International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2017; **20:** 1728–1750

ORIGINAL ARTICLE

A systematic review of the epidemiology, disease characteristics and management of systemic sclerosis in Australian adults

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Abstract

Objective: Australia has one of the highest prevalence rates of systemic sclerosis (SSc) worldwide. In order to highlight management deficiencies and key areas for further research, it is essential to understand its local epidemiological patterns, natural history, prognosis and mortality trends over time.

Methods: To identify Australian SSc-specific information through a systematic review focusing on areas of epidemiology, disease characteristics, treatment, functional ability, disease burden and health-related quality of life (HRQoL).

Results: MEDLINE, EMBASE and the Cochrane Library were searched on 14 September, 2016. All original full text articles on SSc in Australia were included. Of the 54 articles included in this review, the majority of studies recruited from South Australia, Victoria and New South Wales. The prevalence of SSc in Australia is increasing and is similar among the general population and the Aboriginal population. Despite improvements in care over the last three decades, morbidity and mortality remain high, with an overall standardized mortality ratio of 3.4 and a 10-year survival of 84% in a newly diagnosed patient. Cardiorespiratory manifestations are the leading cause of SSc-related death. Malignancy is the leading cause of non-SSc-related death. The role of autoantibodies in predicting disease subtype, visceral involvement and their use as a prognostic marker is becoming increasingly recognized.

Conclusion: Information on SSc in Australia, particularly unmet healthcare needs, HRQoL and economic burden, is limited. As a heterogenous condition, SSc requires a multi-disciplinary approach to care. Research aimed at quantifying HRQoL and burden of disease in Australia is essential for advocacy and resource allocation.

Key words: systemic sclerosis, scleroderma, epidemiology, Australia.

INTRODUCTION

Systemic sclerosis (SSc) is a rare but potentially devastating connective tissue disease (CTD) with no cure.[1]

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Worldwide prevalence varies with estimates ranging from 7/million to 489/million population, with the highest prevalence reported in the USA (276/million population in 1990) and in Australia (233/million population in 1999).[2]

The pathogenesis remains unknown and is likely a multifactorial process involving immune system alteration, genetic and environmental factors. A family history of SSc is an important risk factor for

developing SSc.[3,4] Furthermore, occupational exposure to silica dusts and hydrocarbons have been described[5–7] in addition to spatiotemporal and regional clustering.[8]

Despite an improvement over the last few decades, morbidity and mortality in SSc remain high with years of life lost (YLL) of up to 11.3 for women and 25.8 for men.[9–11] Cardiopulmonary manifestations, namely pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), remain the leading cause of SSc-related death having superseded scleroderma renal crisis (SRC) in the last two decades.[12] As SSc progresses, patients experience functional disability, disfigurement, pain and psychological consequences, including depression, helplessness and diminished health-related quality of life (HRQoL).[13,14]

Given the high prevalence of SSc in Australia, it is essential to understand its local epidemiological patterns, natural history, prognosis and mortality trends over time. This information highlights current deficiencies and key areas for future research. To identify Australian SSc-specific information, we conducted a systematic review focusing on areas of epidemiology, disease characteristics, treatment, disease burden and HRQoL.

METHODS

Database search

MEDLINE (through PUBMED and OVID), EMBASE and the Cochrane Library were searched on 14 September, 2016, using search terms (Medical Subject Heading (MeSH), EMTREE and/or free text) from the following categories: (i) systemic sclerosis, scleroderma; (ii) Australia, Victoria, Tasmania, New South Wales, Western Australia, South Australia, Northern Territory, Queensland; (iii) epidemiology, prevalence, incidence; (iv) disease characteristics, disease attributes, morbidity, mortality, management and outcomes ([morbidity or cost of illness].mp, [mortality or survival or outcome].mp, [disease attributes or disease characteristics].mp, [Raynaud's disease or digital ulcers or pulmonary arterial hypertension or interstitial lung disease or gastrointestinal motility disorder or gastro-esophageal reflux disease or renal crisis].mp, [quality of life or health related quality of life].mp, [treatment or guidelines or disease management].mp, [disease course or prognosis].mp.); and (v) quality of life, health-related quality of life. Search terms were combined using 'OR' and 'AND'. All MeSH and EMTREE terms were exploded. There were no limits to the search. The EMBASE (through OVID) search is illustrated in Figure 1.

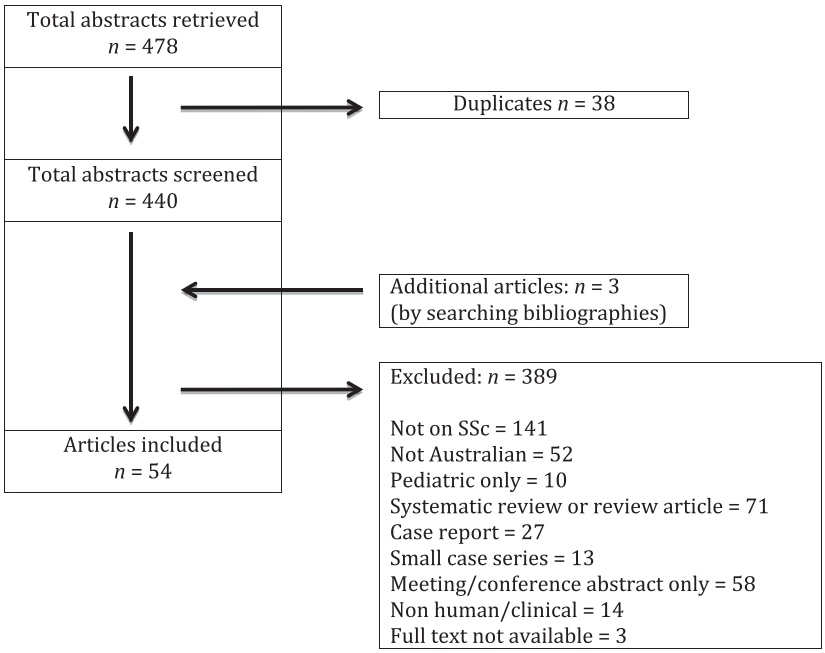

Figure 1 Systematic review flow chart (14 September, 2016). SSc, systemic sclerosis; scleroderma.

Article selection

Two reviewers (authors KM, MN) conducted the literature search, screened each record retrieved and identified appropriate articles for full-text review. These were then approved for inclusion by the other co-authors. All original research articles involving Australian patients were included. Review articles, conference abstracts, non-human trials, pediatric studies, case reports and small case series were excluded. Research articles limited to SSc pathogenesis were excluded. Conference abstracts were excluded if the full-text article was not found following an extensive search and /or contacting the corresponding author. This was done to ensure consistency across results as results can change between abstract and full-text article. The bibliographies of relevant articles identified using our search strategy were reviewed for additional studies.

Extraction of data/information

All studies reported quantitative data. Information on study design, patient characteristics (SSc defined by standard diagnostic criteria respective to the time period), treatment details, outcomes measures and results (as available) were extracted into a predefined spreadsheet. We evaluated the potential for bias in studies assessing SSc epidemiology including disease frequency and survival.

RESULTS

Literature search results

A total of 478 articles were identified in the literature search, of which 38 were duplicates and an additional 389 were excluded; three additional articles were identified from bibliographies (Fig. 1). A total of 54 articles were included in this review.

Epidemiology and overall disease characteristics of SSc (Tables 1 and 2)

The prevalence of SSc in Australia appears to be increasing over time from 0.46 per 10^5 in 1974, to 20.0 per 10^5 in 1993 to the most recently reported prevalence ranging from 86 to 23.3 per 10^5, with an estimated point incidence of 2.28 per 10^5.[15,16] These figures are based primarily on data from South Australia (SA) and New South Wales (NSW). The prevalence of SSc in Aboriginal Australians was only reported in one small study ($n = 5$) estimating similar prevalence to that of the general population but different autoantibody profiles.[17] SSc in Australia primarily affects women, with the highest female-to-male ratio reported of 5 : 1, and is predominantly of the limited disease subtype (lcSSc) accounting for 70–80% of SSc.[18] Although the pathogenesis remains unknown, Australian data indicate that family history is one of the most important determinants of disease.[4] However, genetics are not the sole contributor, with another study indicating no association between SSc and birth order, parity, age at first child or family size[19] and another suggesting the role of a common environmental exposure leading to geographical clustering in a rural town in Victoria.[8] Furthermore, another study reported a four-fold higher odds of men developing SSc following environmental exposure to silica with a disease latency of two decades.[5] This association has not been established in women, with two studies showing no association between silicone gel breast implants and subsequent development of SSc.[20,21]

Multiple small studies have described disease characteristics in Australian SSc patients (Table 3). The 'neck sign' (defined as ridging and tightening of the skin of the neck on extending the head) was described in 1989 by a Victorian physician and found to have a high sensitivity and specificity in distinguishing SSc patients from those with primary Raynaud's disease.[22] At that time, patients with early SSc were not identified using the Australian Rheumatology Association (ARA) criteria (which included patients with proximal scleroderma (skin sclerosis proximal to the metacarpophalangeal joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram).[23] This sign enabled patients to be identified earlier in their disease course.

