Clinical characteristics and mortality rate of Thai elderly-onset systemic sclerosis

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ABSTRACT

Objective. *To identify the clinical differences and mortality rate between adult and elderly-onset systemic sclerosis (SSc).*

Methods. *We conducted a historical cohort study of SSc patients during January 2007-December 2011. The SSc patients were 60 and over classified as elderly-onset SSc. Cox regression analysis was used to estimate the probability of survival and for assessing the factors associated with mortality.*

Results. *The medical records of 350 SSc patients were reviewed; 53 (15.1%) had elderly-onset SSc. According to the multivariate analysis, elderly-onset SSc has a higher WHO functional class, more frequent weakness, more frequent hyperCKaemia, and less pulmonary fibrosis than adult-onset SSc (p=0.004, 0.02, 0.02, 0.02, respectively). The incidence of mortality was 3.8 per 100 person-year with a median survival rate of 15.9 years (95%CI 12.4-17.3). The mortality rate of elderly SSc onset was significantly higher than that of adult SSc onset (HR 5.71; 95%CI 3.54-9.20). The median survival of elderly and adult-onset SSc was 4.9 years and 16.1 years, respectively. The Cox regression analysis indicated that presence of digital ulcer and tendon friction rub had a respective HR of 7.39 (95%CI 1.28-42.60) and 37.23 (95%CI 2.10-659.09) for predicting mortality of elderly-onset SSc.*

Conclusion. *Myopathy and limitation of physical activity were frequently found among elderly-onset SSc over against pulmonary involvement than in adult-onset SSc. Mortality of elderly-onset SSc was 5.7 times higher, and median survival was 11 years shorter, than adult-onset SSc.*

Introduction

Systemic sclerosis (SSc) is a rare systemic connective tissue disease, characterised by skin tightness and fibrosis of internal organs (including the heart, lungs, oesophagus, and intestine). The age of disease onset among Caucasians is reported to be between 65 and 74 in females and over 75 in males (1), but it is between 40 and 60 years among Thais (2) - about 10 years younger than among Caucasians.

Early symptoms of SSc can also be non-specific (*i.e.* puffy hands, weight loss, and fatigue) (3). Skin tightness is a classical symptom of the disease. The tightness can progress either slowly (2) or rapidly (within a few months) of onset (4), and sometimes it can undergo regression on its own (5).

The mortality of the SSc patients who had short duration of disease particularly within 4 years of disease onset had higher mortality rate than overall SSc patients (6). The previous study found that the common cause of death was SSc related death and the renal death rate was decreased in year 2000-2009 while the pulmonary death rate was not changed when compare to 1990-1999 (7).

Poor prognostic factors for SSc include male sex (8, 9), the diffuse cutaneous SSc (dcSSc) subset (9, 10), internal organ involvement (particularly pulmonary fibrosis) (8, 9, 11), pulmonary arterial hypertension (PAH) (8, 9, 11), cardiomyopathy (9, 10, 12), and scleroderma renal crisis (SRC) (13, 14). Old age was also associated with high mortality among SSc patients (9, 11, 12, 15).

The number of elderly people is trending higher than those in the work-force age group. Since an aging population has more underlying diseases and health problems - including the need for caregivers and more medical instruments - there is a cost to the economy. A recent, large series of US Caucasian SSc cohort compared clinicals between

early and late age onset SSc and found that late onset SSc (≥65 years) had a greater risk for PAH, renal impairment, cardiac disease, and muscle weakness than in younger onset SSc (16). Another series from Europe revealed that late onset SSc (≥75 years) was associated with a higher prevalence of pulmonary hypertension (by echocardiography), cardiac involvement (conduction block, diastolic dysfunction), and limited cutaneous SSc (lcSSc) (17). Both series reported less digital ulcers but more frequent anti-centromere antibody positive in late onset than in younger onset SSc (16, 17). A comparison of the mortality rate, predictor of mortality and causes of death between late onset and younger onset SSc has, however, not been reported.

