Author/s:
Fairley, JL;Hansen, D;Proudman, S;Sahhar, J;Ngian, GS;Apostolopoulos, D;Walker, J;Host, LV;Stevens, W;Nikpour, M;Ross, L

Title:
The Prognostic and Functional Impact of Multimorbidity in Systemic Sclerosis

Date:
2025-04

Citation:
Fairley, J. L., Hansen, D., Proudman, S., Sahhar, J., Ngian, G. S., Apostolopoulos, D., Walker, J., Host, L. V., Stevens, W., Nikpour, M. & Ross, L. (2025). The Prognostic and Functional Impact of Multimorbidity in Systemic Sclerosis. ACR Open Rheumatology, 7 (4), https://doi.org/10.1002/acr2.70034.

Persistent Link:
https://hdl.handle.net/11343/360513

ACR Open Rheumatology
Vol. 7, No. 4, April 2025, e70034
DOI 10.1002/acr2.70034

American College of Rheumatology
Empowering Rheumatology Professionals

BRIEF REPORT

The Prognostic and Functional Impact of Multimorbidity in Systemic Sclerosis

Jessica L. Fairley,[1] Dylan Hansen,[2] Susanna Proudman,[3] Joanne Sahhar,[4] Gene-Siew Ngian,[4] Diane Apostolopoulos,[4] Jennifer Walker,[5] Lauren V. Host,[6] Wendy Stevens,[1] Mandana Nikpour,[7] and Laura Ross[1]

Objective. Our objective was to define the frequency and impact of multimorbidity in systemic sclerosis (SSc).

Method. Australian Scleroderma Cohort Study participants meeting American College of Rheumatology/EULAR criteria were included. Charlson Comorbidity Index scores were calculated at each visit, with multimorbidity defined as scores ≥4. Generalized estimating equations were used to model longitudinal data in multivariable models including age, sex, subclass, interstitial lung disease, and pulmonary arterial hypertension status. Survival was analyzed using Cox hazard modeling.

Results. Of 2,000 participants, 85% were female, 27% had diffuse SSc, and 20% had multimorbidity. Among those with multimorbidity, key comorbidities were hypertension (81%), dyslipidemia (67%), obstructive lung disease (50%), malignancy (49%), and ischemic heart disease (IHD) (40%). Multimorbidity was associated with worse survival (hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.30–1.91, $P < 0.01$). Renal disease had the largest impact (HR 2.41, 95% CI 1.46–3.98, $P < 0.01$), followed by left ventricular dysfunction (HR 1.76, 95% CI 1.21–2.57, $P < 0.01$), anticoagulation (HR 1.64, 95% CI 1.28–2.08, $P < 0.01$), and IHD (HR 1.45, 95% CI 1.16–1.80, $P < 0.01$). In multivariable modeling, multimorbidity was associated with poorer physical function (regression coefficient [RC] +0.17 units, 95% CI 0.13–0.21, $P < 0.01$). Peripheral vascular disease had the largest impact on physical function (RC +0.26 units, 95% CI 0.18–0.34, $P < 0.01$), followed by left ventricular dysfunction (RC +0.23 units, 95% CI 0.14–0.33, $P = 0.01$), IHD (RC +0.22 units, 95% CI 0.17–0.28, $P < 0.01$), and obstructive lung disease (RC +0.19 units, 95% CI 0.14–0.24, $P < 0.01$).

Conclusion. Multimorbidity occurred in 20% of patients in a large SSc cohort and was an important determinant of both prognosis and physical function. Effective treatment of non-SSc morbidity may improve outcomes for patients with SSc.

INTRODUCTION

Multimorbidity is an increasing public health challenge and an important adverse prognostic factor in both the general population and in rheumatic diseases.[1,2] In particular, cardiovascular risk factor management is an important priority in those with rheumatic diseases including systemic sclerosis (SSc) and rheumatoid arthritis (RA),[3] which confer increased risk of cardiovascular disease.[4,5]

The Australian Scleroderma Cohort Study is supported by Janssen, Boehringer Ingelheim, Scleroderma Australia, Scleroderma Victoria, Arthritis Australia, Musculoskeletal Australia (muscle, bone and joint health), Australian Rheumatology Association, and St. Vincent's Hospital Melbourne IT Department and Research Endowment Fund. Dr Fairley's work was supported by a National Health and Medical Research Council (NHMRC) Postgraduate Scholarship (GNT2013842), the University of Melbourne John Hayden Research Fellowship, an Avant Foundation Grant and an Australian Government Research Training Program Scholarship. Dr Nikpour's work was supported by an NHMRC Investigator Grant (GNT1176538). Dr Ross's work was supported by a Royal Australasian College of Physicians and the Australian Rheumatology Association, D.E.V. Starr Research Establishment Fellowship, and the University of Melbourne Paul Desmond Senior Research Fellowship.

[1]Jessica L. Fairley, MBBS, FRACP, Wendy Stevens, MBBS, FRACP, Laura Ross, MBBS, FRACP, PhD: The University of Melbourne and St. Vincent's Hospital Melbourne, Melbourne, Australia; [2]Dylan Hansen, MBiostatistics: St. Vincent's Hospital Melbourne, Melbourne, Australia; [3]Susanna Proudman, MBBS, FRACP: University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia; [4]Joanne Sahhar, MBBS, FRACP, Gene-Siew Ngian, MBBS, FRACP, PhD, Diane Apostolopoulos, MBBS, FRACP, PhD: Monash Health and Monash University, Melbourne, Australia; [5]Jennifer Walker, MBBS, FRACP, PhD: Royal Adelaide Hospital and Flinders University of South Australia, Adelaide, Australia; [6]Lauren V. Host, MBBS, FRACP: Fiona Stanley Hospital, Murdoch, Australia; [7]Mandana Nikpour, MBBS, FRACP, PhD: University of Sydney School of Public Health, Royal Prince Alfred Hospital Sydney and University of Sydney, Sydney, Australia.

