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Review

Humanistic and cost burden of systemic sclerosis: A review of the literature

Aryeh Fischer [a], Evelina Zimovetz [b], Caroline Ling [b], Dirk Esser [c], Nils Schoof [c,*]

[a] University of Colorado School of Medicine, Denver, CO, USA
[b] RTI Health Solutions, Manchester, United Kingdom
[c] Boehringer Ingelheim GmbH, Ingelheim, Germany

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ABSTRACT

Background: Systemic sclerosis (SSc), or systemic scleroderma, is a chronic multisystem autoimmune disease characterised by widespread vascular injury and progressive fibrosis of the skin and internal organs. Patients with SSc have decreased survival, with pulmonary involvement as the main cause of death. Current treatments for SSc manage a range of symptoms but not the cause of the disease. Our review describes the humanistic and cost burden of SSc.

Methods: A structured review of the literature was conducted, using predefined search strategies to search PubMed, Embase, and the Cochrane Library. Grey literature searches also were conducted.

Results: In total, 2226 articles were identified in the databases and 52 were included; an additional 10 sources were included from the grey literature. The review identified six studies reporting relevant cost estimates conducted in five different countries and four studies that assessed the humanistic burden of SSc. Total direct annual medical costs per patient for Europe varied from €3544 to €8452. For Canada, these costs were reported to be from Can$5038 to Can$10,673. In the United States, the total direct health care costs were reported to be US$17,365 to US$18,396. Different key drivers of direct costs were reported, including hospitalisations, outpatients, and medication. The total annual costs per patient were reported at Can$18,453 in Canada and varied from €11,074 to €22,459 in Europe. Indirect costs represented the largest component of the total costs. EQ-5D utility scores were lower for patients with SSc than those observed in the general population, with reported mean values of 0.49 and 0.68, respectively. The average value of the Health Assessment Questionnaire for patients with SSc was significantly higher than the control population (0.94), and the average value of the SF-36 was significantly lower than the control population: 49.99 for the physical dimension and 58.42 for the mental dimension.

Conclusions: Overall, there is a paucity of information on the burden of SSc. Nonetheless, our review indicates that the quality of life of patients with SSc is considerably lower than that of the general population. In addition, SSc places a considerable economic burden on health care systems and society as a whole.

Contents

Abbreviations: AIDS, acquired immunodeficiency syndrome; CI, confidence interval; DALY, disability-adjusted life-year; dcSSc, diffuse cutaneous SSc; DRG, diagnosis-related group; EQ-5D-5L, five-level EQ-5D; ERS, European Respiratory Society; ESC, European Society of Cardiology; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; HIV, human immunodeficiency virus; HRQOL, health-related quality of life; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; PAH, pulmonary arterial hypertension; QOL, quality of life; SD, standard deviation; SF-36, short form-36; SSc, systemic sclerosis; US, United States; VAS, visual analogue scale.

* Corresponding author at: Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim am Rhein, Germany.
E-mail addresses: aryeh.fischer@ucdenver.edu (A. Fischer), ezimovetz@rti.org (E. Zimovetz), cling@rit.org (C. Ling), dirk.esser@boehringer-ingelheim.com (D. Esser), nils.schoof@boehringer-ingelheim.com (N. Schoof).

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1. Introduction

Systemic sclerosis (SSc), or systemic scleroderma, is a chronic multisystem autoimmune disease characterised by widespread vascular injury and progressive fibrosis of the skin and internal organs [1,2]. Systemic sclerosis is most commonly diagnosed in women (female:male ratio, 3:1 to 14:1 in different studies) who are 30 to 50 years old [3,4]. Early identification of SSc can be difficult owing to its significant clinical heterogeneity and a vast array of organ complications [2].

The pathogenesis of SSc is not fully understood, but it is clear that autoimmunity has a major role in the fibrogenic processes of the condition [5]. Based on the extent of skin fibrosis, SSc is subdivided into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) types [6]. In lcSSc, skin sclerosis is restricted to the distal portion of the limbs, including hands, and also the face; whereas in dcSSc, skin involvement extends proximal to the elbows and knees [6].

More than half of patients with SSc develop associated interstitial lung disease (SSc-ILD). The symptoms of SSc-ILD range from subclinical lung involvement to major pulmonary disease progressing to respiratory failure and death [7]. Patients with SSc are also at risk of developing pulmonary arterial hypertension, internal organ fibrosis, and hypertensive renal crisis [5].

The rarity and heterogeneous clinical presentation of SSc have made reliable epidemiological studies difficult to conduct [8]. Prevalence varies widely between studies and is estimated to be from 3 to 24 per 100,000 population globally [8]. The incidence of SSc has increased significantly since the 1950s and 1980s, probably due to greater physician awareness and more reliable diagnosis [8]. Patients with SSc have a higher mortality rate than the general population and pulmonary involvement is the main cause of death (standardised mortality ratio, 2.72), although the rate appears to have decreased since 1990 [9]. Survival from diagnosis has been estimated to be 74.9% at 5 years and 62.5% at 10 years [9].

Treatments for SSc have traditionally targeted the various symptoms rather than the root cause of the disease [10]. The European League Against Rheumatism (EULAR) and Canadian Scleroderma Research Group have published guidelines that provide recommendations on pharmacotherapies for different manifestations of SSc, while other guidelines, such as the American College of Chest Physicians and European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, focus on treatment of PAH (including PAH associated with SSc) [10–13].

