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ORIGINAL ARTICLES

Pulmonary arterial hypertension in systemic sclerosis: a national inpatient analysis

Sami H[1], Sami F[2], Razok A[2], Dasgupta M[2], Gajjar R[2]

Background: Pulmonary arterial hypertension (PAH) is a progressive, and eventually fatal complication of Systemic Sclerosis (SSc) that affects the prognosis, quality of life, and mortality rate. Non-specific manifestations of PAH can result in delayed diagnosis and therefore in poorer outcomes.
Objectives: We aim to study the prevalence and epidemiology of pulmonary arterial hypertension in SSc, and the impact of PAH on SSc hospitalizations in the United States population.
Methods: We utilized the National Inpatient Sample (NIS) from 2016-2019 to obtain adult hospitalizations with the primary/secondary diagnosis of SSc and coexistent PAH (SSc-PAH). Epidemiological variables, mortality rates, and secondary outcomes were studied including pulmonary embolism, atrial flutter, atrial and ventricular fibrillation, pneumonia, sepsis, cardiac arrest and cardiac & renal failure, and ventilator requirement. Healthcare burden was estimated from total hospital charges (THC) and length of stay (LOS). Statistical analysis was performed on STATA 16.1, using linear and logistic regression analyses.
Results: Out of 126,685 adult systemic sclerosis hospitalizations, 16.89% had PAH (SSc-PAH). The SSc-PAH group had significantly more females (85.4 % vs. 83.8%) and higher mean age (64.85±13.29 vs. 62.56±14.51). More African Americans were in this group than in the control group (19.5% vs. 14.6, p-value<0.001) while Whites (61.3% vs. 65.6%, p<0.001) and Asians (18.0 % vs. 2.8%, p<0.001) were less common. Charlson comorbidity index was higher for the SSc-PAH population (3.42 vs. 2.94, p-value<0.001). SSc-PAH group had a higher adjusted odds ratio (aOR) for mortality (aOR: 1.39, p<0.001), increased LOS (6.64 vs. 6.0 days, p<0.001) increased THC ($83,813 vs. $71,016, p <0.001). For the SSc-PAH group, there were also significantly higher odds of cardiac failure (aOR 3.13), ventilator requirement (aOR 2.15), cardiac arrest (aOR 1.39), kidney failure (aOR 1.63), pulmonary embolism (aOR 1.84), atrial flutter (aOR 1.86) atrial fibrillation (aOR1.56) and pneumonia (aOR 1.22). No significant difference in ventricular fibrillation, sepsis, or respiratory failure was noted.
Conclusion: Pulmonary arterial hypertension in SSc is associated with worse outcomes in terms of mortality and morbidity, and higher healthcare burden compared to SSc without PAH. Also, PAH disproportionately affects White, African American & Asian populations. There remains a pressing need to continue efforts for early diagnosis and management of PAH in SSc patients.

Keywords: Pulmonary hypertension; Scleroderma; Systemic sclerosis; Outcome measures; Hospitalized patients.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder (CTD) that is characterized by progressive fibrosis and deposition of extracellular matrix involving the skin, blood vessels, and various other organ systems such as gastrointestinal, pulmonary, and cardiovascular[1]. Although SSc is considered one of the less common autoimmune conditions, with a prevalence of 0.05% in the U.S., it is associated with a high burden of morbidity and mortality[2]. This stems from its association with many life-threatening and progressive conditions such as pulmonary arterial hypertension (PAH), systemic sclerosis renal crisis, and interstitial lung disease (ILD)[3,4]. It was estimated that the annual healthcare expenses per SSc patient in the U.S. can be as high as $18,396 USD, reflecting the total healthcare economic burden of the disease[5].

PAH is a frequent and dreadful complication of SSc. It occurs in up to 10% of SSc patients, and its pathophysiology is thought to be related to a combination of fibrosis and vasculopathy of the pulmonary vasculature bed[6]. The mechanism of PAH in SSc is not yet well understood but it is speculated that pulmonary vascular remodeling, intraluminal microthrombosis, and fibrosis secondary to chronic inflammation leads to elevated pulmonary vascular pressures.[7] [7]. PAH is thought to be the leading cause of mortality in SSc patients with a

[1] Shalamar Medical and Dental College, Lahore, Pakistan
[2] Department of Internal Medicine, Cook County Hospital

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Correspondence to Faria Sami
E-mail: farialatifsami@gmail.com

48.9% survival rate within 3 years of diagnosis.[8] Compared with idiopathic PAH, SSc-associated PAH carries a three times higher mortality risk.[8].

