

# Gastrointestinal manifestations associated with systemic sclerosis: results from the nationwide inpatient sample

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## Abstract

**Background** Systemic sclerosis (SSc) is a multisystem disease associated with significant morbidity and increased mortality. The prevalence of different gastrointestinal (GI) manifestations has been investigated in multiple, but mainly small, retrospective studies. In this study, we investigated the prevalence and risk for a broad spectrum of GI disorders and malignancies in a large sample of inpatients with SSc in the United States.

**Methods** We conducted a retrospective analysis using the 2010-2011 Healthcare Cost and Utilization Project – Nationwide Inpatient Sample (HCUP-NIS). SSc patients were identified by ICD-9-CM code 710.1. Non-SSc patients (“controls”) were matched to cases 4:1 by age and sex. We examined demographics, clinical characteristics, and a range of GI conditions.

**Results** From 15,824,031 total patients, 13,633 cases of SSc were matched to 54,532 controls. The prevalence of GI manifestations among SSc patients was 59.24% compared to 29.96% for controls ( $P<0.0001$ ). Significantly elevated GI manifestations in SSc patients included dysphagia (4.3% vs. 1.9%,  $P<0.0001$ ), esophageal reflux (34.8% vs. 15.4%,  $P<0.0001$ ), Barrett’s esophagus (1.7% vs. 0.3%,  $P<0.0001$ ), constipation (6% vs. 4.6%,  $P<0.0001$ ), diarrhea (4.5% vs. 2.4%,  $P<0.0001$ ), fecal incontinence (0.4% vs. 0.2%,  $P<0.0001$ ), and celiac disease (0.2% vs. 0%,  $P<0.0001$ ). Some GI disorders were significantly lower in SSc patients, including cholelithiasis (1.6% vs. 2.1%,  $P<0.0001$ ) and GI malignancies (1% vs. 2.2%,  $P<0.0001$ ).

**Conclusions** Our results emphasize the established association between SSc and esophageal disorders, such as dysphagia and reflux disease. Our analysis indicated a significant positive association between SSc and celiac disease, and a negative association between SSc and cholelithiasis.

**Keywords** Gastrointestinal manifestations, systemic sclerosis, prevalence, HCUP, comorbidities

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## Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease characterized by progressive and systemic

deposition of connective tissue in the skin and internal organs. The estimated prevalence of SSc in the United States is around 240 cases per 1 million adults [1]. The gastrointestinal (GI) tract is the most common site of visceral involvement and the esophagus is the organ most commonly affected by the disease [2]. GI involvement in SSc has been estimated to be approximately 70-90% [3,4]. Patients present with a wide variety of symptoms depending on the site of involvement. GI involvement carries a significant morbidity and may adversely impact the quality of life in patients with SSc. Multiple studies investigated the prevalence of upper GI manifestations in SSc patients, but other GI manifestations were only reported in a few case reports or small retrospective studies. In this study, we investigated the prevalence and risk for a broad spectrum of GI disorders and malignancies among a large sample of inpatients with SSc in the United States, utilizing a nationwide database.

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## Materials and methods

The data used in this study were drawn from the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). HCUP combines data from state organizations, hospital associations, private data organizations and the federal government to create a national information resource consisting of patient-level healthcare data. The largest collection of longitudinal hospital care data in the United States is included in HCUP. The HCUP database represents 96% of the U.S. population and includes over 32 million observations. HCUP consists of multiple databases; however, the database used in this study was the Nationwide Inpatient Sample (NIS) for the years 2010 and 2011, which includes 15,824,031 patients. This database has inpatient data from over 1000 hospitals and up to 44 states in the United States.

The study included individuals who were at least 18 years of age and had an ICD-9 diagnosis code for SSc. The NIS database allows up to 25 diagnoses per patient. Controls were excluded if they had one or more ICD-9 diagnosis codes for over 100 different autoimmune diseases or were under the age of 18. SSc patients and controls were randomized and matched by age and sex. Four controls were matched to each SSc patient (13,633 SSc and 54,532 controls).

The comorbid conditions used in this analysis totaled 25 and were variables included in the NIS database obtained from the AHRQ comorbidity software. This comorbidity software assigns variables that identify comorbidities in discharge records using ICD-9-CM codes.

## Statistical analysis

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). Frequency distributions between categorical variables were assessed using the  $\chi^2$  test.

An odds ratio with 95% confidence interval was calculated for each variable. Logistic regression models were used to compare patients with and without SSc for 25 different comorbidities. The survey logistic procedures were used in this analysis to include the weight variable provided in the database. The presence of SSc was used as the dependent variable in these models. Each model was weighted and controlled for the comorbid condition as well as race and urban/rural location. A P-value of <0.05 was considered statistically significant.

