The burden of illness of the organ manifestations of systemic sclerosis: a pragmatic, targeted review

V. Smith[1], Z. Marjenberg[2], E.R. Volkmann[3]

[1]Internal Medicine, Ghent University, Ghent, Belgium; Rheumatology, Ghent University Hospital, Ghent, Belgium; VIB Inflammation Research Center (IRC), Unit for Molecular Immunology and Inflammation, Ghent, Belgium; [2]Maverex Ltd, Newcastle-upon-Tyne, UK; [3]Department of Medicine, Division of Rheumatology, University of California, Los Angeles, USA.

Vanessa Smith, MD, PhD
Zoe Marjenberg, PhD
Elizabeth R. Volkmann, MD, MS

Please address correspondence to:
Elizabeth Volkmann
1000 Veteran Ave., Suite 32-59,
Los Angeles, CA 90024, USA.
E-mail: evolkmann@mednet.ucla.edu

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ABSTRACT

Objective. *This structured, targeted literature review aimed to assess the mortality, humanistic and economic burden of eight organ manifestations which are commonly experienced by systemic sclerosis patients.*

Methods. *Identification of relevant literature was carried out by searching in Ovid MEDLINE and EMBASE, PubMed, and NHS Economic Evaluation Database in August 2023. Studies reporting original data on patients with systemic sclerosis with at least one of eight organ manifestations (interstitial lung disease and/or pulmonary hypertension, skin, peripheral vascular, musculoskeletal, gastrointestinal, cardiac or renal involvement) published within the last 15 years were included. Meta-analyses with no publication limits were also included.*

Results. *A total of 50 studies were identified; 37 reported mortality outcomes (including 4 meta-analyses), 9 reported humanistic burden and 11 reported economic burden outcomes. Pulmonary hypertension, cardiac and renal manifestations were generally associated with a poorer survival prognosis. Furthermore, gastrointestinal, skin and peripheral vascular manifestations were found to negatively impact health-related quality of life outcomes. Pulmonary manifestations were associated with substantial economic costs; however, the cost burden of other manifestations is insufficiently reported, despite evidence that they often require healthcare resource use.*

Conclusion. *Organ manifestations experienced by patients with systemic sclerosis significantly affect patient quality of life and mortality. The economic burden of organ manifestations that are widely experienced by SSc patients such as gastrointestinal issues, is poorly understood and requires further research to quantify and understand. Improvements in diagnosis and clinical management of these systemic sclerosis-associated organ manifestations have the potential for significant alleviation of disease-related burdens.*

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterised by inflammation and fibrosis of multiple organs (1). There are two main subtypes of SSc: limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), which have differences in disease progression, severity, and survival (2). The incidence of SSc increased dramatically from the 1950s to the 1980s, potentially due to greater physician awareness and more reliable diagnosis (3). A recent meta-analysis estimated the pooled prevalence of SSc to be 17.6 per 100,000 and the pooled incidence at 1.4 per 100,000 person-years (4). Incidence and prevalence estimates varied considerably between studies and based on the different criteria used to define SSc [*e.g.* 1980 American Rheumatism Association criteria (5), 2001 LeRoy and Medsger revised criteria (6), 2013 American College of Rheumatology [ACR]/European League Against Rheumatism [EULAR] criteria (7)].

Very early SSc is characterised by Raynaud's phenomenon (RP) (puffy fingers), disease-specific autoantibodies and abnormal capillaroscopy results (6, 8). The clinical heterogeneity and the vast array of organ complications can make early identification and diagnosis of SSc challenging (9). Various organ-based manifestations of SSc are observed in all patients, and may include gastrointestinal (GI) complications, lung involvement, cardiac involvement or renal crises (10, 11). The prevalence of organ manifestations in SSc can be

high. Peripheral vascular involvement with RP affects nearly all SSc patients. The GI tract is also commonly affected; approximately 90% of SSc patients report a change in GI function over the disease course (12). SSc-associated interstitial lung disease (ILD) is present in 19-47% of patients in Europe and 30–65% in North America (13, 14), while pulmonary hypertension (PH) is present in 5–12% of SSc patients (15).

Longitudinal evidence from a *post hoc* analysis of the European Scleroderma Trials and Research (EUSTAR) database suggests that approximately half of all organ manifestations become evident within the first two years after RP onset in SSc patients (16). Manifestations develop simultaneously rather than sequentially; a steep increase in manifestations during the first two years after RP was observed across all organ manifestation studies, with the development of severe complications becoming apparent at both early and later stages of disease (16). The rate of organ damage in the early stages of SSc may also indicate further damage in later disease; in a study of SSc patients with ≥10 years of follow-up, those patients with higher organ damage scores within the first two years of disease had the highest rate of damage accumulation in the following years (17).

While the burden of SSc has been previously collated (18-21), the overall burden of individual organ manifestations in patients with SSc, as a group, needs to be understood and communicated. The purpose of this review is to understand the mortality, human and economic burdens of eight organ system manifestations of SSc (ILD and/or PH, skin, peripheral vascular, musculoskeletal, GI, cardiac, or renal involvement).

Methods

Semi-systematic literature review

A semi-systematic literature review approach was used to ensure identification of relevant studies. This process involved searches for full-text reports containing original data, run in Ovid MEDLINE and EMBASE, PubMed, and NHS Economic Evaluation Database (up to 31/03/2015) in August 2023. These searches were limited to the last 15 years (studies published from 2008 onwards) and included thesaurus terms (MeSH and Emtree for MEDLINE and Embase, respectively), and subject headings combined with free-text keywords. The process also involved hand-searching literature, including reviewing the reference lists of relevant studies, and citation tracking of the included studies.