In a retrospective cohort study using data from the PHAROS registry (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma), 54% of patients had at least one hospitalization between 2005 and 2016, 34% of which had at least one re-admission. Having an etiology related to PAH in the index hospitalization was the strongest risk factor for re-admission in the subsequent 12 months[9]. For all the above reasons, identifying SSc-associated PAH in the early stages is crucial in the overall management. In this study, we aim to better determine the prevalence, risk factors, healthcare expenses and burden of SSc-associated PAH in the U.S. We also aim to investigate the impact of PAH on the hospitalization rate of SSc patients.

METHODS

Study Design and Data Sources

We designed a retrospective cohort study of systemic sclerosis hospitalizations using the National Inpatient Sample (NIS) recorded between 2016-2019. NIS is an all-payer inpatient database provided by the Agency for Healthcare Research and Quality. All hospitalizations are weighted to represent all non-federal hospitals that provide acute care in the United States (U.S.). Hospitals submit billable data to statewide data organizations which is then included in the database and represents about 97% of the U.S. population. Based on the teaching status, bed size, geographical location of the hospital, rural/urban status, the data is stratified. Twenty percent of this stratified data is collected and weighted to represent national-level data, representative of the whole country. We included data from four years (2016-2019), which has hospitalization records from 47 states and about 4000 acute care hospitals.

The database can identify patient and hospital characteristics based on several variables. These variables include primary and secondary diagnoses, hospital bed size, location, teaching status, urban or rural location, insurance type, and median household income based on zip code. The coding system used is the 'International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System (ICD-10-CM/PCS)', for all diagnoses. These can be categorized into principal, primary, or secondary diagnoses. Principal diagnosis represents the reason for hospitalization and secondary diagnoses can be other active and inactive comorbidities for the patients.

Inclusion Criteria and Study Variates

We extracted all adult hospitalizations (age>18) with a principal diagnosis of SSc between 2016-2019 using the ICD- 10 code of M34.0, M34.1, M34.2, M34.81, M34.82, M34.83, M34.89, M34.9. We used ICD-10 codes I2.70, I27.20, I27.21, I27.22, I27.23, I27.24, and I27.29 to identify all the patients with a secondary diagnosis of PAH. I is representative of the patient population included in our study.

The study variables include hospital characteristics as well as social and demographic characteristics such as age, race, gender, primary payer method, mean household income, disposition, hospital bed size, hospital location and hospital teaching status which were included in the database. The comorbidity burden was assessed using Sundararajan's adaptation of the modified Deyo's Charlson comorbidity index (CCI) which has been adjusted for population-based research. This categorizes the CCI into 4 groups based on increasing risk of mortality.

Clinical Outcomes and Definitions

The primary outcome of our analysis was the mortality rate in SSc patients with and without PAH. Several secondary outcomes that were analyzed using ICD-10 codes in both groups included congestive heart failure (CHF), pulmonary embolism (PE), pneumonia, cerebrovascular accident, atrial flutter/atrial fibrillation, ventilator requirement, respiratory failure, and sepsis. To assess the healthcare economic burden, we compared the means of length of stay and total hospital cost of stay in SSc patients with and without PAH.

Statistical Analysis

STATA® version 16.1 (StataCorp, College Station, TX) was used for statistical analysis. Year-based discharge weights supplied by Healthcare Cost and Utilization (HCUP) were used to obtain weighted national estimates, and proportions were compared using the Fisher exact test.

The independent t-test was used for the comparison of means of continuous data. We calculated the odds ratio (OR) with univariate regression analysis. From the results obtained for each secondary outcome, we filtered variables with a p-value of less than 0.2 and to adjust for confounders, included them in multivariable logistic regression analysis. Following the general rule of analysis, logistic regression analysis was implied for binary variables and linear regression analysis was used for continuous outcomes. The cut-off for the p-value to determine significance was 0.05. The Charlson Comorbidity Index was calculated for both groups as well.. Multivariate regression analysis was used to adjust for confounders for mortality in SSc.

