>	MMF (N=12)	NA
<p>Zamora AC, Wolters PJ, Collard HR, Connolly MK, Elicker BM, Webb WR, King TE, Golden JA. Use of mycophenolate</p>	MMF (N=17)	NA

Reference	Intervention	Comparison
mofetil to treat scleroderma-associated interstitial lung disease. Respir Med. 2008;102(1):150-5.  DOI: <a href="https://doi.org/10.1016/j.rmed.2007.07.021">10.1016/j.rmed.2007.07.021</a>		AZA azathioprine; MMF mycophenolate mofetil; RTX rituximab; SLS Scleroderma Lung Study.

### Disease progression

Reference	Instrument capturing progression
Adamali HI, Delgado CM, Stock C, Lindhal GE, Molyneaux P, Russell AM, Wells A, Renzoni EA, Maher T. Telomere (TL) shortening is associated with disease severity in scleroderma (SSC) associated interstitial lung disease (ILD). Eur Respir J. 2012;40(Suppl 56):4532.	Telomere shortening
Adler S, Huscher D, Siegert E, Allanore Y, Czirjak L, DelGaldo F, Denton CP, Distler O, Frerix M, Matucci-Cerinic M, Mueller-Ladner U, Tarner IH, Valentini G, Walker UA, Villiger PM, Riemekasten G. Systemic sclerosis associated interstitial lung disease - individualized immunosuppressive therapy and course of lung	DL <sub>CO</sub> or FVC

Reference	Instrument capturing progression
function: results of the EUSTAR group. Arthritis Res Ther. 2018;20(1):17.  DOI: <a href="https://doi.org/10.1186/s13075-018-1517-z">10.1186/s13075-018-1517-z</a>	
Aozasa N, Asano Y, Akamata K, Noda S, Masui Y, Tamaki Z, Tada Y, Sugaya M, Kadono T, Sato S. Clinical significance of serum levels of secretory leukocyte protease inhibitor in patients with systemic sclerosis. Mod Rheumatol. 2012;22(4):576-83.	Secretory leukocyte protease inhibitor
Baqir M, Makol A, Osborn TG, Bartholmai BJ, Ryu JH. Mycophenolate mofetil for scleroderma-related interstitial lung disease: A real world experience. PloS One. 2017;12(5):e0177107.	FVC
DOD: <a href="https://doi.org/10.1371/journal.pone.0177107">10.1371/journal.pone.0177107</a>	
Bosello S, Occhipinti ME, Canestrari G, De Lorenzis E, Parisi F, Natalello G, Leuconeo G, Larici AR, De Waure G, Ferraccioli G.	Quantitative CT evaluation
Quantitative CT evaluation in Diffuse Interstitial Lung Involvement in Systemic Sclerosis: Usefulness of Lung Texture Analysis to Predict the Functional Change over Time. Arthritis	

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**Reference****Instrument capturing  
progression**

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Rheumatol. 2017;69(Suppl 10):[Abstract ID – 742].

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CCL C-C motif chemokine ligand; CD cluster of differentiation; CT computed tomography; CXCL C-X-C motif chemokine ligand 10; DL <sub>CO</sub> diffusing capacity of the lungs for carbon monoxide; FDG fluorodeoxyglucose; FVC forced vital capacity; HNP human neutrophil peptide; HRCT high-resolution computed tomography; IL interleukin; ILD interstitial lung disease; IRF5 Interferon Regulatory Factor 5; KCO ratio of DL <sub>CO</sub> to alveolar volume; KL-6 Krebs von den Lungen 6; MCP-1 monocyte chemoattractant protein-1; miR microRNA; mRSS modified Rodnan skin score; NT-proBNP N-terminal pro-brain natriuretic peptide; PET position emission tomography; PFT pulmonary function test; PINP procollagen type I N propeptide; PIIINP procollagen type III N-terminal peptide; QILD quantitative ILD; QLF quantitative lung fibrosis; SpO <sub>2</sub> oxygen saturation; SSc systemic sclerosis; TAA tumour-associated antigen; TGF-β transforming growth factor beta; Th17 T helper 17 cell; TLC total lung capacity.	
<b><u>Biomarkers for risk stratification and disease progression</u></b>	
<b>Reference</b>	<b>Biomarker</b>
Aozasa N, Asano Y, Akamata K, Noda S, Masui Y, Tamaki Z, Tada Y, Sugaya M, Kadono T, Sato S. Clinical significance of serum levels of secretory leukocyte protease inhibitor in patients with systemic sclerosis. <i>Mod Rheumatol</i> .	Secretory leukocyte protease inhibitor

Reference	Biomarker
2012;22(4):576-83. DOI: <a href="https://doi.org/10.1007/s10165-011-0553-1">10.1007/s10165-011-0553-1</a>	ACAs and ATAs
Arandia NI, Pilar C, Castillo MD, Argüelles DC, Martínez LT, Hernandez G, Saez L, Comet MD, Egurbide MV, Arberas MD. Influence of antibody profile in clinical features and prognosis in a cohort of Spanish patients with systemic sclerosis. Clin Exp Rheumatol.	
2017;35(106):S98-S105.	
Assassi S, Wu M, Tan FK, Chang J, Graham TA, Furst DE, Khanna D, Charles J, Ferguson EC, Feghali-Bostwick C, Mayes MD. Skin gene expression correlates of severity of interstitial lung disease in systemic sclerosis. Arthritis Rheum. 2013;65(11):2917-27. DOI: <a href="https://doi.org/10.1002/art.38101">10.1002/art.38101</a>	CCL2 and sPSGL-1
Atilla N, Yildirim G, Balkarli A. Association of neutrophil/lymphocyte ratio with the degree of interstitial lung disease in systemic sclerosis. Turk J Med Sci. 2016;46:1871-4. DOI: <a href="https://doi.org/10.3906/sag-1601-87">10.3906/sag-1601-87</a>	Neutrophil/lymphocyte ratio
Benyamine A, Heim X, Resseguier N, Bertin D, Gomez C, Ebbo M, Harle JR, Kaplanski G, Rossi	KL-6

