Mortality in the Waikato Hospital Systemic Sclerosis Cohort

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Abstract

Objective: To characterize the causes of mortality and standardised mortality ratio in a cohort of patients with Systemic Sclerosis (SSc).

Methods: A cohort of 132 patients enrolled at the Waikato Systemic Sclerosis clinic was prospectively followed from 2005 to 2016. Patient demographics, diagnoses and lab reports were used to assess risk of mortality and generate standardised mortality ratios (SMR). Survival was analysed using Kaplan-Meier methods.

Results: Of the cohort of 132 patients, 20 (15%) were deceased by the end of the study period. The median age of diagnosis and death was 52 years (range 13-86) and 71 years (range 42-87) respectively. Seventy percent of deaths were SSc related and the leading causes of death were due to pulmonary arterial hypertension (PAH), interstitial lung disease (ILD) and scleroderma renal crisis (SRC). Patients diagnosed after the age of 60, had renal or cardiac manifestations were associated with a significantly increased risk of mortality. The overall SMR was 2.59 (95% CI 1.67-4.01) and was higher in those with diffuse versus limited SSc (6.46, 95% 3.08-13.54 vs 1.93, 95% CI 1.10-3.41) and males (4.17, 95% CI 1.74-10.02 vs 2.30, 95% CI 1.39-3.81).

Conclusion: This study demonstrated an increased risk of mortality in patients with SSc relative to that of the general population. An excess in risk was observed particularly in those with diffuse SSc and in males. Renal and cardiac involvement were found to be significant indicators of mortality and reinforces the necessity of screening of screening for these complications.

Introduction

Systemic sclerosis (SSc) is a chronic heterogeneous autoimmune connective tissue disorder characterized by specific antibody production, vasculopathy and fibrosis of the skin and other internal organs. This condition is associated with higher mortality and morbidity, on account of its multisystem involvement. Pathogenesis of SSc is not completely understood and current treatments are seldom effective in preventing disease progression [1-3].

SSc is classified into two defined subsets, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) based on the extent of skin involvement. DcSSc is frequently more aggressive and involves multiple organ systems such as the lungs, heart and kidneys at an early stage [1, 4]. Major known causes of mortality in SSc include pulmonary arterial hypertension (PAH), pulmonary fibrosis (PF), scleroderma renal crisis (SRC), malabsorption and cardiomyopathy [5]. Recommendations have been made regarding appropriate screening to facilitate early detection of these complications [6-8].

Several studies have explored the mortality in SSc in various geographical areas from America, Australia, Canada, Europe, Japan, and Singapore [9-23].

We aimed to assess and analyse the predictors of mortality in our cohort of SSc patients diagnosed from 1976-2016 and followed up prospectively since 2005 in comparison with other international studies.

Methods

Data Collection

The Waikato Hospital patient database was used as the primary source for extracting data. This database was based on information that had been gathered prospectively from the Waikato Systemic Sclerosis Cohort from 2005. The clinic operates in a secondary and tertiary capacity, drawing patients from neighbouring regions. Both inpatients and out-patients with systemic sclerosis are included in the cohort. Sources of information including clinical notes, referral letters, laboratory results and admission histories were consulted. Where information was not available for referred patients from surrounding regions, clinical records were requested from their respective hospitals and practices. The date of diagnosis was defined as the date SSc was formally diagnosed and first documented in the patient's clinical notes. Whilst this was available for the majority of patients,

when unclear, laboratory results were reviewed to assess the dates of antibody testing to serve as a proxy and approximate the date of diagnosis.

Additional information was collected with the patient's consent for The European Scleroderma Trials and Research Group (EUSTAR) registry. This included demographic data and measures such as a modified Rodnan Skin Score (mRSS). Data was collected up until the 14th of December 2016, which defined the censoring date for the mortality estimates. The current study has been approved by the NZ Health and Disability Ethics Committee.