Ethical Considerations

This study is exempted from the requirement of the

TABLE I. DEMOGRAPHICS AND HOSPITAL CHARACTERISTICS OF ADULT SYSTEMIC SCLEROSIS HOSPITALIZATIONS WITH AND WITHOUT PULMONARY ARTERY HYPERTENSION

Hospitalization Characteristics	SSc without PAH N = 105295	SSc with PAH N = 21930	P-Value
Female (%)	83.8	85.4	0.023
Age in years (Mean/SD)	62.56/14.51	64.85/13.29	<0.001
18 – 40 (%)	7.9	4.5	<0.001
40 – 60 (%)	30	27	<0.001
60 – 80 (%)	50.5	55.2	<0.001
80 or more (%)	11.5	12.9	0.014
Race			
White (%)	65.6	61.3	<0.001
African American (%)	14.6	19.5	<0.001
Hispanic (%)	11.2	11.4	0.721
Asian (%)	18.0	2.8	<0.001
Native American (%)	0.8	0.9	0.699
Charlson comorbidity Index (Mean)	2.94	3.42	<0.001
Insurance Status			
Medicare (%)	62.0	69.4	<0.001
Medicaid (%)	10.2	7.9	<0.001
Private Insurance (%)	23.6	19.8	<0.001
Self-Pay (%)	1.8	1.3	0.043
Other (%)	1.6	1.3	0.115
Hospital Bed size			
Small Bed Size (%)	17.7	15.2	0.002
Medium Bed Size (%)	26.5	23.6	0.006
Large Bed Size (%)	55.7	61.0	<0.001

Abbreviations: SS=Systemic sclerosis, PAH=Pulmonary Arterial Hypertension, SD= standard deviation.

Cook County Health Institutional Review Board (IRB) approval as NIS includes only de-identified data. The data is also readily publicly available at https://www.hcup-us.ahrq.gov. In accordance with the HCUP guidelines, our study did not require IRB approval.

RESULTS

Hospitalization characteristics

From the NIS, between the duration of 2016-2019, a total of 121,099,120 adult hospitalizations (age>18) were extracted, of which 126,685 patients were hospitalized with a principal or a secondary diagnosis of Systemic Sclerosis based on the ICD-10 codes. Among these, 21,390 (16.89%) SSc patients also had concurrent PAH as a principle or a secondary diagnosis. Therefore, SSc was divided into two groups: i.e. those with and those without PAH. Table I represents the clinical characteristics of these SSc hospitalizations for both groups.

Compared to SSc patients without PAH, females were significantly more in the group with PAH (SSc-PAH), representing approximately 85% of total admissions versus 83.84% (p-value= 0.023, odds ratio (OR 1.12). Patients with PAH had a higher mean age (64.85 years ± standard deviation (SD) of 13.29 vs. 62.56 years ± SD of 14.51, p-value<0.001) as well. In terms of racial demographics, there was a significantly higher proportion of African Americans in the group of SSc patients with PAH (19.5% vs. 14.6%, p-value=0.000). It was also noted that there were significantly fewer Asians in the study group with PAH (2.8% vs. 18%, p-value<0.001) as well as Whites (61.3% vs. 65.6%, p<0.001)

Morbidity and mortality

The Charlson Comorbidity Index (CCI) was 3.42 for the SSc-PAH group compared to 2.94 for the control group (p value <0.001). PAH was associated with higher odds of mortality in the SSc-PAH group (OR: 1.39, p<0.001) with a mortality rate of 6.42% compared to

TABLE II. PRIMARY OUTCOMES OF ADULT SYSTEMIC SCLEROSIS HOSPITALIZATIONS WITH AND WITHOUT PULMONARY ARTERY HYPERTENSION

Primary Outcome	SSc without PAH N = 105295	SSc with PAH N = 21930	P-Value OR
Died (%)	4.1	6.4	<0.001 1.39
Length of Stay (LOS) (Mean/SD)	7.7	7.3	<0.001
THC (USD)	71, 016	83, 813	<0.001

Abbreviations: SS=Systemic sclerosis, PAH=Pulmonary Arterial Hypertension, THC=Total hospital charges, USD= U.S. Dollar, SD= standard deviation, OR= odds ratio.

4.05% (p-value <0.001).