Reference	Biomarker
P, Bardin N, Granel B. Elevated serum Krebs von den Lungen-6 in systemic sclerosis: a marker of lung fibrosis and severity of the disease. <i>Rheumatol Int.</i> 2018;38(5):813-9. DOI: <a href="https://doi.org/10.1007/s00296-018-3987-3">10.1007/s00296-018-3987-3</a>	
Betteridge ZE, Woodhead F, Lu H, Shaddick G, Bunn CC, Denton CP, Abraham DJ, du Bois RM, Lewis M, Wells AU. Brief Report: Anti-Eukaryotic Initiation Factor 2B Autoantibodies Are Associated With Interstitial Lung Disease in Patients With Systemic Sclerosis. <i>Arthritis Rheumatol.</i> 2016;68(11):2778-83. DOI: <a href="https://doi.org/10.1002/art.39755">10.1002/art.39755</a>	Anti-eIF2B
Caetano J, Nihtyanova S, Harvey J, C.P. D, Ong VH. Distinctive clinical phenotype of anti-centromere antibody positive diffuse systemic sclerosis. <i>Arthritis Rheumatol.</i> 2016;68(Suppl 10):111-12. DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	ACAs
Caetano J, Nihtyanova SI, Denton CP, Ong VH. The distinctive clinical phenotype of anti-centromere antibody positive diffuse systemic sclerosis. <i>Rheumatology (Oxford).</i>	ACA positivity

Reference	Biomarker
2017;56(Suppl2):kex062.059. DOI: <a href="https://doi.org/10.1093/rheumatology/kex062.059">10.1093/rheumatology/kex062.059</a>	
Celeste S, Santaniello A, Caronni M, Franchi J, Severino A, Scorza R, Beretta L. Carbohydrate antigen 15.3 as a serum biomarker of interstitial lung disease in systemic sclerosis patients. Eur J Intern Med. 2013;24(7):671-6. DOI: <a href="https://doi.org/10.1016/j.ejim.2013.04.004">10.1016/j.ejim.2013.04.004</a>	Carbohydrate antigen 15.3
Chilukuri B, Sankaralingam R, Chinnadurai S, Tamilselvam TN, Mahendran B, Ramamoorthy R, Annamalai SV, Mantharam V. Serum CXCL4 makes its mark !-As a biomarker of disease activity in systemic sclerosis. Indian J Rheumatol. 2016;11(5):S79.	CXCL4
Chinnadurai S, Sankaralingam R, Mahendran B, Chilukuri B, Selvakumar B. Serum vascular endothelial growth factor levels as a marker of skin thickening, digital ischemia, and interstitial lung disease in systemic sclerosis. Indian J Rheumatol. 2016;11(5):S69-70.	VEGF
De Lauretis A, Sestini P, Pantelidis P, Hoyles R, Hansell DM, Goh NS, Zappala CJ, Visca D, Maher TM, Denton CP, Ong VH, Abraham DJ,	IL-6

<b>Reference</b>	<b>Biomarker</b>
Kelleher P, Hector L, Wells AU, Renzoni EA.  Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. <i>J Rheumatol.</i> 2013;40(4):435-46.  DOI: <a href="https://doi.org/10.3899/jrheum.120725">10.3899/jrheum.120725</a>	
De Luca G, Bosello SL, Berardi G, Rucco M, Canestrari G, Mirone L, Forni F, Di Mario C, Danza FM. Tumour-associated antigens in systemic sclerosis patients with interstitial lung disease: association with lung involvement and cancer risk. <i>Rheumatology (Oxford)</i> . 2015;54(11):1991-9.  DOI: <a href="https://doi.org/10.1093/rheumatology/kev204">10.1093/rheumatology/kev204</a>	TAAs; PINP and PIIINP
Devi S, Tripathy R, Sahoo R, Panda A, Das B. Plasma TGF- $\beta$ in systemic sclerosis: patients display lower levels and inversely correlate with disease severity. <i>Int J Rheum Dis.</i> 2016;19(S2):225.  DOI: <a href="https://doi.org/10.1111/1756-185X.12962">10.1111/1756-185X.12962</a>	TGF- $\beta$
Dubey S, Patel Z, Kakde G, Balkrishnan C, Samant R. Role of biomarkers KL-6, SP-D and CCL-18 in assessing disease severity of	Serum KL-6, SP-D and CCL18

<b>Reference</b>	<b>Biomarker</b>
interstitial lung disease in systemic sclerosis. Indian J Rheumatol. 2017;12(5):S36.	
Elhaj M, Charles J, Pedroza C, Liu X, Zhou X, Estrada Y, Martin RM, Gonzalez EB, Lewis DE, Draeger HT, Kim S, Arnett FC, Mayes MD, Assassi S. Can serum surfactant protein D or CC-chemokine ligand 18 predict outcome of interstitial lung disease in patients with early systemic sclerosis? J Rheumatol. 2013;40(7):1114-20.	SP-D and CCL18
DOI: <a href="https://doi.org/10.3899/jrheum.120997">10.3899/jrheum.120997</a>	
Fava A, Cimbro R, Wigley FM, Liu Q-R, Rosen A, Boin F. Frequency of circulating topoisomerase-I-specific CD4 T cells predicts presence and progression of interstitial lung disease in scleroderma. Arthritis Res Ther. 2016;18(1):99.	Topoisomerase-I-specific CD4 T cells
DOI: <a href="https://doi.org/10.1186/s13075-016-0993-2">10.1186/s13075-016-0993-2</a>	
Fritzler MJ, Hudson M, Choi MY, Mahler M, Wang M, Bentow C, Milo J, Baron M. Bicaudal D2 is a novel autoantibody target in systemic sclerosis that shares a key epitope with CENP-A but has a distinct clinical phenotype. Autoimmun	Anti-BICD2