All patients fulfilled the 2013 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for systemic sclerosis [24]. Further classification into lcSSc, dcSSc and scleroderma overlap syndrome (SOS) subtypes of systemic sclerosis were made according to LeRoy's criteria [25]. Patients who exhibited features of other connective tissue disease overlapping with systemic sclerosis were classified as SOS.

Comorbidities were categorised into three groups; renal, cardiac and pulmonary manifestations. Renal comorbidities were defined as a documented diagnosis of renal failure and SRC. Cardiac comorbidities were defined as heart failure, cardiomyopathy and pericardial effusions whilst respiratory comorbidities included PAH and ILD [2].

Antibodies were detected using the EUROIMMUN Systemic Sclerosis (Nucleoli) EUROLINE (IgG) test kit, to assess for the presence of specific SSc antibodies. These included Scl-70, CENP-A, CENP-B, RP11, RP115, Fib, NOR90, Th/To, PM100, PM75, Ku, PDGFR and Ro-52 [26].

Mortality data

Mortality data was collected from the database based on the established date of death recorded from confirmed death certificates. The cause of death was identified in the patient's clinical documentation. Where uncertain, causes of death and relation to SSc were adjudicated by two consultant rheumatologists (KS & DW). A Standardised Mortality Ratio (SMR) was derived from the cohort comparing the relative rate of mortality between the study group and the general population within the study period. Annual death rates by age (5 year groups) and gender from 1976 to 2015 were provided by Statistics New Zealand. Statistics New Zealand is a government organisation tasked with the collection and management of statistical data, in areas such as the economy, society and the environment [27]. Mortality rates for 2016 were assumed to be the same as 2015. Mortality rates

for those aged 13-19 (3 patients were diagnosed at age <20 years) were assumed to be the same as those aged 20-24 and birthdays were assumed to be on the 1st of January each year.

Statistical analysis

Data was entered and analysed using Microsoft Excel and IBM SPSS Statistics version 23. Descriptive statistics were computed as mean (standard deviation) or median (range) where appropriate. Survival analysis for the cohort was completed using the Kaplan-Meier method and comparisons between groups were tested using the Log Rank test. For all statistical tests a P value of <0.05 was considered as statistically significant.

Results

Demographics

A total of 132 individuals who fulfilled the ACR/EULAR criteria for systemic sclerosis were identified and recruited for this study. The cohort consisted of 115 female patients (87%) and 17 male patients (13%). The majority of patients identified as NZ European ethnicity (n=99, 77%), followed by Other European (n=11, 39%), Māori (n=8, 6%), Indian (n=6, 5%), Asian (n=3, 2%), Tongan (n=1, 1%), and four were not identified (3%). The median age of diagnosis was 52 years (range 13-86), with the median duration of follow up being 7 years (range 0-41). Median age of first non-Raynaud phenomenon was 50 (range 20-78). A total of 1287 patient follow up years was recorded. In assessing smoking status for patients, 54 (41%) patients have smoked at least once in the past, 67 (51%) have never smoked and 11 (8%) are unaccounted for (table 1).

Diagnosis and relevant investigations

In diagnosis of specific SSc subtypes, 89 (67.4%) were diagnosed with lcSSc, 33 (25.0%) with dcSSc and 10 (7.6%) with SOS. The average maximum mRSS for patients with lcSSc was 5.53 (SD 4.25), dcSSC 17.50 (SD 11.92) and SOS 3.22 (SD 2.54). Measures were unavailable for 10 patients. Of the cohort assessed, 127 (96%), 42 (32%) and 15 (18%) tested positive for Anti-nuclear antibodies (ANA), Anti-centromere antibodies (ACA) and Anti-Scl-70 antibodies (Scl-70) respectively (table 1).

Mortality

By the end of the study period (December 14, 2016) 20 patients had died (15 female, 5 male). Based on lcSSc, dcSSc and SOS subtypes, 12 (13.5%), 7 (21.2%) and 1 (10.0%) individual(s) respectively were deceased. The median age at death was 71 years (range 42-87). The median age at death for those

with lcSSc was 70 years (range 42-87), dcSSc 71 years (range 67-87) and a single -patient with SOS passed away at the age of 69.