## Results

Between 2010 and 2011, there were 13,633 admissions with SSc listed as principal diagnosis (5%) or secondary diagnosis (95%) for admission (Table 1). The majority of patients admitted were white females admitted to hospitals in urban locations. In each year, patients admitted with SSc as principal diagnosis were significantly younger than patients admitted with SSc as secondary diagnosis.

Table 2 shows the baseline characteristics of SSc patients and controls. Comparisons of demographic variables for SSc patients and controls revealed equal distributions for age and sex. On the other hand, there were significantly more blacks among the SSc group. The SSc group also had more admissions to hospitals in urban locations.

Table 3 shows a list of the frequency of the GI manifestations among SSc and non-SSc patients. The prevalence of GI manifestations included in our analysis was 59.24% among SSc patients compared to 29.96% among non-SSc ( $P<0.0001$ ). Esophageal reflux constituted the major GI manifestation experienced by SSc patients, with a prevalence of 34.8% compared to 15.4% in the control group ( $P<0.0001$ ). Other significantly elevated GI manifestations in SSc patients included dysphagia (4.3% vs. 1.9%,  $P<0.0001$ ), esophageal reflux (34.8% vs. 15.4%,  $P<0.0001$ ), Barrett's esophagus (1.7% vs. 0.3%,  $P<0.0001$ ), constipation (6% vs. 4.6%,  $P<0.0001$ ),

**Table 1** Hospital admissions with systemic sclerosis (SSc) as principal or secondary diagnosis by demographics and year of admission

Variable	2010		2011		Total SSc cases n=13,633
	Principal n=345	Secondary n=6363	Principal n=338	Secondary n=6587	
Sex					
Female (%)	79.4	85.2	79.6	85.2	84.9
Race					
White (%)	51.7	70.4	61.0	72.0	70.4
Black (%)	27.9	16.2	23.0	13.7	15.5
Hispanic (%)	14.7	8.2	8.9	9.6	9.1
Other (%)	5.7	5.2	7.1	4.7	5
Location*					
Urban (%)	92.0	90.0	95.8	91.3	90.8
Age (mean $\pm$ SD)	54.7 $\pm$ 15.5	61.8 $\pm$ 15.1	56.0 $\pm$ 15.1	62.2 $\pm$ 14.8	61.7 $\pm$ 15.0

\*Based on hospital location in rural or urban area

diarrhea (4.5% vs. 2.4%,  $P<0.0001$ ), fecal incontinence (0.4% vs. 0.2%,  $P<0.0001$ ), and celiac disease (0.2% vs. 0%,  $P<0.0001$ ). On the other hand, cholelithiasis was found to be significantly less common in SSc patients (1.6% vs. 2.1%,  $P<0.0001$ ). There was no significant association between SSc and diverticulosis, peptic ulcer disease or other gallbladder diseases.

**Table 2** Distribution of systemic sclerosis (SSc) and non-SSc in relation to demographic variables

Variable	SSc N=13,633	Non-SSc N=54,532	P-value
Sex			
Female (%)	84.9	84.9	-
Age (mean $\pm$ SD)	61.7 $\pm$ 15.0	61.9 $\pm$ 15.9	0.1524
Race			
White (%)	70.4	71.1	0.0002
Black (%)	15.5	14.0	
Hispanic (%)	9.1	9.6	
Other (%)	5.0	5.3	
Location*			
Urban (%)	90.8	86.6	<0.00001

\*Based on hospital location in rural or urban area

Table 4 lists the frequencies of a broad spectrum of GI malignancies among SSc and non-SSc patients. Total GI malignancies were found to be significantly lower in SSc patients (1% vs. 2.2%,  $P<0.001$ ). Analysis by type of cancer showed significantly lower frequency of colon (0.2% vs. 0.8%,  $P<0.001$ ), liver (0.1% vs. 0.3%,  $P<0.001$ ), and pancreatic cancers (0.1% vs. 0.4%,  $P<0.001$ ) among the SSc patients compared to the control group. No significant difference between groups was seen in other GI malignancies, including esophageal, gastric and gallbladder malignancies.

