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Differences in clinical presentation and incidence of cardiopulmonary involvement in late-onset versus early-onset systemic sclerosis: inception cohort study

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Abstract

Introduction: Data regarding the incidence rate (IR) of cardiopulmonary involvement in comparison between late-onset SSc and early-onset SSc are limited.

Objective: To compare the prevalence of clinical manifestations and the IR of cardiopulmonary involvement compared between the two subgroups.

Methods: An inception cohort of SSc patients seen at the Rheumatology Clinic, Maharaj Nakorn Chiang Mai Hospital, between January 2010 and June 2016, was used. All patients were assessed for clinical manifestations and underwent electrocardiograph, echocardiography and high-resolution computed tomography at the study entry and every 12 months thereafter.

Result: One hundred and fifteen patients (69 female and 90 diffuse cutaneous SSc [dcSSc]) with a mean (SD) disease duration of 11.6 months (8.8) at cohort entry were enrolled during a mean (SD) observation period of 3.8 years (1.6). Patients were classified into two groups: age ≥ 50 years (late onset) and age < 50 years (early onset). The late-onset group included 78 patients (67.8%). At enrollment, the late-onset group had higher prevalence of digital pitting scars (60.3% *vs*. 35.1%, $P = 0.012$), dry eye symptoms (17.9% *vs*. 2.7%, $P = 0.035$), and hypertension (20.5% *vs*. 5.4%, $P = 0.037$) compared to the early-onset group. In the last visit, it was found that the late-onset group had higher cumulative prevalence of joint contracture (61.5% *vs*. 37.8%, $P = 0.017$) compared to the early-onset group. The late-onset group had no significant IR of left ventricular ejection fraction < 50% (3.04 *vs*. 4.45 per 100 person-years, $P = 0.486$), right ventricular dysfunction (5.17 *vs*. 2.73 per 100 person-years, $P = 0.269$), interstitial lung disease (49.45 *vs*. 42.03 per 100 person-years, $P = 0.462$), and systolic pulmonary arterial pressure ≥ 50 mmHg (2.57 *vs*. 1.07 per 100 person-years, $P = 0.267$) compared to the early-onset group.

Conclusion: Our study cohort found that digital pitting scar, xerophthalmia, hypo–hyperpigmentation, joint contracture, and hypertension are more prevalent in late-onset SSc than early-onset SSc. However, no significant differences regarding the IR of cardiopulmonary involvement between the two subgroups, the majority of which were dcSSc, in the early phase of the disease.

Key words: early-onset, elderly, incidence, late-onset, systemic sclerosis.

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INTRODUCTION

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease, and its etiopathogenesis is from

endothelial injury, autoimmune-mediated inflammation and fibroblast overactivity, resulting in fibrosis of skin and visceral organs. The disease commonly occurs in the fifth decade of life, although its onset also occurs in both younger and older than the average onset age.[1] Moreover, aging has been associated with differences in the clinical presentation and the clinical course of SSc patients.[2–7] Reports from large prevalence cohort studies have determined that late-onset SSc patients have higher cumulative prevalence of heart conduction defects,[2,6] diastolic dysfunction[6] and pulmonary hypertension[2,6,8] compared to early-onset SSc patients.

Most reports that carried out a comparison between late-onset and early-onset SSc on the prevalence of clinical manifestations are from Western countries (Europe[2,4,6,7] and USA[5,8]); study populations in these reports were varied in the phase of the disease course. In addition, it has been reported that Thai SSc patients have a higher prevalence of diffuse cutaneous SSc (dcSSc) (68.6–78.0%)[9,10] than patients from Western countries (23.4–58.3%).[2,4–8] The difference seen in Thailand in the characteristics of SSc patients may affect the clinical presentation and incidence of cardiopulmonary involvement when compared to the earlier studies. Therefore, this study aimed to compare the differences in the clinical presentation and incidence rate (IR) of cardiopulmonary involvement between late-onset and early-onset Thai SSc patients, of whom the majority belonged to the dcSSc subset with a mean duration of disease of 1 year from the first non-Raynaud's phenomenon (NRP), using an inception cohort study.

PATIENTS AND METHODS

The Ethics Committee of the Faculty of Medicine, Chiang Mai University, approved the protocol of this research. This research conforms to the provisions of the World Medical Association's Declaration of Helsinki.

Study design

This was an inception cohort study.

Study population

This study cohort was recruited from the Rheumatology Clinic, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Thailand, and included all consenting, consecutive adults (≥ 18 years), consisting of early diagnosed SSc patients (disease duration ≤ 3 years from first NRP), from January 2010 to June 2016. All patients fulfilled the 1980 classification criteria of SSc[11] and/or the American College of Rheumatology/European League Against Rheumatism criteria 2013 for the classification of SSc.[12] The patients were classified as dcSSc or limited cutaneous systemic sclerosis (lcSSc) according to LeRoy and Medsger's classification criteria.[13]

Patients were excluded if they had any of the following conditions: (i) follow-up duration from study entry to last visit as less than 1 year, or (ii) any overlapping syndrome (SSc with systemic lupus erythematosus [SLE] or SSc with rheumatoid arthritis [RA]).

