Clinical Characteristics and Mortality in Systemic Sclerosis: A Comparison between Early- and Late-Referred Diseases

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Objective: *To determine if there is any significant difference in the clinical characteristics and mortality between early-and late-referred systemic sclerosis (SSc).*

Material and Method: *An historical cohort study was performed among referred-SSc patients at Srinagarind Hospital between January 2006 and December 2010. 'Early referrals' occurred during the edematous phase while 'late referrals' occurred after that.*

Results: *Forty two percent of the SSc cases (229 of 543) were referred; 108 (47.2%) were early-referrals. Early referrals were for proper management (49.1%) and diagnosis (41.7%), whereas the majority of late referrals (79.3%) were for proper management, followed by additional investigations (10.7%). The respective median duration of disease at referral between early and late was 3.7 (IQR 2.6-5.6) and 20.7 months (IQR 12.2-37.4). Joint contracture, cardiac involvement and pulmonary fibrosis presented more frequently among late-referrals ($p<0.001$, $p = 0.03$ and $p = 0.04$, respectively). The respective mortality rate among early- vs. late-referrals was 15.1 (95% CI 10.0-21.8) vs. 23.0 (95% CI 15.8-32.3) per 100 person-year. Two-thirds of deaths were associated with the disease, pulmonary fibrosis being most common among both early- and late-referrals (50 and 42.7%, respectively).*

Conclusion: *The number of early vs. late referrals was comparable and cardiopulmonary involvement and joint contracture were common presentations in late-referrals. Late-referral was associated with high mortality commonly from pulmonary fibrosis.*

Keywords: *Systemic sclerosis (SSc), Scleroderma, Refer, Mortality, Autoimmune disease*

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Systemic sclerosis (SSc) is a rare disease for which skin tightness is the hallmark. Disease progression has been subdivided into (1) edematous stage, (2) indurative stage, and (3) atrophic phase[1]. In the edematous phase, the initial clinical manifestations, which could include puffy hands, sclerodactyly and/or Raynaud's phenomenon[1], are insufficient for confirming the diagnosis because the classical skin tightness is not yet detectable. An abnormal capillary nailfold pattern-such as giant capillary loop and presentation of specific autoantibodies (i.e., anti-centromere antibody or anti-topoisomerase-I) are the most appropriate markers for the diagnosis of early SSc[2]. Whereas skin tightness is the classical presentation of the indurative phase of the disease, the extension of which is classified into two major subsets, (a) limited cutaneous systemic sclerosis (LcSSc), and (b) diffuse cutaneous systemic sclerosis (DcSSc)[1]. The skin tightness of LcSSc is limited to the face, hands, feet, forearms, and legs, whereas the skin tightness of DcSSc extends proximal to the elbows and knees, or includes the trunk. Rapid skin thickness progression was reported in DcSSc patients[3] and is associated with a poor survival outcome and development of a scleroderma renal crisis within the first two years of the disease[3].

Fibrosis is a predominant pathological finding in SSc, presenting not only in the skin but also in the internal organs (i.e., the kidney, lung, heart, and intestines)[4-9]. Internal organ involvement could be detected in the early course of the disease, particularly among patients with DcSSc[4]: these patients trended to be referred to secondary or tertiary centers[10]. Since internal organ involvement is associated with significant morbidity and mortality in both LcSSc and DcSSc[4,11], these patients should be closely followed-up in order to monitor any

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internal organ involvement and for initiation of early treatment.

There are no recent reports on the clinical characteristics of referred patients with SSc and a comparison of the mortality rate in patients who were referred early vs. late. When these are released, they should reflect whether the healthcare and referral system is working appropriately for SSc patients. If the mortality rate among late-referred SSc is high, the preliminary data should provide some guidance vis-à-vis evaluating SSc patients and could be used to improve the care of SSc patients in daily practice.

Our objectives were (1) to identify the clinical characteristics of Thai patients referred with systemic sclerosis (2) to determine the clinical difference between early referred and late referred patients and (3) to determine the mortality rate of patients referred early vs. late.

