ORIGINAL RESEARCH

Economic Burden and Management of Systemic Sclerosis-Associated Interstitial Lung Disease in 8 European Countries: The BUILDup Delphi Consensus Study

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a rare chronic autoimmune disease characterised by microvascular damage, immune dysregulation and fibrosis, affecting the skin, joints and internal organs. Interstitial lung disease (ILD) is frequently associated with systemic sclerosis (SSc-ILD), leading to a poor prognosis and a high mortality rate. The aim of the BUILDup study (BUrden of Interstitial Lung Disease Consensus Panel) was to investigate the overall disease management and to estimate the social and economic burden of SSc-ILD across 8 European countries.

Methods: A modified Delphi method was used to obtain information on the management of SSc-ILD patients among 40 specialists (panellists) from 8 European countries. Average annual costs per patient and country were estimated by means of a direct cost-analysis study.

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Results: The panellists had managed 805 SSc-ILD patients in the last year, 39.1% with limited (L-SSc-ILD) and 60.9% with extensive (E-SSc-ILD) disease. Of these, 32.8% of the panellists started treatment at diagnosis, 42.3% after signs of deterioration/progression and 24.7% when the disease had become extensive. The average annual cost of SSc-ILD per patient ranged from €6191 in Greece to €25,354 in Sweden. Main cost drivers were follow-up procedures, accounting for 80% of the total annual costs. Hospitalisations were the most important cost driver of follow-up costs. Healthcare resource use was more important for E-SSc-ILD compared to L-SSc-ILD. Early retirement was taken by 40.4% of the patients with an average of 11.9 years before the statutory retirement age.
Conclusions: SSc-ILD entails not only a clinical but also a social and economic burden, and is higher for E-SSc-ILD.

Key Summary Points

What is already known about this subject?

The manifestation of interstitial lung disease (ILD) in systemic sclerosis (SSc) patients impacts patient quality of life and prognosis. Data available on the cost and clinical burden of SSc-ILD are scarce, especially in Europe

Through a Delphi methodology, this study assesses the clinical and economic burden of two forms of SSc-ILD: limited (L-SSc-ILD) and extensive (E-SSc-ILD)

What does this study contribute?

This study shows the important loss of productivity for SSc-ILD patients and a significant societal impact for patients and their carers. Moreover, the study suggests that healthcare resource use increases with greater severity of SSc-ILD

How might this study impact clinical practice or future developments?

This study further underscores the need to modify the course of SSc-ILD

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.13095629.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterised by inflammation, vasculopathy and fibrosis. Its clinical manifestations are mainly skin thickening, on which basis three subsets of SSc are defined: limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc) and SSc without skin involvement [1]. Apart from skin lesions, lung, heart and kidney involvement is common, and, among pulmonary manifestations, interstitial lung disease (ILD) and pulmonary hypertension are the most severe complications of the disease.

Worldwide, SSc-ILD affects mostly women between 30 and 55 years of age [2]. In Europe, the prevalence of SSc ranges from 8.2 to 30.7 per 100,000 persons, and between 47.0 and 66.4% of these patients suffer from ILD (SSc-ILD) [3–14], which accounts for up to 35% of SSc-related mortality [15]. Thus, the early detection of lung involvement with high-resolution computed tomography (HRCT) and pulmonary function tests is crucial in order to plan the best management for these patients with the overall purpose of optimizing prognosis [16, 17]. Goh et al. showed that the combination of an increased extent of lung fibrosis on HRCT and a low forced vital capacity (FVC) was associated with higher mortality, and therefore proposed a simple staging system for SSc-ILD (limited/extensive) that has been shown to provide discriminatory prognostic information [18].

However, the clinical heterogeneity of SSc renders management challenging. The current guidelines for SSc treatment indicate that methotrexate can be used to treat the skin manifestations of early dcSSc, but positive effects on other organ manifestations have not been established. Cyclophosphamide treatment may be considered, especially in patients with SSc with progressive ILD, despite its potential toxicity [19]. In the SLS-II study in which 142 patients were enrolled, no significant difference was observed between cyclophosphamide and mycophenolate mofetil (MMF) in the course of forced vital capacity as a percentage of predicted value (FVC %) over 24 months, although MMF was better tolerated and was associated with less toxicity [20]. Recently, a phase III trial tested nintedanib in SSc-ILD and showed a reduction in FVC decline of 44% compared to best supportive care, and an acceptable safety profile over 1 year [21]. Lung transplantation and haematopoietic stem cell transplantation may be considered in patients with rapidly progressive SSc-ILD at risk of organ failure. However, there is a high risk of side effects, and choice of treatment must be considered individually [19].

The cost data available for SSc-ILD are scant. The objective aim of the BUILDup study (BUrden of Interstitial Lung Disease Consensus Panel) was to evaluate the level of consensus on the current management of the disease and to estimate health resource consumption and costs, as well as the social burden of SSc-ILD patients across several European countries. The study took both the limited (L-SSc-ILD) and extensive (E-SSc-ILD) forms of the disease into account according to the Goh classification [18].

METHODS

Study Design

We used a modified Delphi method to explore the management and economic burden of SSc-ILD in 8 European countries: Belgium, Denmark, Finland, Greece, the Netherlands, Norway, Portugal and Sweden. This study was part of a broader study elucidating the burden of ILD, in which the impact of progression in fibrosing ILD has been published elsewhere [22].

The Delphi method is a prospective research technique that makes it possible to evaluate the degree of consensus and the points of disagreement between experts. This Delphi approach was implemented in several phases, including the formation of the Steering Committee, the definition of criteria for selecting panellists, the design of the Delphi questionnaire, the administration of the Delphi survey (in two rounds) and data collection, analysis and interpretation [23].

The objective of the Delphi methodology is to obtain a consensual opinion about a specific topic based on the judgment of a group of experts. For this purpose, as the experts were asked to give their opinion on their experience without retrieving any patient data or information, no ethics committee approval or informed consent was required.

Participants: Steering Committee and Panellists

The Steering Committee included 8 members, from Belgium (WW), Denmark (JRD), Finland (MK), Greece (SP and EM), The Netherlands (JM) and Portugal (AM and CRC). The Steering Committee was responsible for designing a Delphi questionnaire, selecting the panellists and interpreting the data. Panellists from the 8 European countries (Belgium, Denmark, Finland, Greece, The Netherlands, Norway, Portugal and Sweden) were invited to participate in the project. The panellists (pulmonology or rheumatology specialists) were selected according to their experience in the management of patients with SSc-ILD at public hospitals (including academic centres) in the above-mentioned countries.