Clinical evaluation

At cohort entry, demographic data, first clinical presentation, clinical manifestations, underlying diseases, current medications, routine laboratory tests (complete blood count, creatinine, creatine kinase [CK], erythrocyte sedimentation rate [ESR], and prohormone of brain natriuretic peptide [Pro-BNP]), and test findings for antinuclear and anti-centromere antibodies (by immunofluorescence on Hep2 cells), and anti-topoisomerase I antibodies (enzyme-linked immunosorbent assay: ELISA) were recorded. The severity of the skin involvement was assessed by modified Rodnan skin score (mRSS).[14] All participants underwent electrocardiography (ECG), echocardiography and high-resolution computed tomography (HRCT) at study entry and annually thereafter. The ECG and echocardiography results were assessed by cardiologists (N.P.) blinded to the clinical data. The HRCT results were interpreted by an experienced thoracic radiologist (J.E.) blinded to the clinical data. The patients were seen at regular intervals of 1–3 months and they received all medical treatments as recommended by their attending rheumatologist by following the standards of care.

Complete data, including clinical manifestations and blood tests, were recorded every 6 months. At the last visit, the cumulative clinical manifestations were recorded. The survival statuses of the participants were obtained with regard to all the patients, in June 2016, either during the regular follow-up visit or by telephone call directly to the patients or their families in the cases of patients who had been referred to other hospitals or failed to follow up.

Definitions

Based on the mean ± SD value of the age at disease onset of the study population (51.4 ± 8.5 years), the patients were later classified into two groups: (i) age ≥ 50 years (late-onset group) and (ii) age < 50 years (early-onset group). Another rationale to use this

cut-off age was that usual onset age of SSc is after 50 years; therefore, the cut-off age at onset of 50 years was reasonable for subgroupings the disease onset in the real natural course of the disease. Onset of SSc is defined as the time of the first NRP attributable to SSc, including swollen skin, skin thickening, digital pitting scars, digital ulcers, or arthritis as reported by the patients. Duration of disease is calculated as the interval between the disease onset and the time at the cohort entry. Duration of follow up is calculated as the interval between the cohort entry and the time at the last follow up or death. Initial clinical characteristic is defined as the organ involvement detected at the cohort entry. Cumulative clinical characteristic is defined as the presence of organ involvement being ≥ 1 in the recorded data during the observational period. The presence of organ involvement was assessed as 'yes' or 'no' according to the following definitions.

Peripheral vascular manifestations are defined by the presence of Raynaud's phenomenon (RP), digital pitting scar, digital ulcer or telangiectasia. Digital ulcer is defined as active or healed ulceration which is present at the volar aspect of the digital pulp.

Skin manifestation is defined by the presence of hypo–hyperpigmentation. Musculoskeletal manifestations are defined by the presence of arthritis, myositis, joint contracture or tendon friction rub. Suspected myositis is when CK levels elevate to ≥ 500 IU/L in the absence of other explainable causes such as statin use or hypothyroidism. Joint contracture is defined as presence of stiffness in any joints, which decreases the range of motion and prevents full extension.

Gastrointestinal involvements are defined as the presence of gastroesophageal reflux symptoms (GERD) or dysphagia symptoms reported by the patient.

Cardiac involvements are defined by the presence of any of the following, which are detected by echocardiography, in the absence of other explainable causes: (i) pericardial effusion; (ii) left ventricular ejection fraction lower than 50% (LVEF < 50%); or (iii) right ventricular (RV) dysfunction. RV dysfunction is defined as present when the tricuspid annular plane systolic excursion (TAPSE) is less than 1.6 cm or the right ventricular annular velocity is less than 10 cm/s or the right ventricular fraction area change is less than 35%, or a localized right ventricular aneurysmal change is detected.[15] In addition, cardiac involvement is also defined as the presence of (iv) conduction alteration detected by ECG, which includes any bundle branch block, second or third degree atrioventricular block, QRSD > 120 ms, or prolonged QTc interval. Furthermore, prevalence of left ventricular diastolic dysfunction was also reported. Prior to 2016, diagnosis of diastolic dysfunction was based on the 2009 recommendations for evaluation of left ventricular diastolic dysfunction by echocardiography.[16] After that, the diagnosis was based on the 2016 recommendations for the evaluation of left ventricular diastolic function by echocardiography.[17]

Pulmonary involvement is defined by the presence of interstitial lung disease (ILD) determined by HRCT in the absence of other explainable causes; suspected pulmonary hypertension (PH) is defined as estimated systolic pulmonary arterial pressure (sPAP) being ≥ 50 mmHg at rest, with normal LVEF determined by echocardiography.[18]

Scleroderma renal crisis is defined as present if the criteria of the International Scleroderma Crisis Study Group[19] are fulfilled.