Inclusion criteria

We included full publications of studies in English that included patients with SSc with at least one of the eight organ manifestations (ILD and/or PH, skin, peripheral vascular, musculoskeletal, GI, cardiac, or renal involvement). Studies were required to include a comparator group without manifestations, and report any of the following outcomes: mortality, humanistic burden (including patient/carer health-related quality of life [HRQoL] and patient-reported outcome or experience measures [PROMs/PREMs]), or economic burden (including healthcare resource use [HCRU] healthcare costs, and productivity losses). Meta-analyses reporting these outcomes were also included; no limit on publication date was applied to these studies.

Data extraction and synthesis

Data from the eligible studies were extracted by one reviewer into a standardised data-extraction template, and a second reviewer performed an independent data check of the extracted data. Manifestations were categorised according to organ, while the data-extraction spreadsheet included the full manifestation description reported by the included studies. The results were then synthesised narratively, grouped by outcome.

Results

Literature search results

The search identified 1,984 unique records. After title/abstract and full-text screening, 116 articles met the inclusion criteria, and a further six articles were identified by hand-searching. Due to the large number of included studies, only those reporting mortality and humanistic outcomes published from 2018 onwards, and those detailing economic outcomes from 2013 onwards were included (meta-analyses from any timepoint were also included).

In total, 50 studies were included (Fig. 1). Of these, 34 reported mortality outcomes (22-55), and 4 meta-analyses that reported pooled risks of mortality in patients with SSc were also identified (19, 47, 69, 70), 9 reported humanistic burden outcomes (23, 39, 46, 56-61) and 11 reported economic burden outcomes (26, 42, 46, 50, 62-68) One publication included both original data from an observational study and a meta-analysis (47). Searches by the four meta-analyses were performed up to May 2021 (Xiong 2022 (69); PH), July 2017 (Pokeerbux 2019 (47); PH, ILD, cardiac, musculoskeletal, and renal manifestations), July 2013 (Rubio-Rivas 2014 (19); PH, ILD, cardiac, and renal manifestations), and July 2010 (Komócsi 2012 (70); PH, ILD, cardiac, and renal manifestations).

Full study and patient characteristics are available in Supplementary Tables S1 and S2. In summary, the studies were conducted in 18 different countries, including Australia (9 studies), USA (5 studies), and China (4 studies). Twenty were performed in different European countries. The number of participants in the included studies ranged from 30 to 179,669. In terms of patient characteristics, the mean age ranged from 38.4 to 71 years and the median age from 46.7 to 55 years. The percentage of female participants ranged from 57.6% to 100%. Average SSc duration in the participants ranged from 0.7 to 17.4 years, with most of the studies reporting an SSc duration of six years or more, indicating a more prevalent rather than incident SSc cohort. The majority of studies used the first non-Raynaud phenomenon manifestation as the definition of disease onset.

Mortality

The association of organ manifestation in SSc and mortality or survival outcomes were reported in 34 studies (22-55), and four meta-analyses (19, 47, 69, 70). Associations of manifestations with mortality, reported by multivariate analyses and published meta-analyses, are presented in Figures 2, 3 and 4. Ka-

plan-Meier survival estimates, which ranged from 5 to 60 years in the identified studies, are presented in Supplementary Table S3.

Pulmonary manifestations were generally associated with a significantly increased risk of mortality (Fig. 2). Nearly all included studies (n=21) reported that ILD was significantly associated with mortality (22-28, 32-34, 37, 39, 40, 42-44, 47, 48, 53-55), while increasing severity of ILD was associated with higher mortality (23, 37). Kaplan-Meier estimates from five studies also reported a significantly (p<0.005) poorer prognosis for SSc-ILD patients (23, 24, 27, 44, 51). Three meta-analyses reported significantly increased pooled risk ratios of 2.34 (1.78, 3.08) (47), 2.89 (2.24, 3.72) (19), and odds ratio (OR) 2.58 (1.98, 3.37) (70). PH was generally associated with even poorer survival than ILD; nearly all identified studies (n=24) reported that PH was a significant predictor of mortality (22-24, 26-28, 31-35, 37, 39, 40, 42, 44, 45, 47-49, 51, 53-55), while four of these also reported significantly poorer survival from Kaplan-Meier estimates (22-24, 51). Four meta-analyses reported significantly increased pooled risk ratios of 3.12 (2.44, 3.98) (69), 3.44 (2.59, 4.58) (or 5.27 [2.98, 9.31] when analysis was limited to only PH diagnosed by right heart catheterisation) (47), 2.62 (1.64, 4.17) (19), and 3.50 (1.94, 6.30) (70). Combined PH-ILD in SSc patients was also significantly associated with a significantly increased risk of mortality by three of four studies (22-24, 42); significantly poorer prognosis in Kaplan-Meier estimates was also reported by three of them (22-24).

Definitions of cardiac manifestations were highly heterogeneous across studies (n=15). Associations were reported for "cardiac involvement" by some, while other reported manifestations included heart conditions such as arrythmia and atrial fibrillation, heart failure, pericarditis, ventricular dysfunction, and atrioventricular or bundle branch block. Both significant and non-significant associations with increased mortality were reported by 15 studies (Fig. 3A) (25, 26, 28, 30, 32, 35, 37, 39, 41, 42, 47, 51-53, 55). However, all three meta-analyses reported that cardiac involvement in SSc was associated with significantly increased mortality risks of 4.35 (2.28, 8.29) (47), 3.43 (1.35, 8.70) (19), and 3.15 (2.33, 4.26) (70).

