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ORIGINAL ARTICLE

Indications for hospitalization and in-hospital mortality in Thai systemic sclerosis

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Abstract This study aimed to identify the indications for hospitalization, hospital mortality rate, predictors of hospital mortality, and clinical parameters affecting length of stay (LOS) among Thai systemic sclerosis (SSc). A retrospective study was performed in SSc patients admitted in Khon Kaen University, Thailand, between January 2008 and December 2010. The respective clinical factors affecting LOS and predictors of mortality were analyzed using the Spearman's rank correlation and the Cox regression model. There were 202 hospital admissions among 131 SSc patients. The female-to-male ratio was 1.6:1. The median age at admission was 54.7 years (interquartile range (IQR) 49.2–62.9), the duration of disease at admission was 2.9 years (IQR 1.1–7.8), and the LOS was 5 days (IQR 2–10). The indications for hospitalization were divided equally between SSc-related and non-SSc-related events (53.5 vs. 46.5 %, respectively). The most common indication for hospitalization was infection (23.3 %) and pneumonia is the most common cause of infection (58.0 %). Prolonged LOS was related to fatigability status ($p<0.01$), intestinal involvement ($p<0.01$), electrolyte disorders ($p<0.01$), multiple comorbidities ($p<0.01$), modified Rodnan skin score ≥20 points ($p=0.01$), disease duration under 5 years ($p=0.02$), cardiac arrhythmia ($p=0.04$), and deficiency anemia ($p=0.04$). Hospital mortality was 16.8 per 100 person-years (95 % confidence interval (95 % CI) 10.8–24.3). Infection (59.1 %) was the most common cause of death, particularly from bacterial pneumonia. Clinical predictors of mortality were: disseminated intravascular coagulation related to infection (hazard ratio (HR) 52.73; 95 % CI 1.26–403.74), cardiac arrhythmia (HR 32.89; 95 % CI 3.00–359.95), electrolyte disorders (HR 15.66; 95 % CI 2.04–119.98), renal crisis (HR 13.38; 95 % CI 1.80–99.36), intestinal involvement (HR 10.42; 95 % CI 2.58–42.01), admission due to a non-SSc-related condition (HR 8.93; 95 % CI 2.21–36.13), and disease duration under 5 years (HR 6.67; 95 % CI 1.21–36.52). Infection was the most common cause of hospitalization. Prolonged LOS and hospital mortality should be warning signs in patients with shorter disease duration, presence of intestinal involvement, cardiac arrhythmia, and multiple comorbidities.

Keywords Cause of death · Hospitalization · Length of stay · Mortality · Scleroderma · Systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease, characterized by skin and internal organ fibrosis and vasculopathy [1]. The two main subsets of SSc are defined by the extent of skin involvement: limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [2].

The prognosis for dcSSc is worse than for lcSSc because of the severe internal organ involvement in the former, especially in the early course of the disease [3]. Patients who have internal organ involvement are significantly associated with morbidity and mortality [4, 5] and trend to be referred to secondary or tertiary centers for care [5].

