

# Work Productivity and Economic Burden of Systemic Sclerosis in a Multiethnic Asian Population

Ling Xiang,<sup>1</sup> Sandra M. Y. Kua,<sup>2</sup> and Andrea H. L. Low<sup>3</sup>

**Objective.** To assess work productivity, identify associated factors and evaluate the economic burden of systemic sclerosis (SSc) in a multiethnic Asian population.

**Methods.** Data on employment status and work productivity loss were collected. Associations between demographic and disease characteristics and unemployment status, work productivity loss, and activity impairment were examined using logistic and linear regression analyses, as appropriate. Costs of unemployment and work productivity loss were estimated using the human capital approach.

**Results.** Of 111 patients with a mean disease duration of 9.1 years, 33 (29.7%) were unemployed. Their mean age at unemployment was 44.2 years, equating to 22.8 years of lost employment. No demographic and disease characteristics were significantly associated with unemployment status in multivariable analysis. Of 73 employed patients, 39 (53.4%) reported work productivity loss, accounting for 45.9% of the working week. The presence of hyperlipidemia (coefficient  $-19.01$ ,  $P = 0.03$ ) was associated with work productivity loss in multivariable analysis. In total, 37 of 78 employed patients (47.4%) and 19 of 33 unemployed patients (57.6%) reported activity impairment, accounting for 42.2% and 50.0%, respectively, of the preceding week. The presence of hyperlipidemia (coefficient  $-18.56$ ,  $P < 0.01$ ) was associated with activity impairment in multivariable analysis. Annual cost of unemployment and work productivity loss were estimated to be \$53,244 and \$13,045 (Singapore dollar) per patient, respectively.

**Conclusion.** SSc imposes significant unemployment and work productivity loss and causes a substantial economic burden to both affected individuals and society. Modifying the identified factors associated with unemployment and work productivity loss may reduce the burden of SSc.

## INTRODUCTION

Systemic sclerosis (SSc) is a less common autoimmune rheumatic disease characterized by excessive production and accumulation of collagen in the skin and other tissues such as the joints, tendons, blood vessels, muscles, gastrointestinal tract, lungs, kidneys, and heart. SSc significantly impacts physical function and leads to a reduced capacity to participate in activities of daily life such as self-care/maintenance, household chores, and professional activities such as work and studies (1–5). Affected individuals in the workforce may experience work disability, namely reduced work productivity (presenteeism), absence from work (absenteeism), change of jobs/careers (work transitions), and work cessation (unemployment/early retirement) due to illness before reaching retirement age (6–9). Work disability has

been reported among 18–89% of patients with SSc in published studies (10–12). Since SSc affects mostly patients of an economically productive age (10), it can lead to a substantial burden to both affected individuals and society (11,13,14).

The economic burden of disease has been mainly studied in the more common autoimmune rheumatic diseases, including rheumatoid arthritis (RA), axial spondyloarthritis, and systemic lupus erythematosus (SLE) (15–17). Studies on SSc have been mostly conducted in Europe, North America, and Australia (11,13,14,18–22). There is a paucity of reports from Asian countries, where the clinical manifestations of SSc have been shown to differ from those in other populations (23). The primary aim of this study was to assess work productivity and identify associated factors in patients with SSc in a multiethnic Asian population. The secondary aim was to evaluate the

<sup>1</sup>Ling Xiang, MBBS, MMed: Singapore General Hospital and Yong Loo Lin School of Medicine, National University of Singapore, Singapore; <sup>2</sup>Sandra M. Y. Kua, BSc: Singapore General Hospital, Singapore; <sup>3</sup>Andrea H. L. Low, BMedSci, BMBS, MRCP, FAMS: Singapore General Hospital and Duke-NUS Medical School, Singapore.

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Address correspondence to Andrea H. L. Low, BMedSci, BMBS, MRCP, FAMS, Department of Rheumatology and Immunology, Singapore General Hospital, Academia Building, Level 4, 20 College Road, Singapore, 169856. Email: andrea.low.h.l@singhealth.com.sg.

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**SIGNIFICANCE & INNOVATIONS**

- Nearly 30% of the patients with systemic sclerosis (SSc) were unemployed at a mean age of 44 years.
- Considerable work productivity loss was reported in over half of employed patients.
- SSc imposes a substantial economic burden to both affected individuals and society.
- Modifying identified factors for work productivity may reduce the burden of SSc.

economic burden of unemployment and work productivity loss in these patients.

**PATIENTS AND METHODS**

**Patients.** Patients who were enrolled in the Systemic Sclerosis Cohort in Singapore (SCORE) (24) and who were seen at the scleroderma clinic in Singapore General Hospital were consecutively recruited between October 2017 and January 2020. All patients fulfilled the 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for SSc (25) or the Very Early Diagnosis of Systemic Sclerosis criteria (26), and were age  $\geq 18$  years. Written consent was obtained from all patients. This study was approved by the SingHealth Centralized Institutional Review Board (ref. 2007/011/E). Data on employment status, work productivity loss, and demographic and disease characteristics were collected from all patients.

