


## Original article

# Disease frequency, patient characteristics, comorbidity outcomes and immunosuppressive therapy in systemic sclerosis and systemic sclerosis-associated interstitial lung disease: a US cohort study

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## Abstract

**Objectives.** To investigate prevalence estimates and incidence rates (IRs) for SSc and SSc-associated interstitial lung disease (SSc-ILD) cohorts and describe patient characteristics, immunosuppressive therapy (IST) and comorbid outcomes among incident SSc and SSc-ILD cohorts.

**Methods.** Data were obtained from the US IBM MarketScan (2008–2017) claims database using algorithms developed with expert consultation. For the SSc cohort, newly diagnosed patients (aged  $\geq 18$  years) had one or more diagnostic claim for SSc. For the SSc-ILD cohort, patients had an additional ILD claim. Sensitivity analyses using two or more claims or alternative ILD diagnostic codes were also conducted.

**Results.** When requiring one or more diagnostic claim, the prevalence of SSc and SSc-ILD per 100 000 persons was 72.1 and 19.0. The IR for SSc and SSc-ILD per 100 000 person-years was 18.3 and 4.3. Sensitivity analyses requiring two or more claims yielded much lower prevalence (SSc: 41.5; SSc-ILD: 13.3) and IR (SSc: 8.8; SSc-ILD: 1.6) estimates. Patients with SSc-ILD were older, with increased comorbidities and diagnostic procedures at baseline. MTX and MMF were the most common ISTs; 12.7% of the SSc-ILD cohort received therapy at baseline vs 8.2% for SSc. A total of 42.5% and 45.0% of the SSc and SSc-ILD cohorts, respectively, started a stable IST regimen and 21.7% and 19.4% of these had an escalation. Skin disorders were the most common comorbid outcome in both cohorts during follow-up.

**Conclusions.** SSc, with or without associated ILD, is a rare disease in the US. Newly diagnosed patients with SSc-ILD had received more IST and had more comorbidities compared with newly diagnosed SSc.

**Key words:** systemic sclerosis, scleroderma, interstitial lung disease, rheumatology, epidemiology, rare disease

## Rheumatology key messages

- SSc-ILD, with an incidence of 4.3/100 000 person-years, presents more incident comorbid outcomes compared with SSc.
- Of patients with SSc-ILD, 12.7% initiated immunosuppressive therapy after diagnosis vs 8.2% for SSc.
- MTX and MMF were the most common immunosuppressive therapies for both cohorts.

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## Introduction

SSc is a rare, heterogeneous chronic connective tissue disease characterized by progressive fibrosis of the skin and internal organs [1, 2]. The clinical course is variable, but organ manifestations tend to occur early in the course of the disease [2, 3]. Interstitial lung disease (ILD) is a common occurrence and the leading cause of death in SSc, responsible for approximately one-third of

SSc-related deaths [4–7]. Previous studies suggest that progressive ILD affects 19–47% of patients with SSc (depending on the definition of ILD used) [6, 8–11] and most patients that develop ILD do so within the first 5 years following the onset of SSc symptoms [12]. The majority of patients with ILD associated with SSc (SSc-ILD) show a non-specific interstitial pneumonia pattern of fibrosis on high-resolution CT (HRCT) [13].

As SSc-ILD follows a variable clinical course, treatment decisions need to be made on a case-by-case basis, which can be aided by a better understanding of the natural history of SSc-ILD and patient characteristics. While most patients experience a slow decline in lung function, some patients progress rapidly, with progression defined as decreased lung function and an increased extent of fibrosis on HRCT scans [7]. Patients experience extensive disease burden, including greater absenteeism and higher medication use, healthcare costs and resource utilization compared with matched controls [14].

Given that no targeted treatments were available [15] until the approval of the tyrosine kinase inhibitor nintedanib in 2019 [16], patients with SSc, especially SSc-ILD, have a high unmet medical need. Although treatment recommendations are available [15], there is no established treatment algorithm for SSc-ILD. The lack of targeted therapies and known immune system involvement has led to immunosuppressive therapies (ISTs) such as CYC, MTX and MMF being used as the main treatment option [17]. MTX has been shown to improve the skin score in early dcSSc, but beneficial effects in other systems, including the lungs, have not yet been established [15]. CYC may slow ILD progression [18], but its known toxicity limits its duration of use [15]. Although the Scleroderma Lung Study (SLS) II indicated that MMF was better tolerated and equally effective compared with CYC [19], it is not currently included in the treatment guidelines for SSc or SSc-ILD [15]. There is a need to better understand current clinical treatment patterns and efficacy, especially for ISTs, in SSc-ILD.