In the near future, Thailand will have a predominantly aging society. The clinical characteristics and disease outcomes in elderly-onset *versus* adult-onset SSc are of interest. There are clinical differences between Thai and Caucasian SSc, in particular the younger age at SSc onset and more dcSSc among Thais than among Caucasians; so we sought to investigate the clinical differences and clinical outcome between elderly and adult-onset Thai SSc patients. Our study objectives were (a) to identify the clinical differences between adult and elderly-onset systemic sclerosis patients and (b) to determine the mortality of adult and elderly-onset SSc patients.

Methods

We conducted a historical cohort study of SSc patients, 18 and over who were followed up at the Out-patient Unit at Srinagarind Hospital, Khon Kaen University, Thailand, between January 2006 and December 2010. The review performed included details on age, age at SSc diagnosis, sex, SSc subset, date of first detected SSc symptom, date of last follow-up or date of death, modified Rodnan skin score, internal organ involvement, baseline comorbidities, medical treatment, final status (survive or deceased), and causes of death (where relevant).

Operational definitions

A diagnosis of systemic sclerosis (SSc) was based on the 2013 ACR/EULAR Classification Criteria for Systemic Sclerosis (18). SSc is classified as the limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) subset, following the classification by LeRoy *et al*. (19).

Elderly-onset SSc was defined by age of the first SSc symptom being when the person was 60 or over, as per the definition of elderly by the United Nations. Adult-onset SSc was defined when the age of the first SSc symptom occurred when the person was under 60 (20).

Pulmonary fibrosis was confirmed when interstitial fibrosis was detected by either chest radiographic or high resolution computed tomography (HRCT) of the chest. HyperCKaemia was confirmed when the muscle enzyme (creatine phosphokinase; CK) was above 200 IU/L. Pulmonary arterial hypertension (PAH) was defined by a mean pulmonary arterial pressure ≥25 mmHg and a pulmonary capillary wedge pressure <15 mmHg from right heart catheterisation (21). Renal impairment was defined as serum creatinine (Cr) >1.4 mg/dL. Anaemia was confirmed when Hb <12.0 g/dL in females and <13.0 in males. Baseline comorbidities were defined according to the modified version of Elixhauser's Methodology (22), and included any of the following: congestive heart failure, arrhythmia, hypertension, valvular heart disease, pulmonary circulation disease, peripheral vascular disease, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, diabetes with chronic complications, hypothyroidism, renal failure, liver disease, peptic ulcer disease with bleeding, acquired immune deficiency syndrome (AIDS), lymphoma, metastatic cancer, solid tumour without metastasis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, chronic blood loss anaemia, deficiency anaemias, alcohol abuse, drug abuse, psychoses, and depression.

Statistical analysis

Clinical characteristics were categorised according to the theory being studied. Each was divided into a dichotomous or polytomous variable or a continuous variable. The differences in clinical characteristics between adult-onset and elderly-onset patients were investigated. The categorical data were tested for significance using the *Chi*-square or Fisher's exact test. The continuous data were analysed using the student *t*-test or the Wilcoxon Rank-sum as appropriate.

The mortality rate and median survival rate were described. The hazard ratio with 95%CI and *p*-value were used to evaluate the clinical characteristics with respect to the mortality rate. The variables with a *p*-value <0.10 were entered into a multiple logistic regression model or a Cox regression analysis. The backward elimination method was used for model fitting. Variables were tested for significance using the Wald X^2 statistic. All statistical tests were two-tailed. A *p*-value of <0.05 was considered to be statistically significant.

All of the data analyses were performed using STATA v. 11.2 (StataCorp., College Station, TX, USA).

Results

The study comprised 350 SSc patients; the female to male ratio was 1.8 to 1 (225 *vs*. 125). The majority (266 cases; 76%) had the dcSSc subset, while 53 patients (15.1%) had elderly-onset SSc. According to the univariate analysis, elderly-onset SSc (*vs*. adult-onset SSc) had a short duration of disease, Raynaud's phenomenon, hyperCKaemia, pulmonary fibrosis, anaemia at the onset, high WHO functional class, hand deformity, muscle weakness, and anaemia during follow-up (Table I).