**Outcome measures.** All patients were administered a standardized questionnaire during their clinic visit, with the following options for employment status: employed, unemployed due to medical condition, unemployed due to nonmedical condition, full-time student, homemaker, national service (compulsory service in Singapore), and retired. Unemployment was defined as being unemployed due to a medical condition or being unemployed due to a nonmedical condition in this study. Patients who were a full-time student, a homemaker, on national service, or retired were excluded from analysis.

Work productivity was measured using the Work Productivity and Activity Impairment (WPAI) specific health problem (SSc) questionnaire (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24521/abstract>) (27). There are 6 items on the WPAI concerning employment status (item 1), hours missed from work due to SSc (item 2) and other reasons (item 3), total hours worked (item 4), and the impact of SSc on work productivity (item 5) and daily activities (item 6) during the preceding week. For employed patients, we calculated absenteeism (time absent from work), presenteeism (time at work with reduced productivity), and work productivity loss (overall work impairment

calculated from absenteeism and presenteeism). For both employed and unemployed patients, we calculated activity impairment (activity limitation outside work for the employed). All these 4 scores from the WPAI were expressed as impairment percentages (possible range 0–100), with a higher score indicating greater impairment.

**Independent variables.** Demographic characteristics included age, sex, ethnicity, date of first non-Raynaud's phenomenon manifestation, date of WPAI survey, and smoking history. Disease duration at the time of the survey was derived from the date of the first non-Raynaud's phenomenon manifestation. Physician-diagnosed comorbidities, including hypertension, ischemic heart disease, hyperlipidemia, diabetes mellitus, renal impairment, stroke, and malignancy were extracted from the medical records.

Disease characteristics included SSc subtype, cumulative clinical manifestations, skin thickness score, pulmonary function, autoantibodies, and treatment received. Patients were classified as having limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc) according to the criteria established by LeRoy et al (28), or SSc overlap if SSc occurred with 1 or more of the following defined connective tissue diseases: SLE, RA, or inflammatory myositis.

Cumulative clinical manifestations captured in the SCORE cohort were described elsewhere (29) and included joint involvement (arthritis or joint contracture), tendon friction rub, mild peripheral vasculopathy (Raynaud's phenomenon, digital pitting, pulp atrophy, or telangiectasia), severe peripheral vasculopathy (digital ulcers or gangrene), calcinosis, inflammatory myositis, upper gastrointestinal involvement (reflux/dysphagia, vomiting, gastric antral vascular ectasia, or bloating/distension), lower gastrointestinal involvement (diarrhea, constipation, fecal soilage, or malabsorption), interstitial lung disease (ILD; diagnosed by high-resolution computed tomography) and pulmonary arterial hypertension (PAH; diagnosed by right heart catheterization), renal involvement (renal crisis, creatinine above the upper limit of normal on 3 or more occasions, and proteinuria) and cardiac involvement.

Skin thickness was measured using the maximum modified Rodnan skin score (30). Pulmonary function was quantified using the forced vital capacity (FVC). Treatment received included immunosuppression (methotrexate, azathioprine, cyclophosphamide, and mycophenolate mofetil) and treatment for peripheral vasculopathy and PAH (prostacyclin, phosphodiesterase type 5 inhibitor, and endothelin receptor antagonists).

**Estimation of economic burden.** In Singapore, employers are required to provide re-employment to employees who turn 62 (retirement age), until age 67 years (re-employment age) (31). In an epidemiologic survey conducted among the Singapore general population in 2017, only 1.8% of the residents

