Hospitalization Rates are Highest in the First 5 Years of Systemic Sclerosis: Results from a Population-based Cohort (1980-2016)

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Short Running Head: Hospitalization in Systemic Sclerosis

Abstract

Objective: Few studies have estimated the healthcare resource usage of patients with systemic sclerosis (SSc). The purpose of this study was to compare hospitalization among incident cases of SSc vs age- and sex-matched comparators.

Methods: A retrospective, population-based cohort of patients with SSc in Olmsted County, MN from Jan 1, 1980 to Dec 31, 2016 was assembled. A 2:1 cohort of age- and sex-matched patients without SSc from the same population was randomly selected for comparison. All hospitalizations in the geographic area from Jan. 1, 1987 to Sept. 30, 2018 were obtained. Rates of hospitalization, lengths of stay, and readmissions were compared between groups.

Results: 76 incident SSc cases and 155 non-SSc comparators (mean age of 56 ± 16 years at diagnosis/index, 91% female) were included. Rates of hospitalization among cases and comparators were 31.9 and 17.9 per 100 person-years, respectively (rate ratio [RR]:1.78; 95% confidence interval (CI):1.52-2.08). Hospitalization rates were higher in patients with SSc than comparators during the first 5 years after SSc diagnosis (RR: 2.16; 95%CI: 1.70-2.74). This difference decreased over time and was no longer significant at ≥15 years after SSc incidence/index. Lengths of stay (median (IQR) 4 (2-6) vs 3(2-6); p=0.52) and readmission rates (25% vs 23%; p=0.51) were similar between groups.

Conclusion: Patients with SSc were hospitalized more frequently than comparators, indicating high inpatient care needs in this population. Hospitalization rates were highest during the first 5 years following SSc diagnosis.

Introduction

Systemic sclerosis (SSc) is a rare systemic inflammatory disease characterized by widespread fibrosis of the skin and internal organs, microvascular injury and autoimmunity. SSc affects multiple organ systems and is associated with high morbidity and mortality, which exceeds that of other rheumatic diseases (1) and of the general population (2). Patients frequently develop internal organ complications from SSc, including digital ischemia, renal crisis, pulmonary arterial hypertension (PAH), progressive interstitial lung disease (ILD), cardiomyopathy, arrhythmias, gastrointestinal dysmotility and pseudo-obstruction. While the large majority requires close outpatient follow up, many SSc related complications may require in-hospital care. Cardiopulmonary disease is the major driver of mortality in SSc (3).

Given the severity and multi-system involvement of SSc, patients have tremendous health care needs in the inpatient and outpatient settings. Hospitalizations, medications, and outpatient appointments are reported to make up the bulk of medical costs for patients with SSc (4). A previous population-based study from the United States (U.S) reported that patients with SSc are more frequently hospitalized than unaffected matched controls, with longer lengths of inpatient stay (5). Healthcare costs were also higher in patients with SSc than controls, including costs for inpatient care which are estimated to make up 31% of total annual healthcare cost (5). Among U.S. patients with SSc, hospitalization has been consistently reported as more commonly occurring in women than men, with hospitalization rates increasing with age in 1995, 2002-2003, and 2012-2013 U.S. hospital cohorts (6-8). Presence of ILD has been associated with frequency of hospitalization in an Australian cohort of SSc patients (9).

The purpose of this study was to compare hospitalization rates between incident cases of SSc vs age- and sex-matched comparators without SSc, in a geographically-based, U.S. population over 36 years. This is, to our knowledge, the most recent study of its kind to evaluate inpatient care utilization in a population-based, incident U.S. population, allowing for assessment of trends over the course of disease in recent years. Case identification and data collection in this study was conducted via comprehensive individual medical record review, while the majority of similar studies have used insurance-based or code-based data which can be subject to many limitations. Indications for hospitalization, length of stay, and readmission rates were also examined.