Healthcare Economic Burden

SSc hospitalizations with PAH had significantly increased LOS (6.64 vs. 6.0 days, p-value <0.001) and increased total hospital charges (THC) ($83813 vs. $71016, p <0.001) as well. This is shown in Table II. Multivariate regression analysis for the length of stay for patients of the SSc-PAH group showed that increasing age, higher Charlson Comorbidity Index, African American race, renal failure, and essential hypertension increased the length of stay. Length of hospital stay was also higher for these patients if they were admitted to a small bed size hospital, acute care center in the Midwest, or an urban non-teaching hospital.

Multivariate regression analysis for total hospital charges was able to define increasing age, female gender, African American and Asian ethnicities, renal failure, essential hypertension, small bed size, and non-teaching hospital status as risk factors for increasing total hospitalization charges.

Complications of interest

Several secondary outcomes were also studied for SSc and SSc-PAH groups. These secondary outcomes were adjusted for confounders with logistic regression analysis which included age, gender, race, renal failure, essential hypertension, insurance type, weekend admission, bed size, teaching status, and hospital region.

The SSc-PAH group had significantly higher adjusted odds for cardiac failure (aOR 3.13, p-value<0.001) and ventilator requirements (aOR 2.15, p-value<0.001). SSc-PAH hospitalizations also had a higher prevalence of cardiac arrest (aOR 1.39, p-value <0.001), kidney failure (aOR 1.62, p-value<0.001), pulmonary embolism (aOR 1.84, p-value <0.001), atrial flutter (OR 1.86, p-value<0.001), atrial fibrillation (aOR 1.56, p-value<0.001), and pneumonia (aOR 1.22, p-value<0.001). No significant difference in ventricular fibrillation, sepsis, and respiratory failure was noted (p-value >0.005). Table III summarizes the secondary outcomes of systemic sclerosis hospitalizations with and without PAH.

TABLE III. SECONDARY OUTCOMES IN ADULT HOSPITALIZATIONS WITH PULMONARY ARTERY HYPERTENSION COMPARED TO ADULT SYSTEMIC SCLEROSIS HOSPITALIZATIONS WITHOUT PULMONARY ARTERIAL HYPERTENSION.

Secondary outcomes	Odds ratio	P – Value
Cardiac Arrest	1.39	0.024
Pulmonary Embolism	1.84	<0.001
Heart failure	3.13	<0.001
Atrial Flutter	1.86	<0.001
Atrial Fibrillation	1.56	<0.001
Ventricular Fibrillation	1.01	0.975
Sepsis	0.96	0.658
Pneumonia	1.22	<0.001
Ventilator requirements	2.15	<0.001
Respiratory failure	0.77	0.185

DISCUSSION

PAH is an independent risk factor for mortality in patients with SSc and according to some studies, it is the leading cause of death even exceeding deaths from ILD in SSc patients[6]. This large retrospective study observed a significant prevalence and higher mortality, healthcare economic burden, frequency of cardiac failure and arrest, ventilator requirement, kidney failure, pulmonary embolism, atrial flutter/fibrillation, and pneumonia among SSc patients hospitalized with PAH compared to those without PAH in the U.S. from 2016-2019. We also identified important patient-related characteristics of SSc-PAH hospitalizations and compared to them

those without PAH.

Between 2016-2019, there were 126,685 adult systemic sclerosis hospitalizations of which 21,930 (16.89%) had a concurrent PAH diagnosis. This is an impressively high proportion of SSc patients with PAH. Prior studies have reported high prevalence and rising incidence as well. A review article including 9,804 patients discussed that 6.4% of SSc patients had PAH. [10]Another smaller single-center study with 140 patients done in Turkey reported one-fourth of patients had PAH. [11] A meta-analysis involving the European population reported the prevalence to be between 5-12% among SSc patients. [12] Similarly, the DETECT study by Coghlan JG, et al. including 466 patients in a cross-sectional design reported prevalence to be as high as 19% in high-risk SSc patients. [13] While prevalence has been variable in different studies depending on geographical and demographic features, it is important to acknowledge the findings of current study representative of all populations in the U.S. with the prevalence as high as 17%.