**Table 1.** Demographic and disease characteristics of SSc patients (n = 111)\*

	Overall (n = 111)	Employed (n = 78)	Unemployed (n = 33)	P
Female sex	97 (87.4)	67 (85.9)	30 (90.9)	0.55
Age at survey, mean ± SD years	49.4 ± 10.5	48.2 ± 10.7	52.2 ± 9.5	0.07
Age at unemployment, mean ± SD years	-	-	44.2 ± 9.3	-
Disease duration from first non-RP symptom onset to survey, mean ± SD years	9.1 ± 6.7	8.8 ± 6.8	9.7 ± 6.8	0.52
Ethnicity				0.91
Chinese	78 (70.3)	55 (70.5)	23 (69.7)	-
Malay	13 (11.7)	10 (12.8)	3 (9.1)	-
Indian	6 (5.4)	4 (5.1)	2 (6.1)	-
Others	14 (12.6)	9 (11.5)	5 (15.2)	-
Smoking history (previous or current smoker)	10 (9.0)	7 (9.0)	3 (9.1)	>0.99
Comorbidities				
Hypertension	19 (17.1)	11 (14.1)	8 (24.2)	0.20
Ischemic heart disease	3 (2.7)	2 (2.6)	1 (3.0)	>0.99
Hyperlipidemia	21 (18.9)	16 (20.5)	5 (15.2)	0.51
Diabetes mellitus	4 (3.6)	4 (5.1)	0 (0.0)	0.32
Renal impairment	4 (3.6)	2 (2.6)	2 (6.1)	0.58
Stroke	2 (1.8)	2 (2.6)	0 (0.0)	>0.99
Malignancy	4 (3.6)	3 (3.9)	1 (3.0)	>0.99
Cumulative clinical manifestations				
SSc subtype				0.07
lcSSc	48 (43.2)	37 (47.4)	11 (33.3)	-
dcSSc	38 (34.2)	22 (28.2)	16 (48.5)	-
SSc overlap	24 (21.6)	19 (24.4)	5 (15.2)	-
Joint involvement	83 (74.8)	61 (78.2)	22 (66.7)	0.20
Tendon friction rub	5 (4.5)	3 (3.9)	2 (6.1)	0.83
Mild peripheral vasculopathy	105 (94.6)	74 (94.9)	31 (93.9)	>0.99
RP	89 (80.2)	64 (82.1)	25 (75.8)	0.45
Digital pitting	56 (50.5)	37 (47.4)	19 (57.6)	0.33
Pulp atrophy	75 (67.6)	51 (65.4)	24 (72.7)	0.45
Telangiectasia	64 (57.7)	42 (53.9)	22 (66.7)	0.21
Severe peripheral vasculopathy	18 (16.2)	8 (10.3)	10 (30.3)	0.01
Digital ulcers	17 (15.3)	8 (10.3)	9 (27.3)	0.02
Digital gangrene	6 (5.4)	1 (1.3)	5 (15.2)	0.01
Calcinosis	12 (10.8)	7 (9.0)	5 (15.2)	0.34
Inflammatory myositis	18 (16.2)	12 (15.4)	6 (18.2)	0.28
Gastrointestinal involvement	90 (81.1)	62 (79.5)	28 (84.9)	0.51
Upper	78 (70.3)	53 (68.0)	25 (75.8)	0.41
Lower	63 (56.8)	43 (55.1)	20 (60.6)	0.59
ILD	46 (41.4)	32 (41.0)	14 (42.4)	0.14
PAH	8 (7.2)	4 (5.1)	4 (12.1)	0.41
Renal involvement	15 (13.5)	7 (9.0)	8 (24.2)	0.03
Cardiac involvement	3 (2.7)	0 (0.0)	3 (9.1)	0.03
Maximum MRSS, median (IQR)	6.0 (2.0–15.0)	6.0 (2.0–12.0)	8.0 (3.0–21.0)	0.12
FVC, % predicted, median (IQR)	72.0 (61.0–79.0)	74.0 (62.0–81.0)	65.5 (54.0–76.0)	0.02
Anti-Scl-70	43 (38.7)	32 (41.0)	11 (33.3)	0.71
Anticentromere	16 (14.4)	11 (14.1)	5 (15.2)	0.74
Immunosuppressive treatment	83 (74.8)	60 (76.9)	23 (69.7)	0.42
Methotrexate	44 (39.6)	32 (41.0)	12 (36.4)	0.65
Azathioprine	10 (9.0)	8 (10.3)	2 (6.1)	0.72
Cyclophosphamide	26 (23.4)	17 (21.8)	9 (27.3)	0.53
Mycophenolate mofetil	44 (39.6)	32 (41.0)	12 (36.4)	0.65
Medication for peripheral vasculopathy	10 (9.0)	7 (9.0)	3 (9.1)	>0.99
Prostacyclin	1 (0.9)	0 (0.0)	1 (3.0)	0.30
PDE5i	10 (9.0)	7 (9.0)	3 (9.1)	>0.99
ERA	1 (0.9)	1 (1.3)	0 (0.0)	>0.99
Medication for PAH	4 (3.6)	1 (1.3)	3 (9.1)	0.08
Prostacyclin	1 (0.9)	0 (0.0)	1 (3.0)	0.30
PDE5i	4 (3.6)	1 (1.3)	3 (9.1)	0.08
ERA	1 (0.9)	0 (0.0)	1 (3.0)	0.30

\* Values are the number (%) unless indicated otherwise. ERA = endothelin receptor antagonist; dcSSc = diffuse cutaneous systemic sclerosis; FVC = forced vital capacity; ILD = interstitial lung disease; IQR = interquartile range; lcSSc = limited cutaneous SSc; MRSS = modified Rodnan skin score; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type 5 inhibitor; RP = Raynaud's phenomenon.

age 60–74 years became unemployed, 42.9% continued to work, 31.6%, were retired, and 23.6% were homemakers (32). We therefore chose 67 as the upper cutoff age for the estimation of economic burden. Only patients up to age 67 years were included in this study.