As there is now a new treatment option available, it is increasingly important to understand existing IST patterns, real-world epidemiology and clinical outcomes in SSc and SSc-ILD. To address these evidence gaps, the present study investigated SSc and SSc-ILD in a major US claims database using algorithms that were developed in consultation with experts. We aimed to investigate prevalence estimates and incidence rates (IRs) for SSc and SSc-ILD among commercial claims, patient characteristics among patients with incident SSc and SSc-ILD, ISTs and dose escalations among each cohort with sufficient follow-up and, finally, comorbidity outcomes.

## Methods

### Data source and ethics

We used the US IBM MarketScan claims database from 2008 to 2017 to identify patients with SSc and SSc-ILD

as defined by International Classification of Diseases (ICD) 9th and 10th revision diagnostic codes appearing on medical claims. The database consists of de-identified outpatient, inpatient and pharmaceutical claims of ~40–50 million privately insured patients each year originating from >150 large employer-sponsored health insurance plans across the US. In this study, a new algorithm was developed in consultation with a rheumatologist specializing in CTD-associated lung diseases, including ILD, to identify patients with SSc and SSc-ILD from the database (Supplementary Table S1, available at *Rheumatology* online). The study protocol was reviewed and approved by the New England Independent Review Board (#120180270).

### Study population

All patients who were  $\geq 18$  years of age with a continuous enrolment of  $\geq 365$  days between 2009 and 2017 were included in the general population cohort used to calculate the prevalence proportion and IR estimates. Among which, a newly diagnosed SSc cohort included all patients with any inpatient or outpatient diagnostic claim for SSc (ICD-9-CM 710.1 or ICD-10-CM M34.x; Supplementary Table S1, available at *Rheumatology* online) requiring a 365-day washout to determine a new diagnosis. The date of the first SSc diagnosis was defined as the index date.

For the newly diagnosed SSc-ILD cohort, patients were included if they met the inclusion criteria for the newly diagnosed SSc cohort and additionally had an ILD claim (Supplementary Table S1, available at *Rheumatology* online) within 365 days prior to, on or any time after the first SSc diagnosis date. The date of the latter of either the first SSc diagnosis or the first ILD diagnosis was defined as the index date.

For both the SSc and SSc-ILD cohorts, the baseline period was the 365 days prior to and ending 1 day prior to the index date. The follow-up period was defined as the index date until either disenrolment from the health plan, inpatient death or the end of the study period, whichever was first. Follow-up for IR of SSc and SSc-ILD was further censored upon diagnosis with SSc or SSc-ILD, respectively.

In order to evaluate the initiation of ISTs, subsequent SSc and SSc-ILD cohorts further excluded patients with IST during the baseline period.

### Outcomes

The primary outcome of the study was initiation of IST (first therapy per patient), defined as initiation of one or more of the following therapies during the follow-up period: CYC, MMF, AZA, rituximab, MTX, tocilizumab, tacrolimus, ciclosporin or anti-TNF drugs. Further outcomes included prevalence estimates (new or existing diagnosis, allowing existing diagnosis to occur in 2008 prior to satisfying the 365-day enrolment criteria) and IRs (new diagnosis). Prevalence proportions and IRs are presented as the number of patients with the condition

per 100 000 patients and 100 000 person-years, respectively. Objectives also included the following events during the follow-up period (considered independently of each other and evaluated among patients without each condition during baseline): escalation of IST during the follow-up period, lung transplantation, acute respiratory failure, pulmonary hypertension, pulmonary arterial hypertension, digital ulcers, gastrointestinal perforation, major adverse cardiovascular events, bleeding and the frequency of comorbidities during follow-up. Inpatient mortality was also determined and included deaths that occurred within the hospital setting. Escalation of IST was defined as a dose increase or switching or adding of IST after  $\geq 180$  days of a stable IST regimen. Because 180 days were required to qualify for each stable regimen, escalation events could only be evaluated among patients with sufficient enrolment during follow-up and only the first two escalation events were assessed.

### Covariates

Covariates included age, gender, geographic region, length of enrolment prior to the index date, cohort entry year, comorbidities and medical treatments or procedures.

### Analyses

All analyses were performed using the Aetion Evidence Platform (version 3.12; Aetion, New York, NY, USA). Baseline characteristics, IST course and outcomes during follow-up were analysed with descriptive statistics.

Incident SSc and SSc-ILD cohorts were described according to covariates during baseline and selected a priori, including demographics, medical and dispensing drug/treatment history, comorbidities and healthcare utilization. The prevalence of comorbidities during baseline was calculated as the number of patients in the cohort with the condition during the 365-day baseline period divided by the total number of patients in the cohort.