According to the multivariate analysis, elderly-onset SSc had a higher WHO functional class, more frequent muscle weakness, hyperCKaemia, and less pulmonary fibrosis than adult-onset SSc (*p*=0.004, 0.02, 0.02, 0.02, respectively). Muscle weakness in elderly-onset SSc was not associated with hyperCKaemia (*p*=0.91) nor WHO functional class (*p*=0.67). Moreover, neither muscle weakness nor hyperCKaemia was significantly associated with lipid lowering agent use among sufferers of elderly-onset SSc (*p*=0.47 and 0.32, respectively).

Of the total 2,399 person-years, 90 patients died (27 of whom were elderly-

Table I. Clinical differences between adult-onset and elderly-onset SSc.

Data	Adult-onset SSc n=n297 (%)		Elderly-onset SSc n=53 (%)		*p*-value
Female	193	(65.0)	32	(60.4)	0.52
Duration of disease (years): median (IQR)	6.4	(3.4-10.0)	3.6	(2.0-5.3)	<0.001*
Diffuse cutaneous SSc	226	(76.1)	40	(75.5)	0.92
Clinical characteristics at the onset					
Functional class					0.32
I	83 of 176	(47.2)	11 of 32	(34.4)	
II	82 of 176	(46.6)	21 of 32	(65.6)	
III	9 of 176	(5.1)	0 of 32	(0)	
IV	1 of 176	(0.6)	0 of 32	(0)	
Raynaud phenomenon	198	(66.9)	28	(52.8)	0.048*
Digital ulcer	73	(24.6)	14	(26.4)	0.78
Digital gangrene	11	(3.7)	2	(3.8)	1.00
Telangiectasia	60	(20.2)	6	(11.3)	0.13
Calcinosis cutis	12	(4.0)	1	(1.9)	0.70
Salt and pepper appearance	151	(50.8)	24	(45.3)	0.46
Oedematous skin	85	(28.6)	10	(18.9)	0.14
Tendon friction rub	24	(8.1)	8	(15.1)	0.10
Hand deformity	93	(31.3)	20	(37.7)	0.36
Arthritis	36	(12.1)	5	(9.4)	0.82
Muscle weakness	17	(5.7)	6	(11.3)	0.13
Nerve entrapment	17	(5.7)	2	(3.8)	0.75
Dysphagia	111	(37.4)	20	(37.7)	0.96
GERD	98	(33.0)	15	(28.3)	0.50
Stomach involvement	80	(26.9)	14	(26.4)	0.94
Constipation	41	(13.8)	9	(17.0)	0.54
Weight loss	54	(18.2)	7	(13.2)	0.38
HyperCKaemia	19 of 295	(6.44)	8	(15.1)	0.03*
Alveolitis	41 of 295	(13.9)	9	(17.0)	0.56
Pulmonary fibrosis	77 of 296	(26.0)	5	(9.4)	0.01*
Pulmonary arterial hypertension	13 of 290	(4.5)	2 of 52	(3.9)	1.00
Anaemia	108 of 296	(36.5)	27	(50.9)	0.047*
FVC <70%predicted	25 of 53	(47.2)	4 of 4	(100)	0.11
LVEF <50%	0 of 59	(0)	0 of 7	(0)	NA
RVSP >45mmHg	5 of 48	(10.4)	1 of 4	(25)	0.40
mRSS >20 point	44	(14.8)	8	(15.1)	0.96
Clinical characteristics during follow-up					
Functional class					<0.001*
I	118 of 208	(56.7)	5 of 34	(14.7)	
II	71 of 208	(34.1)	26 of 34	(76.5)	
III	16 of 208	(7.7)	3 of 34	(8.8)	
IV	3 of 208	(1.4)	0 of 34	(0)	
Raynaud phenomenon	168	(56.6)	30	(56.6)	1.00
Digital ulcer	72	(69.6)	10	(18.9)	0.40
Digital gangrene	1	(0.34)	1	(1.89)	0.28
Telangiectasia	92	(31.0)	11	(20.8)	0.13
Calcinosis cutis	13	(4.4)	1	(1.9)	0.70
Salt and pepper appearance	113	(38.1)	17	(19.7)	0.41
Oedematous skin	24	(8.1)	4	(7.6)	1.00
Tendon friction rub	27	(9.1)	5	(9.4)	1.00
Hand deformity	116	(39.1)	12	(22.6)	0.02*
Arthritis	13	(4.4)	1	(1.9)	0.70
Muscle weakness	14	(4.7)	8	(15.1)	0.004*
Nerve entrapment	6	(2.0)	2	(3.8)	0.35
Dysphagia	91	(30.6)	20	(37.7)	0.31
GERD	95	(32.0)	18	(34.0)	0.78
Stomach involvement	41	(13.8)	8	(15.1)	0.80
Constipation	37	(12.5)	9	(17.0)	0.37
HyperCKaemia	36 of 296	(11.5)	8	(15.1)	0.46
Alveolitis	61 of 296	(20.6)	16	(30.2)	0.12
Pulmonary fibrosis	135 of 296	(45.6)	27	(50.9)	0.47
Pulmonary arterial hypertension	26 of 296	(8.8)	2	(3.8)	0.28
Anaemia	131 of 296	(44.3)	32	(60.4)	0.03*
FVC <70%predicted	8 of 16	(50)	8 of 16	(50)	0.46
LVEF <50%	0 of 10	(0)	1 of 2	(50)	0.17
RVSP >45mmHg	2 of 9	(22.2)	0 of 1	(0)	1.00
mRSS >20 point	36	(12.1)	7	(13.2)	0.82
Coexisting disease					
Diabetes mellitus	27	(9.1)	7	(13.2)	0.35
Dyslipidaemia	51	(17.2)	12	(22.6)	0.34
Essential hypertension	34	(11.5)	13	(24.5)	0.01*
Renal impairment	8	(2.7)	8	(15.1)	<0.001*
Hypothyroidism	10	(3.4)	4	(7.6)	0.15
Cardiovascular disease	19	(6.4)	5	(9.4)	0.42

