Nationwide analysis of adult hospitalizations with hematologic malignancies and systemic sclerosis

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Abstract

Introduction: Systemic sclerosis (SSc) is a connective tissue disease with multi-system involvement and it has an increased risk of developing hematologic malignancies. This study aims to report the association between hematologic malignancies with SSc and to characterize in-hospital demographics and outcomes in patients with hematologic malignancies with and without SSc.

Methods: We performed a retrospective review of pooled data from the National Inpatient Sample (NIS) database from 2016 to 2020. Crude prevalence of hematologic malignancies among hospitalized patients with and without SSc was calculated. Logistic regression was used for statistical significance of differences in prevalence while adjusting for confounders. Demographic characteristics and outcomes of patients with hematologic malignancies with and without SSc was compared. Statistical analysis was done using chi-square and multivariate logistic regression.

Results: Among all adult hospitalizations, the prevalence of hematologic malignancy was 1.87% compared to 2.66% among patients with SSc (adjusted odds ratio (aOR) 1.52, p <0.01). Relative to the non-SSc group, the SSc group had higher odds of in-patient mortality (OR 1.43; 95% confidence interval (CI) 1.11 – 1.87; p<0.01). The prevalence of lymphoma was 0.71% compared to 1.04% among patients with SSc (aOR 1.6, p < 0.01). Relative to the non-SSc group, the lymphoma-SSc group had similar odds of in-patient mortality (OR 0.93; 95% CI 0.55 – 1.59; p=0.80). The prevalence of leukemia was 0.79% compared to 1.28% among patients with SSc (aOR 1.74, p < 0.01). The leukemia-SSc group had higher odds of in-patient mortality (OR 1.78; 95% CI 1.29 – 2.46; p<0.01). For myeloma, there was no difference in the prevalence in adults with and without SSc (0.4 vs. 0.38%, aOR 0.96, p=0.64) and there was no difference of in-hospital mortality.

Conclusions: There is a positive significant association between hematologic malignancies including lymphoma and leukemia, and SSc. This association was not seen between myeloma and SSc. There is increased in-hospital mortality of patients with leukemia and SSc.

Keywords: Systemic sclerosis; Hematologic malignancy; Lymphoma; Leukemia; Myeloma.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease with multi-system involvement primarily integumentary, vascular, and visceral. Emerging data have established a 1.5 to 4 times aggravated risk of developing cancers in SSc patients[1]. More recently there has been compelling evidence to support the idea of a paraneoplastic mechanism driving SSc pathogenesis which could explain the finding of high prevalence of malignancies in this population[2].

Several risk factors may be associated with the heightened risk of malignancies. These include the antibody profile (presence of anti-RNA Polymerase III, anti-PM/Scl antibodies), late age of onset, and diffuse scleroderma[3]. While systemic inflammatory diseases portend a greater risk of malignancy secondary to the chronic inflammation process and T/B cell immune dysregulation as well as state of immunosuppression enabling tumorigenesis, in SSc patients, vascular impairment and aberrant fibrogenesis are added risk factors[2]. Malignancies remain among one of the most common causes of non-scleroderma-related deaths in SSc patients with the mortality rate from malignancies reported to be as high as 38%[4-6]. Overall, hematopoietic malignancies and lymphoma are observed to be more prevalent in SSc patients when compared to the general population[7].

Given the increased risk of hematologic malignancy in patient with SSc, this study aims to describe the association of hematological malignancies and SSc using a large in-patient NIS database of the United States of America (USA). It focuses on the prevalence of hematologic malignancies, detailed descriptive analysis of the epidemiological profile and in-hospital outcomes of hematologic malignancy patients with and without SSc.