For patients that initiated IST, we analysed data for the percentage of patients, time from index date to initiation, initial dose and combination of therapies. For patients on a stable regimen, we analysed dose, combination of therapies and number of patients who escalated therapies. For patients who escalated therapy, we analysed dose and combination of therapies at the first two escalation events.

The IR of study outcomes during the follow-up period was calculated as the number of patients in the cohort with an incident outcome divided by the sum of person-time at risk for the outcome.

Two sensitivity analyses were conducted. In the first sensitivity analysis, the newly diagnosed SSc cohort required two or more claims for SSc and the newly diagnosed SSc-ILD cohort required two or more claims for SSc and two or more claims for ILD. The index date was defined as the date of the second SSc claim for the newly diagnosed SSc cohort and the latest date of

either the first two SSc claims or the first two ILD claims in the SSc-ILD cohort. This represents a more specific algorithm for defining these two diseases, which had a higher probability of the true presence of disease compared with the more sensitive algorithm in the main analysis. In the second sensitivity analysis, the algorithm for newly diagnosed patients in the SSc cohort was the same as the main analysis; however, a subset of diagnostic codes for ILD (Supplementary Table S1, available at *Rheumatology* online) was used to define the SSc-ILD cohort, further ruling out some patients whose ILD may not have resulted from SSc.

## Results

### Population prevalence and incidence

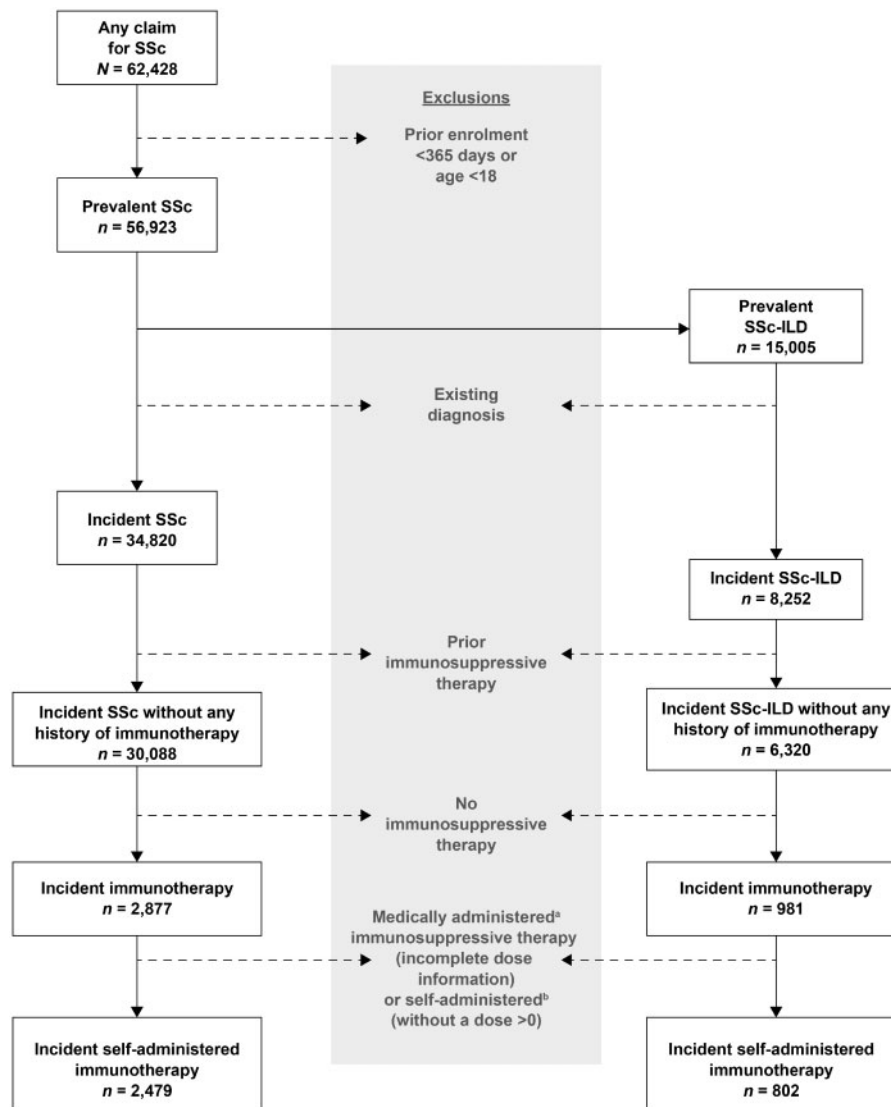
Among a total of 62 428 patients with one or more claim for SSc, there were 56 923 and 15 005 patients satisfying the inclusion criteria for prevalent SSc and SSc-ILD, respectively (Fig. 1). In the main analysis, among the population at risk ( $N=78\,964\,708$ ), the prevalence of SSc and SSc-ILD per 100 000 persons was 72.1 and 19.0, respectively (Table 1), and higher among females (115.8 and 30.2) than males (24.0 and 6.7). There were 34 820 patients with incident SSc and 8252 with incident SSc-ILD overall (18.3 and 4.3 per 100 000 patient-years), and more females (29.0 and 6.7) than males (6.3 and 1.7).