Material and Method

The authors conducted an historical cohort study of SSc patients over 15 years of age, diagnosed with SSc and referred to Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand, between January 1, 2006 and December 31, 2010. Any patients who had an overlap with any other connective tissue disease were excluded from the study.

All medical records indicating a diagnosis of SSc with a referral from a local hospital were reviewed. Clinical characteristics according to the theory being studied were categorized. The differences in clinical characteristics between early- and late-referred patients were reviewed. Our primary outcome was the clinical characteristics of referrals. The secondary outcome was the mortality rate of the late referrers from a local hospital.

Operation definition

A diagnosis of systemic sclerosis (SSc) was based on the American College of Rheumatology Criteria[12] SSc was classified as a limited or diffused type as per the classification by LeRoy et al[13]. A referred patient was defined as a patient referred from any hospital. An early referral was indicated when the patient was referred during the edematous phase of the disease, after which any referred patient was defined as a late referral.

The 'start date' was the date when the patients had any first SSc symptoms while the 'end date' was the 'date of decease' (if the patient died), or the last meeting date (if the patient was lost to follow-up or the patient was still alive before December 31, 2011). The 'referral date' was the date the patient was sent from the local hospital. 'Time to event' (death) was the time calculated by subtracting the 'end date' from the 'start date'.

Pulmonary fibrosis was defined when interstitial fibrosis was detected by either chest radiographic or high-resolution computed tomography (HRCT) chest. Alveolitis was diagnosed when ground glass opacity was detected by HRCT chest and the other causes of the finding, particularly infection, were excluded. Stomach involvement was defined when the patient had such a clinical of early satiety, delayed gastric emptying, or upper gastrointestinal bleeding related to telangiectasia. Intestinal involvement was defined when the patient had any intestinal symptoms of SSc such as malabsorption, constipation, ileus or pseudo-intestinal obstruction that need to rest bowel and use total parenteral hyperalimentation. Myositis was diagnosed if the muscle enzyme, creatine phosphokinase was elevated or an abnormal finding from the electromyography was found. Pulmonary arterial hypertension (PAH) was defined by the right ventricular systolic pressure (RVSP) from echocardiogram >40 mmHg[14].

Statistical analysis

The categorical data were tested for significance using the Chi-square or Fisher's exact test while the continuous data were analyzed using the student t-test or the Mann-Whitney test, as appropriate. Each mortality rate was described together with its 95% confidence interval and described separately between early and late referrals. The hazard ratio, 95% CI and p-value were used to assess the clinical characteristics associated with mortality. The variables with a p-value <0.05 were entered into a multiple logistic regression model and the best model fitted using the backward elimination method. Variables were tested for significance using the Wald X^2 statistic. Cox regression model was used to assess the factors associated with death. All statistical tests were two-tailed. A p-value of <0.05 was considered statistically significant. All of the data analyses were performed using STATA version 11.0 (Stata Corp., College Station, TX, USA).

The present study was designed by the authors and approved by the Human Research Ethics Committee of Khon Kaen University (HE541341). The sponsors had no role in this study.

Results

Two hundred twenty nine of 543 new SSc cases (42.2%) were referred from local hospitals; 108 (47.2%) were early-referrals. The female to male ratio was 2.3:1. The mean age at referral was 50.6±11.6 (range, 16.7-84.1). The respective median duration of disease at referral between early and late was 3.7 (IQR 2.6-5.6) and 20.7 (IQR 12.2-37.4) months. The mean age at disease onset for the late referrals was significantly less than among the early referrals; whereas, there was no statistically significant difference for mean age at referral (Table 1).