Renal manifestations in the included studies (n=16), were predominantly scleroderma renal crisis, but also included chronic renal disease, proteinuria, and low glomerular filtration rate (28, 30, 31, 33-35, 37, 39-42, 44, 47, 48, 53). Renal crisis was associated with a significant association with mortality by half of all multivariate analyses (Fig. 3B). Three meta-analyses of renal involvement manifestations also reported significantly increased pooled risks of 2.79 (1.95, 3.99) (or 3.89 [2.38, 6.36] when analysis limited to only renal crisis) (47), 4.22 (3.42, 5.19) (19), and 2.76 (1.91, 4.00) (70).

Most studies reporting an association of mortality with GI manifestations (n=11) found that these manifestations do not significantly impact survival (Fig. 3C). However, severe malabsorption may be an independent predictor of mortality, as three studies, two of which reported multivariate analyses, found a significantly higher hazard ratio of between 2.22 and 2.59 (39, 40, 42).

Evidence of a significant association with increased mortality was not observed in most identified studies for musculoskeletal manifestations (30, 41, 44, 47, 49) (Fig. 4A), while peripheral vascular (22, 34, 35, 41, 42, 44, 47-49, 52, 55) (Fig. 4B) and skin (34, 35, 39, 41, 44, 47-49) (Fig. 4C) manifestations were only significant in some. A single meta-analysis of 4 studies reported a non-significantly higher pooled mortality hazard ratio of 1.32 (0.82, 2.12) for joint involvement manifestations (47).

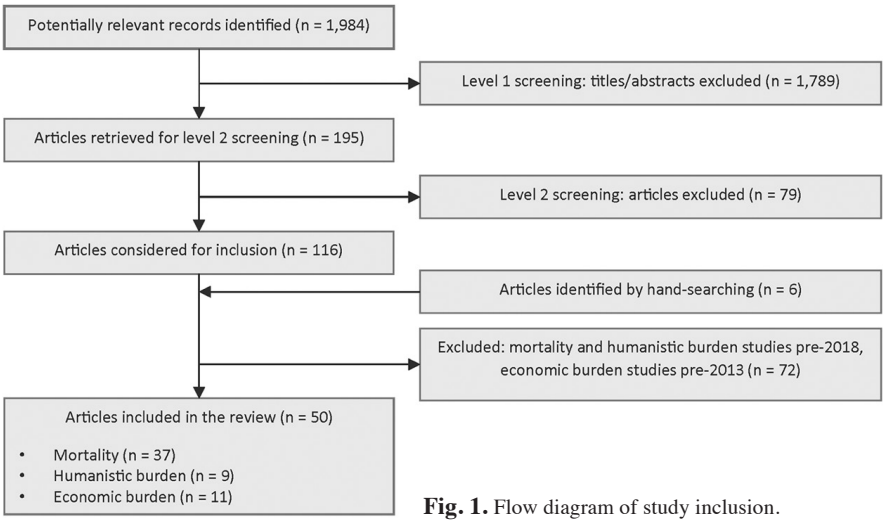

Fig. 1. Flow diagram of study inclusion.

Humanistic burden

Nine studies reporting humanistic burden outcomes were identified (23, 39, 46, 56-61) These used a total of 11 different validated HRQoL instruments that evaluated generic, scleroderma-specific, disability-specific, and work impairment quality of life impact (Table I).

There was a trend for poorer HRQoL reported for patients with GI manifestations. Patients with SSc and GI manifestations reported a significant association with poorer physical HRQoL (59) and a significantly greater decline in HRQoL over time compared with those without GI manifestations (39, 57). Diarrhoea was also reported to be an independent risk factor for impaired social and emotional function for patients with SSc and GI involvement (61). However, this was not consistent across all studies; one reported no significant impact of GI symptoms on quality of life (60), while another reported a significant association with a lower chance of worsening HRQoL over a median follow-up of 7 years (56).

Peripheral vascular and skin manifestations were also associated with poorer HRQoL. Three studies reported that peripheral vascular manifestations can have a significant impact on quality of life (46, 57, 58); mental and physical quality of life, including hand disability