In the first sensitivity analysis (SSc: two or more SSc claims; SSc-ILD: two or more SSc claims plus two or more ILD claims), prevalence was 41.5 and 9.8 per 100 000 persons and the IR was 8.8 and 1.6 per 100 000 person-years for SSc and SSc-ILD, respectively. When requiring two claims, the prevalence of SSc and SSc-ILD dropped by 42.4% and 48.4% compared with the main analysis; IRs also dropped by 51.9% and 62.8% for SSc and SSc-ILD. In the second sensitivity analysis of SSc-ILD only, where patients had a more specific set of ILD diagnostic codes, prevalence was 13.3 per 100 000 persons and the IR was 2.7 per 100 000 person-years.

Incident cohorts of patients with SSc ( $n=34\,820$ ) and SSc-ILD ( $n=8252$ ) were largely female (83.7% and 81.8%), with mean ages of 53.6 and 58.3 years, respectively (Table 2).

Patients with SSc-ILD had more respiratory-related diagnostic procedures during baseline than all patients with SSc during baseline, including pulmonary function tests (46.0% vs 15.9%) and HRCT (29.9% vs 7.4%; Table 2). Rates of procedures were consistent within both cohorts irrespective of whether patients were IST naïve. The prevalence of comorbidities during the baseline period was higher among newly diagnosed patients in the SSc-ILD cohort compared with the SSc cohort, including general or any skin disorders (34.5% vs 28.8%), gastroesophageal reflux disease (GERD; 28.5% vs 17.9%) and chronic obstructive pulmonary disease (COPD; 20.7% vs 7.6%) (Table 3).

Fig. 1 Cohort inclusion flowchart



SSc was defined as an inpatient or outpatient diagnostic claim for SSc. SSc-ILD was defined as an inpatient or outpatient diagnostic claim for lung fibrosis occurring within 365 days prior to SSc or on or after SSc. If prior to SSc, the SSc-ILD event date was assigned based on the SSc date. <sup>a</sup>Medically administered therapy was defined as therapy that needed to be given by healthcare providers, such as drugs given intravenously or through injection, and were captured via inpatient or outpatient medical claims. <sup>b</sup>Self-administered therapy was defined as therapy that could be taken by patients themselves, such as oral drugs or auto-injectable devices, and were captured via outpatient prescription claims.

### IST

Among IST-naïve patients in the SSc and SSc-ILD cohorts [30 088/34 820 (86.4%) and 6320/8252 (76.6%) patients, respectively] with a median follow-up of 599 and 517 days (Fig. 1), 9.6% and 15.5% initiated IST (either medically or self-administered) a median of 152 and 114 days after diagnosis, respectively. For self-administered IST, where dose information is available via prescription claims, 8.2% and 12.7% had a new

prescription claim a median of 145 and 115 days after diagnosis (Table 4), respectively. The most frequently initiated ISTs in the SSc cohort were MTX (48.4%), MMF (31.3%) and AZA (13.3%); in the SSc-ILD cohort these were MMF (52.6%), MTX (23.4%) and AZA (14.6%).

Among patients with  $\geq 180$  days of follow-up (SSc: 2002; SSc-ILD: 653), 42.5% and 45.0% started a stable regimen within a median of 88 and 87 days after IST initiation. The main therapies during the first stable