We used the human capital approach to estimate the economic burden (33). Since data on monthly income were not collected, we used the median gross monthly income in Singapore in 2018 (Singapore dollar [SGD] \$4,437) instead (34). For patients who were unemployed at the time of the survey, we estimated the cost of unemployment from their age at unemployment until the re-employment age. For patients who were employed at the time of the survey, we estimated the costs of absenteeism, presenteeism, and work productivity loss. We also estimated the economic burden of unemployment and work productivity loss to Singapore based on an estimated prevalence of 78–100 per million population and a reported resident population of 4,026,200 in 2019 (35). The prevalence of SSc in Singapore was estimated based

on the prevalence in other Asian countries and our own hospital data (36,37). All estimated costs were expressed in 2018 value without inflation or discounting.

**Statistical analysis.** Continuous variables such as age, disease duration, and WPAI scores are expressed as mean  $\pm$  SD or median (interquartile range), while categorical variables such as sex, ethnicity, and disease characteristics are expressed as frequency (percentage). We assessed differences between employed and unemployed patients using student's *t*-test/Wilcoxon's rank sum test for continuous variables and chi-square test/Fisher's exact test for categorical variables, as appropriate. We examined the associations between independent variables (demographic and disease characteristics) and unemployment status (dichotomous variable: unemployed/employed) in all patients using logistic regression analysis. We examined the associations between these independent variables and 1) work productivity loss (continuous variable,

**Table 2.** Factors associated with unemployment status in SSc patients (n = 111)\*

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
Female sex	1.64 (0.43, 6.32)	0.47	2.28 (0.40, 12.82)	0.35
Age at survey	1.04 (1.00, 1.09)	0.07	1.04 (0.91, 1.07)	0.11
Disease duration, first non-RP symptom onset to survey	1.02 (0.96, 1.08)	0.52	0.99 (0.91, 1.07)	0.77
Smoking history	1.00 (0.24, 4.13)	>0.99	–	–
Comorbidities				
Hypertension	1.95 (0.70, 5.41)	0.20	–	–
Ischemic heart disease	1.19 (0.10, 13.57)	0.89	–	–
Hyperlipidemia	0.69 (0.23, 2.08)	0.51	–	–
Diabetes mellitus†	–	–	–	–
Renal impairment	2.45 (0.33, 18.19)	0.38	–	–
Stroke†	–	–	–	–
Malignancy	0.78 (0.08, 7.80)	0.83	–	–
SSc subtype (ref. lcSSc)				
dcSSc	2.45 (0.96, 6.21)	0.06	–	–
SSc overlap	0.89 (0.27, 2.92)	0.84	–	–
Joint involvement	0.56 (0.23, 1.37)	0.20	–	–
Tendon friction rub	1.63 (0.26, 10.31)	0.60	–	–
Mild peripheral vasculopathy	0.84 (0.15, 4.81)	0.84	–	–
Severe peripheral vasculopathy	3.80 (1.34, 10.79)	0.01	3.07 (0.79, 11.96)	0.11
Calcinosis	1.81 (0.53, 6.19)	0.34	–	–
Inflammatory myositis	1.27 (0.43, 3.74)	0.67	–	–
Gastrointestinal involvement	1.45 (0.48, 4.34)	0.51	–	–
ILD	0.64 (0.25, 1.64)	0.35	–	–
PAH	2.46 (0.57, 10.59)	0.23	–	–
Renal involvement	3.25 (1.07, 9.87)	0.04	3.68 (0.98, 13.76)	0.05
Cardiac involvement†	–	–	–	–
Maximum MRSS	1.04 (1.00, 1.09)	0.05	1.01 (0.95, 1.07)	0.71
FVC, % predicted	0.97 (0.94, 0.99)	0.02	0.97 (0.93, 1.00)	0.06
Anti-ScI-70	0.70 (0.30, 1.67)	0.42	–	–
Anticentromere	1.18 (0.37, 3.78)	0.78	–	–
Immunosuppressive treatment	0.69 (0.28, 1.71)	0.42	–	–
Medication for peripheral vasculopathy (ref. none)	1.01 (0.25, 4.19)	0.98	–	–
Medication for PAH (ref. none)	7.70 (0.77, 76.97)	0.08	0.66 (0.03, 13.04)	0.79

\* 95% CI = 95% confidence interval; dcSSc = diffuse cutaneous systemic sclerosis; FVC = forced vital capacity; ILD = interstitial lung disease; lcSSc = limited cutaneous SSc; MRSS = modified Rodnan skin score; OR = odds ratio; PAH = pulmonary arterial hypertension; RP = Raynaud's phenomenon.

† Odds ratio was not calculated as no/all patients with the condition were unemployed.