Early referrals were for proper management (53 cases; 49.1%), diagnosis (45 cases; 41.7%), patient request (9 cases; 8.3%) and additional investigation(s) (1 case; 0.9%). By comparison, the majority of late referrals (96 cases; 79.3%) were for proper management, followed by additional investigation(s) (13 cases, 10.7%) and patient request (12 cases; 9.9%). Almost all of the cases were referred due to disease

Table 1. Comparison of clinical presentation at referral between early and late referrals

Data	Early referrals (n = 108)	Late referrals (n = 121)	p-value
Female	78 (72.2%)	81 (67.8%)	0.46
Age at onset; mean ± SD	50.7±11.9	47.3±11.4	0.03*
Age at refer; mean ± SD	51.0±11.9	50.1±11.2	0.56
MRSS at refer; median (IQR)	11 (6-17)	14 (6-24)	0.08
Anti-Scl70 positive	48 of 61 (78.7%)	42 of 49 (85.7%)	0.34
DcSSc subset	70 (65.1%)	99 (82.1%)	0.02*
Primary diagnosis at referral			
SSc related	102 (94.4%)	110 (90.0%)	0.31
Non-SSc related	6 (5.6%)	11 (9.1%)	
Localized infection	4	3	
Gastric ulcer with gastrointestinal bleeding	0	1	
Liver disease	1	0	
Deep venous thrombosis	1	0	
Coronary artery disease	0	3	
Cancer	0	4	
SSc clinical presentations at referral			
Raynaud's phenomenon	84 (77.7%)	87 (72.5%)	0.36
Digital ulcer	10 (9.3%)	15 (12.5%)	0.43
Digital gangrene	5 (4.6%)	9 (7.5%)	0.37
Hand deformity	3 of 77 (3.9%)	30 of 90 (33.4%)	<0.001*
Arthralgia	42 (38.9%)	36 (30.0%)	0.16
Synovitis	7 (6.5%)	5 (4.2%)	0.43
Muscle weakness	14 (12.9%)	8 (6.7%)	0.11
Myositis	35 (32.5%)	43 (35.7%)	0.68
Tendon friction rub	6 (5.6%)	8 (6.7%)	0.73
Dysphagia	49 of 106 (46.3%)	40 of 120 (33.4%)	0.05
Reflux symptoms	16 (14.9%)	120 (16.7%)	0.72
Stomach involvement	27 (25.0%)	21 (17.5%)	0.17
Intestinal involvement	7 (6.5%)	8 (6.7%)	0.96
Pulmonary fibrosis	58 (53.7%)	80 (66.1%)	0.04*
Alveolitis	19 (17.6%)	18 (15.0%)	0.60
Renal crisis	3 (2.8%)	2 (1.7%)	0.57
Cardiac evaluation	n = 8	n = 19	
Diastolic dysfunction	1 (12.5%)	4 (21.1%)	0.03*
Pericardial effusion	4 (50.0%)	11 (57.9%)	0.71
Pulmonary arterial hypertension	2 (25.0%)	8 (42.1%)	0.04*

* $p<0.05$

IQR = interquartile range; MRSS = modified Ronan skin score; SSc = systemic sclerosis; DcSSc = diffuse cutaneous systemic sclerosis

related conditions and around 10% of the total referred SSc patients were referred due to non-SSc-related conditions (Table 1), among whom localized infection was the most common early referral and cancer the most common late referral.

A comparison of clinical presentations between early and late referral is presented in Table 1. Joint contracture, DcSSc subset, cardiac involvement and pulmonary fibrosis presented significantly more frequently among late than early referrals ($p<0.001$, $p = 0.02$, $p = 0.03$ and $p = 0.04$, respectively). None of the late referrals had been screened for PAH by echocardiography and none evaluated for the severity of pulmonary fibrosis or for alveolitis.

Low-dose steroid was prescribed in the first 2 weeks after referrals for edematous skin treatment in 33 early-referred patients (30.6%) and moderate-dose steroid for myositis treatment in 9 early (8.3%) and 4 late referrals (3.3%). Immunosuppressant was prescribed for active alveolitis treatment in 19 early referrals (17.6%) and 18 late referrals (14.9%). The number of patients on steroid therapy among early referrals was significantly larger than for late referrals ($p = 0.001$); however; the number of immuno-suppressants prescribed was not different ($p = 0.71$).