Sicca symptoms are defined as present when ocular or oral dryness is reported by the patients.

The causes of death were reviewed from the medical records. The primary causes of death of the SSc patients were determined based on the evaluation and decision of the attending rheumatologists and primary physicians.

Statistical analysis

The data are presented in percentages or as mean $\pm$ SD. For the comparison of proportions between the two groups, the chi-square test or Fisher's exact test was used. For the comparison of continuous variables between the two groups, Student's *t*-test or Mann–Whitney *U*-test was used. The time from the study entry to the first diagnosed LVEF < 50% and RV dysfunction, as well as the time from the first NRP to ILD and sPAP ≥ 50 were analyzed using the Kaplan–Meier plot. Patient data were censored when: (i) any of the first cardiopulmonary involvements were detected (LVEF < 50%, RV dysfunction, ILD or sPAP ≥ 50); and (ii) any event consisted of death, or when the end of the study was reached. Univariable analysis for the difference between late-onset and early-onset SSc regarding cumulative incidence of LVEF < 50%, RV dysfunction, ILD, and sPAP ≥ 50 used the log-rank test. The incidence rate of the cardiopulmonary involvement between the two groups was compared using Mantel–Haenszel method. *P*-values < 0.05 were considered statistically significant. Statistical analyses were performed using Stata for Windows version 13.0 (StataCorp, College Station, TX, USA).

RESULT

Demographic

Of the 115 early-SSc patients fulfilling the inclusion criteria, 69 (60%) were female and 90 (78.3%) were classified as having dcSSc. Their mean ± SD MRSS at cohort entry was 18.9 ± 10.5. Tests for anti-topoisomerase I and anti-centromere antibodies were positive in 91 (79.1%) and seven (6.1%) patients, respectively. Their mean ± SD age at disease onset was 51.4 ± 8.5 years. A total of 78 patients (67.0%) were found to have been diagnosed with SSc at age ≥ 50 years. Their mean ± SD disease duration from disease onset to study entry was 11.6 ± 8.8 months and the mean ± SD follow-up period was 3.8 ± 1.6 years. The most common initial clinical presentations were combined manifestations including RP and swollen skin or arthritis (54.8%) and the second common manifestation was RP and swollen skin (20.9%). There were patients who were initially found to have presented with swollen skin, RP, or arthritis at 18.3%, 16.5%, and 6.1%, respectively. Fourteen (12.2%) patients had no RP at first presentation.

The late-onset group had significantly higher age at disease onset (56.1 ± 4.9 *vs*. 41.7 ± 5.6, $P < 0.001$) and higher proportion of underlying hypertension (20.5% *vs*. 5.4%, $P = 0.037$) than the early-onset group. However, no differences existed between the two groups regarding gender, disease subtype, immunologic features, first clinical presentation, other underlying diseases, as well as mean ± SD disease duration and follow-up duration (data not shown).

Comparison of initial clinical characteristics between late and early onset of SSc at cohort entry

At cohort entry, the late-onset group had significantly higher proportion of digital pitting scars (60.3% *vs*. 35.1%, $P = 0.012$) and dry eye symptoms (17.9% *vs*. 2.7%, $P = 0.035$) than the early-onset group. There were no significant differences with regard to the initial clinical manifestations between the two groups with respect to involvement of other systems including skin, musculoskeletal, gastrointestinal, cardiac, pulmonary and renal (Table 1). Regarding the initial laboratory test (data not shown), the early-onset group had higher levels of hemoglobin than the late-onset group (13.0 ± 1.4 *vs*. 12.3 ± 1.6, $P = 0.016$). However, the late-onset group had higher mean ± SD levels of creatinine (0.9 ± 0.2 *vs*. 0.8 ± 0.2, $P = 0.025$), ESR (41.9 ± 29.4 *vs*. 31.2 ± 23.8, $P = 0.055$), and median [interquartile range 1, 3] of pro-BNP (172.6 [91.5, 425.1] *vs*. 73.3 [43.7, 253.5], $P = 0.002$), than the early-onset group.

In addition, regarding the initial echocardiographic data, the early-onset group had similar mean ± SD values with respect to LVEF (68.9 ± 7.9 *vs*. 66.9 ± 7.0, $P = 0.202$), TR velocity (m/s) (248.8 ± 39.2 *vs*. 235.8 ± 39.4, $P = 0.132$), sPAP (mmHg) (33.6 ± 10.0 *vs*. 29.7 ± 9.7, $P = 0.089$), and deceleration time (seconds) (0.22 ± 0.05 *vs*. 0.21 ± 0.04, $P = 0.191$), compared with the early-onset group. The late-onset group had lower mean ± SD value of mitral E/A ratio than the late-onset group (0.97 ± 0.26 *vs*. 1.24 ± 0.37, $P < 0.01$). However, the prevalence of left ventricular diastolic dysfunction was comparable in both groups (53.8% *vs*. 37.8%, $P = 0.109$), although the late-onset group tended to have a higher proportion.