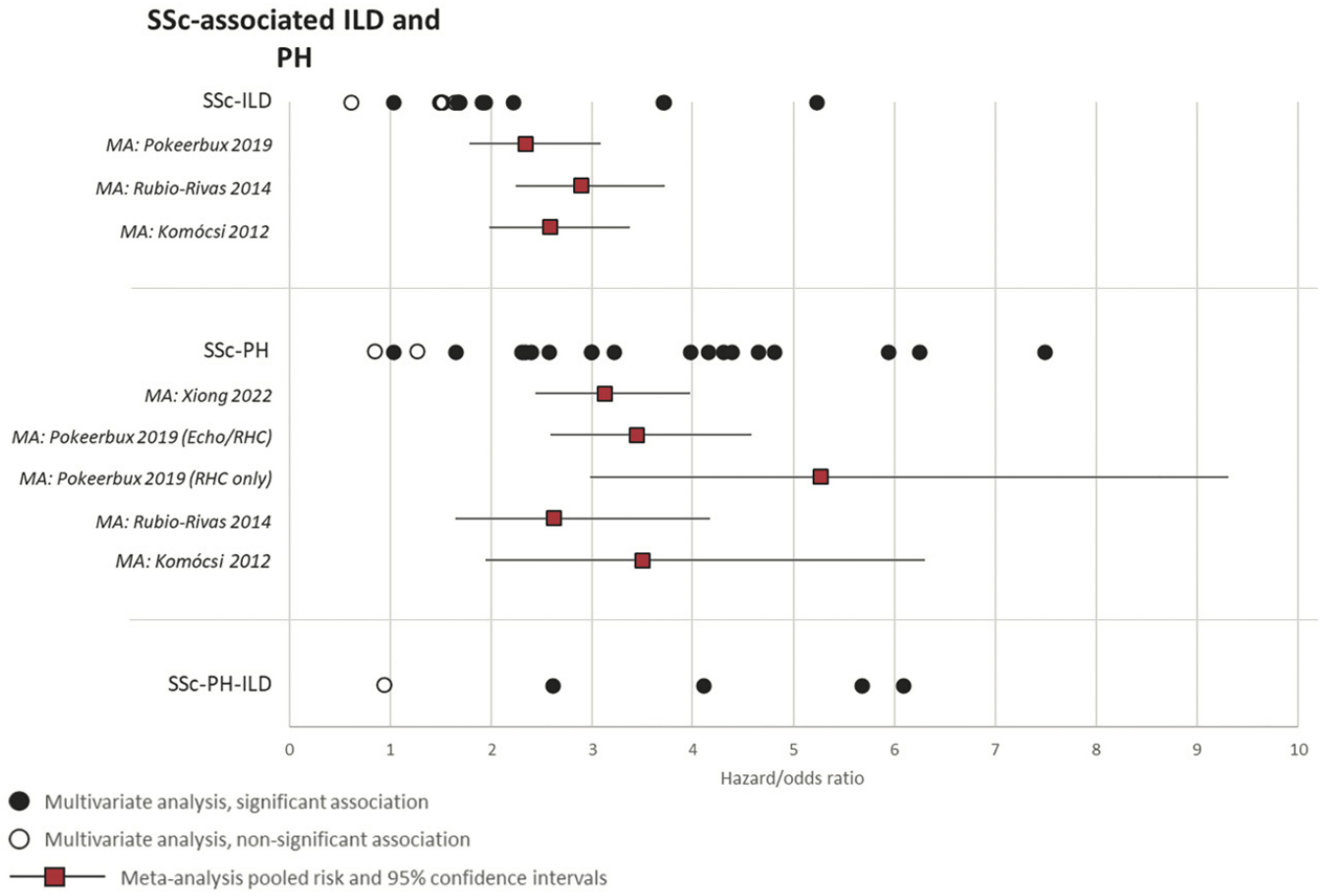

Fig. 2. Overview of associations of SSc-associated ILD and PH with mortality compared with SSc patients without organ manifestation in studies published 2018-2022 (multivariate analyses only) and meta-analyses.
Meta analyses: *SSc-ILD*: Pokeerbux 2019: SSc-ILD, 14 studies in analysis (47); Rubio-Rivas 2014: SSc-ILD, 6 studies in analysis (19); Komócsi 2012: SSc-ILD, 12 studies in analysis (70).
SSc-PH: Xiong 2022: SSc-PH, 16 studies in analysis (69); Pokeerbux 2019: SSc-PH (ecohocardiography or right heart catheterization), 13 studies in analysis (47); Pokeerbux 2019: SSc-PH (right heart catheterization only), 5 studies in analysis (47); Rubio-Rivas 2014: SSc-PH, 6 studies in analysis (19); Komócsi 2012: SSc-PH, 6 studies in analysis (70).
Echo: echocardiography; ILD: interstitial lung disease; MA: meta-analysis; PH: pulmonary hypertension; RHC: right heart catheterisation.

and capacity for day-to-day activities (58), were particularly impacted. Three other studies found no significant association between poorer quality of life and peripheral vascular involvement in SSc (56, 59, 60). Skin manifestations in patients with SSc were associated with poorer HRQoL, including physical, mental and emotional quality of life, compared with those without skin involvement (57, 59, 61). A single study reported no significant impact of skin manifestations on quality of life in patients with SSc (56).

There was less evidence for significant associations between pulmonary and cardiac manifestations. Significantly increased odds of poorer physical or mobility-related quality of life were reported for patients with SSc and PH compared with those without PH by one study (23). Two other studies reported no significant association between baseline SSc-PAH and reduced quality of life (56, 57); however, one of these studies did report that PH contributed to a significant decrease in HRQoL over an 8-year follow-up in patients with long-standing disease (≥2 years) (57). ILD was reported to impact physical and emotional quality of life in patients with SSc by two studies (23, 61), whereas no significant association between SSc-ILD and poorer HRQoL were reported by three others (39, 56, 57). The HRQoL of patients with both ILD and PAH was evaluated in only one study, which found that patients were at very high risk of poor quality of life, greater than patients with only PH or ILD (23). Two studies found no significant association between cardiac involvement in patients with SSc and HRQoL (39, 56), however one study found that at an early stage of disease, cardiac involvement was reported to significantly affect patients' mental quality of life (57).

Quality of life was not reported to be significantly impacted by musculoskeletal involvement by two studies (56, 57), and that the change in quality of life over time was not significantly affected by renal involvement by three studies (39, 56, 57).

