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Inflammatory Arthritis in Systemic Sclerosis: Its Epidemiology, Associations, and Morbidity

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Objective. To describe the epidemiology, associations, and impact of inflammatory arthritis (IA) in systemic sclerosis (SSc).

Methods. Patients with SSc prospectively enrolled in the Australian Scleroderma Cohort Study were included. IA was defined clinically as the presence of synovitis on examination. Logistic regression was used to determine the associations of IA with SSc manifestations and serological parameters. Patient-reported outcome measures were used to capture physical function and health-related quality of life (HRQoL).

Results. IA was a common SSc manifestation affecting one-third (33.3%) of patients over a median follow-up of 4.3 (1.7–8.4) years. Associations of IA included diffuse SSc (odds ratio [OR] 1.33, 95% confidence interval [95% CI] 1.01–1.74, $P = 0.042$), concurrent musculoskeletal manifestations (joint contractures and tendon friction rubs, OR 1.70, 95% CI 1.34–2.15, $P < 0.001$); myositis (OR 2.11, 95% CI 1.39–3.20, $P < 0.001$), and sicca symptoms (OR 1.57, 95% CI 1.14–2.16, $P = 0.006$), whereas IA was negatively associated with pulmonary arterial hypertension (OR 0.52, 95% CI 0.35–0.78, $P = 0.002$). Neither the presence of rheumatoid factor nor U1 small nuclear RNP were associated with IA (OR 1.13, 95% CI 0.88–1.44, $P = 0.331$, OR 1.46, 95% CI 0.89–2.39, $P = 0.129$ respectively). Positive anticyclic citrullinated protein antibodies, although at low frequency, were more common in those with IA compared with those without IA (7.5% vs 1.5%, $P < 0.001$). IA was associated with significantly lower HRQoL score ($P < 0.001$) and more physical disability than in those without IA ($P < 0.001$).

Conclusion. IA is a common disease manifestation that is more frquently seen in diffuse disease. IA is associated with poor HRQoL and physical disability. Further research is needed into the effective management of IA in SSc.

INTRODUCTION

Systemic sclerosis (scleroderma, SSc) is an autoimmune connective tissue disease characterized by fibrosis of the skin and internal organs.[1] SSc can be distinguished into two clinical subtypes based on the extent of skin involvement, with limited SSc having skin involvement distal to the elbows and knees, but including face and upper chest, whereas diffuse SSc (dcSSc) has skin involvement proximal to elbows and knees and involving the face, chest, and abdomen. The pathogenesis of SSc is complex and not fully understood but includes a combination of vasculopathy, excess immune activation, and increased collagen deposition by fibroblasts, resulting in the characteristic skin and organ fibrosis.[1] Given the heterogeneous multisystem nature of SSc, clinical manifestations can vary widely with almost any organ being involved. Despite an improvement over the last three decades, the morbidity and mortality in SSc remains high.[2] With emerging therapies and improved survival in SSc, improving patients' morbidity and health-related quality of life (HRQoL) is becoming an increasingly important focus for clinicians and patients alike.

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SIGNIFICANCE & INNOVATIONS

- Inflammatory arthritis (IA) is a common systemic sclerosis (SSc) disease manifestation occurring in a third of Australian patients with SSc.
- The presence of IA was associated with the diffuse SSc disease subtype, the presence of other musculoskeletal manifestations, myositis, and sicca symptoms.
- The presence of IA was associated with poor patient-reported quality of life and physical function.

Musculoskeletal (MSK) involvement, manifested by arthralgia, myalgia, inflammatory arthritis (IA), tendon friction rubs (TFRs), and joint contractures (JCs), is a common occurrence in Sjogren syndrome with a prevalence of 24% to 97% and can result in significant disability and psychosocial and economic burden.[3] The prevalence and impact of IA in SSc, either in isolation or as part of an overlap syndrome, such as SSc-rheumatoid arthritis (RA), is less well understood than in other rheumatic conditions, such as RA and psoriatic arthritis. In the latter, significant research has demonstrated the impact that IA has on patients' physical function and HRQoL.[4–6] As such, this study sought to determine the prevalence of IA in a large Australian SSc cohort and determine its treatment, disease associations, and impact on outcomes.