Both the EULAR and Canadian Scleroderma Research Group recommend proton pump inhibitors for the prevention of SSc-related gastrointestinal disease [13,14]. For SSc-related digital vasculopathy (including Raynaud's phenomenon and digital ulcers), these guidelines recommend calcium channel blockers as first-line treatment [13,14]. Angiotensin-converting enzyme inhibitors are recommended for the treatment of scleroderma renal crisis [13,14]. Methotrexate may be considered for treatment of SSc-related skin involvement [13,14]. Both the EULAR and Canadian guidelines recommend cyclophosphamide for the treatment of SSc-ILD [10,13]. Other treatments may include mycophenolate mofetil or azathioprine depending on patient characteristics [13]. Treatment options for patients with associated PAH depend on the severity of disease and include endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids [11,12].

The objective of our review was to identify and report on key studies on the burden of SSc, including ILD associated with SSc, to gain insight into the clinical, economic, and humanistic burden (in terms of the impact on patient's quality of life and daily functioning) of SSc; to describe the epidemiology of SSc; and to outline currently available treatment options for SSc. This article presents only the review findings associated with the humanistic and economic burden of SSc.

2. Methods

Searches were conducted on 25 August 2015 using PubMed, Embase, and Cochrane Library literature databases and limited to human studies published from January 1990 (for epidemiology) or 2000 (for other aspects). Treatment guidelines were identified using the Agency on Health care Research and Quality's National Guideline Clearinghouse (www.guideline.gov).

A search strategy was development in PubMed and was translated to Embase and Cochrane syntax. Search terms were categorised as follows: condition of study (e.g., "Scleroderma, Systemic," OR "Scleroderma, Diffuse," OR "Scleroderma, Limited"), economic burden (e.g., "Scleroderma, Systemic/economics", "Health Resources/utilization", "Cost of Illness"), humanistic burden (e.g., "Quality of Life", "activities of daily living", "Caregivers"), clinical burden (e.g., "Symptom" OR "Comorbidity"), treatment (e.g., "mycophenolate" OR "cyclophosphamide" OR "bosentan"), and epidemiology (e.g., ("Scleroderma, Systemic/epidemiology" OR "Incidence" OR "Prevalence"). The full PubMed search strategy used is presented in Supplementary material 1.

A review of the titles and abstracts was conducted iteratively, initially including a broader set of potentially relevant articles and narrowing the review before screening full texts of included studies to identify the most robust sources. Key studies on the burden of SSc were selected, with the focus on Australia, Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States.

3. Results

3.1. Literature search results

The search identified 2226 unique articles; 2091 of these were excluded, as it was clear from their titles that they were not relevant to the goals of the study or that SSc was not the focus. The full text of the remaining 135 articles was obtained; of these, 52 sources were included in the full review. Ten additional sources were identified through searches for treatment guidelines. The review included 10 key publications that reported on the humanistic (4 articles) and economic burden (6 articles) of SSc and therefore were relevant for inclusion in this article. Fig. 1 shows the decision process from identification to title/abstract review and full-text selection.

3.2. Economic burden of SSc

The review identified six studies reporting relevant cost estimates conducted in five different countries: the US [15], Canada [16,17], France [18], Italy [19], and Spain [20]. The studies used various methods, including database analyses [15,17], surveys [18,20], an analysis of registry data [16], and a retrospective cohort study based on data from a single hospital [19]. Most studies were cross-sectional, and only one longitudinal analysis reported the trend in direct medical costs [17]. The review of the identified studies indicated that SSc is associated

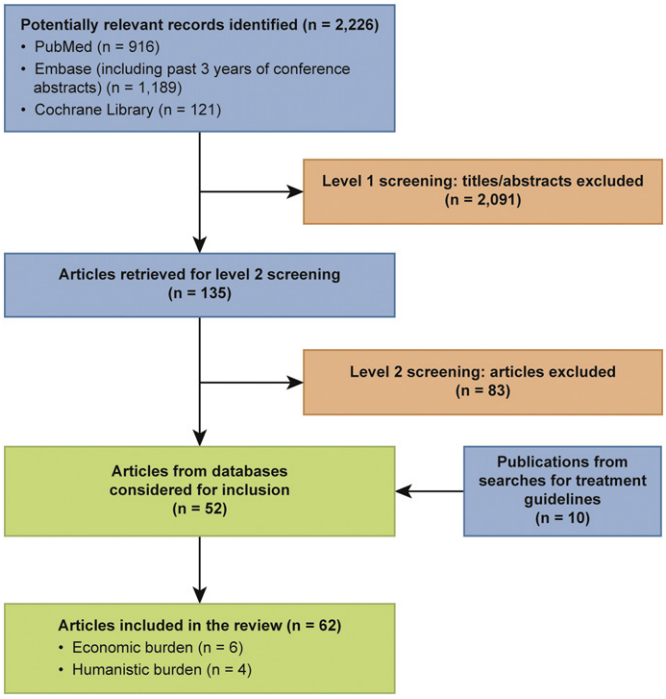


Fig. 1. Study selection diagram.

with a large economic burden to individual patients and to society. Table 1 presents summaries of the six studies assessing the economic burden of SSc.

Most studies (4 out of 6) reported both direct and indirect costs [16,18–20]. Fig. 2 presents the variation in the relative proportions of direct and indirect costs of total costs among the included studies. Direct health care costs constituted between 27% and 39% of the total costs in all four studies, with the remainder a combination of direct non-health care and indirect costs.

Different key drivers of direct health care costs were reported by the identified studies as indicated in Fig. 3. Hospital stays, medications, and outpatient appointments were the main sources of direct medical costs, but the contribution of each to the overall costs varied considerably between studies. Two studies compared costs associated with the diffuse form of SSc and the limited form of SSc [16,19].