Drs Nikpour and Ross contributed equally to this study.

Additional supplementary information cited in this article can be found online in the Supporting Information section (http://onlinelibrary.wiley.com/doi/10.1002/acr2.70034).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/acr2.70034.

Address correspondence via email to Jessica Fairley, MBBS, FRACP, at jessica.fairley@svha.org.au.

Submitted for publication December 30, 2024; accepted in revised form March 16, 2025.

Increasingly, rheumatologists are encouraged to take an active role in the management of key comorbidities in patients with rheumatic diseases to improve outcomes, particularly regarding cardiovascular disease.[5] This is especially true in the setting of socioeconomic deprivation, in which individuals are less likely to access care from multiple services, so an integrated approach is needed.[6]

The Charlson Comorbidity Index (CCI) is a tool commonly used to define comorbidity burden in large, population-based cohorts.[7] A series of key comorbidities are each assigned a weighted score according to perceived severity.[7] Multimorbidity, or significant comorbidity burden, defined as a CCI score of 4 or higher, is a threshold reached by only 6.5% of the general population, of whom account for 23% of health care costs.[8] Australian data also suggest that those with multimorbidity have a twofold increased risk of high health care utilization.[9] In the Australian Scleroderma Cohort Study (ASCS), multimorbidity defined by CCI score has been associated with a variety of adverse outcomes including malnutrition, myopathy, and cardiovascular disease.[10–13] Limited data describe the frequency and types of multimorbidity in SSc and suggest that multimorbidity is associated with poorer survival.[14] However, no data describe its impact on physical function. Accordingly, we performed this study to define the frequency and impact of multimorbidity as measured by the CCI and to establish which components of multimorbidity most impact both survival and physical function.

PATIENTS AND METHODS

Participants were recruited from the ASCS, a prospective longitudinal study of SSc. All participants meeting 2013 American College of Rheumatology/EULAR criteria for SSc[15] recruited between 2007 and July 2024 with a definable disease subclass according to LeRoy criteria (diffuse [dcSSc] or limited SSc)[16] were included. The ASCS has been approved by all human research ethics committees at participating sites with St Vincent's Hospital Melbourne as the coordinating site (HREC-A 020/07). Written informed consent was obtained from all participants.

CCI scores were calculated at each study visit for all participants. Thirteen key comorbidities were identified and defined in accordance with the CCI (cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease [COPD] or asthma, hypertension, diabetes, ischemic heart disease [IHD], peripheral vascular disease [PVD], chronic kidney disease [CKD], rheumatic disease, malignancy, leukemia, lymphoma, or anticoagulation use; Supplementary Table S1). Data for a further seven CCI variables are not collected as part of the ASCS protocol (depression, cellulitis or skin ulcers, liver disease, peptic ulcer disease, hemiplegia, HIV/AIDS, and dementia) and were omitted from the CCI calculation in this study. The CCI was not modified to included SSc disease features (eg, pulmonary arterial hypertension [PAH] and interstitial lung disease [ILD]) to ensure this reflected general comorbidity burden rather than SSc-specific determinants. Multimorbidity was defined as a CCI score[8] ≥4, with the highest possible score in this study being 17.

Clinical Data. Health Assessment Questionnaire Disability Index (HAQ-DI) scores were collected annually at study visits. Demographic and disease data and medication usage were collected at each visit. Self-reported race was collected and grouped as White or from a racial and ethnic minority group (Asian, Black, Aboriginal or Torres Strait Islander, Hispanic, Polynesian, Middle Eastern, or other). SSc onset was defined as the first non-Raynaud phenomenon SSc manifestation, with SSc duration defined as the time from this date to ASCS recruitment. Disease manifestations were considered present if they were recorded at any time from SSc diagnosis.

The presence of IHD, diabetes, dyslipidemia, hypertension, smoking, and medication use were recorded at each visit from patient-reported history and medical record review. Upper gastrointestinal involvement was defined as the presence of symptoms (reflux, dysphagia, vomiting) or history of Barrett esophagus, esophageal stricture, dysmotility, or gastric antral vascular ectasia. Lower gastrointestinal involvement was defined as the presence of symptoms of fecal incontinence, constipation, diarrhea, or bloating or confirmation of bowel dysmotility or pseudo-obstruction. Clinical examination features were recorded by the study physician at each visit (including tendon friction rubs, synovitis, and proximal weakness on manual muscle testing [with weakness defined as scores <5/5]). All participants underwent annual transthoracic echocardiography and pulmonary function testing as screening for PAH and ILD. Right heart catheterization or high-resolution computed tomography was performed if abnormalities were detected by clinical assessment or screening investigations. PAH was defined according to the revised classification criteria[17] (mean pulmonary artery pressure [mPAP] >20 mm Hg, pulmonary vascular resistance [PVR] >2 Wood units, and a pulmonary arterial wedge pressure [PAWP] ≤15 mm Hg), or if PVR was unavailable, according to previous classification criteria (mPAP ≥ 25 mm Hg, PAWP <15 mm Hg)[18]. ILD was diagnosed in the presence of typical radiographic abnormalities on high-resolution computed tomography of the chest. Myositis was defined by a positive muscle biopsy. Raised C-reactive protein (CRP) levels were defined as values >5 IU/L. Polypharmacy was defined as the use of five or more concurrent medications recorded in the ASCS. The ASCS does not record a complete list of medications, but rather specific classes of medication (Supplementary Material S1).