Comparison of cumulative clinical manifestations between late onset and early onset of SSc at the last visit

At the last visit, with a mean (SD) observation period of 3.8 years (1.6), the late-onset subgroup also had a higher proportion of cumulative clinical manifestations consisting of hypo–hyperpigmentation ((97.4% *vs*. 81.1%, $P = 0.005$) and joint contracture (61.5% *vs*. 37.8%, $P = 0.017$) than the early-onset group. No significant differences in symptoms regarding the cumulative clinical manifestations between the two groups with respect to other systems including peripheral vascular, gastrointestinal, cardiopulmonary, renal and sicca were observed (Table 2).

Cardiopulmonary outcomes

After the cohort entry, with a mean observational period of 4 years, there were 14 patients (12.2%) who developed LVEF < 50%, 17 (14.8%) who developed RV dysfunction, 10 (8.7%) who developed ILD, and five patients (4.3%) with sPAP ≥ 50. Six patients (7.7%) died, all in the late-onset group. Two out of six deceased patients died because of pulmonary hypertension (one was determined by right heart catheterization and one was determined by echocardiography: sPAP 69 mmHg) with severe right ventricular dysfunction. One patient died from non-ischemic cardiomyopathy determined by echocardiography and left heart catheterization. There was one patient each who died from *Klebsiella* pneumonia, small bowel volvulus and intracerebral hemorrhage. No statistical differences regarding the mentioned outcomes were observed between the two

groups, either beginning from the study entry (Fig. 1) or from the first NRP (data not shown).

Cumulative incidence of LVEF < 50%

Over the observational time, the cumulative incidence of LVEF < 50% complications from the study entry were comparable between the late-onset and the early-onset groups ($P = 0.500$) (Fig. 2). In addition, the incidence rate of LVEF < 50% complications showed no significant statistical difference between the late-onset group and the early-onset group (3.04 per 100 person-years *vs*. 4.45 per 100 person-years, $P = 0.486$.

Cumulative incidence of RV dysfunction

Over the observational time, the cumulative incidence of RV dysfunction complications from the study entry showed no statistically significant difference between the late-onset and the early-onset groups ($P = 0.224$) (Fig. 3). In addition, the incidence rate of RV dysfunction complication showed no significant statistical difference between the late-onset group and the early-onset group (5.17 per 100 person-years *vs*. 2.73 per 100 person-years, $P = 0.269$.

Cumulative incidence of ILD

Similar high cumulative incidence of ILD complications from NRP were observed in the late-onset and the early-onset groups over the observational time ($P = 0.366$) (Fig. 4). In addition, the incidence rate of ILD complications showed no significant statistical difference between the late-onset group and the early-onset group (49.45 per 100 person-years *vs*. 42.03 per 100 person-years, $P = 0.462$.

Cumulative incidence of sPAP ≥ 50

The cumulative incidence of sPAP ≥ 50 from NRP was similar between the late-onset and the early-onset

Table 1 Comparison of initial clinical characteristics between late and early-onset of SSc at cohort entry

Clinical manifestation at entry	Late onset ($N = 78$)	Early onset ($N = 37$)	*P*-value
Peripheral vascular manifestation			
Raynaud's phenomenon	70 (89.7)	32 (86.5)	0.310
Digital pitting scar	47 (60.3)	13 (35.1)	**0.012**
Digital ulcer	7 (9.0)	3 (8.1)	1.000
Telangiectasia	24 (30.8)	10 (27.0)	0.681
Skin manifestation			
Hypo–hyperpigmentation	61 (78.2)	23 (62.2)	0.070
Musculoskeletal manifestation			
Arthritis	19 (24.4)	12 (32.4)	0.362
Joint contracture	37 (47.4)	16 (43.2)	0.673
Tendon friction rub	11 (14.1)	1 (2.7)	0.100
Suspected myositis	13 (16.7)	6 (16.2)	0.952
Gastrointestinal involvement			
Gastroesophageal reflux	32 (41.0)	16 (43.2)	0.822
Dysphagia	18 (23.1)	11 (29.7)	0.443
Cardiac involvement			
Conduction alteration	11 (14.1)	3 (8.1)	0.543
Pericardial effusion	4 (5.1)	1 (2.7)	1.000
LVEF < 50%	2 (2.6)	0	1.000
RV dysfunction	4 (5.1)	0	0.304
Pulmonary involvement			
ILD	59 (75.6)	28 (75.7)	0.997
sPAP ≥ 50 mmHg	5 (6.4)	1 (2.7)	0.662
Scleroderma renal crisis	0	0	
Sicca symptom			
Dry eyes	14 (17.9)	1 (2.7)	**0.035**
Dry mouth	27 (34.6)	9 (24.3)	0.266

P-values in bold are statistically significant. The data are presented as *n* (%). ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; RV, right ventricular; sPAP, estimated systolic pulmonary artery pressure; SSc, systemic sclerosis.