Another crucial finding of our study is that SSc patients with PAH had higher odds of mortality. Our findings are in accordance with previous studies that report increased mortality in patients with SSc-PAH compared to those without PAH. A 2013 meta-analysis comprising 22 studies with 2,244 patients with SSc-PAH reported the survival rates at one-, two-, and three-year to be 81%, 64%, and 52%, respectively. [14] Similarly, a meta-analysis of 11 studies of randomized-controlled trials with a total of 4,329 patients of patients with connective tissue disease-associated PAH found a lower survival rate in this group (most of which were SSc-PAH patients) when compared to other types of patients with PAH (3-year survival rate 62% versus 72%).[15] Another study conducted using the PHAROS registry, including 160 SSc patients with PAH reported 52% of deaths were secondary to PAH, which is an impressively high number. [16] All these studies, including ours, continue to emphasize the significance of PAH management in SSc patients.

Our study also found that those with SSc-PAH had an increased hospital stay and total healthcare economic burden. These findings agree with a prospective multicenter study using the Australian Scleroderma Cohort Study (ASCS) database with a sample size of 5,527 SSc patients between 2008-2015 demonstrating higher hospital charges for these individuals. [17] The median THC in SSc-PAH was also significantly higher in a retrospective U.S. study during a 5-year follow-up period with a total cohort of 1,957 SSc patients with lung involvement. [18] It is important to understand the economic impact of PAH on the healthcare system to accelerate our efforts on prompt and aggressive management of PAH as a comorbidity in SSc patients.

In our analysis, SSc patients with PAH were also noted to have a higher frequency of cardiac failure with a three-fold higher risk than patients without PAH. This is a crucial finding as congestive cardiac failure has been associated with higher mortality in SSc patients. In a retrospective study from South Carolina, it was noted that SSc in-hospital deaths were associated with the presence of congestive heart failure.[19] SSc patients with PAH should be regularly screened and aggressively managed for heart failure to address high mortality risks. In our study, kidney failure, pulmonary embolism, atrial flutter/fibrillation, and pneumonia were also more frequent in the SSc-PAH group. While there is lack of literature on specifically SSc patients with PAH who develop pulmonary embolism, atrial flutter/fibrillation, and pneumonia, there have been different studies that demonstrated increased mortality in SSc patients who have renal involvement, especially if associated with other vasculopathies. This further emphasizes the need to do PAH surveillance in SSc patients with renal involvement. [20,21]

Whether survival is increasing with PAH-directed therapies in SSc patients remains unclear and continues to be a topic that requires further exploration. Data to date on increased survival related to novel therapies is conflicting. One observational study from 1996-2010 reported unchanged mortality rates of SSc-PAH even after the introduction of oral vasodilator therapy in 2002. [22] In contrast, a prospective cohort study found that of 504 SSc-PAH patients diagnosed between 2010-2021, transplant-free survival improved significantly with nearly four years longer than patients diagnosed between 1999-2010 attributing the findings to earlier detection and better therapeutic options.[23] This remains an area for further investigation to assess potential gaps for the improvement in mortality and outcomes in patients with SSc-PAH.

While our study has several strengths including the representation of population from across the U.S. and includes a large population sample, the limitations of this study remain worthy of discussion. Since the diagnosis of PAH must be confirmed by the measurements of mean pulmonary pressures and resistance via right heart catheterization, there is no way to determine diagnostic accuracy when data is obtained from ICD-10 codes. It involves reliance on the diagnoses of other clinicians and the human error involved cannot, therefore, be accounted for. Another point for consideration is that this data is obtained from SSc hospitalizations, and it is unclear how accurately it represents SSc patients seen in outpatient settings, since these patients are potentially sicker or have a high disease burden. Additionally, NIS data does not give details on clini-

cal presentations, disease severity, and therapeutic regimens that may have been used while hospitalized; this leaves out important details for a comparison study and the impact of different treatments cannot be evaluated. However, this large registry analysis representative of the U.S. population provides relevant epidemiologic and clinical information to add to the foundation for future studies on the topic.

CONCLUSION

Pulmonary arterial hypertension in SSc patients is associated with worse overall outcomes in terms of mortality and morbidity, as well as a much higher healthcare burden compared to that for SSc patients without PAH. Also, PAH disproportionately affects African American & Asian populations. Although advancements have been made in the treatment of PAH in SSc, there remains room for efforts directed toward early diagnosis and management to further improve outcomes for SSc patients.

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