Methods

This study was approved by the Mayo Clinic and Olmsted Medical Center institutional review boards (17-005603 and 033-OMC-17). A retrospective, population-based cohort of physician-diagnosed patients with SSc in Olmsted County, MN from Jan 1, 1980 to Dec 31, 2016 was assembled. The need for informed consent was waived.

Patients

Patients were identified using the resources of the Rochester Epidemiology Project (REP), which allows for identification of nearly all clinically-recognized cases of SSc due to complete access to inpatient and outpatient records from all healthcare facilities and providers in the geographic area (10). Medical records of patients with a diagnosis or suspicion of SSc were reviewed manually. Included patients were age ≥18 years, diagnosed with incident SSc by a rheumatologist between January 1, 1980 and December 31, 2016. Patients who declined to authorize the use of their medical records for research purposes were not included.

Fulfillment of 2013 ACR/EULAR classification criteria for SSc was ascertained. An index date was assigned corresponding to the date of clinical diagnosis of SSc, made by a physician, as documented in the medical record. A 2:1 cohort of age- and sex-matched non-SSc patients from the same population base was randomly selected for comparison. Both matched non-SSc patients were given the same index date as their comparator with SSc. Inclusion as a comparator required age within ± 3 years of the patient with SSc, same sex, and absence of diagnosis of SSc. Comparators were also excluded if their medical records contained diagnosis of another rheumatic condition such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic vasculitis or others.

Data Collection

A retrospective review of records was performed and data on demographics, disease characteristics, autoimmune serologies, diagnosis of limited versus diffuse systemic sclerosis, organ system involvement both at diagnosis (± 12 months) and at time of last follow-up, and treatments were abstracted. Charlson Comorbidity Index (CCI) was used to assess baseline comorbidities prior to the index dates (11). Inpatient hospitalization data were obtained from the electronic medical record beginning 12 months prior to the SSc incidence/index date.

All hospitalizations in the geographic area from Jan 1, 1987 to Sep 30, 2018 were obtained. Data on admission and discharge dates were retrieved electronically. Cases and comparators who died or emigrated from Olmsted County prior to 1987 were excluded from analysis. Primary discharge diagnosis information was available for hospitalizations in 1995 to present, with primary diagnosis made by the healthcare provider(s) caring for the patient at the time of

hospital stay. For analyses using primary discharge diagnoses, cases and comparators who died or emigrated from Olmsted County prior to 1995 were excluded from analysis.

Primary discharge diagnoses were grouped based upon Clinical Classifications Software (CCS) for ICD-9-CM and ICD-10-CM from the Healthcare Cost and Utilization Project (12), which classifies diagnoses each into one of 18 chapters (categories). Systemic sclerosis is categorized in Chapter 13: Disease of the Musculoskeletal System and Connective Tissue. Primary discharge diagnoses were also manually reviewed by a physician (CMC) to determine whether the primary diagnosis represented an infectious etiology, and whether the diagnosis was a direct consequence of SSc or not.

Readmission was defined as occurring within 30 days of a discharge. Readmissions were treated as unique hospitalizations for the purposes of comparison of hospitalization rates between groups. Patients were followed from the latter of index date or January 1, 1987 (defined as baseline) until death, migration from the geographic area or Sep 30, 2018.

Statistical Analysis

Descriptive statistics (means, medians, percentages) were used to summarize the characteristics of patients with SSc and comparators. Chi-square and rank sum tests were performed to compare the baseline characteristics between patients with SSc and comparators. Rates of hospitalization of cases and comparators were analyzed using person-year methods and rate ratios. Poisson regression models with smoothing splines were used to examine trends over time to allow for non-linear effects. Length of stay was analyzed using generalized linear models adjusted for age, sex and calendar year, with random intercepts to account for multiple hospitalizations per patient. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, U.S.) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). A p-value of less than 0.05 was considered statistically significant for analyses.