Methods

Study design:

We performed a retrospective review of pooled data from the NIS database from 2016 to 2019 (available online at https://www.hcup-us.ahrq.gov). The NIS is the largest all-payer inpatient database in the USA and part of the databases developed for the Healthcare Cost and Utilization Project (HCUP) which includes state wide data of 48 States and the District of Columbia. Data for each year is a stratified probability sample representing around 20% of all admissions and

weighted to obtain national estimates[8]. Ethics/Institutional Review Board approval was not pursued as data in the NIS is de-identified and publicly available.

Inclusion criteria and study variables:

The initial analysis included all adult hospitalizations (age ≥ 18). Prevalence of SSc and hematologic malignancies was obtained using ICD-10-CM/PCS (M34 for SSc; C81, C82, C83, C84, C85, C86 for lymphoma; C91, C92, C93, C94, and C95 for leukemia; and C90 for myeloma). We later selected only patients with a diagnosis of hematological malignancy for demographic and outcome analysis. Study variables included age, gender, race/ethnicity, insurance and median household income. Median household income by zip code was divided into quartiles (Q1-Q4). In 2020 the dollar values for each quartile were as follows: Q1=$ 1- 49,999; Q2 = $ 50,000 - 64,999; Q3=$ 65,000 - 85,999; and Q4 ≥ $86,000. We assessed the comorbidity burden using Sundararajan's adaptation of the modified Deyo's Charlson comorbidity index (CCI)[9].

Outcomes:

Crude prevalence of hematologic malignancies among hospitalized patients with and without SSc was calculated. Outcomes were compared between patients with hematologic malignancies with and without SSc. These included length of stay (LOS), total hospital charges (THC) and in-hospital mortality.

Statistical Analysis:

Analyses were performed using STATA, version 17.0. Logistic regression was used to calculate the adjusted prevalence of hematological malignancies in patients with SS and in the general population, while adjusting for race, age and gender. Descriptive statistics included weighted counts, percentages, means and 95% CI, and chi-square was used to assess statistical significance of demographic differences. For LOS, THC and mortality, multivariate analysis was performed to obtain ORs, adjusting for race, age, gender, and CCI.

Results

There were 149,000,000 adult hospitalizations in the 2016 to 2020 NIS database. Of those, 154,860 had SSc and 2,783,104 had hematologic malignancy (1,063,330 had lymphoma, 1,182,380 had leukemia and 591,744 had myeloma).

Hematologic malignancy:

The prevalence of hematologic malignancy among all adult hospitalizations was 1.87% in patients without SSc compared to 2.66% among patients with SSc (aOR 1.52, p <0.01) (Table I). Relative to the non-SSc group, the SSc group was younger (mean age 61 vs 66 years; p<0.01) with higher proportion in age 45-64 years (40.6% vs 28.2%; p<0.01), had more females (66.9% vs 43.1%; p<0.01), similar proportion in terms of race (p=0.19) with whites having the highest percentage (71.4% vs 70%) and higher CCI mean (4.7 vs 3.9; p<0.01). Household income, LOS and total charges were similar between the SSc and non-SSc groups. (Table II)

Lymphoma:

The prevalence of lymphoma among all adult hospitalizations was 0.71% in patients without SSc compared to 1.04% among patients with SSc (aOR 1.6, p <0.01) (Table I). There was no difference in age between the SSc and non-SSc with a mean of 64 years in both groups (p=0.61). Relative to the non-SSc group, the SSc group has more females (75.2% vs 42.5%; p <0.01), similar proportion in terms of race (p=0.96) with whites having the highest percentage (72.7% vs 71.6%) and higher CCI mean (4.6 vs 3.8; p<0.01). Household income, LOS and total charges were similar between the SSc and non-SSc groups. (Table III)

Leukemia:

The prevalence of leukemia among all adult population was 0.79% in patients without SSc compared to 1.28% among patients with SSc (aOR 1.74, p <0.01) (Table I). Relative to the non-SSc group, the SSc group was younger (mean age 58 vs 66 years; p<0.01) with higher proportion in age 18 – 44 years (22.5% vs 13.1%; p<0.01) and in age 45 – 64 years (41.5% vs 25.2%; p<0.01) but lower proportion in age ≥65 years (36% vs 61.8%; p<0.01). The SSc group also had more females (58.7% vs 42.8%; p<0.01), similar proportion of whites (74.2% vs 72.9%), less African Americans (4.8% vs 9.3%) and higher Hispanics (11.1% vs 8.7%) but this was not significant (p=0.06). Also, the SSc group had higher CCI mean (4.7 vs 3.8; p<0.01). Household income, LOS and total charges were similar between the SSc and non-SSc groups. (Table IV)

Myeloma:

For myeloma, there was no difference in the prevalence in adults with and without SSc (0.4% vs. 0.38%, aOR 0.96, p=0.64) (Table I). Relative to the non-SSc group, the SSc group was younger (mean age 66 vs 70 years; p<0.01) with higher proportion in age 45 – 64 years (47% vs 29.6%; p<0.01) but lower proportion in age ≥65 years (51.3% vs 68.3%; p<0.01). The SSc group also had more females (70.9% vs 44.3%; p<0.01), similar proportion in terms of race (p=0.81) with whites

having the highest percentage (59% vs 61.7%) and higher CCI mean (5 vs 4.4; p<0.01). Household income, LOS and total charges were similar between the SSc and non-SSc groups. (Table V)

Mortality:

When analyzing any hematologic malignancy with and without SSc a difference of in-hospital mortality was observed (8% vs 5%; p<0.01) with higher odds of mortality seen in people with SSc (OR 1.43; 95% CI 1.11 – 1.87). Higher odds of in-hospital death were associated to age ≥65 years (OR 2.25; 95% CI 2.11 – 2.41; p<0.01) and CCI (OR 2.13; 95% CI 2.06 – 2.22; p<0.01). While lower odds of in-hospital death were associated to being female (OR 0.87; 95% CI 0.85 – 0.90; p<0.01). In lymphoma, in-hospital mortality was similar between patients with SSc and without SSc (5%; OR 0.93; 95% CI 0.55 – 1.59; p=0.80). In leukemia, there was a difference of in-hospital mortality when comparing patients with and without SSc (10% vs 6%; p<0.01) with higher odds of mortality seen in people with SSc (OR 1.78; 95% CI 1.29 – 2.46; p<0.01). In myeloma, the difference of in-hospital mortality when comparing patients with and without SSc was not significant (7% vs 5%; p=0.36) with OR 1.39 and 95% CI of 0.68 – 2.86.

Discussion

The association of SSc and cancer has been widely explored in medical literature. Several studies have reinforced this association with variable temporal associations between the two diseases. In the epidemiological study by Roumm *et al.,* the authors reported an increased overall incidence of cancers in patients with SSc compared to patients without SSc[10]. The most prevalent cancers being breast, lung and hematologic malignancies with this study focusing on hematologic malignancies[11].

Our study showed a statistically significant association between SSc and hematologic malignancies, namely leukemia and lymphomas. The trend of elevated incidence of hematological malignancies in patients with SSc is well reported in previous medical literature, particularly with regards to non-Hodgkin lymphoma and hematopoietic tumors[7, 12, 13]. In general, it is proposed that development of hematologic malignancies in autoimmune diseases is due to increased malignant transformation of autoreactive B-cells and the autoantigen-driven immune stimulation. However, the exact mechanism responsible for SSc hematologic cancer is not well defined[14]. A cohort study including 1,727 SSc patients reported a greater risk of hematologic malignancies in the absence of anti-RNP Polymerase III antibodies and greater age of disease onset[15]. Also, a case series on SSc patients with hematological malignancies reports that most malignancies presented within the first year of scleroderma diagnosis, were mostly B-cell

neoplasms and co-occurrence of other autoimmune conditions was also noted[14]. Given this risk, new unexplained cytopenias should warrant hematology referral[1]. On the other hand, we found that myeloma is less likely to be associated with SSc. Coexistence of multiple myeloma and SSc is extremely rare and only few cases have been previously reported[16-18]. In the literature, this association seems to be more coincidental with the possibility of inflammation and molecular dysregulation proceeding clonal proliferation of plasma cells[16].