<b>Reference</b>	<b>Biomarker</b>
Rev. 2018;17(3):267-75.  DOI: <a href="https://doi.org/10.1016/j.autrev.2018.01.006">10.1016/j.autrev.2018.01.006</a>	
Garthwaite H, Denton C, Groves A, Porter J. A prospective cohort study to assess the use of fluodeoxyglucose positron emission tomography (FDG-PET) in assessing treatment response in patients with systemic sclerosis associated interstitial lung disease. Am J Respir Crit Care Med. 2017;195.	18F-FDG-PET combined with a single breath hold HRCT
DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5425">10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5425</a>	
Goh NS, Veeraraghavan S, Desai SR, Cramer D, Hansell DM, Denton CP, Black CM, du Bois RM, Wells AU. Bronchoalveolar lavage cellular profiles in patients with systemic sclerosis-associated interstitial lung disease are not predictive of disease progression. Arthritis Rheum. 2007;56(6):2005-12.	Bronchoalveolar lavage cellular profiles
DOI: <a href="https://doi.org/10.1002/art.22696">10.1002/art.22696</a>	
Gonçalves DR, Fonseca R, Aguiar F, Martins-Rocha T, Bernardes M, Costa L. SAT0221 Determinants Associated with Interstitial Pulmonary Involvement in Patients with Systemic	ANAs, topoisomerase I DNA (Scl70) and ACAs

Reference	Biomarker
Sclerosis-A Cross-Sectional Study. Ann Rheum Dis. 2016;75:748. DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.6115">10.1136/annrheumdis-2016-eular.6115</a>	
Hant FN, Ludwicka-Bradley A, Wang HJ, Li N, Elashoff R, Tashkin DP, Silver RM. Surfactant protein D and KL-6 as serum biomarkers of interstitial lung disease in patients with scleroderma. J Rheumatol. 2009;36(4):773-80. DOI: <a href="https://doi.org/10.3899/jrheum.080633">10.3899/jrheum.080633</a>	KL-6 and SP-D
Hesselstrand R, Wildt M, Bozovic G, Andersson Sjoland A, Andreasson K, Scheja A, Westergren-Thorsson G, Bjermer L, Wuttge DM. Biomarkers from bronchoalveolar lavage fluid in systemic sclerosis patients with interstitial lung disease relate to severity of lung fibrosis. Respir Med. 2013;107(7):1079-86. DOI: <a href="https://doi.org/10.1016/j.rmed.2013.03.015">10.1016/j.rmed.2013.03.015</a>	CXCL4, CXCL5, CXCL4, CXCL8, S100A8/A9, COMP and KL-6
Hizal M, Bruni C, Romano E, Mazzotta C, Guiducci S, Bellando Randone S, Blagojevic J, Lepri G, Tufan A, Matucci Cerinic M. Decrease of LL-37 in systemic sclerosis: a new marker for interstitial lung disease? Clin Rheumatol. 2015;34(4):795-8.	LL-37

Reference	Biomarker
DOI: <a href="https://doi.org/10.1007/s10067-014-2854-1">10.1007/s10067-014-2854-1</a>	
Hoa S, Hudson M, Troyanov Y, Proudman S, Walker J, Stevens W, Nikpour M, Assassi S, Mayes MD, Wang M, Baron M, Fritzler MJ. Single-specificity anti-Ku antibodies in an international cohort of 2140 systemic sclerosis subjects: clinical associations. Medicine. 2016;95(35):e4713.	Single-specificity anti-Ku antibodies
DOI: <a href="https://doi.org/10.1097/MD.00000000000004713">10.1097/MD.00000000000004713</a>	
Hoffmann-Vold A, Huyen R, Volkmann ER, Midtvedt O, Palchevskiy V, Brit Lund M, Garen T, Aalokken TM, Tennøe AH, Weigt SS, Shino M, Saggar R, Ross D, Lynch J, Ueland T, Fishbein M, Aukrust P, Molberg Ø, Belperio JA. High level of chemokine CCL2 is associated with lung fibrosis progression and reduced survival in two independent systemic sclerosis cohorts. Arthritis Rheumatol. 2016;68(Suppl 10):1102-4.	Chemokine CCL2
DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	
Hoffmann-Vold AM, Huynh R, Volkmann E, Palchevskiy S, Midtvedt Ø, Garen T, Der Hovanessian A, Weigt S, Fishbein M, Ardehali A, Ross D, Saggar R, Lynch J, Aukrust P, Ueland	CX3CL1