Results

The cohort included 76 patients with incident SSc and 155 comparators without SSc. Mean age of included subjects was 56 ± 16 years at diagnosis/index, and both groups were 91% female. Baseline characteristics are displayed in Table 1. Sixty-nine of 76 (91%) patients with SSc met ACR/EULAR 2013 classification criteria. Median length of follow-up from

baseline date was 10.3 (IQR 4.0-17.1) years for patients with SSc and 12.7 (IQR 6.4-19.7) years for comparators. Only 5 of the 76 patients were diagnosed with SSc prior to Jan 1, 1987.

Hospitalization rates

Rates of hospitalization among cases and comparators were 31.9 and 17.9 per 100 person-years (py), respectively (rate ratio [RR] 1.78; 95% confidence interval (CI) 1.52-2.08)(Table 2). Hospitalization rates were significantly higher among patients with SSc than comparators. Both men (RR: 4.33; 95%CI: 2.58-7.60) and women (RR: 1.63; 95%CI: 1.38-1.92) with SSc had substantially higher hospitalization rates than comparators of the same sex. Among all age groups, patients with SSc ages 20-49 years (RR: 2.54; 95% CI 1.73-3.75), 50-64 years (RR: 2.29; 95% CI 1.70-3.09), and 65 years and older (RR 1.46; 95% CI 1.18-1.80) were hospitalized more frequently than their non-SSc counterparts. Rates of hospitalization increased with age in both groups of patients with SSc and non-SSc subjects (Table 2). Rates of hospitalization also increased among those with SSc in later calendar years (Table 2).

Hospitalization rates were higher in patients with SSc compared with non-SSc comparators during the first 5 years following SSc diagnosis (RR: 2.16; 95%CI: 1.70-2.74). This difference decreased over time and was no longer significant for ≥15 years after SSc incidence/index (Figure).

Overall, most common primary discharge diagnoses for hospitalizations among patients with SSc were categorized as diseases of the circulatory system (6.5 hospitalizations per 100 py), respiratory system (5.1 per 100 py), digestive system (4.8 per 100 py), and musculoskeletal system and connective tissue (3.6 per 100 py), the latter category including a primary diagnosis of SSc (Table 2). Among those without SSc, most common primary discharge diagnosis for hospitalizations were categorized as diseases of the circulatory system (3.3 hospitalizations per 100 py), respiratory system (2.0 per 100 py), musculoskeletal system and connective tissue (2.0 per 100 py), and injury or poisoning (2.0 per 100 py) (Table 2). Patients with SSc were more frequently hospitalized for infections and diseases involving circulatory, digestive, and respiratory systems than comparators, with ratios ranging from 1.96 to 3.90 (Table 2).

Regardless of the CCS Category in which primary discharge diagnosis was grouped, manual review demonstrated that 81 of 259 (31%) hospitalizations of patients with SSc with available discharge diagnosis information were directly due to underlying SSc. 64 of the 259 (25%) hospitalizations in patients with SSc were related to infection. Of these hospitalizations, 37 of 64 (58%) involved patients with SSc on immunosuppressant medications.

Risk Factor Analysis

Analysis of risk factors for hospitalizations following SSc baseline date was performed, with adjustments made for age, sex, and calendar year. Presence of coronary artery disease (HR 1.64, 95% CI 1.01, 2.64; p=0.0435), diabetes (HR 2.99, 95% CI 1.71, 5.22; p=0.0001), hypertension (HR 1.83, 95% CI 1.33, 2.52; p=0.0002), and pulmonary arterial hypertension (HR 2.08, 95% CI 1.26, 3.43; p=0.0041) were associated with higher risk of hospitalization. Patients with diffuse cutaneous vs limited cutaneous involvement or sine scleroderma were less likely to be hospitalized (HR 0.54, 95% CI 0.34, 0.87; p=0.0101). Current (HR 1.15, 95% CI 0.80, 1.66) or ever (HR1.20, 95% CI 0.88, 1.63) smoking, interstitial lung disease (HR 1.84, 95% CI 0.86, 3.93), digital ulcers (HR 0.99, 95% CI 0.61, 1.62), and SSc-specific antibodies such as anti-centromere (HR 0.84, 95% CI 0.44, 1.61), topoisomerase/Scl-70 (HR 0.98, 95% CI 0.49, 1.96), and RNA polymerase III (HR 2.23, 95% CI 0.92, 5.44) did not have significant associations with hospitalization in this cohort.