3.2.1. United States and Canada

A claims-database analysis in the US compared medical costs of SSc in a cohort of 1648 patients with SSc versus 4944 matched controls and found that mean overall annual medical costs were higher among patients with SSc than controls (see Table 1) [15]. Compared with controls, significantly higher proportions of patients with SSc had outpatient visits, emergency department visits, and inpatient hospital stays. Ambulatory costs accounted for the largest portion of overall health care costs among patients with SSc (38.7% of total costs) (Table 1) [15]. The second-largest driver of overall medical costs was inpatient costs (31.0% of total costs), followed by pharmacy costs (22.2% of total costs) (see Table 1) [15].

Overall total health care costs were also modelled with a generalised linear model. The analysis showed that several SSc-related conditions (diagnosed within 1 year following the index date) were associated with increased costs, including lung disease (cost ratio = 2.298; $P < 0.001$), gastrointestinal bleeding (cost ratio = 1.894; $P < 0.001$), and renal disease (cost ratio = 3.074; $P < 0.001$) [15].

A cross-sectional analysis of registry data based on the Canadian Scleroderma Research Group composed of 15 centres estimated the average total annual cost of SSc at Can$18,453 (95% confidence interval [CI], Can$16,598–$20,308) (2007 prices) per patient [16]. In the sample of 457 patients with SSc, the average direct cost per patient was Can$5038 per year (95% CI, Can$4400–$5676) [16]. The value of potential productivity loss related to paid labour was estimated at an average of Can$5345 per patient per year (95% CI, Can$4598–$6092), and the cost of lost productivity related to unpaid labour contributed another Can$8070 per patient annually. Total annual costs were strongly associated with younger age, greater disease severity, and poorer health status [16].

The study stratified costs by disease subset (diffuse versus limited disease). Although patients with diffuse disease tended to have higher costs for some direct cost components, the 95% CIs for these estimates overlapped with the estimates for patients with limited disease. However, regarding indirect costs, patients with diffuse disease had higher annual costs related to lost productivity related to paid labour, which was an average of Can$7092 (95% CI, Can$5694–$8490) per patient with diffuse disease versus Can$4101 (95% CI, Can$3314–$4887) per patient with limited disease [16].

A population-based, longitudinal analysis evaluated the direct medical costs of patients with SSc in Canada over a duration of 15 years [17]. Over this period, the cumulative costs for SSc cases totalled Can$83,507,123 and averaged $10,673 per patient per year with Can$2475 (23%) from outpatient services, Can$5360 (50%) from hospitalisations, and Can$2838 (27%) from prescription medications. The study found that, from 1996 to 2010, outpatient and hospital costs decreased and medication use and costs increased. After adjustment to 2010 Canadian dollars, from 1996 to 2010, annual mean per-patient-per-year costs increased by 8%, mean per-patient-per-year outpatient costs decreased by 14%, and hospital costs decreased by 15% (see Table 1). In contrast, mean per-patient-per-year prescription costs increased by 109%, and the mean number of prescriptions per patient per year increased by 56% (from 29 to 46). The authors concluded that, given there were no specific disease-modifying antirheumatic drugs for SSc during the period of the study, the long-term costs of SSc may be driven by ongoing complications and comorbidities of the disease [17].

3.2.2. Europe

A survey of 147 patients with SSc conducted in France reported the average annual direct health care costs for SSc were €8452 per patient (2012 prices) [18]. Hospitalisation was the key cost driver, representing 60% of the direct health care costs, with medications accounting for only a small part of annual direct health care costs (€145 per patient) (see Table 1 for other costs) [18]. Annual direct non-health care formal costs were estimated at €1606 per patient. Social services was the largest component, with costs for professional caregivers and non-health care transport being minimal (see Table 1) [18]. The average total annual cost of SSc per patient was estimated to be €22,459 [18]. The major contributors to the economic burden of SSc were indirect costs, representing 47% of the total annual cost, with early retirement being the most costly component (77%) and loss of productivity accounting for the rest (see Table 1) [18].

Based on estimates of the prevalence of SSc in France—from 132.2 to 158.3 cases per 1,000,000 adults [21,22]—the study estimated the total national economic burden of SSc to be from €194 million to €232 million per year [18].

Annual costs for patients who were moderately dependent or worse (Barthel Index ≤ 90) were found to be 3.5 times higher than for those who were slightly dependent (Barthel Index > 90). The greatest differences were observed for direct health care costs (mainly due to hospitalisation) and indirect costs (cost of early retirement was 4 times higher) [18].

High costs of SSc were suggested in one Italian study, with an average total yearly per-patient cost of €11,074 (2001 prices) [19]. The total yearly economic impact of SSc in Italy was calculated at €249 million [19]. The authors estimated annual economic burden based on a prevalence of 375 cases per 1,000,000 without giving their source. However,

Table 1
Summary of costs related to systemic sclerosis.