Table 2 Comparison of cumulative clinical manifestations between late and early onset of SSc at the last visit

Cumulative clinical manifestation	Late onset (N = 78)	Early onset (N = 37)	P-value
Peripheral vascular manifestation			
Raynaud's phenomenon	77 (98.7)	36 (97.3)	0.542
Digital pitting scar	65 (83.3)	27 (73.0)	0.194
Digital ulcer	29 (37.2)	12 (32.4)	0.620
Telangiectasia	63 (80.8)	28 (75.7)	0.530
Skin manifestation			
Hypo–hyperpigmentation	76 (97.4)	30 (81.1)	**0.005**
Musculoskeletal manifestation			
Arthritis	33 (42.3)	17 (45.9)	0.713
Joint contracture	48 (61.5)	14 (37.8)	**0.017**
Tendon friction rub	24 (30.8)	8 (21.6)	0.307
Suspected myositis	12 (15.4)	8 (21.6)	0.410
Gastrointestinal involvement			
Gastroesophageal reflux	66 (84.6)	35 (94.6)	0.220
Dysphagia	40 (51.3)	18 (48.6)	0.792
Cardiac involvement			
Conduction alteration	16 (20.5)	8 (21.6)	0.891
Pericardial effusion	4 (5.1)	0	0.304
LVEF < 50%	10 (12.8)	6 (16.2)	0.623
RV dysfunction	17 (21.8)	4 (10.8)	0.154
Pulmonary involvement			
ILD	66 (84.6)	31 (83.8)	0.909
sPAP ≥ 50 mmHg	9 (11.5)	2 (5.4)	0.499
Scleroderma renal crisis	0	0	
Sicca symptom			
Dry eyes	47 (60.3)	16 (43.2)	0.087
Dry mouth	43 (55.1)	14 (37.8)	0.083

P-values in bold are statistically significant. The data are presented as *n* (%). ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; RV, right ventricular; sPAP, estimated systolic pulmonary artery pressure; SSc, systemic sclerosis.

groups over the observation time (P = 0.248) (Fig. 5). In addition, the incidence rate of sPAP ≥ 50 showed no significant statistical difference between the late-onset group and the early-onset group (2.57 per 100 person-years *vs*. 1.07 per 100 person-years, P = 0.267.

DISCUSSION

This is the first inception cohort study of early SSc patients reported in theliterature to have determined the differences in the clinical presentation and

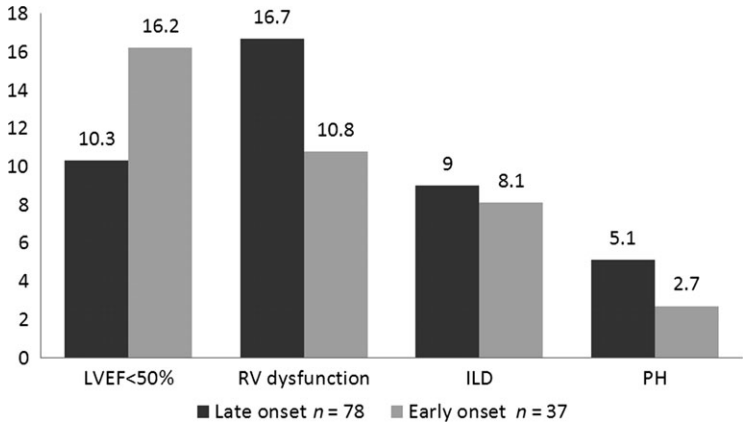

Figure 1 The cardiopulmonary outcome.

incidence of cardiopulmonary involvement in a comparison between late-onset and early-onset SSc. Prior reports are prevalence cohort studies in design which included participants with a variety of disease durations.[2,4,6,8] The population cohort in this study was homogeneous in the early phase of the disease, with mean disease duration from the first NRP of 1 year. Patients who were diagnosed with SSc after the age of 50 years (late onset) accounted for 67.0% of all the study population. However, this study's cut-off for defining late-onset SSc (50 years) is lower than the cut-off of 60–75 years used in the prior studies.[2,4–8]