Delphi Questionnaire

The Delphi questionnaire was developed based on a literature search in the PubMed database (using the MESH terms "systemic sclerosis" and "interstitial lung disease" as search terms) to obtain information about the clinical

management of the disease and resource use and on the clinical experience of the Steering Committee members. The questionnaire addressed 4 topics in SSc-ILD: epidemiology of SSc-ILD, expertise in SSc-ILD, current management of SSc-ILD patients and the economic and social burden of SSc-ILD patient management. For the management of SSc-ILD, a distinction was made between L-SSc-ILD and E-SSc-ILD in order to better capture the difference in management between the two forms of disease. For simplicity, no additional questions were asked that would distinguish between initiation and maintenance treatment. The resources used to manage the exacerbations of the associated ILD were also collected. Exacerbations in connective tissue disease associated with ILD have been described in the literature [24]. In our study, we arbitrarily defined exacerbations as acute, clinically significant respiratory deteriorations characterised by the evidence of new, widespread alveolar abnormalities meeting all the following criteria: acute worsening or development of dyspnoea (typically of < 1 month duration), CT with new bilateral ground-glass opacity or consolidation superimposed on a background pattern consistent with fibrosing ILD, while deterioration not fully explained by cardiac failure or fluid overload. Infection was not an exclusion criterion for an acute exacerbation [25].

The final Delphi questionnaire was pilot-tested by the members of the Steering Committee, and its final version can be found in Appendix 1.

The Delphi questionnaire was administered through an online platform that ensured data anonymity and confidentiality, and was sent out in two rounds of voting, held between 15 February and 23 April 2019 and 7 and 21 June 2019. A total of 138 panellists (about 15 per country) were contacted to participate in the study. Panellists had to have more than 5 years of experience in their speciality, be working in public hospitals and have experience in the management of SSc-ILD. They were asked to answer all the questions and check "Don't know" as necessary. All the questions in which no consensus was reached in the first round were repeated in a second wave. The review of

the results of the first wave pointed to the need to also include the "Don't know" response option for several other questions. During the second round of voting for each question, the panellists found the value that they had inserted during the first wave together with the aggregate results from the total sample of all the panellists.

Data Collection, Analysis and Interpretation

A descriptive analysis of the results was performed. All items measured with a Likert-type 9-position scale were subsequently converted into 3 categories of agreement: 1–3 ("disagreement"), 4–6 ("neither disagreement nor agreement"), and 7–9 ("agreement"). The median score, mean, quartile 1 (Q1) and 3 (Q3) and the percentage of panellists falling into each interval of agreement were calculated for each item. When more than 75% of panellists fell inside one of the extreme intervals ("disagreement" or "agreement"), the item was considered to have reached a "consensus". Otherwise, the item was repeated in the second wave. We used two waves of questions to avoid panellist fatigue and to ensure a high response rate. The results present items for which consensus was reached during the first or second wave, as well as the items for which consensus was not reached. The percentage of panellists was determined for numeric discrete variables, with consensus being when > 75% panellists chose a specific value. For numeric continuous variables, the mean, Q1 and Q3 were calculated. Consensus was determined with the mean value. A comparative analysis by panellist speciality was carried out with a Chi-square test or ANOVA test for categorical and continuous variables, respectively. The data were analysed with SPSS v.22, and a p value < 0.05 was considered to be statistically significant.

The final results from the Delphi questionnaire were further evaluated and discussed by the Steering Committee. No statements or level of consensus were modified at any point.

Cost Analysis

Average annual costs per patient and country were estimated by a direct cost-analysis study. Healthcare resources used (HCRU) for the diagnosis of the disease, patient follow-up management, management of adverse events, exacerbations of the associated ILD and end-of-life care were obtained from the panellists' answers.

These resources included specialist visits, diagnostic tests, pharmacological and non-pharmacological treatments and hospitalisations.

Direct costs were calculated by multiplying the number of HCRU by their corresponding unit costs. Unit costs were obtained from local health economists through official national or regional official databases, whenever possible, for the country in question, or from equivalent or alternative organisations.

When needed, unit costs were converted to 2019 value prices using the published consumer price index. Moreover, costs were converted into Euros for countries not using the currency. The list of sources per country can be found in Appendix 2.

Treatment costs were obtained by multiplying the mean doses used of the selected medication and the estimated treatment time (or 1-year treatment for chronic medication prescribed for follow-up). To calculate adverse event (AE) costs in cases where the AE required hospitalisation, the cost of hospitalisation for this specific cause was used, otherwise the cost of one visit to a general practitioner or specialist was applied.

SSc-ILD exacerbation costs included hospitalisation costs plus outpatient costs for a period of 6 months after the event. For end-of-life event cost calculation, the percentage of patients dying in the intensive care unit (ICU), hospital, home or nursing home was obtained. The cost of one admission to the ICU or the hospital was assumed for cases dying in such departments, and the sum of costs for cases dying at home or in the nursing home was based on outpatient visits, tests and treatment resources.

Annual costs were measured by diagnosis (based on total cost divided by number of years of diagnosis), follow-up management costs and exacerbation costs (determined by frequency of exacerbation). Costs for SSc-ILD were calculated from a weighted average of the costs for E-SSc-ILD and L-SSc-ILD. End of-life costs were event-based and not estimated as annual costs.

Sensitivity Analyses

Successive univariate sensitivity analyses were conducted on key values to test their impact on costs. Specific variables were varied one at a time across a plausible range, while the remaining ones were maintained at baseline values. For HCRU, the alternative values used were Q1, median and Q3. For costs, we successively tested the impact of a 25% decrease or the increase in the unit costs for outpatient visits, hospitalisations, tests and treatment (including drugs, long-term oxygen therapy and lung transplantation).

RESULTS

Characteristics of Participant Panellists

Of the 138 panellists invited to participate in the survey, a total of 40 specialists (32 pulmonologists and 8 rheumatologists) completed the questionnaire for both rounds of the survey. Of them, 37.5% had between 5 and 20 years of experience and 25% more than 20 years. Regarding the type of work centre, all of them were employed in public hospitals and 70% practised in teaching hospitals. A full description of the sample of participant panellists is provided In the Supplementary Table S1.

Characteristics and Diagnosis of SSc-ILD Patients

Of the patients managed by the panellists, 39.1% presented L-SSc-ILD and 60.9% presented E-SSc-ILD according to the Goh classification [18]. Overall, comorbidities affecting the course of the disease and reported by the panellists in

the course of the last year included gastroesophageal reflux disease (53.8% of patients), fatigue (40.3%), pulmonary hypertension (23.7%), depression (22.6%), pulmonary infections (20.8% patients), osteoporosis (19.0%) and diabetes (8.7%) (Supplementary Table S2). When focusing on the social characteristics of the SSc-ILD patients, the panellists stated that 42.6% of them were retired.

Based on the panellists' clinical experience, the number of years between onset of symptoms and the definitive diagnosis was 2.1 years [Q1–Q3: 1–3], and the most important professionals involved in the definitive diagnosis of SSc-ILD, categorised by importance, were rheumatologists, pulmonologists and internal medicine physicians. When considering the resources routinely used in their clinical practice to obtain the definitive diagnosis of SSc-ILD, the panellists indicated a mean of 4.2 outpatient visits, 9.2 laboratory tests and 9.5 other tests in total (Table 1).

Non-Pharmacological and Pharmacological Management of SSc-ILD

When the monitoring of SSc-ILD was considered, rheumatologists, pulmonologists and cardiologists were specified as the professionals mainly involved in both L-SSc-ILD and E-SSc-ILD follow-up.