Reference, country, cost year	Study population	Methods	Health care resource, direct and indirect costs, and productivity reported
Furst et al. [15] United States, 2009	N = 1648 (matched to 4944 controls) Mean age: 50.8 years Female: 87%	• Database analysis. • Patients aged ≥18 years with claims-based evidence of SSc identified from a health plan database from 2003 to 2008. • Patients matched to unaffected controls, based on index date, age, sex, geographic region, time on insurance, and comorbidity score. • Costs and resource use identified during the 12-month postindex period. • A generalised linear model used to estimate costs, controlling for demographic and clinical characteristics.	Average annual postindex medical costs: Ambulatory costs: US $6713 Inpatient costs: US $5390 Pharmacy costs: US $3856 Other medical costs: US $1229 Emergency services costs: US $177 Average annual unadjusted total medical costs: US $17,365 (US $5508 for controls, $P < 0.001$) Average annual adjusted[a] total medical costs: US $18,396 (US $5316 for controls) Annual postindex per-patient resource use, mean number of visits (%) (SSc patients [n = 1648] vs. controls [n = 4944]): Ambulatory visits: 23.98 (19.70) vs. 11.15 (12.44) Visits to primary care physician: 5.16 (5.19) vs. 3.36 (3.50) Visits to nephrologist: 0.10 (1.06) vs. 0.01 (0.34) Visits to rheumatologist: 2.96 (3.12) vs. 0.06 (0.61) Visits to dermatologist: 0.78 (3.40) vs. 0.32 (1.10) Emergency department visits: 1.00 (3.66) vs. 0.54 (2.60) Inpatient hospital stays: 0.33 (0.76) vs. 0.09 (0.35) Total length of inpatient stay, days: 2.19 (7.92) vs. 0.44 (2.71)
Bernatsky et al. [16] Canada, 2007	N = 457 Mean age: 55.1 years Female: 87.7% Adult-onset disease: > 99% Mean duration of SSc: 10.5 years Mean modified Rodnan skin score: 10.4 Prevalence of lung involvement (including mild disease): 80.4%	• Cross-sectional analysis of registry data. • Data included clinical variables and standardised measures of health resource use and time loss. • Annualised averages of direct medical costs calculated by multiplying health service utilisation levels by appropriate unit prices, determined from government fee schedules, professional associations, and other sources. • Indirect costs calculated from patients' self-reported time loss related to illness and to seeking health care, and caregiver time losses. • Opportunity cost method used to estimate the value of lost time in market work. • Replacement cost method used to assign values to unpaid work losses.	Average direct per-patient costs, mean (95% CI)[b]: Outpatient visits: Can$756 (Can$638–$875) Diagnostic tests: Can$736 (Can$643–$828) Medications: Can$1575 (Can$1184–$1967) Assistive devices: Can$208 (Can$144–$273) Outpatient surgical procedures: Can$222 (Can$165–$280) Acute-care hospitalisations: Can$1448 (Can$1115–$1780) Rehabilitation hospital stays: Can$92 (Can$39–$145) Total: Can$5038 (Can$4400–$5676) Average indirect per-patient costs in 2007 Can$, mean (95% CI)[b] Lost productivity, paid labour: Can$5345 (Can$4598–$6092) Lost productivity, unpaid labour: Can$8070 (Can$7167–$8973) Total indirect costs: Can$13, 415 (Can$11,840–$14,990)
McCormick et al. [17] Canada, 2010	N = 1456 Mean age: 55.3 years Female: 82%	• Population-based, longitudinal analysis. • Cohort of SSc identified using: (1) diagnosis of SSc on at least two visits within a 2-year period between January 1990 and December 2010 by a non-rheumatologist physician; (2) diagnosis of SSc on at least one visit by a rheumatologist or from hospitalisation. To increase specificity, we excluded cases not confirmed by a rheumatologist if they were seen at a later time. • Costs for outpatient services and prescriptions were summed directly from paid claims. • Case-mix methodology was used to cost hospitalisations.	Direct annual health care costs per patient, mean (in 1996): Outpatients: Can$2714 Hospital: Can$5059 Medications: Can$1740 Total: Can$9513 Direct annual health care costs per patient, mean (in 2010): Outpatients: Can$2333 Hospital: Can$4287 Medications: Can$3641 Total: Can$10,261
Chevreul et al. [18] France, 2012	N = 147 Mean age: 53.8 years Female: 90.5% Mean age at disease onset: 42.3 years Mean duration of SSc: 11.5 years Mean Barthel Index: 93.5	• Cross-sectional, retrospective online survey. • Patients recruited through French scleroderma patients' association. – For patients with informal caregivers, the principal caregiver (person who spent most hours helping the patient) was also asked to complete a separate questionnaire. • Data collected through the online form included patient demographics, use of health care resources and social services (services provided to the patient other than formal medical care such as day or residential centres, hydrotherapy, supportive home care, or psychosocial support for family members), informal care, and absence from the labour market. • Health-related quality of life data on both patients and caregivers also compiled.	Direct annual health care costs per patient, mean (SD)[c]: Drugs: €145 (€121) Medical tests: €648 (€571) Medical visits: €1077 (€1348) Hospitalisations: €5075 (€12,559) Health material: €1466 (€2023) Transport: €41 (€142) Total: €8452 (€14,480) Direct annual non-health care formal costs per patient, mean (SD)[c]: Professional carer: €23 (€210) Transport: €146 (€281)

Table 1 (*continued*)