Economic burden

Outcomes relating to economic burden were reported by 11 data sources (26, 42, 46, 50, 62-68). Direct costs were

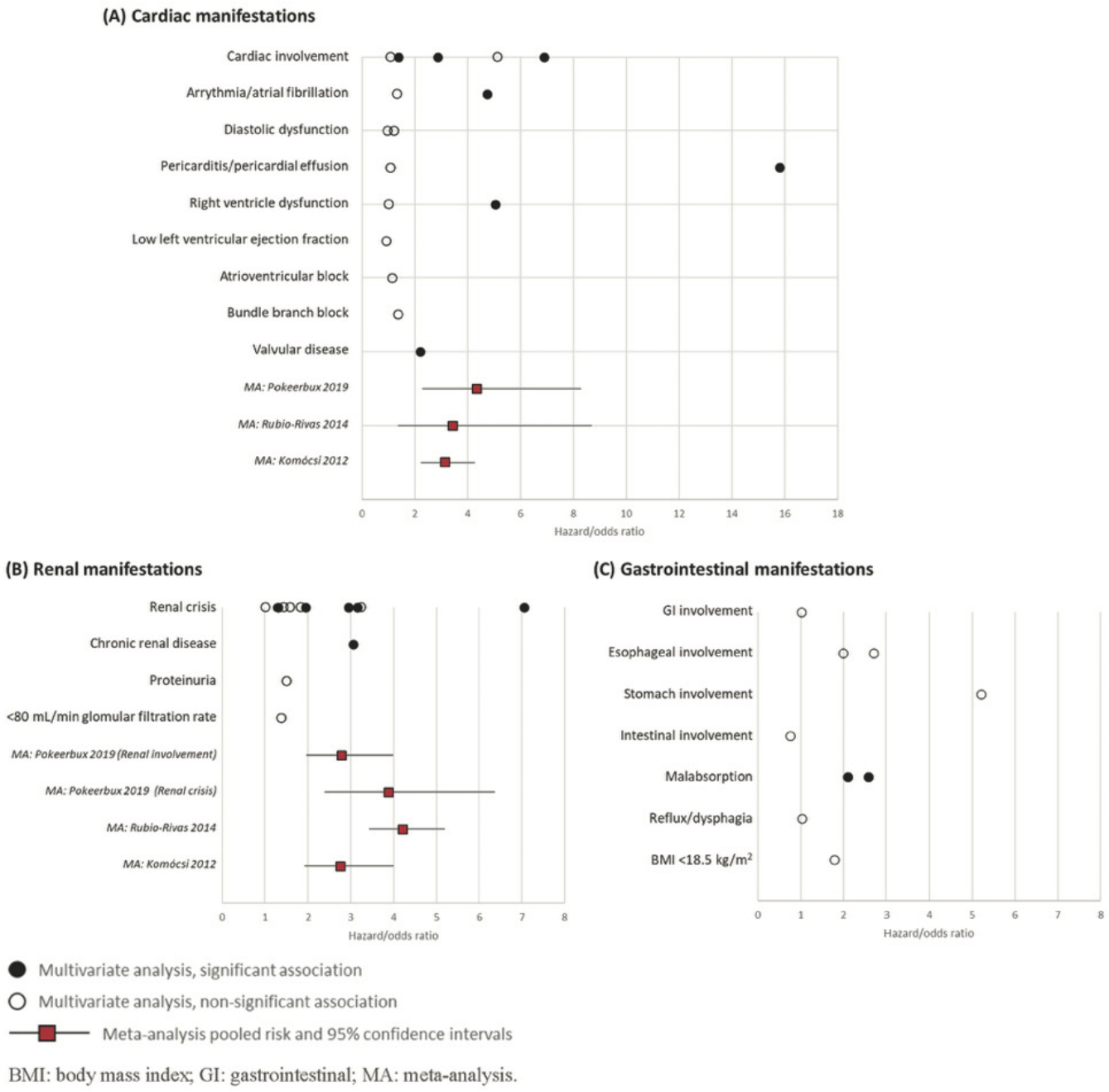

Fig. 3. Overview of associations of cardiac (**A**), renal (**B**), and gastrointestinal (**C**) SSc manifestations with mortality compared with SSc patients without organ manifestation in studies published 2018-2022 (multivariate analyses only) and meta-analyses.
Meta analyses: *Cardiac manifestations*: Pokeerbux 2019: cardiac involvement, 7 studies in analysis (47); Rubio-Rivas 2014: cardiac involvement, 5 studies in analysis (19); Komócsi 2012: cardiac involvement, 11 studies in analysis (70).
Renal manifestations: Pokeerbux 2019: renal involvement, 9 studies in analysis (47); Pokeerbux 2019: scleroderma renal crisis, 10 studies in analysis (47); Rubio-Rivas 2014: renal involvement, 8 studies in analysis (19); Komócsi 2012: Renal involvement, 12 studies in analysis (70).

reported by five studies (46, 50, 64-66), healthcare resource use by nine studies (26, 42, 46, 50, 62, 64-67), and indirect costs reported by three studies (62, 68, 69). Total mean or median direct healthcare costs were higher for patients with SSc and ILD (50, 64, 65), PH (50, 66), or digital ulcers (46) (Table II). Direct costs were not reported for other manifestations; however, one study reported significantly higher median hospital costs associated with PH and renal manifestations, significantly higher median outpatient care costs associated with PH and synovitis, and significantly higher median medication costs associated with ILD, synovitis, and GI manifestations (67).