Table 1 Definitions of clinical parameters determined from medical records

Clinical parameters	Definitions
Pulmonary fibrosis	Interstitial fibrosis detected either by chest radiography or HRCT of the lung
Myositis	Elevated creatine phosphokinase (CK) ≥200 IU/dL or an abnormal finding from the electromyogram
Fatigability	Lethargy, fatigue, and muscle weakness
Cardiac involvement	Heart failure, pericardial effusion, cardiac arrhythmia that needs antiarrhythmic drug therapy, or abnormal findings from echocardiography including systolic and diastolic dysfunction but excluding other causes of abnormalities
Pulmonary arterial hypertension (PAH)	Either by echocardiogram RVSP >40 mmHg or right heart catheterization, mean pulmonary arterial pressure >25 mmHg at rest, and pulmonary capillary wedge pressure <15 mmHg [10]
Renal insufficiency	Elevated serum creatinine (Cr) >1.3 mg/dL
Renal crisis	Triad of elevated blood pressure, unexplained microangiopathic hemolytic anemia, and rapidly progressive rising serum creatinine
Esophageal involvement	Any esophageal symptoms of SSc such as esophageal dysphagia, heartburn, or reflux symptoms
Gastrointestinal involvement	Any gastrointestinal symptoms of SSc such as malabsorption, constipation, ileus, or pseudo-intestinal obstruction that require resting the bowel and/or using total parenteral hyperalimentation
Medication	Use of corticosteroid, antimalarial agent (chloroquine and hydroxychloroquine), and immunosuppressant (cyclophosphamide and methotrexate) within 2 weeks of admission
Range of corticosteroid	Subdivided into 3 groups: low dose <15 mg, moderate dose 15–30 mg, and high dose >30 mg that is equivalent to prednisolone therapy
Infection	Evidence of clinical infection confirmed by microbial culture or diagnosed clinically by a specialist in infectious disease or rheumatology
Opportunistic infection	Infection caused by a pathogen not usually found in a normal immune function host
Disease duration	Duration of first SSc symptom to first date of admission
Indications of hospitalization	Classified into two groups: 1. SSc-related condition such as intestinal pseudo-obstruction, renal crisis, and/or pulmonary arterial hypertension 2. Non-SSc-related condition such as infection, malignancy, and/or coronary artery disease
Length of stay (LOS)	Duration from first date of admission to date of discharge
Congestive heart failure	Defined according to the cause: 1. Related to SSc 2. Not related to SSc
Comorbidities	According to a modified version of Elixhauser's methodology [11] as follows: congestive heart failure, arrhythmia, hypertension, valvular heart disease, pulmonary circulation disease, peripheral vascular disease, paralysis, other neurological disorders, chronic pulmonary disease, diabetes, diabetes with chronic complications, hypothyroidism, renal failure, liver disease, peptic ulcer disease with bleeding, acquired immune deficiency syndrome, lymphoma, metastatic cancer, solid tumor without metastasis, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, chronic blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression Comorbidity divided into 2 categories: 1. Baseline comorbidity: occurred before admission 2. Hospital comorbidity: occurred during hospital stay
Anemia	When hemoglobin <12 g/dL in females and 13 g/dL in males
Electrolyte disorder	When patient has any of the followings: hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypomagnesemia, hypermagnesemia, hypercalcemia, or hypocalcemia

RVSP right ventricular systolic pressure

Hospital mortality and length of stay (LOS) among SSc patients range between 6.3–7.1 and 6.6–7.5 days, respectively [6, 7]. Meta-analysis of individual patient data indicates that most SSc-related mortality involves a cardiac component with hazard ratio (HR) of 2.8 (95 % confidence interval (95 % CI) 2.1–3.8) [7]. Hospital mortality is associated with emergency

admission, older age, male sex, high numbers of diagnoses, congestive heart failure, SSc-related internal organ involvement, and anti-Scl 70 antibody (anti-topoisomerase I antibody) [7, 8]. Based on these studies [7, 8], SSc disease itself was the most common primary indication for hospitalization. Respiratory infection and respiratory failure are the second most common indications for hospitalization [6].

Based on the literature, the prevalence of SSc is 30–240 cases per million, which varies geographically. The majority of these studies investigating mortality risk are from the USA and Europe where the studied populations were mostly Caucasian which may not represent Asians generally and Southeast Asians specifically. For example, in Japan, the prevalence is 38 cases per million [8]. We therefore explored the indications for hospitalization, LOS, and predictors of hospital mortality for the Thai population. The primary objective of our study was to identify the indications for hospitalization among Thais with SSc and the subsidiary objectives were to determine the hospital mortality rate, mortality risks, and clinical parameters which affect LOS in this population.

Materials and methods

A retrospective, cross-sectional study was performed at Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand. The studied population included all SSc patients admitted to Srinagarind Hospital between January 2008 and December 2010. We excluded patients if they were: (a) diagnosed with an overlapping syndrome, (b) in for an elective surgery, or (c) in for an intervention/diagnostic procedure(s).