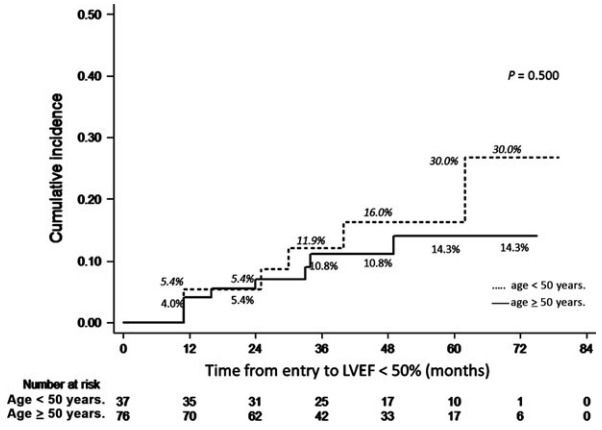

Figure 2 The cumulative incidence of left ventricular ejection fraction < 50% (LVEF < 50%) in early systemic sclerosis (SSc) patients, with late onset compared with early onset. The *P*-value was from the log-rank test.

Sixty percent of this study's participants were female, which is lower than the 83–91.2% reported in Western studies.[2,4–8] This study found a higher proportion of women than man in the late-onset SSc, which is similar to the findings of prior studies.[2,5–8] Furthermore, 78.3% of this study's population was found to belong to the dcSSc subtype, similar to previous studies from Thailand,[9,10] which is higher than the range of 23.4–58.3% reported by Western studies.[2,4–8] Regarding SSc subsets, it was found that the dcSSc subset was predominantly comparable between late-onset and early-onset SSc. Contrarily, Alba *et al.*[2] reported that lcSSc is the more frequent subtype in late-onset SSc. The discrepancy of the result may be attributable to the different study populations and genetic backgrounds.

In this study, the most common first clinical manifestation of the disease was combined manifestation consisting of RP and swollen skin or arthritis (54.8%), which was the same in both late-onset and early-onset SSc. In contrast, some studies[2,7] in which the majority of participants belonged to the lcSSc subset reported that RP was the most common (83.8–98.5%) initial manifestation of the disease. Only 16.5% of this report's patients had only RP as the initial presentation. Higher prevalence of the early phase of the dcSSc subset in this study's population may be the possible explanation for the differences in the first manifestation of the disease, since in dcSSc there is more rapid progression of the disease.

At the cohort entry, more prevalence of hypertension was found in late-onset SSc, similar to the reports of Alba *et al.*[2] and Hügle *et al.*[6] Further, concordant with

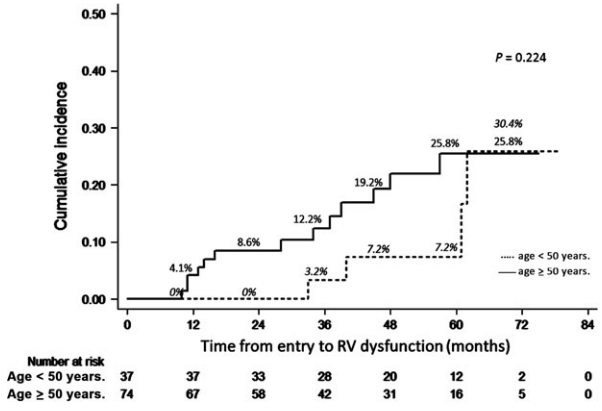

Figure 3 The cumulative incidence of right ventricular (RV) dysfunction in early systemic sclerosis (SSc) patients, with late onset compared with early onset. The *P*-value was from the log-rank test.

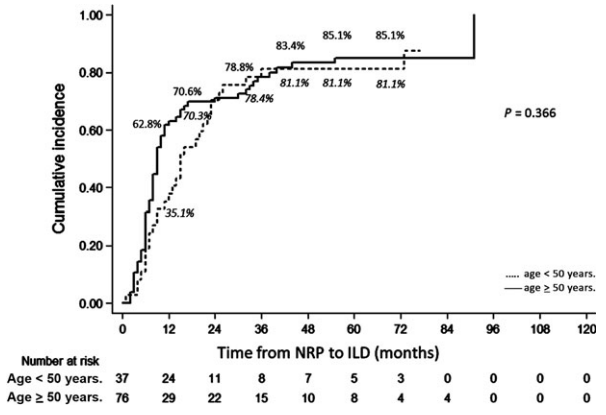

Figure 4 The cumulative incidence of interstitial lung disease (ILD) in early systemic sclerosis (SSc) patients, with late onset compared with early onset. The *P*-value was from the log-rank test.