In terms of in-hospital mortality, our study demonstrated an increased in-hospital mortality of patients with hematological malignancies who had SSc compared to those who did not. This was seen in the leukemia group. SSc cancer patients have a higher all-cause mortality than those without cancer with a two-fold increased mortality rate as seen in the cohort by Morrisroe *et al.*[15].

An interesting finding within our study was noted to be the increased presence of hematologic malignancy in female patients with SSc. This finding is in contrast to studies done by Onishi *et al.* which showed an increased risk of cancer development in male patients with SSc when compared to female patients[12]. Generally, men with SSc are at higher risk of hematological and immune related cancers than women[19].

Several theories have been proposed for the association of SSc with malignancies. Some argue that the inflammatory state of the condition and the therapies used for treatment predispose to the development of cancer[20]. Other theories try to explain cancer-induced autoimmunity as an inciting factor for the development of SSc[20]. While others mention that patients with SSc have an increased cumulative exposure to radiation as part of disease management which predispose to the development of malignancies[20]. Our study has re-demonstrated the association of SSc and hematological malignancies. Current recommendations of cancer-screening in patients of SSc are similar to the general population based on age and risk-factors. However, the possibility of disease-specific cancer screening guidelines should be explored. The presence of certain autoantibodies, including anti-RNAP III and anti-PM-Scl in patients with SSc is also linked with increased incidence of malignancies and may play a key role in the development of such guidelines[21].

Our study has its strengths as the NIS is a large inpatient database representative of all USA hospitalizations allowing us to report hematologic malignancy hospitalizations in relation to a rare disease as SSc. We performed odds ratio for the association of hematologic malignancy with

SSc and we analyzed inpatient characteristics with and without SSc. There are also some limitations to our analysis. First, since we used ICD-10 billing codes we were not able to confirm if the diagnoses of hematologic malignancies and SSc met standard diagnostic criteria. Second, even though we used a large inpatient database, the number of patients with hematologic malignancies in the outpatient setting is also big and not taken into account in this study. Previous literature uses patient registry that include inpatient and outpatient database[15, 19]. Third, data in the NIS does not give information regarding the characteristics, disease onset, organ involvement, auto-antibodies, severity or comorbidities associated to underlying SSc.

CONCLUSIONS

We performed an analysis of the NIS to report the association of SSc and hematologic malignancies. There is a positive significant association between hematologic malignancies such as lymphoma and leukemia and SSc. These results confirm what has been seen in previous literature but using a larger in-patient database. Inpatient with hematologic malignancy and SSc were predominantly female. Also, there is increased in-hospital mortality of patients with hematologic malignancies, especially leukemia and SSc. This information can help clinicians to better use recommendations of cancer-screening in patients with SSc including working-up new cytopenias in patients with SSc.

Tables and Figures

Table I. Prevalence of hematologic malignancy in adults with and without SSc from the 2016 to 2020 National Inpatient Sample.

	With SSc (n=154,860)	Without SSc (n=148,845,140)	aOR	P-value
Any Hematologic Malignancy	2.66%	1.87%	1.52	<0.01
Lymphoma	1.04%	0.71%	1.6	<0.01
Leukemia	1.28%	0.79%	1.74	<0.01
Myeloma	0.4%	0.38%	0.96	0.64

SSc, Systemic sclerosis; aOR, adjusted Odds Ratio

Table II. Descriptive Characteristics of Any Hematologic Malignancy Hospitalizations with and without SSc from the 2016 to 2020 National Inpatient Sample (n=2,783,104)