METHODS

Patient selection. Adult (>18 years) patients with SSc fulfilling the American College of Rheumatology/EULAR Classification criteria for SSc[7] enrolled in the Australian Scleroderma Cohort Study (ASCS) were included. The ASCS database collects comprehensive demographic and disease-related data on an annual basis. Written informed consent from all patients and ethical approval from all participating hospitals were obtained.

ASCS clinical data. SSc disease onset was defined as the time of the first non-Raynaud phenomenon SSc disease manifestation. Clinical manifestations and autoantibody status were defined as present if ever reported from the time of SSc diagnosis. Most autoantibodies were assayed systemically except for anticyclic citrullinated protein antibodies (CCP), which has recently been added to the database and was only recorded in 36.9% of patients (633/1,717). IA was defined as the presence of synovitis in one or more joints on clinical examination documented by the treating physician. SSc-RA overlap was physician diagnosed based on the presence of U1 small nuclear RNP (U1RNP), SSc, and clinical features consistent with IA. The presence of positive RhF and CCP was not compulsory for a diagnosis of SSc-RA overlap. Myositis was defined as present if the following were recorded: muscle weakness on examination, elevated creatine kinase two-fold above the upper limit of normal, and evidence of muscle inflammation on magnetic resonance imaging, electromyography, or muscle biopsy. Sicca symptoms were defined as present if dry eyes and/or dry mouth requiring daily treatment was reported. Interstitial lung disease was defined as present by characteristic fibrotic changes on high-resolution computed tomography lung.[7] Pulmonary arterial hypertension (PAH) was defined as present if diagnosed by right heart catheterization according to international criteria.[8] Medication use, prescribed at the discretion of the treating physician(s), from IA diagnosis was recorded. Annual patient-reported outcome measures (PROMs), such as HRQoL measured using the Medical Outcome Short Form-36 (SF-36) and Patient-Reported Outcomes Measurement Information System (PROMIS), in addition to physical function measured using the Health Assessment Questionnaire (HAQ) and SSc specific HAQ, were reviewed. These questionnaires are all validated for use in SSc.[9,10]

Statistical analysis. Data are presented as mean ± SD with *P* value calculated by two sample *t*-tests for normally distributed and median (25th -75th) with *P* value calculated by Wilcoxon rank-sum test for nonnormally distributed continuous variables and as number (percentage) for categorical variables. Differences in frequency were tested using chi-square and Fisher's exact tests. Univariable and multivariable logistic regression were used to determine the associations of IA with clinical manifestations and serological parameters. Variables with a *P* value less than 0.05 in univariable regression or variables deemed to be of clinical significance to the outcome (IA) a priori were included in the multivariable logistic regression analysis. A two-tailed *P* value of 0.05 or less was considered statistically significant. PROMs including the SF-36, PROMIS, HAQ, and scleroderma specific HAQ (sHAQ) scores were evaluated to estimate the impact of IA on HRQoL and physical function. All statistical analyses were performed using STATA 15.1 (StataCorp LP).

Data are available on request from the authors. Written informed consent from all patients and ethical approval from all participating hospitals were obtained. The dataset supporting the conclusions of this article can be made available on request through the corresponding author.

RESULTS

Patient characteristics. In our cohort of 1,717 patients with SSc, a third of patients with SSc experienced IA (572 [33.3%]) over a median follow-up of 4.3 (1.7–8.4) years. The median age at IA onset was 59.5 (50.4–67.7) years with a median SSc disease duration to IA onset of 7.9 (3.0–16.7) years. Those who experienced IA compared with those who did not experience IA were more likely to have dcSSc (30.1% vs 22.7%, $P = 0.001$) and more likely to experience other MSK

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manifestations, including JC and TFR (50.1% vs 36.3%, $P < 0.001$ and 12.3% vs 8.0%, $P = 0.004$), myositis (11.2% vs 5.3%, $P < 0.001$), and sicca symptoms (86.5% vs 79.3%, $P < 0.001$). IA occurred less frequently in those with PAH (7.2% vs 11.3%, $P = 0.007$). There was no significant difference between those with and without IA in terms of age at SSc onset, sex, ethnicity, or smoking status. Patient characteristics by IA status are summarized in Table 1.