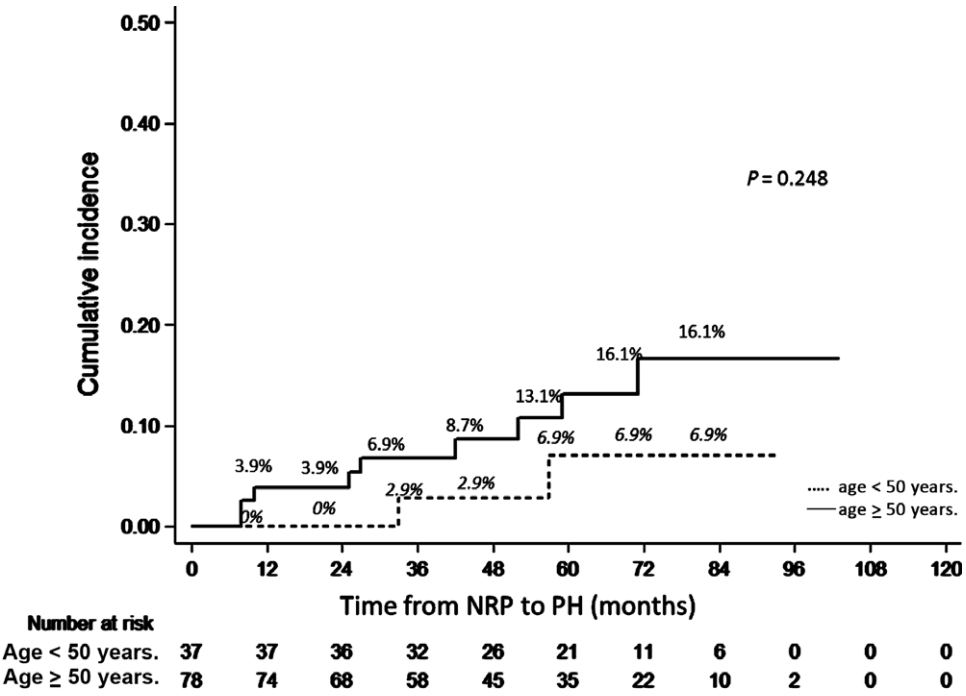

Figure 5 The cumulative incidence of estimated systolic pulmonary artery pressure (sPAP) ≥ 50 mmHg (pulmonary hyperstension) in early systemic sclerosis (SSc) patients, with late onset compared with early onset. The *P*-value was from the log-rank test.

Pérez-Bocanegra *et al.*'s[7] report, dry eye symptoms were observed in this study as well to be more prevalent in late-onset SSc. The physiologic change in the elderly and the high prevalence of some diseases in elderly patients, such as hypertension, xerophthalmia and xerostomia[20] could be attributed to the differences between the two subgroups. In addition, based on the finding regarding the late-onset group, there is higher proportion of digital pitting scars, but not digital ulcers. Contrarily, some prior studies reported higher cumulative prevalence of digital ulcers[2,6] and digital ischemia[8] in early-onset SSc. The explanation for this discrepancy might be due to the fact that the majority of their participants[2,6,8] belonged to the lcSSc subset in the late phase of the disease. However, data obtained through inception cohort studies regarding prevalence of organ involvement at study entry are limited.

At the last visit, during the mean observational period of 3.8 years, there were some differences in organ involvement as regards the late-onset group, which consisted of higher cumulative prevalence of skin hypo–hyperpigmentation and joint contracture. Nevertheless, there has been no prior study to directly support these findings; however, Czirjak *et al.*[4] found that the majority of late-onset SSc showed rapid disease course, which is in agreement with this report. Further, regarding cumulative prevalence of internal organ involvement, no significant differences were observed between the late-onset group and the early-onset group in this study's cohort. Contrarily, cardiac involvement consisting of conduction defect[2,6,7] and diastolic dysfunction,[6] as well as pulmonary involvement consisting of PH[2,5–8] and ILD[5,7] were reported as having more prevalence in late-onset SSc. In addition, some studies have reported high prevalence of esophageal involvement[2,7] and myositis[2,7] in early-onset SSc. The discrepancies regarding the prevalence of organ involvement between late-onset SSc and early-onset SSc might be explained as having arisen from differences in study design, study population, cut-off age for defining late-onset, and definition of organ involvement as well as follow-up duration, as summarized in Table 3. This report's cohort comprised the early phase of SSc patients with short durations of follow-up, as well as use of a younger cut-off age for defining late-onset SSc (50 years) compared to the other studies (60–75 years).[2,4–8] Further inception cohort studies with large sample sizes and different cut-off ages defining late-onset are needed to confirm the findings of this study.