**Table 3.** Work productivity loss and activity impairment in SSc patients\*

	Patients, no.	Work time %, mean $\pm$ SD	Work time %, median (IQR)
Absenteeism			
All employed patients	73	6.2 $\pm$ 19.8	0.0 (0.0–0.0)
Employed reporting absenteeism due to SSc	9	50.5 $\pm$ 31.6	34.8 (32.7–60.0)
Presenteeism			
All employed patients	78	19.7 $\pm$ 25.5	5.0 (0.0–30.0)
Employed reporting presenteeism due to SSc	39	39.5 $\pm$ 22.8	30.0 (20.0–60.0)
Overall work impairment (work productivity loss)			
All employed patients	73	24.5 $\pm$ 30.2	10.0 (0.0–50.0)
Employed reporting absenteeism or presenteeism due to SSc	39	45.9 $\pm$ 26.9	46.2 (20.0–67.4)
Activity impairment			
All employed and unemployed patients	111	22.6 $\pm$ 28.8	10.0 (0.0–40.0)
Employed and unemployed reporting activity impairment due to SSc	56	44.8 $\pm$ 25.4	40.0 (25.0–70.0)
All employed patients	78	20.0 $\pm$ 27.4	0.0 (0.0–30.0)
Employed reporting activity impairment due to SSc	37	42.2 $\pm$ 25.4	30.0 (20.0–70.0)
All unemployed patients	33	28.8 $\pm$ 31.5	20.0 (0.0–50.0)
Unemployed reporting activity impairment due to SSc	19	50.0 $\pm$ 25.4	50.0 (30.0–70.0)

\* IQR = interquartile range; SSc = systemic sclerosis.

possible range 0–100) in employed patients, and 2) activity impairment (continuous variable, possible range 0–100) in all patients using linear regression analysis. We reported odds ratios (ORs) from logistic regression and coefficients from linear regression. Independent variables with a *P* value less than 0.1 in the univariate analysis were included in the corresponding multivariable analysis, with adjustments for age, sex, and disease duration. All analyses were performed using Stata software, version 15.0.

## RESULTS

**Demographic and disease characteristics.** Among 195 patients with SSc who consented and completed the WPAI questionnaire, 54 patients who were above the age of 67 years (re-employment age), and 30 patients who were a full-time student, a homemaker, on national service, or retired were excluded from analyses (Table 1). The remaining 111 patients had a mean  $\pm$  SD age of 49.4  $\pm$  10.5 years and a mean  $\pm$  SD disease duration of 9.1  $\pm$  6.7 years at the time of the survey. The majority were female (87.4%) and of Chinese ethnicity (70.3%). Approximately 18.9% of patients had hyperlipidemia and 17.1% had hypertension. The other comorbidities were present in <5.0% of patients. Overall, lcSSc (43.2%) was the most common subtype of SSc, followed by dcSSc (34.2%) and SSc overlap (21.6%).

**Unemployment.** Of 111 patients, 33 (29.7%) were unemployed at the time of the survey; 23 were unemployed due to their medical condition and 10 were unemployed due to a nonmedical condition. Unemployed patients did not differ from employed patients in terms of demographic characteristics (Table 1).

Factors associated with unemployment status are shown in Table 2, with values shown as the odds ratios (ORs) and 95% confidence intervals (95% CIs). The presence of severe peripheral

vasculopathy (OR 3.80 [95% CI 1.34, 10.79]; *P* = 0.01), renal involvement (OR 3.25 [95% CI 1.07, 9.87]; *P* = 0.04), and FVC (OR 0.97 [95% CI 0.94, 0.99]; *P* = 0.02) were significantly associated with unemployment status in univariate analysis. However, they were not significant in the multivariable analysis after adjustment for age, sex, and disease duration.

**Work productivity loss.** Of 73 employed patients with relevant data on the WPAI, 9 (12.3%) reported absenteeism, accounting for 50.5% of the working week (Table 3). Of 78 employed patients, 39 (50.0%) reported presenteeism, accounting for 39.5% of the working week. Of 73 employed patients, 39 (53.4%) reported work productivity loss (incorporating both absenteeism and presenteeism), accounting for 45.9% of the preceding week.

Factors associated with work productivity loss are shown in Table 4. Smoking history was associated with work productivity loss in univariate analysis (coefficient 26.30 [95% CI 2.79, 49.81]; *P* = 0.03). The presence of hyperlipidemia was associated with work productivity loss in both univariate analysis (coefficient –21.64 [95% CI –38.47, –4.81]; *P* = 0.01) and multivariable analysis (coefficient –19.01 [95% CI –36.39, –1.63]; *P* = 0.03) after adjustment for age, sex, and disease duration.

