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

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Abstract

Objective: Australia has amongst 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 14th September 2016. All original full text articles on SSc in Australia were included.

Data synthesis: 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 standardised mortality ratio (SMR) of 3.4 and a ten-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 recognised.

Conclusion: Information on SSc in Australia, particularly unmet healthcare needs, HRQoL and economic burden, is limited. As a heterogeneous 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.

Keywords

- Systemic sclerosis
- Scleroderma
- Epidemiology
- Australia

Introduction

Systemic sclerosis (SSc) is a rare but potentially devastating connective tissue disease (CTD) with no cure [1]. Worldwide prevalence varies with estimates ranging from 7/million to 489/million, with the highest prevalence reported in the USA (276/million in 1990) and in Australia (233/million 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 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 14th 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, (Raynauds disease or digital ulcers or pulmonary arterial hypertension or interstitial lung disease or gastrointestinal motility disorder or gastro-oesophageal 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.

Article selection

Two reviewers (author 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 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 pre-defined 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; 3 additional articles were identified from bibliographies (Figure 1). A total of 54 articles were included in this review.

Epidemiology and Overall Disease Characteristics of SSc (Table 1 and Table 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 [19]. 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 [20] 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 [21, 22].

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 [23]. 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) [24]. 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) [25]. 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%) [26]. ACA is consistently associated with lcSSc,

female gender, calcinosis, reflux oesphagitis, sicca symptoms, increased risk of PAH, protective of ILD and improved survival compared to other subtypes [26]. Anti-Scl-70 has a prevalence of 14.6-18% across studies and is consistently associated with dcSSc, digital ulcers, joint contractures, SRC, ILD and poor survival compared with ACA [26]. 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% of patients and is associated with dcSSc, joint contractures, SRC, poor survival and increased risk of malignancy within the first five years of disease onset [26]. 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 (Table 1 and Table 2). Survival is well below age and gender matched controls, with an overall SMR of 3.4 and a ten-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 [27] 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 algorithm' incorporating N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) with 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 [28, 29]. This algorithm allows rationalisation of the use of limited resources with TTE only required for screen positive

patients. This algorithm has been shown to reduce the cost per case of PAH diagnosed by AUD\$1,057 [30]. Another algorithm incorporates both asymmetric dimethylarginine (ADMA) and NT-proBNP in detecting PAH [31]. 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 mPAP, lower 6MWT, higher functional class and presence of pericardial effusion [32]. Mean survival is five years from diagnosis. Monotherapy with bosentan improves survival and HRQoL measured by the SF-36 form [33]. Sequential and combination therapy, in the event of deterioration on monotherapy, has been shown in two studies to prolong survival [32, 34]. Anticoagulation was shown in one study to have an additional survival advantage [32]. 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 [35, 36].

The prevalence of SSc-ILD ranges from 17.4-26.6% and can be detected earlier by screening with serial pulmonary function tests (PFTs) (Supplementary Table 1). Although HRCT is essential in diagnosis of SSc-ILD, there is no need for serial high-resolution computer tomography (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 corrected for haemoglobin (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 diffusing capacity for carbon monoxide (DLCO), DLCO/VA and forced vital capacity (FVC) at baseline and a decline of 15% in DLCO or DLCO/VA in the first year [37, 38]. Conversely, lcSSc and stable PFTs in the first four years are protective [39]. 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 [40].

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%)[41]. 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 [41]. 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 [42].

Peripheral vascular involvement

Three studies indicate a higher risk of macrovascular disease in SSc (Supplementary Table 2). The earliest study, performed in NSW, reported an increased prevalence of ulnar artery narrowing in the absence of atherosclerosis [43]. 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 [44]. 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 [45]. 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, hypercholesterolaemia 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 [46]. 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 [47].

Cancer

There appears to be a higher prevalence of cancer in SSc patients (Supplementary Table 3), that is higher in men and in dcSSc as seen in a large prospective study of 441 SSc patients [48]. Lung cancer followed by breast cancer had the highest standardised incidence rates and were further explored in retrospective studies indicating that SSc

itself appears to be an independent risk factor [49] [50]. The aetiology 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, mycophenolate (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 4) [51-53]. Functional disability is associated with unemployment and reduced HRQoL amongst Australian SSc patients [54]. 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 amongst 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 generalisability 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, 20]. 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 CTD, such as systemic lupus erythematosus, which has a higher reported prevalence among the indigenous Australian population [55]. 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 “centres 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 [56, 57]. Not only is the presence of certain autoantibodies in SSc, such as ACA, helpful in making the diagnosis of SSc, but the 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 [56, 57].