Autoantibodies in SSc

Autoantibodies are common in Australian SSc patients and are useful in predicting the disease subtype, visceral involvement and as a prognostic marker (Table 4). The three most prevalent autoantibodies are anticentromere antibody (ACA), anti-Scl-70 antibody and RNA polymerase III antibody (RNAP).[24] They have strong clinical correlations and generally do not co-exist in the same patient. Antinuclear antibody (ANA) is present in almost all SSc patients (93–96%).[25] ACA is consistently associated with lcSSc, female gender, calcinosis, reflux esophagitis, sicca symptoms, increased risk of PAH, protective of ILD and improved survival compared to other subtypes.[25] Anti-Scl-70 has a prevalence of 14.6–18.0% across studies and is consistently associated with dcSSc,

Table 1 Original research articles on epidemiology in Australian patients with SSc published before 2000

Study	Study design, dates (location), inclusion criteria	Patient characteristics *n*, (% women), % subtype mean age (years)	Key findings	
			Epidemiology	Disease outcome
Barnett, 1978[78]	Prospective study (VIC) Characteristic skin changes and RP	118, (76%), onset age: 45	Gender: M : F ratio: 1 : 3. Survival rate: 80% at 5 years, 68% at 10 years.	Survival rate: 80% at 5 years, 68% at 10 years. Predictors of mortality: type 3 ($P < 0.0005$), older age (>40 years old), SRC
Barnett, 1988[79]	Prospective study 1953–83 (VIC) ARA Criteria or RP and bilateral symmetrical skin stiffness	177 †Disease subtype Type 1: 49%, Type 2: 37%, Type 3: 14%	Gender: M : F ratio: 1 : 4 Autoantibodies: ANA+ (100%), ACA+ (71% in type 1, 24% type 2), anti-SCL-70+ (29% in type 3) ACA correlated with calcinosis and telangiectasia ($P < 0.05$).	Predictors of mortality: type 3 ($P < 0.001$), males ($P = 0.001$), older age at onset (>40) Cause of death: 50% in type 2 and three due to SRC
Englert, 1994[20]	Retrospective case control 1989–91 (NSW) ACR or ‡study-specific criteria	SSc: 315 (80%) Controls: 371 (78%)	Rate of augmentation mammoplasty was similar in SSc and controls (RR 0.9, 95%CI 0.2–3.4). No association between silicone breast implantation and subsequent development of SSc	
Chandran, 1995[80]	Retrospective review of medical records 1987–93 (SA)	115 lcSSc: 70% dcSSc: 11% Overlap: 18%	Point prevalence: 208 per 10^6. Mortality rate: 4.0 per 10^6 Gender: M : F ratio 4 : 1. Subtype: lcSSc: dcSSc: overlap: 6:1:1.6 RP was the first symptom in all patients. Scl-70 more common in dcSSc (38%), ACA more common in lcSSc (66%), RNP more common in overlap (48%)	Abnormal nailfold capillaroscopy: type IV and V had a sensitivity and specificity of 100% and 63% for dcSSc
Englert. 1996[21]	Retrospective case control 1974–88 (NSW) ACR or † study-specific criteria	SSc: 556 Controls: 289	No association between silicone gel augmentation mammography and scleroderma (OR 1, 95%CI, 0.16–6.16).	
Englert, 1999[16]	Retrospective review 1974–88 (NSW) ACR Criteria study-specific*	715 (77%) lcSSc: 79%	Prevalence: increased from 1975 to 1988 from 4.52 per 100 000 to 8.62 per 100 000 Subtype: lcSSc: dcSSc: 4.2 : 1 Gender: F : M 5.1 :1 Males more likely to have dcSSc (OR 2.1, 95%CI 1.35–3.26)	Mortality rates: 0.17 (0.03–0.32) in 1976 and 0.21 (0.06–0.36) in 1988. 46% of deaths were attributed to SSc.
Englert, 1999[4]	Retrospective cohort 1974–88 (NSW) ARA or †study-specific criteria	SSc: 340 SSc families:338 Controls: 371 Control families:371	Ratio of SSc in family members: controls 10:0 Familial SSc prevalence: 1.4% (95%CI 0.8–2.2), RRE: 11–158, ARR: 1.4%, 80% were lcSSc, 75% female Both horizontal and vertical transmission.	

SA, South Australia; VIC, Victoria; NSW, New South Wales; ACR, American College of Rheumatology Classification Criteria; RP, Raynaud's phenomenon; lcSSc, limited scleroderma; dcSSc, diffuse scleroderma; ACA, anticentromere antibody; RNP, ribonucleoprotein antibody; ANA, antinuclear antibody; SRC, scleroderma renal crisis; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; SMR, standardized mortality rate; YLL, years of life lost; RRE, relative risk estimate; ARR, absolute relative risk; OR, odds ratio; RF, risk factor; ARA, Australian Rheumatology Association classification criteria: proximal scleroderma (skin sclerosis proximal to the metacarpophalangeal joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram.

†Disease subgroup: type 1: sclerodactyly only, type 2: skin stiffness proximal to the metacarphalangeal joints but sparing the trunk, type 3: diffuse skin stiffness including the trunk.

‡Study specific criteria = sclerodactyl and at least two of: Raynaud's phenomenon, esophageal dysmotility, calcinosis, telangiectasia, or an elevated ANA titer.

digital ulcers, joint contractures, SRC, ILD and poor survival compared with ACA.[25] The presence of anti-Scl-70 should prompt frequent monitoring of blood pressure, renal function and urinary protein to allow early detection of SRC. RNAP is present in 13.8–16.0% of patients and is associated with dcSSc, joint contractures, SRC, poor survival and increased risk of malignancy within the first 5 years of disease onset.[25] The presence of RNAP should encourage SRC monitoring as above, but also ensure patients are up-to-date with their age and sex appropriate cancer surveillance.

Mortality, survival and prognostic factors

Despite an improvement over the last three decades, morbidity and mortality in SSc remains high (Tables 1 and 2). Survival is well below age and gender matched controls, with an overall standardized mortality ratio (SMR) of 3.4 and a 10-year survival of 84% in a newly diagnosed patient.[11] Poor prognostic features include male gender, diffuse disease subtype (dcSSc), presence of PAH or SRC and the presence of Scl-70 antibody.[11] SSc is the predominant cause of death in most studies, accounting for 62.1% of deaths.[11] Cardiopulmonary involvement now supersedes SRC as the primary cause of SSc-related death while malignancy is the leading cause of non-SSc related death.[11]

Pulmonary involvement

Cardiopulmonary manifestations of SSc, namely ILD and PAH, are the most feared complications. SSc-PAH accounts for 42% of patients on the Australian PAH Bosentan registry[26] and has a prevalence of 10% in an asymptomatic SSc cohort and 11–50% in a symptomatic SSc cohort (Table 5). SSc-PAH can be detected early by screening. A novel Australian screening model, the 'ASIG (Australian Scleroderma Interest Group) algorithm' incorporating N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) with pulmonary function tests (PFTs), identifies patients at risk of developing SSc-PAH with the same sensitivity and negative predictive power as the DETECT algorithm, but with higher specificity.[27,28] This algorithm allows rationalization of the use of limited resources with transthoracic echocardiogram only required for screening positive patients. This algorithm has been shown to reduce the cost per case of PAH diagnosed by AUD$1057.[29] Another algorithm incorporates both asymmetric dimethylarginine (ADMA) and NT-proBNP in detecting PAH.[30] Predictors of SSc-PAH include older age, female gender, lcSSc, ACA and higher functional class (II/III).[11] Predictors of mortality in SSc-PAH include more severe PAH at diagnosis demonstrated by higher mean pulmonary arterial pressure, lower 6-minute walk test, higher functional class and presence of pericardial effusion.[31] Mean survival is 5 years from diagnosis. Monotherapy with bosentan improves survival and HRQoL measured by the Short Form-36.[32] Sequential and combination therapy, in the event of deterioration on monotherapy, has been shown in two studies to prolong survival.[31,33] Anticoagulation was shown in one study to have an additional survival advantage.[31] Multidisciplinary clinics have been shown in two studies to result in rapid diagnosis and early treatment of SSc-PAH with the potential of improved survival.[34,35]

The prevalence of SSc-ILD ranges 17.4–26.6% and can be detected earlier by screening with serial PFTs (Supplementary Table S1). Although high-resolution computer tomography (HRCT) is essential in diagnosis of SSc-ILD, there is no need for serial HRCT scans to monitor progression, as the same prognostic information is obtained through serial PFTs, allowing reduction in radiation exposure and cost. A diffusing capacity for carbon monoxide by alveolar volume ratio corrected for hemoglobin (DLCO/ VA) <60% is specific for pulmonary parenchymal or vascular disease.