SSc: systemic sclerosis; IQR: interquartile range; GERD: gastroesophageal reflux disease; FVC: forced vital capacity; LVEF: left ventricular ejection fraction; RVSP: right ventricular systolic pressure; mRSS: modified Rodnan skin score; NA: data not available; *statistically significant.

onset and 63 were adult-onset SSc) for an overall mortality rate of 3.8 per 100 person-year with a median survival rate of 15.9 years (95%CI 12.4–17.3). The mortality rate among elderly-onset SSc was 12.7 per 100 person-years while it was 2.9 per 100 person-years for adult-onset SSc. The mortality rate for elderly-onset SSc was significantly higher than for adult-onset SSc (hazard ratio 5.71 (95%CI 3.54–9.20). The respective median survival rate for adult-onset and elderly-onset SSc was 16.1 years (95%CI 14.8–23.4) and 4.9 years (95%CI 3.8–7.4).

The respective 1-, 5-, and 10-year survival rate for elderly-onset SSc was 88.7%, 47.8%, and 22.3%. While the respective 1-, 5-, and 10-year survival rate for adult-onset SSc was 97.6%, 91.5%, and 76.0%. The Kaplan-Meier survival graph comparison between elderly and adult-onset SSc is presented in Figure 1.

The mortality risk for elderly-onset according to the Cox regression analysis included (a) the presence of tendon friction rub and (b) digital ulcers at the onset hazard ratio 37.23 (95%CI 2.1-689.09) and 7.39 (95%CI 1.28-42.60), respectively (Table II). The SSc subset, severity of skin tightness, and internal organ involvement - which was associated with mortality risk in the univariate analysis - had no statistical significance in the Cox regression analysis (data not shown). Meanwhile, the mortality risk for adult-onset SSc according to the Cox regression analysis included the presence of Raynaud's phenomenon, salt and pepper skin, oedematous skin, hyperCKaemia, PAH at onset, and extensive skin tightness during follow-up (Table II).