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 [58, 59]. 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 [60], 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 [61] and has been shown to improve both survival and HRQoL [33]. Australia has developed, validated and shown

cost benefits with the 'ASIG algorithm', which integrates a blood test (NT-proBNP) with PFTs [44] [62].

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]. It's frequency, albeit declining in both Australian SSc patients and other SSc cohorts [63, 64], is still a feared complication of SSc and associated with poor five year survival [63, 64].

Peripheral vascular disease

Although SSc is considered a fibrosing disease of the tissues, the presence of vasculopathy in its pathogenesis is becoming increasingly recognized [65, 66]. The increased risk of CVD has been reported before in SSc cohorts despite the absence of traditional cardiovascular risk factors [67]. 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 [68] 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 [69]. 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 [70] and is associated with substantial disability [71], therefore addressing HRQoL is an important aspect of patient care and has been recommended as a key area for future research [72, 73]. 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 [73] [74] [75]. The medical care of SSc patients should involve a patient-centred approach as this has been shown to increase patient satisfaction, HRQoL, engagement, and to reduce anxiety [76].

Unmet healthcare need 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) [77]. This unmet need has been confirmed across Europe [78] and in the US [79]. 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 personalised 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 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 thirty-seven 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 generalisability 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.

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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 ^[80]	Prospective study (VIC) Characteristic skin changes and RP	118, (76%), onset age: 45	Gender: M:F ratio: 1:3. Survival rate: 80% at 5years, 68% at 10years.	Survival rate: 80% at 5years, 68% at 10years. Predictors of mortality: type 3 (p<0.0005), older age (>40years old), SRC
Barnett 1988 ^[81]	Prospective study 1953-83 (VIC) ARA Criteria or RP and bilateral symmetrical skin stiffness	177 *Disease subtype Type1: 49%, Type2: 37% Type3: 14%	Gender M:F Ratio: 1:4 Autoantibodies: ANA +ve (100%), ACA +ve (71% in type 1, 24% type 2), anti-SCL-70 +ve (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 3 due to SRC
Englert 1994 ^[21]	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 ^[82]	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 ^[22]	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.	

Abbreviations: South Australia (SA), Victoria (VIC), New South Wales (NSW), American College of Rheumatology Classification Criteria (ACR), Raynaud's phenomenon (RP), Limited Scleroderma (lcSSc), Diffuse Scleroderma (dcSSc), anticentromere antibody (ACA), Ribonucleoprotein (RNP) antibody, antinuclear antibody (ANA), Scleroderma renal crisis (SRC), Interstitial lung disease (ILD), Pulmonary arterial hypertension (PAH), Standardised mortality rate (SMR), Years of life lost (YLL), relative risk estimate (RRE), absolute relative risk (ARR), risk factor (RF)

Australian Rheumatology Association (ARA) classification criteria: proximal scleroderma (skin sclerosis proximal to the MCP 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, Type2: skin stiffness proximal to the metacarpophalangeal joints but sparing the trunk, Type 3: diffuse skin stiffness including the trunk

**Study specific criteria = sclerodactyl and at least 2 of: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody titre.

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

Study	Study Design, dates	Patient Characteristics	Key Findings
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	(location), Inclusion Criteria	n, (%women), %Subtype mean age (years)	Epidemiology	Disease Outcome
Englert 2000 ^[83]	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 in 1993 to 2.28 per 10 ⁵ in 1999 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 2 cases and 3 first degree relatives of controls. No one 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 (2.5fold 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)
Hissaria 2011 ^[84]	Prospective study (SARS), but retrospective record review 1993- 2007 (SA) ARA Criteria Study Specific *	786(80%) lcSSc: 64%, dcSSc: 19% Overlap: 7%, Unclassified: 10%	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),	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

		Age: 46.7 (16.2)	dcSSc: 2.92 (2.2-3.89), overlap: 2.41 (1.37-4.24) 10yr survival: 91% for lcSSc, 74% for dcSSc	(0.37- 0.74), nailfold capillary dropout: 1.6 (1.06-2.42), cancer (p<0.0006)
Russo 2014 ^[20]	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%).