**TABLE 2** Patient characteristics at baseline among patients with newly diagnosed SSc and SSc-ILD

Characteristics	All patients		IST-naïve patients	
	SSc (n = 34 820)	SSc-ILD (n = 8252)	SSc (n = 30 088)	SSc-ILD (n = 6320)
Age, years, mean (s.d.)	53.6 (14.48)	58.3 (13.46)	54.0 (14.56)	59.4 (13.45)
Sex, n (%)				
Female	29 141 (83.7)	6750 (81.8)	25 171 (83.7)	5169 (81.8)
Diagnostic procedures at baseline, n (%)				
Chest X-ray	12 147 (34.9)	5296 (64.2)	9950 (33.1)	3978 (62.9)
Chest CT	4678 (13.4)	3658 (44.3)	3605 (12.0)	2719 (43.0)
HRCT	2588 (7.4)	2465 (29.9)	1948 (6.5)	1797 (28.4)
Auto-antibodies	12 598 (36.2)	3328 (40.3)	10 798 (35.9)	2519 (39.9)
Heart ultrasound	1765 (5.1)	776 (9.4)	1464 (4.9)	597 (9.4)
Abdomen ultrasound	4229 (12.1)	1435 (17.4)	3486 (11.6)	1064 (16.8)
Regular lab tests	28 130 (80.8)	6946 (84.2)	23 915 (79.5)	5219 (82.6)
Any pulmonary function test <sup>a</sup>	5546 (15.9)	3794 (46.0)	4369 (14.5)	2746 (43.4)
Spirometry	5282 (15.2)	3623 (43.9)	4162 (13.8)	2621 (41.5)
Lung volume	1619 (4.6)	1450 (17.6)	1201 (4.0)	1004 (15.9)
Six-minute walk test	834 (2.4)	767 (9.3)	579 (1.9)	518 (8.2)

<sup>a</sup>Any pulmonary function test included spirometry, lung volume test or 6-min walking test in addition to pulmonary stress tests. Spirometry often co-occurred with other pulmonary function tests.

**TABLE 3** Prevalence of comorbidities during baseline among patients with newly diagnosed SSc and SSc-ILD

Comorbidity, prevalence per 100 persons (95% CI)	SSc (n = 34 820)	SSc-ILD (n = 8252)
Skin disorders	28.8 (28.3, 29.3)	34.5 (33.4, 35.5)
GERD	17.9 (17.5, 18.3)	28.5 (27.5, 29.4)
Upper respiratory tract infections	11.1 (10.8, 11.5)	11.3 (10.6, 12.0)
Type 2 diabetes mellitus	10.2 (9.8, 10.5)	13.2 (12.5, 13.9)
COPD	7.6 (7.3, 7.9)	20.7 (19.8, 21.5)
RP	7.8 (7.5, 8.1)	14.5 (13.8, 15.3)
Cardiac arrhythmia	6.5 (6.3, 6.8)	12.3 (11.6, 13.0)
Chronic and acute renal failure or insufficiency	6.7 (6.4, 6.9)	12.2 (11.5, 12.9)
Arterial hypertension	6.3 (6.0, 6.5)	13.8 (13.1, 14.6)
Pulmonary hypertension	3.2 (3.0, 3.4)	11.2 (10.6, 11.9)
Pneumonia	3.3 (3.1, 3.5)	11.4 (10.7, 12.1)
Urinary tract infections	6.3 (6.0, 6.5)	8.7 (8.1, 9.4)
Acute respiratory failure	1.5 (1.3, 1.6)	5.1 (4.6, 5.6)
Pulmonary arterial hypertension	0.1 (0.1, 0.2)	0.5 (0.3, 0.6)

regimen were MTX (41.8%) and MMF (37.5%) in the SSc cohort and MMF (60.2%) and MTX (17.3%) in the SSc-ILD cohort.

Of those patients who achieved a stable regimen for  $\geq 180$  days (SSc: 850; SSc-ILD: 294), 21.7% and 19.4% had an escalation after a median duration of 289 and 292 days of stable use, respectively. Among patients with SSc at first escalation, 7.6% ( $n = 14$ ) had an SSc-ILD diagnosis in the 14 days prior and 12.5% ( $n = 23$ )

had an SSc-ILD diagnosis within 30 days prior ([Supplementary Table S2](#), available at *Rheumatology* online). Among patients with sufficient enrolment to determine a subsequent stable regimen (141 and 44 patients), 61.0% and 66.0% were able to achieve a second stable regimen for median durations of 397 and 365 days. The median time between the start of the first and second stable regimen was 436 and 451 days. The main therapies during the second stable IST regimen

TABLE 4 Initiation and escalation of IST

Time, days, median (IQR)	SSc (n = 30 088)	SSc-ILD (n = 6320)
Time from index date to initiation of medically or self-administered IST <sup>a</sup>	152 (36–512)	114 (34–404)
Time from index date to initiation of self-administered IST with dose >0	145 (34–505)	115 (32–405)
Time from initiation of self-administered IST to start of first stable regimen <sup>b</sup>	88 (1–258)	87 (1–226)
Duration of first stable regimen	289 (221–426)	292 (22–455)
Time from first stable regimen to start of second stable regimen	436 (331–660)	451 (346–560)
Duration of second stable regimen	397 (268–515)	365 (240–477)