A diagnosis of systemic sclerosis was based on the American College of Rheumatology criteria [9]. SSc was classified as the limited or diffuse type, according to the classification by Le Roy et al. [2]. Table 1 provides a summary of the: definition of disease duration, indication of hospitalization, length of stay, comorbidities, and internal organ involvement in SSc. The

Table 2 Indications for hospitalization based on primary diagnosis

Indication of hospitalization	Number of hospitalizations
Admission due to SSc	108 (53.5 %)
Pulmonary arterial hypertension	34.3 %
Scleroderma renal crisis	11.1 %
Gastrointestinal involvement	10.2 %
Severe myositis	8.3 %
Congestive heart failure	5.6 %
Admission due to non-SSc condition	94 (46.5 %)
All infection	47.9 %
Congestive heart failure	8.5 %
Coronary artery disease	6.4 %
Malignancy	4.3 %
Sepsis	3.2 %

Table 3 Clinical parameters correlated with length of stay (LOS)

Variables	Rho	*p* value
Female sex	−0.08	0.24
Age at admission	−0.01	0.99
Disease duration <5 years	0.16	0.02*
Diffuse cutaneous systemic sclerosis subset	0.08	0.27
Positive anti-Scl 70 antibody	0.05	0.49
Modified Rodnan skin score ≥20 points	0.17	0.01*
Body mass index ≤18 kg/m^2	0.13	0.08
Raynaud's phenomenon	0.03	0.62
Digital ulcer	0.04	0.60
Myositis	−0.03	0.59
Fatigability	0.19	<0.01*
Tendon friction rub	0.01	0.90
Dysphagia	0.03	0.64
Reflux esophagitis	0.10	0.14
Intestinal involvement	0.23	<0.01*
Pulmonary fibrosis	−0.07	0.35
Alveolitis	0.03	0.67
Renal crisis	0.09	0.18
Cardiac involvement included pulmonary arterial hypertension	−0.03	0.64
Corticosteroid therapy	−0.04	0.56
Antimalarial therapy	0.01	0.95
Immunosuppressant therapy	0.01	0.96
Baseline comorbidity		
Heart failure	0.01	0.94
Arrhythmia	0.14	0.04*
Hypertension	−0.01	0.89
Diabetes	0.07	0.34
Hypothyroidism	−0.07	0.33
Renal insufficiency	0.11	0.12
Electrolyte disorder	0.18	<0.01*
Deficiency anemia	0.001	0.99
In-hospital comorbidity		
Heart failure	0.02	0.79
Arrhythmia	0.07	0.35
Hypertension	NA	NA
Diabetes	NA	NA
Hypothyroidism	NA	NA
Renal insufficiency	0.08	0.23
Electrolyte disorder	0.32	<0.01*
Deficiency anemia	0.14	0.04*
Baseline comorbidities ≥4	0.22	<0.01*
In-hospital comorbidities ≥4	0.31	<0.01*

NA not available

*$p<0.05$; statistically significant

indications for hospitalization and discharge status were defined according to the primary diagnosis, and the number of admissions was counted for each patient individually.

Statistical analysis

In-hospital mortality was expressed with 95 % CI. The HR was calculated to assess the hospital mortality risk. The Spearman's rank correlation was applied to identify the clinical parameters correlated with LOS. All of the variables with a p value of less than 0.10 were entered into a Cox regression model. The backward elimination method was applied for model fitting. The variables were tested for significance using the Wald χ^2 statistic. All of the statistical tests were two-tailed and a p value <0.05 was considered statistically significant. All data analyses were performed using STATA version 11.2 (Stata Corp. College Station, TX, USA).

The variables used for analysis of hospital mortality risks included: age at admission, sex, disease duration, SSc clinical subset, modified Rodnan skin score (mRSS), Raynaud's phenomenon, digital ulcer, findings of internal organ involvement (including esophageal, gastrointestinal, pulmonary, cardiac, renal, tendon friction rub, and myositis), anti-Scl 70 antibody, corticosteroid use, antimalarial use, and immunosuppressant therapy, baseline and in-hospital comorbidities, number of baseline and in-hospital comorbidities, indication(s) for hospitalization, and number of admissions.