In terms of autoantibody profile, those with IA compared with those without IA, were more likely to be positive for antitopoisomerase-1 antibody, RNA Polymerase III antibody, and U1RNP antibody (18.4% vs 13.1%, $P = 0.004$; 18.1% vs 11.7%, $P = 0.002$; and 8.2% vs 5.7%, $P = 0.050$, respectively). There was no significant difference in the frequency of RhF antibody positivity between those with and without IA with a third of both groups being positive for RhF (31.7% vs 29.5%, $P = 0.354$). Although present at low frequency, positive anti-CCP antibodies were more common in those with IA than in those without IA (7.5% vs 1.5%, $P < 0.001$). The presence of IA was associated with a higher frequency of raised markers of inflammation, reflected in both a raised C-reactive protein (CRP) and erythrocyte sedimentation rate, compared with those without IA

Table 1. Patient characteristics by IA status*

Patient characteristics	IA (n = 572)	No IA (n = 1,145)	*P* value
Demographics			
Age at SSc onset, mean (SD), y	47.0 (14.04)	46.8 (14.45)	0.764
Age IA onset, median (IQR 25th–75th), y	59.54 (50.38–67.70)	—	—
Female, n (%)	494 (87.0)	976 (85.3)	0.354
Caucasian ethnicity, n (%)	493 (89.8)	978 (91.4)	0.290
Diffuse disease subtype, n (%)	168 (30.1)	256 (22.7)	0.001
Smoking history,[a] n (%)	286 (50.1)	579 (51.1)	0.692
Antibody profile positivity, n (%)			
ANA (n = 1,685)	542 (95.4)	1,071 (95.9)	0.659
Anti-Scl70 (n = 1,644)	103 (18.4)	142 (13.1)	0.004
RNA Polymerase III (n = 1,208)	78 (18.1)	91 (11.7)	0.002
Anti- Scl/PM (n = 1,636)	9 (1.6)	18 (1.7)	0.943
U1RNP (n = 1,643)	46 (8.2)	62 (5.7)	0.050
RhF (n = 1,570)	172 (31.7)	303 (29.5)	0.354
Anti-CCP (n = 633)	18 (7.5)	6 (1.5)	<0.001
Anti-Ro (n = 1,641)	53 (9.5)	106 (9.8)	0.847
Anti-La (n = 1,640)	11 (2.0)	23 (2.1)	0.066
Markers of inflammation, n (%)			
CRP,[b] mg/L (n = 1,658)	330 (58.6)	547 (50.0)	<0.001
ESR,[b] mm/hr (n = 1,652)	294 (52.3)	470 (43.1)	<0.001
Clinical manifestations,[c] n (%)			
Digital ulcers	282 (49.3)	509 (44.5)	0.058
Telangiectasia	509 (89.5)	1,003 (88.1)	0.420
Calcinosis	260 (45.5)	474 (41.6)	0.119
Joint contractures	285 (50.1)	411 (36.3)	<0.001
Tendon friction rubs	70 (12.3)	90 (8.0)	0.004
Myositis	64 (11.2)	61 (5.3)	<0.001
GORD	547 (95.6)	1,075 (94.0)	0.154
GIT dysmotility	158 (27.6)	295 (25.8)	0.410
Renal crisis	18 (3.1)	45 (3.9)	0.416
ILD	175 (30.6)	321 (28.0)	0.270
PAH	41 (7.2)	129 (11.3)	0.007
Myocarditis	56 (9.8)	97 (8.5)	0.366
Sicca symptoms	493 (86.5)	893 (79.3)	<0.001
Overlap syndrome, n (%)			
Overlap with RA	60 (63.2)	0 (0)	<0.001
Overlap with SS	19 (20.2)	29 (43.9)	0.001
Overlap with SLE	15 (16.0)	13 (19.7)	0.540
Overlap with PM	14 (14.9)	15 (22.4)	0.223
Overlap with DM	2 (2.1)	4 (6.1)	0.197

* ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; GIT, gastrointestinal; GORD, gastro-oesphageal reflux disease; IA, inflammatory arthritis; ILD, interstitial lung disease; IQR, interquatile range; PAH, pulmonary arterial hypertension; PM, polymyositis; RA, rheumatoid arthritis; RhF, rheumatoid factor; RNAP III, anti RNA Polymerase III; Scl-70, antitopoisomerase-1; SS, Sjogren syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; U1RNP, U1 small nuclear RNP.
[a] Current or ever smoking history.
[b] CRP and ESR defined as positive if level above the upper limit of normal.
[c] Clinical manifestations ever reported from SSc disease onset.

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(58.6% vs 50.0%, $P < 0.001$ and 52.3% vs 43.1%, $P < 0.001$ respectively) (Table 1). Given the higher prevalence of U1RNP in those with IA, we evaluated the frequency of overlap syndrome in our cohort and found those with IA were more likely to have a diagnosis of an overlap syndrome with RA (63.2% vs 13.6%, $P < 0.001$).

Treatment of IA. Those with IA compared with those without IA were more likely to receive a disease modifying antirheumatic drug (DMARD), including both conventional and biological DMARDs (Table 2). All patients who experienced IA were treated with at least one agent following their IA diagnosis. The most used agents in those with IA were prednisolone (61.9%), methotrexate (46.0%), and hydroxychloroquine (44.9%). Other DMARDs and their frequency in IA included leflunomide (4.2%) and mycophenolate mofetil (18.5%). Biological DMARDs were used less frequently than the synthetic DMARDs with 3.0% of patients with IA using rituximab, 1.6% using tocilizumab, and 1.6% using abatacept. No patients were treated with an antitumor necrosis factor inhibitor.

Associations of IA. Associations of IA by univariable logistic analysis are summarized in Table 3. Associations with IA include the presence of dcSSc (odds ratio [OR] 1.46, 95% confidence interval [95% CI] 1.16–1.98, $P = 0.001$), other MSK manifestations (JC [OR 1.76, 95% CI 1.43–2.16, $P < 0.001$]) and TFR [OR 1.63, 95% CI 1.17–2.26, $P = 0.004$]), myositis (OR 2.24, 95% CI 1.55–3.23, $P < 0.001$), and sicca symptoms (OR 1.67, 95% CI 1.26–2.21, $P < 0.001$). IA was less frequent in those with PAH (OR 0.61, 95% CI 0.42–0.88, $P = 0.008$). In terms of autoantibodies, anticentromere positivity was negatively associated with IA with an OR of 0.90, a 95% CI of 0.49–0.73, and a P less than 0.001. Positivity for antitopoisomerase-1, RNA Polymerase III positivity, and anti-CCP were associated with the presence of IA (OR 1.50, 95% CI 1.14–1.98, $P = 0.004$; OR 1.67, 95% CI 1.20–2.31, $P = 0.002$; and OR 5.23, 95% CI 2.05–13.37, $P = 0.001$, respectively). Furthermore, the presence of raised markers of inflammation (CRP and erythrocyte sedimentation rate) were both significantly associated with IA (OR 1.42, 95% CI 1.16–1.74, $P = 0.001$ and OR 1.45, 95% CI 1.18–1.78, $P = 0.001$).

Using multivariable logistic regression analysis (outlined in Table 4), after adjusting for age and sex, associations of IA included the dcSSc (OR 1.33, 95% CI 1.01–1.74, $P = 0.042$), the presence of other MSK manifestations (JC and TFR) (OR 1.70, 95% CI 1.34–2.15, $P < 0.001$), myositis (OR 2.11, 95% CI 1.39–3.20, $P < 0.001$), and sicca symptoms (OR 1.57, 95% CI 1.14–2.16, $P = 0.006$). IA was negatively associated with PAH (OR 0.52, 95% CI 0.35–0.78, $P = 0.002$). Neither the presence of RhF or U1RNP were associated with the presence of IA (OR 1.13, 95% CI 0.88–1.44, $P = 0.331$ and OR 1.46, 95% CI 0.89–2.39, $P = 0.129$, respectively). Anti-CCP was not included in the multivariable logistic regression model as its prevalence was so low, being present in only 18 patients, and there was significant missing data in those without IA.

