The Impact of Systemic Sclerosis Manifestations on Survival, Humanistic Burden, and Economic Burden: A Targeted Literature Review

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- Systemic sclerosis (SSc) is a rare autoimmune disease characterized by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs.
- Key organ systems impacted by SSc are the skin, gastrointestinal (GI) tract and lungs.
- The severity and type of organ involvement in SSc varies between patients which poses a challenge for assessment of the impact of organ manifestations on mortality, health-related quality of life (HRQoL), and economic burden.
- Given the systemic nature of SSc, an understanding of how individual manifestations contribute to mortality, humanistic and economic burden is critical.

Objective

To understand the overall additional mortality risk, humanistic burdens, and economic burdens of eight organ manifestations in patients with SSc: Pulmonary hypertension (PH) and/or interstitial lung disease (ILD), skin, peripheral vascular, musculoskeletal, gastrointestinal (GI), cardiac, and renal involvement.

色 Methods

A semi-systematic literature review approach was used to identify relevant studies, combining electronic searches of Ovid MEDLINE and EMBASE, PubMed, and NHS Economic Evaluation Database. Searches were run in August 2023. Hand-searching was also performed.

Depulation	Dationts with CCo
Population	Patients with SSc
Comparison	SSc patients with one of eight organ manifestations vs. SSc patients without the manifestation
Outcomes	Mortality: Association (hazard ratios or odds ratios) with mortality, Kaplan-Meier survival estimates Humanistic burden: patient HRQoL and patient-reported outcome or experience measures Economic burden: direct and indirect healthcare-related costs, healthcare resource use (HCRU), productivity/employment losses
Study design	Non-interventional (observational) studies, systematic literature reviews (SLRs) & meta-analyses (MAs)
Dates published	Mortality & humanistic burden: 2018-2023; Economic burden: 2013-2023 SLRs and meta-analyses: no limitations

Data from identified studies were extracted and synthesized narratively by manifestation & outcome.

Findings **Observational studies: Economic burden studies: 6** countries publications identified North Mortality America: **7** 2 (including 4 meta-analyses) Asia: **11** Cardiac Renal Humanistic burden Europe: 19 (*)1 Musculoskeletal South Australia: 9 Peripheral vascular America: Economic burden Skin N studies identified **Mortality Humanistic burden Economic burden** 6, 30, 31 1, 8, 20, 25, 32-34 **7** studies **3** studies 26 studies 4 meta-analyses **Pulmonary** Difference in median **Higher direct costs** \$2,463 ~3-fold risk of increased mortality Poorer physical or mobility-related HRQoL, total direct costs hypertension (increased hospitalization & between SSc with & and poorer HRQoL over time 5 years \$115,373 MAs report pooled risks between 2.62 and 3.50 outpatient services) without PH: 2–10, 12–14, 16–21, 23, 25–29, 35, 37 8, 20, 25, 33, 34, 39–41 6, 17, 30, 31, 38 5 studies 24 studies 3 meta-analyses studies 1 year \$1,192 **Interstitial lung** Poorer physical or emotional HRQoL Difference in median ~2.5-fold risk of increased mortality 5 years **Higher direct costs** total direct costs reported by some studies, but no impact \$42,478 disease between SSc with & MAs report pooled risks between 2.34 and 2.89 (increased hospitalization) reported by others without ILD: **£4,879** 1 study 1 study 4 studies **Higher hospitalization** reported, but full burden **PH-ILD** Risk of poor HRQoL, including physical ~4-6-fold increased risk of death, but limited unclear due to limited studies and direct costs are HRQoL studies available unknown 3 studies studies 3 meta-analyses 2 studies ~3-4-fold increased risk of death Cardiac Some manifestations associated with higher Poorer mental QoL in early SSc reported MAs report pooled risks between **3.15** and **4.35**, but hospitalization, but full burden unclear due to by a single study definitions of involvement are highly heterogeneous limited studies across studies 17, 30, 31 20, 33, 39 2-4, 10, 11, 13–21, 23, 26, 27, 29, 42, 44, 45 3 studies 3 studies 3 meta-analyses Associated with higher hospitalization, but full Renal ~3-fold risk of increased mortality No evidence of impact on HRQoL burden unclear due to limited studies MAs report pooled risks between 2.76 and 4.22 17, 30, 31, 38, 47, 48 2, , 5, 9, 17–21, 24, 26, 29, 35, 46 8, 20, 33, 34, 39 13 studies 6 studies 5 studies While advanced GI manifestations such **Gastrointestinal** Increased hospital, outpatient care, and medication costs, Poorer mental and physical QoL, as severe malabsorption may increase the risk of as well as higher unemployment and impacted social functioning death, other GI manifestations are unlikely to impact the risk of mortality

2, 19, 21, 24, 26, 42

2, 5, 14, 15, 19–21, 23, 24, 26, 29, 43, 49

2, 14, 15, 17, 19, 21, 23, 24, 26

1 meta-analysis

Not associated with a significant increase in risk

of mortality

Limited evidence of an association with

increased mortality – most studies report **no**

significant impact

Mixed evidence, skin involvement defined

differently across studies

13 studies

9 studies

Conclusions

Skin

Musculoskeletal

Peripheral vascular



The burden of SSc manifestations is high and varied across organs. Pulmonary, cardiac, and renal manifestations are associated with significantly higher mortality, while gastrointestinal, skin, and peripheral vascular manifestations often have a significant impact on physical and mental HRQoL.



2 studies

6 studies

4 studies

No recent evidence of impact on HRQoL,

however older literature implies patients

experience physical HRQoL limitations and

pain

Reynaud phenomenon associated with poorer

physical and mental HRQoL

Digital ulcers cause hand disabilities affecting

multiple aspects of daily activities

Poorer physical and mental HRQoL

30, 31, 47–50

30, 31, 38, 47

The economic burden of many organ manifestations of SSc is currently poorly understood, and further research is needed to quantify their direct and indirect costs.

3 studies

6 studies

1 study

Burden currently **poorly understood**; a single study reports no

association with productivity loss/unemployment, but direct costs

and HCRU currently unknown

Higher total healthcare costs,

hospitalization, & emergency

visits

Higher outpatient and medication cost and work

unemployment, but full burden unclear due to limited

studies

Difference in median total

with & without digital

ulcers:

direct costs between SSc \$794



New therapies to target organ involvement in SSc may reduce the burdens associated with manifestations.

Conflict of interest

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). VS has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received consultancy fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received consultancy fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and has received speaker fees from BI, Janssen-Cilag and Galapagos, and Galapago



33, 34, 39

8, 20, 33, 36, 39, 49