Systemic sclerosis among hospitalized patients in Poland: a study based on a national hospital registry

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Abstract

Introduction: Systemic sclerosis (SSc) is a rare autoimmune disease with possible life-threatening internal organ involvement. Because of its rarity and heterogeneous clinical presentation, studies on this disease may be difficult to carry out. We sought to describe patients at first hospitalization for SSc in Poland from 2013 to 2019. The study measured SSc incidence trend, comorbidities, and factors related to this disease among hospitalized patients in Poland.

Material and methods: We conducted a retrospective, population-based study using hospital discharge records compiled by the National Institute of Public Health.

Results: The study group consisted of 4,633 patients hospitalized with SSc diagnosis for the first time in 2013–2019. The mean and median age were 53.9 (95% CI: 53.4–54.3, SD = 16.6) and 57 years (IQR: 44–66). In the study group, female patients accounted for 81.3% of all patients, and they were significantly older than male patients (54.6 vs. 50.4 years; $p < 0.001$). The crude incidence was estimated at 1.72 per 100 000 person-years (95% CI: 1.67–1.77). The SSc incidence rate was significantly higher in urban than rural areas of Poland (1.83 vs. 1.46 per 100,000; $p < 0.001$). In patients with progressive systemic sclerosis in comparison to other forms of SSc we observed a significantly rare presence of selected groups of diseases.

Conclusions: Presented data on SSc in Poland may also be helpful in comparative analyses in the European context. Territorial factors may have a significant impact on the occurrence of SSc in Poland.

Key words: epidemiology, hospitalization, comorbidities, rural regions, urban regions.

Introduction

Systemic sclerosis (SSc) is a rare immune-mediated rheumatic disease characterized by tissue fibrosis of the skin and internal organs, and vasculopathy. In 2013, a joint committee of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) presented classification criteria for SSc [1].

Systemic sclerosis is a rare disease. The reported prevalence of SSc was 7.2–33.9 and 13.5–44.3 per 100,000 individuals in Europe and North America, respectively. Annual incidence estimates were 0.6–2.3 and 1.4–5.6 per 100,000 individuals in Europe and North America, respectively [2]. In a systematic review and meta-analysis, the incidence rate of SSc ranged from 0.77 per 100,000 person-years in the Netherlands to 5.6 per 100,000 person-years in the USA. Reported prevalence ranged from 3.8 per 100,000 in Taiwan to 50 per 100,000 in the USA [3]. In another systematic review and meta-analysis the overall pooled prevalence of SSc was 17.6 per 100,000 and the overall pooled incidence rate of SSc was 1.4 per 100,000 person-years [4].

The pathogenesis of SSc is still unclear, although it may result from interactions between environmental factors and epigenetic features, leading to the onset and progression of SSc in the group of genetically susceptible patients. The association between SSc and occupational exposure may be variable according to gender [5]. A correlation is reported to exist between occupational exposure to crystalline silica/solvents and more severe forms of SSc characterized by: diffuse cutaneous involvement, interstitial lung disease, general microangiopathy, and association with cancer [6]. Occupational exposure to silica or solvents is highly prevalent in male patients with systemic sclerosis [7]. The effect of low median household income is demonstrated to be a factor raising the risk of death in SSc patients [8]. Other risk factors reported are age between 45 and 64 years, female sex, positive family history and exposure to silica [9]. Men with SSc were found to be exposed to a higher risk of developing cancer than women [10]. In another study, age at disease onset, male sex, diffuse cutaneous SSc, cardiac and renal involvement, interstitial lung disease, pulmonary hypertension, and malignancy were found to be associated with a worse prognosis [11].