The major cause of death in both elderly-onset and adult-onset SSc was related to the SSc itself while heart failure was the most common cause of death in both groups. The causes of death in the elderly and adult-onset SSc groups are presented in Figure 2.

Discussion

The prevalence of elderly-onset SSc among Thais was not common and in fact was lower than the prevalence in American and European cohorts; de-

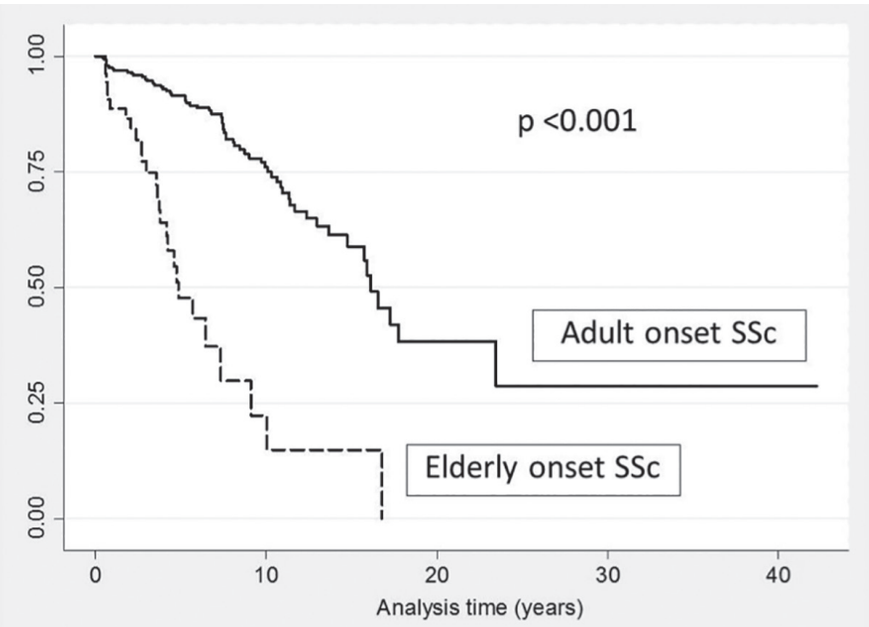

Fig. 1. Kaplan-Meier survival graph comparison between elderly and adult-onset SSc.

Table II. Cox regression analysis mortality risk in elderly and adult-onset SSc.

Data	Hazard ratio (95%CI)	
	Adult-onset SSc	Elderly-onset SSc
Female	0.48 (0.19-1.20)	-
Diffuse cutaneous SSc	0.62 (0.12-3.16)	-
Presence of anti-topoisomerase I	2.74 (0.76-9.97)	-
Clinical characteristics at the onset		
Raynaud's phenomenon	4.96 (1.90-12.93)*	-
Digital ulcer	-	7.39 (1.28-42.6)*
Digital gangrene	10.60 (0.39-288.55)	35.54 (0.15-8434.24)
Salt and pepper appearance	2.78 (1.08-7.12)*	0.62 (0.11-3.59)
Oedematous skin	4.27 (1.12-16.35)*	3.43 (0.18-64.13)
Tendon friction rub	0.66 (0.15-2.80)	37.23 (2.10-659.09)*
Hand deformity	0.80 (0.29-2.15)	-
Muscle weakness	0.82 (0.16-4.14)	-
HyperCKaemia	2.88 (1.03-8.06)*	-
Nerve entrapment	-	8.00 (0.48-134.59)
Alveolitis	1.53 (0.44-5.28)	2.96 (0.60-14.56)
Pulmonary arterial hypertension	3.98 (1.52-10.34)*	-
mRSS >20 points	0.55 (0.17-1.75)	0.14 (0.01-1.60)
Clinical characteristics during follow-up		
Raynaud phenomenon	-	5.05 (0.89-28.72)
Digital ulcer	-	2.69 (0.32-22.91)
Telangiectasia	-	3.05 (0.33-28.37)
Salt and pepper appearance	1.05 (0.40-2.77)	1.30 (0.21-8.24)
Oedematous skin	-	0.13 (0.01-1.59)
Tendon friction rub	0.38 (0.06-2.56)	-
Arthritis	2.21 (0.53-9.13)	-
Gastroesophageal reflux disease	-	1.03 (0.17-6.29)
Stomach involvement	-	5.21 (0.48-56.54)
mRSS>20	7.88 (2.26-27.53)*	4.55 (0.60-34.15)
Weight loss	1.92 (0.49-7.56)	-
Underlying disease		
Hypothyroidism	-	2.10 (0.39-11.15)
Cardiovascular disease	1.57 (0.34-7.21)	-