Statistical analysis. Characteristics of study participants are presented as means with SDs for normally distributed continuous variables, medians with interquartile ranges (IQRs) for non-normally distributed continuous variables, and as numbers with percentages for discrete variables. Comparisons between demographic and clinical characteristics between groups were

performed using the two-sample *t*-test for normally distributed continuous variables, the Wilcoxon rank-sum test for nonnormally distributed continuous variables, and the chi-square test for discrete variables. Cox proportional hazard modeling using CCI scores as a time-varying covariate was used to evaluate the impact of multimorbidity on survival. To identify which comorbidities contributed most to prognosis, the impact of both multimorbidity and each separate CCI element were tested in separate multivariable models. All multivariable models included demographic and SSc-specific variables known to be significant predictors of mortality and morbidity that did not violate the proportional hazards assumption: age, sex, dcSSc, PAH, and ILD status. Results are reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Generalized estimating equations using an exchangeable correlation structure were used to model longitudinal data to determine the associations of multimorbidity over time. The impact of multimorbidity and each separate CCI element were assessed in these models adjusting for the key covariates identified as important in survival modeling (age, sex, dcSSc, PAH, and ILD status), with results presented as regression coefficients (RCs) and 95% CIs. Subgroup analyses were also performed examining the impact of multimorbidity and individual comorbidities on both survival and HAQ-DI scores in four subgroups with specific antibody profiles (antinuclear antibody [ANA] centromere positivity, Scl-70 positivity, RNA polymerase III positivity, and ANA positivity without an additional SSc-specific antibody). This sensitivity analysis was only performed for comorbidities that met statistical significance in the primary models and was adjusted for age, sex, PAH, and ILD status. Analysis was performed using Stata version 17.0 (StataCorp).

RESULTS

Of 2,000 included participants (Figure S1), 85% were female, 27% had dcSSc, and the median age was 47 (IQR 36–57) years (Table 1). Median SSc duration at recruitment was 7 (IQR 3–16) years, and median follow-up duration was 4 (IQR 1–9) years. Participants had median baseline CCI scores of 2 (IQR 1–2). Among the cohort overall, common comorbidities included hypertension (48%), COPD or asthma (30%), malignancy (14%), IHD (14%), diabetes (9%), PVD (9%), and cerebrovascular disease (7%). In terms of SS-specific complications, PAH was identified in 11% of patients, ILD was identified in 28% of patients, digital ulcers were identified in 53% of patients, synovitis was identified in 42% of patients, SSc renal crisis (SRC) was identified in 3.6% of patients, and myositis was identified in 2.6% of patients, and more than 80% of patients had gastrointestinal involvement.

Characteristics of multimorbidity. Multimorbidity was identified ever during follow-up in 401 participants (20%), at a median of 12 (IQR 6–21) years following SSc onset. Among those with multimorbidity, key comorbidities were hypertension (81%), dyslipidemia (67%), COPD or asthma (50%), and malignancy (49%; subtypes presented in Supplementary Table S2). IHD was present in 40% of patients, one-quarter of patients had PVD, 23% of patients had diabetes, and 19% of patients had a history of cerebrovascular disease. Left ventricular ejection fraction (LVEF) <50% occurred in 13% of patients, CKD occurred in 6% of patients, lymphoma occurred in 6% of patients, and leukemia occurred in 1% of patients.

Participants with multimorbidity had an older age at SSc onset, longer disease duration at recruitment, and longer duration of follow-up ($P < 0.01$) (Table 1). Multimorbidity was increasingly frequent in those with longer disease duration, rising in frequency from 18% of those with <7 years SSc duration at recruitment to 23% of those with SSc duration ≥7 years at recruitment (Figure S2A). The frequency of IHD, malignancy, PVD, asthma or COPD, anticoagulation, and dyslipidemia all increased with longer SSc duration at recruitment (Figure S2B).

Participants with multimorbidity were more likely to be smokers ($P = 0.01$). Participants with multimorbidity were less likely to have Scl-70 positivity ($P < 0.01$), without other differences in autoantibody profile. Multimorbid participants were also less likely to be from a racial and ethnic minority group ($P < 0.01$). There was no difference in the frequency of dcSSc between groups ($P = 0.10$). Specific SSc disease features were more common in those with multimorbidity, including PAH, ILD, SRC, and both upper and lower gastrointestinal involvement (all $P < 0.01$). Proximal weakness ($P < 0.01$) and synovitis ($P < 0.01$) were more common in those with multimorbidity, as were tendon friction rubs, although this did not meet statistical significance ($P = 0.07$). Raynaud phenomenon was more frequent in those with multimorbidity ($P = 0.03$), as only a small number of participants did not experience Raynaud phenomenon (n = 18), who tended to have ANA-negative diffuse disease with a shorter follow-up duration and did not meet criteria for multimorbidity. There was no difference in the frequency of digital ulcers between the two groups ($P = 0.93$). Raised CRP levels and anemia were more common in those with multimorbidity (both $P < 0.01$) as was the use of prednisolone ($P < 0.01$) but not nonglucocorticoid immunosuppression ($P = 0.14$). Polypharmacy and PAH treatment were more common in those with multimorbidity ($P < 0.01$).