Length of Stay and Readmission

Lengths of stay (median (IQR) 4 (2-6) vs 3(2-6); p=0.52) were similar among cases and comparators. There were comparable rates of readmission in the groups, with 55 readmissions among patients with SSc (25% of 219 subsequent hospitalizations) and 64 readmissions (23% of 283 subsequent hospitalizations) among comparators (p=0.51).

Discussion

This study reports hospitalization rates among 76 patients with incident SSc compared with age- and sex-matched comparators without SSc within the same geographic population in the U.S., with a median duration of follow-up of 10.3 (IQR 4.0-17.1) years. SSc is a chronic condition affecting multiple organ systems which is associated with high morbidity and mortality. Not surprisingly, the rate of hospitalization of SSc patients, at 31.9 hospitalizations per 100 py, was significantly higher than comparators without SSc at 17.9 per 100 py (Table 2). The increased rate of hospitalization observed in SSc patients was seen in both sexes, and in all age groups despite similar comorbidities suggesting that the increased need for inpatient hospital care relates to the presence of SSc and its sequelae. Rates of readmission and lengths of stay did not differ between groups.

The findings of this study are consistent with prior research, showing that healthcare costs, inpatient care, and outpatient healthcare utilization are higher in SSc patients than in those without SSc (5). Furst et al. demonstrated in 2012 that patients with SSc had a significantly higher rate of inpatient hospital stays with 0.33 hospitalizations per patient per year compared with 0.09 for those without SSc in the same managed care network in the U.S (5). The rates of hospitalization from the Furst et al. study are similar to findings from the current study despite differences in methodology, including utilizing data from multiple geographic areas within a managed care organization, and including

SSc subjects based upon diagnosis code at any phase of the disease process rather than incident SSc as in the current study. In an international population of Australian SSc patients, an average of 2.8 annual hospitalizations per patient without ILD and 3.9 annually per SSc patient with ILD were reported (9). Additionally, prior research has shown that hospitalization occurs more frequently in patients with other rheumatologic conditions than the general population, including in giant cell arteritis (13), and sarcoidosis (14).

In this study population, men with SSc had higher rates of hospitalization than both women with SSc, as well as their male non-SSc comparators. Sex differences have previously been described in systemic sclerosis, with women more frequently affected and at a younger age than men (15). However, men with SSc are more likely to have ILD, and have worse survival than women with SSc (15). While specific reasons for sex-related differences in hospitalization rates were not examined, we hypothesize that more severe disease and organ manifestations may underlie the increased rates of hospitalization observed in male patients. Prior studies have reported a predominance of female SSc patients hospitalized (6-8) in the U.S., however this likely reflects the fact that females are more likely to be affected by SSc and comparing rates of hospitalization among all SSc patients was not possible due to the methodology of these studies, using cross-sectional samples of hospitalization events rather than population-based cohorts.

The findings from the current study suggest that hospitalization rates are highest early in the course of SSc, with rate ratio of 2.16 for patients with SSc compared with comparators during the first 5 years after SSc diagnosis/index, a difference that decreased over time. This finding persisted after adjusting for patient age and sex. The higher hospitalization rates observed early in the disease process may parallel development of morbidity during the course of SSc, as a large majority of organ manifestations such as cardiac disease, interstitial lung disease, and renal crisis occur during the first five years of disease onset. Alternatively, hospitalization may relate to symptoms that ultimately result in establishing a diagnosis of SSc, or result from early complications of SSc due to inadequate disease control or delayed initiation of treatment in the first five years of disease. Reasons for this difference were not specifically explored and will be an interesting topic for further study.