Results

Our analysis included 202 hospitalizations by 131 patients. The female-to-male ratio was 1.6:1. The majority of the patients studied were diagnosed with dcSSc (81.7 %). The respective median age on admission and disease duration was 54.7 years (IQR 49.2–62.9) and 2.9 years (IQR 1.1–7.8). Nearly 60 % of the admitted patients were positive for anti-Scl 70 antibody. Eighty-three patients (63.4 %) had one admission, 33 (25.2 %) had two, 10 (7.6 %) had three, 3 (2.3 %) had four, and 2 (1.5 %) had more than four admissions. The median length of stay was 5 days (IQR 2–10). Eight patients (6.1 %) were readmitted within 28 days with a similar problem as their previous hospitalization, viz., coronary arterial disease, scleroderma renal crisis, pulmonary arterial hypertension, severe myositis, lung cancer, congestive heart failure, esophageal stricture, or intestinal pseudo-obstruction.

Indications for hospitalization were quite similar between SSc-related and non-SSc-related events (Table 2). Pulmonary arterial hypertension (PAH) was the most common cause of hospitalization among the SSc-related events, while for those with a non-SSc-related condition, infection was the most common. The sources of infection included pneumonia (58.0 %), diarrhea (12.0 %), and urinary tract infection (4.0 %) and the causative agents were mostly bacterial; two cases of which were pulmonary tuberculosis. There was no association between respiratory tract infection and any of the following: dysphagia (p=0.52), dcSSc subset (p=0.41), reflux esophagitis (p=0.97), pulmonary fibrosis (p=0.87), use of corticosteroid (p=0.36), or immunosuppressive drugs (p=0.71).

Three quarters of our patients received low-dose steroid therapy for edematous skin and alveolitis within 2 weeks prior to admission. The remaining patients had a moderate steroid dosage for inflammatory myopathy. Thirty-five of the 131 patients received immunosuppressants. Oral daily cyclophosphamide was prescribed for the treatment for 28 SSc patients with active alveolitis, azathioprine for 3 with myositis, methotrexate for 3 with myositis, and mycophenolate mofetil for 1 with active alveolitis.

Clinical parameters related to LOS are presented in Table 3. The LOS was affected by fatigability (p<0.01), gastrointestinal symptoms (p<0.01), both baseline and in-hospital electrolyte disorders (p<0.01), both baseline and in-hospital multiple comorbidities (p<0.01), (p<0.01), disease duration under 5 years (p value 0.02), mRSS ≥20 points (p=0.01), baseline cardiac arrhythmia (p=0.04), and in-hospital deficiency anemia (p=0.04).

Clinical improvement at discharge occurred in 180 admissions (89.1 %). Twenty-two patients died and the hospital mortality rate was 16.8 per 100 person-years (95 % CI 10.8–24.3). The causes of death are summarized in Table 4. Most (68.2 %) of the patients who died were admitted due to non-SSc-related conditions. The most common cause of death was infection (59.1 %), followed by congestive heart failure (18.2 %).

Analysis of the variables predictive of hospital mortality is presented in Table 5. The clinical parameters affecting hospital mortality according to the Cox regression analysis included: coagulopathy due to disseminated intravascular coagulation, arrhythmia, electrolyte disorder, scleroderma

Table 4 Causes of death

Causes of death	Number of patients (%) N=22
Non-systemic sclerosis-related events	15 (68.2 %)
Bacterial pneumonia	73.2
Pulmonary tuberculosis	6.7
H1N1 pneumonitis	6.7
Bronchoalveolar cancer	6.7
Massive pulmonary embolism	6.7
Systemic sclerosis-related events	7(31.8 %)
Congestive heart failure	57.1
Intestinal pseudo-obstruction	14.3
Scleroderma renal crisis	14.3
Severe malnutrition	14.3