Impact of multimorbidity on survival. In multivariable regression modeling, multimorbidity was associated with worse survival (HR 1.57, 95% CI 1.30–1.91, P <0.01) (Table 2, Supplementary Tables S3 and S4). Among CCI comorbidities, CKD had the largest impact on survival (HR 2.41, 95% CI 1.46–3.98, $P < 0.01$), followed by LVEF <50% (HR 1.76, 95% CI 1.21–2.57, $P < 0.01$), anticoagulation (HR 1.64, 95% CI 1.28–2.08, $P < 0.01$), and IHD (HR 1.45, 95% CI 1.16–1.80, $P < 0.01$). PVD (HR 1.41, 95% CI 1.04–1.93, $P = 0.03$), cerebrovascular disease (HR 1.38, 95% CI 1.01–1.90, $P = 0.04$), malignancy (HR 1.29, 95% CI 1.02–1.65, $P = 0.04$), and COPD or asthma (HR 1.21,

Table 1. Description of the Australian Scleroderma Cohort Study population*

Variable[a]	Overall cohort (N = 2,000, 100%)	Multimorbidity[b] (n = 401, 20.1%)	No multimorbidity (n = 1,599, 79.9%)	*P* value
Age at SSc onset (n = 1,871), median (interquartile range), y	47.4 (36.5–57.2)	54.3 (42.1–62.1)	45.7 (35.4–55.0)	<0.01
Male sex (n = 1,999), n (%)	292 (14.6)	66 (16.5)	226 (14.1)	0.24
Diffuse cutaneous SSc (n = 2,000), n (%)	540 (27.0)	95 (23.7)	445 (27.8)	0.10
Racial and ethnic minority group (n = 1,881), n (%)	170 (9.0)	21 (5.5)	149 (9.9)	<0.01
Disease duration at recruitment (n = 1,869), median (interquartile range), y	7.1 (2.5–15.7)	9.6 (3.1–18.0)	6.6 (2.4–15.2)	<0.01
Follow-up (n = 2,000), median (interquartile range), y	4.2 (1.3–8.5)	5.2 (2.5–9.4)	4.0 (1.1–8.3)	<0.01
Died (n = 1,995), n (%)	569 (28.5)	195 (48.6)	374 (23.5)	<0.01
Smoking[c] (n = 2,000), n (%)	999 (50.0)	223 (55.6)	776 (48.5)	0.01
BMI (highest)[c] (n = 1,941), median (interquartile range)	26.6 (23.3–30.5)	28 (24.2–32)	26.3 (23.1–30.2)	<0.01
Serology				
ANA positive (n = 1,953), n (%)	1,866 (95.5)	379 (95.0)	1,487 (95.7)	0.54
ANA centromere (n = 1,935), n (%)	895 (46.3)	194 (49.0)	701 (45.5)	0.22
Scl-70 (n = 1,902), n (%)	287 (15.1)	39 (10.1)	248 (16.4)	<0.01
RNA polymerase III (n = 1,346), n (%)	194 (14.4)	49 (16.1)	145 (13.9)	0.35
SSc manifestations				
PAH[c] (n = 2,000), n (%)	222 (11.1)	67 (16.7)	155 (9.7)	<0.01
SRC[c] (n = 2,000), n (%)	72 (3.6)	28 (7.0)	44 (2.8)	<0.01
ILD[c,d] (n = 2,000), n (%)	566 (28.3)	138 (34.4)	428 (26.8)	<0.01
MRSS (highest recorded, n = 1,948), median (interquartile range)	8 (4–16)	8 (5–16)	8 (4–16)	0.96
Upper gastrointestinal involvement[c,e] (n = 2,000), n (%)	1,771 (88.5)	370 (92.3)	1,401 (87.6)	<0.01
Lower gastrointestinal involvement[c,f] (n = 2,000), n (%)	1,622 (81.1)	351 (87.5)	1,271 (79.5)	<0.01
Myositis (biopsy-proven, n = 2,000),[c] n (%)	52 (2.6)	15 (3.7)	37 (2.3)	0.11
Proximal weakness[c,g] (n = 1,954), n (%)	431 (22.1)	134 (33.8)	297 (19.1)	<0.01
Synovitis[c] (n = 1,985), n (%)	833 (42.0)	195 (48.6)	638 (40.3)	<0.01
Raynaud's phenomenon[c] (n = 2,000), n (%)	1,982 (99.1)	401 (100.0)	1,581 (98.9)	0.03
Digital ulcers[c] (n = 2,000), n (%)	1,061 (53.0)	212 (52.9)	849 (53.1)	0.93
Tendon friction rubs (n = 1,961), n (%)	176 (9.0)	45 (11.3)	131 (8.4)	0.07
Charlson Comorbidity Index components				
IHD[c,h] (n = 1,976), n (%)	276 (14.0)	161 (40.1)	115 (7.3)	<0.01
LVEF <50%[c] (n = 1,763), n (%)	97 (5.5)	49 (13.1)	48 (3.5)	<0.01
Anticoagulation[c] (n = 2,000), n (%)	206 (10.3)	110 (27.4)	96 (6.0)	<0.01
Cerebrovascular disease[c] (n = 1,842), n (%)	120 (6.5)	76 (19.4)	44 (3.0)	<0.01
Peripheral vascular disease[c] (n = 1,439), n (%)	124 (8.6)	79 (23.7)	45 (4.1)	<0.01
Chronic kidney disease[c,i] (n = 2,000), n (%)	30 (1.5)	24 (6.0)	6 (0.4)	<0.01
Hypertension[c] (n = 1,978), n (%)	948 (47.9)	323 (80.5)	625 (39.6)	<0.01
Diabetes mellitus[c] (n = 1,851), n (%)	170 (9.2)	89 (22.7)	81 (5.6)	<0.01
COPD or asthma[c] (n = 1,978), n (%)	597 (30.2)	202 (50.4)	395 (25.0)	<0.01
Malignancy[c,j] (n = 2,000), n (%)	287 (14.3)	196 (48.9)	91 (5.7)	<0.01
Leukemia[c] (n = 2,000), n (%)	6 (0.3)	5 (1.2)	1 (0.1)	<0.01
Lymphoma[c] (n = 2,000), n (%)	26 (1.3)	24 (6.0)	2 (0.1)	<0.01
Other comorbidities				
Dyslipidemia[c] (n = 1,823), n (%)	732 (40.2)	260 (67.2)	472 (32.9)	<0.01
CRP >5 IU/L[c] (n = 1,892), n (%)	998 (52.7)	262 (65.8)	736 (49.3)	<0.01
Anemia[c,k] (n = 1,934), n (%)	765 (39.6)	220 (54.9)	545 (35.6)	<0.01
Treatment				
Prednisolone[c] (n = 2,000), n (%)	920 (46.0)	221 (55.1)	699 (43.7)	<0.01