Abbreviations: South Australia (SA), Victoria (VIC), New South Wales (NSW), Limited Scleroderma (lcSSc), Diffuse Scleroderma (dcSSc), anticentromere antibody (ACA), Ribonucleoprotein (RNP) antibody, antinuclear antibody (ANA), Scleroderma renal crisis (SRC), Interstitial lung disease (ILD), Pulmonary arterial hypertension (PAH), Standardised mortality rate (SMR), Years of life lost (YLL), American College of Rheumatology Classification Criteria (ACR)

Australian Rheumatology Association (ARA) classification criteria: proximal scleroderma (skin sclerosis proximal to the MCP joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram.

*Study specific criteria = sclerodactyl and at least 2 of: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody titre.

** Disease subgroup: Type 1: sclerodactyl only, Type2: skin stiffness proximal to the metacarpophalangeal joints but sparing the trunk, Type 3: diffuse skin stiffness including the trunk

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 ^[23]	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 positive in all SSc patients. ANA Speckled: type 1: 53%, type 2: 58%, type 3: 70%. ACA: type1: 71%, type2: 24%, type3: 0%. Scl-70: type 1: 9%, type2: 38%, type3: 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 ^[47]	Cross sectional analysis of longitudinally collected data (SA) ARA or Study Specific * criteria Enrolled: LSSc 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 positive, 40% had PAH, ACA positivity: SSc without PAH: 100%, SSc with PAH: 75%, Controls: 0% Nailfold capillaroscopy: - 3 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 ^[85]	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). Telangiectasia were randomly distributed No correlated between telangiectasia number and calcification surface area or capillary diameter or density in 12 LSSc patients. HHT: the number and distribution of telangiectasia was similar to SSc patients. Control group: 0% had telangiectasia
Roberts-Thompson 2002 ^[46]	Cross sectional analysis of longitudinally collected data (SA)	Total SSc = 53 lcSSc: 72%, (90%), 64	Telangiectasia frequency: SSc: 76%, Rheumatic controls: 12%, Controls: 13% Correlations of telangiectasia in SSc:

	ARA and Study Specific * Criteria Rheumatic controls: 30%RA, 15%OA 13%SLE/Sjogren, 42%soft tissue or inflammatory disorder, Controls: hospital staff	dcSSc: 23%, (67%), 50 Overlap: 5.6% (100%), 51 Rheumatic controls: 100 (78%), 58 Healthy controls: 30 (73%), 44	- mean $\pm$ SD number on hands 22.9 $\pm$ 30.1, 7.3% were >1mm 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 (>1mm) telangiectasia, PAH and git bleed
Walker 2003 ^[41]	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: 15months (1week-11years) Scl-70 associated with reduced risk of SRC (p=0.03) Presentation: Severe hypertension 94%, Heart failure 56%, Microangiopathic anaemia 81%, Cr normal in 47% Despite treatment: 5 died, 5 dialysis, 3 renal recovery, 2 renal transplant
Lu 2005 ^[86]	Retrospective review 1993- 2002 (SA) ARA Criteria and Study Specific * SSc-myositis: proximal muscle weakness with CK>2xULN; inflammatory myopathic changes 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 1129U/L (38-5968) - EMG (tested in 10 patients): 80% had inflammatory myopathic changes - muscle biopsy (in 13patients): 92% had positive histology - ANA positive in 100%, anti-Pm-Scl in 25% (2 patients, both had overlap)
Swaminathan 2008 ^[87]	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 (29patients), 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 ^[42]	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-.097), late referral (early OR0.39, 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 (OR 0.32, 0.14-0.71) SSc Survival on dialysis was associated with a: higher mortality (p<0.05) most commonly CVD, median survival was shorter (p<0.001), survival at 1year: 72%, 2years: 55%, 5years: 29% Renal recovery: better in SSc patients (10%) (p<0.001) and occurred within the first 12-18months of dialysis
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Abbreviations: Not reported (NR), South Australia (SA), South Australian Scleroderma Registry (SASR), Victoria (VIC), connective tissue disease (CTD), cardiovascular disease (CVD), Limited Scleroderma (lcSSc), Diffuse Scleroderma (dcSSc), anticentromere antibody (ACA), Ribonucleoprotein (RNP) antibody, antinuclear antibody (ANA), Raynaud's phenomenon (RP), Primary Raynaud's disease (PRD), Hereditary haemorrhagic telangiectasia (HHT), connective tissue disease (CTD), Upper limit of normal (ULN), electromyogram (EMG), Creatine Kinase (CK) Australian Rheumatology Association (ARA) classification criteria: proximal scleroderma (skin sclerosis proximal to the MCP joints) and at least two of the following minor criteria: sclerodactyly, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram. American College of Rheumatology Classification Criteria (ACR)