Reference, country, cost year	Study population	Methods	Health care resource, direct and indirect costs, and productivity reported
		• Data on resource utilisation extracted from the questionnaire, which retrospectively covered the 6 months before the study, except for hospitalisations, which were assessed over a 1-year period. Valuation then carried out by extrapolating all the data over a 1-year period.	Social services: €1437 (€8628) Total: €1606 (€8663) Direct annual non-health care informal costs per patient, mean (SD)[c]: Main informal carer: €1834 (€6963) Other informal carers: €41 (€436) Total: €1875 (€6982) Indirect annual costs per patient, mean (SD)[c]: Productivity loss: €2403 (€7990) Early retirement: €8123 (€14,312) Total: €10,526 (€15,145) Total annual cost per patient, mean (SD)[c]: €22,459 (€29,354)
Belotti Masserini et al. [19] Italy, 2001 (translated from Italian)	N = 106 (57 limited, 49 diffuse) Mean age: 57 years Female: 97% Mean disease duration: 8.9 years	• Retrospective study. • Patients with SSc recruited in 2001 from one Italian hospital. • Direct health care costs derived using DRG codes for connective tissue disease with and without complications and units of resource. • Drug costs from national pharmaceutical reference book. • Direct non-health care costs derived using distance travelled for care and number of work days lost receiving treatment. • Indirect cost estimate based on extrapolation.	Direct annual health care per-patient costs mean[b]: Outpatient: €282 Inpatient: €2385 (ordinary admissions) Inpatient: €580 (day hospital) Total: €3247 Total direct annual non-health care per-patient cost, mean[b]: €297 Total direct annual per-patient cost, mean[b]: €3544 Total indirect annual per-patient cost, mean[b]: €7530
Lopez-Bastida et al. [20] Spain, 2011	N = 147 Mean age: 45 years Female: 85%	• Cross-sectional, retrospective survey. • Demographic and clinical data collected from questionnaires completed by patients with SSc or their caregivers recruited from the Scleroderma Spanish National Alliance (September 2011 and February 2012). • Questionnaires solicited information covering the 6-month period prior to the study (12 months for hospital admissions). Data for the preceding 6 months were extrapolated to the entire year. • Temporary and permanent sick leave or early retirement used to estimate losses of labour productivity. Informal carers' time also included in the analysis. • All unit costs obtained from national sources; gross wage figures obtained from the Wage Structure Survey of the Spanish National Statistics Institute.	Annual direct health care per-person costs, mean (SD): Medication: €4158 (€6637) Tests: €521 (€411) Outpatients and primary health care visits: €1572 (€22,286) Acute hospitalisation: €1474 (€3754) Devices: €505 (€1484) Health care transportation: €6 (€63) Total: €8235 (€9574) Annual direct non-health care per-person costs, mean (SD): Social services: €929 (€2795) Caregiver's time costs (informal costs)[d]: €4574 (€14,634) Main caregivers: €4053 (€12,533) Secondary caregivers: €521 (€3889) Total: €5503 (€14,742) Total annual direct per-person costs, mean (SD): €13,738 (€19,085) Productivity loss per-person costs, mean (SD): Sick leave[e]: €1411 (€5009) Early retirement[f]: €5891 (€9244) Total lost productivity costs: €7303 (€9685) Total annual per-person cost, mean (SD): €21,041 (€24,037)

CI = confidence interval; DRG = diagnosis-related group; SD = standard deviation; SSc = systemic sclerosis.

[a] Clinical and demographic characteristics were adjusted for using a generalised linear model.

[b] This study also reported these costs separately for patients with limited and diffuse SSc.

[c] This study also reported these costs separately by age groups, gender, disease duration, and level of functioning assessed by the Barthel Index.

[d] Caregiver's time was valued at €13.19/h.

[e] Sick leave was valued at €14.50/h.

[f] Early retirement was valued at €25,001/year for men and €19,502/year for women.

this study was limited because elements of indirect cost were based on extrapolations rather than data obtained from a sample of patients with SSc. Similar to the findings from the study by Bernatsky et al. [16], this study found that medical costs in patients with SSc correlated with poor health status and disease severity. Costs related to the diffuse form of the disease were statistically significantly higher ($P = 0.0006$) when compared with those of the limited form [19]. Similarly, it was found that significantly higher costs were detectable in patients who showed parameters of worse organ functions (e.g., high pulmonary artery pressure, reduced diffusing capacity for carbon monoxide, presence of pulmonary fibrosis) regardless of the form of the disease [19].

A survey of 147 patients with SSc and their caregivers conducted in Spain estimated the total average annual cost of SSc per patient to be €21,042 (2011 prices) [20]. Of this, 39% were direct health care costs, 26% were direct non-health care costs, and 35% was loss of labour productivity (see Table 1). Medication costs accounted for 50.5% of the health care costs and 19.8% of total costs (Table 1). Early retirement costs accounted for 80.7% of loss of labour productivity and 28.0% of total costs (Table 1) [20].

The authors compared the estimated annual cost per SSc patient with the equivalent costs of patients with other chronic illnesses in Spain. The cost of patients with SSc was higher than costs of patients with human immunodeficiency virus (HIV) and acquired

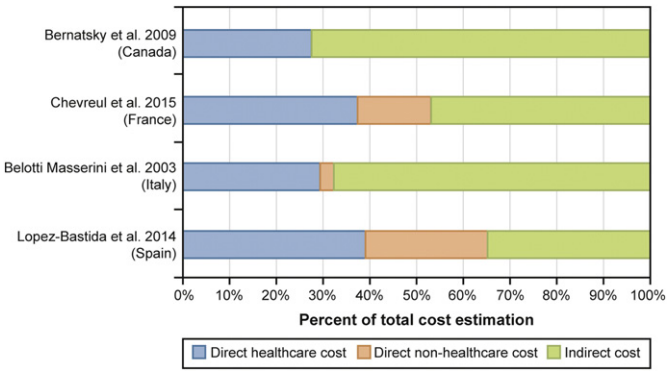


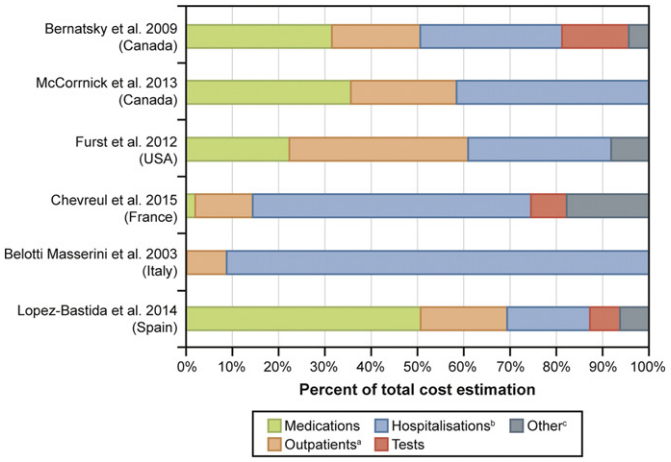
Fig. 2. Proportion of direct and indirect costs in total cost estimation [16,18–20].

immunodeficiency syndrome (AIDS) (€13,823); ataxias (€18,776); and stroke survivors during the first year after stroke (€13,826) [20].