## Discussion

This study aimed to examine the prevalence of GI manifestations among SSc patients, based on hospital admissions data, and also to investigate the association between GI manifestations and SSc compared to controls. The prevalence of GI manifestations among SSc patients included in our analysis was 44.4%, and was significantly higher compared to 26.6% among non-SSc. GI manifestations are known to be significantly more common in SSc patients [4]. The estimated prevalence of GI manifestations has been

**Table 3** Distribution of selected gastrointestinal disorders between patients with and without systemic sclerosis (SSc)

Disorder	SSc N (%)	Non-SSc N (%)	OR 95% CI	P-value
Diverticulosis	556 (4.1)	2049 (3.8)	1.09 0.99-1.20	0.085
Celiac	34 (0.2)	0 (0.0)	.*	<0.0001
Peptic ulcer	71 (0.5)	243 (0.4)	1.18 0.91-1.54	0.276
Dysphagia	584 (4.3)	1026 (1.9)	2.36 2.13-2.62	<0.0001
Fecal incontinence	53 (0.4)	96 (0.2)	2.19 1.57-3.08	<0.0001
Constipation	822 (6.0)	2506 (4.6)	1.34 1.23-1.45	<0.0001
Diarrhea	620 (4.5)	174 (2.4)	14.88 12.57-17.63	<0.0001
Esophageal reflux	4743 (34.8)	8424 (15.4)	2.93 2.81-3.05	<0.0001
Barrett's esophagus	232 (1.7)	174 (0.3)	5.41 4.44-6.59	<0.0001
Cholelithiasis	214 (1.6)	1128 (2.1)	0.75 0.64-0.87	0.0002
Other gallbladder diseases	147 (1.1)	517 (0.9)	1.14 0.95-1.37	0.166
Total	8076 (59.24)	16337 (29.96)	3.4 3.27-3.53	<0.0001

\*Not calculable

OR, odds ratio; CI, confidence interval

**Table 4** Distribution of gastrointestinal malignancies between patients with and without systemic sclerosis (SSc)

Malignancy	SSc N (%)	Non-SS N (%)	OR 95% CI	P-value
Oropharyngeal	2 (0.01)	6 (0.01)	1.3 0.27-6.61	0.72
Oral	14 (0.1)	66 (0.1)	0.85 0.48-1.51	0.576
Esophageal	23 (0.2)	64 (0.1)	1.44 0.89-2.32	0.135
Stomach	16 (0.1)	99 (0.2)	0.65 0.38-1.09	0.1
Small intestine	1 (0.0)	23 (0.0)	0.17 0.02-1.29	0.086
Colon	28 (0.2)	417 (0.8)	0.27 0.18-0.39	<0.0001
Rectum	31 (0.2)	168 (0.3)	0.74 0.5-1.08	0.12
Liver	11 (0.1)	145 (0.3)	0.3 0.16-0.56	<0.0001
Gallbladder	4 (0.02)	32 (0.1)	0.45 0.18-1.41	0.191
Pancreas	17 (0.1)	197 (0.4)	0.34 0.21-0.57	<0.0001
Peritoneum	3 (0.01)	49 (0.1)	0.24 0.08-0.79	0.018
Other gastrointestinal location	0 (0.0)	9 (0.01)	0.21 0.01-3.62	0.282

OR, odds ratio; CI, confidence interval

reported to be approximately 70-90% [3,4]. However, one study that investigated the frequency of GI symptoms based on a multi-symptom questionnaire suggested that, in reality, a much higher percentage of patients than expected (98.9%, i.e. nearly all) suffer from GI symptoms, regardless of the stage of their disease [5].

In this study, we found a significantly higher prevalence of gastroesophageal reflux disease, Barrett's esophagus and dysphagia in patients with SSc, consistent with the current knowledge regarding esophageal involvement in SSc. Esophageal involvement is the most common GI involvement in SSc patients, with an incidence that varies from 70-90% depending upon the technique of detection [6-8]. These manifestations are related to a weakened lower esophageal sphincter and altered peristaltic activities, secondary to fibrosis and abnormalities in smooth muscle function, that occur in SSc patients [9,10].

Our study also showed a significantly higher prevalence of constipation in SSc patients. Colonic dysmotility in patients with SSc could explain the higher risk of constipation. We also found a significant association with diarrhea and fecal incontinence. These colonic manifestations were evaluated by Trezza *et al* [11] in a case-series study involving 83 participants. They reported that 20% of SSc patients have colorectal dysfunction resulting in some or major restriction of social

activities or the quality of life [11]. The colonic manifestations included in their analysis were diarrhea, constipation, and fecal incontinence.

One of the other colonic manifestations examined in this study was colonic diverticulosis. Our analysis found no significant association between SSc and colonic diverticulosis. Heinz *et al* described a characteristic roentgenological appearance of wide-mouth diverticula typical of SSc, found in 9 of 19 cases who had a barium enema examination [12]. Our results suggest that this finding could be random among patients with SSc compared to controls, or it may be underdiagnosed.