Sixty-five cases died (28.4%) during the follow-up period; 30 (27.8%) were early referrals and 35 (28.9%) late referrals. The respective mortality rate of early- vs. late-referrals was 15.1 (95% CI 10.0-21.8) vs. 23.0 (95% CI 15.8-32.3) per 100 person-year. Although the mortality rate among late referrals was higher than early referrals, there was no association between referral status and mortality risk (hazard ratio 1.49; 95% CI 0.90-2.46). The Kaplan-Meier survival estimates the survival rate between the early vs. late referrals is presented in Fig. 1. Two-thirds of deaths were associated with the disease: pulmonary fibrosis being most common among both early- and late-referrals (50 and 42.7%, respectively) (Fig. 2). Heart failure was the second most common cause of death among early referrals whereas cancer was the second most common in late referrals (viz., cervical cancer, cholangiocarcinoma, hepatocellular carcinoma, and squamous cell cancer of unknown origin).

Age of onset >60 years, modified Rodnan skin score (MRSS) >20, digital gangrene, myositis, renal crisis, and diastolic dysfunction at referral were associated with mortality risk among early referrals (Table 2). There was, however, no significant association between those clinical parameters and mortality risk after using the Cox regression analysis (Table 3). By comparison, among later referrals only age at onset >60 years was associated with the mortality risk according to the Cox regression analysis with adjusted hazard ratio (HR) 3.13 (95% CI 1.14-8.59) (Table 3).

Discussion

Around 40% of SSc patients in our center were referred from local hospitals, among whom late referrals were slightly more common than early referrals. The most common reasons for referral among the early referrals were for proper management and diagnosis whereas the majority of late referrals were for proper management. The data may reflect the difficulty of making a diagnosis at the early edematous phase of the disease[2]; consequently, nearly half of the patients were referred because of an

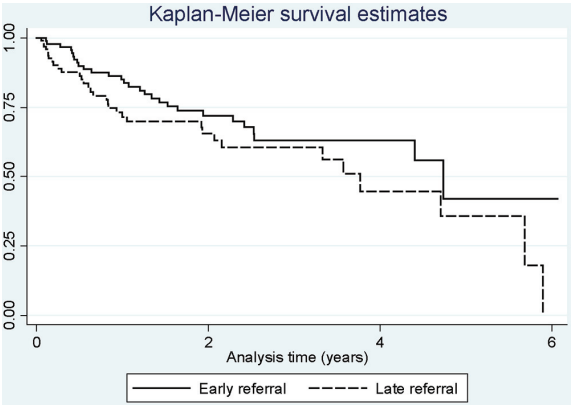

Fig. 1 Comparison of Kaplan-Meier curves between early- and late referrals.

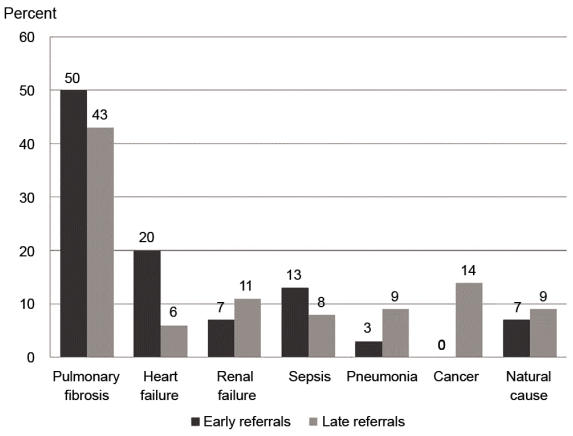

Fig. 2 Causes of death categorized by early and late referrals.