**Activity impairment.** Of 78 employed and 33 unemployed patients, 37 (47.4%) and 19 (57.6%), respectively, reported activity impairment, accounting for 42.2% and 50.0% of the preceding week (Table 3). Factors associated with activity impairment are shown in Table 5. The presence of hyperlipidemia (coefficient –17.90 [95% CI –31.39, –4.42]; *P* = 0.01), severe peripheral vasculopathy (coefficient 17.44 [95% CI 3.04, 31.84]; *P* = 0.02), and calcinosis (coefficient 22.30 [95% CI 5.28, 39.32]; *P* = 0.01) were associated with activity impairment in univariate analysis. After adjustment for age, sex, and disease duration, the

**Table 4.** Factors associated with work productivity loss in employed SSc patients (n = 78)\*

	Univariate analysis		Multivariable analysis	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Female sex	-13.35 (-32.96, 6.27)	0.18	9.27 (-16.10, 34.64)	0.47
Age at survey	0.05 (-0.61, 0.71)	0.88	-0.08 (-0.72, 0.56)	0.81
Disease duration, first non-RP symptom onset to survey	-0.07 (-1.16, 1.02)	0.90	-0.01 (-1.11, 1.10)	0.99
Smoking history	26.30 (2.79, 49.81)	0.03	27.45 (-1.35, 56.25)	0.06
Comorbidities				
Hypertension	-4.62 (-24.46, 15.22)	0.64	-	-
Ischemic heart disease	43.46 (-16.82, 103.74)	0.16	-	-
Hyperlipidemia	-21.64 (-38.47, -4.81)	0.01	-19.01 (-36.39, -1.63)	0.03
Diabetes mellitus	10.19 (-20.94, 41.33)	0.52	-	-
Renal impairment	-4.59 (-65.73, 56.55)	0.88	-	-
Stroke	-25.22 (-68.35, 17.91)	0.25	-	-
Malignancy	-18.63 (-54.16, 16.90)	0.30	-	-
SSc subtype (ref. lcSSc)				
dcSSc	-4.19 (-21.14, 12.75)	0.62	-	-
SSc overlap	-0.73 (-18.53, 17.07)	0.94	-	-
Joint involvement	8.11 (-8.59, 24.82)	0.34	-	-
Tendon friction rub	-17.54 (-53.04, 17.96)	0.33	-	-
Mild peripheral vasculopathy	-15.23 (-50.85, 20.40)	0.40	-	-
Severe peripheral vasculopathy	10.35 (-12.27, 32.98)	0.37	-	-
Calcinosis	22.90 (-0.62, 46.43)	0.06	20.76 (-5.74, 47.27)	0.12
Inflammatory myositis	-8.82 (-28.58, 10.93)	0.38	-	-
Gastrointestinal involvement	-0.54 (-18.59, 17.52)	0.95	-	-
ILD	7.06 (-11.28, 25.39)	0.44	-	-
PAH	13.15 (-16.80, 43.11)	0.38	-	-
Renal involvement	15.13 (-10.51, 40.76)	0.24	-	-
Cardiac involvement†	-	-	-	-
Maximum MRSS	-0.40 (-1.27, 0.47)	0.36	-	-
FVC	-0.16 (-0.65, 0.33)	0.52	-	-
Anti-Scl-70	-0.68 (-15.55, 14.19)	0.93	-	-
Anticentromere	3.90 (-16.23, 24.04)	0.70	-	-
Immunosuppressive treatment (ref. none)	4.43 (-12.72, 21.58)	0.61	-	-
Medication for peripheral vasculopathy (ref. none)	13.22 (-12.47, 38.91)	0.31	-	-
Medication for PAH (ref. none)	-4.59 (-65.73, 56.55)	0.88	-	-

\* 95% CI = 95% confidence interval; dcSSc = diffuse cutaneous systemic sclerosis; FVC = forced vital capacity; ILD = interstitial lung disease; lcSSc = limited cutaneous SSc; MRSS = modified Rodnan skin score; PAH = pulmonary arterial hypertension; RP = Raynaud's phenomenon.

† Coefficient was not calculated as all patients with the condition were unemployed.

presence of hyperlipidemia (coefficient -18.56 [95% CI -32.22, -4.90];  $P < 0.01$ ) was associated with activity impairment in multivariable analysis.

**Economic burden of unemployment and work productivity loss.** For unemployed patients, their mean  $\pm$  SD age at unemployment was  $44.2 \pm 9.3$  years, equating to 22.8 years of lost employment. The annual cost of unemployment (lost earning) was estimated to be SGD \$53,244 per patient. The overall cost of unemployment in the remaining working life of unemployed patients was estimated to be SGD \$1,213,963 per patient. For employed patients, the annual cost of work productivity loss was estimated to be SGD \$13,045 per patient. The annual cost of absenteeism and presenteeism was estimated to be SGD \$3,301 and \$9,744 per patient, respectively.

Based on an estimated prevalence of 78–100 per million population in Singapore, the annual cost of unemployment and work productivity loss was estimated to be \$5.0–6.4 million and

\$2.9–3.7 million, respectively. The overall cost of unemployment in the remaining working life of unemployed patients was estimated to be SGD \$113–145 million.