Previous research involving U.S.-based patients with SSc has shown that these patients were most commonly hospitalized for diseases involving the circulatory, gastrointestinal, musculoskeletal, and respiratory systems (7,8). In the most recent reports based upon data from the National Inpatient Survey, infection was the most common reason for hospitalization, representing 17.4% of all hospitalizations among patients with SSc in 2012-2013 (8). Our findings were comparable with prior research, showing that diseases of the circulatory, digestive/gastrointestinal, and respiratory systems were the most common primary reasons for hospitalization. However when relying upon CCS

codes, hospitalization for infection (Group 1 referring to ”Infectious and Parasitic Diseases”) occurred at a rate of only 1.3 hospitalizations per 100 py, representing 3.9% of all hospitalization events in the SSc group during the study interval. Hospitalizations for infection by CCS Group 1 were nearly 4-fold more frequent in patients with SSc than in comparators. When a physician reviewed each hospitalization’s primary diagnosis individually, re-classifying diagnoses such as cellulitis (CCS Group 12, Diseases of the Skin and Subcutaneous Tissue), as infection, we observed that 25% of hospitalizations in patients with SSc were due to infectious causes. We postulate that the use of primary diagnosis coding, as well as systematic assessment of multiple hospital diagnoses historically at the time of the hospitalization, as well as underlying differences in study populations, may have contributed to this difference seen from prior research. We also note that due to this study’s population being geographically-based, severity of disease may be lower than those of other hospital-based or tertiary referral-based SSc populations, contributing to differences seen in reasons for hospitalization.

Strengths of this study include a geographic, population-based cohort with two matched controls for each patient with SSc, data obtained from detailed, individual medical record review, and use of the REP, allowing comprehensive access to information about hospitalizations among all healthcare facilities in the geographic area regardless of insurance status or payer. Use of CCS for categorization of primary diagnoses during hospitalizations allowed for better comparison with prior studies.

A potential limitation of this study is its aforementioned reliance upon historical diagnosis codes and use of primary diagnosis coding. As SSc is a multi-system illness, hospitalization for multiple affected systems is not captured with the use of primary diagnosis only. The primary reason for hospitalization may have been categorized as SSc (Ch. 13) or affected organ (for example, Ch. 8 Diseases of the Respiratory System); this was decided historically by the treating provider rather than a prospective protocol. This study was limited by small sample size despite long study interval, and the fact that cost associated with hospitalizations was outside of the scope of this work, though it has been addressed in prior research. The matched design of this study may potentially allow for bias due to depletion of susceptibles. Additionally, this study was limited to residents of a particular geographic area in the Midwest U.S. and the inpatient care needs of this population may not be generalizable to persons in other regions, nations, or healthcare systems.

Though there is a distinction between ‘classification’ and ‘diagnosis’, the 2013 classification criteria are regarded as the most sensitive particularly in early disease (in comparison to the 1987 ACR criteria), and therefore these criteria were evaluated in all patients diagnosed before and after their development in 2013 for the purposes of reporting in this study. There are limitations to using the 2013 classification criteria for this population given that it is a cohort that

started in 1980. For example, the RNA polymerase III autoantibody, which is now included in 2013 classification criteria, was not widely adopted until more recent years, and therefore not tested in many patients in this study. Likewise, formal video nailfold capillaroscopy was not available until recent years and abnormal nailfold capillaries as part of 2013 classification criteria may not be reported in the medical record in many cases in which bedside examination aided the rheumatologist's diagnosis. Manifestations such as calcinosis, esophageal dysmotility, and inflammatory arthritis are not captured in the 2013 criteria, but may have contributed to clinical picture and eventual diagnosis of SSc in many of the patients included in this study.

In conclusion, this study demonstrates that patients with SSc are hospitalized more frequently than persons in the same geographic population without SSc. Rates of hospitalization were nearly 3-fold higher among male than female patients with SSc. Hospitalization of patients with SSc occurs more frequently in the five years following diagnosis, and rates approach those of the non-SSc population over time. SSc places a large burden on patients and healthcare systems, and continued efforts are needed to reduce the disease burden and to improve care for this group of patients.

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Table 1. Baseline characteristics of patients with systemic sclerosis (SSc) and matched comparators without SSc.

