Rapid skin thickness progression rate is associated with high incidence rate of cardiopulmonary complications in patients with early diffuse cutaneous systemic sclerosis: inception cohort study

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ABSTRACT

Objective. *We aimed to investigate patients with early diffuse cutaneous systemic sclerosis (dcSSc) with regard to: 1. the association between skin thickness progression rate (STPR) at baseline visit and incidence rate of cardiopulmonary complications; 2. comparison of the mortality rate between patients with skin improvers and those with skin non-improvers.*

Methods. *An inception cohort of early dcSSc patients seen at the Rheumatology Clinic, Maharaj Nakorn Chiang Mai Hospital, Thailand, was selected. All patients were assessed for clinical manifestations, and modified Rodnan skin score (mRSS) and underwent echocardiography, and HRCT at study entry and then annually.*

Results. *One hundred and four dcSSc patients (57 of whom were females and 91 anti-topoisomerase I-positive) with a mean disease duration of 11.1±8.6 months were enrolled. Forty-two patients had rapid STPR [RPsp], 38 intermediate STPR [IMsp] and 24 slow STPR [SLsp]. At enrolment, the RPsp group had a significantly shorter disease duration, more prevalent anti-topoisomerase-I-positive, higher mRSS, more prevalent creatine kinase≥500 IU/L and higher NT-proBNP levels compared to the IMSp and SLsp groups. During a mean observation period of 4.5±2.0 years, the RPsp group had a significantly higher incidence rate of LVEF< 50% (6.06 vs. 0 per 100 person-years, p=<0.01) and interstitial lung disease (ILD) (69.69 vs. 34.66 per 100 person-years, p=0.012) than the SLsp group. Skin non-improvers had a significantly higher mortality rate than skin improvers (28.6% vs. 5.8 %, p= 0.004).*

Conclusion. *In this early dcSSc study cohort it was found that skin change determined by STPR at the baseline visit was a useful surrogate marker for cardiac and ILD complications. It was also found that skin improvers assessed 1-year later were a useful surrogate marker of mortality.*

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease in which the aetiopathogenesis originates from vascular injury, autoimmunity and fibroblast dysregulation, resulting in widespread obliterative vasculopathy and inflammation, later turning into fibrosis of the skin and internal organs. Skin thickening is a hallmark of SSc which can be used to categorise the disease population into two major groups, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the maximum extent of skin involvement (1). Patients with dcSSc have more rapid skin thickening, more severe internal organ complications, and also a higher mortality rate than those with lcSSc (2).

Several observational studies have been carried out in Western countries regarding the association between changes in skin thickening score determined by modified Rodnan skin score (mRSS) (3) and internal organ complications and mortality, using a variety of definitions of skin changes. In 2001, in a prospective cohort study, Steen *et al*. studied 278 early-dcSSc patients reporting that patients in a skin improved group categorised by a reduction in their skin score of at least 5 units per year and a >25% overall improvement from their initial or peak skin score had an association with improved survival. However, there were no differences with regard to occurrence of internal organ involvements (4). In 2007, in a retro-

spective cohort study, Shand *et al*. studied 225 early-dcSSc cases and found that patients who had a high baseline skin score with little improvement during follow up had the lowest survival; however, sustained severe skin disease did not predict the burden of internal organ involvement (5). Contrarily, in 2011, in an inception cohort study, Domsic *et al*. studied 826 early-dcSSc cases and reported that in patients with a rapid skin thickness progression rate (rapid STPR) there were found to be independent risk factors of mortality and renal crisis (6). In 2019, using the EUSTAR database, Wu *et al*. studied 1021 dcSSc cases and found that progressive skin fibrosis within 1 year was associated with decline in lung function and a lower survival rate (7). In 2019, in an inception cohort study, Zheng *et al*. studied 154 early-dcSSc cases which showed that patients classed as skin improvers showed a correlation with improved Medsger disease activity score, physician global assessment, and quality of life and function (8). Both reports by Wu *et al*. and Zheng *et al*. supported skin change determined by mRSS as a surrogate marker for dcSSc (7, 8).

In Thailand approximately 70–80% of SSc patients are the dcSSc subtype with anti-topoisomerase I antibody-positive (9-11), a cohort in which there was a high incidence of interstitial lung disease (ILD) (9). It has also been shown that cardiac involvement is the main SSc-related cause of death in Thai patients with early-SSc (12), which is a challenging problem for our country. Our hypothesis was that skin thickness change at the baseline and one-year visits can be used as a surrogate marker for the development of cardiopulmonary involvement as well as high mortality in early-dcSSc.

We therefore aimed to investigate Thai patients with an early-diagnosis of dcSSc with regard to: (1) the association between skin thickness progression rate (STPR) at baseline visit, the incidence rate of cardiopulmonary complications, specifically a left ventricular ejection (LVEF) less than 50%, ILD and suspected pulmonary hypertension (PH); (2) comparison of the mortality rate between patients classed as skin improvers and those as skin non-improvers at a 1-year follow-up visit, using an inception cohort study.