Predictors of SSc-ILD include dcSSc and the presence of anti-Scl-70 antibody. Predictors of deterioration and mortality are related to disease extent on baseline HRCT, older age, abnormal DLCO, DLCO/VA and forced vital capacity (FVC) at baseline and a decline of 15% in DLCO or DLCO/VA in the first year.[36,37] Conversely, lcSSc and stable PFTs in the first 4 years are protective.[38] Mycophenolate mofetil (MMF) and azathioprine have been shown to have equal efficacy in the treatment of ILD with stability of both FVC and DLCO at 12, 24 and 36 months of follow-up in an observational study.[39]

Renal involvement

SRC, although rare, is a feared complication of SSc (Table 3). South Australian data support its rarity, with a prevalence of 2.8% in their cohort, all occurring in patients with dcSSc (prevalence in dcSSc 14%).[14] SRC occurred early in the disease process (mean of 15 months) and despite aggressive treatment, 33% died, 33% remained on long-term dialysis and 13% experienced renal recovery.[40] SSc-end stage renal failure (ESRF) has a prevalence of 0.3% and is an independent predictor of death on dialysis, a shorter time to death but also a predictor of renal recovery.[41]

Table 2 Original research articles on epidemiology in Australian patients with SSc published after 2000

Study	Study design, dates (location), inclusion criteria	Patient characteristics *n*, (% women), % subtype mean age (years)	Key findings	
			Epidemiology	Disease outcome
Englert, 2000[5]	Retrospective case control (NSW) Cases: silica-exposed SSc men ACR or study specific† criteria controls: men without silica exposure	Cases: 64 interviewed Controls: 83 interviewed Age: cases: 59 Control: 59.7	Silica exposure occurred more commonly in SSc patients: OR 3.93 (95%CI 1.84–8.54) Disease latency: 22.6 years to first disease symptom, 22.8 years to second disease symptoms and 24 years to disease diagnosis	Disease characteristics in idiopathic and silica-exposed SSc were the same. This study supports the concept of silica as a causal determinant in male SSc.
Roberts-Thomson, 2001[15]	Prospective study 1993–99 (SA) ARA criteria Study specific†	447 lcSSc: 69%, dcSSc: 24% Overlap = 7%	Prevalence increased from 20.0 per 10^5 in 1993 to 23.3 per 10^5 in 1999. Incidence increased from 1.51 per 10^5 in1993 to 2.28 per 10^5 in1999 SSc prevalence in siblings: 0.6% (95% CI 0.16–1.15%) Gender: M : F: 1 : 5. lcSSc more common	Survival from first symptom (years, 95%CI): • lcSSc: 27.6 (22.9–32.2), • dcSSc: 9.56 (7.2–12), • Overlap: 24.5 (18.7–30.3)
Zurauskas, 2005[17]	Cross sectional analysis of longitudinally collected data (SA) SSc: ARA study specific criteria	SSc in Aborigines: 5 lcSSc: 40%, dcSSc: 40%, Overlap: 20% Age: 33	Proportion of Aboriginal patients was no different to that in the general population Autoantibody profile: ACA (0%), nucleolar (40%), RNP (20%), homogenous (20%), mixed (20%)	
Englert, 2005[8]	Case control 1986–96 (VIC) ACR classification criteria	SSc: 13 (50%)	Prevalence of SSc in Edenhope: 6.1/10 000 • 10.2-fold higher prevalence than Sydney (95%CI, 4.5–23, $P < 0.0001$) • Gender ratio: M : F: 1 : 1	Family history of SSc in one case and RP in first degree relatives of two cases and three first degree relatives of controls. No single exposure or occupation was common to all.
Roberts-Thomson, 2006[18]	Prospective study 1993–2002 (SA) ARA criteria Study specific†	353 dcSSc: 22%	Prevalence rate: 21.1 per 10^5 (95%CI 20.2–22.6) Incidence rate: 1.5 per 10^5 (95%CI 1.32–1.73) Gender: M : F ratio: 1 : 5 RF: European birthplace (2.5-fold risk, $P < 0.001$)	Cumulative survival, years (95% CI): • dcSSc: 9.56 (7.2–12) to 22 (16.8–27.2), • lcSSc: 27.6 (22.9–32.2) to 39.7 (35.5–43.9)

Table 2 (continued)

Study	Study design, dates (location), inclusion criteria	Patient characteristics *n*, (% women), % subtype mean age (years)	Key findings	
			Epidemiology	Disease outcome
Hissaria, 2011[81]	Prospective study (SARS), but retrospective record review 1993–2007 (SA) ARA criteria Study specific†	786 (80%) lcSSc: 64%, dcSSc: 19% Overlap: 7%, Unclassified:10% Age: 46.7 (16.2)	Mortality: 43% died, mean age 70 (SD 13.2), mean disease duration 16.4 years Death by subtype (%) and mean age (years): lcSSc: 41%, 74.1, dcSSc: 46%, 62.9, overlap: 32%, 57.8. SMR (95%CI): overall 1.46 (1.28–1.69), lcSSc: 1.3 (1.11–1.53), dcSSc: 2.92 (2.2–3.89), overlap: 2.41 (1.37–4.24) 10 year survival: 91% for lcSSc, 74% for dcSSc	Predictors of death: older age at disease onset ($P < 0.00001$), male gender (RR 2.6, 95%CI 1.88–3.52), dcSSc ($P < 0.0001$), SRC: 4.69 (2.67–8.24), ILD: 2.34 (1.55–3.53), PAH: 2.17 (1.4–3.36), anti-Scl-70: 1.83 (1.14–2.96) or ACA: 0.53 (0.37–0.74), nailfold capillary dropout: 1.6 (1.06–2.42), cancer ($P < 0.0006$)
Russo, 2014[19]	Cross-sectional analysis of longitudinally collected data 1993–2011 (SA) ARA criteria Study specific† Controls: hospital staff	SSc: 374 (84%) lcSSc: 73%, dcSSc: 22%, Overlap 6% Controls: 347 (84%) Age controls: 51.57	No association between SSc and • family size at birth ($P = 0.21$) • birth order ($P = 0.36$) • parity ($P = 0.07$) • age at first child ($P = 0.28$) • gender of first child ($P = 0.29$)	
Hao, 2016[11]	Prospective study 2007–14 (VIC) ACR criteria, Medsger criteria for lcSSc	Overall 1800 (88.6%) Prevalent: 1411 (87%), lcSSc: 72.8%, dcSSc: 27.2% Inception: 389 (81.8%) lcSSc: 59.8%, dcSSc: 40.2% Age: prevalent: 46.2, incident 52.1	Inception cohort: SMR overall: 3.4 (2.3–4.5), YLL: 11.3 women, 25.8 men Prevalent cohort: SMR overall 2.8 (2.4–3.3), YLL: 11.9 women, 17.2 men Predictors of mortality in inception cohort: HR (95%CI): male gender: 3.4 (1.4–3.7), dcSSc: 1.8 (1.1–2.9), PAH: 2.4 (1.3–4.3), SRC: 1.9 (1.0–3.5)	Cause of SSc-related death: 62.1% (PAH 30.4%, ILD 21.7%, PAH-ILD 17.4%, GIT 13.0%, SRC 13.0%) Cause of non-SSc-related death: malignancy (50.0%), sepsis (10.0%), CVD (20.0%), IHD (10.0%).