Hospitalization characteristics	**Heme malignancy with SSc (n=4,115)**	**Heme malignancy without SSc (n=2,778,989)**	**P-value**
Age, mean in years (95% CI)	61.2 (59.7 - 62.7)	66.2 (66.0 - 66.4)	<0.01
Age Groups (n, %)			<0.01
Age 18 - 44 years	601 (14.6%)	294573 (10.6%)	
Age 45 - 64 years	1671 (40.6%)	783675 (28.2%)	
Age ³65 years	1844 (44.8%)	1700741 (61.2%)	
Gender (n, %)			<0.01
Women	2753 (66.9%)	1197744 (43.1%)	
Male	1362 (33.1%)	1581245 (56.9%)	
Race (%)			0.19
White	71.4%	70%	
Black	9.1%	11.9%	
Hispanic	10.1%	8.9%	
Other	9.4%	9.2%	

CCI mean (95% CI)	4.7 (4.5 - 4.8)	3.9 (3.9 - 3.9)	<0.01
Insurance (%)			<0.01
Medicare	62%	62.5%	
Medicaid	5.7%	9.4%	
Private	31.6%	26.2%	
Self pay	0.7%	1.9%	
Household income (%)			< 0.01
Q1	19.2%	24.6%	
Q2	23.8%	25.3%	
Q3	28.4%	25.4%	
Q4	28.6%	24.7%	
LOS mean (95% CI)	8.4 (7.6 - 9.1)	7.5 (7.4 - 7.6)	0.16
Total charges mean (95% CI)	113,402.8 (96,403.7 – 130,401.9)	95,545.2 (92,970.5 – 98,119.8)	0.11
In-hospital mortality (n, %)	320 (8%)	150065 (5%)	<0.01

Heme, Hematologic; SSc, Systemic sclerosis; n, number; CI, confidence interval; CCI; Charlson Comorbidity Index; LOS, length of stay

Table III. Descriptive Characteristics of Lymphoma Hospitalizations with and without SSc from the 2016 to 2020 National Inpatient Sample (n=1,063,330)

Hospitalization characteristics	Lymphoma with SSc (n=1615)	Lymphoma without SSc (n=1061715)	P-value
Age, mean in years (95% CI)	64.1 (62.5 - 65.8)	64.6 (64.4 - 64.8)	0.61
Age Groups (n, %)			0.02
Age 18 - 44 years	145 (9%)	131653 (12.4%)	
Age 45 - 64 years	615 (38.1%)	327008 (30.8%)	
Age ³65 years	854 (52.9%)	603054 (56.8%)	
Gender (n, %)			<0.01
Women	1215 (75.2%)	451229 (42.5%)	
Male	401 (24.8%)	610486 (57.5%)	
Race (%)			0.96
White	72.7%	71.6%	
Black	8.4%	9.2%	
Hispanic	9.6%	9.4%	
Other	9.3%	9.8%	

CCI mean (95% CI)	4.6 (4.4 - 4.8)	3.8 (3.76 - 3.81)	<0.01
Insurance (%)			<0.01
Medicare	62%	57.9%	
Medicaid	4.1%	10.3%	
Private	33.2%	29.5%	
Self pay	0.6%	2.2%	
Household income (%)			0.50
Q1	22.4%	23.6%	
Q2	22.1%	25.1%	
Q3	28.6%	25.6%	
Q4	27%	25.7%	
LOS mean (95% CI)	7.9 (7.1 - 8.8)	6.8 (6.8 - 6.9)	0.09
Total charges mean (95% CI)	103,206.1 (84,595.4 – 121,816.7)	91,248.9 (88,812.0 – 93,685.8)	0.31
In-hospital mortality (n, %)	85 (5%)	52236 (5%)	<0.01

SSc, Systemic sclerosis; n, number; CI, confidence interval; CCI; Charlson Comorbidity Index; LOS, length of stay