Material and methods

Patients

This study was a sub-study of the inception cohort study of natural history of Northern Thai patients with early-diagnosed SSc patients conducted at the Rheumatology Clinic, Maharaj Nakorn Chiang Mai Hospital, Thailand, between January 2010 and December 2017. All consecutive adult (≥18 years) SSc patients with a disease duration of less than 3 years from the first non-Raynaud's phenomenon (NRP) contributing to SSc were enrolled. All patients fulfilled the 1980 classification criteria of SSc (13) and/or the ACR/EULAR criteria 2013 for the classification of SSc (14). Exclusion criteria were: (i) SSc with an overlapping syndrome (SSc with systemic lupus erythematosus (SLE) or SSc with rheumatoid arthritis); and (ii) patients with follow-up duration less than 1 year.

Clinical and laboratory assessment

All patients had an initial visit with an evaluation of clinical manifestations, physical examination, laboratory testing including serum creatine kinase (CK) and N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP) levels and a serologic test including testing for anti-nuclear and anti-centromere antibodies (by immunofluorescence on Hep2 cells), anti- topoisomerase-I antibodies (enzyme-linked immunosorbent assay; ELISA). Skin involvement was assessed by an experienced rheumatologist (SW) using a modified Rodnan skin score (mRSS) (15) and patients were classified as diffuse cutaneous SSc (dcSSc) or limited cutaneous SSc (lcSSc) according to LeRoy and Medsger's classification criteria (16).

All participants underwent echocardiography, and high-resolution computed tomography (HRCT) at enrolment and annually thereafter. Echocardiographic data were reviewed by an experienced cardiologist (N.P.) and HRCT findings were reviewed by an experienced thoracic radiologist (J.E.). Patients were visited regularly every 1–3 months based on their disease activity and received medication as recommended by the attending rheumatologists following the prescribed standard of care. Complete data were recorded every 6 months. The survival status of the patients was recorded for all patients in December 2017, either during the regular follow-up visit or by additional direct contact to the patients or their families in the case of patients who had been referred to other hospitals or were lost to follow-up. For more details of the study cohort please refer to our previous article (12).

This study was conducted in accordance with the declaration of Helsinki and was approved by the Research Ethics Committee of Chiang Mai University (study code MED-2561-05577). All patients provided written informed consent at study entry.

Definitions

The onset of SSc was defined as the time of the first NRP attributed to SSc manifestation as reported by the patient. Disease duration was the interval between the disease onset and the study entry. Follow-up duration was the interval between the cohort entry and the time of the last follow-up or death. The presence of organ involvement was defined as previously published with regard to digital ulceration, left ventricular diastolic dysfunction, or gastrointestinal, musculoskeletal, and renal involvement (17). Interstitial lung disease (ILD) was determined by HRCT. Suspected pulmonary hypertension (PH) was defined as presence of (i) peak tricuspid velocity ≥3.4 m/s or (ii) peak tricuspid velocity ≥2.9 m/s concomitant with the presence of at least 2 out of 3 echocardiographic signs suggesting PH according to the 2015 ESC/ERS guidelines (18).

Skin thickness progression rate (STPR) was calculated as the mRSS at the study entry divided by the duration of skin thickening (in years) from patient reports based on the method used by Domsic *et al*. (6). We further categorised STPR into 3 groups based on the reports by Perera *et al*. as: (i) rapid STPR (RPsp)-with an STPR≥40 units per year, (ii) intermediate STPR (IMsp)-

with an STPR of 15-39 units per year, and (iii) slow STPR (SLsp) -with an STPR of <15 units per year (19). Additionally, skin improvers were defined as dcSSc patients with a ≥25% reduction in the mRSS at one-year visit compared with study entry and those with a ≥25% increase in mRSS were defined as skin non-improvers. This cut-off point was modified from the studies of Wu *et al*. (7) and Shand *et al*. (5).

Statistical analysis

The descriptive data are presented as frequency (percentage), mean ± standard deviation (SD), or median (IQR). Comparison of categorical variables between the three STPR groups including RPsp, IMsp and SLsp were carried out using a Chi-square or Fisher's exact test. Comparison of continuous variables between the three groups was performed using an ANOVA or Kruskal-Wallis test. The patient data were censored when any of the following events occurred: LVEF less than 50%, ILD, suspected PH, death or reached the end of the study. Cumulative survival was analysed using the Kaplan-Meier method. The comparison of the survival between subgroupings was determined by the Log-rank test. The incidence rate (IR) of death between the two subgroups was compared using the Mantel Haenszel method. *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata for Windows v. 14.0 (Texas, USA).

Results

Patient's characteristics

Out of the 145 early-SSc patients initially recruited, 41 were excluded (29 with lcSSc subtype, 11 had a follow-up period less than 1 year, and one later developed an overlapping syndrome with SLE), leaving a cohort of 104 dcSSc patients for final analysis. Of the 104 early-dcSSc patients, 57 (54.8%) were female, 91 (87.5%) were anti-topoisomerase I antibody-positive, and 4 (3.8%) were anti-centromere antibody-positive. Their mean±SD age was 53.2±8.8 years and mean disease duration was 11.1±8.6 months. The mean ± SD follow-up period was 4.5±2.0 years. At enrolment, their mean±SD mRSS was 21.8±9.0 and the median STPR was 30.7 units per year, with a range of 1.64–252 units per year. We divided patients into 3 subgroups by STPR: (i) 42 (40.4%) patients with RPsp; (ii) 38 (36.5%) IMsp and; (iii) 24 (23.1%) SLsp. The mean ± SD peak mRSS was 24.1±9.5 and median (IQR 1, 3) duration of peak skin score from the disease onset was 12 (7, 20.5) months. In addition, at the 1-year visit, we also categorised patients into 2 groups including 69 (66.3%) patients with skin improvers and 35 (33.7%) with skin non-improvers.