Mixed findings for the impact of SSc organ manifestations on healthcare resource use were reported (Suppl. Table S4). While significant associations between SSc manifestations and increased hospitalisation, emergency room visits, and outpatient visits were reported by some studies, others reported no significant association, and the number of

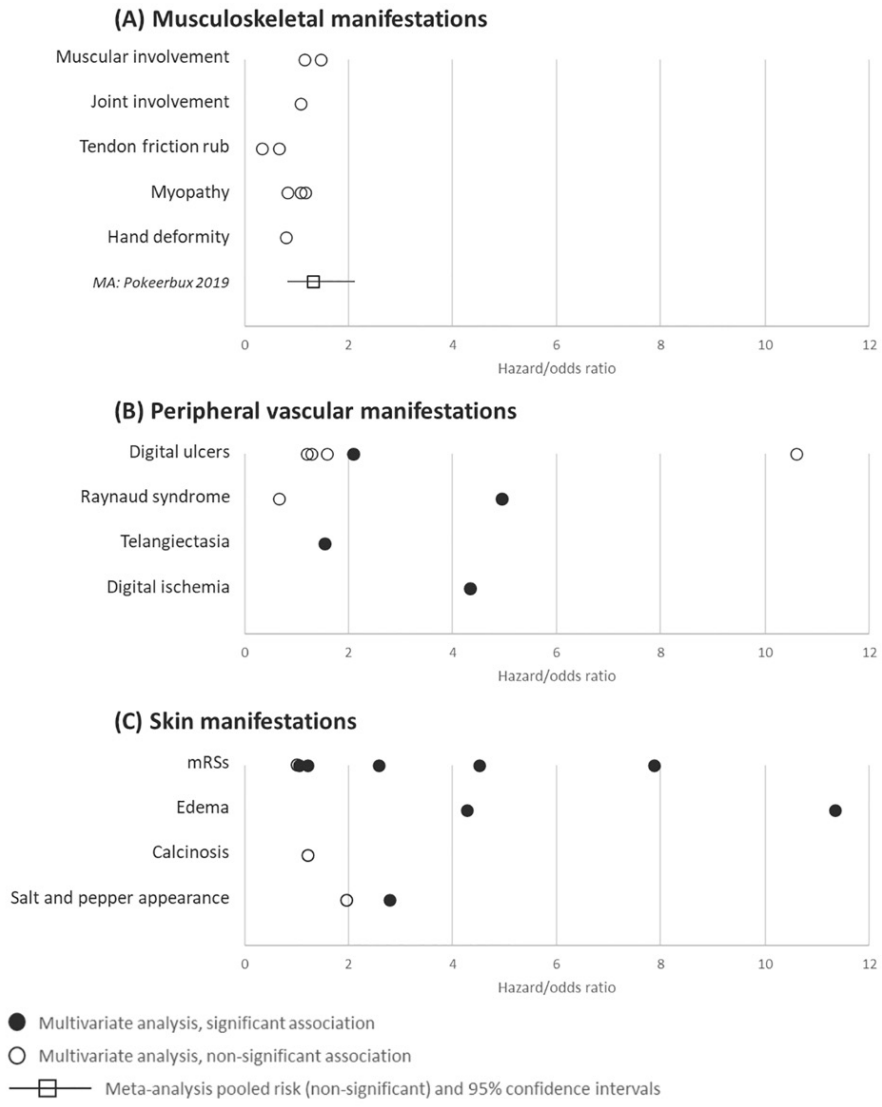

Fig. 4. Overview of associations of musculoskeletal (**A**), peripheral vascular (**B**), and skin (**C**) SSc manifestations with mortality compared with SSc patients without organ manifestation in studies published 2018-2022 (multivariate analyses only) and meta-analyses.
Meta analyses: *Musculoskeletal manifestations*: Pokeerbux 2019: joint involvement, 4 studies in analysis (47).
MA: meta-analysis; mRSs: modified Rodnan's skin score.

studies for each manifestation was too low to draw overall conclusions.

Indirect costs, reported by two studies, included increased odds of being unemployed (68), and association with work productivity loss and unemployment (63). The presence of GI symptoms, musculoskeletal symptoms, and PH in Australian SSc patients was associated with increased odds of being unemployed (68). None of the eight organ manifestations were associated with unemployment or work productivity loss in Singapore; however, nearly one-third of this cohort was unemployed and among the employed patients, over 50% reported work productivity loss (63). A third indirect cost study reported that SSc patients with digital ulcers required an accompanying person significantly more than SSc patients without digital ulcers (54% *vs*. 38%; p=0.025) and had a significantly higher mean number of hours spent by the accompanying person (17.9 *vs*. 11.5 hours; p=0.01) (62).

Discussion

This review evaluated the mortality, humanistic, and economic burdens of SSc as they relate to specific organ manifestations. A focus on recent studies was chosen to ensure that these burdens reflect current treatment practice. However, we also chose to include systematic literature reviews reporting pooled burden outcomes from studies published at any time point to provide a more comprehensive overview and for a comparison with the burden reported by recent literature. Furthermore, this review included studies that compared SSc burden outcomes with manifestations that are impactful for patients to SSc patients without those manifestations, allowing for identification of the manifestation impact separate from the burden imposed by SSc itself.