Reference	Biomarker
T, Elashoff R, Molberg Ø, Belperio J. Augmented Concentrations of Cx3cl1 Are Associated with Progressive Interstitial Lung Disease in Systemic Sclerosis. Ann Rheum Dis. 2016;75(Suppl 2):527.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.4406">10.1136/annrheumdis-2016-eular.4406</a>	
Hoffmann-Vold AM, Tennøe AH, Garen T, Midtvedt Ø, Abraityte A, Aaløkken TM, Lund MB, Brunborg C, Aukrust P, Ueland T, Molberg Ø. High Level of Chemokine CCL18 Is Associated With Pulmonary Function Deterioration, Lung Fibrosis Progression, and Reduced Survival in Systemic Sclerosis. Chest. 2016;150(2):299-306.  DOI: <a href="https://doi.org/10.1016/j.chest.2016.03.004">10.1016/j.chest.2016.03.004</a>	CCL18
Jiang Z, Tao JH, Zuo T, Li XM, Wang GS, Fang X, Xu XL, Li XP. The correlation between miR-200c and the severity of interstitial lung disease associated with different connective tissue diseases. Scand J Rheumatol. 2017;46(2):122-9.  DOI: <a href="https://doi.org/10.3109/03009742.2016.1167950">10.3109/03009742.2016.1167950</a>	miR-200c

<b>Reference</b>	<b>Biomarker</b>
Karagiannis K, Sato H, Stock C, Handa T, Antoniou KM, Maher TM, Wells A, Lindahl G, Renzoni EA. Activin A And Follistatin Like-3 Levels In Bronchoalveolar Lavage Fluid Of Patients With Systemic Sclerosis Related Interstitial Lung Disease. Am J Respir Crit Care Med. 2014;189:[Abstract ID – A1997]. DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A1997">10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A1997</a>	Activin A
Kennedy B, Branagan P, Moloney F, Haroon M, O'Connell OJ, O'Connor TM, O'Reagan K, Harney S, Henry MT. Biomarkers to identify ILD and predict lung function decline in scleroderma lung disease or idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2015;32(3):228-36.	Serum KL-6, SP-D and MMP7
Kowal-Bielecka O, Chwiesko-Minarowska S, Bernatowicz PL, Allanore Y, Radstake T, Matucci-Cerinic M, Broen J, Hesselstrand R, Krasowska D, Riemekasten G. The arachidonate 5-lipoxygenase activating protein gene polymorphism is associated with the risk of scleroderma-related interstitial lung disease: a	ALOX5AP single nucleotide polymorphisms

Reference	Biomarker
multicentre European Scleroderma Trials and Research group (EUSTAR) study.  Rheumatology (Oxford). 2017;56(5):844-52.  DOI: <a href="https://doi.org/10.1093/rheumatology/kew499">10.1093/rheumatology/kew499</a>	
Kozi J NK, Granton JT, Silkoff PE, Thenganatt J, Chakravorty S, Johnson SR. Exhaled Nitric Oxide in Systemic Sclerosis Lung Disease. Can Respir J. 2017;2017:Article ID 6736239.  DOI: <a href="https://doi.org/10.1155/2017/6736239">10.1155/2017/6736239</a>	Exhaled nitric oxide
Kranenburg P, van den Hombergh WM, Knaapen-Hans HK, van den Hoogen FH, Fransen J, Vonk MC. Survival and organ involvement in patients with limited cutaneous systemic sclerosis and anti-topoisomerase-I antibodies: determined by skin subtype or auto-antibody subtype? A long-term follow-up study.  Rheumatology (Oxford). 2016;55(11):2001-8.  DOI: <a href="https://doi.org/10.1093/rheumatology/kew298">10.1093/rheumatology/kew298</a>	ATAs
Kranenburg P, Van Den Hombergh WMT, Knaapen-Hans HK, van den Hoogen FH, Fransen J, Vonk MC. AB0650 Survival and Organ Involvement in Patients with Limited Cutaneous Systemic Sclerosis and Anti-	ATAs

<b>Reference</b>	<b>Biomarker</b>
Topoisomerase Antibodies. Ann Rheum Dis. 2016;75(Suppl 2):1126-7.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.2842">10.1136/annrheumdis-2016-eular.2842</a>	
Kumar U, Mittal S, Guleria R, Seith Bhalla A, Mohan A, Mathur S, Sreenivas V. HRCT chest score and bronchoalveolar lavage fluid cytology in assessment of disease activity of systemic sclerosis associated interstitial lung disease. Int J Rheum Dis. 2013;16(Suppl. 1):[Abstract ID – APLAR-0280].	Bronchoalveolar lavage levels of IL-6 and IL-7
Kuwana M, Shirai Y, Takeuchi T. Elevated Serum Krebs von den Lungen-6 in Early Disease Predicts Subsequent Deterioration of Pulmonary Function in Patients with Systemic Sclerosis and Interstitial Lung Disease. J Rheumatol. 2016;43(10):1825-31.  DOI: <a href="https://doi.org/10.3899/jrheum.160339">10.3899/jrheum.160339</a>	KL-6
Liaskos C, Marou E, Simopoulou T, Barmakoudi M, Efthymiou G, Scheper T, Meyer W, Bogdanos DP, Sakkas LI. Disease-related autoantibody profile in patients with systemic sclerosis. Autoimmunity. 2017;50(7):414-21.  DOI: <a href="https://doi.org/10.1080/08916934.2017.1357699">10.1080/08916934.2017.1357699</a>	ATA, anti-CENP and anti-NOR90