Table 3 Clinical manifestation comparing early versus late-onset SSc in this study and other selected studies

References	Publication year	Study design	Number (total/ late-onset)	Mean age at onset (years)	Cut-off for defining late-onset (years)	Female (%)	dcSSc (%)	Mean disease duration (years)	Mean follow-up duration (years)	Most common first manifestation	Higher cumulative clinical prevalence in late-onset SSc	Higher cumulative clinical prevalence in early-onset SSc
This study	2017	Inception cohort	115/78	56.1 (L) 41.7 (E)	≥ 50	60	78.3	11.6 months	3.8	RP and swollen skin (20.9%)	-Initial visit: digital pitting scar, hypertension, higher ESR, BNP, creatinine, anemia -Last visit: skin hypo-hyperpigmentation, joint contracture	
Alba *et al.*[2] (Spain)	2014	Prevalence cohort	1037/191	45	≤ 30 31–59 ≥ 60	88	26.1	—	5.2	RP (83.8%)	lcSSc, heart conduction defect, hypertension, sPAP > 40 mmHg	Digital ulcer, esophageal involvement, myositis
Manno *et al.*[8] (USA)	2011	Prevalence cohort	2300/216	45.5	≥ 65	83	37	2 (L) 6 (E)	4 (L) 5 (E)	—	Muscle weakness, renal impairment, cardiac disease, higher cumulative incidence of PH at 5 years	Digital ischemia
HÜgle *et al.*[6] (EUSTAR)	2011	Prevalence cohort	8554/123	78 (L) 45 (E)	≥ 75	86	17.8 (L) 32.5 (E)	30 (L) 75 (E) months	—	—	Conduction block, diastolic dysfunction, PH, hypertension, elevated acute phase reactant	Digital ulcer
Pérez-Bocanegra *et al.*[7] (Spain)	2010	Retrospective	319/67	71.7	≥ 65	91	7.5 (L) 23.4 (E)	6.9 (L) 11 (E)	13.2 (L) 17.7 (E)	RP (L 98.5% E 90.5%)	ILD, PAH, cardiac, conduction defect, sicca syndrome, death	Esophageal involvement
Derk *et al.*[5] (USA)	2006	Case (late-onset)–control (c)	36 (L) 12 (c)	77.5 (L) 43.3 (c)	> 75 (L) < 60 (c)	83.3	58.3	—	3	—	Pulmonary involvement, higher ESR, malignancy, death	
Czirja'k *et al.*[4] (Hungary)	1992	Prevalence cohort	114/9	72.2 (L) 49.3 (E)	> 60	91.2	29.8	10.7	5.1	—	Similar to early-onset, but majority of late-onset SSc showed rapid disease course	

BNP, brain natriuretic peptide; dcSSc, diffuse cutaneous systemic sclerosis; E, early-onset SSc; ESR, erythrocyte sedimentation rate; ILD, interstitial lung disease; L, late-onset SSc; lcSSc, limited cutaneous SSc; PAH, pulmonary artery hypertension; PH, pulmonary hypertension; RP, Raynaud's phenomenon; sPAP, estimated systolic pulmonary artery pressure.

Regarding incidence rate of cardiopulmonary involvement, in this study it was found that there was low incidence rate of LVEF < 50% (3.04 per 100 person-years *vs*. 4.45 per 100 person-years), RV dysfunction (5.17 per 100 person-years *vs*. 2.73 per 100 person-years), and sPAP ≥ 50 mmHg (2.57 per 100 person-years *vs*. 1.07 per 100 person-years), and the late-onset group and the early-onset group were similar in this case. Contrarily, Manno *et al.*[8] reported higher cumulative incidence of sPAP ≥ 50 in late-onset SSc, using a prevalence cohort study with a mean follow-up duration of 5 years. However, similar high incidence rates of ILD (49.45 per 100 person-years *vs*. 42.03 per 100 person-years) were observed in the late-onset group and the early-onset group, which is concordant with the high prevalence of positive anti-Scl 70 in the two subgroups (83.3% *vs*. 70.3%). To the authors' knowledge, data regarding the incidence rate of cardiopulmonary involvement that carries out a comparison between late-onset SSc and early-onset SSc are limited.

The main limitations of this study include the small sample size of early-SSc patients; as a tertiary referral SSc center for northern Thailand, most patients had severe organ-based complications and high frequency of dcSSc. With a mean follow-up period of 4 years from the study entry; therefore, the findings of this study should be interpreted with caution because of the short duration of the follow-up period. Also, it should be taken into consideration that the researchers abstained from including early immunosuppressive treatment in the analysis due to the potential for bias in an observational study, the effect of which is that it may skew the real incidence rate of organ involvement. Another major limitation is that PH was not determined by right heart catheterization.

This study has several strengths. This is the first inception cohort study of early-SSc patients with mean disease duration of 1 year from first NRP to determine the difference in the clinical manifestations and incidence rate of cardiopulmonary involvement in a comparison between late-onset and early-onset SSc. In addition, single-center assessment with a limited number of investigators and uniform clinical and radiologic assessment were also strengths in this study.

CONCLUSION

Our study cohort found that digital pitting scars, xerophthalmia, hypo–hyperpigmentation, joint contracture and hypertension are more prevalent in late-onset SSc than early-onset SSc. However, no significant differences regarding the incidence rates of LVEF < 50%, RV dysfunction, ILD and sPAP ≥ 50 between the two subgroups, the majority of whom were dcSSc, were noted in the early phase of the disease.

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DISCLOSURES

All authors declare no conflicts of interest.

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