The resources routinely used in patient follow-up were differentiated by category of SSc-ILD and the panellists indicated a mean total number of outpatient visits of 7.5 for E-SSc-ILD and 5.3 for L-SSc-ILD per year, including visits to pulmonologists, rheumatologists and dermatologists. The mean number of hospitalisations, laboratory tests and other tests (e.g. HRCT, pulmonary function tests and bronchoscopy) were also estimated, all of which were higher for E-SSc-ILD versus L-SSc-ILD during follow-up (Table 2).

Regarding maintenance treatment, 40% of the panellists followed a "watch and wait" approach for L-SSc-ILD patients versus 20% for E-SSc-ILD patients. According to the drug used in maintenance treatment, MMF was stated as the main option for treating L-SSc-ILD (50.0% of panellists) followed by systemic corticosteroid therapy (35.0%). These data translated into 35.4% of the L-SSc-ILD patients on MMF and 10.6% of patients on systemic corticosteroid therapy. In contrast, for E-SSc-ILD, the main treatment options were MMF (82.5% of panellists), cyclophosphamide (77.5%), systemic corticosteroids (60.0%), rituximab (47.5%) and azathioprine (37.5%) (Table 3), corresponding to 64.5% of patients on MMF, 27.7% on cyclophosphamide, 30.5% on systemic corticosteroids, 13.1% on rituximab and 10.3% on azathioprine, respectively (Table 3). With regard to other non-pharmacological treatments, the panellists stated that the annual proportion of patients receiving a lung transplantation was 0.1% for L-SSc-ILD and 1.5% for E-SSc-ILD, whereas the proportions of patients to whom long-term oxygen therapy was prescribed were 3.5% and 11.7% for L-SSc-ILD and E-SSc-ILD, respectively. The mean number of rehabilitation sessions and the duration of these sessions were also higher in E-SSc-ILD versus L-SSc-ILD (Supplementary Table S3).

Panellists reported that they never stop maintenance treatment in 44.7% of SSC-ILD patients and that the most important indicator to define treatment success is oxygen saturation with exercise (100% of panellists) followed by FVC stabilisation or improvement (61.1%) and symptoms stabilisation or improvement (42.1%).

The proportion of panellists that indicated the initiation of treatment of SSc-ILD at diagnosis was 32.8%. However, 42.3% waited until signs of deterioration/progression and 24.7% until the disease became extensive. Notably, the panellists stated that they would prescribe an antifibrotic in 19.5% of L-SSc-ILD and 55.3% of E-SSc-ILD if a new reimbursed treatment was approved.

Tumour necrosis factor inhibitors, systemic corticosteroids, antifibrotics and immunomodulatory agents were considered to be associated with AE in 40.0%, 23.9%, 18.8% and 16.6% of the patients, respectively. The panellists indicated that, while most of the AE required a visit either to the general practitioner or to the specialist, the percentage of AE that required

Table 1 Description of resources used for the diagnosis of SSc-ILD

Resource, n = number of responders among panellists[a]	Number of visits or tests, mean [q1–q3]
Diagnostic visits	
Pulmonologist visits, n = 39	1.8 [2–2]
Rheumatologist visits, n = 36	2.2 [2–3]
Dermatologist visits, n = 33	0.4 [0–1]
Total number of visits per patient[b], n = 39	**4.2 [3–5]**
Laboratory tests	
Complete blood count, n = 39	1.4 [1–2]
Sedimentation rate, n = 39	1.1 [1–1]
Hepatic profile, n = 39	1.2 [1–1]
CPK, n = 39	1.1 [1–1]
ACE, n = 38	0.5 [0–1]
Rheumatoid factor, n = 39	1.1 [1–1]
Antinuclear antibodies, n = 39	1.2 [1–4]
Urinalysis, n = 39	0.9 [0–1]
Other[c], n = 20	1.2 [1–1]
Total number of laboratory tests per patient[b], n = 39	**9.2 [7–9]**
Imaging or other tests	
Chest X-ray, n = 38	1.0 [1–1]
HRCT, n = 38	1.2 [1–2]
Computed tomography pulmonary angiogram, n = 37	0.2 [0–0]
Bronchoscopy, n = 37	0.5 [0–1]
Sputum assessment, n = 36	0.1 [0–0]
Bronchoalveolar lavage, n = 36	0.5 [0–1]
Transbronchial biopsy, n = 36	0.2 [0–0]
Ventilation/perfusion scintigraphy, n = 36	0.3 [0–0]
Blood gases, n = 36	0.7 [0–1]
Spirometry, n = 37	1.3 [1–2]
Body plethysmography, n = 36	1.1 [1–1]
Diffusing capacity for carbon monoxide, n = 37	1.5 [1–2]
6-min walk test, n = 37	1.0 [1–1]
Other, n = 19	0.3 [0–1]
Total number of imaging or other tests per patient[b], n = 38	**9.5 [6–12]**

Number of patients = 805

ACE angiotensin-converting enzyme, *CPK* creatine-phosphokinase, *HRCT* high-resolution computed tomography

[a] All panellists (n = 40) answered all questions. n indicates the number of panellists who estimated a value per resource. The remaining panellists answered 'Don't know'

[b] The total may not add up due to missing values (different number of respondents in each row)

[c] Verbatims: Anti-ENA, complement analysis, CRP, CRP, kidney profile, ionogram, ECG, ENA screen, Nailfold capillaroscopy, pHmetry, NT-proBNP or other autoantibodies renal profile or other autoantibodies, missing

Table 2 Description of the resources used for the follow-up of SSc-ILD patients, per year

Limited SSc-ILD Number of patients = 315		Extensive SSc-ILD Number of patients = 490	
Resource, n = number of panellists[a]	Number of visits or tests per year, mean [Q1–Q3]	Resource, n = number of panellists[a]	Number of visits or tests per year, mean [Q1–Q3]
Follow-up visits			
Pulmonologist visits, $n = 37$	1.8 [1–2]	Pulmonologist visits $n = 37$	2.7 [2–4]
Rheumatologist visits, $n = 33$	2.5 [2–3]	Rheumatologist visits, $n = 33$	3.0 [2–4]
Dermatologist visits, $n = 27$	0.5 [0–1]	Dermatologist specialist, $n = 28$	0.5 [0–1]
Nurse (or other healthcare professionals), $n = 27$	0.9 [0–1]	Nurse (or other healthcare professionals), $n = 28$	1.3 [0–2]
Social workers, $n = 26$	0.1 [0–0]	Social workers, $n = 27$	0.2 [0–0]
Emergency room visits, $n = 24$	0.3 [0–0]	Emergency room visits, $n = 25$	0.8 [0–1]
Total number of visits per patient[b], n = 197	**5.3 [4–6]**	**Total number of visits per patient[b], n = 227**	**7.5 [5–9]**
Hospitalisations			
Hospital admissions, $n = 30$	0.4 [0–1]	Hospital admissions, $n = 32$	1.4 [1–2]
Duration of a hospital admission (days), $n = 7$	3.1 [2–4]	Duration of a hospital admission (days), $n = 21$	4.6 [3–6]
Hospitalisations at the pulmonary department, $n = 27$	0.1 [0–0]	Hospitalisations at the pulmonary department, $n = 29$	1.0 [0–1]
Duration of a hospitalisation at the pulmonary department (days), $n = 2$	2.0 [2–2]	Duration of a hospitalisation at the pulmonary department (days), $n = 15$	5.2 [3–7]
Hospitalisation at the intensive care unit, $n = 26$	0 [0–0]	Hospitalisation at the intensive care unit, $n = 28$	0.3 [0–0]
Duration of a hospitalisation at the intensive care unit (days), $n = 23$	–	Duration of a hospitalisation at the intensive care unit (days), $n = 5$	3.8 [2–5]
Total number of hospitalisations per patient[b], n = 14	**0.5 [0–1]**	**Total number of hospitalisations per patient[b], n = 82**	**2.6 [1–4]**
Number of laboratory tests			
Complete blood count, $n = 32$	2.1 [1–3]	Complete blood count, $n = 33$	3.1 [2–4]
Sedimentation rate, $n = 31$	1.5 [1–2]	Sedimentation rate, $n = 32$	2.2 [0.5–4]
Hepatic profile, $n = 31$	2.1 [1–3]	Hepatic profile, $n = 32$	3.2 [2–4]
CPK, $n = 31$	1.2 [1–2]	CPK, $n = 32$	1.9 [1–3]