Patients receiving IST	Number with event/total qualifying, n	% (95% CI)	Number with event/total qualifying, n	% (95% CI)
Initiation of medically or self-administered IST	2877/30 088	9.6 (9.2, 9.9)	981/6320	15.5 (14.6, 16.4)
Initiation of self-administered IST with dose >0	2479/30 088	8.2 (7.9, 8.6)	802/6320	12.7 (11.9, 13.5)
Reaching first stable regimen after initiation, N (100%) <sup>b</sup>	850/2002 <sup>c</sup>	42.5 (40.3, 44.6)	294/653 <sup>c</sup>	45.0 (41.2, 48.8)
Escalation of IST after first stable regimen	184/850	21.7 (18.9, 24.4)	57/294	19.4 (14.9, 23.9)
Reaching second stable regimen after initiation <sup>c</sup>	86/141 <sup>c</sup>	61.0 (52.9, 69.0)	29/44 <sup>c</sup>	65.9 (51.9, 79.9)
Escalation of IST after the second stable regimen	15/86	17.4 (9.4, 25.5)	7/29	24.1 (8.6, 39.7)

<sup>a</sup>Medically administered therapy was defined as therapy that needed to be given by healthcare providers, such as drugs given intravenously or through injection, and were captured via inpatient or outpatient medical claims. Self-administered therapy was defined as therapy that could be taken by patients themselves, such as oral drugs or auto-injectable devices, and were captured via outpatient prescription claims. <sup>b</sup>Stable regimen defined as without escalation of IST for at least 6 months. <sup>c</sup>Total patients qualifying is reduced due to 180 days of continuous enrolment that is required in order to determine 180 days of stable regimen.

TABLE 5 Comorbid outcomes during follow-up

Comorbidity, IR per 100 person-years (95% CI) <sup>a</sup>	SSc (n = 34 820)	SSc-ILD (n = 8252)
Skin disorders	20.3 (19.9, 20.8)	23.3 (22.2, 24.4)
GERD	14.4 (14.1, 14.7)	22.6 (21.6, 23.6)
Arterial hypertension	6.1 (5.9, 6.3)	11.1 (10.5, 11.7)
COPD	4.2 (4.1, 4.4)	10.8 (10.1, 11.4)
RP	6.8 (6.6, 7.0)	9.9 (9.3, 10.5)
Pneumonia	3.2 (3.1, 3.4)	9.7 (9.2, 10.3)
Chronic and acute renal failure or insufficiency	4.2 (4.1, 4.4)	7.8 (7.4, 8.3)
Pulmonary hypertension	2.7 (2.6, 2.9)	8.3 (7.8, 8.8)
Upper respiratory tract infections	6.3 (6.1, 6.5)	6.8 (6.4, 7.3)
Cardiac arrhythmia	4.2 (4.1, 4.4)	7.5 (7.0, 8.0)
Urinary tract infections	4.7 (4.5, 4.8)	6.3 (5.8, 6.7)
Bleeding	3.8 (3.7, 4.0)	5.9 (5.5, 6.3)
Lower respiratory tract infections	1.8 (1.7, 1.9)	3.2 (2.9, 3.4)
Lung transplant	0.1 (0.1, 0.1)	0.5 (0.4, 0.6)

<sup>a</sup>Without the event previously occurring during the 365-day baseline period.

were MTX (53.5%) and MMF (26.7%) for the SSc cohort and MMF (48.3%) and MTX (27.6%) for the SSc-ILD cohort.

### Selected outcomes during follow-up

Incident comorbid outcomes were more frequent in the SSc-ILD cohort ( $n=8252$ ) compared with the SSc cohort ( $n=34\ 820$ ) over a median follow-up of 527 and 606 days (Table 5), including general or any skin disorders (23.3 vs 20.3 per 100 person-years), GERD (22.6 vs 14.4), arterial hypertension (11.1 vs 6.1), RP (9.9 vs 6.8) and COPD (10.8 vs 4.2) for SSc-ILD vs SSc, respectively. The inpatient mortality rate was higher in the SSc-ILD cohort than the SSc cohort (21.54 vs 6.76 per 1000 person-years).