Table I. Demographic data of 104 early dcSSc patients by STPR**.** Values are expressed as mean± standard deviation or n (%).

	RPsp (n=42)	IMsp (n=38)	SLsp (n=24)	*p*-value
Age (years)[a]	55.7 ± 8.7	51.6 ± 8.4	51.6 ± 8.9	0.067
Female	18 (42.9)	24 (63.2)	15 (62.5)	0.131
Disease duration (months)[a]	5.3 ± 2.3	11.5 ± 6.0	20.7 ± 10.3	<0.001
Follow-up duration (years)[a]	4.5 ± 2.0	4.3 ± 1.9	4.8 ± 1.9	0.624
Immunologic features				
Anti-Scl 70 antibody	40 95.2)	29 (76.3)	22 (91.7)	0.037
Anti-centromere antibody	1 (2.4)	1 (2.6)	2 (8.3)	0.543
Current medication				
Prednisolone	21 (50.0)	18 (47.4)	10 (41.7)	0.808
Cyclophosphamide	8 (19.0)	17 (44.7)	8 (33.3)	0.047
Methotrexate	3 (7.1)	2 (5.3)	2 (8.3)	0.891
Mycophenolate mofetil	4 (9.5)	0	1 (4.2)	0.133

RPsp: rapid skin progression; IMsp: intermediate skin progression; SLsp: slow skin progression; a: ANOVA.

Demographic and clinical characteristics of early dcSSc by STPR

The demographic of the early dcSSc population by STPR are shown in Table I. At enrolment, the RPsp group had a shorter disease duration and higher prevalence of anti-topoisomerase I antibody-positive than IMsp and SLsp groups. Patients with IMsp and SLsp were concurrently treated with cyclophosphamide more frequently than RPsp patients. However, no significant differences were observed in corticosteroid and other immunosuppressive treatments.

Baseline clinical characteristics of the early dcSSc population by STPR are shown in Table II. Patients with RPsp had significantly higher mRSS, a higher proportion of CK≥500 IU/L, and higher serum NT-proBNP levels than those with IMsp and SLsp groups. There were no significant differences regarding other organ involvement as well as other laboratory results between the three groups.

Incidence rate of LVEF<50%, ILD and suspected PH by STPR

Over the mean entire follow-up period of 4.5±2.0 years, there were 19 patients (18.3%) who developed an LVEF less than 50% and 25 (24.0%) developed suspected PH complications. Two out of 104 dcSSc had ILD at the first NRP; we therefore excluded them from the analysis of ILD incidence, and we found 87 (85.3%) out of 102 dcSSc developed ILD after NRP. Patients with RPsp had a significantly higher incidence rate of an LVEF less than 50% than those with IMsp and SLsp (6.06 *vs*. 4.46 and 0 per 100 person-years, *p*=0.009) (Fig. 1). In addition, patients with RPsp tended to have a higher incidence rate of ILD than IMsp and SLsp groups (69.69 *vs*. 50.37 and 34.66 per 100 person-years, *p*=0.054) (Fig. 2). Nevertheless, patients with RPsp had a significantly higher incidence rate of ILD than those with SLsp with an incidence rate ratio of 2.01 (1.13–3.68, *p*=0.012). No significant differences regarding cumulative incidence of suspected PH was observed between the three groups (6.45 *vs*. 5.10 and 3.43 per 100 person-years, *p*=0.582) (Fig. 3).

Mortality and survival of early dcSSc by changes in skin score

At the end of the study, there were 14 all-cause deceased patients (13.5%) including 7 with SSc-related death (4

Table II. Baseline clinical characteristics of 104 early dcSSc patients by STPR. Values are expressed as mean ± standard deviation or n (%).

	RPsp (n=42)	IMsp (n=38)	SLsp (n=24)	*p*-value
Organ involvement				
Baseline mRSS[a]	26.1 ± 7.9	22.1 ± 8.3	13.8 ± 6.5	< 0.001
Peak mRSS[a]	29.4 ± 8.5	22.9 ± 8.2	16.6 ± 7.6	<0.001
Digital ulcer	3 (7.1)	3 (7.9)	2 (8.3)	1.000
Telangiectasia	11 (26.2)	12 (31.6)	12 (50.0)	0.136
Interstitial lung disease	30 (71.4)	31 (81.6)	20 (83.3)	0.421
% FVC[a] (n=27, 24, 15)	73.9 ± 16.1	66.1 ± 14.6	78.8 ± 21.5	0.069
Suspected pulmonary hypertension	3 (7.1)	3 (7.9)	1 (4.2)	1.000
TR velocity (m/sec)[a] (n=38, 33, 22)	2.5 ± 0.3	2.5 ± 0.5	2.3 ± 0.4	0.052
LVEF (%)	68.5 ± 7.2	67.2 ± 7.4	67.0 ± 7.8	0.653
Diastolic dysfunction	17 (40.5)	11 (28.9)	7 (29.2)	0.480
Gastroesophageal reflux disease	14 (33.3)	19 (50.0)	13 (54.2)	0.174
Dysphagia	17 (40.5)	11 (28.9)	5 (20.8)	0.231
Arthritis	13 (31.0)	12 (31.6)	5 (20.8)	0.613
Joint contracture	26 (61.9)	23 (60.5)	11 (45.8)	0.404
Tendon friction rub	4 (9.5)	7 (18.4)	3 (12.5)	0.538
Laboratory investigations				
Creatinine[a] (mg/dL)	0.9 ± 0.2	0.8 ± 0.3	0.9 ± 0.3	0.633
ESR[b] (mm/hr)	52.1 ± 94.9	46.6 ± 36.6	32.5 ± 22.3	0.524
Creatine kinase ≥500 (IU/L)	14 (33.3)	7 (18.4)	1 (4.2)	0.018
NT-proBNP[b] (ng/L) (n=39, 37, 23)	913.7 ± 2273.9	734.0 ± 1367.9	163.9 ± 225.3	0.001