3.3. Humanistic burden of SSc

The experience of living with scleroderma is complex [23]; patients perceived that clinical aspects of their disease, such as limitations in mobility and hand function, pain, fatigue, difficulty breathing, gastrointestinal problems, sleep disturbance, depression, sexual dysfunction, pruritus, body image, and distress from disfiguring changes in appearance (e.g., pigment changes, hand contractures, and facial telangiectasias), were debilitating or distressing and were associated reduced QOL and impaired ability to work [24,25]. Emotional distress, including depression, low self-esteem, concerns with physical appearance, and uncertainty about future outcomes, has a major impact on patient's overall well-being [26]. Consequently, patients experience significant disruptions in their social lives, a burden considered by many as the worst consequence of their disease [26].

The review identified four studies that assessed the humanistic burden of SSc (Table 2). Three of these studies also reported costs and are discussed above. All four studies were conducted in Europe. Various measures of health-related quality of life (HRQOL) were used. The most recent study used the five-level EQ-5D (EQ-5D-5L) health questionnaire [18]; Lopez-Bastida et al. [20] used the EQ-5D (version not stated); Belotti Masserini et al. [19] used the Short Form-36 (SF-36) for the evaluation of the quality of life (QOL) and the Health Assessment Questionnaire (HAQ) for the evaluation of disability; and Villaverde-Hueso et al. [27] measured the burden of SSc in terms of the disability-adjusted life-years (DALYs), composed of years of life lost and years lived with disability.



[a]This includes visits to health care professionals and outpatient surgical procedures in [16] and both outpatients and primary health care visits in [20].
[b]This includes acute-care hospitalisations and rehabilitation hospital stays in [16] and ordinary admissions and hospital days in [19].
[c]This category includes devices [16, 20], health material [18], transport [18, 20], emergency services, and any costs that could not be assigned to pharmacy, ambulatory, emergency services, or inpatient categories [15].

Fig. 3. Reported direct health care cost components [15–20].

Quality of life is considerably lower for patients with SSc than in the general population. EQ-5D utility scores derived in a study in France were lower for patients with SSc than those observed in the general population, (mean values, 0.49 and 0.83, respectively) [18]. Similarly, in a study in Spain, the average EQ-5D index score of people with SSc was 0.68, which was much lower than the HRQOL of the general population (0.85) [20] (Fig. 4).

A study in Italy reported the average value of the HAQ for patients with SSc as significantly higher than the control population (0.94 [SD, 0.72]) and the average value in the SF-36 as significantly lower than the control population (49.99 [SD, 19.16] for the physical dimension and 58.42 [27.71] for the mental dimension) [19]. Means for the control population were not presented. This study also suggested that the diffuse form of SSc resulted in lower HRQOL compared with the limited form; however, this finding was not statistically significant [19]. One study measured the burden of SSc in Spain using DALYs and found that the major contributing factor to SSc-related DALYs was years lived with disability (68%), with years of life lost, in contrast, accounting for only 32% of total DALYs [27].

4. Discussion

Our review evaluated the economic and humanistic burden associated with SSc. Although SSc is an orphan disease, the total cost of SSc is estimated to account for US$1.9 billion per year across North America and up to €3.1 billion per year across Europe [16]. One identified study compared the cost of SSc with other chronic illnesses and concluded that patients with SSc have higher mean annual costs compared with patients with other illnesses, such as HIV, AIDS, ataxias, and stroke [20]. Our review showed that total direct annual medical costs per patient for Europe varied from €3544 to €8452. For Canada, these costs were reported to be from Can$5038 to Can$10,673. In the US, the total direct health care costs were reported to be US$17,365 to US$18,396. A recent US-based study, identified as an abstract since our review, reported similar direct health care costs for patients with SSc without lung involvement, but higher costs for patients with SSc-ILD and pulmonary hypertension (5-year direct health care costs of US$101,839, US$191,107 and US$254,425, respectively) [29]. They concluded that the presence of ILD and/or pulmonary hypertension is associated with significant increases in health care costs compared with SSc alone [29].

Different key drivers of direct costs were reported by the identified studies, including hospitalisations [17–19], outpatient costs [15], and medication [20]. The variety of drivers probably reflects the differences in health care systems across the countries, cost component data considered, methodologies across the included studies, and the timings of these studies.

Four of the six identified studies reported both direct and indirect costs [16,18–20]. The total annual costs per patient were reported to be Can$18,453 in Canada [16] and varied from €11,074 to €22,459 in Europe [18,19]. In most of the included studies, indirect costs represented the largest component of the total costs, with the relative proportion of indirect costs of total costs varying among the included studies from 35% to 73%. Early retirement was a key driver of indirect costs [16,18–20].

As expected, costs associated with the diffuse form of SSc were higher than those of the limited form of disease [16]. Disease severity, health status, and younger age had a great impact on economic burden. Similarly, the presence of SSc-related complications was associated with increased costs [17].

The burden of SSc is not only economic, as the QOL of patients is also significantly reduced. Our review showed that the QOL of patients with SSc is considerably lower than the general population or other chronic illnesses [18–20,27]. One study reported a mean EQ-5D-5L score of

Table 2
Effect of systemic sclerosis on patient's quality of life.