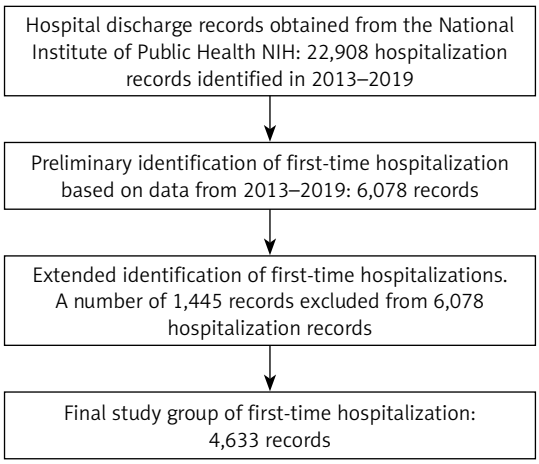

Figure 1. Flow chart. Study group identification

Patients with SSc have higher mortality rates than the general population [12, 13]. The worldwide age-standardized mortality rate in systemic sclerosis (deaths per million) was reported to be 1.46 in 2014 [14]. In high-income societies, SSc has a poor prognosis, as in about 55% of affected patients the disease is a direct cause of death [15]. In another study, respiratory failure from interstitial lung disease (ILD) was reported to be the main cause of death in most SSc-ILD patients [16]. In a study from Denmark, one fifth of all deaths were attributable to cardiovascular causes, one fourth to pulmonary diseases, and 15% of deaths were caused by cancer [17]. In a study from the United Kingdom, survival at 1, 5, and 10 years was found to be 94.2, 80.0, and 65.7%, respectively [18]. In a multicenter French cohort study the overall survival rates at 1, 3, 5, and 10 years from diagnosis were 98.0%, 92.5%, 85.9%, and 71.7% respectively. In a study conducted in Australia, an overall standardized mortality ratio of 3.4 and a 10-year survival of 84% were reported in newly diagnosed patients [19].

Various comorbidities were associated with substantial and significant differences in the risk of in-hospital mortality [20]. Moreover, SSc is associated with an increased risk of cancer, particularly lung, liver, hematologic, and bladder cancers [10, 21]. Another meta-analysis revealed a higher mortality rate in SSc patients with associated digital ulcers [22].

Systemic sclerosis is considered to be an economic burden on health care systems [23–25]. There are studies on the SSc epidemiology or comorbidities in SSc in Poland [26–33]. However, research on this rare disease based on national hospital morbidity registers may be justified and necessary.

We sought to describe patients at the time of first hospitalization for SSc in Poland between 2013 and 2019. The study measured the SSc incidence trend, comorbidities, and factors related to this disease among hospitalized patients in Poland.

Material and methods

The study is a retrospective study based on data from hospital discharge records that included an SSc diagnosis. Data were obtained from the National Institute of Public Health NIH – National Research Institute in Poland and they covered 22,908 all first-time and subsequent hospitalization cases reported between 2013 and 2019. For the extended identification of first-time hospitalizations, data on hospitalizations from previous years were also used [26]. The study group consisted of 4,633 first-time hospitalization cases of SSc patients in the studied period of time as presented in the flow chart in Figure 1. We analyzed the records of

patients hospitalized for SSc diagnosed as the primary or secondary disease. All hospitals in Poland, except for psychiatric facilities, are required under the law to submit electronically data from hospitalization to the institute using the official form MZ/Szp-11. The data are anonymous and they contain information on ICD10 code diagnoses, hospital admission and discharge data, the sex of the patient, their date of birth and place of residence. The local bioethics committee was informed about the study. Based on the information obtained from the committee, in the case of retrospective and non-invasive research studies, the ethics committee does not issue an opinion. SSc often requires advanced differential diagnostic procedures and treatment during hospitalization. Therefore, cases of hospitalized patients may provide a good basis for estimating incidence. We assumed that SSc diagnoses were made in hospitals on the basis of the most current and widely used diagnostic criteria.

Statistical analysis

To perform the statistical analyses, Statistica [34] and WINPEPI [35] were used. The following statistical measures were computed: means, medians, and ranges for continuous variables, counts and percentages for categorical variables. The incidence was calculated per 100,000 person-years and the prevalence was calculated per 100,000 for the period 2013–2019. To assess trends, we used linear regression and time series analysis. The statistical analysis was performed using Student's *t*-test with respect to an assumption of normal distribution in sufficiently large samples in public health research [36]. When normality assumptions were not met, non-parametric tests (χ^2 test, Mann-Whitney *U*-test) were applied. For comparison of nominal variables the χ^2 test was used. A two-sided p value of less than 0.05 was considered to be statistically significant. Data on the overall population of Poland were taken from Statistics Poland [37, 38]. In the analyses of comorbidities, selected groups of diseases according to the ICD-10 classification were compared.