Studies identified by this review confirmed that pulmonary (ILD and PH), cardiac, and renal SSc manifestations are associated with a poor survival prognosis. It is important to note that these manifestations still have a significant mortality burden despite recent improvement in treatments, such as angiotensin converting enzyme (ACE) inhibitors for renal crisis, vasodilator drugs for PH, and immunosuppressive therapy for myocarditis (71). Overall, there was inconclusive (or very little) evidence of musculoskeletal, peripheral vascular, or skin manifestations significantly impacting mortality. However, serious GI manifestations such as gastric antral vascular ectasia (GAVE) may contribute to poor prognosis, and further studies to investigate this are warranted. Several systematic reviews and meta-analyses have previously summarised the impact of different organ manifestations on mortality; we identified four meta-analyses reporting pooled associations of manifestations with decreased survival (19, 47, 69, 70). Although most of the studies included in these meta-analyses were published prior to the 2018-2023 time period our review limited non-systematic review studies to, the pooled associations reported by these meta-analyses generally agreed with the range of associations reported by our included studies.

Manifestations that have limited impact on prognosis may still significantly impact SSc patients through their humanistic burden. GI, skin, and periph-

Table I. Impact of SSc organ manifestations on humanistic burden.

Study	HRQoL instruments	Summary of reported significant impact on HRQoL compared with SSc patients without manifestation
ILD		
Fairley 2023 (23)	SHAQ SF-36	Significant association with poorer SHAQ and SF-36 physical HRQoL (p<0.001)
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D SF-36	NS (change over 8-year follow-up)
Allanore 2020 (39)	HAQ-DI	NS (change over a 1-year follow-up)
Yang 2019 (61)	SSC-GIT 1.0	Significant association with poorer emotional well-being (p=0.013)
PH		
Fairley 2023 (23)	SHAQ SF-36	Significant association with poorer SHAQ and SF-36 physical HRQoL (p<0.001)
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D SF-36	Significant association with a decrease in SF-36 physical (p=0.0004) and EQ-5D HRQoL (p<0.001) in prevalent SSc over an 8-year follow-up
ILD and PH		
Fairley 2023 (23)	SHAQ SF-36	Significant association with poorer SHAQ and SF-36 physical HRQoL (p<0.001)
Cardiac		
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D SF-36	Significant association with a decrease in SF-36 mental HRQoL in incident SSc over an 8-year follow-up (p=0.0001)
Allanore 2020 (39)	HAQ-DI	NS (change over a 1-year follow-up)
Musculoskeletal		
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D SF-36	NS (change over 8-year follow-up)
Gastrointestinal		
Liem 2023 (56)	HAQ-DI	Significant association with a lower chance of worsening HAQ-DI over a median 7-year follow-up (OR 0.6 [95% CIs 0.4, 0.9])
Leeuwen 2021 (57)	EQ-5D SF-36	Significant association between severe GI issues and: • a decrease in SF-36 mental SF-36 HRQoL in incident SSc over an 8-year follow-up (p=0.007) • a decrease in SF-36 mental (p<0.001) and physical (p=0.002) SF-36 HRQoL and EQ-5D HRQoL (p=0.001) in prevalent SSc over an 8-year follow-up
Allanore 2020 (39)	HAQ-DI	Significant association between oesophageal symptoms with a decrease in HRQoL over a 1-year follow-up (p=0.001); NS change for stomach or intestinal symptoms
Park 2019 (59)	EQ-5D-3L SF-36	Significant association with poorer SF-36 physical HRQoL (p<0.001)
Sierakowska 2019 (60)	SScQoL	NS
Yang 2019 (61)	SSC-GIT 1.0	SSc patients with abnormal social functioning had significantly worse distension (p=0.029) and diarrhoea (p=0.004) statuses. SSc patients with abnormal emotion well-being had significantly worse diarrhoea statuses (p=0.001)
Renal		
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D SF-36	NS (change over 8-year follow-up)
Allanore 2020 (39)	HAQ-DI	NS (change over a 1-year follow-up)
Skin		
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D, SF-36	Significant association with a decrease in EQ-5D HRQoL in incident (p=0.003) and prevalent (p=0.02) SSc, and a decrease in physical SF-36 HRQoL in incident SSc (p=0.002) over an 8-year follow-up
Park 2019 (59)	EQ-5D-3L SF-36	Significant association with poorer physical (p=0.001) and mental (p=0.021) SF-36 HRQoL and EQ-5D-3L HRQoL (p=0.021)
Yang 2019 (61)	SSC-GIT 1.0	Significant association with poorer emotional HRQoL (p=0.009)
Peripheral vascular		
Liem 2023 (56)	HAQ-DI	NS (change over median 7 years follow-up)
Leeuwen 2021 (57)	EQ-5D SF-36	Significant association between Raynaud phenomenon and: • a decrease in SF-36 mental (p=0.003) and physical (p=0.007) HRQoL in incident SSc over an 8-year follow-up • a decrease in SF-36 mental (p=0.001) and physical (p=0.001) HRQoL and EQ-5D HRQoL (p=0.009) in prevalent SSc over an 8-year follow-up Significant association between digital ulcers and: • a decrease in SF-36 physical (p=0.002) HRQoL in incident SSc over an 8-year follow-up • a decrease in SF-36 mental (p=0.04) and physical (p=0.009) HRQoL in prevalent SSc over an 8-year follow-up
Castellví 2019 (58)	CHFS SHAQ SHAQ-VAS WPAI-SHP VAS	Significant association with poorer CHFS hand function (p<0.002), pain (p=0.013) and a significantly limited capacity for daily life activities (p=0.002)
Morrisroe 2019b (46)	SF-36	Significant association with poorer physical SF-36 HRQoL (p<0.001); physical HRQoL deteriorates with increasing digital ulcer severity
Park 2019 (59)	EQ-5D-3L SF-36	NS
Sierakowska 2019 (60)	SScQoL	NS