SSc: systemic sclerosis; mRSS: modified Rodnan skin score. *statistically significant.

spite having a cut-off age for elderly-onset SSc in our definition that was less than in other series. The low prevalence could be attributed to the epidemiology of the disease as the peak age at onset for SSc among Thais was approximately 10 years younger than among Caucasians, so it results in low number of elderly-onset SSc patients in ours.

Internal organ involvement presented equally in both elderly and adult-onset SSc in our study. This result contrasts with previous studies in which PAH and cardiac involvements presented more frequently in elderly-onset than younger onset SSc (16, 17). The result might be explained by the difference in the SSc subset. The majority of our patients had the dcSSc subset – whether elderly or adult-onset – in contrast to others series where the lcSSc subset predominated (16, 17). Owing to the higher prevalence of internal organ involvement - particularly pulmonary fibrosis and cardiac involvement in the dcSSc subset over against the lcSSc subset (23-25) - internal organ involvement occurred in our elderly and adult-onset SSc patients at the same rate. However, elderly-onset SSc patients in our series had shorter duration of disease than in adult-onset SSc, so PAH which was the late complication in SSc (26) might be underestimated in our elderly-onset SSc patients.

The reports of the features of skin involvement in elderly-onset SSc vary. A small series of elderly-onset without a control group revealed that extensive skin tightness in elderly-onset SSc patients (17). Some limited series reported mild form of disease (both skin and internal organ involvement) in elderly-onset SSc (27, 28). Our study did not confirm different skin features between elderly and adult-onset SSc. Despite of the predominance of the dcSSc subset in our patients; there was a low proportion of patients with extensive severe skin tightness but a high prevalence of internal organ involvement in both elderly and adult-onset SSc, and particularly pulmonary fibrosis. The results might reflect that the severity of skin tightness in Thai SSc is not in proportion to internal organ involvement.

Muscle weakness was commonly found among elderly-onset Thai SSc patients after adjusting the analysis for the WHO functional class, hyperCKaemia, and associated medical treatment. The finding was also revealed in other study (16). According to the structural