Table 2. The mortality risk of early- and late referrals

Data	Early referrals HR (95% CI)	p-value	Late referrals HR (95% CI)	p-value
Female	1.66 (0.67-4.12)	0.28	0.70 (0.35-1.41)	0.32
Age at onset >60 years	2.68 (1.23-5.86)	0.01*	3.39 (1.25-9.17)	0.02*
MRSS at refer >20	6.96 (1.52-31.92)	0.01*	1.77 (0.59-5.31)	0.30
Anti-Scl70 positive	1.18 (0.26-5.32)	0.21	1.27 (0.16-10.39)	0.82
DcSSc subset	1.44 (0.39-5.25)	0.58	1.43 (0.42-4.91)	0.57
SSc clinical presentations at referral				
Raynaud's phenomenon	1.25 (0.50-3.12)	0.63	0.71 (0.34-1.49)	0.37
Digital ulcer	1.03 (0.31-3.43)	0.96	1.79 (0.77-4.20)	0.18
Digital gangrene	5.13 (1.73-15.14)	0.003*	3.61 (1.04-12.48)	0.04*
Hand deformity	0.95 (0.12-7.24)	0.96	1.12 (0.48-2.60)	0.79
Arthralgia	0.87 (0.41-1.87)	0.73	0.78 (0.36-1.68)	0.53
Synovitis	0.47 (0.06-3.52)	0.47	NA	NA
Muscle weakness	1.30 (0.49-3.43)	0.60	1.06 (0.25-4.48)	0.94
Myositis	3.19 (1.23-8.27)	0.02*	2.70 (0.99-7.33)	0.05
Tendon friction rub	1.65 (0.39-7.01)	0.49	0.62 (0.15-2.60)	0.51
Dysphagia	0.85 (0.40-1.82)	0.68	1.12 (0.55-2.27)	0.76
Reflux symptoms	0.60 (0.18-1.99)	0.41	0.19 (0.05-1.82)	0.54
Stomach involvement	0.39 (0.13-1.15)	0.09	0.84 (0.36-1.97)	0.68
Intestinal involvement	0.42 (0.05-3.33)	0.41	2.34 (0.70-7.84)	0.17
Pulmonary fibrosis	1.78 (0.82-3.88)	0.15	1.82 (0.69-4.77)	0.22
Alveolitis	0.90 (0.31-2.62)	0.85	0.62 (0.22-1.79)	0.38
Renal crisis	7.95 (1.81-34.92)	0.01*	5.50 (1.27-23.85)	0.02*
Diastolic dysfunction	6.13 (2.44-15.38)	<0.001*	1.49 (0.64-3.49)	0.35
Pericardial effusion	1.70 (0.33-8.62)	0.52	1.14 (0.21-6.35)	0.88
Pulmonary hypertension	1.72 (0.28-10.46)	0.55	1.69 (0.33-8.60)	0.53

* p<0.05
HR = hazard ratio; CI = confidence interval; MRSS = modified Ronan skin score; SSc = systemic sclerosis; DcSSc = diffuse cutaneous systemic sclerosis; NA = not available

Table 3. Cox regression model of clinical parameters for prediction of death in early and late referrals

Data	Early referrals		Late referrals	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Age at onset >60 years	2.68 (1.23-5.86)	7.95 (0.83-76.00)	3.39 (1.25-9.17)	3.13 (1.14-8.59)*
MRSS at refer >20	6.96 (1.52-31.92)	4.75 (0.53-42.72)		
Digital gangrene	5.13 (1.73-15.14)	NA	3.61 (1.04-12.48)	3.32 (0.92-11.97)
Myositis	3.19 (1.23-8.27)	3.14 (0.25-40.07)		
Renal crisis	7.95 (1.81-34.92)	1.80 (0.17-3.92)	5.50 (1.27-23.85)	NA
Diastolic dysfunction	6.13 (2.44-15.38)	5.24 (0.49-56.43)		

* p<0.05
HR = hazard ratio; CI = confidence interval; MRSS = modified Ronan skin score; NA = not available because of too low number

unknown definite diagnosis. Once the skin presented obvious tightness, particularly at the indurative phase, the patient would be referred when complicated internal organ involvement was detected and/or the disease needed special additional investigation.