Table 2 continued

Limited SSc-ILDNumber of patients = 315		Extensive SSc-ILDNumber of patients = 490	
Resource, *n* = number of panellists[a]	Number of visits or tests per year, mean [Q1–Q3]	Resource, *n* = number of panellists[a]	Number of visits or tests per year, mean [Q1–Q3]
ACE, *n* = 31	0.1 [0–0]	ACE, *n* = 32	0.1 [0–0]
Rheumatoid factor, *n* = 31	0.5 [0–1]	Rheumatoid factor, *n* = 31	0.4 [0–1]
Antinuclear antibodies, *n* = 31	0.6 [0–1]	Antinuclear antibodies, *n* = 33	0.7 [0–1]
Urinalysis, *n* = 31	1.3 [1–2]	Urinalysis, *n* = 32	1.8 [1–2]
Other, *n* = 18	0.2 [0–0]	Other, *n* = 18	0.3 [0–0]
Total number of laboratory tests per patient[b], n = 294	**9.2 [6–12]**	**Total number of laboratory tests per patient[b], n = 435**	**13.2 [10–18]**
Other tests			
Chest X-ray, *n* = 33	1 [1–1]	Chest X-ray, *n* = 34	1.3 [1–2]
HRCT, *n* = 32	0.6 [0–1]	HRCT, *n* = 34	1.1 [1–1]
Computed tomography pulmonary angiogram, *n* = 31	0.1 [0–0]	Computed tomography pulmonary angiogram, *n* = 32	0.2 [0–0]
Bronchoscopy, *n* = 31	0.1 [0–0]	Bronchoscopy, *n* = 32	0.3 [0–1]
Sputum assessment, *n* = 31	0.1 [0–0]	Sputum assessment, *n* = 32	0.3 [0–1]
Bronchoalveolar lavage, *n* = 31	0 [0–0]	Bronchoalveolar lavage, *n* = 32	0.2 [0–0]
Ventilation/perfusion scintigraphy, *n* = 31	0.1 [0–0]	Ventilation/perfusion scan, *n* = 32	0.2 [0–0]
Blood gases, *n* = 31	0.5 [0–1]	Blood gases, *n* = 32	1.1 [0–1]
Pulmonary function tests, *n* = 30	1.7 [1–2]	Respiratory function tests *n* = 31	2.4 [2–4]
Spirometry, *n* = 31	1.7 [1–2]	Spirometry, *n* = 32	2.1 [1–3]
Body plethysmography, *n* = 30	0.9 [0–1]	Body plethysmography, *n* = 31	1.4 [0–2]
DLCO, *n* = 31	1.7 [1–2]	DLCO, *n* = 32	2.3 [2–3]
6-min walk test, *n* = 31	0.9 [0–1]	6-min walk test, *n* = 32	1.5 [1–2]
Other, *n* = 16	0.1 [0–0]	Other, *n* = 17	0.2 [0–0]
Total number of other tests per patient[b], n = 294	**8.9 [6–12]**	**Total number of other tests per patient[b], n = 485**	**14.3 [10–18]**

ACE angiotensin-converting enzyme, *CPK* creatine-phosphokinase, *DLCO* diffusing capacity for carbon monoxide, *HRCT* high-resolution computed tomography

[a] All panellists (*n* = 40) answered all questions. *n* indicates the number of panellists who estimated a value per resource. The remaining panellists answered 'Don't know'

[b] The total may not add up due to missing values (different number of respondents in each row)

Table 3 Description of the maintenance treatments used during the follow-up of limited and extensive SSc-ILD patients

Agents for maintenance	Limited SSc-ILD Number of patients = 315				Extensive SSc-ILD Number of patients = 490			
	Number of panellists using the drug, n (%)	% of patients using the drug[d]	Number of panellists using the dose	Mean dose used (± SD), (mg/day)	Number of panellists using the drug, n (%)	% of patients using the drug[d]	Number of panellists using the dose	Mean dose used (± SD), (mg/day)
No treatment. Watch and wait	16 (40.0%)	26.1	–	–	8 (20.0%)	5.5	–	–
MMF[b] (mg/day)	20 (50%)	35.4	12	1833.3 ± 325.9	33 (82.5%)	64.5	23	1908.7 ± 477.7
Systemic corticosteroid[b] (mg/day)	14 (35.0%)	10.6	11	9.5 ± 5.8	24 (60.0%)	30.5	17	9.6 ± 5.0
Cyclophosphamide[b] (mg/day)	10 (25%)	9.1	6	101.7 ± 55.4	31 (77.5%)	27.7	15	143.3 ± 106.1
Azathioprine[b] (g/day)	7 (17.5%)	3.4	7	0.15 ± 0	15 (37.5%)	10.3	14	0.157 ± 0.182
Hydroxychloroquine[b] (g/day)	7 (17.5%)	4.7	6	0.3583 ± 0.8	3 (7.5%)	2.0	3	0.2667 ± 0.1155
Rituximab[b] (mg/day)[a]	7 (17.5%)	3.8	3	67.7 ± 114.6	19 (47.5%)	13.1	5	41 ± 53.9
Methotrexate[b] (mg/week)	4 (10%)	5.0	2	17.5 ± 3.5	4 (10.0%)	2.8	3	16.7 ± 2.9
Tocilizumab[b]	0 (0.0%)	0.0	0		3 (7.5%)	0.4	2	81.5 ± 113.8
Tacrolimus[b]	0 (0.0%)	0.0	0		1 (2.5%)	0.3	1	5.0
Other[c]	2 (5%)	2.2	1		2 (5%)	1.1	1	

No panellist answered that they prescribed anti-tumour necrosis factor or antifibrotic such as pirfenidone

MMF mycophenolate mofetil, *SD* standard deviation

[a] Assumed over a period of 14 days

[b] In monotherapy or in combination

[c] Although the "other" parameter has been marked, it was not specified

[d] % of patients using the agent weighted by the number of patients indicated by each panellist

hospitalisation was 13.1% for immunomodulatory agents, 5% of AEs due to systemic corticoids and 2.8% of AEs related to antifibrotics (Supplementary Table S4).