Results

In the study group females predominated (81.3% vs. 18.7% males) with the female to male ratio at 4.34 to 1, as well as in the subgroup of patients with progressive SSc (81.8%) and the subgroup of all other forms of SSc (81%). The mean and median age were 53.9 (95% CI: 53.4–54.3, SD = 16.6) and 57 years (IQR: 44–66, min.–max.: 1–106). The age distribution in the study group is presented in Figure 2. Female patients were significantly older than males in the study group (54.6 vs. 50.4 years, $p < 0.001$). We observed no significant increasing or decreasing trends in SSc incidence in the study group in the analyzed period of time. The crude incidence was estimated at 1.72 per 100,000 person-years (95% CI: 1.67–1.77). The crude SSc incidence rate was significantly higher in urban than rural areas of Poland (1.83 vs. 1.46 per 100,000; $p < 0.001$). The prevalence was estimated at 12 per 100,000 during the study period. The most common groups of co-morbidities among patients in the study group were cardiovascular diseases (23.6%), diseases of the musculoskeletal system and diseases of connective tissue other than SSc (17.7%), endocrine, nutritional and metabolic diseases (13.6%), diseases of the respiratory system (11.1%), and digestive system diseases (7.1%), with other groups of diseases being below 5% each. Patients with neoplasms accounted for 2% of SSc patients. In the study group most often observed were neoplasms of uncertain behavior of the middle ear and respiratory and intrathoracic organs (ICD-10 code: D38) – 10 cases, malignant neoplasm of the bronchus and lung (ICD-10 code: C34) – 9 cases, malignant neoplasm of the breast (ICD-10 code: C50) – 8 cases, lymphoid leukemia (ICD-10 code: C91) – 8 cases. In the study group among the cardiovascular disease most of them were arterial hypertension (14.7%), Raynaud's syndrome (3.5%), heart failure (2.5%), and chronic ischemic heart disease (1.8%). Pulmonary hypertension (ICD-10 code: I27.0, I27.2) was observed in 0.6% of the study group. Other interstitial pulmonary diseases (ICD-10 code: J84) were observed in 6.5% of the study group.

Among groups of diseases of the musculoskeletal system and diseases of connective tissue other than SSc most of them were polyosteoarthritis (ICD-10 code: M15) – 196 cases, spondylosis (ICD-10 code: M47) – 177 cases, or other systemic involvement of connective tissue (ICD-10 code: M35) – 117 cases.

In the study group endocrine, nutritional and metabolic diseases were more often observed in

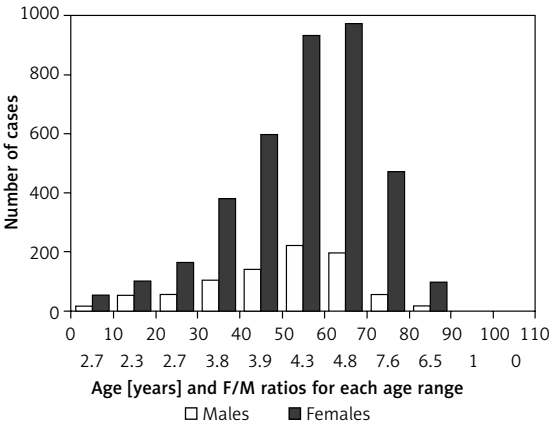

Figure 2. Age distribution of SSc cases in the study group by gender 2013–2019

females than males (14.6% vs. 8.1%, $p < 0.001$). Diseases of the respiratory system were more often observed in males than females (13.7% vs. 10.5%, $p < 0.01$). Diseases of the digestive system were more often observed in males than females (8.9% vs. 6.6%, $p < 0.03$). Neoplasms were more often observed in males than females (3.1% vs. 1.8%, $p < 0.05$).