Because of the high frequency of raised markers of inflammation (CRP) in dcSSc compared with limited SSc (61.4% vs 47.8%, $P < 0.001$) and presence of collinearity, a second multivariable logistic regression was performed highlighting similar associations with IA as above, but with the presence of a raised CRP significantly associated with IA (OR 1.27, 95% CI 1.01–1.59, $P = 0.043$) (Table 4).

Association of IA on PROMs. The association of IA on quality of life is highlighted in Table 5. The HRQoL reported among our SSc cohort is well below 50 in both the physical (PCS) and mental component scores (MCS) of SF-36, indicating that patients with SSc experience worse HRQoL than age- and sex-matched population controls. The presence of IA in SSc is associated with a significantly lower score than those without IA, indicating a worse reported HRQoL in both the physical and mental domains of quality of life (PCS 28.6 vs 32.6, $P < 0.001$ and MCS 39.0 vs 41.5, $P = 0.003$). Furthermore, the association of IA on physical function is highlighted in the higher HAQ and sHAQ scores in those with IA compared with those without IA, indicating more difficulty with physical function and activities of daily living (HAQ 1.25 vs 0.88, $P < 0.001$ and sHAQ 23.0 [14.0–23.0] vs 18.0 [9.0–28.0], $P < 0.001$, respectively) (Table 5). Other impacts of IA on HRQoL are highlighted across all domains of the PROMIS questionnaire with those with IA indicating a higher frequency of pain (12.0 vs 9.0, $P < 0.001$), sleep

Table 2. Treatment of inflammatory arthritis

Immunosuppressive therapy	Inflammatory arthritis (n = 572), n (%)	No inflammatory arthritis (n = 1,145), n (%)	*P* value
Prednisolone	354 (61.9)	218 (38.1)	<0.001
Plaquenil	257 (44.9)	150 (13.1)	<0.001
Methotrexate	263 (46.0)	160 (14.0)	<0.001
Leflunomide	24 (4.2)	4 (0.3)	<0.001
Mycophenolate mofetil	106 (18.5)	134 (11.7)	<0.001
Rituximab	17 (3.0)	6 (0.5)	<0.001
Tocilizumab	9 (1.6)	3 (0.3)	0.002
Abatacept	9 (1.6)	0 (0.0)	<0.001

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Table 3. Determinants of IA in univariable analysis*

Patient characteristics	Odds ratio	95% CI	*P* value
Demographics			
Age at SSc disease onset, y	1.00	0.99–1.01	0.764
Female	1.15	0.86–1.54	0.354
Diffuse disease subtype	1.46	1.16–1.84	0.001
Caucasian ethnicity	0.83	0.58–1.17	0.290
Employment	0.73	0.52–1.05	0.089
Smoking history (current or ever)	0.96	0.79–1.17	0.692
Antibody profile positivity			
ANA	0.60	0.55–1.46	0.660
Anticentromere	0.90	0.49–0.73	<0.001
Anti-Scl70	1.50	1.14–1.98	0.004
Anti-Scl/PM	0.97	0.43–2.18	0.943
RNA Polymerase III	1.67	1.20–2.31	0.002
U1RNP	1.48	1.00–2.20	0.051
RhF	1.11	0.89–1.39	0.354
Anti-CCP	5.23	2.05–13.37	0.001
Anti-Ro	0.97	0.69–1.37	0.864
Anti-La	0.93	0.45–1.92	0.847
Elevated CRP[a]	1.42	1.16–1.74	0.001
Elevated ESR[a]	1.45	1.18–1.78	0.001
Clinical manifestations (ever)			
Digital ulcers	1.22	0.99–1.49	0.058
Telangiectasia	1.14	0.83–1.58	0.420
Calcinosis	1.17	0.96–1.44	0.119
Joint contractures	1.76	1.43–2.16	<0.001
Tendon friction rubs	1.63	1.17–2.26	0.004
Myositis	2.24	1.55–3.23	<0.001
GORD	1.40	0.88–2.24	0.156
GIT dysmotility	1.10	0.88–1.38	0.410
SSc renal crisis	0.79	0.46–1.38	0.417
ILD	1.13	0.91–1.41	0.270
PAH	0.61	0.42–0.88	0.008
Myocarditis	1.17	0.83–1.66	0.366
Sicca symptoms	1.67	1.26–2.21	<0.001

* ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GIT, gastrointestinal; GORD, gastro-oesphageal reflux disease; IA, inflammatory arthritis; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PM, polymyositis; RhF, rheumatoid factor; RNAP III, anti RNA Polymerase; Scl-70, antitopoisomerase-1; SSc, Systemic sclerosis; U1RNP, U1 small nuclear RNP.
[a] CRP and ESR levels elevated above the upper limit of normal.

disturbance (13.0 vs 12.0, $P = 0.007$), fatigue (13.0 vs 12.0, $P < 0.001$), anxiety (9.0 vs 8.0, $P = 0.019$), and depression (9.0 vs 8.0, $P = 0.007$) than those without IA. Additional evidence of the morbidity associated with IA is the higher frequency of unemployment among those with IA compared with those without IA (25.9% vs 19.2%, $P = 0.014$).

Table 4. Determinants of inflammatory arthritis in multivariable logistic regression*

Models	With disease subtype		With acute-phase reactants	
Patient characteristics	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age at SSc disease onset	1.00 (1.00–1.01)	0.337	1.00 (0.99–1.01)	0.314
Female	1.27 (0.91–1.77)	0.168	1.26 (0.91–1.77)	0.167
Diffuse disease subtype	1.33 (1.01–1.74)	0.042	—	—
RhF	1.13 (0.88–1.44)	0.331	1.09 (0.86–1.39)	0.473
U1RNP	1.46 (0.89–2.39)	0.129	1.47 (0.94–2.29)	0.093
MSK (JC+TFR)	1.70 (1.34–2.15)	<0.001	1.77 (1.41–2.23)	<0.001
Myositis	2.11 (1.39–3.20)	<0.001	2.30 (1.53–3.47)	<0.001
PAH	0.52 (0.35–0.78)	0.002	0.50 (0.34–0.75)	0.001
Sicca symptoms	1.57 (1.14–2.16)	0.006	1.51 (1.09–2.08)	0.012
Raised acute phase reactants	—	—	1.27 (1.01–1.59)	0.043

* CI, confidence interval; MSK, musculoskeletal manifestations (defined as the presence of joint contractures [JC] and or tendon friction rub [TFR], acute phase reactants [include both elevated C-reactive protein and or erythrocyte sedimentation rate]); OR, odds ratio; PAH, pulmonary arterial hypertension; RhF, rheumatoid factor; SSc, systemic sclerosis; U1RNP, U1 small nuclear RNP.

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Table 5. Impact of inflammatory arthritis on physical function and HRQoL*