Management of Exacerbations

When exacerbations of SSc-ILD were considered, the proportion of patients with ≥ 1 acute exacerbation was higher among patients with E-SSc-ILD (12.5%) than among patients with L-SSc-ILD (2.5%). HCRU for the management of an exacerbation and its 6-month management of follow-up included hospitalisations (mean 1.7), outpatient visits to any specialist (mean 4.4), laboratory tests (mean 8.9) and other tests (mean 10.6) (Table 4). The main pharmacological approach to exacerbation treatment included prednisone (34.8%), methylprednisolone (17.9%) and both sequentially (1.7%).

End-of-Life Care

Palliative care was estimated to last 5.8 months. Palliative care was reported as provided at home (37.8%), in hospitals (36.2%), in nursing homes (11.1%), in intensive care units (6.6%) and in other places (4.5%) (the total does not add up due to missing values).

Social Burden of SSc-ILD

Early retirement was reported in 40.4% of the patients, with an average of 11.9 years between early retirement due to the disease and the statutory retirement age. The panellists responded that 8.5% of patients with L-SSc-ILD and 44.7% of those with E-SSc-ILD had permanent disability and that 5.0% and 29.3% lost their job due to their SSc-ILD, respectively (Supplementary Table S5).

Of the patients with SSc-ILD, 2.0% would require the support of a paid caregiver (e.g. a nurse), while 37.7% would need the support of an unpaid caregiver (e.g. a family member) for an average of 22.3 h per week (Supplementary Table S5).

Consensus was reached among panellists for all the aspects tested regarding the impact of SSc-ILD on the quality of life of unpaid caregivers (sleep and health impact; emotional impact; social impact; impact on daily activities; financial impact).

Economic Burden

The total annual costs of diagnosis, follow-up and exacerbation management per country per patient with either L-SSc-ILD or E-SSc-ILD were calculated and are provided in Table 5. The average annual cost of SSc-ILD per patient ranged from €6191 in Greece to €25,354 in Sweden.

Table 5 shows the total costs of SSc-ILD categorised at diagnosis, follow-up and end-of-life care. In general, the main cost drivers were follow-up procedures, which accounted for up to 80% of the total annual costs. Hospitalisations were the most important cost driver in follow-up costs.

Sensitivity Analysis

The lowest cost (− 62.9% vs. base case) was observed when we used the Q1 for all resources used values (average yearly cost: €5004), while the highest was obtained by using the Q3 for all resources used values (+ 29.9% vs. base case). Cost variations had less impact than Q1, median and Q3. The most important cost driver was hospitalisation, for which a 25% cost variation represented an overall variation of 15.2% of total yearly costs (Fig. 1).

DISCUSSION

SSc-ILD is a chronic and progressive disease and the main cause of SSc-related death [26, 27]. To our knowledge, the BUILDup study is the first study to describe overall disease management and to shed light on the economic and social burden associated with SSc-ILD in several European countries.

As the development or progression of ILD involvement can occur at any time, patients should be monitored regularly after the

Table 4 Description of resources used for the management of SSc-ILD exacerbations and their 6-month follow-up

SSc-ILD number of patients = 805

Resource, n = number of respondents among panellists[a]	Number of visits or tests, mean [Q1–Q3]
Outpatient visits	
Pulmonologist specialist, n = 33	1.7 [1–2]
Rheumatologist specialist, n = 30	1.6 [0–2]
Dermatologist specialist, n = 28	0.1 [0–0]
Nurse (or other healthcare professionals), n = 27	0.7 [0–1]
Home nurse (or other homecare healthcare professionals), n = 30	0.1 [0–0]
Emergency room visit, n = 28	0.9 [0–1]
Total number of visits per patient[b], n = 150	**4.4 [2–6]**
Hospitalisations	
Hospital admissions, n = 27	1.0 [0–1]
Mean duration of a hospital admission (days), n = 19	6.4 [4–7]
Hospitalisations in the pulmonary department, n = 25	0.6 [0–1]
Mean duration of a hospitalisation in the pulmonary department (days), n = 11	6.2 [4–10]
Hospitalisation in the intensive care unit, n = 25	0.2 [0–0]
Mean duration of a hospitalisation in the intensive care unit (days), n = 3	2.7 [1–5]
Total number of hospitalisations per patient[b], n = 46	**1.7 [1–2]**
Laboratory tests	
Complete blood count, n = 30	2.6 [2–4]
Sedimentation rate, n = 29	1.3 [0–2]
Hepatic profile, n = 28	2.4 [1–4]
CPK, n = 29	1.5 [0–2]
ACE, n = 29	0.2 [0–0]
Rheumatoid factor, n = 29	0.1 [0–0]
Antinuclear antibodies, n = 29	0.2 [0–0]
Urinalysis, n = 29	0.9 [0–1]
Other[c], n = 21	0.1 [0–0]
Total number of laboratory tests, per patient[b], n = 268	**8.9 [6–12]**
Other tests	
Chest X-ray, n = 31	1.3 [1–2]
HRCT, n = 31	1.1 [1–1]

Table 4 continued

SSc-ILD number of patients = 805	
Resource, n = number of respondents among panellists[a]	Number of visits or tests, mean [Q1–Q3]
Computed tomography pulmonary angiogram, n = 30	0.3 [0–0]
Bronchoscopy, n = 30	0.2 [0–0]
Sputum assessment, n = 30	0.6 [0–1]
Bronchoalveolar lavage, n = 30	0.2 [0–0]
Transbronchial biopsy, n = 30	0.1 [0–0]
Ventilation/perfusion scan, n = 30	0.1 [0–0]
Blood gases, n = 30	1.5 [0–2]
Respiratory function tests, n = 30	1.3 [0–2]
Spirometry, n = 30	1.3 [0–2]
Body plethysmography, n = 30	0.4 [0–0]
Diffusing capacity for carbon monoxide, n = 30	1.4 [0–2]
6-min walk test, n = 30	0.4 [0–1]
Other[d], n = 17	0 [0–0]
Total number of other tests per patient[b], n = 330	**10.6 [6–16]**

ACE angiotensin-converting enzyme, *CPK* creatine-phosphokinase, *HRCT* high-resolution computed tomography

[a] All panellists (n = 40) answered all questions. n indicates the number of panellists who estimated a value per resource. The remaining panellists answered "Don't know"

[b] The total may not add up due to missing values (different number of respondents in each row)

[c] Verbatims for "other laboratory tests": CRP, missing

[d] Verbatims for "other laboratory tests": heart ultrasound, missing

diagnosis of SSc-ILD and treatment initiation is crucial before an irreversible loss of lung function occurs [28]. Thus, it is essential to limit disease progression in SSc-ILD as far as possible to minimise the patient's burden of disease while maintaining healthcare system sustainability.