SA, South Australia; VIC, Victoria; NSW, New South Wales; ACR, American College of Rheumatology Classification Criteria; RP, Raynaud's phenomenon; lcSSc, limited scleroderma; dcSSc, diffuse scleroderma; ACA, anticentromere antibody; RNP, ribonucleoprotein antibody; ANA, antinuclear antibody; SRC, scleroderma renal crisis; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; CVD, cardiovascular disease; IHD, ischemic heart disease; GIT, gastrointestinal tract; SMR, standardized mortality rate; YLL, years of life lost; RRE, relative risk estimate; ARR, absolute relative risk; OR, odds ratio; RF, risk factor; ARA, Australian Rheumatology Association classification criteria: proximal scleroderma (skin sclerosis proximal to the metacarpophalangeal joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram.
†Study specific criteria = sclerodactyly and at least two of: Raynaud's phenomenon, esophageal dysmotility, calcinosis, telangiectasia, or an elevated NA titer.

Peripheral vascular involvement

Three studies indicate a higher risk of macrovascular disease in SSc (Supplementary Table S2). The earliest study, performed in NSW, reported an increased prevalence of ulnar artery narrowing in the absence of atherosclerosis.[42] A Victorian study found that arterial stiffness is higher in SSc patients compared with age and sex matched controls and was associated with age, disease duration and blood pressure.[43] As arterial stiffness is an independent predictor of cardiovascular events and all-cause mortality, the same authors addressed this concern in another large Victorian study.[44] They found more than a three-fold increased risk of cardiovascular disease in patients with SSc compared with age and sex matched controls. Male gender, older age, hypercholesterolemia and the presence of PAH were independent risk factors for the development of CVD in SSc patients. The frequency and clinical association of telangiectasia reported in two South Australian studies identified a correlation between lcSSc, ACA and an increased risk of PAH and gastrointestinal bleeding.[45] Reduced capillary density on nailfold capillaroscopy may aid as a prognostic tool in identifying patients with lcSSc who are at a higher risk of developing PAH.[46]

Cancer

There appears to be a higher prevalence of cancer in SSc patients (Supplementary Table S3), that is higher in men and in dcSSc as seen in a large prospective study of 441 SSc patients.[47] Lung cancer followed by breast cancer had the highest standardized incidence rates and were further explored in retrospective studies indicating that SSc itself appears to be an independent risk factor.[48,49] The etiology of this increased risk is unknown. Hypotheses proposed relate to the disease itself, including an underlying fragile genome and /or exposure to an environmental agent that contributes to both the development of SSc and cancer, and the treatment of the disease with immunosuppressives including cyclophosphamide, MMF and prednisolone. Additionally, the increased risk of lung cancer may arise in some people from previously damaged or fibrotic lung.

Functional ability assessments

SSc is a chronic progressive condition with significant morbidity, functional disability and reduced life expectancy. Despite this, there is a paucity of Australian studies focusing on functional ability, disease burden, treatment guidelines and HRQoL. Only three studies were found by the same author addressing functional ability, in particular hand function (Supplementary Table S4).[50–52] Functional disability is associated with unemployment and reduced HRQoL among Australian SSc patients.[53] This highlights an important area of unmet need for Australian SSc patients that requires further study.

DISCUSSION

This systematic review, the first to focus on SSc in Australia, presents evidence of the heterogeneous nature of disease characteristics, significant disease-related morbidity and mortality, and the potential role of autoantibodies in predicting disease characteristics and course. In addition, our review highlights an increase in risk of malignancy among SSc patients and the paucity of data in this country regarding patient-centered care, burden of disease and HRQoL.

Epidemiology and overall disease characteristics of SSc

Published data on SSc prevalence confirm a higher prevalence in Australia (208 and 233 per million) than in other countries.[2] The Australian studies of prevalence recruited patients from SA and NSW only, thus their generalizability to the wider Australian population is uncertain. Genetic and shared environmental factors may play a role in this high prevalence, although the studies to date have been inconclusive.[4,5,19] In addition, there was only one study focusing on the epidemiology of SSc among the Indigenous population ($n = 5$), demonstrating a similar prevalence to non-Indigenous Australians. This is discordant with the prevalence of other CTDs, such as systemic lupus erythematosus, which has a higher reported prevalence among the Indigenous Australian population.[54] It is unclear whether the increasing prevalence of SSc in Australia is due to better case ascertainment due to greater awareness, more sophisticated methods of low prevalent disease attainment with the advent of 'centers of excellence' or due to a true increase in disease prevalence.

Autoantibodies

The prevalence of autoantibodies and their clinical correlations in Australian SSc patients are consistent with that of other international SSc cohorts.[55,56] Not only is the presence of certain autoantibodies in SSc, such as ACA, helpful in making the diagnosis of SSc, but the

Table 3 Original research articles on disease characteristics in Australian patients with SSc

Study	Study design, dates (location) inclusion criteria	Patient characteristics *n*, (% women), % subtype‡ Age, years (mean)	Key findings
Barnett, 1989[22]	Cross-sectional study (VIC) SSc = RP and skin stiffness PRD: RP with no signs of SSc Control: without CTD Disease subtype**	Total SSc = 76 Type 1: 58%, (84%) 62 Type 2: 28%, (86%) 54 Type 3: 9%, (86%) 43 Type 4: 5%, (75%) 50 Primary RD = 7, (57%) 52 Controls = 57, (88%) 53	ANA+ in all SSc patients. ANA speckled: type 1: 53%, type 2: 58%, type 3: 70%. ACA: type1: 71%, type 2: 24%, type 3: 0%. Scl-70: type 1: 9%, type 2: 38%, type 3: 29% Presence of ≥ 1 antibody was common Presence of 'neck sign': SSc: 92%; primary RP: 0%, controls: 0% Neck sign is highly sensitive and specific tool for the diagnosis of SSc.
Ong, 1998[46]	Cross sectional analysis of longitudinally collected data (SA) ARA or study specific† criteria Enrolled: lcSSc who lived near the hospital Controls: hospital staff	lcSSc: 20 (90%) Without PAH:60%(83%) With PAH: 40% (100%) Controls: 10 Age: SSc without PAH: 58 SSc with PAH:64.6 Controls: 35	lcSSc: 90% ACA+, 40% had PAH, ACA positivity: SSc without PAH: 100%, SSc with PAH: 75%, controls: 0% Nailfold capillaroscopy: - three-fold increase in capillary diameter in SSc compared with healthy controls ($P < 0.01$) - reduction in capillary density in SSc compared with healthy controls ($P < 0.01$) - reduction in density in those with PAH compared with those without PAH ($P < 0.01$) - no correlation between disease duration and capillary diameter or density. The immunological process responsible for capillary loss in nailbed is the same in the lung vascular bed. Capillaroscopy may identify those at risk of PAH
Mould, 2000[82]	Cross sectional analysis of longitudinally collected data (SA) ARA and study specific† criteria HHT patients Controls: patients without a CTD	Total SSc = 38 lcSSc: 76%, (90%) dcSSc: 24%, (67%) HHT: 3 (NR) Controls: 50 (NR) Age: lcSSc: 63.4, DSSc: 48.4 HHT: NR, Controls: NR	Telangiectasia number (range): lcSSc: 35 (0–150) dcSSc: 23(0–135) Correlation between telangiectasia number on hands, face ($P = 0.014$) and disease duration ($P = 0.009$). Telangiectasias were randomly distributed No correlated between telangiectasia number and calcification surface area or capillary diameter or density in 12 lcSSc patients. HHT: the number and distribution of telangiectasias was similar to SSc patients. Control group: 0% had telangiectasia

Table 3 (continued)