## DISCUSSION

This study examined the work productivity and economic burden of unemployment and work productivity loss among patients with SSc in a multiethnic Asian population. Nearly 30% of patients with SSc were unemployed in our study cohort. They averaged an age of 44.2 years at unemployment, which equates to 22.8 years of lost employment in Singapore. Work productivity loss was present in approximately half (53.4%) of the employed patients, while activity impairment was also reported in approximately half of both the employed patients (47.4%) and unemployed patients (57.6%), both affecting nearly 50% of the working week. This is the first study investigating the work productivity and economic burden of SSc in Southeast Asia. Findings

**Table 5.** Factors associated with activity impairment in all SSc patients (n = 111)\*

	Univariate analysis		Multivariable analysis	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
Female	-2.73 (-19.13, 13.66)	0.74	8.36 (-8.78, 25.49)	0.34
Age at survey	0.08 (-0.44, 0.60)	0.77	0.09 (-0.42, 0.60)	0.73
Disease duration, first non-RP symptom onset to survey	0.34 (-0.50, 1.18)	0.43	0.05 (-0.80, 0.89)	0.91
Smoking history	2.60 (-16.51, 21.71)	0.79	-	-
Comorbidities				
Hypertension	6.37 (-8.03, 20.78)	0.38	-	-
Ischemic heart disease	-6.11 (-39.67, 27.45)	0.72	-	-
Hyperlipidemia	-17.90 (-31.39, -4.42)	0.01	-18.56 (-32.22, -4.90)	<0.01
Diabetes mellitus	12.85 (-16.27, 41.97)	0.38	-	-
Renal impairment	23.22 (-5.66, 52.11)	0.11	-	-
Stroke	-17.94 (-58.73, 22.86)	0.39	-	-
Malignancy	-2.71 (-31.92, 26.50)	0.85	-	-
SSc subtype (ref. dcSSc)				
lcSSc	-1.24 (-13.78, 11.30)	0.85	-	-
SSc overlap	3.96 (-10.48, 18.39)	0.59	-	-
Joint involvement	8.27 (-4.17, 20.71)	0.19	-	-
Tendon friction rub	0.17 (-26.41, 26.75)	0.99	-	-
Mild peripheral vasculopathy	-7.81 (-31.85, 16.23)	0.52	-	-
Severe peripheral vasculopathy	17.44 (3.04, 31.84)	0.02	14.82 (-0.95, 30.58)	0.07
Calcinosis	22.30 (5.28, 39.32)	0.01	18.92 (-0.03, 37.88)	0.05
Inflammatory myositis	-0.60 (-15.45, 14.24)	0.94	-	-
Gastrointestinal involvement	6.75 (-7.10, 20.59)	0.34	-	-
ILD	3.72 (-9.68, 17.12)	0.58	-	-
PAH	-2.97 (-24.46, 18.52)	0.78	-	-
Renal involvement	12.40 (-3.36, 28.15)	0.12	-	-
Cardiac involvement	21.74 (-11.32, 54.81)	0.20	-	-
Maximum MRSS	0.14 (-0.46, 0.75)	0.64	-	-
FVC	-0.26 (-0.63, -0.10)	0.16	-	-
Anti-Scl-70	1.38 (-9.97, 12.73)	0.81	-	-
Anticentromere	-0.55 (-17.04, 15.93)	0.95	-	-
Immunosuppressive treatment (ref. none)	-4.15 (-16.66, 8.37)	0.51	-	-
Peripheral vasculopathy medication (ref. none)	11.42 (-7.48, 30.31)	0.23	-	-
Medication for PAH (ref. none)	12.85 (-16.27, 41.97)	0.38	-	-

\* 95% CI = 95% confidence interval; dcSSc = diffuse cutaneous systemic sclerosis; FVC = forced vital capacity; ILD = interstitial lung disease; lcSSc = limited cutaneous SSc; MRSS = modified Rodnan skin score; PAH = pulmonary arterial hypertension; ref. = reference; RP = Raynaud's phenomenon.

from this study could provide some insights into interventions to mitigate work impairment in patients with SSc and reduce the disease burden in the population.

The unemployment rate in our cohort of SSc patients (29.7%) was relatively lower than those reported in other populations (approximately one-third to two-thirds) (2,7,18,38,39). Work productivity loss was also reported by a smaller proportion of employed patients in our study (53.4%) compared to the study by Morrisroe et al in Australia (63.6%) (18), but the extent of work productivity loss (the proportion of the working week impaired) experienced by our patients was greater (45.9% versus 38.4%). The mean work productivity loss in all employed SSc patients (24.5%) was comparable to SSc patients in Australia (24.4%) (18) and axial spondyloarthritis patients in Singapore (27.6%) (40). While different disease characteristics, including disease duration and severity across study populations, may partly explain this variation, other factors including work and psychosocial characteristics may have also influenced a patient's employment status and work productivity (12,41). In addition to

unemployment and work productivity loss, other measures of work disability, such as reduced work ability and work transitions/changes, have also been reported among patients with SSc. In the study by Sandqvist et al, 72.9% of the employed patients with SSc reported poor or moderate work ability after a mean disease duration of 13 years (38). In the studies by Nguyen et al (42), Bérezné et al (2), Decuman et al (7), and Morrisroe et al (18), 31.0–56.0% of patients with SSc reported work transitions/changes after their diagnosis of SSc.