RPsp: rapid skin progression; IMsp: intermediate skin progression; SLsp: slow skin progression; mRSS: modified Rodnan skin score; pFVC: predicted forced vital capacity; LVEF: left ventricular ejection fraction; TR: tricuspid regurgitation; ESR: erythrocyte sedimentation rate; NT-proBNP: N-terminal pro brain natriuretic peptide.
a: ANOVA; b: Kruskal-Wallis test.

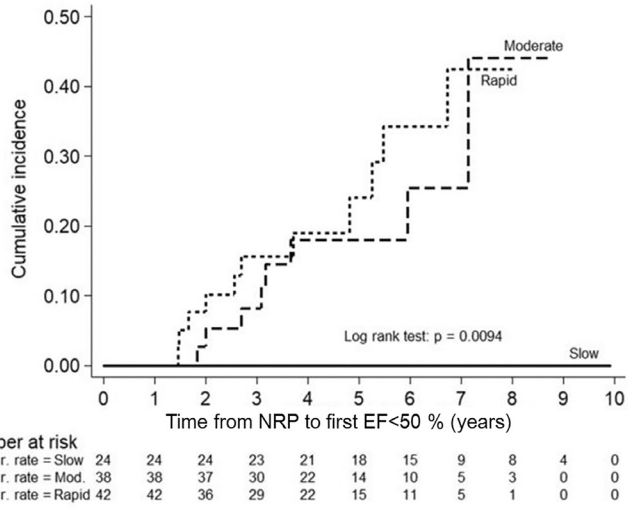

Fig. 1. Cumulative incidence of left ventricular ejection fraction <50% by STPR. *p*-value was calculated by Log-rank test.

congestive heart failure associated with PH, 2 congestive heart failure, 1 sudden death at home) and 7 with non-SSc related death (1 breast cancer, 3 pneumonia, 1 small bowel volvulus, 1 intracerebral haemorrhage and 1 liver abscess). Of those 14 deceased patients, 7 patients were RPsp, 5 were IMsp and 2 were SLsp. There were no significant differences in mortality rate between the three groups (3.65 *vs*. 3.06 and 1.74 per 100 person-years, p=0.586).

However, within the categories of skin-improvers and skin non-improvers, we found that skin non-improvers had a significantly higher mortality (10 of 35 [28.6%] *vs*. 4 of 69 [5.8%], p=0.004) and higher mortality rate (6.71 *vs*.1.24 per 100 person-years, p<0.001) than skin improvers, resulting in a mortality rate ratio of 5.40 (95% CI 1.56–23.58, p=0.003). Survival rate of skin-improvers at 1, 3 and 5 years after study entry was 100%, 96.9%, and 96.9%, respectively; while survival rate of skin-non improvers at 1, 3 and 5 years was 91.3%, 88.2%, and 74.9%, respectively. Patients within the skin-non improvers group had a significantly decreased survival rate in comparison to skin-improvers (p=0.0008) as shown in Figure 4.

Discussion

This is a first inception cohort study in an Asian country that investigates the relationship between changes in skin thickness with the incidence rate of cardiopulmonary involvement and mortality in early-diagnosed dcSSc. There have been several observational studies prior to this in Caucasian (4-8, 19) and Asian (10, 11, 20) populations regarding the association between changes in skin thickness and internal organ complications and/or mortality in SSc using a variety of study designs. In this study, the prevalence of females was 53.9% which was lower than previously reported in Western (4-8, 19) and Asian (10, 20) countries which ranged from 74.0–89.4%. Our homogeneous early dcSSc population cohort in the early disease phase with a mean disease duration of less than 3 years was similar to previously studies by Zheng *et al*. (8), Wu *et al*. (7), Domsic *et al*. (6), Perera *et al*. (19), Shand *et al*. (5), and Steen *et al*. (4). Contrarily, the prevalence of anti-topoisomerase I antibody-positive in this study was 87.5% which was not dissimilar to the 75.3% previously reported from Thailand (10), but was higher than previously reported in Western studies [range 23–62.9% (5-7)], suggesting differences in genetic susceptibility between Thai and Caucasian populations. There has been a report stating that the strongest association is between the HLADRB1* 11:04, DQA1*05:01, DQB1*03:01 haplotype, and the DQB1 alleles encoding a non-leucine residue at position 26 with Caucasian and Hispanic SSc patients (21); while the allele frequency of DRB1*15:02 and HLA-DRB5*01:02 was reported as significantly higher in Thai SSc patients and SSc with anti-topoisomerase I antibody-positive (22). At enrolment, we found that the RPsp had a shorter disease duration than those with IMsp and SLsp which con-