Sixty-one patients were found with at least one comorbidity relevant to the renal, cardiac and pulmonary systems. Of the total cohort, 11 (8.3%) had renal involvement, 17 (12.9%) had cardiac involvement and 50 (37.9%) had pulmonary involvement (table 1). Deaths were then categorised as related or unrelated to SSc: 65% of deaths recorded during the study period were SSc related. Of these, PAH was the leading cause of death (35%) followed by ILD (15%) and SRC (10%). Further SSc related deaths in the cohort occurred from factors including sepsis (5%) and severe malnutrition due to gastrointestinal involvement (5%).

Deaths unrelated to SSc included prostate cancer, metastatic melanoma, other malignancies, ischaemic heart disease (IHD), and traumatic subdural haemorrhage [2] (table 2).

Survival

An age and gender adjusted SMR was calculated for the cohort and further sub-categories according to gender and SSc subtype. The SMR for the cohort studied demonstrated a 2.59 (95% CI 1.67-4.01, p<0.001) times increased risk of mortality compared the national population (table 3). Differences were observed between the SMR of lcSSc (1.93, 95% CI 1.10-3.41) and dcSSc (6.46, 95% CI 3.08-13.54) subtypes. SMR for females (2.30, 95% CI 1.39-3.81) was lower than males (4.17 95% CI 1.74-10.02) .

Kaplan-Meier curves were also generated and the results of log rank tests were used to analyse the association between patient features and mortality within the cohort. Renal involvement (x^2=14.84, P<0.001), cardiac involvement (x^2=8.44, P=0.02), pulmonary involvement (x^2=5.63, P= 0.018), being diagnosed after the age of 60 (x^2=33.50, P<0.001) and maximum mRSS (x^2=91.48, P<0.001) showed significant effects on survival (table 3).

Discussion

This is the first study to date investigating survival in a New Zealand cohort of SSc patients. The overall SMR obtained from our cohort was 2.59, comparable to several studies in Japan (2.76), Denmark (2.90) and Canada (2.69); this was within reasonable expectations as highlighted by an international meta-analysis in 2012 observing a pooled SMR of 3.53 and another done in 2005 with SMRs ranging from 1.5 to 7.2 [10, 15, 17, 19, 23]. These results reinforce the notion that an excess risk of

mortality can be associated with SSc relative to the general population. The dcSSc demonstrated a significant difference in mortality in our patients compared to those with lcSSc, consistent with the prognosis of dcSSc and the findings of previous literature [9, 10, 15, 19, 21, 22]. In comparing SMRs for gender, no significant differences were seen between males and females, also in line with findings reported in studies such as those by Hesselstrand, Jacobsen and Scussel-Lozentti [17, 19, 20, 23]. In contrast, differences in gender have been noted in some studies whereby male gender was associated with a higher SMR. Results observed by Hashimoto and Hussein have indicated a poorer prognosis of SSc in male patients attributed to multisystem organ involvement. These findings however were inconclusive and acknowledged the potential of confounding factors unrelated to gender [10, 28]. It is worth acknowledging that these comparisons should not be overestimated due to the relatively few participants in our study resulting in wide confidence intervals. Despite the increased overall SMR in the cohort, no other sub-category showed significant differences in mortality compared to the general population.

In our study, the presence of renal, cardiac and pulmonary manifestations within the cohort were significantly associated with increased mortality as demonstrated through Kaplan-Meier analysis (table 3). In observing the distribution of comorbidities, the percentage of patients with lung involvement (38%) appeared similar to that of other studies which have reported a range of 24-50%. Cardiac involvement, observed in 24% of our patient cohort was also relatively comparable to figures reported in literature varying from 10-40%. Likewise the rates of renal comorbidities in our study (8%) were consistent with the range reported in international literature of 6-17%, in addition to uniform counts for SRC at approximately 3% (table 4) [9, 10, 13, 17, 18, 22]. With the exception of a study conducted by Ferri et al (2002) which showed lung involvement at 81% and SRC counts at 10% of the cohort, findings were otherwise relatively consistent across all studies [9-15, 17-23].