Table 5 Clinical parameters associated with hospital mortality

Variables	Improved (%)	Died (%)	Crude HR (95 % CI)	*p* value	Adjusted HR (95 % CI)	*p* value
Female sex	61.7	63.6	0.96 (0.40–2.28)	0.92		
Age at admission >60 years	29.4	27.3	0.92 (0.36–2.36)	0.87		
Length of stay >7 days	32.8	59.1	2.93 (1.25–6.87)	0.01*	0.52 (0.15–1.75)	0.29
Disease duration <5 years	61.1	90.9	9.67 (2.26–41.42)	0.002*	6.67 (1.22–36.52)	0.03*
dsSSc subset	83.9	90.9	2.21 (0.52–9.46)	0.29		
Positive anti-Scl 70 antibody	56.1	72.7	2.12 (0.83–5.42)	0.12		
Modified Rodnan skin score ≥20 points	17.8	18.2	1.43 (0.49–4.25)	0.51		
Body mass index ≤18 kg/m^2	29.9	42.9	2.15 (0.90–5.11)	0.08	0.98 (0.33–2.97)	0.98
Raynaud's phenomenon	59.4	54.6	1.01 (0.43–2.33)	0.99		
Digital ulcer	11.1	13.6	0.79 (0.23–2.69)	0.71		
Myositis	28.3	33.3	1.80 (0.73–4.48)	0.20		
Fatigability	18.3	18.2	1.67 (0.56–4.99)	0.36		
Tendon friction rub	9.0	13.6	2.52 (0.73–8.64)	0.14		
Dysphagia	43.9	50.0	1.87 (0.80–4.36)	0.15		
Reflux esophagitis	32.2	31.8	1.11 (0.45–2.75)	0.82		
Intestinal symptoms	15.0	27.3	2.26 (0.88–5.78)	0.09	10.42 (2.58–42.01)	0.001*
Pulmonary fibrosis	58.3	40.9	0.34 (0.14–0.80)	0.01*	0.38 (0.10–1.59)	0.19
Alveolitis	16.7	27.3	2.55 (0.98–6.65)	0.06	0.28 (0.05–1.47)	0.13
Renal crisis	3.3	13.6	5.30 (1.54–18.27)	0.01*	13.38 (1.80–99.35)	0.01*
Cardiac involvement included PAH	13.3	27.3	1.81 (0.70–4.70)	0.23		
Corticosteroid therapy	49.4	50.0	1.05 (0.45–2.44)	0.90		
Antimalarial therapy	6.2	9.1	1.19 (0.28–5.13)	0.82		
Immunosuppressant therapy	17.2	18.2	1.27 (0.43–3.78)	0.67		
In-hospital comorbidity						
Heart failure	5.0	13.6	2.04 (0.27–15.63)	0.49		
Arrhythmia	3.9	31.8	6.11 (2.41–15.49)	<0.001*	32.89 (3.01–359.95)	0.004*
Renal insufficiency	0.6	13.6	24.07 (5.92–97.87)	<0.001*	0.40 (0.01–27.39)	0.67
Coagulopathy	0	13.6	44.65 (9.83–202.89)	<0.001*	52.73 (1.26–403.74)	0.04*
Electrolyte disorder	21.1	68.2	6.07 (2.36–14.98)	<0.001*	15.66 (2.04–119.98)	0.01*
In-hospital comorbidities ≥4	0.6	13.6	2.15 (1.67–2.77)	<0.001*	0.75 (0.25–2.23)	0.61
Admission due to non-SSc condition	43.3	72.7	3.34 (1.30–8.58)	0.01*	8.93 (2.21–36.12)	0.002*

SSc systemic sclerosis

*$p<0.05$; statistical significant

renal crisis, intestinal symptoms, admission due to non-SSc condition, and disease duration under 5 years.