As work characteristics, including employment status, occupation, and work productivity and ability, may change with different health status conditions and other contextual factors, longitudinal studies are required to capture the dynamic change of work disability and to explore its relationship with various contextual factors. Sandqvist et al found that the relative risk for sick leave or disability pension in patients with SSc compared to an age- and sex-matched reference group increased from 2.09 at 1 year from disease onset to 2.41 at 3 years (43). Sharif et al found that 26.7% of patients who were employed at baseline

self-reported work disability after an average of 4 years of follow-up (44). Hudson et al found that the odds of reporting work disability increased by ~15% with every 5 additional years of disease (45). However, in our study, we did not find an association between disease duration and unemployment or work productivity loss.

Exploring risk factors for unemployment and work productivity loss among patients with SSc can provide a basis for the development of interventions to prevent and mitigate the impact of disease on work. Currently identified factors for unemployment and productivity loss vary across studies, including demographic (2,38,39,43,44), disease-related (2,7,38,39,42,44–47), work-related (38,46), and sociopsychologic characteristics (42,44), many of which are potentially modifiable with appropriate interventions. In accordance with findings from previous studies (2,7,10,38,44,45), organ involvement such as kidney, severe peripheral vasculopathy, and severity of lung involvement (FVC) were associated with unemployment. Lung involvement (ILD and PAH) is the most common cause of mortality in SSc (48). Notably, while the presence of ILD and PAH was not associated with unemployment, the severity of disease with lower FVC was associated with unemployment. However, none of these associations were significant in multivariable analysis after adjustment for age, sex, and disease duration, possibly due to the small sample size.

Hyperlipidemia was negatively associated with work productivity loss and activity impairment, i.e., patients with hyperlipidemia compared to those without hyperlipidemia had better outcomes. This finding could be due to the fact that the majority of these patients (57%, data not shown) were treated with a statin, which has been shown to improve impaired endothelial function, lower high-sensitivity C-reactive protein and immune complex production (49), and improve skin microvascular function in SSc (50). Therefore, the treatment of hyperlipidemia with statins, rather than hyperlipidemia per se, may have been associated with better outcomes of work productivity and activity impairment. Disease duration, which was found to be associated with work disability in some studies (2,7,45,47) was not significant in our study. Decuman et al studied work participation and transition among SSc patients of working age and found that patients who reported work transitions had significantly longer disease duration compared to those with no work transition (6.3 versus 2.7 years) (7). Hence, patients may have received job accommodation/work transitions or have adjusted themselves to the demands at work, all of which may have offset the impact of more severe disease or disease damage due to longer disease duration.

Several systematic reviews have been conducted on the factors associated with work impairment of SSc, which yielded inconsistent findings. Schouffoer et al found only moderate evidence for the associations with disease-specific symptoms, functional disability, and quality of life (12). Decuman et al found that, among the factors with a strong association (global disability, income,

muscle/skin involvement, and demands at work), only global disability was reported frequently in the literature (10). McCormick et al found that the productivity loss was mainly driven by more generalized factors such as pain, fatigue, depression, cognitive dysfunction, and being overweight (11), which we did not investigate in our study. While this inconsistency could be mainly attributed to the diversity of contextual factors examined in various studies, it also highlights the importance of defining the essential contextual factors in studying the impact of disease on work (41).

Significant economic burden of SSc has been reported in the literature, despite different components of the cost estimated and data resources used across studies (11,13). In this study, we estimated the cost of SSc associated with unemployment and work productivity loss among affected individuals. Nearly 30% of our patients with SSc were unemployed at the time of this study. They lost an average of 22.8 years of employment, which was much longer than those reported in other published studies and hence a much higher cost of unemployment (lost earning) to society (14,18–22,39). Our estimated cost of work productivity loss was also relatively higher compared to the cost reported in the study by Morrisroe et al, in which the same measurement of work productivity loss (WPAI) was used (18).

There are several limitations in this study. First, data on employment status before and at disease onset were not collected. Possibly some of our patients were unemployed before the onset of SSc. Thus, the impact of SSc on unemployment status might have been overestimated in our study. Second, other than the demographic and disease characteristics examined in this study, other factors, including work and sociopsychologic characteristics that were not examined, may have also played important roles in the unemployment and work impairment in our patients. This possibility would be the subject of future studies, which require a larger sample size to examine multiple factors. Last, we studied patients attending a tertiary referral center who might have more severe disease compared to those who were seeking treatment in nontertiary clinics and those who were not seeking treatment in the community. The impact and burden of SSc might thus have been overestimated in our population.

SSc imposes significant unemployment and work productivity loss and causes substantial economic burden to both affected individuals and society. Modifying the identified factors associated with unemployment and work productivity loss may reduce the burden of SSc.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Low had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Xiang, Low.

**Acquisition of data.** Kua.

**Analysis and interpretation of data.** Xiang, Low.



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