Previous studies have shown that pulmonary, renal and cardiac involvement are associated with increased mortality and poor prognosis [5, 12, 15, 21, 23]. It is possible the lack of significance shown by pulmonary involvement in our study could be attributable to various limitations of our study discussed later on.

The percentage of deceased patients in our study (15%) appeared to be in the lower ranges compared to other studies observed. Of these deaths, however, SSc related deaths (70%) was relatively similar across international cohorts (table 4) [12, 15, 23]. This was consistent with the recent meta-analysis of international studies with 27% of patients reported deceased and 64% SSc related

deaths [23]. Additionally, of the deaths in our cohort, PAH (30%) and ILD (15%) were notably the most common followed by SRC (10%) (table 3). This may be suggestive of the trends observed by Steen and Medsger: an increasing proportion of deaths due to PAH and pulmonary fibrosis (PF) with fewer SRC related deaths following advances in screening and the introduction of ACE inhibitors [5].

Several limitations of this study exist. One of the difficulties encountered in the study was in relation to the size of the cohort and implications on validity and comparability. With a total patient number of 132 with no loss of follow up, this was among the smaller studies done with relation of SSc and mortality. Nonetheless, taking into consideration the relatively small size of New Zealand's population (approximately 4.8 million), these results give a reasonable indication of population representation [29]. Accordingly, statistical methods involving the use of Kaplan-Meier curves and Cox proportional hazards models to assess mortality were limited in their power to explore associations within our cohort. Additionally, months lived with SSc from the age at diagnosis was used as a baseline measure of survival. This gives rise to an element of age dependency in our cohort when comparing results to other studies. However, the distribution of the mean age at diagnosis in international cohorts appear to be similarly clustered around 50 years and therefore use of this measure would not affect comparisons to a significant degree (table 4). It is possible that those with milder disease will not be referred for secondary or tertiary care and would not therefore form part of this cohort with SSc. However, this established clinic is recognised as local centre of excellence in the management of systemic sclerosis and it is routine practice in neighbouring centres to refer all potential cases for assessment. The demographics and patient characteristics of this cohort are consistent with other published cohorts reinforcing that this is a representative cohort.

With regards to ethnicities, New Zealand is a predominantly European country with a growing Māori, Pacific Peoples and Asian population [30]. As a consequence, analysis on potential ethnic disparities in the risk of mortality for SSc could not be achieved to a satisfactory level given the small numbers in our cohort. To improve the accuracy of our analysis, Māori and Pacific ethnic groups were combined as traditionally these groups have faced similar inequities in health outcomes [31, 32]. Results were suggestive of an earlier onset of SSc in this group which is in line with other studies who made comparisons with ethnic minorities [16]. At present, further analysis in this area was not possible given the number of patients in the study but provides an avenue for further research to pursue in later studies as our cohort continues to grow.

Conclusion

In summary, our cohort had a significantly higher rate of mortality compared to that of the general population. Those with dcSSc, renal involvement, cardiac involvement and diagnosis after the age of 60 demonstrated a marked increase in mortality within our cohort. Leading causes of death included PAH followed by ILD and SRC. Our results suggest consistent practices and management of SSc within our cohort compared to that of international studies.

In identifying these risk factors within our cohort, increased awareness, education and management of screening practices can be undertaken to reduce SSc related mortality.

Funding declaration & Conflict of interest

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Declaration: No Conflict of Interest has been declared by the authors.

Key Messages:

- Increased mortality associated with cohort.
- Significance of organ involvement supports screening practices and protocol.