Patient characteristics	Inflammatory arthritis (n = 572)	No inflammatory arthritis (n = 1,145)	*P* value
HRQoL,[a] median (IQR 25th–75th)			
Physical component score	28.56 (22.99–38.34)	32.69 (24.59–44.38)	<0.001
Mental component score	39.01 (29.90–48.11)	41.53 (31.90–50.98)	0.003
General HAQ,[a] median (IQR 25th–75th)	1.25 (0.63–1.75)	0.88 (0.25–1.50)	<0.001
Scleroderma specific HAQ,[a] median (IQR 25th–75th)	23.00 (14.00–32.00)	18.00 (9.00–28.00)	<0.001
PROMIS,[a] T score (SD)	T score (SD)	T score (SD)	
Physical function	15.7 (4.7)	16.0 (4.7)	0.364
Pain intensity	12.2 (4.6)	10.2 (4.1)	<0.001
Sleep disturbance	13.5 (3.8)	12.4 (4.0)	<0.001
Anxiety	9.5 (5.2)	8.7 (4.0)	0.013
Depression	9.4 (4.6)	8.6 (4.3)	0.007
Fatigue	13.4 (6.3)	12.2 (4.8)	0.002
Satisfaction with social role	13.7 (4.8)	14.3 (5.0)	0.110
PROMIS,[a] median (IQR 25th–75th)			
Physical function	17.00 (13.00–19.00)	18.00 (13.00–20.00)	0.065
Pain intensity	12.00 (8.00–16.00)	9.00 (6.00–14.00)	<0.001
Sleep disturbance	13.00 (11.00–16.00)	12.00 (10.00–15.00)	<0.001
Anxiety	9.00 (6.00–12.00)	8.00 (5.00–12.00)	0.019
Depression	9.00 (5.00–12.00)	8.00 (4.00–12.00)	0.009
Fatigue	13.00 (9.00–16.00)	12.00 (8.00–16.00)	0.007
Satisfaction with social role	14.00 (11.00–18.00)	15.00 (11.00–20.00)	0.056
Unemployment, N/n (%)	572/90 (25.9)	1,245/135 (19.2)	0.014
Age of unemployment, median (IQR 25th–75th), y	53.46 (44.98–59.58)	56.32 (48.12–61.40)	0.109

* HAQ, health assessment questionnaire; HRQoL, health-related quality of life; IQR, interquartile range; PROMIS, Patient-Reported Outcomes Measurement Information System (PROMIS); sHAQ, scleroderma specific health assessment questionnaire.
[a] Highest ever score.

DISCUSSION

This study is the first Australian study and second largest international study, after the EULAR Scleroderma Trial and Research Group (EUSTAR) network study,[11] to describe the epidemiology, clinical characteristics, associations, and impacts of IA in SSc. In our SSc cohort of 1,717 patients, IA was a common SSc disease manifestation, occurring in a third of Australian patients with SSc at a median age of 59.5 years. Our findings demonstrate that the presence of IA is independently associated with the dcSSc disease subtype, the presence of other MSK manifestations namely JC and TFR, the presence of myositis, and sicca symptoms, and was negatively associated with the presence of PAH. Unlike RA, the presence of RhF in our cohort was not independently associated with the presence of IA, and in fact more than a third of our cohort regardless of IA status were positive for RhF. However, the presence of anti-CCP was associated with IA, although only present in a small number of patients with IA (7.5%). Finally, but of upmost importance, our results reveal the significant impact that IA has on patients, with the presence of IA being negatively associated with employment, physical function, and HRQoL.

MSK manifestations have previously been evaluated in SSc in the EUSTAR registry[11] showing a prevalence of synovitis in 16%, TFR of 11%, and JC 31% consistent with our results. The most affected joints in their study included the small joints of the hands, specifically the metacarpophalangeal and proximal interphalangeal joints, and the wrists. Like our results, this study found an independent association between the presence of synovitis and the dcSSc, the presence of muscle weakness, elevated acute phase reactants, and the concurrence of synovitis with other MSK manifestations, specifically TFR and JC. Interestingly, in the EUSTAR cohort, they found an association between the presence of synovitis and PAH (which they defined by a systolic pulmonary arterial pressure >40 mmHg on transthoracic echocardiogram), which is contrary to our results, which showed a negative association between the presence of IA and PAH (defined on right heart catherisation [RHC]). A potential reason behind this conflicting finding may lie in the definition of PAH, namely they used transthoracic echocardiogram rather than RHC parameters and, as such, an elevated systolic pulmonary arterial pressure may result from other causes of pulmonary hypertension, such as left heart disease or lung disease. Given the strong association between the presence of synovitis and raised acute phase reactants indicating systemic inflammation and the known association between uncontrolled systemic inflammation and heart disease, this may account for this difference. The presence of RhF and or anti-CCP was not documented in the EUSTAR cohort, nor was the treatment of IA or the impact of synovitis on SSc-related morbidity, so comparison between autoantibody status and differences in treatments cannot be made.