Reference, country	Study design and QOL measure	Results
Chevreul et al. [18] France	• N = 147 • Cross-sectional, retrospective survey. • Patients recruited through the French scleroderma patients' association. • Data collected through the online form included patient demographics, use of health care resources and social services, informal care, absence from the labour market, and HRQOL. • HRQOL of patients and caregivers assessed with the EQ-5D-5L health questionnaire.	• Mean EQ-5D-5L utility score (SD): – Patients (n = 134): 0.49 (0.25); their caregivers (n = 14): 0.66 (0.41) • Mean EQ-5D-5L VAS score (SD): – 59 (18) for patients; 76 (25) for caregivers • Mean EQ-5D-5L utility score (SD): – Patients with a Barthel Index <90 (n = 22): 0.19 (0.25) – Patients with a Barthel Index ≥90 (n = 110): 0.54 (0.21)
Belotti Masserini et al. [19] Italy	• N = 106 (57 limited, 49 diffuse) • Retrospective study. • Recruited patients with SSc in 2001 at G. Pini Orthopaedic Institute of Milan. • All patients were administered the SF-36 QOL and the HAQ.	• HAQ, mean (SD): 0.94 (0.72) • SF-36, mean (SD): – Physical dimension: 49.99 (19.16) • Mental dimension: 58.42 (27.71)
Lopez-Bastida et al. [20] Spain	• N = 147 • Cross-sectional, retrospective study. • Demographic and clinical data collected from the questionnaires completed by patients with SSc or their caregivers recruited from the Scleroderma Spanish National Alliance (September 2011 and February 2012). • Information about HRQOL collected from patients with SSc through the generic EQ-5D questionnaire.	• EQ-5D score (n = 114)[a], mean (SD): 0.68 (0.23) • VAS score (n = 123)[a], mean (SD): 64 (19.1)
Villaverde-Hueso et al. [27] Spain	• N = 41,116,842 (population of Spain, 2001) • Burden of disease estimated following the procedures used in the Global Burden of Disease study described by Murray and Lopez [28]. • DALY were obtained from the addition of 2 components: years of life lost and years lived with disability.	• Scleroderma resulted in the loss of 1732 DALYs: – 562 (32%) years of life lost – 1170 (68%) years lived with disability

DALY = disability-adjusted life-year; EQ-5D-5L = five-level EQ-5D; HAQ = Health Assessment Questionnaire; HRQOL = health-related quality of life; QOL = quality of life; SD = standard deviation; SF-36 = Short Form-36; VAS = visual analogue scale.
[a] Number of patients who completed the EQ-5D or VAS.

0.49 for patients versus 0.83 for the general population [18], and another study reported a mean EQ-5D score of 0.68 versus 0.85, respectively [20]. Estimated EQ-5D utility and visual analogue scale scores from one study were lower than those observed in patients with HIV or type 2 diabetes [18]. The major contributing factor to SSc-related DALYs was years lived with disability (68%), with years of life lost accounting for only 32% of total DALYs.

Some limitations of the study design should be acknowledged. Our review was not performed as a systematic review; therefore, study selection was not as rigorous. The review was targeted to identify studies on the burden of SSc and therefore was not fully comprehensive. The cost data were presented as reported (without being inflated to current prices and converted into a single currency) because of the existing methodological challenges hindering such cross-country comparisons, which are driven by differences in health care systems, cost component data, and methodologies across the included studies. Owing to these challenges, cost summaries are presented as percentage contributions of different cost components, and any cost comparisons that can be drawn from the reported data should be interpreted with caution. Future economic burden studies in SSc would benefit from a common approach to study design and cost component data, thus enabling a more transparent analysis.

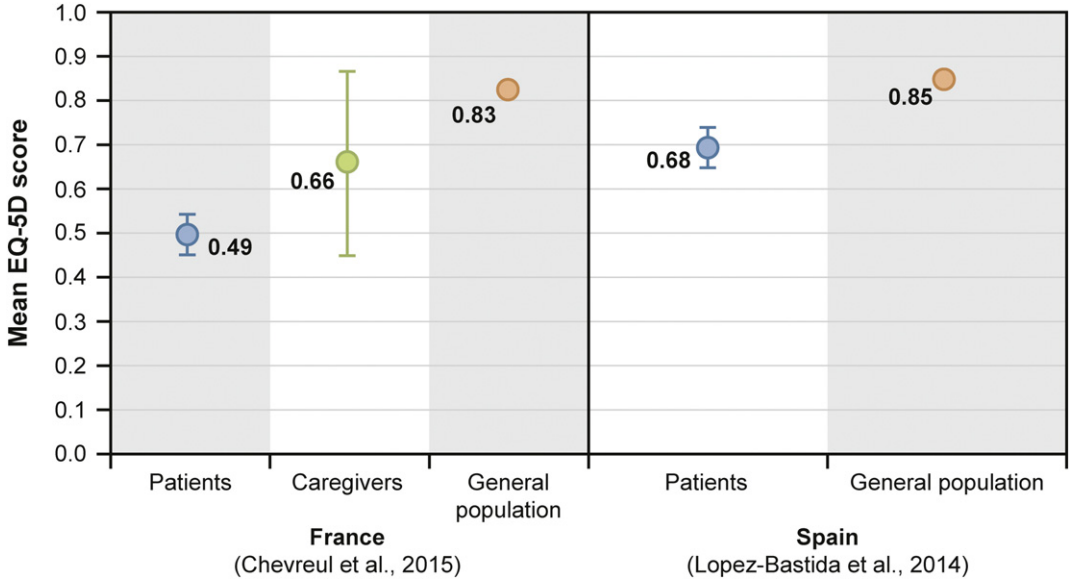


Fig. 4. Reported mean EQ-5D scores [18,20].

5. Conclusions

Overall, there is a paucity of information on the burden of SSc. Future research should concentrate on quantifying the economic and humanistic burden of SSc, particularly of its complications, such as ILD. The review indicates that SSc places a considerable economic burden on health care systems and society as a whole. In addition, the QOL of patients with SSc is considerably lower than that of the general population. Novel treatment approaches for SSc are needed to ameliorate the existing unmet need.