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Table 1: Demographic profile of cohort

	Whole cohort (n=132)	Living (n= 112)	Deceased (n=20)
Demographics			
Females	115 (87.1)	100 (89.3)	15 (75.0)
Males	17 (12.9)	12 (10.7)	5 (25.0)
Median age (range)	63 (20-87)	61 (20-85)	71 (42-87)
Median age at diagnosis (range)	52 (13-86)	51 (13-81)	67 (86-36)
Median duration of disease (range)	7.1 (0-41)	7.7 (0-41)	2.5 (0-30)
Maximum mRSS (S.D.)	8.6 (8.9)	8.2 (8.1)	11.4 (13.5)
Subtype of SSc			
- Limited SSc	89 (67.4)	77 (68.8)	12 (60.0)
- Diffuse SSc	33 (25.0)	26 (23.2)	7 (35.0)
- Overlap	10 (7.6)	9 (8.0)	1 (5.0)
Serology ±			
- Anti-Scl-70 (n=83)	15 (18.1)	14 (16.9)	1 (6.7)
- Anti-Centromere (n=82)	42 (51.2)	39 (47.6)	3 (15.0)
- Anti-nuclear (n=130)	127 (97.7)	108 (83.1)	17 (89.5)
- RNA Pol III (n=74)	14 (18.9)	12 (16.2)	2 (10.0)
- RP 155 (n=74)	13 (18.1)	11 (14.9)	2 (10.0)
Organ involvement			
- Pulmonary	50 (37.9)	38 (10.7)	12 (60.0)
- Cardiac	17 (12.9)	9 (8.0)	8 (40.0)
- Renal	11 (8.3)	5 (4.5)	6 (30.0)
Smoking status			
Ever smoked	54 (40.9)	47 (21.4)	7 (35.0)

± Size of patient group stated in brackets (n)

Table 2: Causes of death for the 20 patients with SSc

Cause of death	Number = 20 (n%)
Related to SSc	
Pulmonary arterial hypertension	7 (35)
Interstitial lung disease	3 (15)
Scleroderma renal crisis	2 (10)
Malnutrition	1 (5)
Unrelated to SSc	
Ischemic heart disease (CAD)	1 (5)
Prostate cancer	1 (5)
Traumatic subdural haemorrhage	1 (5)
Suspected malignancy	1 (5)
Metastatic melanoma	1 (5)
Infection and dementia	1 (5)
Cervical myelopathy	1 (5)

Table 3: Survival analysis

Standardised Mortality Ratios

	Observed	Expected	SMR	95% CI
Cohort	20	7.73	2.59	1.67-4.01
lcSSc	12	6.20	1.93	1.10-3.41
dcSSc	7	1.08	6.46	3.08-13.54
SOS	1	0.44	2.27	0.11-11.19
Females	15	6.53	2.30	1.39-3.81
Males	5	1.19	4.17	1.74-10.02

Kaplan-Meier analysis

	Chi-square (Log-rank)	p value
Gender	3.5	0.061
Māori vs non-Māori	0.2	0.636
Cardiac involvement	9.7	**0.02**
Pulmonary involvement	5.6	**0.018**
Renal involvement	14.8	**<0.001**
Diagnosed after the age of 60	33.5	**<0.001**
Maximum mRSS	91.5	**<0.001**
Ever smoked	0.1	0.824
Use of any DMARD	0.2	0.596
Scl-70	0.3	0.598
ANA	2.6	0.110
ACA	0.6	0.431
RP11	0.3	0.572
RP155	1.0	0.314
Ro52	1.4	0.231
NOR90	0.2	0.632
Fib	0.2	0.682