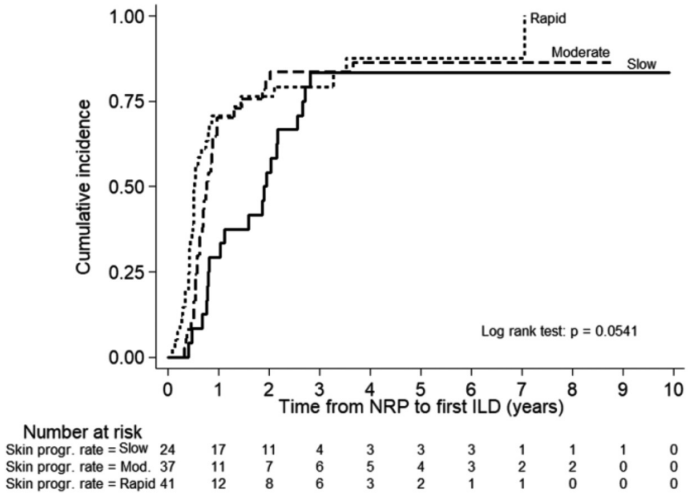

Fig. 2. Cumulative incidence of interstitial lung disease by STPR.
p-value was calculated by Log-rank test.

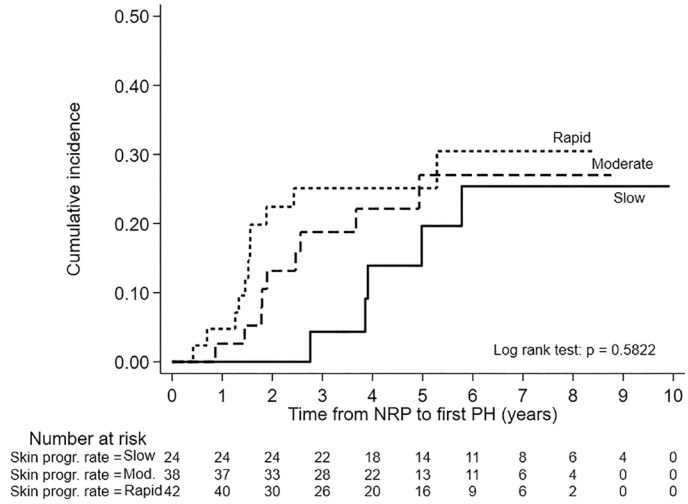

Fig. 3. Cumulative incidence of pulmonary hypertension by STPR.
p-value was calculated by Log-rank test.

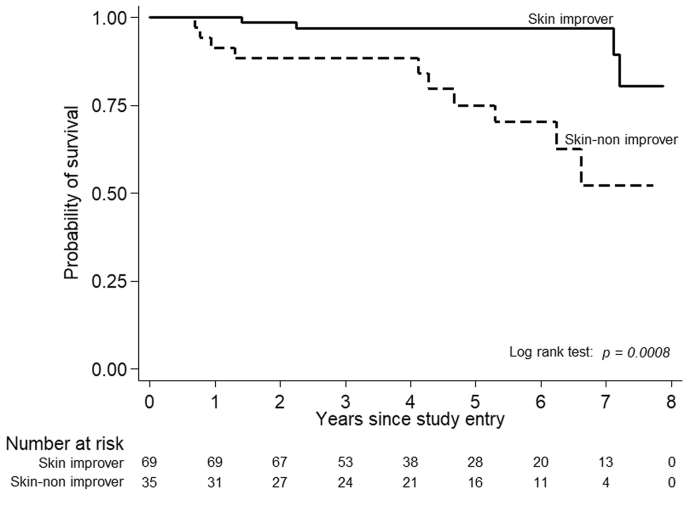

Fig. 4. Estimated survival of early dcSSc patients between skin improvers and skin non-improvers.
p-value was calculated by Log-rank test.

firmed the findings in Domsic *et al*. (6) and Perera *et al*. reports (19). We found that the RPsp group also had a significantly higher prevalence of anti-topoisomerase I antibody-positive than those of the IMsp and SLsp groups. In addition, anti-topoisomerase I antibody-positive dcSSc patients show a positive association with high mRSS and RPsp, similar to Perera *et al*. findings (19). However, the high prevalence of ILD was equally distributed between our three groups (6). Furthermore, we found that the RPsp group had a significantly higher proportion of CK levels ≥500 IU/L and higher serum levels of NT-pBNP than those of IMsp and SLsp, suggesting more severe suspected myositis and cardiac involvement in the RPsp group. Contrarily, Domsic *et al*. reported that the RPsp group had a significantly higher prevalence of -anti-RNA polymerase III antibody-positive and scleroderma renal crisis than the IMsp and SLsp groups (6). The discrepancies between the studies may be explained by differences in the genetics of the study populations and the definition of organ involvement.