(Continued)

Table 1. (*Cont'd*)

Variable[a]	Overall cohort (N = 2,000, 100%)	Multimorbidity[b] (n = 401, 20.1%)	No multimorbidity (n = 1,599, 79.9%)	*P* value
Nonglucocorticoid immunosuppression[c,l] (n = 2,000), n (%)	961 (48.0)	206 (51.4)	755 (47.2)	0.14
Polypharmacy[c] (n = 2,000), n (%)	903 (45.1)	314 (78.3)	589 (36.8)	<0.01
PAH treatment[c,m] (n = 2,000), n (%)	381 (19.1)	111 (27.7)	270 (16.9)	<0.01

*ANA, antinuclear antibody; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ENA, extractable nuclear antigen; IHD, ischemic heart disease; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; MRSS modified Rodnan skin thickness score; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; SRC, systemic sclerosis renal crisis.

[a]Number of variables available for analysis presented.

[b]Multimorbidity defined as Charlson Comorbidity Index scores ≥4.

[c]Denotes ever recorded from SSc onset.

[d]ILD diagnosed on high-resolution computed tomography of the chest.

[e]Upper gastrointestinal involvement defined as ever reporting reflux symptoms, Barrett esophagus, esophageal dysmotility, esophageal stricture, dysphagia, vomiting, or gastric antral vascular ectasia.

[f]Lower gastrointestinal involvement defined as ever reporting bowel dysmotility, pseudo-obstruction, fecal incontinence, constipation, diarrhea, or bloating.

[g]Proximal weakness defined as power <5/5 on physical examination.

[h]IHD defined as patient-reported ischemic chest pain or abnormal coronary angiography.

[i]Chronic kidney disease defined as history of creatinine higher than 265 umL/L, dialysis, or renal transplantation.

[j]History of malignancy, excluding nonmelanoma skin cancer as well as lymphoma and leukemia, which are presented separately.

[k]Anemia defined as hemoglobin <120 g/L.

[l]Nonglucocorticoid immunosuppression exposure defined as use of conventional synthetic or biologic immunosuppressants.

[m]Polypharmacy defined as use of ≥5 medications routinely recorded in the Australian Scleroderma Cohort Study concurrently. Note that the Australian Scleroderma Cohort Study does not record a complete list of medications, but rather specific categories/groups (abatacept, ace inhibitors [any], ambrisentan, angiotensin II receptor blockers [any], beta-blockers [any], other antiarrhythmic drugs [any], aspirin or other antiplatelets [any], azathioprine, B cell depletion including rituximab, bosentan, calcium channel antagonists [any], cisapride or other prokinetics, cyclophosphamide, cyclosporine, diuretics [any], epoprostenol, histamine receptor antagonist [any], hormone replacement therapy [any], hydroxychloroquine, leflunomide, lipid lowering therapy [any], macitentan, methotrexate, mycophenolate, nonsteroidal anti-inflammatories [any], opioids [any], warfarin, other anticoagulation [any], penicillamine, prednisolone, proton pump inhibitors [any], riociguat, selexipag, sildenafil, sitaxasen, tadalafil, tumor necrosis factor alpha inhibitors [any], tocilizumab, vitamin D supplementation).

Table 2. Impact of each element of CCI score as a time-varying covariate on death and physical function as measured by HAQ-DI score at each study visit in individual multivariable models*

	Death				HAQ-DI score			
CCI score component	N	HR	95% CI	*P* value	N	Coeff	95% CI	*P* value
Multimorbidity: CCI ≥4	9,242	1.57	1.30 to 1.91	<0.01	5,999	0.17 units	0.13 to 0.21	<0.01
CCI IHD[a]	8,644	1.45	1.16 to 1.80	<0.01	5,852	0.22 units	0.17 to 0.28	<0.01
CCI LVEF <50%	6,982	1.76	1.21 to 2.57	<0.01	4,602	0.23 units	0.14 to 0.33	0.01
CCI anticoagulation	9,242	1.64	1.28 to 2.08	<0.01	5,999	0.18 units	0.11 to 0.25	<0.01
CCI cerebrovascular disease	8,216	1.38	1.01 to 1.90	0.04	5,634	0.11 units	0.02 to 0.19	0.01
CCI peripheral vascular disease	6,677	1.41	1.04 to 1.93	0.03	4,551	0.26 units	0.18 to 0.34	<0.01
CCI chronic kidney disease[b]	9,242	2.41	1.46 to 3.98	<0.01	5,999	0.12 units	0.02 to 0.21	0.01
CCI hypertension	8,643	0.86	0.71 to 1.05	0.14	5,840	0.06 units	0.01 to 0.10	<0.01
CCI diabetes mellitus	8,540	1.08	0.80 to 1.45	0.61	5,799	0.06 units	−0.03 to 0.15	0.20
CCI COPD or asthma	8,662	1.21	1.00 to 1.48	0.05	5,863	0.19 units	0.14 to 0.23	<0.01
CCI malignancy[c]	9,242	1.29	1.02 to 1.65	0.04	5,999	0.02 units	−0.02 to 0.05	0.33
CCI leukemia	9,242	1.64	0.94 to 2.87	0.08	5,999	0.15 units	−0.08 to 0.38	0.21
CCI lymphoma	9,242	1.46	0.78 to 2.73	0.23	5,999	0.08 units	−0.01 to 0.18	0.08