Prevalence estimates for comorbidities at initiation of IST (Supplementary Table S3, available at *Rheumatology* online) showed an increased prevalence of skin disorders (14.3 vs 11.6 per 100 persons) for the SSc vs SSc-ILD cohort. However, there was a higher prevalence of GERD (13.8 vs 9.1) and RP (13.2 vs 10.5) for the SSc-ILD vs SSc cohort, respectively. At the first escalation of IST, the cohort sizes were small (SSc: 184; SSc-ILD: 57) and there were no incident cases for several comorbidities.

At initiation of IST, more than half of patients were receiving corticosteroids in both the SSc (51.1%) and SSc-ILD cohorts (51.5%), with the next most common ISTs being MTX (46.3% and 24.1%, respectively) and MMF (32.9% and 52.7%, respectively) (Supplementary Table S4, available at *Rheumatology* online). This pattern continued at the first escalation of IST.

At the initiation of IST, patients in the SSc and SSc-ILD cohorts also received drugs for pulmonary hypertension (50.1% and 60.1%), drugs for digital ulcers (40.5% and 45.9%) and treatment for GERD (36.1% and 40.2%), respectively (Supplementary Table S4, available at *Rheumatology* online); these patterns of the drugs received and the relative proportions for SSc and SSc-ILD remained similar upon the first escalation of IST.

## Discussion

We conducted an analysis of a US cohort of patients with SSc or SSc-ILD based on the MarketScan claims database over a 9-year period. Prevalence estimates and IRs of SSc and SSc-ILD were higher among females than males. Patients with SSc-ILD were older, with a higher burden of disease than patients with SSc, as reflected by the higher frequency of comorbidities and diagnostic procedures. Skin disorders were the most common comorbidity in both the SSc and SSc-ILD cohorts.

We found that 13.6% (SSc) and 23.4% (SSc-ILD) of patients were receiving IST at baseline and 8.2% and 12.7%, respectively, initiated IST during follow-up. In our study and a similar study in patients with SSc, approximately half of patients received corticosteroids at

baseline [20], despite limited evidence of efficacy [15]. MTX and MMF were the next most used ISTs in both cohorts across baseline, initiation and escalation time points. In Thomason *et al.* [21], a higher proportion of patients received IST at baseline, with 38–51% receiving one or more line of therapy during follow-up, in particular MTX for SSc and MMF for SSc-ILD.

Approximately 20% of patients in both cohorts escalated IST after a stable regimen of a median of 289–292 days, with  $\geq 17\%$  requiring a second escalation. This indicates that patients were not stable and their conditions not well controlled, necessitating IST dose increases or other regimen changes, highlighting the need for better treatments and clearer guidelines. However, due to the nature of claims data, we can only know with certainty which drugs were dispensed; we do not have prescribing information to determine indication.

There are no established treatment algorithms for SSc-ILD, although patients generally receive CYC based on clinical trials and following the current EULAR guidelines [15, 22]. However, in a consensus review of treatment algorithms determined in 2012, experts had 69% agreement on MMF, CYC and rituximab as the recommended induction therapy for SSc-ILD, with MMF as the first-line maintenance treatment; MTX was not included in the algorithm, in contrast to the findings of our study and despite current guidelines [23]. Given the fact that ISTs are widely used among patients with SSc and SSc-ILD, there is a clear need for further guidance on ISTs in SSc and SSc-ILD to advise on which patients would benefit and when.

Previous studies used different algorithms to define SSc [24–27] and SSc-ILD patients [25], which resulted in lower prevalences and IRs. For example, patients with SSc in a US care-managed organization were identified using an algorithm requiring one or more inpatient claim or two or more office or emergency room visits, potentially limiting cases to those with more progressive disease, and a sensitivity analysis limited to specific clinical and treatment characteristics [20]. For the current study, work on refining these earlier algorithms was done in consultation with an external expert.

The epidemiological findings of the current study also differ from those of a systematic review of studies published between January 2000 and February 2016 including patients with SSc and SSc-ILD [11], which covers the time period of the current study. Based on our main analysis, which required only one diagnostic code, prevalence was higher in the present study compared with another North American cohort. This may be attributed to the methodology—the authors [11] noted that prevalence estimates varied according to the data source used: studies based on healthcare databases (current study) gave higher annual estimates of SSc (3.6–5.6 per 100 000 persons) compared with medical chart reviews (1.4–2.4 per 100 000 persons).

When two claims were required for diagnosis in the sensitivity analysis, prevalence estimates and IRs were reduced, becoming more comparable to other studies



[11]. Fan *et al.* [25] also used both one-claim and two-claim definitions of SSc and SSc-ILD. While IRs were similar to ours, prevalence proportions were much lower, more closely reflecting those found by Bergamasco *et al.* [11]. Incidence and prevalence estimates generated from the MarketScan data are representative of a subset of the general population and may differ from the population and methodologies used in other studies. For example, younger age may be associated with a lower incidence and prevalence. Therefore results should be interpreted with caution.