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References

[1] Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of morbidity and mortality of systemic sclerosis in Canada. Semin Arthritis Rheum 2010;39:269–77.
[2] Kowal-Bielecka O, Bielecki M, Kowal K. Recent advances in the diagnosis and treatment of systemic sclerosis. Pol Arch Med Wewn 2013;123:51–8.
[3] Scleroderma Foundation. What is scleroderma? http://www.scleroderma.org/site/PageNavigator/patients_whatis.html#.Vh_ZCvPD-M8; 2015, Accessed date: 15 October 2015.
[4] Wells AU, Margaritopoulos GA, Antoniou KM, Denton C. Interstitial lung disease in systemic sclerosis. Semin Respir Crit Care Med 2014;35:213–21.
[5] Postlethwaite AE, Harris LJ, Raza SH, Kodura S, Akhigbe T. Pharmacotherapy of systemic sclerosis. Expert Opin Pharmacother 2010;11:789–806.
[6] Romanowska-Prochnicka K, Walczyk M, Olesinska M. Recognizing systemic sclerosis: comparative analysis of various sets of classification criteria. Reumatologia 2016;54:296–305.
[7] Hoffmann-Vold AM, Aalokken TM, Lund MB, Garen T, Midtvedt O, Brunborg C, et al. Predictive value of serial high-resolution computed tomography analyses and concurrent lung function tests in systemic sclerosis. Arthritis Rheumatol 2015;67:2205–12.
[8] Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev 2010;9:A311–8.
[9] Rubio-Rivas M, Royo C, Simeon CP, Corbella X, Fonollosa V. Mortality and survival in systemic sclerosis: systematic review and meta-analysis. Semin Arthritis Rheum 2014;44:208–19.
[10] Kowal-Bielecka O, Delcroix M, Vonk-Noordegraaf A, Hoeper MM, Naeije R. Outcome measures in pulmonary arterial hypertension associated with systemic sclerosis. Rheumatology 2009;47:39–41.
[11] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903–75.
[12] Taichman DB, Ornelas J, Chung L, Klinger JR, Lewis S, Mandel J, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST guideline and expert panel report. Chest 2014;146:449–75.
[13] Walker KM, Pope J. Treatment of systemic sclerosis complications: what to use when first-line treatment fails—a consensus of systemic sclerosis experts. Semin Arthritis Rheum 2012;42:42–55.
[14] Kowal-Bielecka O, Landewe R, Avouac J, Chwiesko S, Miniati I, Czirjak L, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009;68:620–8.
[15] Furst DE, Fernandes AW, Iorga SR, Greth W, Bancroft T. Annual medical costs and healthcare resource use in patients with systemic sclerosis in an insured population. J Rheumatol 2012;39:2303–9.
[16] Bernatsky S, Hudson M, Panopalis P, Clarke AE, Pope J, Leclercq S, et al. The cost of systemic sclerosis. Arthritis Rheum 2009;61:119–23.
[17] McCormick N, Marra CA, Sayre EC, Avina-Zubieta JA. Longitudinal analysis of direct medical costs for systemic sclerosis patients: a population-based study. Arthritis Rheum 2013;65(Suppl. 10):S429–30.
[18] Chevreul K, Brigham KB, Gandre C, Mouthon L. The economic burden and health-related quality of life associated with systemic sclerosis in France. Scand J Rheumatol 2015;44:238–46.
[19] Belotti Masserini A, Zeni S, Cossutta R, Soldi A, Fantini F. Cost-of-illness in systemic sclerosis: a retrospective study of an Italian cohort of 106 patients. Reumatismo 2003;55:245–55.
[20] Lopez-Bastida J, Linertova R, Oliva-Moreno J, Posada-de-la-Paz M, Serrano-Aguilar P. Social economic costs and health-related quality of life in patients with systemic sclerosis in Spain. Arthritis Care Res 2014;66:473–80.
[21] Le Guern V, Mahr A, Mouthon L, Jeanneret D, Carzon M, Guillevin L. Prevalence of systemic sclerosis in a French multi-ethnic county. Rheumatology (Oxford) 2004;43:1129–37.
[22] El Adssi H, Cirstea D, Virion JM, Guillemin F, de Korwin JD. Estimating the prevalence of systemic sclerosis in the Lorraine region, France, by the capture-recapture method. Semin Arthritis Rheum 2013;42:530–8.
[23] Joachim G, Acorn S. Life with a rare chronic disease: the scleroderma experience. J Adv Nurs 2003;42:598–606.
[24] Almeida C, Almeida I, Vasconcelos C. Quality of life in systemic sclerosis. Autoimmun Rev 2015;14:1087–96.
[25] Stamm TA, Mattsson M, Mihai C, Stöcker J, Binder A, Bauernfeind B, et al. Concepts of functioning and health important to people with systemic sclerosis: a qualitative study in four European countries. Ann Rheum Dis 2011;70:1074–9.
[26] Suarez-Almazor ME, Kallen MA, Roundtree AK, Mayes M. Disease and symptom burden in systemic sclerosis: a patient perspective. J Rheumatol 2007;34:1718–26.
[27] Villaverde-Hueso A, Sanchez-Valle E, Alvarez E, Morant C, Carreira PE, Martin-Arribas MC, et al. Estimating the burden of scleroderma disease in Spain. J Rheumatol 2007;34:2236–42.
[28] Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases injuries and risk factors in 1990 and projected to 2020. Global Burden of Disease and Injury Series. Boston: Harvard University Press; 1996.
[29] Raimundo K, Farr A, Cole A, Fischer A. Assessment of mortality and healthcare costs associated with systemic sclerosis with and without lung involvementACR/ARHP Annual Meeting. Washington, D.C.; 2016.