We found that patients with SSc have a significantly higher prevalence of celiac disease than controls. The association between celiac disease and SSc has been evaluated in a few studies in the literature. In addition to some case reports [13,14], we identified three studies that discussed this association, though with non-consistent results. Two studies reported a higher prevalence of celiac disease in SSc patients (7-8%) compared to the general population (1%). These two studies were limited by small sample sizes (n=30 and n=50) [15,16]. The third study, conducted by Forbess *et al*, tested 72 SSc patients for celiac disease serology then biopsy [17]. They reported the prevalence of celiac antibodies in SSc population as 3/72 (4%), but no cases of celiac disease confirmed by biopsy were seen in

their SSc cohort [17]. They also found no important differences with respect to GI symptoms in the celiac antibody-positive compared with antibody-negative SSc patients. Given these inconsistent results and the small sample sizes in the three previous studies, there was a need for a large comparative study to detect any difference between the two groups. Our study is the largest observational comparative study to evaluate the association between celiac disease and SSc. Celiac disease is known to be associated with an increased risk of multiple autoimmune disorders in patients and their relatives [18-20].

In this study we found that there was no significant difference in gallbladder diseases between SSc patients and controls. Regarding cholelithiasis, it was significantly lower in SSc patients compared to controls. Two studies in the literature showed that gallbladder motility in patients with SSc was not significantly reduced when compared to controls [21,22], consistent with our findings.

Our study found a significantly lower prevalence of all GI cancers in SSc patients. The risk of all malignancies in SSc is controversial. Some studies have suggested that these patients have an increased total risk of malignancies compared to the general population, which, in most cases, was attributable to lung cancer, with a non-consistent increase in some other types of malignancy [23-30]. On the other hand, a few other studies showed that there is no difference in the risk of malignancy in patients with SSc compared to the general population [31-34]. One study included GI cancer as a subgroup and showed no significant difference between SSc and the general population in the standardized incidence ratio of all GI malignancies [27].

In our study we found no significant difference in esophageal and oropharyngeal cancer between SSc patients and controls. Esophageal cancer was reported to be more frequent in a subgroup analysis of two studies [28,29], while five other studies showed no significant difference [23,24,30,33-35]. One study reported a higher risk of oropharyngeal cancer in SSc patients [28].

Our analysis showed that the risk of liver cancer was significantly lower in SSc patients. Chatterjee *et al* [33] found that black females with scleroderma had significantly higher rates of liver cancer, which was not evident in other subgroups. Additionally, two other studies found a higher incidence of liver cancer in SSc patients [29,35]. However, one of these studies reported only one case and the calculated standardized incidence ratio had a wide confidence interval, which calls into question the clinical significance of this finding [29].

Our study has several important strengths. We used a national database representing 96% of the U.S. population, with over 32 million patients. Of those, 15,824,031 records were screened and used in our analysis, enabling a clear picture of the prevalence of GI problems among SSc patients on a countrywide basis. Furthermore, the GI problems identified in this study were based on doctor-diagnosed diseases and not on self-reporting by patients.

There are also several potential weaknesses in the design of this study. First, the data were limited to hospitalized patients; therefore, not all patients suffering from SSc were investigated. Additionally, HCUP data may not reflect the true prevalence

## Summary Box

### What is already known:

- Gastrointestinal (GI) manifestations are common among patients with systemic sclerosis (SSc)
- Esophagus is the most common GI organ involved in SSc

### What the new findings are:

- Our results emphasize the established association between SSc and esophageal disorders such as dysphagia and reflux disease
- There was a significant positive association between SSc and celiac disease, and a negative association with cholelithiasis and GI malignancies

of GI manifestations, as the database relies on an inpatient coding system. Coding errors would affect the reliability and validity of our results. In addition, the data do not include the level of workup and investigation used to reach the diagnoses code; however, these are physician-based diagnoses, which increases their reliability. Furthermore, because HCUP is limited to hospitalized patients, the SSc patients included in this study was sicker than the other group of SSc patients seen on outpatient setting and were not included in this database, thereby hospitalized patients possibly presented with a higher prevalence of certain types of GI problems the group included in this study was sicker than the SSc patients not requiring hospitalization, thereby possibly presenting with a higher prevalence of certain types of GI problems. Multiple admissions for the same patient might be problematic. However, there is no reason to believe that the pattern of admission differed between the SSc patients and the controls.

In conclusion, GI manifestations are common among patients with SSc. Our results emphasized the established association between SSc and esophageal disorders such as dysphagia and reflux disease. Moreover, our analysis advocated a significant positive association between SSc and celiac disease, and a negative association with cholelithiasis and some GI malignancies. These results could be confirmed by further studies.

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