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Management pitfalls and prevalence of lost to follow-up due to unpredicted death in systemic sclerosis

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Abstract

Lost to follow-up in systemic sclerosis (SSc) is reported. Unpredicted death before visit schedule might be the result of pitfalls in patients care management. We aimed to define the prevalence of lost to follow-up due to unpredicted death in SSc and management pitfalls. A retrospective study was performed using scheduled visits to the Scleroderma Clinic, Khon Kaen University, between January 2019 and April 2020. A direct telephone call was performed when lost to follow-up was identified. If no response was received, the medical records were reviewed, and health status was requested from the Civil Registration Bureau. A total of 497 adult SSc patients with 2,040 follow-ups from 53 visits were reviewed, of whom 37 were lost to follow up due to unpredicted death for a prevalence of 7.4% (95% cumulative incidence (CI) 5.3-10.1). The respective median time from death to the next scheduled visit and median duration of disease was 19.7 days (Interquartile Range (IQR) 2.9-34) and 3.8 years (IQR 1.7-7.5). Six cases were defined as an improper interval of follow-up and monitoring that led to death before the scheduled visit. All had cardiopulmonary involvement. One case was defined as improper management given for cardiac involvement. Pneumonia and sepsis were the causes of death in 4 of 14 cases that received the immunosuppressant. Death before the scheduled follow-up visit occurred among SSc patients, particularly among those with cardiopulmonary involvement and inadequate monitoring or management. Close monitoring should be the norm for SSc patients with cardiopulmonary involvement to avoid unpredicted death.

Keywords: Scleroderma, Systemic sclerosis, Loss follow-up, Mortality, Pitfalls

1. Introduction

Systemic sclerosis (SSc) is a rare systemic disease which skin thickness is the classical clinical feature. The area of skin thickness is categorized into two subsets (a) diffuse cutaneous systemic sclerosis (dcSSc) and (b) limited cutaneous systemic sclerosis (lcSSc) [1]. Extent of skin involvement in lcSSc is limited to the face, forearms, hands, legs, and feet, while in dcSSc, the skin thickness extends proximal to elbows and knees and/or includes the trunk. the skin thickness extends proximal to the elbows and knees and/or includes the trunk. Rapid progression of skin thickening is related to poor outcomes and associated with a scleroderma renal crisis particularly in an early onset of disease [2].

Fibrosis presents in the skin and the internal organs (i.e., the kidney, lung, heart, and intestines) [3-8]. Internal organ fibrosis can be revealed early in the disease, especially in dcSSc patients [3]. Currently, such patients are referred to secondary center or tertiary centers [9,10]. Since internal organ fibrosis is related to significantly high mortality and morbidity in both dcSSc and lcSSc [3,11], and these patients should be followed closely and monitored for any internal organ involvement that could be treated.

Ours is a supra-tertiary care center that receives many referred SSc cases from the northeastern region of Thailand [10]. Despite tracking referrals (i.e., from primary and secondary centres to our tertiary care centre), the number of cases lost to follow-up remains a concern. A good way to decrease losses to follow up is for the

attending physician (or team designate) to contact the patient as soon as they are flagged as lost to follow up to ask about their health status. We have found that some patients were unable to be contacted by telephone or had died before the scheduled visit. We aimed to define the prevalence of lost to follow-up due to unpredicted death in SSc and the pitfalls that had occurred in the management of those patients. The findings should help get better care for SSc inpatients by informing attending physicians how to identify the clinical characteristics associating with a poor outcome and the management pitfalls of SSc patients.

2. Materials and methods

This retrospective study was performed using scheduled visits to the Scleroderma Clinic, Khon Kaen University, Thailand, between 1 January 2019 and 30 April 2020. The Scleroderma Clinic was open on Wednesdays, with at least 30 patients scheduled every week. All patients were over 18 and had a definition of SSc per the American College of Rheumatology (ACR) criteria [12] and the 2013 ACR/EULAR Classification for Scleroderma [13]. The SSc subset was either dcSSc or lcSSc [14]. We included the patients who were lost to follow-up between 1 January 2019 and 30 April 2020. When the lost to follow-up cases were identified, the attending physician called to ask the patient how they were doing and why they did not come to the scheduled visit. The reasons for lost to follow-up were recorded and requested for the new visit follow-up. If no response was received, the medical charts of those patients were evaluated for gathering medical problems, health status, and medical treatment during the last visit. In addition, the living status of patients was checked against the Civil Registration Bureau. We excluded any patients coming to the clinic in the "prior visit due to any causes," "coming late for the next visit," "receiving a medical assessment for SSc," and "follow-up at the same hospital outside the Scleroderma Clinic by an internist or doctor in training in Internal Medicine.