*Each model is adjusted for age at each review, sex, dcSSc, PAH, and ILD status. Complete models are presented in Supplementary Tables S3 and S9. CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; Coeff, regression coefficient; HAQ-DI, Health Assessment Questionnaire Disability Index; HR, hazard ratio; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction.
[a]IHD defined as patient-reported ischemic chest pain or abnormal coronary angiography.
[b]Chronic kidney disease defined as history of creatinine higher than 265 umL/L, dialysis, or renal transplantation.
[c]History of malignancy, excluding nonmelanoma skin cancer as well as lymphoma and leukemia, which are presented separately as per CCI items.

95% CI 1.00–1.48, $P = 0.05$) were also associated with worse survival, as was leukemia, although this did not meet statistical significance (HR 1.64, 95% CI 0.94–2.87, $P = 0.08$). Hypertension, diabetes, and lymphoma were not associated with worse survival.

In a subgroup analysis, multimorbidity was associated with an adverse prognosis in subgroups with ANA centromere positivity, Scl-70 positivity, and RNA polymerase III positivity, although not in those with ANA positivity alone (Supplementary Tables S5–-S8). Cardiovascular and renal disease continued to have a dominant prognostic impact, with further detail about the impact of individual comorbidities available in the electronic supplement (Supplementary Tables S5–S8).

Impact of multimorbidity on physical function. In multivariable regression modeling examining the impact of multimorbidity at each study visit, multimorbidity was associated with a significant increase (worsening) of HAQ-DI scores (RC +0.17 units, 95% CI 0.13–0.21, $P < 0.01$) (Table 2, Supplementary Tables S9 and S10). Among the CCI comorbidities, PVD was associated with the largest impact on physical function (RC +0.26 units, 95% CI 0.18–0.34, $P < 0.01$), followed by LVEF <50% (RC +0.23 units, 95% CI 0.14–0.33, $P = 0.01$), IHD (RC +0.22 units, 95% CI 0.17–0.28, $P < 0.01$), COPD or asthma (RC +0.19 units, 95% CI 0.14–0.24, $P < 0.01$), and anticoagulation (RC +0.18 units, 95% CI 0.11–0.25, $P < 0.01$). CKD (RC +0.12 units, 95% CI 0.02–0.21, $P = 0.01$), cerebrovascular disease (RC +0.11 units, 95% CI 0.02–0.19, $P = 0.01$), and hypertension (RC 0.06 units, 95% CI 0.01–0.10, $P < 0.01$) were also associated with worse HAQ-DI scores, as was lymphoma, although this did not meet statistical significance (RC 0.08 units, 95% CI −0.01 to 0.18, $P = 0.08$). Presence of solid organ malignancy, diabetes, and leukemia had no impact on physical function.

In a subgroup analysis, multimorbidity was associated with an adverse impact on function in all autoantibody subgroups (Supplementary Tables S11–S14). Cardiovascular and PVD continued to have a dominant impact on function, with further detail about the impact of individual comorbidities available in the electronic supplement (Supplementary Tables S11–S14).

DISCUSSION

Multimorbidity was identified in 20% of patients in a large, longitudinal SSc cohort. Multimorbidity was associated with significantly poorer survival and physical function after adjusting for older age and SSc-specific features. Multimorbidity also continued to have an adverse prognostic and functional impact consistently across almost all autoantibody subgroups. To our knowledge, this is the largest study to explore multimorbidity in SSc and the only study to explore the impact of multimorbidity on patient-reported outcomes. These findings highlight the contribution of non-SSc factors to both morbidity and mortality in SSc, identifying a non-SSc–specific factor that places patients at increased risk of adverse outcomes.

It is well recognized that multimorbidity and comorbidity burden contribute to adverse outcomes in rheumatic diseases, particularly in RA. In this study, we have identified that multimorbidity is associated with a poorer prognosis independently

of age and severe cardiopulmonary disease in patients with SSc. Elsewhere, multimorbidity was also shown to be associated with higher SSc disease activity scores.[14] We identified a particular contribution of cardiac, vascular, and renal disease to increased death risk. Other studies have identified an increase in IHD in SSc[4] and suggested that cardiovascular comorbidities are similarly frequent in SSc and RA. Shared risk factors may exist for cardiac and vascular comorbidities in rheumatic diseases, including smoking and glucocorticoid exposure. In addition to its well-recognized role in the development of cardiovascular, cerebrovascular, and PVD, smoking is a risk factor for RA development and can exacerbate SSc disease features such as Raynaud phenomenon and digital ulceration.[19] Smoking cessation is important in both managing cardiovascular risk and in preventing SSc complications.[20,21] Furthermore, prednisolone exposure was identified as more frequent in those with multimorbidity in our cohort, with a relatively high frequency overall. ASCS data are collected from 2007, so this relatively high rate of prednisolone exposure ever may reflect historic prescribing practices and previous exposure or seeing non-SSc rheumatologists before referral to a subspecialist SSc center.