With a mean ± SD entire follow-up duration of 4.5±2.0 years, we found the RPsp had higher incidence rate of developing LVEF<50% than SLsp. Domsic *et al*. and Perera *et al*. reported that the RPsp group had a significantly higher proportion of cardiac involvement and renal crisis than IMsp and SLsp groups (6, 19). Contrarily, no scleroderma renal crisis was observed in our population study. The strategy of avoiding the prescription of a prednisolone dose more than 10 mg/day in early cases of dcSSc may be a possible reason for this finding besides the low prevalence of anti-RNA polymerase III in our population. We also found that the RPsp group had a higher incidence of developing ILD in comparison to the SLsp group, supporting previous published findings that worsening skin score is associated with worse pulmonary complications, although different definitions of skin progression were used (7, 10, 20). Contradictory findings were found in several prior published data reports in which no differences were found between skin thickness change and ILD complications (6, 11, 19). Nevertheless, our findings that no differences in incidence rate of developing suspected PH with STPR were in agreement with previous reports that stated there were no significant relationships between a worse skin thickness and occurrence of PH with a variety of its definition (5-7, 10, 11, 19). We found no significant difference in mortality across the STPR subgroups of which main dcSSc-related causes of death were attributed to congestive

Table III. Association between skin score changes and clinical outcome in this study and other selected studies.

Author	Publication year	Study Design	n (%dcSSc)	Age (yrs.)	Female (%)	Disease duration	FU duration	Baseline mRSS	Change of skin thickness	Clinical outcome
This study	2020	Inception cohort	104 (100)	53.2	54.8	11.1±8.6 mo. (mean)	4.5±2.0 yrs. (mean)	21.8±9.0 (mean)	[a]- RPsp: 42 (40.4%) - IMsp: 38 (36.5%) - SLsp: 24 (23.1%) [b] Skin improvers: 69 (66.3%) Skin non-improvers: 35 (33.7%)	- RPsp is associated with higher incidence rate of LVEF <50% and ILD complications than those of SLsp. - Skin non-improvers had higher mortality than skin improvers.
Matsuda *et al*. (20) (Japan)	2019	Retrospective	198 (46.8)	55.4	89.4	7.3±8.8 yrs.	3.2±2.3 yrs.	NA	- N/A	- mRSS significantly negative correlation with FVC and DLco of the lungs.
Zheng *et al*. (8) (Canada)	2019	Inception cohort	154 (100)	49.1	76.0	2.2±1.3 yrs. (mean)	1.0 yrs. (last FU)	22.5±9.3 (mean)	[c]- Skin improvers: 64 (41.0%) - Skin worseners: 90 (58.0%)	- Skin improvers in early dcSSc correlate with improved Medsger DSS, physician global assessments, quality of life and function. - Skin changes may be reasonable surrogate outcome for global disease in early dcSSc.
Wu *et al*. (7) (EUSTAR database)	2019	Prevalence cohort	1021 (100)	52.0	75.7	7.7±7.5 yrs. (mean)	3.4 yrs. (median)	16.9±7.7 (mean)	[d]- Skin progressors: 78 (7.6%) - Skin non-progressors: 943 (92.4%)	- Progressive skin fibrosis within 1 year is associated with decline in lung function (FVC decline) and lower survival in dcSSc during follow-up. - These results confirm mRSS as a surrogate marker in dcSSc.
Wannarong *et al*. (10) (Thailand)	2018	Prevalence cohort	118 (78.0)	49.8	81.4	3.3 IQR (1, 6.8) yrs. (median)	1.0 yrs. (last FU)	7.5 IQR (1.8,14.3) (median)	[e]- Low TA-mRSS: 39 (33.0%) - Intermediate TA-mRSS: 40 (33.9%) - High TA-mRSS: 39 (33.0%)	- Higher cumulative course of mRSS over a 1-year period was significantly associated with internal organ involvement (usually interstitial pneumonia, diastolic dysfunction, gastrointestinal dysmotility).
Foocharoen *et al*. (11) (Thailand)	2012	Retrospective	117 (70.1)	49.8	59.8	N/A	3 yrs.	N/A	- Slow progression to peak then slow improvement (65.8%) - Continuous slow progression (31.6%) - Continuous intermediate progression (1.7%) - Slow progression to peak then intermediate improvement (0.9%)	- Skin thickness pattern does not correlate with SSc subsets and internal organ involvement.
Domsic *et al*. (6) (USA)	2011	Inception cohort	826 (100)	49.0	75.0	0.9 IQR (0.6, 1.4) yrs. (median)	2.0 yrs. (last FU)	26.0±11.4 (mean)	[f]- RPsp: 272 (33.1%) - IMsp : 277 (33.7%) - SLsp : 274 (33.3%)	-The STPR is an easy measure to identify those dcSSc patients who are at increased risk of mortality and renal crisis during the following 2 years.
Perera *et al*. (19) (USA)	2007	Retrospective cohort	212 (87.3)	48.0	74.0	0.9 Range (0.1-2.0) (mean)	N/A	RPsp: 30.7±11.0 IMsp: 24.9±10.1 SLsp: 13.4±5.9 (mean)	[a]- RPsp : 60 (35.1%) - IMsp : 82 (47.9%) - SLsp : 29 (16.9%)	-Anti-topoisomerase I antibody-positive dcSSc patients with a rapid STPR have reduced survival rates, primarily due to early and often fatal renal and cardiac involvement.
Shand *et al*. (5) (UK)	2007	Retrospective	225 (100)	44.0	82.0	10.0±0.6 mo. (mean)	N/A	30.0±11.0 (mean)	[g]- Low baseline, improver: 67 (34.9%) - High baseline, improver: 40 (20.8%) - High baseline, non-improver: 24 (12.5%) - Unclassified: 61 (31.8%)	-Mortality was highest in dcSSc -patients who had high baseline skin score with little improvement during FU. -Sustained severe skin disease does not predict number of visceral organ complications.
Steen *et al*. (4) (USA)	2001	Prospective cohort	278 (100)	46/: 47 yrs.	75.0	Improved: 1.2±1.0 yrs. Non-improved: 1.3±1.3 yrs. (mean)	2 (last F/U)	Improved : 25.0±11.8 No-Improved : 22.0±13.1 (mean)	[h]- Improvement: 174 (63%) - No improvement: 99 (36%)	-Improvement in skin thickening of dcSSc patients is associated with improved survival. -No significant differences in the occurrence of severe organ involvement between two groups during the first 2 years.