Data collection included date of the scheduled visit, age, sex, duration of disease, clinical characteristics of SSc, comorbid diseases, laboratory results, and medical treatment on the visit before being lost to follow-up, living status, and cause of death (if died).

2.1 Operation definitions

The 'initial date' was the date of first non-Raynaud SSc symptoms and the 'last date' was the last meeting date or the 'date of death' (if the patient died). Lost to follow-up was defined when the SSc patients did not come to hospital according to the scheduled visit. The definition of unpredicted death is fulfilled when the patient dies before coming for the scheduled visit. The causes of death were labeled according to the death certificate from the Civil Registration Bureau. Pulmonary fibrosis was defined when fibrosis was revealed by either pulmonary radiograph or high-resolution computed tomography (HRCT) of chest. The definition of pulmonary arterial hypertension (PAH) was defined when the mean pulmonary artery pressure was > 20 mmHg using right heart catheterization [15]. Cardiac involvement included a left ventricular ejection fraction < 50% or pericardial effusion detection by echocardiography without any other cause. Esophageal involvement included heartburn, esophageal dysphagia, or reflux symptoms. Stomach involvement was defined when any stomach symptoms were revealed (i.e., early satiety, dyspepsia, or bloating).[16] Hand deformity included flexion contractures of finger joints resembling claw deformities [17]. Anemia was defined as hemoglobin (Hb) level < 13 g/dL in men and < 12 g/dL in non-pregnant women [18].

2.2 Statistical analysis

The data were set as categorical or continuous. The continuous data were displayed as appropriate as means±standard deviations (SD) or medians and interquartile ranges (IQR). The categorical data were displayed as proportions or percentages. In order to define the prevalence of lost to follow-up due to unpredicted death in SSc, the prevalence and its 95% confidence interval of lost to follow-up due to unpredicted death in SSc was assessed. The management pitfalls were evaluated, particularly those associated with lost to follow-up due to unpredicted death in SSc. The statistics were analysed using STATA version 16.0 (StataCorp., Texas, USA).

3. Results and discussion

A total of 497 adult patients with SSc who were attended at the Scleroderma Clinic during the study period were included, of whom the majority were female (330 cases; 66.4%). Of the 2,040 follow-up visits (based on 53 clinic sessions with at least 30 patients/session), 272 cases (54.7%) were lost to follow-up. The most common reasons for lost to follow-up were "forgetting the scheduled visit" (176 cases; 64.7%), followed by "unpredicted death" (37 cases; 13.6%), then "receiving treatment" and "following up at local hospital" (30 cases; 11.0%), and "unable to contact" (29 cases; 10.7%) (Figure 1). All patients that forgot the scheduled visit returned after rescheduling their visit.

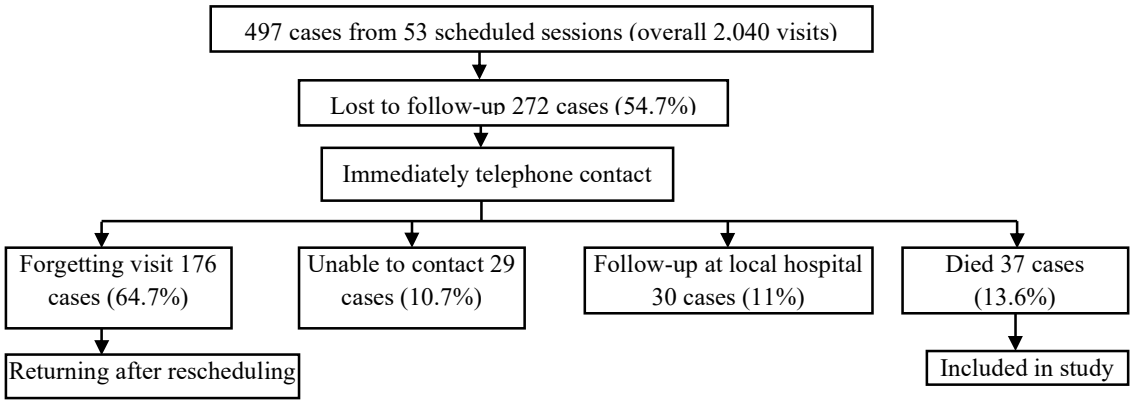

Figure 1 Flow of patients at the Scleroderma Clinic during the study period.