<b>Reference</b>	<b>Biomarker</b>
Liu X, Mayes M, Tan F, Harper B, Gonzalez EB, Draeger R, Sharif J, Reveille F, Arnett FC, Assassi, S. S.2.4 IL-8 and IL-10 correlate with severity of interstitial lung disease in SSc. Rheumatology (Oxford). 2012;51:ii3-5.  DOI: <a href="https://doi.org/10.1093/rheumatology/ker468">//doi.org/10.1093/rheumatology/ker468</a>	IL-8 and IL-10
Liu X, Mayes MD, Pedroza C, Draeger HT, Gonzalez EB, Harper BE, Reveille JD, Assassi S. Does C-reactive protein predict the long-term progression of interstitial lung disease and survival in patients with early systemic sclerosis? Arthritis Care Res. 2013;65(8):1375-80.  DOI: <a href="https://doi.org/10.1002/acr.21968">10.1002/acr.21968</a>	C-reactive protein
Martyanov V, Kim GJ, Hayes W, Du S, Ganguly BJ, Sy O, Lee SK, Bogatkevich GS, Schieven GL, Schiopu E, Marangoni RG, Goldin J, Whitfield ML, Varga J. Novel lung imaging biomarkers and skin gene expression subsetting in dasatinib treatment of systemic sclerosis-associated interstitial lung disease. PLoS One. 2017;12(11):e0187580.  DOI: <a href="https://doi.org/10.1371/journal.pone.0187580">10.1371/journal.pone.0187580</a>	Serum biomarker assays and skin biopsy-based gene expression

Reference	Biomarker
Masui Y, Asano Y, Takahashi T, Shibata S, Akamata K, Aozasa N, Noda S, Taniguchi T, Ichimura Y, Toyama T, Tamaki Z, Sumida H, Yanaba K, Tada Y, Sugaya M, Sato S, Kadono T. Clinical significance of monitoring serum adiponectin levels during intravenous pulse cyclophosphamide therapy in interstitial lung disease associated with systemic sclerosis. <i>Mod Rheumatol.</i> 2013;23(2):323-9. DOI: <a href="https://doi.org/10.1007/s10165-012-0660-7">10.1007/s10165-012-0660-7</a>	Serum adiponectin levels
Mathai SK, Gulati M, Peng X, Russell TR, Shaw AC, Rubinowitz AN, Murray LA, Siner JM, Antin-Ozerkis DE, Montgomery RR, Reilkoff RA, Bucala RJ, Herzog EL. Circulating monocytes from systemic sclerosis patients with interstitial lung disease show an enhanced profibrotic phenotype. <i>Lab Invest.</i> 2010;90(6):812-23. DOI: <a href="https://doi.org/10.1038/labinvest.2010.73">10.1038/labinvest.2010.73</a>	Circulating monocytes
Morrisroe KB, Stevens W, Nandurkar H, Prior D, Thakkar V, Roddy J, Zochling J, Sahhar J, Tymms K, Sturgess A, Major G, Kermene F, Hill C, Walker J, Nash P, Gabbay E, Youssef P, Proudman SM, Nikpour M. The association of	Antiphospholipid antibodies

Reference	Biomarker
antiphospholipid antibodies with cardiopulmonary manifestations of systemic sclerosis. Clin Exp Rheumatol. 2014;32(6 Suppl 86):S-133-7.	
Nakashita T, Motojima S, Jibatake A, Yoshida A, Yamamoto Y. Serum level of KL-6, a biomarker of interstitial lung disease (ILD), is higher in diffuse SSC than in limited SSC and RA even when the activity of ILD is low. Arthritis Rheumatol. 2016;68(Suppl 10):3861-2.	Serum level of KL-6
DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	
Nan J, Li MT, Zeng XF. Correlation of th17 cells and CD4+CD25+ regulatory T cells with clinical parameters in patients with systemic sclerosis. Chin Med J. 2014;127(20):3557-61.	Th17 cells and CD4+CD25+ regulatory T cells
DOI: <a href="https://doi.org/10.3760/cma.j.issn.0366-6999.20141395">10.3760/cma.j.issn.0366-6999.20141395</a>	
Nicola S, Fusaro E, Rolla G, Bucca C, Peroni C, et al. AB0643 Th-17 Cytokines and Interstitial Lung Involvement in Systemic Sclerosis. Ann Rheum Dis. 2016;75(Suppl 2):1124.	Th17-related cytokines
DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.5626">10.1136/annrheumdis-2016-eular.5626</a>	
Odani T, Yasuda S, Ota Y, Fujieda Y, Kon Y, Horita T, Kawaguchi Y, Atsumi T, Yamanaka H,	HLA-DRB5 and HLA-DRB5*01:05 allele

Reference	Biomarker
Koike T. Up-regulated expression of HLA-DRB5 transcripts and high frequency of the HLA-DRB5* 01: 05 allele in scleroderma patients with interstitial lung disease. <i>Rheumatology (Oxford)</i> . 2012;51(10):1765-74.  DOI: <a href="https://doi.org/10.1093/rheumatology/kes149">10.1093/rheumatology/kes149</a>	
Olewicz-Gawlik A, Danczak-Pazdrowska A, Kuznar-Kaminska B, Gornowicz-Porowska J, Katulska K, Trzybulska D, Batura-Gabryel H, Silny W, Poplawski D, Hrycaj P. Interleukin-17 and interleukin-23: importance in the pathogenesis of lung impairment in patients with systemic sclerosis. <i>Int J Rheum Dis</i> . 2014;17(6):664-70.  DOI: <a href="https://doi.org/10.1111/1756-185X.12290">10.1111/1756-185X.12290</a>	IL-17, IL-21 and IL-23
Pauling JD, Salazar G, Lu H, Betteridge ZE, Assassi S, Mayes MD, McHugh NJ. Presence of anti-eukaryotic initiation factor-2B, anti-RuvBL1/2 and anti-synthetase antibodies in patients with anti-nuclear antibody negative systemic sclerosis. <i>Rheumatology (Oxford, England)</i> . 2018;57(4):712-7.  DOI: <a href="https://doi.org/10.1093/rheumatology/kex458">10.1093/rheumatology/kex458</a>	Anti-eIF2B