Although observational data suggest an increase in cardiovascular risk with glucocorticoid use in RA,[22,23] these risks are not substantiated by limited randomized controlled data,[24] potentially due to confounding by disease severity.[25] Regardless, glucocorticoid-exposed individuals are a group requiring careful cardiovascular risk factor monitoring, and guidelines recommend dose minimization when possible.[3] In RA, the importance of aggressive cardiovascular risk modification is well recognized because of the associated 50% increase in cardiovascular risk and accelerated atherosclerotic disease.[20,26] Cardiovascular risk factor modification in RA is now considered the expected standard of care.[3] Although EULAR guidelines for RA recommend that the rheumatologist monitors and initiates treatment for key cardiovascular comorbidities including hypertension and dyslipidemia, in practice, this can be difficult to prioritize in a busy outpatient clinic.[5] It has been shown that referral to a cardiology outpatient clinic in patients with RA results in a significantly higher chance of preventive treatment being initiated than patients seen in rheumatology clinics alone.[20] Increasing the visibility of multimorbidity and its impact in rheumatic diseases including SSc may help to identify those needing both monitoring and treatment. However, it is important to recognize that patients with multimorbidity face unique health care challenges and require specific configuration and integration of services to achieve optimal outcomes.[27]

A novel finding in our study was that multimorbidity was associated with poorer physical function, even accounting for age, sex, and presence of dcSSc, PAH, and ILD. Comorbidity burden has been associated with poorer physical function in inflammatory arthritis[28,29] and increased symptom burden in patients with cancer.[30] Interestingly, most factors that adversely impacted survival also impacted function, particularly PVD, CKD, IHD, LVEF <50%, and COPD or asthma. Hypertension was observed to adversely affect physical function, but not survival. The mechanism of this discrepancy is unclear. Hypertension has been associated with physical disability in general population studies without established cardiovascular disease, perhaps related to subtle or so-called preclinical cardiovascular disease that impairs physical function and exercise tolerance.[31] It may be that the prognostic impact of this preclinical cardiovascular disease is attenuated by adjustment for overt cardiovascular disease. On the other hand, malignancy contributed to poorer survival but not physical function. Although it is unsurprising that malignancy determines prognosis, in SSc, other disease features (eg, PAH) seem to have a larger effect on physical function than comorbid cancer.

A limitation of this work is that although the CCI is a well-established tool for measurement of multimorbidity, this tool was modified for application retrospectively to the ASCS database because not all variables were available for analysis. We deliberately applied the CCI in a conservative way, to avoid overestimating the frequency and impact of multimorbidity in our cohort. When clearly comparable measures were presented (eg, COPD or asthma), these were used; however, for other measures, a surrogate marker was used (eg, cardiac failure).[7] We were unable to assess the impact of comorbidities including dementia, depression, liver disease, and peptic ulcer disease because these variables are not collected in the ASCS (Supplementary Table S1). This means we have likely underestimated the frequency of multimorbidity in our cohort. However, our estimated frequency of 20% of patients having multimorbidity is similar to other studies, suggesting that multimorbidity occurs in 20% to 40% of patients with SSc depending on the definition applied.[14,32] Furthermore, the ASCS is also characterized by a degree of "survivor bias," in which more unwell individuals are less likely to survive to recruitment. However, these results are likely generalizable to an outpatient cohort of patients with chronic SSc, for whom non-SSc determinants of prognosis and function are of greatest interest.

Although we identified an association of prednisolone use with multimorbidity, we do not collect data about medication dose or formulation in the ASCS to quantify precise exposure and further explore the role prednisolone exposure may have in the accrual of comorbidities. Some of the included CCI comorbidities are also likely to have been contributed to by SSc-specific complications, particularly CKD, which was moderately correlated with SRC. However, severe SSc complications such as SRC, which can cause lasting damage, are also likely to also have serious implications for patients, including accelerated vascular disease, which may also lead to faster accrual of multimorbidity. Finally, multimorbidity was more common in those with Raynaud

phenomenon, although this manifestation was highly frequent overall (>98% of the cohort). The small number of individuals without Raynaud phenomenon tended to have diffuse disease with shorter follow-up duration, and thus this finding may reflect this shorter disease duration rather than a meaningful difference.

Multimorbidity was identified in 20% of patients in a large, longitudinal SSc cohort, with cardiovascular disease and key cardiovascular risk factors being major contributors to the frequency of multimorbidity. Multimorbidity was associated with both poorer survival and physical function, even after adjusting for severe SSc complications. Similar comorbidities determined prognosis and functional disability in our data. These data suggest a role for aggressive management of comorbid cardiac and renal disease to potentially improve outcomes in SSc.

ACKNOWLEDGMENT

Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Fairley confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