Discussion

In the current study, more than 200 hospitalizations were recorded over 3 years. The number of hospitalizations of Thais diagnosed with SSc was much higher than in the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample (HCUP-NIS) database in the USA, which includes ~20,000 discharges from 1,000 hospitals in 2002–2003 [6]. The majority of their studied patients were diagnosed with the dcSSc subset positive for the anti-Scl70 antibody, which trends to have severe internal organ involvement and high mortality [3, 10, 11]. Indications for hospitalization in our study were similar between SSc-related and non-SSc-related conditions, whereas the SSc-related condition was more prominent in the HCUP-NIS database [6]. The differences could be explained by low socioeconomic status, endemic area of infections, and/or differences among ethnic groups.

Most of the patients studied had one to two admissions (88.5 %) during the study period. Approximately 6 % had a readmission within 28 days due to the same malady as in the

previous admission (mostly SSc-related events); once admitted because of the disease itself, readmission was likely—particularly for cardiopulmonary or gastrointestinal sequelae.

Among the SSc-related conditions, PAH was the most common cause of admission, whereas pulmonary infections were the most common cause among non-SSc-related conditions. Notwithstanding, the most common cause of death in the current series was a lower respiratory tract infection caused by common bacterial infection. Opportunistic infection was not found among our observations, despite immunosuppressant therapy. The analysis cannot be used to differentiate which clinical predictors were responsible for lower respiratory tract infection, neither for esophageal involvement, reflux esophagitis, dcSSc subset, pulmonary fibrosis, and use of corticosteroid or immunosuppressive drugs.

Not surprisingly, the presence of coagulopathy became the strongest predictor of hospital mortality as it is the result of severe infection complicated by disseminated intravascular coagulation (DIC). It is well-known that DIC can increase the risk of organ failure and death [12].

SSc patients who had shorter disease duration had a high mortality risk if admitted. These patients tend to have severe internal organ involvement(s), especially intestinal involvement and renal crisis, which are also related to hospital mortality. According to the natural course of SSc, disease progression such as skin tightness and internal organ involvement was revealed within the first 3–5 years [3, 13, 14] and associated with mortality among sufferers of SSc [4, 5].

The LOS among our observations was affected by fatigability, intestinal symptoms, both baseline and hospital electrolyte disorder, ≥4 both baseline and hospital comorbidities, disease duration under 5 years, modified Rodnan skin score ≥20 points, BMI ≤18 kg/m^2, and hospital deficiency anemia. The Canadian Scleroderma Research Group database reported a high mortality risk among malnourished SSc patients, particularly those with a shorter disease duration [15]. Lim et al. found that malnourished patients had a significantly prolonged LOS [16]. Approximately 10 % of intestinal involvements in our studied patients had a lower BMI, electrolyte disorder, and deficiency anemia that needed enteral or parenteral nutritional supports to improve nutritional status for several days during admission. It is, therefore, necessary to evaluate and monitor the nutritional status among SSc patients in daily practice, especially those who have intestinal symptoms; in order to prevent the progression of malnutrition, leading to multiple comorbid developments and affecting LOS.

Our study was primarily limited by the retrospective nature of the data collection. The major cause of death depended upon clinical information available in the medical records as most of the cases that had died in hospital had not undergone autopsy to determine the pathology. None of the patients included had been assessed for a systemic sclerosis activity score [17]: we, therefore, could not effectively investigate the association between disease activity and causes of hospitalization or death. Our data nonetheless included other details of SSc clinical characteristics; SSc subsets, specific autoantibodies, modified Rodnan skin score, disease duration at the time of admission, and readmission data. To our knowledge, these parameters have never before been analyzed for their association with the course of hospitalization and hospital mortality. The findings of the current study, therefore, yield new information for evaluating hospitalized Thai SSc patients; some of which can be used for improving the care of SSc patients with PAH and gastrointestinal involvement.

Conclusion

Infection was the most common cause of hospitalization among Thai SSc patients followed by PAH. Risk factors for prolonged hospital stay and high hospital mortality were found to be shorter disease duration, presence of intestinal involvements, cardiac arrhythmia, and the presence of four or more comorbidities. The causes of death among hospitalized SSc patients were due to non-SSc-related conditions and the most common cause was bacterial pneumonia.

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