<b>Reference</b>	<b>Biomarker</b>
Raslan A, Stermer C, Hsu V. The clinical relevance of common ANA patterns in systemic sclerosis. <i>Arthritis Rheumatol.</i> 2016;68(Suppl 10):3895-7.  DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	ANA patterns (homogeneous, speckled, nucleolar, centromere, and mixed) and SSc autoantibodies: RNA Polymerase III, ATA, U-1 RNP, and ACA.
Riemekasten G, Siegert E, Heidecke H. Antibodies against the chemokine receptors CXCR3 and cxcr4 predict progressive lung fibrosis in systemic sclerosis (SSC). <i>Arthritis Rheumatol.</i> 2017;69:[Abstract ID – 724].	Anti-CXCR3 and anti-CXCR4 antibody
Rocha TM, Fonseca R, Rosa-Gonçalves D, Aguiar F, Meirinhos T, Bernardes M, Bernado A, Costa L. Anti-Ssa/ro Antibodies in A Cohort of Systemic Sclerosis Patients: The Association with Interstitial Lung Disease. <i>Ann Rheum Dis.</i> 2016;75:1125.  DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.2573">10.1136/annrheumdis-2016-eular.2573</a>	Anti-SSA/Ro
Rolla G, Fusaro E, Nicola S, Bucca C, Peroni C, Parisi S, Cassinis MC, Ferraris A, Angelino F, Heffler E, Boita M, Brussino L. Th-17 cytokines and interstitial lung involvement in systemic sclerosis. <i>J Breath Res.</i> 2016;10(4):046013.	Th17-related cytokines (IL1- $\beta$ , IL-6, IL-17, IL-21, IL-22, IL-23, TGF- $\beta$ ) and proinflammatory (TNF- $\alpha$ ) and anti-inflammatory (IL-10)

Reference	Biomarker
DOI: <a href="https://doi.org/10.1088/1752-7155/10/4/046013">10.1088/1752-7155/10/4/046013</a>	
Rotondo C, Praino E, Lanciano E, Fornaro M, Lopalco G, Nivuori MG, Iannone F, Lapadula G.  Residual volume: A candidate as early marker of interstitial lung disease in systemic sclerosis patients? Clin Exp Rheumatol. 2014;32(2):S83.	Residual volume
Saigusa R, Asano Y, Nakamura K, Yamashita T, Ichimura Y, Takahashi T, Toyama T, Taniguchi T, Yoshizaki A, Miyazaki M, Tamaki Z, Sato S.  Plasma plasmin- $\alpha$ 2-plasmin inhibitor complex levels may predict the effect of cyclophosphamide for systemic sclerosis-related interstitial lung disease. Mod Rheumatol. 2017;27(4):618-22.	Plasma PIC levels
DOI: <a href="https://doi.org/10.1080/14397595.2016.1226472">10.1080/14397595.2016.1226472</a>	
Sakamoto N, Kakugawa T, Hara A, Nakashima S, Yura H, Harada T, Ishimoto H, Yatera K, Kuwatsuka Y, Hara T, Ichinose K, Obase Y, Ishimatsu Y, Kohno S, Mukae H. Association of elevated alpha-defensin levels with interstitial pneumonia in patients with systemic sclerosis.  Respir Res. 2015;16:148.	HNPs and IL-8
DOI: <a href="https://doi.org/10.1186/s12931-015-0308-1">10.1186/s12931-015-0308-1</a>	

<b>Reference</b>	<b>Biomarker</b>
Salazar G, Kuwana M, Wu M, Ying J, Charles J, Mayes MD, Assassi S. KL-6 and not CCL-18 is a predictor of early progression in systemic sclerosis related interstitial lung disease. <i>Arthritis Rheumatol.</i> 2016;68(Suppl 10):1097-8. DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	KL-6
Sfriso P, Cozzi F, Oliviero F, Caso F, Cardarelli S, Facco M, Fitta C, Del Rosso A, Matucci-Cerinic M, Punzi L, Agostini C. CXCL11 in bronchoalveolar lavage fluid and pulmonary function decline in systemic sclerosis. <i>Clin Exp Rheumatol.</i> 2012;30(2 Suppl 71):S71-5.	CXCL11
Sosnovskaya A, Fomin V, Novikov P, Frerix M, Mukhin N. Serum Surfactant Protein D in Systemic Sclerosis Lung Fibrosis by Presence or Absence of Gastroesophageal Reflux: A Crossectional Monocentric Study. <i>Ann Rheum Dis.</i> 2015;74(Suppl 2):592. DOI: <a href="https://doi.org/10.1136/annrheumdis-2015-eular.5054">10.1136/annrheumdis-2015-eular.5054</a>	SP-D levels
Takahashi T, Asano Y, Akamata K, Aozasa N, Taniguchi T, Noda S, Masui Y, Ichimura Y, Toyama T, Tamaki Z, Tada Y, Sugaya M, Kadono T, Sato S. Dynamics of serum Angiopoietin-2	Angiopoietin-2