Study	Study design, dates (location) inclusion criteria	Patient characteristics *n*, (% women), % subtype‡ Age, years (mean)	Key findings
Roberts-Thompson, 2002[45]	Cross sectional analysis of longitudinally collected data (SA) ARA and study specific† criteria Rheumatic controls: 30% RA, 15% OA 13% SLE/Sjogren, 42% soft tissue or inflammatory disorder Controls: hospital staff	Total SSc = 53 lcSSc: 72%, (90%), 64 dcSSc: 23%, (67%), 50 Overlap: 5.6% (100%), 51 Rheumatic controls: 100 (78%), 58 Healthy controls: 30 (73%), 44	Telangiectasia frequency: SSc: 76%, rheumatic controls: 12%, controls: 13% Correlations of telangiectasia in SSc: - mean ± SD number on hands 22.9 ± 30.1, 7.3% were >1 mm in size - higher number in lcSSc and on the ventral surface of the digits - hand telangiectasia was associated with face and lip telangiectasia (P = 0.001), disease duration (P = 0.002), calcinosis surface area (P = 0.03), ACA (P = 0.005) - trend for correlation between multiple large (>1 mm) telangiectasia, PAH and GIT bleeding
Walker, 2003[40]	Retrospective medical record analysis of longitudinally collected data 1993–2000 (SA)	SSc total: 539 (NR) SRC: 15 (NR) Age:54.5	SRC prevalence: SSc: 2.8% (all had dcSSc). Time to SRC: 15 months (1 week to 11 years) Scl-70 associated with reduced risk of SRC P = 0.03) Presentation: severe hypertension 94%, heart failure 56%, microangiopathic anemia 81%, Cr normal in 47% Despite treatment: 5 died, 5 dialysis, 3 renal recovery,2 renal transplant
Lu, 2005[83]	Retrospective review 1993–2002 (SA) ARA criteria and study specific† SSc-myositis: proximal muscle weakness with CK >2 × ULN; inflammatory myopathic chances on EMG or characteristic biopsy	SSc-myositis = 20 dcSSc 40% (40%) Overlap 40% (87%) lcSSc 20% (100%) Age: 47.3	Prevalence of myositis: 3.3%. Gender: F : M ratio: 3 : 1 Subtype: dcSSc 40%, overlap 40%, lcSSc 20% Characteristics: - 100% had proximal weakness with functional impairment - 10% developed dyspnea, 15% neck weakness, 10% severe dysphagia - CK (tested in 18 patients): 85% elevated, mean 1129 U/L (38–5968) - EMG (tested in 10 patients): 80% had inflammatory myopathic changes - muscle biopsy (in 13 patients): 92% had positive histology - ANA+ in 100%, anti-Pm-Scl in 25% (2 patients, both had overlap)

Table 3 (continued)

Study	Study design, dates (location) inclusion criteria	Patient characteristics *n*, (% women), % subtype‡ Age, years (mean)	Key findings
Swaminathan, 2008[84]	Cross-sectional analysis of longitudinally collected data 1998–2006 (SA) ARA or study specific† criteria Sicca symptom prevalence determined from questionnaire	Total SSc: 193 lcSSc: 61% (83%), dcSSc: 24%, (85%), overlap: 0.7%, (80%), not specified: 7%, (79%) Age: lcSSc: 58.3, dcSSc: 49.2, overlap: 44.6, not specified:55.2	Sicca symptoms prevalence: lcSSc: 59%, dcSSc: 49%, overlap: 40% Mean sicca score: lcSSc 13.22, dcSSc 10.15, overlap 9.5, not specified 9 Higher sicca score associated with: anticholinergic use (14 patients), thyroxine (29 patients), ACA presence and anti-M3R-blocking antibodies Autoantibody and association with sicca symptoms: ACA: 40%, speckled 14%, Scl-70 10%, nucleolar 9.5%, Ro/La 5.4% Sicca symptoms were independent of the presence of Ro/La
Siva, 2011[41]	Retrospective study 1963–2005	Dialysis registry 40 238 127 SSc	Prevalence of ESRF secondary to SSc: 0.3%. ESRF secondary to SSc had odds (95%CI) of: female (OR 4.17, 2.38–7.3), lower BMI (OR 0.92, 0.88–0.097), late referral (early OR 0.39, 0.2–0.77), chronic lung disease (OR 2.83, 1.64–4.9), peripheral vascular disease (OR 4.19, 2.23–7.68), absence of coronary artery disease (OR 0.39, 0.2–0.77), absence of cerebrovascular disease (OR 0.2, 0.06–0.67), and absence of diabetes (OR0.32, 0.14–0.71) SSc survival on dialysis was associated with: higher mortality ($P < 0.05$) most commonly CVD, median survival was shorter ($P < 0.001$), survival at 1 year: 72%, 2 years: 55%, 5 years: 29% Renal recovery: better in SSc patients (10%) ($P < 0.001$) and occurred within the first 12–18 months of dialysis

NR, not reported; SA, South Australia; SASR, South Australian Scleroderma Registry; VIC, Victoria; NSW, New South Wales; ACR, American College of Rheumatology Classification Criteria; RP, Raynaud's phenomenon; RPD, primary Raynaud's disease; HHT, hereditary hemorrhagic telangiectasia; lcSSc, limited scleroderma; dcSSc, diffuse scleroderma; ACA, anticentromere antibody; RNP, ribonucleoprotein antibody; ANA, antinuclear antibody; SRC, scleroderma renal crisis; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; CTD, connective tissue disease; CVD, cardiovascular disease; IHD, ischemic heart disease; GIT, gastrointestinal tract; SMR, standardized mortality rate; YLL, years of life lost; RRE, relative risk estimate; ARR, absolute relative risk; OR, odds ratio; RF, risk factor; ULN, upper limit of normal; EMG, electromyogram; CK, creatine kinase; ARA, Australian Rheumatology Association classification criteria: proximal scleroderma (skin sclerosis proximal to the metacarpophalangeal joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram.

†Study specific criteria = sclerodactyly and at least two of: Raynaud's phenomenon, esophageal dysmotility, calcinosis, telangiectasia, or an elevated NA titer.

‡Disease subgroup: type 1: sclerodactyly only, type 2: skin stiffness proximal to the metacarphalangeal joints but sparing the trunk, type 3: diffuse skin stiffness including the trunk, type 4: 'atypical' included patients with Raynaud's phenomenon, telangiectasia and characteristic involvement of internal organs, but no typical skin stiffness.

Table 4 Original research articles on autoantibodies in Australian patients with SSc

Study	Study design, dates (location), inclusion criteria	Patient characteristics *n*, (% women), % subtype mean age (years)	Key Findings
Nikpour, 2011[25]	Cross sectional analysis of longitudinally acquired data 2007–2010 ACR criteria, Medsger criteria for lcSSc	451 (88%) lcSSc: 70.7% dcSSc: 29.3% Age: 46.5 (13.7)	Antibodies: ANA:96% patients, anti-Scl-70: 7.7%, RNAP: 15.3%, anti-Ro: 6.1%, ANCA: 16.7%, Rhf: 29.8%, APLA: 31.7%, RNAP were associated with: OR (95%CI): SRC: 3.8 (1.2–11.5, $P = 0.02$), dcSSc: 6.4 (2.9–13.8, $P < 0.0001$), joint contractures: 2.5 (1.2–5.3, $P = 0.02$), anti-Scl-70: 0.01 (0.0–0.11, $P < 0.0001$), ACA: 0.13 (0.1–0.4, $P = 0.0005$) Anti-RNAP had high NPV for: myositis: 99.5%, SRC: 98.2%, malignancy within 5 years of SSc onset: 96.1% OR (95%CI) of developing cancer within 5 years of SSc skin onset: RNAP: 4.2 (1.3–13.4), older age at onset: 1.1 (1.1–1.2) Highest mRSS was independently associated with: anti-Scl-70 antibodies: OR 4.4 ($P < 0.0001$), RNAP: OR 7.7 ($P < 0.0001$) and joint contractures: OR 8.5 ($P < 0.0001$)
Graf, 2012[85]	Prospective study 1993–2007 (SA) ARA or study specific† criteria	Cohort 1: 129 Cohort 2: 768 Age by antibody: ACA: 42.8, Scl70: 39.1, RNAP: 45.8, U1RNP: 33.2, Th/To: 45.5, Pm/Scl: 49.8, Ku: 50	Antibody prevalence in cohort 1: 85%: consisting of: ANA: 40%, Scl-70: 18%, RNAP3: 16%, U1RNP: 7%, Th/To: 6%, Pm/Scl: 7%, Ku: 6%; 11% had multiple antibodies present Disease subtype by autoantibody status: lcSSc: ACA: 96%, Th/To 75%, Pm/Scl 56%, Ku 50%, dcSSc: Scl70: 61%, RNAP3: 90%, overlap: U1RNP: 78% Organ involvement by autoantibody status: ILD was associated with Scl70 (30%, $P = 0.004$) and absence of ACA, PAH was associated with U1RNP (44%, $P = 0.0006$) and Th/To (38%, $P = 0.034$), SRC was associated with RNAP3 (20% $P = 0.002$) and Scl-70(4%, $P = 1.00$), myositis was associated with U1RNP (22%, $P = 0.12$) and Ku (17%, $P = 0.36$) If ≥1 autoantibody present, the one with the highest titer determined the clinical phenotype Survival (cohort 2): ACA is protective, Scl-70 has the worst survival, followed by RNAP3 and U1RNP Scl70, RNAP3, U1RNP were associated with reduced survival compared with ACA ($P = 0.0004$)