*Study specific criteria = sclerodactyl and at least 2 of: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody titre.

** Disease subgroup: Type 1: sclerodactyl only, Type2: skin stiffness proximal to the metacarpophalangeal joints but sparing the trunk, Type 3: diffuse skin stiffness including the trunk, Type4: "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 ^[26]	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 5years of SSc onset: 96.1% OR (95%CI) of developing cancer within 5years 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: OR (p-value) anti-Scl-70 antibodies: 4.4 (p<0.0001), RNAP: 7.7 (p<0.0001) and joint contractures: 8.5 (p<0.0001)
Graf 2012 ^[88]	Prospective study 1993-2007 (SA) ARA or Study Specific * criteria	Cohort1: 129 Cohort2: 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 cohort1: 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 titre 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)
Morrisroe 2013 ^[89]	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 titres corresponding with increased risk (OR 4.6, 95%CI 1.0-20.8, p =0.047), ACA-IgM and ACA-IgG were associated 2.0 and 1.8 increased risk of ILD, with higher titres associated with increased risk (moderate titre ACA-IgM: OR 2.4, 95%CI 1.2-4.8p=0.016, moderate titre 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 Raynaud's phenomenon (OR2.4, 95%CI 1.1-5.3 p=0.03)

Patterson 2015 ^[90]	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 1autoantibody, 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 oesphagitis (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%).
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Abbreviations: South Australia (SA), Victoria (VIC), Limited Scleroderma (lcSSc), Diffuse Scleroderma (dcSSc), antinuclear antibody (ANA), anticentromere antibody (ACA), RNA Polymerase III antibody (RNAP3), anti-neutrophil cytoplasmic antibodies (ANCA), anti-phospholipid antibodies (APLA), Topoisomerase 1 (anti-Scl-70), Scleroderma renal crisis (SRC), Interstitial lung disease (ILD), Pulmonary arterial hypertension (PAH), modified rodnan skin score (mRSS), Gastric antral vascular ectasia (GAVE), Raynaud's phenomenon (RP), Negative predictive value (NPV). American College of Rheumatology Classification Criteria (ACR); Australian Rheumatology Association (ARA): proximal scleroderma (skin sclerosis proximal to the MCP joints) and at least two of the following minor criteria: sclerodactyl, digital pitting scars and bilateral pulmonary fibrosis on chest radiogram. *Study specific criteria = sclerodactyl and at least 2 of: Raynaud's phenomenon, oesophageal dysmotility, calcinosis, telangiectasia, or an elevated antinuclear antibody titre.

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 ^[91]	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%	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 15-20years, DLCO 44%, PAP 64%

		Overlap:7.8%, Uncertain:8%	Deceased PAH patients had more digital ulcers (p=0.06) than deceased without PAH Cumulative survival from diagnosis: 2.5years
Keogh 2006 ^[33]	Prospective study 2001-03 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 3months 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 ^[92]	Prospective study 2005-07 (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<40mmHg: 0%, RVSP 41-55mmHg: 40%, RVSP >50mmHg: 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 v 402, p=0.02), PVR (884 v 486dynes/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
Keogh 2011 ^[34]	Prospective study 2005-09 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 year 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 316m to 406m, reduced sPAP from 86mmHg to 77mmHg, reduced RV systolic dysfunction from 2.8 to 2.4 and TR from 2.9 to 2.4.
Keogh 2011 ^[27]	Prospective registry 2004-07	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 >70years, disease severity (functional class >III), aetiology (SSc-PAH). Survival was better in those who continued therapy
Bagga	Prospective cohort study	47 patients (72%) 8 had PAH	Multidisciplinary clinic involves cardiology, respiratory, rheumatology, rehabilitation physician and allied