Reference	Biomarker
angiopoietin-2 levels correlate with efficacy of intravenous pulse cyclophosphamide therapy for interstitial lung disease associated with systemic sclerosis. Mod Rheumatol. 2013;23(5):884-90. DOI: <a href="https://doi.org/10.3109/s10165-012-0755-1">10.3109/s10165-012-0755-1</a>	
Takekoshi D, Arami S, Sheppard TJ, Cole- Saffold P, Michel JC, Kondos GT, Schraufnagel DE. Computed tomography of the esophagus in scleroderma and lung disease. Tohoku J Exp Med. 2015;237(4):345-52. DOI: <a href="https://doi.org/10.1620/tjem.237.345">10.1620/tjem.237.345</a>	Oesophageal dysfunction
Taniguchi T, Asano Y, Akamata K, Aozasa N, Noda S, Takahashi T, Ichimura Y, Toyama T, Sumida H, Kuwano Y, Yanaba K, Tada Y, Sugaya M, Kadono T, Sato S. Serum levels of ADAM12-S: possible association with the initiation and progression of dermal fibrosis and interstitial lung disease in patients with systemic sclerosis. J Eur Acad Dermatol Venereol. 2013;27(6):747-53. DOI: <a href="https://doi.org/10.1111/j.1468-3083.2012.04558.x">10.1111/j.1468-3083.2012.04558.x</a>	ADAM12-S
Thakkar V, Patterson K, Stevens W, Byron J, Moore O, Roddy J, Zochling J, Sahhar J, Nash	ICAM-1 and VCAM-1

Reference	Biomarker
P, Tymms K, Youssef P, Proudman S, Hissaria P, Nikpour M. Serum ICAM-1 levels are related to the presence of interstitial lung disease in systemic sclerosis. <i>Pulm Circ.</i> 2011;1:S38-8.	
Tiev KP, Riviere S, Hua-Huy T, Cabane J, Dinh-Xuan AT. Exhaled NO predicts cyclophosphamide response in scleroderma-related lung disease. <i>Nitric Oxide.</i> 2014;40:17-21.	Baseline alveolar concentration of nitric oxide
DOI: <a href="https://doi.org/10.1016/j.niox.2014.04.011">10.1016/j.niox.2014.04.011</a>	
Truchetet ME, Bremilla NC, Montanari E, Allanore Y, Chizzolini C. Increased frequency of circulating Th22 in addition to Th17 and Th2 lymphocytes in systemic sclerosis: association with interstitial lung disease. <i>Arthritis Res Ther.</i> 2011;13(5):R166.	Circulating Th22 cells
DOI: <a href="https://doi.org/10.1186/ar3486">10.1186/ar3486</a>	
Volkmann E, Tashkin D, Elashoff R, Tseng CH, Khanna D, Mayes M, Charles J, Clements P, Roth M, Furst D, Assassi S. Change in CXCL4 Levels May Predict Treatment Response in Systemic Sclerosis-Related Interstitial Lung Disease (SSC-ILD). <i>Ann Rheum Dis.</i>	CXCL4

Reference	Biomarker
2016;75:535.1. DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.3799">10.1136/annrheumdis-2016-eular.3799</a>	
Volkmann ER, Tashkin DP, Hant FN, Bogatkevich GS, Roth M, Hyun K, Goldin J, Akter T, Wilhalme H, Tseng C-H. Surfactant Protein D and Krebs Von Den Lungen-6 Predict Severity of Systemic Sclerosis-Related Interstitial Lung Disease in Two Independent Cohorts. Arthritis Rheumatol. 2016; 68(Suppl 10):4339-40. DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	KL-6 and SP-D
Volkmann ER, Tashkin DP, Roth MD, Clements PJ, Khanna D, Furst DE, Mayes M, Charles J, Tseng C-H, Elashoff RM, Assassi, S. Changes in plasma CXCL4 levels are associated with improvements in lung function in patients receiving immunosuppressive therapy for systemic sclerosis-related interstitial lung disease. Arthritis Res Ther. 2016;18:305. DOI: <a href="https://doi.org/10.1186/s13075-016-1203-y">10.1186/s13075-016-1203-y</a>	CXCL4
Wangkaew S, Euathrongchit J, Wattanawittawas P, Kasitanon N, Louthrenoo W. Incidence and predictors of interstitial lung disease (ILD) in Thai	ATAs, and absence of ACAs

Reference	Biomarker
patients with early systemic sclerosis: Inception cohort study. Mod Rheumatol. 2016;26(4):588-93. DOI: <a href="https://doi.org/10.3109/14397595.2015.1115455">10.3109/14397595.2015.1115455</a>	
Watanabe S, Saeki K, Waseda Y, Takato H, Ichikawa Y, Murata A, Hara J, Sone T, Abo M, Kimura H. KL-6 As A Predictor Of Progression In Scleroderma-Associated Interstitial Lung Disease. Am J Respir Crit Care Med. 2017;195:[Abstract ID – A5424]. DOI: <a href="https://doi.org/10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5424">10.1164/ajrccm-conference.2017.195.1_MeetingAbstracts.A5424</a>	KL-6
Weigold F, Günther J, Pfeiffenberger M, Cabral- Marques O, Siegert E, Dragun D, Philippe A, Regensburger A-K, Recke A, Yu X. Antibodies against chemokine receptors CXCR3 and CXCR4 predict progressive deterioration of lung function in patients with systemic sclerosis. Arthritis Res Ther. 2018;20(1):52. DOI: <a href="https://doi.org/10.1186/s13075-018-1545-8">10.1186/s13075-018-1545-8</a>	CXCR3 and CXCR4
Wodkowski M, Hudson M, Proudman S, Walker J, Stevens W, Nikpour M, Assassi S, Mayes MD, Wang M, Baron M, Fritzler MJ. Monospecific	Anti-Ro52/TRIM21 antibodies