Management and Social Burden

Currently, the treatment of SSc-ILD is based on immunosuppressive treatment. In this study, we found a more significant proportion of patients reported as having been treated with MMF, cyclophosphamide, azathioprine and rituximab in patients with E-SSc-ILD compared to L-SSc-ILD, indicating a greater need for immunosuppression in the more severe presentations of SSc-ILD disease. In our study, systemic corticosteroids are prescribed to a significant proportion of SSc-ILD patients as maintenance treatment or for the treatment of exacerbations. Current SSc guidelines recommend careful monitoring of blood pressure and renal function in patients receiving systemic corticosteroids due to an increased risk of scleroderma renal crisis [19].

The impact of SSc-ILD is not only limited to the patient's clinical status as the impact on society and patient quality of life must also be

Table 5 Cost of SSc-ILD per patient, by country

	Yearly costs				End-of-life costs
	Total	Diagnosis	Follow-up	Exacerbations	
Denmark	**€17,480.57**	€1950.04	€14,380.95	€1149.59	€2524.30
Portugal	**€8696.84**	€319.61	€7677.75	€699.48	€2500.79
Greece	**€6191.34**	€122.17	€5481.55	€587.63	€2091.06
Netherlands	**€10,751.40**	€1157.43	€8909.93	€684.03	€1638.32
Belgium	**€9293.58**	€383.07	€8212.60	€697.91	€3387.86
Norway	**€16,333.22**	€1050.83	€14,036.42	€1245.97	€3346.89
Finland	**€13,857.60**	€1341.51	€11,612.83	€903.26	€1955.26
Sweden	**€25,354.25**	€2376.00	€20,963.70	€2014.55	€4711.17
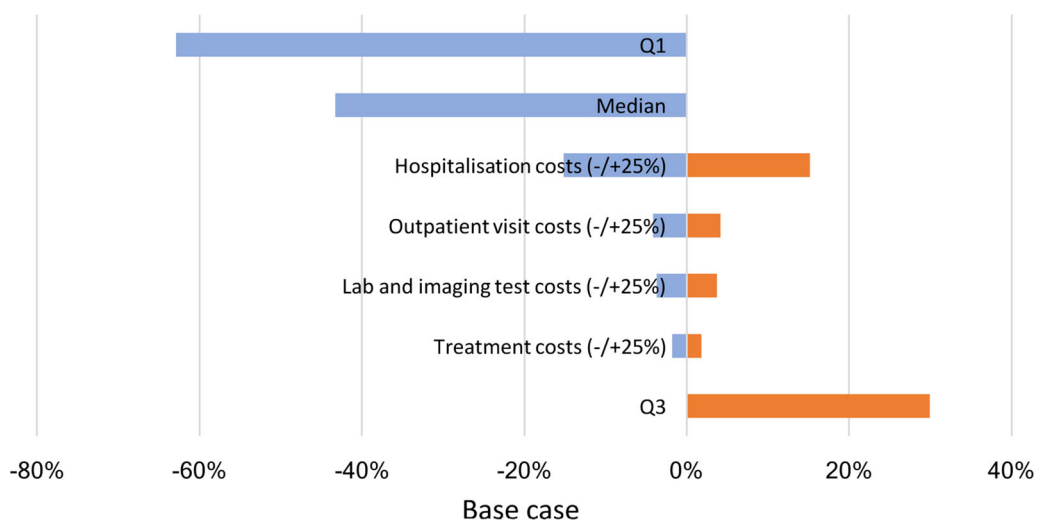
Fig. 1 Univariate deterministic sensitivity analysis

considered. SSc patients have reported significant effects on health-related quality of life compared to the general population or other chronic diseases [29–31]. In our study, there was consensus among physicians, who reported an apparent negative impact of SSc-ILD on social life, and that the decline in pulmonary function impacts patient quality of life. The results of our Delphi study showed that, according to the panellists, most SSc-ILD patients suffer from a number of comorbidities, such as gastroesophageal reflux disease (53.8%), fatigue (40.3%) or depression (22.6%). These results are consistent with the reports in the literature for SSc or SSc-ILD patients [32–34].

Economic Burden of SSc-ILD

Apart from the clinical and social burden, the economic burden of SSc-ILD management is also significant. Nevertheless, very little data have been published in this regard.

Given the prevalence and morbidity associated with SSc and the lack of effective treatment options, higher healthcare costs associated with

the disease have been reported in SSc patients compared to matched controls [35]. A systematic review reported a total direct annual medical cost for SSc per patient in Europe ranging from €3544 to €8452 [29]. According to our study, the average annual healthcare cost per patient for SSc-ILD ranged from €6191 to €25,354 according to the country. Fischer et al. reported an average annual all-cause healthcare cost per-patient ranging from $31,285 to $55,446 during a 5-year follow-up period in patients with incident SSc-ILD in the US [36]. Recently, Zhou et al. reported annual direct healthcare costs of SSc-ILD in the US of $33,195 [37], and Morrisroe et al. reported AUD 48,368 total cost per patient in Australia, with increased cost and impact on quality of life with more severe forms of SSc-ILD [38].

The different healthcare costs observed in the US and Australian studies in comparison to ours can be accounted for by geographic scope, differences in healthcare systems, the methodology used (claims analysis based on incident cases in the US, registry data in the paper from Australia, Delphi method based on incident and prevalent cases with potential recall bias in BUILDup) and the approach used (all-cause healthcare in the US, national health service for Australia and BUILDup).

The BUILDup study highlights the differences in healthcare resource utilisation between L-SSc-ILD and E-SSc-ILD, with a higher consumption for the latter. The clinical impact of increasing disease severity in E-SSc-ILD compared to L-SSc-ILD are in line with Goh et al., who demonstrated that extensive disease (i.e. increasing disease severity) is a predictor of mortality [18]. It is still unclear whether L-SSc-ILD evolves into E-SSc-ILD or if both diseases are different entities. Nevertheless, Goh et al. recognised that treatment should be initiated earlier in the course of the disease, hoping to prevent progression to the 20% HRCT extent or 70% FVC thresholds [18].

Furthermore, patients with SSc-ILD may experience periods when the disease progresses more rapidly. In our study, we arbitrarily used the definition of exacerbation used for idiopathic ulmonary fibrosis to describe these periods of progression. Several definitions of acute exacerbations are currently used in the literature [39–41]. Further research is needed to understand the incidence of such events and to describe their impact on quality of life and prognosis. Exacerbation in connective tissue disease associated with ILD has been described in the literature but with a much lower frequency than in our study (1.25% vs. 14.6% for E-SSc-ILD and 2.7% for L-SSc-ILD in BUILDup), and most exacerbations were rheumatoid arthritis associated with ILD or Sjogren Syndrome associated with ILD [24]. One possible reason for the higher frequency in our study could be, for instance, the fact that the panellists might not have always distinguished between acute exacerbation and hospitalisation and an infection related to immunosuppression.