Table 4: Comparisons of international cohorts

	(Ooi, 2017)	(Elhai, 2011)	(Ioannidis, 2005)	(Hissaria, 2011)	(Hashimoto, 2011)	(Mayes, 2003)	(Strickland, 2013)	(Vettori, 2010)	(Hesselstrand, 1998)	(Jacobsen, 1998)	(Scussel-Lonzetti, 2002)	(Ferri, 2002)	(Santosa, 2015)	(Joven, 2010)
Demographics														
Total patients	132	2691	1645	786	405	706	223	251	249	344	309	1012	349	204
Female	115 (87.1)	2230 (82.9)	1320 (80.2)	630 (80.2)	376 (92.8)	591 (83.7)	179 (87.7)	220 (87.6)	178 (71.5)	278 (81)	266 (86.1)	895 (88.5)	304 (87)	182 (89)
lcSSc	89 (67.4)	1705 (63.4)	-	501 (63.7)	273 (67.4)	460 (65.2)	164 (80.4)	200 (79.7)	186 (74.7)	226 (66)	152 (49.2)	407 (64)	122 (35)	121 (59)
dcSSc	33 (25.0)	713 (26.5)	734 (44.6)	152 (19.3)	132 (32.6)	246 (34.8)	59 (26.5)	51 (20.3)	63 (25.3)	118 (34)	29 (9.4)	89 (14)	133 (38)	62 (31)
SOS	10 (7.6)	-	-	53 (6.7)	-	-	-	-	-	-	-	-	91 (26)	21 (10)
Mean age at diagnosis (S.D.)	51.4 (15.6)	50.1	-	46.7 (16.2)	-	46.1	51.6 (8.8)	46.2 (15)	49.6 (13.8)	-	49.2 (12.7)	-	46.2 (15)	49 (17)
Median age at diagnosis (range)	52 (13-86)	(47.1-59.8)	-	-	47	-	-	-	-	-	-	-	-	-
Organ involvement														
Lung	50 (37.9)	890 (43.2)	280 (31.7)	-	204 (50.4)	-	-	-	-	-	74 (23.9)	515 (81)	-	-
- ILD	-	-	-	-	-	-	65 (32.3)	168 (66.9)	-	-	-	-	-	78 (38)
- PAH	-	-	-	40 (7.6)	65 (16.0)	-	23 (11.6)	3 (1.62)	-	-	-	-	-	31 (15)
Heart	17 (12.9)	447 (24.6)	165 (10.1)	-	79 (19.6)	-	25 (13.2)	36 (14.3)	-	-	28 (9.1)	223 (35)	-	82 (40)
Renal	11 (8.3)	-	172 (10.5)	-	-	-	-	42 (16.7)	-	-	-	-	-	12 (6)
- SRC	3 (2.3)	-	-	19 (3.6)	13 (3.2)	-	5 (2.8)	-	-	-	6 (2.0)	64 (10)	-	6 (3)
Gastrointestinal	-	-	-	-	187 (46.4)	-	187 (83.9)	188 (74.9)	-	-	-	-	-	114 (56)
Serology														
Scl-70+	15 (18.1)	337 (22.8)	315 (25.3)	47 (10.7)	82 (23.3)	39 (19.6)	33 (16.2)	90 (36.6)	-	-	37 (12)	229 (36)	-	46 (23)
ACA+	42 (51.2)	499 (33.8)	309 (22.3)	199 (49.4)	127 (36.1)	112 (22.1)	96 (47.1)	95 (38.6)	-	-	135 (43.7)	248 (39)	-	75 (38)
ANA+	127 (97.7)	-	-	-	-	482 (89.3)	-	61 (24.8)	-	-	-	127 (20)	-	187 (93)
Mortality														
SMR	2.59	3.53	1.5-7.2	1.46	2.76	-	1.34	-	4.59	2.9	2.69	-	-	-
Number of deaths	20 (15.2)	732 (27.2)	578 (35.1)	331 (42.1)	86 (21.2)	215 (30.5)	53 (23.6)	20 (8.6)	49 (19.7)	160 (46.5)	66 (21.3)	279 (27.6)	35 (10)	44 (23)
Related deaths (n% of deaths)*	13 (65.0)	-	-	-	-	-	19 (30)	12 (60.0)	15 (30.6)	41 (88.2)	35 (53)	87 (52)	20 (57.1)	36 (81.8)

*Numbers were inclusive of categories definitely SSc related and probably SSc related where applicable