mRSS: modified Rodnan skin score; RPsp: rapid skin progression; IMsp: intermediate skin progression; SLsp: slow skin progression; DSS: disease severity score; FVC: forced vital capacity; TA-mRSS: time-adjusted accrual-modified Rodnan skin score; STPR: skin thickness progression rate; LVEF: left ventricular ejection fraction; N/A: not available.

Definition of change of skin thickness

a. Skin thickness progression rate (STPR): mRSS at first visit/duration, in years, from the onset of skin thickening, in mRSS units per year. Rapid progression (STPR ≥40 units per year), intermediate progression (STPR 15-39 units per year), slow progression (STPR < 15 units per year).

b Skin improvers were defined as those with ra ≥25% reduction in the mRSS at the one-year visit compared with baseline. Skin non improvers were defined as those with or a ≥25% increase in the mRSS at the one-year visit compared with baseline.

c. Skin improvers were defined as those with a ≥5 point and/or a ≥25% reduction in the mRSS at the annual visit compared with baseline. Skin worseners were defined as those with a ≥5 point and/or a ≥25% increase in the mRSS at the annual visit compared with baseline.

d. Skin progressors were defined as those with increase in mRSS >5 units and by ≥25% from baseline to 12 ± 3 months.

e. TA- mRSS: time-adjusted accrual-modified Rodnan skin score.

f. Skin thickness progression rate (STPR): mRSS at first visit/duration of skin thickening (in years) by patient report. Then then STPR was tertiled for analysis. This corresponded to a STPR score less than 25 per year for slow STPR, 25-44 per year for intermediate STPR and over 45 per year for rapid STPR.

g. Skin improvers were defined as those whose skin score decreased by > 25 % at the end of year 3 compared with baseline. Skin non-improvers were defined as those whose skin score decreased by ≤ 5% or increased.

h. Rate of change in skin score= SS1 (or peak score) – SS2 (score closest to 24 months)/ Time2-time1. Improvement required a reduction in their skin score of at least 5 units per year and a > 5% overall improvement from their initial or peak skin score. No improvement was defined as no change or an increase in their skin score during the first 2 years after the first visit. Patients with minimal improvement, *i.e*. from 1 to 4 units of change per year or < 25 % improvement during the 2 years, were excluded from further aspects of the study.

heart failure and PH, which agreed with Elha *et al*. report that cardiac involvement is the most common cause of death in SSc (23). In their reports, Domsic *et al*. and Perera *et al*. stated that the RPsp group has significantly increased risk of mortality due to renal crisis and heart disease (6, 19). Again, differences in the genetics of the study population, number of cohort participants, definition of organ involvement and study period may explain these discrepancies. However, we found that the skin non-improver group had a higher incidence rate of mortality and had lower survival than those in the skin improvers, which supported the findings of other previous studies (4, 5, 7). Table III summarises the observational studies regarding the association between changes in skin thickness determined by a variety of definitions and visceral organ complications and mortality.

The strength of this study was its design as an inception cohort study of early dcSSc with a high prevalence of anti-topoisomerase I antibody-positive status which will provide important observational data regarding the incidence rate of cardiopulmonary complications and mortality according to changes in skin thickness score. In addition, as a single centre study with a homogeneity of serial mRSS examination and cardiopulmonary complication assessment which was systematically recorded entire the study period, the data can be classed as having a high level of reliability.

There are several limitations which should be acknowledged. Firstly, the small number of early-dcSSc cases may have limited the power of the statistical analysis. Secondly, PH was not determined by right heart catheterisation, which is a gold standard for diagnosis of PH. Thirdly, although all participants underwent baseline and serial HRCT, only 66 (63.5%) patients underwent pulmonary function testing. We are therefore unable to completely determine the severity of ILD. The data also need to be interpreted with caution because of the short-term follow-up, mainly in the early phase of the disease. Finally, early immunosuppressive treatment prescribed in early dcSSc may affect the real incidence of cardiopulmonary complications.

In conclusion, our study cohort of early-dcSSc patients with a high prevalence of anti-topoisomerase I antibody found that the patients with baseline RPsp were associated with a significantly higher incidence of cardiac involvement defined as a left ventricular ejection fraction less than 50% and a higher incidence rate of ILD than those with SPsp. This study confirmed that the skin non-improver group had a higher mortality rate than the skin improver group. Therefore, skin changes determined as STPR at the baseline visit are a useful surrogate marker for cardiac and ILD complications and assessment of skin improvers 1-year later gives a useful surrogate marker of mortality which could be conveniently used in general practice.