Table 4 (continued)

Study	Study design, dates (location), inclusion criteria	Patient characteristics *n*, (% women), % subtype mean age (years)	Key Findings
Morrisroe, 2013[86]	Prospective cohort study 2007–12 ACR or Leroy/Medsger criteria	940 (87.7%) lcSSc: 63.5% dcSSc: 25.9% Age: 57.5 (12.5)	Autoantibodies positive: ANA: 93% (ACA pattern in 42.9%), Scl-70: 14.6%, RNAP3: 13.8%, APLA: 24% Prevalence of APLA: ACA-IgM: 14.1%, ACA-IgG: 10.3%, anti-β2GP: 6.7%, LA 0% Associations of APLA: ACA-IgG was associated with PAH (OR 1.7, 95% CI 1.0–2.9, $P = 0.047$), higher titers corresponding with increased risk (OR 4.6, 95%CI 1.0–20.8, $P = 0.047$), ACA-IgM and ACA-IgG were associated with 2.0 and 1.8 increased risk of ILD, with higher titers associated with increased risk (moderate titer ACA-IgM: OR 2.4, 95%CI 1.2–4.8, $P = 0.016$, moderate titer ACA-IgG: OR 2.2, 95%CI 1.0–4.5, $P = 0.041$), ACA-IgG was associated with 2-fold increased risk of ILD-PH (OR 2.1, 95%CI 1.1–4.2, $P = 0.036$) and 1.8-fold increased risk of digital ulcers (OR1.8, 95%CI 1.2–2.7, $P = 0.008$), ACA-IgM was associated with 2.4-fold increased risk of RP (OR 2.4, 95%CI 1.1–5.3, $P = 0.03$)
Patterson, 2015[87]	Cross-sectional analysis of longitudinally acquired data 2007–2013 ACR or LeRoy/Medsger criteria or expert opinion of the attending physician	505 (87.7) lcSSc: 73.3% dcSSc: 26.7% Age: 41.4 (15.77)	Presence of autoantibodies: 45% positive for 1 autoantibody, 33% positive for 2, 9% positive for 3, 2% for ≥3 and 11% had no antibody positivity Prevalence: ANA 94.3% (nucleolar 24.8%, speckled 27.3%, centromere 42%, homogenous 22.4%). ACA, Scl-70 and RNAP3 were the most common and had strong clinical associations. Characteristics of major clusters: Cluster ACA: 41%, were female (95%) with lcSSc (95%) and associations with calcinosis (49%), reflex esophagitis (63%), sicca (dry eyes 73%, dry mouth 84%), telangiectasia (94%), incontinence (45%) and PAH (17%). ILD, joint contractures, tendon friction rubs and synovitis were reduced when compared to other clusters. Cluster RNAP3 'strong': 8%, female (90%) with dcSSc (74%) and associations with joint contractures (82%), SRC (18%), GAVE (41%) and ILD (15%). Cluster Scl-70: 18%: female (82%) with dcSSc (51%) and association with digital ulcers (65%), joint contractures (62%), incontinence (17%) and ILD (74%).

SA, South Australia; lcSSc, limited scleroderma; dcSSc, diffuse scleroderma; ANA, antinuclear antibody; ACA, anticentromere antibody; RNAP3, RNA polymerase III antibody; ANCA, anti-neutrophil cytoplasmic antibodies; APLA, anti-phospholipid antibodies; anti-Scl-70, yopoisomerase 1; SRC, scleroderma renal crisis; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; mRSS, modified Rodnan skin score; GAVE, gastric antral vascular ectasia; RP, Raynaud's phenomenon; NPV, negative predictive value; ACR, American College of Rheumatology classification criteria' ARA, Australian Rheumatology Association: proximal scleroderma (skin sclerosis proximal to the metacarpophalangeal joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram.
†Study specific criteria = sclerodactyly and at least two of: Raynaud's phenomenon, esophageal dysmotility, calcinosis, telangiectasia, or an elevated ANA titer.

Table 5 Original research articles on pulmonary hypertension in Australian patients with SSc

Study	Study design, study dates (location), inclusion criteria	Patients, *n*, (% women) SSc subtype % Age, years mean Duration of SSc, months	Key Findings
Cox, 2005[88]	Cross sectional analysis of longitudinally collected data 1993–2002 (SA) ARA and Study Specific * Criteria	Deceased group: 234 lcSSc: 58%, dcSSc: 23% Overlap: 3.4%, uncertain: 15% Living group: 374 lcSSc: 66%, dcSSc: 19% Overlap: 7.8%, uncertain: 8%	PAH study definition: symptomatic patients with elevated PAP Prevalence of PAH: • deceased: 11% lcSSc, 0% dcSSc, 28% overlap • living: 5% lcSSc, 0% dcSSc, 14% overlap At PAH diagnosis: mean disease duration 15–20 years, DLCO 44%, PAP 64% Deceased PAH patients had more digital ulcers ($P = 0.06$) than deceased without PAH Cumulative survival from diagnosis: 2.5 years
Keogh, 2006[32]	Prospective study 2001–2003 Inclusion: iPAH, SSc-PAH or SLE with WHO functional class III or IV	177 (74%) iPAH: 59% (67%) SSc-PAH: 35% (82) SLE-PAH: 6% (91%) Age: 55.4, duration: 1.22	At baseline: 75.8% of SSc-PAH were WHO functional class III, 24.2% class IV From baseline to 3 months on bosentan: QoL (SF-36 form), improved and were maintained for: physical functioning ($P < 0.0001$), role physical ($P < 0.0001$), vitality ($P = 0.0003$), social functioning ($P < 0.0001$), mental health ($P = 0.005$) and role-emotional ($P = 0.001$). Improvement in QoL scores correlated with improvement in WHO functional class.
Phung, 2009[89]	Prospective study 2005–2007 (WA) ARA criteria Group A: patients referred for screening Group B: patients referred for diagnostic evaluation	Group A: 170 (87.1%) Group B: 14 (85.7%) lcSSc: 76% (87.8%) dcSSc: 24% (84.4%) Age: lcSSc: 56, dcSSc: 58 SSc duration: lcSSc: 120, dcSSc: 126	Prevalence of RHC diagnosed SSc-PAH: 13% (10% of group A, 50% group B) RVSP as a predictor of RHC SSc-PAH: RVSP <40 mmHg: 0%, RVSP 41–55 mmHg: 40%, RVSP >50 mmHg: 71.4%, RVSP not determined: 33% Characteristics of PAH patients: older (mean: 67 years, $P = 0.03$), female (87.5%), shorter 6MWD $P < 0.05$), WHO functional class II or III, LSSc ($P = 0.08$) and ACA positive Disease duration was not predictive Group B had worse: 6MWD (324 *vs.* 402, $P = 0.02$), PVR (884 *vs.* 486 dynes/s per cm^{-5}, $P < 0.01$)), functional class ($P = 0.06$) Prevalence of SSc-ILD: 17.4% DLCO/VA <60%: is specific for pulmonary parenchymal or vascular disease and if between 60–80%: 50% had vascular or parenchymal disease

Table 5 (continued)