Table IV. Descriptive Characteristics of Leukemia Hospitalizations with and without SSc from the 2016 to 2020 National Inpatient Sample (n=1,182,380)

Hospitalization characteristics	**Leukemia with SSc (n=1975)**	**Leukemia without SSc (n=1180405)**	**P-value**
Age, mean in years (95% CI)	57.5 (55.3 - 59.6)	66.1 (65.8 - 66.4)	<0.01
Age Groups (n, %)			<0.01
Age 18 - 44 years	445 (22.5%)	154043 (13.1%)	
Age 45 - 64 years	820 (41.5%)	297108 (25.2%)	
Age ³65 years	710 (36%)	729254 (61.8%)	
Gender (n, %)			<0.01
Women	1160 (58.7%)	504623 (42.8%)	
Male	815 (41.3%)	675782 (57.3%)	
Race (%)			0.06
White	74.2%	72.9%	
Black	4.8%	9.3%	
Hispanic	11.1%	8.7%	
Other	9.9%	9.2%	

CCI mean (95% CI)	4.7 (4.5 - 4.8)	3.8 (3.8 - 3.8)	<0.01
Insurance (%)			0.03
Medicare	15.9%	24.2%	
Medicaid	25.5%	25.7%	
Private	28.8%	25.7%	
Self pay	29.8%	24.5%	
Household income (%)			<0.01
Q1	22.4%	23.6%	
Q2	22.1%	25.1%	
Q3	28.6%	25.6%	
Q4	27%	25.7%	
LOS mean (95% CI)	9.2 (7.9 - 10.5)	8.3 (8.2 - 8.5)	0.59
Total charges mean (95% CI)	133,541.1 (103,784.4 – 163,297.8)	106,208.5 (102,764.7 – 109,652.2)	0.26
In-hospital mortality (n, %)	201 (10%)	73539 (6%)	<0.01

SSc, Systemic sclerosis; n, number; CI, confidence interval; CCI; Charlson Comorbidity Index; LOS, length of stay

Table V. Descriptive Characteristics of Myeloma Hospitalizations with and without SSc from the 2016 to 2020 National Inpatient Sample (n=591,744)

Hospitalization characteristics	**Myeloma with SSc (n=585)**	**Myeloma without SSc (n=591159)**	**P-value**
Age, mean in years (95% CI)	65.7 (63.8 - 67.6)	69.5 (69.4 - 69.6)	<0.01
Age Groups (n, %)			<0.01
Age 18 - 44 years	10 (1.7%)	12769 (2.2%)	
Age 45 - 64 years	275 (47%)	175160 (29.6%)	
Age ³65 years	300 (51.3%)	403230 (68.3%)	
Gender (n, %)			<0.01
Women	415 (70.9%)	261765 (44.3%)	
Male	170 (29.1%)	329394 (55.7%)	
Race (%)			0.81
White	59%	61.7%	
Black	25.6%	21.9%	
Hispanic	7.7%	8.3%	
Other	7.7%	8.2%	

CCI mean (95% CI)	4.9 (4.6 - 5.3)	4.4 (4.4 - 4.4)	<0.01
Insurance (%)			0.21
Medicare	62.6%	69.8%	
Medicaid	5.2%	6.6%	
Private	30.4%	22.4%	
Self pay	1.7%	1.3%	
Household income (%)			0.62
Q1	22.2%	26.9%	
Q2	23.1%	24.6%	
Q3	28.2%	24.8%	
Q4	2.7%	23.7%	
LOS mean (95% CI)	6.3 (5.4 - 7.3)	7.2 (7.1 - 7.3)	0.02
Total charges mean (95% CI)	72213.3 (59,349.7 – 85,076.9)	84251.9 (82,395 – 86,108.6)	0.02
In-hospital mortality (n, %)	40 (7%)	29558 (5%)	0.36

SSc, Systemic sclerosis; n, number; CI, confidence interval; CCI; Charlson Comorbidity Index; LOS, length of stay

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