Almost all of our patients were referred due to a disease related condition and the majority of late referrals were for proper management. Of note, the late referrals had more frequent hand deformities and internal organ involvements (viz., cardiopulmonary) than the early referrals. These patients seemed to have more severe disease at time of referral. It was probably that the local hospital selected the more severe disease presentation for referral to our supra-tertiary center.

Since internal organ involvement is associated with significant morbidity and mortality in SSc[4,11,15,16], it was not surprising that our late referrals patients had a higher mortality rate than the early referrals. There was, however, no clinical parameter associated with mortality risk in both early- and late referrals except age at onset >60 years, which was a predictor of death among our late referrals SSc patients. As in a previous large cohort study[11], age of onset >50 years is a predictor of mortality. This might imply that late disease evaluation and delayed treatment because of late referral increases the mortality risk among SSc patients, particularly among those with elderly onset disease.

According to our observations, the median time between the disease onset and the referral date was a relatively short period, particularly in late referrals (i.e., 20.7 months). This finding may reflect the short period of the skin edematous phase in our SSc patients. This observation should guide the primary physician to be concerned about a progressive skin tightness with or without any early internal organ involvement in SSc patients who present with edematous skin particularly in the first year after disease onset.

The high prevalence of anti-Scl70, myositis and pericardial effusion, the low prevalence of Raynaud's phenomenon, and the significant number of males in our cohort compared to previous studies might be explained by the warm climate and a high prevalence of DcSSc among Thai SSc[17,18] patients over against Western series[19-22], perhaps because of ethnic difference or genetic factors[23]. The high prevalence of DcSSc and internal organ involvement particularly pericardial effusion would be also a reason of poor prognosis in our patients.

PAH is one of the factors indicating a poor prognosis for SSc and the respective 2- and 3-year survival rate was only 71% and 65%, among those who had no PAH treatment[15]. Therefore, annual echocardiographic screening for PAH has been proposed for all SSc patients[24]. None of our late referrals had, however, been screened for PAH before refer and one of the late referrals patients came to us too late with severe PAH with right-side heart failure. These data could reflect the limitation of PAH evaluation-the investigation tool, cardiologist, or knowledge-at the primary center level in Thailand. The results reveal a weak link in the healthcare delivery system that could be addressed in order to provide SSc patients better care continuity.

The present study had several limitations. First, the study was primarily limited by the retrospective nature of the data collection. Second, the first clinical presentation was not always correctly recorded in the referral documentation particularly for the late referrals. Therefore, the authors did not compare the first clinical presentation between the early and late referrals. Third, there was limitation in to perform some specific serologic tests for SSc-PM overlap such as anti PM-Scl, anti-Ku, also muscle biopsy was not routinely performed in SSc patients who had elevation of CPK without proximal muscle weakness, so that SSc-PM overlap could not conclusively excluded even if muscle enzyme was slightly elevated. However, the patients who had positive serological test other than specific serology for SSc such as anti RNP were excluded. Finally, the major cause of death was determined using only the clinical data as most of the cases had not undergone autopsy to determine the precise cause of death. Notwithstanding, the present is the first study to explore the clinical difference and mortality rate between early and late referrals. Ultimately, the data can be used for devising better care of SSc patients at both primary healthcare centers and the follow-on referral centers.

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Author contributions

Retrospective research: all authors; Manuscript preparation: all authors.

Potential conflicts of interest

None.