Reference	Biomarker
anti-Ro52/TRIM21 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects: evidence of an association with interstitial lung disease and worse survival. Clin Exp Rheumatol. 2015;33(4 Suppl 91):S131-5.	
Wu M, Baron M, Hudson M, Fritzler MJ, Pedroza C, Ying J, Salazar G, Charles J, Mayes MD, Assassi S. Serum MCP-1 Levels Predict Long-Term Progression of Interstitial Lung Disease in Systemic Sclerosis. Arthritis Rheumatol. 2016;68 (Suppl 10):[Abstract ID – 3250].	MCP-1
DOI: <a href="https://doi.org/10.1002/art.39977">10.1002/art.39977</a>	
Wu M, Baron M, Pedroza C, Salazar GA, Ying J, Charles J, Agarwal SK, Hudson M, Pope J, Zhou X, Reveille JD, Fritzler MJ, Mayes MD, Assassi S. CCL2 in the circulation predicts long-term progression of interstitial lung disease in patients with early systemic Sclerosis: Data from two independent cohorts. Arthritis Rheumatol. 2017;69(9):1871-8	CCL2
DOI: <a href="https://doi.org/10.1002/art.40171">10.1002/art.40171</a>	
Yamaguchi Y, Shirai Y, Ono J, Kawaguchi Y, Izuhara K, Kuwana M, Aihara M. An elevated	Periostin

Reference	Biomarker
circulating level of periostin in patients with systemic sclerosis: Associations with functional impairment in various affected organs. <i>J Invest Dermatol.</i> 2017;137(5):S62. DOI: <a href="https://doi.org/10.1016/j.jid.2017.02.377">10.1016/j.jid.2017.02.377</a>	
Yamakawa H, Hagiwara E, Kitamura H, Yamanaka Y, Ikeda S, Sekine A, Baba T, Okudela K, Iwasawa T, Takemura T. Serum KL-6 and surfactant protein-D as monitoring and predictive markers of interstitial lung disease in patients with systemic sclerosis and mixed connective tissue disease. <i>J Thorac Dis.</i> 2017;9(2):362. DOI: <a href="https://doi.org/10.21037/jtd.2017.02.48">10.21037/jtd.2017.02.48</a>	KL-6 and SP-D
Yanaba K, Asano Y, Noda S, Akamata K, Aozasa N, Taniguchi T, Takahashi T, Ichimura Y, Toyama T, Sumida H, Kuwano Y, Tada Y, Sugaya M, Kadono T, Sat, S. Increased production of soluble inducible costimulator in patients with diffuse cutaneous systemic sclerosis. <i>Arch Dermatol Res.</i> 2013;305(1):17-23. DOI: <a href="https://doi.org/10.1007/s00403-012-1292-7">10.1007/s00403-012-1292-7</a>	Serum sICOS level

<b>Reference</b>	<b>Biomarker</b>
<p>Yanaba K, Yoshizaki A, Muroi E, Ogawa F, Shimizu K, Sato S. Increased circulating soluble vascular adhesion protein-1 levels in systemic sclerosis: association with lower frequency and severity of interstitial lung disease. <i>Int J Rheum Dis.</i> 2013;16(4):442-7.</p> <p>DOI: <a href="https://doi.org/10.1111/1756-185X.12094">10.1111/1756-185X.12094</a></p>	Vascular adhesion protein-1
<p>Zanatta E, Martini A, Biasiolo A, Pigatto E, Bourji K, Favaro M, Punzi L, POnxisso P, Cozzi F. Squamous cell carcinoma antigen SCCA-IgM is up-regulated in scleroderma patients with reduced DLCO: A new biomarker of pulmonary involvement? <i>Ann Rheum Dis.</i> 2016;75(Suppl 2):522.</p> <p>DOI: <a href="https://doi.org/10.1136/annrheumdis-2016-eular.4283">10.1136/annrheumdis-2016-eular.4283</a></p>	
<p>Zhao J, Wang K, Ye S. Peripheral CD4 + CXCR4 + T cell proportion is a potential diagnostic biomarker for connective tissue disease associated interstitial lung diseases. <i>Int J Rheum Dis.</i> 2016;19(Suppl 2):40.</p> <p>DOI: <a href="https://doi.org/10.1111/1756-185X.12962">10.1111/1756-185X.12962</a></p>	CD4 + CXCR4 + T cell proportion

ACA; anti-centromere antibody; ADAM 12-S ADAM metallopeptidase domain 12-S; ALOX5AP arachidonate 5-lipoxygenase activating protein; ANA antinuclear antibody; ATA anti-topoisomerase I antibody; BICD2 bicaudal D2; CCL C-C motif

chemokine ligand; CD cluster of differentiation; CENP centromere protein; COMP cartilage oligomeric matrix protein; CX3CL1 C-X3-C motif chemokine ligand 1; CXCL C-X-C motif chemokine ligand; CXCR C-X-C motif chemokine receptor; eIF2B anti-eukaryotic initiation factor-2B; FDG-PET fluorodeoxyglucose position emission tomography; HLA human leukocyte antigen; HNP human neutrophil peptide; HRCT high-resolution computed tomography; ICAM intercellular adhesion molecule 1-1; IL interleukin; KL-6 Krebs von den Lungen 6; MCP-1 monocyte chemoattractant protein-1; miR microRNA; MMP matrix metalloproteinase; NOR nucleolus-organising region; PIC plasmin- $\alpha$ 2-plasmin inhibitor complex; PINP procollagen type I N propeptide; PIIINP procollagen type III N-terminal peptide; S100 S100 Calcium-Binding Protein; sICOS serum soluble inducible costimulator; SP-D serum surfactant protein D; sPSGL-1 soluble P-selectin glycoprotein ligand 1; TAA tumour-associated antigen; Th22 T helper 22; TGF- $\beta$  transforming growth factor beta; TNF- $\alpha$  tumour necrosis factor alpha; TRIM21 tripartite motif containing 21; VCAM-1 vascular cell adhesion molecule 1; VEGF vascular endothelial growth factor.