Importantly, no cross-country comparison can be drawn, as the healthcare systems differ widely, particularly with regard to cost of pharmacological treatment. For instance, in Portugal, official medicine prices are retail prices including patient co-pay. For the Netherlands and Belgium, official prices are pharmacy purchasing prices and include value-added tax (VAT), while Denmark does not include VAT. These discrepancies follow the recommendations of local health economists from the different countries.

The cost analyses highlight that many healthcare resources are needed to manage SSc-ILD, particularly E-SSc-ILD. In both L-SSc-ILD and E-SSc-ILD, the main cost drivers are the costs of follow-up management, mainly due to the costs related to hospitalisations, but also to a lesser extent medication costs, visits to healthcare professionals and AE management.

Since SSc-ILD is a systemic disease that may affect multiple organs and patients with the disease present comorbidities, as seen in this study, our results may underestimate the total costs for these patients. With regard to patient burden, our results present the view of the treating physicians and not the actual patients, which could also lead the clinical burden for the patients to be underestimated.

Strengths and Limitations

The main strength of our study stems from the participation of a sample of a pan-European group of experts who provided very detailed information about the clinical management of SSc-ILD patients. Due to the unavailability of healthcare resource utilisation data and difficulties in associating primary and secondary care retrospective data, the Delphi method approach was considered to be the most suitable approach to obtain a good understanding of the management of SSc-ILD in the selected countries, although they present potential recall biases [42, 43]. This method has been used in other therapeutic areas for the same purpose [44–48].

However, the Delphi questionnaire was long and might have led to fatigue among the participants. The number of Delphi rounds was therefore kept to a minimum to ensure a high response rate.

This study has some limitations that should be noted. The participating panellists may not be fully representative of the clinical practice of all the participating countries and obviously not of Europe overall; nevertheless, a sample of answers from 40 panellists illustrates an overall approach to and the understanding of the management of SSc-ILD in medium-sized Western European countries. Moreover, the limited sample size may not make it possible to observe statistically significant differences between specialities, particularly in patient management and treatment. Most of the panellists were pulmonologists who mostly see patients with SSc-ILD with severe structural and functional impairment and/or patients who are mostly symptomatic. This might have introduced a bias into the percentage of patients with limited/extensive disease that they see. Similarly, the Delphi questionnaire included not only questions about SSc-ILD but also about progressive fibrosing ILD (published separately) [22], an area of disease with which pulmonologists are more familiar. This might have introduced a bias into the responses.

The average HCRU of all countries was used in the cost analysis. However, local costs were used for each country. Even if this methodology may dilute the clinical management specificities of each single country, it diminishes the impact of an answer or outlier, given that the sample of panellists per country was low.

The lack of epidemiological data on L-SSc-ILD and E-SSc-ILD in Europe partially affects this cost estimation. The division provided by the panellists was used to estimate the distribution of patients instead. HCRU was asked for the management of SSc-ILD in general and not specifically for the ILD-part, hence it is impossible to draw sound conclusions about the additional costs in the management of the non-ILD part. Given the multiple aspects of a systemic disease, our analysis included other costs, such as medication, hospitalisation, AE associated with other involved organs and their treatment.

Our study showed a significant loss in productivity which was not evaluated from a cost perspective, and any other indirect costs and patient co-payment would have helped to show the impact of SSc-ILD from the societal perspective.

CONCLUSION

Our study indicates that SSc-ILD and its management constitute a clinical, social and economic burden, not only for the patients but also for their caregivers, healthcare systems and more generally for society. Overall disease burden increases with the severity of SSc-ILD.

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Authorship contributions. All the authors reviewed the manuscript for medical and scientific accuracy as well as for intellectual property considerations. All the authors have actively contributed to the development of the work and to the drafting of the manuscript. Montse Pérez designed the questionnaire, was responsible for contacting panellists and analysed the results. Wim Wuyts, Spyridon Papiris, Effrosyni Manali, Jesper Rømhild Davidsen, Jelle Miedema, Carlos Robalo Cordeiro, Maritta Kilpeläinen, Guus Asijee, and Stéphane Soulard reviewed the questionnaire and proposed changes. David Cendoya and Stéphane Soulard performed the cost and sensitivity analyses. At every study milestone, all the authors reviewed and validated the documents (questionnaire, results report and manuscript) to ensure independence and lack of bias.

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Compliance with ethics guidelines. Not applicable in this study because the objective of the Delphi methodology is to obtain a consensus opinion about a specific topic based on the judgment of a group of experts. There is no need to collect any type of patient data or information, hence the approval of an Ethics Committee or patient informed consent is not required.

Data availability. All data generated or analysed during this study are included in this published article [and its supplementary information files].

REFERENCES

1. Wollheim FA. Classification of systemic sclerosis. Vis Real Rheumatol. 2005;44(10):1212–6.

2. Herzog EL, Mathur A, Tager AM, Feghali-Bostwick C, Schneider F, Varga J. Review: interstitial lung disease associated with systemic sclerosis and idiopathic pulmonary fibrosis: how similar and distinct? Arthritis Rheumatol. 2014;66(8):1967–78.

3. Royle JG, Lanyon PC, Grainge MJ, Abhishek A, Pearce FA. The incidence, prevalence, and survival of systemic sclerosis in the UK Clinical Practice Research Datalink. Clin Rheumatol. 2018;37(8):2103–11.

4. García Rodríguez LA, González-Pérez A, Michel A, Sáez ME. Contemporary epidemiology of systemic sclerosis: a population-based cohort study in the United Kingdom. Semin Arthritis Rheum. 2019;49(1):105–11.

5. De Santis M, Bosello SL, Peluso G, Pinnelli M, Alivernini S, Zizzo G, et al. Bronchoalveolar lavage fluid and progression of scleroderma interstitial lung disease. Clin Respir J. 2012;6(1):9–17.

6. Meier FMP, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis. 2012;71(8):1355–60.

7. Allcock RJ, Forrest I, Corris PA, Crook PR, Griffiths ID. A study of the prevalence of systemic sclerosis in northeast England. Rheumatology. 2004;43(5):596–602.

8. Alamanos Y, Tsifetaki N, Voulgari PV, Siozos C, Tsamandouraki K, Alexiou GA, et al. Epidemiology of systemic sclerosis in northwest Greece 1981 to 2002. Semin Arthritis Rheum. 2005;34(5):714–20.

9. Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, et al. Systemic sclerosis in Northwestern Spain: a 19-year epidemiologic study. Medicine (Baltimore). 2008;87(5):272–80.

10. El Adssi H, Cirstea D, Virion J-M, Guillemin F, de Korwin J-D. Estimating the prevalence of systemic sclerosis in the Lorraine region, France, by the capture–recapture method. Semin Arthritis Rheum. 2013;42(5):530–8.

11. Vonk MC, Broers B, Heijdra YF, Ton E, Snijder R, van Dijk APJ, et al. Systemic sclerosis and its pulmonary complications in The Netherlands: an epidemiological study. Ann Rheum Dis. 2009;68(6):961–5.