After focusing on the patients lost to follow-up due to unpredicted death according to the study objective, the prevalence of lost to follow-up due to unpredicted death had a prevalence of 7.4% (95%CI 5.3-10.1), when evaluated with the overall cases in the Scleroderma Clinic. The respective median time from the last visit to death and the median time from death to the next scheduled visit was 40 days (IQR 22-104.8) and 19.7 days (IQR 2.9-34). The clinical characteristics of the SSc patients with unpredicted death are showed in Table 1.

Table 1 Clinical characteristics of patients with unpredicted death at the last visit before lost to follow-up.

Variable	N = 37
Age at onset (years); mean±SD	51.9±10.4
Age at death (years); mean±SD	58.2±7.8
Female sex (%)	19 (51.4)
Duration of disease (years); median (IQR)	3.8 (1.7-7.5)
Time from the last visit to death (days); median (IQR)	40 (22-104.8)
Time from death to the following scheduled visit (days); median (IQR)	19.7 (2.9-34)
Diffuse cutaneous SSc subset (%)	31 (83.8)
Comorbid diseases	
Dyslipidemia (%)	6 (18.2)
Hypertension (%)	5 (13.5)
Thyroid disease (%)	5 (13.5)
Diabetes mellitus (%)	4 (10.8)
Coronary artery disease (%)	4 (10.8)
Cerebrovascular disease (%)	1 (2.7)
Lung cancer	1 (2.7)
Clinical characteristics of SSc	
WHO functional class	
I (%)	5 (13.5)
II (%)	20 (54.1)
III (%)	11 (29.7)
IV (%)	1 (2.7)
Active digital ulcer (%)	5 (13.5)
Digital gangrene (%)	2 (5.4)
Tendon friction rub (%)	12 (32.4)
Hand deformity (%)	20 (54.1)
Muscle weakness (%)	4 (10.8)
Esophageal involvement (%)	19 (51.4)
Stomach involvement (%)	3 (8.1)
Intestinal involvement (%)	4 (10.8)
Pulmonary fibrosis (%)	23 (61.2)
Pulmonary arterial hypertension (%)	12 (32.4)
Cardiac involvement (%)	10 (27.0)
Renal crisis (%)	4 (10.8)
Modified Rodnan skin score (points); mean±SD	13.0±11.6
Laboratory data	
Anemia (%)	29 (80.6)
Serum creatinine (mg/dL); median (IQR)	0.79 (0.58-1.02)
Serum albumin (g/dL); mean±SD	3.5±0.5
Left ventricular ejection fraction < 50% (%)	8 (27.6)
FVC < 40% predicted (%)	5 (17.9)
Medical treatment	
Immunosuppressants	14
Mycophenolate mofetil (%)	8 (21.6)
Cyclophosphamide (%)	4 (10.8)
Methotrexate (%)	1 (2.7)
Azathioprine (%)	1 (2.7)

SD standard deviation; IQR interquartile range; SSc systemic sclerosis; WHO World Health Organization; FVC forced vital capacity

SSc-related death was the most common cause of death (21 cases; 56.8%), of which cardiac involvement (7 cases) and SSc unspecified organ involvement (7 cases) were the most common causes, followed by pulmonary fibrosis (4 cases) and renal crisis (2 cases). While pneumonia was the most common cause of non-SSc-related death (6 cases), followed by coronary artery disease (2 cases) and hypertensive intracranial hemorrhage (2 cases). The causes of death are presented in Figure 2. Three of the patients who died (10.8%) had 4 internal organ involvements, 10 (27.0%) had 3, 13 (35.1%) had 2, and 8 (21.6%) had 1. We found that 3 of the 6 patients who died from pneumonia received mycophenolate mofetil while another 3 had not received the immunosuppressant. The case who died from sepsis received mycophenolate mofetil before death. None of the patients who received the immunosuppressant had taken antibiotic prophylaxis for *Pneumocystis jirovecii* infection.