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References

1. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
2. CLEMENTS PJ, FEGHALI C: Cutaneous involvement in systemic sclerosis. *In*: CLEMENTS PJ, FURST DE (Eds.): Systemic sclerosis. 2nd Ed., Philadelphia, Lippincott, 2004; 129-50.
3. CLEMENTS PJ, LACHENBRUCH PA, SEIBOLD JR *et al*.: Skin thickness score in systemic sclerosis: an assessment of interobserver variability in 3 independent studies. *J Rheumatol* 1993; 20: 1892-6.
4. STEEN VD, MEDSGER TA, JR: Improvement in skin thickening in systemic sclerosis associated with improved survival. *Arthritis Rheum* 2001; 44: 2828-35.
5. SHAND L, LUNT M, NIHTYANOVA S *et al*.: Relationship between change in skin score and disease outcome in diffuse cutaneous systemic sclerosis: application of a latent linear trajectory model. *Arthritis Rheum* 2007; 56: 2422-31.
6. DOMSIC RT, RODRIGUEZ-REYNA T, LUCAS M, FERTIG N, MEDSGER TA, JR: Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. *Ann Rheum Dis* 2011; 70: 104-9.
7. WU W, JORDAN S, GRAF N *et al*.: Progressive skin fibrosis is associated with a decline in lung function and worse survival in patients with diffuse cutaneous systemic sclerosis in the European Scleroderma Trials and Research (EUSTAR) cohort. *Ann Rheum Dis* 2019; 78: 648-56.
8. ZHENG B, NEVSKAYA T, BAXTER CA, RAMEY DR, POPE JE, BARON M: Changes in skin score in early diffuse cutaneous systemic sclerosis are associated with changes in global disease severity. *Rheumatology* (Oxford). 2020; 59: 398-406.
9. WANGKAEW S, EUATHRONGCHIT J, WATTANAWITTAWAS P, KASITANON N, LOUTHRENOO W: Incidence and predictors of interstitial lung disease (ILD) in Thai patients with early systemic sclerosis: Inception cohort study. *Mod Rheumatol* 2016; 26: 588-93.
10. WANNARONG T, MUANGCHAN C: High burden of skin sclerosis is associated with severe organ involvement in patients with systemic sclerosis and systemic sclerosis overlap syndrome. *Rheumatol Int* 2018; 38: 2279-88.
11. FOOCHAROEN C, MAHAKKANUKRAUH A, SUWANNAROJ S, NANAGARA R: Pattern of skin thickness progression and clinical correlation in Thai scleroderma patients. *Int J Rheum Dis* 2012; 15: e90-5.
12. WANGKAEW S, PRASERTWITAYAKIJ N, PHROMMINTIKUL A, PUNTANA S, EUATHRONGCHIT J: Causes of death, survival and risk factors of mortality in Thai patients with early systemic sclerosis: inception cohort study. *Rheumatol Int* 2017; 37: 2087-94.
13. PRELIMINARY CRITERIA FOR THE CLASSIFICATION OF SYSTEMIC SCLEROSIS (SCLERODERMA): Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23: 581-90.
14. 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. *Ann Rheum Dis* 2013; 72: 1747-55.
15. CLEMENTS P, LACHENBRUCH P, SIEBOLD J *et al*.: Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. *J Rheumatol* 1995; 22: 1281-5.
16. LEROY EC, MEDSGER TA, JR: Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573-6.
17. WANGKAEW S, TUNGTEERABUNDITKUL S, PRASERTWITTAYAKIJ N, EUATHRONGCHIT J: Comparison of clinical presentation and incidence of cardiopulmonary complications between male and female Thai patients with early systemic sclerosis: inception cohort study. *Clin Rheumatol* 2020; 39: 103-12.
18. GALIÈ N, HUMBERT M, VACHIERY J-L *et al*.: 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J* 2015; 46: 903-75.
19. PERERA A, FERTIG N, LUCAS M *et al*.: Clinical subsets, skin thickness progression rate,

and serum antibody levels in systemic sclerosis patients with anti-topoisomerase I antibody. *Arthritis Rheum* 2007; 56: 2740-6.

20. MATSUDA KM, YOSHIZAKI A, KUZUMI A *et al*.: Skin thickness score as a surrogate marker of organ involvements in systemic sclerosis: a retrospective observational study. *Arthritis Res Ther* 2019; 21: 129.
21. ARNETT FC, GOURH P, SHETE S *et al*.: Major histocompatibility complex (MHC) class II alleles, haplotypes and epitopes which confer susceptibility or protection in systemic sclerosis: analyses in 1300 Caucasian, African-American and Hispanic cases and 1000 controls. *Ann Rheum Dis* 2010; 69: 822-7.
22. LOUTHRENOO W, KASITANON N, WICHAINUN R *et al*.: Association of HLA-DRB1*15:02 and DRB5*01:02 allele with the susceptibility to systemic sclerosis in Thai patients. *Rheumatol Int* 2013; 33: 2069-77.
23. ELHAI M, MEUNE C, AVOUAC J, KAHAN A, ALLANORE Y: Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. *Rheumatology* (Oxford) 2012; 51: 1017-26.