Study	Study design, study dates (location), inclusion criteria	Patients, *n*, (% women) SSc subtype % Age, years mean Duration of SSc, months	Key Findings
Keogh, 2011[33]	Prospective study 2005–2009 PAH patients on monotherapy with deteriorating WHO functional	112 patients in total (83%) 26% were SSc Age: 51.4	Survival from monotherapy to end of combination therapy at years 1, 2, 3, 4, 5: 98%, 88%, 77%, 69%, 57%. Survival was significantly worse for SSc-PAH Mean time on: monotherapy: 18.7 months, combination therapy: 7.9 months In survivors, combination therapy at 12 months reversed the deterioration in FVC from 3.1 in monotherapy to 2.2, improved 6MWD from 316 m to 406 m, reduced sPAP from 86 mmHg to 77 mmHg, reduced RV systolic dysfunction from 2.8 to 2.4 and TR from 2.9 to 2.4.
Keogh, 2011[26]	Prospective registry 2004–2007	Total patients: 528 iPAH: 58% of patients (71%) SSc: 42% of patients (85%) Age: iPAH: 57, SSc: 62	33% discontinued bosentan similar in iPAH and SSc-PAH, death was the most common reason followed by adverse event Annual death rate: 13.6%: death rate in SSc-PAH (16.6%) was higher than iPAH (11.8%), Predictors of death: age >70 years, disease severity (functional class >III), etiology (SSc-PAH). Survival was better in those who continued therapy
Bagga, 2011[34]	Prospective cohort study (NSW)	47 patients (72%) 8 had PAH lcSSc: 37.5%, dcSSc: 12.5% Age: 71.8,	Multidisciplinary clinic involves cardiology, respiratory, rheumatology, rehabilitation physician and allied health staff (nurse and physiotherapist) Prevalence of PAH: 17% (8 patients, 4 had SSc: 3 lcSSc, 1 dcSSc). Death in three patients (all had SSc)
Ngian, 2012[31]	Prospective study 2002–2009 ACR or Leroy / Medsger criteria PAH diagnosed on RHC	117 with SSc-PAH (89.7%) lcSSc: 72.5%, dcSSc: 21.4% MCTD: 4.5%, SLE: 2.8% RA: 2.8%, undifferentiated CTD: 1.8% Age 61.5 Duration: 2.6	Deaths during follow-up: 27.4% (84.4% SSc group, 90% due to PAH, 10% due to malignancy) PAH therapy: 59% monotherapy, 10% sequential therapy and 29% combination Agent of choice: 88% bosentan, 32.5% sildenafil, 15.4% sitaxentan, 13.4% inhaled iloprost Survival on therapy at 1,2 and 3 years: 94%, 89% and 73%. Mean survival: 5 years Predictors of mortality: higher mean atrial pressure at diagnosis (HR 1.1, 95%CI 1.0–1.2, $P = 0.007$), lower baseline 6MWT (HR = 0.6, 95% CI 0.4–0.9, $P = 0.04$), higher baseline WHO functional class (HR 3.42, 95%CI 1.3–9.4, $P = 0.04$), presence of pericardial effusion (HR 3.39, 95%CI 1.07–10.68, $P = 0.04$) Protective factors: warfarin (HR 0.2, 95%CI 0.1–0.8, $P = 0.02$) and combination PAH therapy (HR 0.2, 95%CI 0.1–0.8, $P = 0.03$)

Table 5 (continued)

Study	Study design, study dates (location), inclusion criteria	Patients, *n*, (% women) SSc subtype % Age, years mean Duration of SSc, months	Key Findings
Thakkar, 2012[90]	Cross-sectional analysis of longitudinally collected data ACR or Leroy / Medsger criteria	Group 1: 15 (80%), (lcSSc: 87%), Group 2: 30 (83%), (lcSSc: 93%), Group 3: 19 (74%), (lcSSc: 32%) Group 4: 30 (100%), (lcSSc: 77%) Age: 40.3–51.5 Duration: 7.8–18.8	Definition: Group 1: SSc-PAH diagnosed on RHC, Group 2: 'at risk' of SSc-PAH with borderline PAH on RHC (mPAP 20–24 mmHg with PCWP <15 mmHg), Group 3: significant ILD but no PAH, Group 4: SSc controls without ILD or PAH Findings: Group 1 had the highest mean NT-proBNP level ($P < 0.0001$), with incremental decline from Group 1 to 4; NT-proBNP > 3000 pg/mL was associated with the most severe PAH at RHC; positive correlation of NT-proBNP level with sPAP on TTE in all groups combined (Pearson correlation coefficient 0.65, $P < 0.001$); and NT-proBNP level was positively correlated with mPAP (correlation coefficient 0.6, $P = 0.01$), PVR (correlation coefficient 0.8, $P = 0.005$), mRAP (correlation coefficient 0.8, $P = 0.006$)
Thakkar, 2013[28]	Prospective study ACR or Leroy / Medsger** criteria considered at high risk of PAH‡ referred for RHC	49 (NR) Age: SSc-PAH: 65.3, no PH: 58.8, ILD-PH: 62.1, LHD-PH: 60.4 Duration: SSc-PAH: 10.2, no PH: 11.1, ILD-PH: 11.4, LHD-PH: 18.3	Screening algorithm: Component A: RFT: DLCOcorr <70% with FVC/DLCOcorr ≥1.8, Component B: NT-proBNP ≥210 pg/m, positive result: A ± B positive (next step = TTE), negative result: A + B negative (next step = regular screen) Using the proposed algorithm: Prevalence of PAH at RHC: 55% (63% SSc-PAH, 22% ILD-PH, 15% LHD-PH) SSc-PAH compared with no PH: female gender (100% *vs.* 73%, $P = 0.03$), ACA presence (65% *vs.* 18%, $P = 0.01$), elevated CRP (11.6 *vs.* 6.1, $P = 0.02$) Signs of PAH: increased $sPAP_{TTE}$, lower $DLCO_{corr}$, lower 6MWD, higher NT-proBNP and $FVC/DLCO_{corr}$ ratio. Performance of the proposed PAH algorithm: sensitivity: 94.1%, specificity 54.5%, PPV 61.5%, NPV 92.3% compared with ESC/ERS algorithm: sensitivity: 94.1%, specificity 31.8%, PPV 51.6% and NPV 87.5% Performance of the proposed algorithm for all PH: 88.9%, 54.5%, 70.6%, 80%

Table 5 (continued)

Study	Study design, study dates (location), inclusion criteria	Patients, *n*, (% women) SSc subtype % Age, years mean Duration of SSc, months	Key Findings
Low, 2013[35]	Prospective study 2005 (NSW)	200 referred (72%) 58 PAH (62%) iPAH: 55% (59%) SSc-PAH: 24% (79%)	Multidisciplinary clinic involves cardiology, respiratory physician, rheumatology and immunology, rheumatology nurse Prevalence of PAH: 29% (iPAH: 55%, SSc-PAH: 24%) Median time from referral to prescription was 16 days (IQR 0–31 days) Cohort survival at 1 year: 92% and 3 years: 56%. SSc-PAH survival at 3 years: 44% (survivors maintained retention rates of 100% for six monthly visits)
Hao, 2015[12]	Prospective study 2007–2012 ACR or Leroy / Medsger criteria	79 SSc-PAH: 27 (93%) (lcSSc: 85%, dcSSc: 15%) Non-PAH: 34 (76%) (lcSSc: 79%, dcSSc: 21%) Age: PAH: 66.8, non-PAH: 61.2 Duration: PAH: 14.9, non PAH: 12.8	Prevalence of RHC diagnosed PAH: 57% PAH patients: older at PAH diagnosis, female (93% *vs.* 76%, $P = 0.03$), lcSSc, ACA positive, presence of telangiectasia, shorter 6MWD, lower DLCO, higher NT-proBNP, larger RA area, higher TRV, higher urate level Comparison of screening model: • DETECT: sensitivity: 100%, specificity: 35.3%, PPV 55.1%, NPV 100%, 45% of patients referred for RHC did not have PAH, missed one patient WHO Group 3 patient • ASIG algorithm: sensitivity 100%, specificity 54.5%, PPV 60%, NPV 100%, 40% were referred for RHC that did not have PAH, missed one WHO Group 2 patient • ESC/ERS guidelines: sensitivity 96.3%, specificity 32.3%, PPV 55.3%, NPV 90.9%, 45% referred for RHC did not have PAH, missed one WHO Group 1 patient

Table 5 (continued)