12. Andréasson K, Saxne T, Bergknut C, Hesselstrand R, Englund M. Prevalence and incidence of systemic sclerosis in southern Sweden: population-based data with case ascertainment using the 1980 ARA criteria and the proposed ACR-EULAR classification criteria. Ann Rheum Dis. 2014;73(10):1788–92.

13. Hoffmann-Vold A-M, Midtvedt Ø, Molberg Ø, Garen T, Gran JT. Prevalence of systemic sclerosis in south-east Norway. Rheumatology. 2012;51(9):1600–5.

14. Butt SA, Jeppesen JL, Fuchs C, Mogensen M, Engelhart M, Torp-Pedersen C, et al. Trends in incidence, mortality, and causes of death associated with systemic sclerosis in Denmark between 1995 and 2015: a nationwide cohort study. BMC Rheumatol. 2018;2:36.

15. Tyndall AJ, Bannert B, Vonk M, Airò P, Cozzi F, Carreira PE, et al. Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. Ann Rheum Dis. 2010;69(10):1809–15.

16. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737–47.

17. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). Respir Res. 2019;20(1):1–10.

18. Goh NSL, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis. Am J Respir Crit Care Med. 2008;177(11):1248–54.

19. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–39.

20. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. 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.

21. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, Stowasser S, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019;380(26):2518–28.

22. Wuyts WA, Papiris S, Manali E, Kilpeläinen M, Davidsen JR, Miedema J, et al. The burden of progressive fibrosing interstitial lung disease: A DELPHI approach. Adv Ther. 2020;20:20.

23. Dalkey N. An experimental study of group opinion: the Delphi method. Futures. 1969;1(5):408–26.

24. Suda T, Kaida Y, Nakamura Y, Enomoto N, Hashimoto D, Takehara Y, et al. Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. Respir Med [Internet]. 2009;103(6):846–53. https://doi.org/10.1016/j.rmed.2008.12.019.

25. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute exacerbation of idiopathic pulmonary fibrosis an international working group report. Am J Respir Criti Care Med. 2016;194:265–75.

26. Rubio-Rivas M, Royo C, Simeón CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44(2):208–19.

27. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis. 2007;66(7):940–4.

28. Steen VD, Medsger TA. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum. 2000;43(11):2437–44.

29. Fischer A, Zimovetz E, Ling C, Esser D, Schoof N. Humanistic and cost burden of systemic sclerosis: A review of the literature. Autoimmun Rev. 2017;16(11):1147–54.

30. Chevreul K, Brigham KB, Gandré C, Mouthon L, Serrano-Aguilar P, Linertová R, et al. The economic burden and health-related quality of life associated with systemic sclerosis in France. Scand J Rheumatol. 2015;44(3):238–46.

31. Bernatsky S, Hudson M, Panopalis P, Clarke AE, Pope J, LeClercq S, et al. The cost of systemic sclerosis. Arthritis Care Res. 2009;61(1):119–23.

32. Basta F, Afeltra A, Margiotta DPE. Fatigue in systemic sclerosis: a systematic review. Clin Exp Rheumatol. 2018;36:S150–60.

33. March C, Huscher D, Preis E, Makowka A, Hoeppner J, Buttgereit F, et al. Prevalence, risk factors and assessment of depressive symptoms in patients with systemic sclerosis. Arch Rheumatol. 2019;34(3):253–61.

34. Foocharoen C, Chunlertrith K, Mairiang P, Mahakkanukrauh A, Suwannaroj S, Namvijit S, et al. Prevalence and predictors of proton pump inhibitor partial response in gastroesophageal reflux disease in systemic sclerosis: a prospective study. Sci Rep [Internet]. 2020;10(1):1–9. https://doi.org/10.1038/s41598-020-57636-0.

35. Furst DE, Fernandes AW, Iorga SR, Greth W, Bancroft TIM. Annual medical costs and healthcare resource use in patients with systemic sclerosis in an insured population. J Rheumatol. 2012;39(12):2303–9.

36. Fischer A, Kong AM, Swigris JJ, Cole AL, Raimundo K. All-cause healthcare costs and mortality in patients with systemic sclerosis with lung involvement. J Rheumatol. 2018;45(2):235–41.

37. Zhou Z, Fan Y, Thomason D, Tang W, Liu X, Zhou ZY, et al. Economic burden of illness among commercially insured patients with systemic sclerosis with interstitial lung disease in the USA: a claims data analysis. Adv Ther. 2019;36(5):1100–13.

38. Morrisroe K, Stevens W, Sahhar J, Ngian G, Ferdowsi N, Hansen D, et al. The clinical and economic burden of systemic sclerosis related interstitial lung disease. Rheumatology. 2019;20:1–11.

39. Singh P, Thakur B, Kumar A, Prasanta M. Clinical features and outcome of acute exacerbation in connective tissue disease-associated interstitial lung disease: a single-center study from India. Int J Rheum Dis. 2018;2019:1–5.

40. Tomiyama F, Watanabe R, Ishii T, Kamogawa Y, Fujita Y, Shirota Y, et al. High prevalence of acute exacerbation of interstitial lung disease in Japanese patients with systemic sclerosis. Tohoku J Exp Med. 2016;20:297–305.

41. Tachikawa R, Tomii K, Ueda H, Nagata K, Nanjo S, Sakurai A, et al. Clinical features and outcome of acute exacerbation of interstitial pneumonia: collagen vascular diseases-related versus idiopathic. Respiration. 2012;0046:20–7.

42. Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs. 2000;32(4):1008–15.

43. Cantrill J, Sibblald B, Buetow S. The Delphi and nominal group techniques in health services. Int J Pharm Pract. 1996;4(2):67–74.

44. Petri M, Bechtel B, Dennis G, Shah M, McLaughlin T, Kan H, et al. Burden of corticosteroid use in patients with systemic lupus erythematosus: Results from a Delphi panel. Lupus. 2014;23(10):1006–13.

45. Yu X, Chen S, Chen X, Jia J, Li C, Liu C, et al. Clinical management and associated costs for moderate and severe Alzheimer's disease in urban China: a Delphi panel study. Transl Neurodegener [Internet]. 2015;4(1):1–9. https://doi.org/10.1186/s40035-015-0038-9.

46. Ferri C, Chisholm D, Van Ommeren M, Prince M. Resource utilisation for neuropsychiatric disorders in developing countries: a multinational Delphi consensus study. Soc Psychiatry Psychiatr Epidemiol. 2004;39(3):218–27.

47. Xie F, Hopkins R, Burke N, Tarride JE, Goeree R. Patient management, and time and health care resource utilization associated with the use of intravenous bisphosphonates for patients with metastatic bone disease: a Delphi study. Hosp Pract (1995). 2012;40(2):131–7.

48. Morell F, Esser D, Lim J, Stowasser S, Villacampa A, Nieves D, et al. Treatment patterns, resource use and costs of idiopathic pulmonary fibrosis in Spain—results of a Delphi Panel. BMC Pulm Med [Internet]. 2016;16(1):1–9. https://doi.org/10.1186/s12890-016-0168-6.