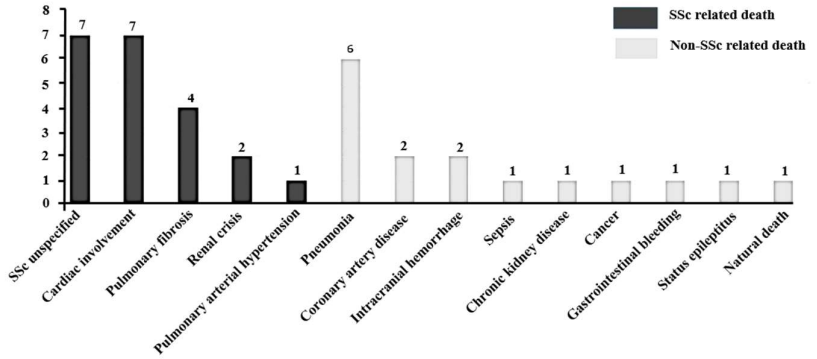

Figure 2 Causes of death.

The patient management pitfalls can be classified into two categories: a) improper interval for follow-up and monitoring, and b) improper management (Table 2). The impact of an overly long interval before follow-up was that patients died before the scheduled visit. In one case, the patient died due to inadequate management of cardiac involvement caused by SSc. The pitfalls of management are presented in Table 2.

Table 2 Pitfalls of management.

SSc subset	Duration of disease	Organ involvements	Causes of death	Detail of pitfalls
Improper interval of follow-up and monitoring				
lcSSc	1 year	Pulmonary fibrosis, cardiac and esophageal involvement with WHO functional class I and normal serum creatinine level	Renal crisis	Died 26 days before scheduled visit Interval of follow-up 12 weeks
dcSSc	1.2 years	Pulmonary fibrosis, PAH, esophageal, and stomach involvement with WHO functional class II	SSc unspecified	Died 2 days before scheduled visit Interval of follow-up 12 weeks
dcSSc	1.7 years	Pulmonary fibrosis and PAH with WHO functional class II	Cardiac involvement	Never performed cardiac monitoring after first visit Died 70 days before scheduled visit Interval of follow-up 14 weeks
dcSSc	4.8 years	Pulmonary fibrosis, PAH and cardiac involvement with WHO functional class II, LVEF 33%, and furosemide treatment	Pulmonary fibrosis	Died 11 days before scheduled visit Interval of follow-up 7 weeks
dcSSc	5.7 years	Pulmonary fibrosis, PAH with WHO functional class II and mycophenolate mofetil treatment	Pneumonia	Died 62 days before scheduled visit Interval of follow-up 14 weeks
lcSSc	5.8 years	PAH with WHO functional class III	PAH	Died 13 days before scheduled visit Interval of follow-up 13 weeks
Improper management				
dcSSc	4.3 years	Cardiac and esophageal involvement with WHO functional class II and LVEF 39.5%, NT-proBNP 5536 pg/mL	Cardiac involvement	No treatment for cardiac involvement despite signs of heart failure (high NT-proBNP)

SSc systemic sclerosis; lcSSc limited cutaneous systemic sclerosis; dcSSc diffuse cutaneous systemic sclerosis; WHO World Health Organization; PAH pulmonary arterial hypertension; LVEF left ventricular ejection fraction, NT-proBNP N-terminal prohormone of brain natriuretic peptide

A significant number of SSc patients are lost to follow-up. Our survey revealed that the rate of lost to follow up was around half of SSc patients. The rate was slightly higher than a study among Thai SSc patients in the last

decade (55% vs. 41%) [19]. The causes of loss follow-up in the previous study included (a) distance to hospital considered too far (63.3%), (b) difficulty ambulating and getting transportation (59.2%), and (c) being dependent on others (38.8%). Almost 92% received healthcare service at clinic near home or local hospital [19]. While "forgetting the appointment" was the most common reason for being lost to follow-up in our study (65%), only a minority (11%) went to a local hospital. The difference in the causes of loss follow-up between the two studies might be improved access to public transportation, more interprovincial highways, and/or greater private ownership of motor vehicles because of an increased Gross Domestic Product [20].