REFERENCES

1. Nunes BP, Flores TR, Mielke GI, et al. Multimorbidity and mortality in older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr 2016;67:130–138.
2. Katz J, Bartels CM. Multimorbidity in rheumatoid arthritis: literature review and future directions. Curr Rheumatol Rep 2024;26(1):24–35.
3. Drosos GC, Vedder D, Houben E, et al. EULAR recommendations for cardiovascular risk management in rheumatic and musculoskeletal diseases, including systemic lupus erythematosus and antiphospholipid syndrome. Ann Rheum Dis 2022;81(6):768–779.
4. Ngian GS, Sahhar J, Proudman SM, et al. Prevalence of coronary heart disease and cardiovascular risk factors in a national cross-sectional cohort study of systemic sclerosis. Ann Rheum Dis 2012; 71(12):1980–1983.
5. Semb AG, Ikdahl E, Wibetoe G, et al. Atherosclerotic cardiovascular disease prevention in rheumatoid arthritis. Nat Rev Rheumatol 2020; 16(7):361–379.
6. Smith SM, Wallace E, O'Dowd T, et al. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. Cochrane Database Syst Rev 2021;1(1):CD006560.
7. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–383.
8. Charlson M, Wells MT, Ullman R, et al. The Charlson comorbidity index can be used prospectively to identify patients who will incur high future costs. PLoS One 2014;9(12):e112479.
9. Kabir A, Conway DP, Ansari S, et al. Impact of multimorbidity and complex multimorbidity on healthcare utilisation in older Australian adults aged 45 years or more: a large population-based cross-sectional data linkage study. BMJ Open 2024;14(1):e078762.
10. Fairley JL, Hansen D, Burns A, et al. Contribution of left ventricular diastolic dysfunction to survival and breathlessness in systemic sclerosis-associated interstitial lung disease. J Rheumatol 2024; 51(5):495–504.
11. Fairley JL, Hansen D, Day J, et al. Proximal weakness and creatine kinase elevation in systemic sclerosis: clinical correlates, prognosis and functional implications. Semin Arthritis Rheum 2024;65:152363.
12. Fairley JL, Hansen D, Quinlivan A, et al. Frequency and implications of malnutrition in systemic sclerosis. Rheumatology (Oxford) 2025;64(3): 1251–1260.
13. Fairley JL, Hansen D, Proudman S, et al. Prognostic and functional importance of both overt and subclinical left ventricular systolic dysfunction in systemic sclerosis. Semin Arthritis Rheum 2024;66: 152443.
14. Orlandi M, Bellando-Randone S, De Angelis R, et al; SPRING-SIR (Systemic Sclerosis PRogression INvestiGation group of the Italian Society of Rheumatology) coworkers. Towards a comprehensive approach to the management and prognosis of systemic sclerosis's patients: the role of comorbidities in the SPRING-SIR registry. Eur J Intern Med 2024;130:130–136.
15. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/-European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013;65(11):2737–2747.
16. LeRoy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988; 15(2):202–205.
17. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53(1). https://doi.org/10.1183/13993003.01913-2018.
18. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol 2013;62(25 Suppl): D42–50.
19. Morrisroe K, Stevens W, Sahhar J, et al. Digital ulcers in systemic sclerosis: their epidemiology, clinical characteristics, and associated clinical and economic burden. Arthritis Res Ther 2019;21(1):299.
20. Aronov A, Kim YJ, Sweiss NJ, et al. Cardiovascular disease risk evaluation impact in patients with rheumatoid arthritis. Am J Prev Cardiol 2022;12:100380.
21. Silva C, Solanki KK, White DHN. The relationship between smoking, Raynaud's phenomenon, digital ulcers, and skin thickness in the Waikato systemic sclerosis cohort. Rheumatol Immunol Res 2022;3(2): 84–89.
22. Ajeganova S, Svensson B, Hafström I; BARFOT Study Group. Low-dose prednisolone treatment of early rheumatoid arthritis and late cardiovascular outcome and survival: 10-year follow-up of a 2-year randomised trial. BMJ Open 2014;4(4):e004259.
23. Aviña-Zubieta JA, Abrahamowicz M, De Vera MA, et al. Immediate and past cumulative effects of oral glucocorticoids on the risk of acute myocardial infarction in rheumatoid arthritis: a population-based study. Rheumatology (Oxford) 2013;52(1):68–75.
24. Boers M, Hartman L, Opris-Belinski D, et al; GLORIA Trial consortium. Low dose, add-on prednisolone in patients with rheumatoid arthritis aged 65+: the pragmatic randomised, double-blind placebo-controlled GLORIA trial. Ann Rheum Dis 2022;81(7):925–936.

25. van der Pol JA, Allaart CF, Lems W, et al. Prednisone use, disease activity and the occurrence of hyperglycaemia and diabetes in patients with early rheumatoid arthritis: a 10-year subanalysis of the BeSt study. RMD Open 2024;10(2):e004246.
26. Panopoulos S, Tektonidou M, Drosos AA, et al. Prevalence of comorbidities in systemic sclerosis versus rheumatoid arthritis: a comparative, multicenter, matched-cohort study. Arthritis Res Ther 2018; 20(1):267.
27. Farmer C, Fenu E, O'Flynn N, et al. Clinical assessment and management of multimorbidity: summary of NICE guidance. BMJ 2016;354: i4843.
28. Radner H, Smolen JS, Aletaha D. Comorbidity affects all domains of physical function and quality of life in patients with rheumatoid arthritis. Rheumatology (Oxford) 2011;50(2):381–388.
29. Lubrano E, Scriffignano S, Azuaga AB, et al. Impact of comorbidities on disease activity, patient global assessment, and function in psoriatic arthritis: a cross-sectional study. Rheumatol Ther 2020;7(4):825–836.
30. Ritchie CS, Zhao F, Patel K, et al. Association between patients' perception of the comorbidity burden and symptoms in outpatients with common solid tumors. Cancer 2017;123(19):3835–3842.
31. Pinsky JL, Branch LG, Jette AM, et al. Framingham disability study: relationship of disability to cardiovascular risk factors among persons free of diagnosed cardiovascular disease. Am J Epidemiol 1985; 122(4):644–656.
32. Makol A, Achenbach S, Hinze A, et al. Multimorbidity in systemic sclerosis: burden and trends in prevalence from an incident population-based cohort (1980-2018) [abstract]. Arthritis Rheumatol 2022;74(Suppl 9).