In the group of all hospitalizations, 243 patients died during hospitalization (5.2% of all patients). In the study group, 56 patients died during hospitalization (1.2% of all patients). Among all 243 fatal hospitalizations the mean and median age were 65.3 (95% CI: 63.7–67, SD = 13.3) and 67 years (IQR: 57–74). Male patients were significantly more often observed in fatal hospitalizations than non-fatal hospitalizations (30% vs. 18%; $p < 0.001$). The most common groups of co-morbidities among 243 patients with fatal hospitalizations were cardiovascular diseases (65.8%), diseases of the respiratory system (50.2%), and diseases of the genitourinary system (23.9%). Neoplasms were observed in 7.4% of SSc patients with fatal hospitalizations. The reported leading underlying causes of in-hospital death were SSc (57%), diseases of the circulatory system (15%), and diseases of the respiratory system (7%); other cases were below 5% each. Among death cases as an underlying or other cause of death heart failure (I50) was reported in 98 cases, other interstitial pulmonary diseases (J84) in 21 cases, and pulmonary hypertension (I27.0, I27.2) in 6 cases.

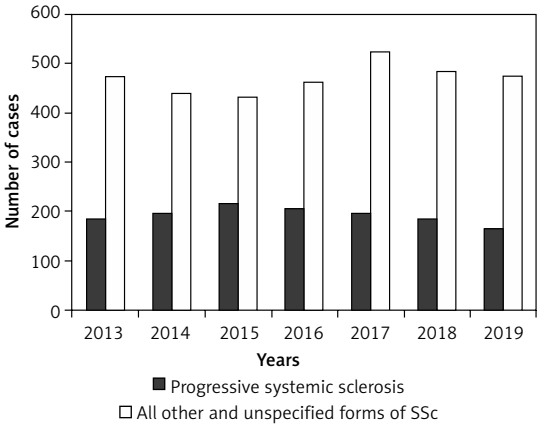

Figure 3. Distribution of SSc forms among first-time hospitalizations by year, 2013–2019

In the present work, patients were divided into two groups of patients with progressive SSc and patients with other forms of SSc. Distribution of these two groups of SSc patients among first-time hospitalizations by year is presented in Figure 3. Patients with progressive SSc accounted for 29% of all SSc patients in the study group. The data concerning the comparison between groups of patients with progressive SSc and other forms of SSc are presented in Table I.

Discussion

Systemic sclerosis is a rare disease and the use of national hospital morbidity registers may contribute to a better understanding of factors related to the disease. The reported incidence was comparable to that reported in many European countries [2]. Additionally, the recent reported SSc incidence was lower than the data collected in an earlier Polish study based on national hospital morbidity registers reporting the crude average annual SSc incidence at the level 1.9 per 100,000 [26]. In our study no significant changes in the trend of SSc occurrence were found. However, in terms of overall SSc incidence, a minor increase was observed in a nationwide cohort study from Denmark over the study period from 1995 to 2015 [17]. It may suggest that the trends in SSC incidence may be related to territorial factors.

Territorial factors are still considered to play an important role in disease development. In a recent study based on data from SSc the southeast region of Romania, the majority of SSc patients came from urban areas [39]. Marked differences in

Table I. Comparison between groups of patients with progressive SSc and other forms of SSc

Parameters	Patients with progressive SSc (coded as M34.0) *N* = 1344	Patients with other forms of SSc *N* = 3289	*P*-value
Female vs. male (%)	81.8 vs. 18.2	81 vs. 19	NS
Age [years], mean, standard deviation	55, 14.9	53.4, 17.2	< 0.01
Percentage of patients living in urban areas (%)	63.9	66.2	NS
Endocrine, nutritional and metabolic diseases, *n* (%)	143 (10.6)	487 (14.8)	< 0.001
Cardiovascular diseases, *n* (%)	260 (19.3)	833, (25.3)	< 0.001
Diseases of the respiratory system, *n* (%)	153 (11.4)	360 (10.9)	NS
Diseases of the digestive system, *n* (%)	82 (6.1)	245 (7.4)	NS
Diseases of the musculoskeletal system and connective tissue other than SSc, *n* (%)	210 (15.6)	608 (18.5)	< 0.05

SSc – systemic sclerosis, p – statistical significance, NS – statistically not significant.

SSc prevalence according to age, sex, and region were also reported in another study from Quebec based on physician billing and hospitalization databases (covering approximately 7.5 million individuals) [40]. In our study, no sufficient information on territorial factors in the nationwide morbidity registry was obtained. However, we noted a significant difference in SSc incidence between urban and rural areas in Poland. This may suggest that there are territorial or environmental factors influencing the risk of SSc in these areas in Poland. However, further research is required to confirm this relationship.