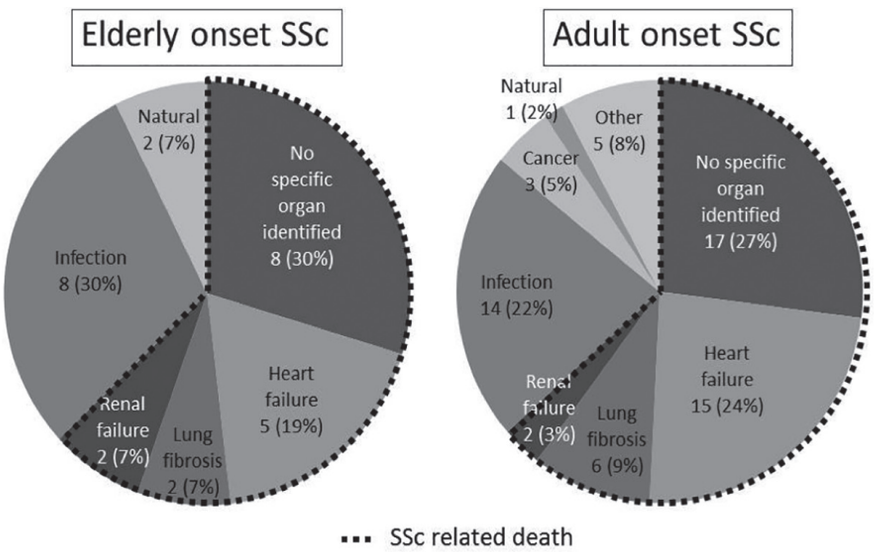

Fig. 2. Causes of death.

and physiological changing of musculoskeletal in aging, low muscle mass and decrease muscle strength with age has been reported (29). Therefore, not only elderly SSc patients but also general elderly population could have muscle weakness. As our analysis and as mentioned above, muscle weakness in elderly-onset SSc might associate with aging physiology rather than disease itself. Notwithstanding, the physician should concern and aware for unexpected fall in those elderly patients.

The mortality rate in our patients with elderly-onset SSc was 5.7 times higher than for adult-onset SSc and the median survival was 10 years less than for adult-onset SSc. Hügle *et al*. similarly found that the mortality rate for elderly-onset SSc was higher than for adult-onset SSc but that median survival was nearly equal between the two (49 *vs*. 41 months); nearly equal to the median survival for our elderly-onset SSc (17). This result might be explained by the difference in the definition of the study population. Our study included a lower age group for elderly-onset SSc than previous studies. The short median survival in our elderly-onset SSc (over against adult-onset SSc) might be related to the significantly higher number of coexisting diseases (particularly hypertension and renal impairment). Even though there was a higher mortality rate for elderly-onset SSc, the major cause of death was SSc-related death in both groups where cardiac involvement was the most common cause of death while infection was the most common non-SSc-related cause of death in both groups. According to our results, adult-onset Thai SSc patients seem to have a good prognosis over against elderly-onset Thai SSc patients but the causes of death between the two groups are not significantly different.

Digital ulcer and tendon friction rub were associated with mortality in our elderly-onset SSc patients whereas internal organ involvement was not statistically associated with mortality. Tendon friction rub (30) and older age are known to be poor prognostic factors for SSc (9, 11, 15), so it was not surprising that tendon friction rub increased mortality among patients with elderly-onset SSc. Digital ulcer is a sign of vasculopathy in SSc and it is reported to be associated with internal organ involvement and severity of the disease (31). Moreover, infection often occurs in digital ulcers (32). According to the physiology of aging and the frequent co-occurrence of diseases in the elderly (*i.e*. hypertension, diabetes mellitus) that can affect vascular health, it is possible that digital ulcers in elderly SSc would be difficult to control and thus be related to a poor prognosis. Once an elderly SSc patient has either tendon friction rub or digital ulcer, they should be closely followed-up and monitored in order to treat complications early, particularly diseases that affect vascular health.

Our study had some limitations. First, there were some missing data, so we could not provide a predictor of mortality for the missing data. Second, most of the patients had not been assessed for cause of death by autopsy, so the major cause of death was only based upon clinical data and laboratory support. Our study did, however, strengths. We compared the mortality and cause of death between elderly and adult-onset SSc and included coexisting diseases such as diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease which are commonly associated diseases among the elderly. Thus, the preliminary data may provide some baseline for evaluating elderly-onset SSc patients for better care of elderly-onset SSc patients in daily practice.

Conclusion

Myopathy and limitation of physical activity over against pulmonary involvement were frequently found among sufferers of elderly-onset SSc *vs*. adult-onset SSc. The mortality rate among elderly-onset SSc was 5.7 times higher than adult-onset SSc and median survival 11 years shorter. Digital ulcers and tendon friction rub were stronly associated with a high mortality rate in elderly-onset SSc.

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