A prompt telephone call can reduce the unintended loss to follow-up. Over 60% of patients were lost to follow-up due to forgetting their appointment, but these patients rescheduled once called. The simple intervention of a call thus improved out-patient care for SSc patients. Some patients (10%) could not be contacted because of a change in telephone number, so regularly updating the patient contact database is advised.

Death before the scheduled visit occurred most commonly because of SSc-related cardiopulmonary involvement (57%). The findings are comparable to the causes of death in the SSc patients who regularly went for follow-up visits [11,21]. Of note, death caused by cardiopulmonary involvement occurred less frequently in our patients than in the previous study (52% vs. 87%).[19] The median duration between lost to follow-up and death in our study was around 40 days or 1.3 months. We found that the median duration between death and the next scheduled visit was less than 1 month (20 days), suggesting that some patients may have an improper interval to follow up and disease monitoring, leading to death before the next scheduled visit.

After examining the management pitfalls, we found that 6 of the patients had an improper interval to follow-up, and most of them had cardiopulmonary involvement, including PAH. At the same time, another case had improper management of cardiac involvement due to a lack of awareness of the early signs of heart failure. The findings underscore the need for close monitoring of SSc patients for better patient management and involvement of a multidisciplinary healthcare team, including the patient and their family.

Although non-SSc-related death was not as high as SSc-related death, the most common cause of death in this group was infection, and pneumonia was the most common infection. None of the patients who had pneumonia and received immunosuppressants were given antibiotics for prophylaxis of *Pneumocystis jirovecii* infection [22]. Unfortunately, we have no information about the etiologic organism of pneumonia in those patients as the Civil Registration Bureau does not record this detail, so we cannot conclude whether antibiotic prophylaxis for *Pneumocystis jirovecii* resulted in unpredicted death in SSc patients who received immunosuppressant therapy.

The interesting point is that 3 (50%) of the patients who died from pneumonia did not receive immunosuppressant therapy. One had pulmonary fibrosis, and one had esophageal involvements that are risks of pulmonary infection [23,24]. The changing or distortion of lung parenchymal structure may reduce local immunity and increase the risk of infection [23]. In addition to esophageal involvement in SSc, esophagus fibrosis causes lower esophageal sphincter dysfunction, gastroesophageal reflux, and risk of aspiration [25,26]. Therefore, the patient who has either pulmonary fibrosis or esophageal involvement should be aware of the risk of pulmonary infection, in order to reduce the mortality and chances of developing pneumonia.

Our study had some limitations, including a) missing data according to the nature of the retrospective study; b) the lack of autopsy to confirm the cause of death, so the cause of death was according to the death certificate from the Civil Registration Bureau; and, c) the limitation to evaluate the extent of pulmonary fibrosis so that we cannot have the information about the severity of PF of those patients who died due to pulmonary fibrosis. The strengths of this study included a) the extensive database on SSc out-patients, b) follow-up visits covering the whole year for all patients followed up at the Scleroderma Clinic; and, c) details of the quality of care in the out-patient unit. Ours is the first study on management pitfalls resulting in patients being lost to follow-up due to unpredicted death. The findings help attending physicians to be aware of the pitfalls when managing SSc patients so as to provide better, more timely care and follow-up.

4. Conclusion

Death before a scheduled follow-up visit was observed in SSc, particularly among those patients with cardiopulmonary involvement and improper monitoring or management of those conditions. Close monitoring and awareness of unpredicted death should be performed for SSc patients with cardiopulmonary involvement. In addition, a multidisciplinary healthcare team together with the patient and their family is needed to avoid pitfalls of poor management, including unpredicted death of SSc patients.

5. Ethical approval

The Human Research Ethics Committee of Khon Kaen University reviewed and approved the study as per the Helsinki Declaration and the Good Clinical Practice Guidelines (HE641076). The need for informed consent was waived by The Human Research Ethics Committee of Khon Kaen University.

6. Acknowledgements

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7. Conflict of interests

Authors declare that they have no conflict of interest.

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