Table 2. Hospitalization rates for patients with and comparators without systemic sclerosis (SSc), overall, and by sex, age, calendar year, and primary diagnosis.

[a]SSc diagnoses were classified under the musculoskeletal system by CCS (CCS Chapter 13).

Figure. Age- and sex- adjusted hospitalization rates among patients with systemic sclerosis (SSc; solid line) and non-SSc comparators (dashed line) according to disease duration.

Characteristic	SSc (n=76)	Non-SSc (n=155)	p-value
Age at original index date, years, mean (SD)	56.4 (15.8)	56.1 (15.5)	0.92
Sex, Female	69 (91%)	141 (91%)	0.96
Race/ethnicity, White	67 (88%)	146 (95%)	0.070
Length of follow-up from baseline to last follow-up, years, median (IQR)	10.3 (4.0, 17.1)	12.7 (6.4, 19.7)	--
Smoking status at original index date			0.44
Never	40 (53%)	83 (55%)	
Former	24 (32%)	38 (25%)	
Current	11 (15%)	30 (20%)	
Body mass index at original index date, kg/m^2, mean (SD)	26.5 (6.0)	30.9 (19.4)	0.004
Fulfill 2013 ACR/EULAR classification criteria	69 (91%)	---	---
Skin involvement		---	---
Limited cutaneous	64 (84%)		
Diffuse cutaneous	10 (13%)		
Sine scleroderma	2 (3%)		

Clinical features		---
Telangiectasias	37 (49%)	
Calcinosis, n/N (%)	18/74 (24%)	
Interstitial lung disease (ILD)	7 (9%)	
Pulmonary arterial hypertension (PAH)	6 (8%)	
Renal crisis, n/N (%)	6/72 (8%)	
Gastrointestinal dysmotility, n/N (%)	37/74 (50%)	
Inflammatory arthritis, n/N (%)	35/73 (48%)	
Raynaud's	71 (93%)	
Digital ulcers	15/31 (48%)	
Positive antinuclear antibodies, n/N (%)	69/74 (93%)	---
Scl-70+, n/N (%)	7/38 (18%)	---
Centromere +, n/N (%)	29/38 (76%)	---
RNA Pol III+, n/N (%)	2/38 (5%)	---

Group	Number of SSc hospitalizations (rate per 100 py)	Number of Non-SSc hospitalizations (rate per 100 py)	Rate Ratio (95% CI)
Overall	278 (31.9)	369 (17.9)	1.78 (1.52-2.08)
Sex			
Women	239 (29.4)	349 (18.1)	1.63 (1.38-1.92)
Men	39 (66.0)	20 (15.1)	4.33 (2.58-7.60)
Age			
20-49	55 (26.8)	48 (10.6)	2.54 (1.73-3.75)
50-64	86 (28.1)	87 (12.3)	2.29 (1.70-3.09)
65+	137 (37.9)	234 (26.0)	1.46 (1.18-1.80)
Calendar Year			
1987-1996	30 (28.5)	49 (23.6)	1.21 (0.76-1.88)
1997-2006	83 (30.5)	115 (18.0)	1.70 (1.28-2.25)
2007-2018	165 (33.3)	205 (16.8)	1.98 (1.61-2.43)
Primary Diagnosis			
Infection	10 (1.3)	6 (0.3)	3.90 (1.50-11.44)
Digestive	38 (4.8)	33 (1.7)	2.77 (1.74-4.43)
Respiratory	41 (5.1)	39 (2.0)	2.54 (1.64-3.94)
Circulatory	52 (6.5)	64 (3.3)	1.96 (1.35-2.82)

Musculoskeletal[a]	29 (3.6)	39 (2.0)	1.80 (1.10-2.89)
Injury	26 (3.3)	38 (2.0)	1.66 (1.00-2.70)
Neoplasms	10 (1.3)	20 (1.0)	1.24 (0.55-2.53)
Mental Illness	1 (0.1)	22 (1.1)	0.16 (0.01-0.55)