Study	Study design, study dates (location), inclusion criteria	Patients, *n*, (% women) SSc subtype % Age, years mean Duration of SSc, months	Key Findings
Thakkar, 2016[91]	Case control study NR (Australia) SSc: ACR or Leroy / Medsger criteria	SSc-PAH: 15 (80%) (lcSSc: 87%) Controls: 30 SSc patients without PAH (100%) (lcSSc: 77%, dcSSc: 23%) Age: SSc-PAH: 62.1, controls: 48.7. Duration: SSc-PAH:19.2, controls:7.8	SSc-PAH group compared with controls: • had higher mean ADMA levels (0.76 ± 0.14 μmol/L, $P < 0.0001$) • lower L-arginine to ADMA ration (97.28 *vs.* 117.45, $P = 0.02$) • ADMA did not correlate with PHC hemodynamics (mPAP, PVR, mRAP) • ADMA level ≥0.7 μmol/L had sensitivity 86.7%, specificity 90%, AUC of 0.86 for diagnosing PAH • NT-proBNP level ≥210 ng/mL had sensitivity 93.3%, specificity 100%, AUC of 0.9 for PAH diagnosis PAH screening model with combination of NT-proNBNP ≥210 ng/mL and ADMA level ≥0.7 μmol/L had sensitivity 100% and specificity 90%
Quinlivan, 2015[29]	Prospective study ACR or Leroy / Medsger criteria	643 (86%) Age: 58.1	Cost reduction with use of ASIG algorithm: $108 904.91 (50%) for screening, $67 753.19 (13%) for screening and RHC, $1057.1 (22%) saved per case of PAH diagnosed and reduced the number of referrals for TTE by 64% and RHC 10% Cost reduction extrapolating to Australian SSc population using ASIG algorithm: $931 535 per annum for screening and $851 400 each subsequent year and reduced number of TTE by 10%
Morrisroe, 2016[53]	Cross-sectional analysis of longitudinally collected data ACR or Leroy / Medsger criteria	1579 (84.9%), lcSSc 68.9%	PAH incidence 0.7%, PAH prevalence 8.4% Mean age at PAH diagnosis 62.3 (±10.5) and disease duration 14 (±12) years. Predictors of PAH included ACA (OR 1.6 (1.1–2.5, $P = 0.03$), esophageal stricture (OR 2.0, 1.2–3.3, $P = 0.01$), calcinosis (OR 1.9 (1.2–2.9, $P = 0.01$), digital ulcers 1.6 (1.0–2.4, $P = 0.03$), ILD (OR 2.3, 1.5–3.7, $P < 0.001$), sicca symptoms (OR 1.6, 1.1–2.5, $P = 0.03$)

SA, South Australia; NSW, New South Wales; WA, Western Australia; ACR, American College of Rheumatology classification criteria; lcSSc, limited scleroderma; dcSSc, diffuse scleroderma; ACA, anticentromere antibody; RNP, ribonucleoprotein; ANA, antibody, antinuclear antibody; ADMA, asymmetric dimethylarginine; NPV, negative predictive value; PPV, positive predictive value; SSc-PAH, SSc-pulmonary arterial hypertension: defined by mean pulmonary arterial pressure (mPAP) ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg; iPAH, idiopathic PAH; LHD-PH, left heart disease associated pulmonary hypertension; AUC, area under the curve; TTE, transthoracic echocardiogram; RVSP, right ventricle systolic pressure; RHC, right heart catheter; TR, tricuspid regurgitation; PAP, pulmonary arterial pressure; ILD, interstitial lung disease; RFT, respiratory function tests; DLCO/VA, diffusing capacity of the lung for carbon monoxide by alveolar volume ratio; FVC, forced vital capacity; HRCT, high-resolution computed tomography scan of the chest; (HRCT).
**High risk of PAH: sPAP ≥40 mmHg and/or $DLCO_{corr}$ ≤50% predicted with FVC >85% and/or fall in $DLCO_{corr}$ ≥20% in last 12 months or unexplained dyspnea.

occurrence of particular antibodies, such as RNAP, can identify patients at increased risk of certain disease manifestations, such as SRC and/ or cancer, allowing the clinician to individualize patient care and monitoring.[55,56]

Mortality, survival and prognosis factors

Information retrieved on mortality in SSc is alarming, with all studies showing significantly reduced life expectancy with an overall SMR of 3.4 for a prevalent cohort and 4.1 for an incident cohort, consistent with other studies.[57,58] Survival is worse in men and dcSSc. This is of particular concern, as we have no cure or effective disease-modifying agents for this disease.

Pulmonary involvement

Consistent with the international literature,[2] cardiopulmonary manifestations are the leading causes of SSc death in Australia, having superseded SRC in the last two decades.[12] Screening for these complications is recommended[59] and has been shown to improve both survival and HRQoL.[32] Australia has developed, validated and shown cost benefits with the 'ASIG algorithm', which integrates a blood test (NT-proBNP) with PFTs.[43,60]

Renal involvement

SRC is no longer the leading cause of SSc-related death since the advent of angiotensin converting enzyme inhibitors in the last two decades.[12] Its frequency, albeit declining in both Australian SSc patients and other SSc cohorts,[61,62] is still a feared complication of SSc and associated with poor 5-year survival.[61,62]

Peripheral vascular disease

Although SSc is considered a fibrosing disease of the tissues, the presence of vasculopathy in its pathogenesis is becoming increasingly recognized.[63,64] The increased risk of CVD has been reported before in SSc cohorts despite the absence of traditional cardiovascular risk factors.[65] The ability to non-invasively monitor peripheral vascular changes through the use of nailfold capillaroscopy is becoming an increasingly important tool in the routine care of SSc patients, highlighted by its introduction in the updated classification criteria for SSc[66] and is an area worthy of future research.

Cancer

The increased risk of cancer in Australian SSc patients is of concern, and has been shown in other countries.[67] These studies involve small patient cohorts. Further studies are required to evaluate this association, which if accurate, may warrant heightened cancer surveillance.

Functional ability assessments

There are no Australian studies focusing on HRQoL or areas of unmet healthcare needs in SSc. SSc encompasses broad multidimensional issues including biological, psychological and social processes,[68] and is associated with substantial disability,[69] therefore addressing HRQoL is an important aspect of patient care and has been recommended as a key area for future research.[70,71] Studies in Europe, Canada, America and China indicate that HRQoL is lower in SSc than other chronic medical conditions including heart disease and diabetes and lower than other rheumatic conditions.[71–73] The medical care of SSc patients should involve a patient-centered approach as this has been shown to increase patient satisfaction, HRQoL, engagemen, and to reduce anxiety.[74]

Unmet healthcare needs in SSc has been studied elsewhere, with 41% of patients reporting at least one unmet healthcare need (dealing with cold fingers) and 86% at least one unmet information need (necessity of certain medical tests).[75] This unmet need has been confirmed across Europe[76] and in the USA.[77] Addressing patients' concerns in addition to treating the physical manifestations of disease is an important component in holistic patient care and may aid us in developing personalized interventions.

A chronic progressive disabling condition with poor HRQoL and high unmet need is undoubtedly associated with a significant economic burden of disease. There are no Australian studies addressing this aspect of the disease.

Implications

Taken together, this Australian-focused systematic review highlights multiple areas within SSc that require further attention, including HRQoL, economic burden and areas of unmet need. This knowledge can be powerful in advocating for better healthcare resource allocation.

Our study is limited by the studies included within the review. This review included a number of retrospective studies which themselves have their own inherent biases and small sample sizes. Additionally, this review spans a 37-year period during which the diagnostic criteria for SSc have been updated. This may have introduced heterogeneity between the study subjects. Furthermore, the majority of studies recruited from three states of Australia (SA, VIC, NSW) and some of

these from the same patient cohorts, which may limit the generalizability to the entire Australian population.

CONCLUSION

Australia has contributed substantially to our current understanding on the nature and impact of SSc. However, the results of our systematic review highlight certain areas which require further attention, particularly unmet healthcare needs, HRQoL and economic burden, which are essential for advocacy and resource allocation.

ACKNOWLEDGEMENTS

Dr Morrisroe is supported by a NHMRC postgraduate scholarship (APP1113954) and an ASIG/Scleroderma Australia Fellowship. Dr Nikpour holds an NHMRC Career Development Fellowship (APP1126370). The authors have no financial interests nor have they received any financial support or other benefits from commercial sources for work reported on this manuscript. The authors have no conflicts of interest.

AUTHORS CONTRIBUTIONS

KM: study design, literature review, preparation of manuscript. WS, SP: preparation of manuscript. MN: literature review, preparation of manuscript. All authors have read and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Original research articles on pulmonary manifestations in Australian patients with SSc
Table S2. Original research articles on peripheral vascular disease in Australian patients with SSc
Table S3. Original research articles on cancer prevalence in Australian patients with SSc
Table S4. Original research articles on functional assessment in Australian patients with SSc