2011 ^[35]	(NSW)	lcSSc: 37.5%, dcSSc: 12.5% Age: 71.8,	health staff (nurse and physiotherapist) Prevalence of PAH: 17% (8patients, 4 have SSc: 3 LSSc, 1 DSSc). Death in three patients (all had SSc)
Ngian 2012 ^[32]	Prospective study 2002-09 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 3years: 94%, 89% and 73%. Mean survival: 5years 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)
Thakkar 2012 ^[93]	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: Group1: SSc-PAH diagnosed on RHC, Group 2: "at risk" of SSc-PAH with borderline PAH on RHC (mPAP20-24mmHg with PCWP<15mmHg), Group 3: significant ILD but no PAH, Group 4: SSc controls without ILD or PAH Findings: Group1 had the highest mean NT-proBNP level (p<0.0001), with incremental decline from Group 1 to 4; NT-proBNP > 3,000pg/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, p0.005), mRAP (correlation coefficient 0.8, p=0.006)
Thakkar 2013 ^[29]	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: DLCO _{corr} <70% with FVC/DLCO _{corr} ≥1.8, Component B: NT-proBNP≥ 210pg/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% v 73%, p=0.03), ACA presence (65% v 18%, p=0.01), elevated CRP (11.6 v 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%

Low 2013 [94]	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 0-31days) Cohort survival at 1 year: 92% and 3year: 56%. SSc-PAH survival at 3years: 44% (Survivors maintained retention rates of 100% for six monthly visits)
Hao 2015 [12]	Prospective study 2007-12 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% v 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 Group3 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
Thakkar 2016 [95]	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 ($0.76 \pm 0.14 \mu\text{M}$, $p < 0.0001$) - lower L-arginine to ADMA ration (97.28 v 117.45 , $p = 0.02$) - ADMA did not correlate with PHC hemodynamics (mPAP, PVR, mRAP) - ADMA level $\geq 0.7 \mu\text{M}$ had sensitivity 86.7%, specificity 90%, AUC of 0.86 for diagnosing PAH - NT-proBNP level $\geq 210 \text{ ng/mL}$ had sensitivity 93.3%, specificity 100%, AUC of 0.9 for PAH diagnosis PAH Screening model with combination of NT-proBNP $\geq 210 \text{ ng/mL}$ and ADMA level $\geq 0.7 \mu\text{M}$ had sensitivity 100% and specificity 90%
Quinlivan 2015 [30]	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, \$1,057.1 (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 ^[96]	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), oesophageal 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)

Abbreviations: South Australia (SA), Victoria (VIC), Western Australia (WA), American College of Rheumatology Classification Criteria (ACR), Limited Scleroderma (lcSSc), Diffuse Scleroderma (dcSSc), anticentromere antibody (ACA), ribonucleoprotein (RNP) antibody, antinuclear antibody (ANA), asymmetric dimethylarginine (ADMA), negative predictive value (NPV), positive predictive value (PPV), SSc-Pulmonary arterial hypertension (SSc-PAH): defined by mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, Idiopathic pulmonary arterial hypertension (iPAH), left heart disease associated PH (LHD-PH), area under the curve (AUC), Transthoracic echocardiogram (TTE), Right ventricle systolic pressure (RVSP), Right heart catheter (RHC), Tricuspid regurgitation (TR), pulmonary arterial pressure (PAP), Interstitial lung disease (ILD), Respiratory function tests (RFT), Diffusing capacity of the lung for carbon monoxide by alveolar volume ratio (DLCO/VA), Forced vital capacity (FVC), High resolution CT scan Chest (HRCT), positive predictive value (PPV), negative predictive value (NPV), Area under curve (AUC)

**high risk of PAH: sPAP ≥ 40 mmHg and/or DLCOcorr $\leq 50\%$ predicted with FVC $> 85\%$ and/or fall in DLCOcorr $\geq 20\%$ in last 12 months or unexplained dyspnea

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