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The association between IA and the presence of raised acute phase reactants as seen in our study and others[11–13] may indicate that the presence of IA in SSc is closely related to systemic inflammation. This hypothesis is further supported by the presence of inflammatory cell infiltration associated with focal microvascular obliteration and fibrin deposition seen on synovial biopsies performed on patients with SSc.[12] Whether IA in SSc represents a more severe SSc disease phenotype whose disease course should be closely monitored is unknown. However, given the association between raised acute phase reactants, disease activity, and morbidity,[14] the presence of IA as a clinical indicator of a more severe phenotype in SSc warrants further consideration.

Consistent with our results, the prevalence of RhF is common in SSc with a reported range in the literature of 30% to 50%.[15] Its presence is not sensitive nor specific for the presence of IA in SSc, nor is it helpful for distinguishing those with SSc-RA overlap.[16] In contrast, the presence of anti-CCP antibody in SSc is specific for IA and highly associated with SSc-RA overlap. However, as in our study, it occurs with a low prevalence in SSc with a reported range of 1% to 8%.[17–19] The prevalence of SSc-RA overlap is low with a reported of 1% to 5% in the literature[19–21] consistent with our study of 3.5%. Distinguishing between SSc-related IA or the presence of SSc-RA overlap is difficult in clinical practice; however, the presence of IA regardless of etiology warrants treatment. Given the lack of robust data to guide evidence-based treatment in SSc-related IA, therapeutic choice in clinical practice is extrapolated from the RA literature taking into account the presence of other SSc disease manifestations.[15] The presence of concurrent interstitial lung disease may influence the physician's decision regarding the biologic agent of choice if unresponsive to conventional DMARDs, for example using tocilizumab or rituximab instead of abatacept.[15] In our cohort, all patients with SSc with IA received treatment with at least one DMARD, most commonly methotrexate, with few patients progressing to a biological DMARDs.

Despite the literature in other rheumatic conditions regarding the impact of IA on physical function and HRQoL,[4–6] there is scarce research on this area in SSc and the studies performed are in small SSc cohorts[22] or in SSc-RA overlap.[19] As such, our study adds to this area of unmet need, highlighting the significant impact that IA has on physical function and HRQoL in SSc. Those with IA have significantly higher physical disability scores and poorer HRQoL scores than those without IA. Furthermore, although not a direct comparison, patients with SSc with IA in our study reported worse physical function and HRQoL scores than those with RA in a recent meta-analysis (PCS 28.9 [93% CI 22.9–38.3] vs 34.1 [95% CI 22.0–46.1]) and MCS (39.0 [95% CI 29.9–48.1] vs 45.6 [95% CI 30.3–60.8]), respectively.[23] We have documented an association between the presence of IA and unemployment, highlighting the impact of synovitis and hand dysfunction on employment in SSc.[24,25] Recognizing the presence of IA in SSc is an important first step as its treatment and monitoring may alleviate some of the associated morbidity.

Strengths of our study include the well-characterized SSc cohort followed prospectively over a substantial period in addition to clearly defined and recorded clinical manifestations, autoantibody profiles, and medication related data. Limitations of this study include that the IA distribution and severity was unable to be assessed, as we do not collect data on pattern of joint involvement, measures of arthritis disease activity, such as an arthritis disease activity score, nor radiographic data. Additionally, the presence of anti-CCP may have been underestimated as only one-third of patients had an anti-CCP recorded. Furthermore, we were unable to assess the effects of DMARD treatment in those with IA. This is an area that warrants further research.

IA is a common SSc disease manifestation, occurring with a prevalence of 33.3% in our SSc cohort, and is associated with a substantial impact on HRQoL and function. Given that IA is a treatable SSc disease manifestation, further research is needed to understand the extent of joint involvement in SSc and optimal strategies for its management.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Morrisroe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Schwender, Nikpour, Morrisroe.

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