CHFS: Cochin Hand Function Scale; Cis: confidence intervals; EQ-5D: EuroQol 5 Dimension; HAQ-DI: Health Assessment Questionnaire-Disability Index; HRQoL: health-related quality of life; NS: not significant; SHAQ: Scleroderma Health Assessment Questionnaire; SF-36: 36-Item Short Form Survey; SSC-GIT 1.0: Scleroderma Gastrointestinal Tract 1.0; SScQoL: Systemic Sclerosis Quality of Life Questionnaire; WPAI-SHP VAS: Work Productivity and Activity Impairment Questionnaire-Specific Health Problem visual analogue score.

Table II. Additional direct healthcare costs of SSc patients with organ manifestations compared with SSc patients without manifestation.

Study	Country (currency, cost year)	Time period	Additional mean cost	Additional median cost
SSc-ILD				
Gayle 2020 (64)	England (GBP, 2016)	Per patient-year	NR	£4,879
Morrisroe 2020 (65)	Australia (AUD, NR)	2008-2015	$17,726	$14,711
		Annual	$1,033	$1,192
Fischer 2018 (50)	USA (USD, 2014)	5 years	$89,268	$42,478
SSc-PH				
Morrisroe 2019a (66)	Australia (AUD, NR)	2008-2015	$1,891	$2,463
		Annual	$34,174	$35,709
Fischer 2018 (50)	USA (USD, 2014)	5 years	$152,586	$115,373
Peripheral vascular (digital ulcers)				
Morrisroe 2019b (46)	Australia (AUD, NR)	2008-2015	NR	$12,474
		Annual	NR	$794

eral vascular manifestations were all reported to be associated with poorer HRQoL outcomes, including poorer physical, mental, and social functioning, by many of the included studies. Mental and social functioning outcomes were limited to associations with HRQoL tool scores rather than specific patient-reported outcomes, however previous studies and systematic literature reviews have highlighted the complexity of the effect of SSc on mental and social functioning, even in those with mild disease (57, 72, 73). Frequent causes include emotional distress from fatigue and pain and the transformation of their appearance, worry over the unpredictable course of the disease and its progression, and deprivation of social function from loss of employment, social isolation, and sexual dysfunction (72, 73). Variation in psychological impact between genders has also been observed, with women often experiencing feelings of unattractiveness and loss of self-esteem (72), while men are more prone to masking the full emotional burden and may be reluctant to readapt their former habits (74). SSc manifestations are also associated with substantial economic costs, particular for pulmonary manifestations, which have also been described by a previous systematic literature review (20).

As a multi-organ system disease, SSc requires a comprehensive and tailored strategy for the prevention and management of complications. Recommendations for standardised screening for early detection of organ involvement promote appropriate treatment with the aim of improving outcomes (75-77). There are, however, still many unmet needs in SSc patients with organ manifestations, and for many of these, current opinion on available treatment regimens varies (78, 79). There is also a need for validated diagnostic and prognostic markers to identify and stratify patients at risk of pulmonary disease and disease progression (78), as well as for reliable outcome measures of organ disease in order to maximise the efficiency of future clinical trials of many promising new target therapies (79, 80). Finally, adding to the burden of SSc disease and its organ manifestations is the impact of comorbid conditions that often occur in the course of SSc disease, such as cardiovascular disease, cancer and infections (81).

This review has some limitations, mainly due to the heterogeneity between studies in terms of study design (*e.g.*, follow-up time) and definitions of organ manifestations, and it is therefore important to be cautious when comparing the results between the studies. Notably, many studies did not report the number of patients with organ manifestations who were assessed for burden impact. Additionally, systemic manifestations of SSc such as fatigue and pain, which are commonly reported by SSc patients, were not assessed by this review, as the causes of these manifestations can often be unclear or related to multiple manifestations. A systematic review approach to determine all three burdens across the different organ manifestations would have returned an extremely large amount of literature to be screened. Therefore, this review was performed pragmatically, and consequently, meta-analyses could not be conducted.

Nonetheless, this study has several strengths, including focusing only on those publications that reflect current clinical practice, providing a comparison of the burdens that the different organ manifestations are associated with, and deepening our insight into which manifestations require further research to understand their current impact on patients and healthcare providers. Furthermore, broad search terms and rigorous selection and screening methodologies were utilised, resulting in a comprehensive review of the currently available literature of SSc manifestations.

Conclusions

The burden of SSc disease is high, and patients with organ manifestations often experience poorer quality of life and may have a significantly higher risk of mortality. The economic burden of many manifestations, including those that are widely experienced by SSc patients such as GI issues, is poorly understood, and there is a need for further high-quality research to quantify the direct and indirect economic burden of these manifestations. Improvements in diagnostic tools and an increased clinical awareness will help to diagnose SSc manifestations as early as possible in order to initiate appropriate treatments and limit their progression. New therapies are also required to treat organ involvement in SSc, with a concomitant reduction in the burdens associated with manifestations.

Competing interests

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