Patients with SSc-ILD had a higher prevalence of baseline comorbidities and higher IR of comorbid outcomes over an average follow-up of 2 years than patients with SSc [25]. Skin disorders and GERD were the most prevalent comorbidities in both cohorts at baseline and remained so during follow-up. Similarly, Bergamasco *et al.* [11] found that patients with SSc-ILD were older and had more comorbidities at baseline than patients with SSc, and that both SSc and SSc-ILD affected 2–3 times more women than men. In addition, in Thomason *et al.*'s analysis of a claims database from 2005–2015 [21], patients with SSc-ILD also had higher levels of comorbidities than SSc at baseline. However, patients recorded a different range of comorbidities, with rheumatic disease (excluding SSc) and COPD being the most frequent. These studies all show a variety of outcomes affecting different organ systems, highlighting the need for innovative treatments as well as clear guidelines to prevent and treat comorbidities and improve patient health.

There were several limitations associated with this study. This study investigated SSc and SSc-ILD in the MarketScan claims database. The database provides a representation of the commercially insured US population who are employed or dependents of the employed. Patients in this study differ from patients in public health insurance plans or those without health insurance and may have broader coverage and financial means to contribute higher co-pays. Overall, 56.0% of the US population had employer-based private health insurance according to the 2017 US census [28]. MarketScan is also a compilation of multiple payers, therefore formularies may vary, and there is a substantial amount of known 'churn' in US commercial claims databases given the nature of shopping around for the best options. Therefore, while a 365-day washout may not exclude all prevalent disease patients with relatively mild disease, it is difficult to expand the look-back used to define a washout period for incident diagnosis further than 1 year without compromising the sample size.

Mortality data are not directly available in the MarketScan database; however, inpatient death can be used to report deaths that occur within the hospital setting in this population. The inpatient mortality rate was higher in the SSc-ILD cohort than the SSc cohort, a pattern similar to that seen in other studies [11].

Analyses of claims databases offer large cohorts of real-world data and information on health resource

utilization from a predefined study purpose. However, conclusions are limited by the extent of information collected for the claims database and there is often a time lag of clinical data or patient-reported outcomes. In addition, because of the differences in insurance coverage and co-pays for certain drugs, the treatment regimen used among patients in this study may also be different from patients not covered by commercial insurance plans or those not able to afford higher co-pays. When using claims data, we can only define patients based on diagnostic codes, which may result in misclassification and thus over- or underestimates of incidence and prevalence. Claims are filed for administrative purposes, therefore codes may not be as accurate as data collected specifically for clinical or research purposes. Clinicians may also code a multisystem disease differently, e.g. they may code all disease manifestations as just SSc or as SSc, ILD and RP separately. This is part of the limitation of not having more granular medical record information. However, we used different algorithms (one vs two claims, different range of ICD codes) to help address this limitation. Due to the way the cohorts were extracted, the SSc-ILD prevalent cohort is a subset of the SSc prevalent cohort. As such, no statistical comparisons were conducted.

In conclusion, compared with all patients with SSc, patients with SSc-ILD were older and had a higher burden of disease, reflected by a higher frequency of comorbidities both at diagnosis and developing over time. One particularly interesting aspect of our study was the insight into the way immunosuppressants are used off-label in clinical practice in patients with SSc-ILD. MTX and MMF were the most common ISTs in the SSc and SSc-ILD cohorts, both at initiation of therapy and over time, and some patients still required treatment escalation. The time delay from diagnosis to treatment initiation was ~3–4 months and may reflect the time for diagnostic procedures to assess the need for ISTs. To our knowledge, ours is the first study to show this. There is a clear need for treatment guidelines that address not only evidence for the use of IST and other therapies, but also when and how to use them.

Future database analyses may give further insights into evolving treatment algorithms; this study lays the foundation for understanding ongoing IST use that will be valuable for assessing the use of nintedanib in the context of other concomitant medications. The tyrosine kinase inhibitor nintedanib has recently been approved in the US and Europe to slow the rate of decline in pulmonary function in patients with SSc-ILD [16, 29], providing a targeted treatment option that slows lung function decline with an acceptable safety profile. Nintedanib adds to the previously limited treatment options and future guidelines will need to make recommendations for its use in disease management. Since the treatment landscape is changing, our data provide valuable information about how patients are currently treated and the burden of disease in patients with SSc-ILD.

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## Supplementary data

**Supplementary data** are available at *Rheumatology* online.

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