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ลักษณะทางคลินิกและการเสียชีวิตของผู้ป่วยโรคหนังแข็ง: เปรียบเทียบระหว่างผู้ป่วยที่ได้รับการส่งตัวมารักษาต่อแต่เนิ่นและส่งตัวช้า

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วัตถุประสงค์: *เพื่อศึกษาความแตกต่างระหว่างลักษณะทางคลินิกและอัตราการเสียชีวิตของผู้ป่วยโรคหนังแข็งที่ได้รับการส่งตัวมารักษาต่อแต่เนิ่นและส่งตัวช้า*

วัสดุและวิธีการ: *การศึกษา cohort แบบย้อนหลังในผู้ป่วยโรคหนังแข็งที่เข้ารับการรักษาที่โรงพยาบาลศรีนครินทร์ ระหว่างเดือนมกราคม พ.ศ. 2549 ถึง เดือนธันวาคม พ.ศ. 2553 การส่งตัวมารักษาต่อแต่เนิ่นคือ การส่งตัวในขณะที่อยู่ในระยะผิวหนังบวมตึง (edematous phase) ขณะที่การส่งตัวช้าคือ การส่งตัวหลังจากระยะผิวหนังบวมตึงผ่านไปแล้ว*

ผลการศึกษา: *ผู้ป่วยโรคหนังแข็งร้อยละ 42 (229 จาก 543 ราย) ได้รับการส่งตัวมารับการรักษาต่อผู้ป่วย 108 ราย (ร้อยละ 47.2) เป็นผู้ป่วยที่ได้รับการส่งตัวมารักษาต่อแต่เนิ่น ผู้ป่วยที่ได้รับการส่งตัวมารักษาแต่เนิ่นถูกส่งมาเพื่อขอรับการรักษาที่เหมาะสม (ร้อยละ 49.1) และเพื่อวินิจฉัย (ร้อยละ 41.7) ในขณะที่ผู้ป่วยที่ถูกส่งตัวมารักษาช้าถูกส่งมาเพื่อขอรับการรักษาที่เหมาะสม (ร้อยละ 79.3) และเพื่อตรวจสืบค้นเพิ่มเติม (ร้อยละ 10.7) ตามลำดับ ค่ากลางของระยะเวลาของโรคจนถึงวันที่ได้รับการส่งตัวมารักษาต่อในผู้ป่วยที่ได้รับการส่งตัวแต่เนิ่นและส่งตัวช้า คือ 3.7 (ช่วง 2.6-5.6) และ 20.7 เดือน (ช่วง 12.2-37.4) ตามลำดับ ภาวะข้อติดงอ พยาธิสภาพที่หัวใจ และภาวะปอด เป็นพังผืดเป็นลักษณะทางคลินิกที่พบได้บ่อยในผู้ป่วยที่ได้รับการส่งตัวช้าเมื่อเทียบกับผู้ป่วยที่ได้รับการส่งตัวแต่เนิ่น (ค่า $p<0.001$, $p = 0.03$ และ $p = 0.04$ ตามลำดับ) อัตราการเสียชีวิตของผู้ป่วยที่ได้รับการส่งตัวแต่เนิ่นและส่งตัวช้า คือ 15.1 (ช่วงเชื่อมั่นร้อยละ 95 = 10.0-21.8) และ 23.0 (ช่วงเชื่อมั่นร้อยละ 95 = 15.8-32.3) ต่อ 100 คน-ปี สองในสามของผู้ป่วยเสียชีวิตจากตัวโรคเองโดยภาวะปอดเป็นพังผืดเป็นสาเหตุการเสียชีวิตหลักของทั้งผู้ป่วยที่ได้รับการส่งตัวแต่เนิ่นและส่งตัวช้า (ร้อยละ 50 และ 42.7 ตามลำดับ)*

สรุป: *การศึกษานี้พบว่าจำนวนผู้ป่วยที่ได้รับการส่งตัวแต่เนิ่นและส่งตัวช้าใกล้เคียงกัน พยาธิสภาพที่หัวใจและปอด รวมทั้งภาวะข้อติดงอเป็นลักษณะทางคลินิกที่พบบ่อยในผู้ป่วยที่ได้รับการส่งตัวช้า และการส่งตัวช้าสัมพันธ์กับอัตราการเสียชีวิตที่สูงขึ้นโดยเฉพาะเสียชีวิตจากภาวะปอดเป็นพังผืด*