Females constituted the majority of patients in our study. Marked female preponderance was also reported in studies analyzed in the recent systematic review [9]. The proportion of women in the study group was lower than in the previous study [26]. Similarly, in a nationwide cohort study from Denmark 76% of all patients with an SSc diagnosis were women and a drop in the proportion of women was reported [17]. In the study group females dominated among all patients and in the subgroup of patients with progressive SSc and the subgroup of all other forms of SSc. Female predominance was also reported in selected groups of SSc patients from the EUSTAR database [41].

In our study male patients were significantly more often observed in fatal hospitalizations than non-fatal hospitalizations. It is possible that the disease presentation in more severe in male patients. Moreover, in a study from Poland it was also suggested that SSc male patients with another selected factor may have severe and rapidly progressive disease [42]. Another study reported that men tend to display a more severe form of the disease including internal organ-based complications and higher mortality than women [43].

In the case of progressive systemic sclerosis, the process of skin and internal organ involvement may be greater, and the course of the disease may be rapid, especially in the initial stage of the disease. It was also reported that clinical phenotypes at disease onset may predict morbidity and mortality in SSc [44]. In the present study, 29% of diagnoses of progressive SSc were observed among all forms of SSc as presented in Figure 3. The percentage of progressive SSc was lower than that presented in a previous study from Poland [26]. In the present work, patients were divided into two groups of patients, those with progressive SSc and those with other forms of SSc. In the first group there were significantly lower incidence rates of selected diseases in comparison to the second group, as presented in Table I. This observation may suggest that the type of comorbidities may be a predictor of a specific form of SSc. Additionally, it is worth highlighting that it was possible to identify this statistically significant difference in the occurrence of certain comorbidities when using the national hospital morbidity registry. Age among the study groups presented in Table I was comparable. In the large multicenter prospective EUSTAR cohort based on observational data of SSc patients aged ≥ 18 years, mean age in groups of limited cutaneous SSc cases and diffuse cutaneous systemic sclerosis cases was comparable and was reported to be 57 and 58 years, respectively [41].

In our study, SSc patients with neoplasms accounted for 2% of all studied patients. In comparison, it was estimated that for every 100,000 people in the Polish population in 2017, 429 people were diagnosed with cancer, and approximately 2,623 lived with a cancer diagnosis over the last 15 years [45]. In the group of patients with fatal hospitalizations in our study the presence of neoplasms was observed in 7.4% of patients. In a study conducted in Australia it was found that cardiorespiratory manifestations were the leading cause of SSc-related deaths, whereas malignancy was reported to be the leading cause of deaths not related to SSc [19]. There is a possibility that a similar relationship may be observed among SSc patients in Poland. Further studies are necessary to perform a better analysis of the cause of death in SSc hospitalized patients in Poland.

In our study we observed relatively low prevalence of pulmonary hypertension. and it may be related to organization of health care in Poland. Relatively low prevalence of pulmonary arterial hypertension associated with connective tissue disease (PAH-CTD) was reported in a study based on data from the Polish Registry of Pulmonary Hypertension. However, among patients with CTD-PAH, the most frequent were diseases of the scleroderma spectrum. The authors of this study suggested that CTD-PAH patients were lost either by never getting a diagnosis or by not reaching the designated PAH center [46].

The reported mortality risks in the study group seem to be low. In a study from the USA among a large cohort from 2011–2019 of SSc patients hospitalized due to SSc and non-SSc related causes, overall inpatient mortality was reported to be 9.3% [47].

Our study also had several limitations. The hospital discharge database analyzed did not include other variables that might be related to SSc. Also, the database included discharge records from inpatient hospitalizations only, which means it excluded SSc patients who were diagnosed or treated as outpatients only. This inaccuracy may result in the underestimation of the incidence rate. For 93 patients (2% of all patients in the study group) no reliable data on the place of residence code were available. The coding practices for SSc-related hospitalizations have not been assessed. This

inaccuracy may have resulted in an imprecise estimation of SSc cases. However, the long observation period and the relatively large amount of data obtained from the national register of hospital morbidity represent advantages of this study.

In conclusion, presented data on SSc in Poland may also be helpful in comparative analyses in the European context. Territorial factors may have a significant impact on the occurrence of SSc in Poland.

Conflict of interest

The authors declare no conflict of interest.

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