Comorbidities associated with Sjögren's syndrome: results from the Nationwide Inpatient Sample

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Although multiple comorbidities associated with Sjögren's syndrome (SS) have been reported, reliable data regarding the prevalence of specific comorbidities among patients with SS remain sparse. In this study, we investigated the prevalence and risk for a broad spectrum of medical conditions among patients with SS in the United States. The Health Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) data was utilized in order to investigate 27 different comorbidities among SS patients. Between the years 2007 to 2009 there were 19,127 admissions with SS listed as principal diagnosis (1.3%) and secondary diagnosis (98.7%). Compared with 57,381 controls, SS patients had significantly higher prevalence of lymphoma (OR 1.6), valvular disease (OR 1.42), congestive heart failure (OR 1.28), hypothyroidism (OR 1.24), paralysis (OR 1.24), deficiency anemia (OR 1.16), depression (OR 1.18), neurological disorders (OR 1.17), chronic pulmonary disease (OR 1.07), and hypertension (OR 1.04). SS is associated with substantial medical conditions that may impact morbidity and mortality as well as quality of life for individuals suffering from SS.

Sjögren's syndrome | autoimmune diseases | comorbidities | HCUP data

Sjögren's syndrome (SS) is an inflammatory disease of the exocrine system, including the lacrimal and salivary glands (1). However, other organs can also be affected by SS including the lungs, nerves, blood vessels, and kidneys (2). SS is often classified into primary Sjögren's syndrome and secondary Sjögren's syndrome. Primary SS is among the most common autoimmune diseases with an estimated prevalence ranging from 0.04% to 4.8% and with a male to female ratio of approximately 1:9 (3). Most women are affected during their 50s after menopause. Secondary SS is closely associated with rheumatoid arthritis and is believed to have a different pathogenesis than primary SS (1).

Comorbid conditions are important when studying autoimmune diseases such as SS because individuals that suffer from autoimmune disease are more susceptible to development of other autoimmune diseases (4, 5). The risk of comorbid conditions among individuals suffering from SS is not well delineated (6). However, there are many known comorbidities that can occur in conjunction with SS. A previous case-controlled study suggested that SS patients are more likely to have hyperlipidemia, cardiac arrhythmias, headaches, migraines, fibromyalgia, asthma, pulmonary circulation disorders, hypothyroidism, liver disease, peptic ulcers, hepatitis B, deficiency anemias, depression and psychoses (6). Other studies have reported higher incidence of other comorbidities such as lymphoma (7), non-Hodgkin's lymphoma (8), celiac disease (9) and dementia (10). Individuals with autoimmune thyroid disorders were found to have a higher rate of comorbid autoimmune diseases such as lupus and SS compared to the general population (11). In other words, an individual having autoimmune disease might be at a higher risk for developing another autoimmune disease. Currently, the long term effects of comorbidities in SS on mortality remain unclear. However, it is known that quality of life is significantly affected by comorbid conditions (12).

Although multiple comorbidities associated with SS have been reported, reliable data regarding the prevalence of specific comorbidities among patients with SS remain sparse. Studies aiming to estimate the prevalence of comorbidities associated with SS in the general population were limited in their scope due to the study population used, as well as the small number of study participants. Furthermore, there is a current deficit of studies that have attempted to capture the prevalence of comorbid conditions among hospitalized SS patients in the United States.

In this study, we investigated the prevalence and risk for a broad spectrum of medical conditions among patients with SS in the United States utilizing a nationwide database.

Methods

Data used in this study is 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 health care data. The largest collection of longitudinal hospital care data in the United States is included in HCUP beginning in 1988. 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 is the Nationwide Inpatient Sample (NIS) for the years 2007 through 2009. This database has inpatient data from over 1,000 hospitals and up to 44 states in the United States. (13).

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Author contributions: TK and SAK designed the study and wrote the manuscript. All other individual authors were involved in data interpretation and writing of the manuscript. All authors have read and approved the manuscript as submitted. SAK takes responsibility for the paper as a whole.

The authors declare no conflict of interest

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Table 1: Hospital admissions with SS as principal or secondary diagnosis by demographics and year of admission

	2007		2008		2009	
Variable	Principal n=90	Secondary n=5423	Principal n=83	Secondary n=6223	Principal n=72	Secondary n=7236
Gender						
% Female	94.44	92.95	75.90	93.35	90.28	91.96
Race						
%White	73.61	83.02	70.42	82.78	67.69	83.04
%Black	6.94	6.03	21.13	6.22	12.31	7.07
%Hispanic	13.89	5.78	5.63	6.12	7.69	5.73
Location*						
%Urban	85.37	82.69	78.48	82.21	90.00	83.92
Age						
mean±sd	58.77±17.06	63.75±15.44	53.76±15.02	63.7±15.23	58.69±16.13	63.52±15.56

*Urban or rural designation based on the country in which the hospital is located

Subjects included in the study consisted of individuals who were at least 18 years of age and had an ICD-9 diagnosis code for Sjøgren's syndrome. The ICD-9 codes do not provide differentiation between primary and secondary SS, therefore the code used in this study to identify all subjects with SS was 710.2. The NIS database allows up to 10 or 15 diagnoses per patient depending on the reporting year. Controls were excluded if they had one or more of over 100 different autoimmune disease ICD-9 diagnosis codes or were under the age of 18. SS patients and controls were randomized and matched by age and sex. Three controls were matched to each SS patient (19, 127 SS and 57,381 Control).

The comorbid conditions used in this analysis totaled 27 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 (13). The 27 comorbidities included in this study are listed in table 2.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). Frequency distributions between categorical variables were assessed using the χ^2 test. Logistic regression models were utilized to compare patients with and without SS for 27 different comorbidities. The survey logistic procedures were used in this analysis to include the weight variable provided in the database. The presence of SS 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 and were used to identify increased occurrence of conditions listed in table 3.

Results

Between 2007 and 2009, there were 19, 127 admissions with SS listed as principal diagnosis (1.3%) or secondary diagnosis (98.7%) for admission (Table 1). The majority of admitted patients were white females admitted to hospitals in urban locations. In each year, patients admitted with SS as principal diagnosis were significantly younger than patients admitted with SS as secondary diagnosis.

Figure 1, displays the frequency of autoimmune diseases coexisting in patients with SS. Rheumatoid arthritis was the most common autoimmune disease coexisting with SS.

Table 2 shows a list of the frequency of the comorbidities among SS patients. Hypertension was the most common comorbidy with a prevalence rate of 42.14%. Other prevalent comorbidities were fluid and electrolytes disorders, chronic pulmonary disease, deficiency anemia, hypothyroidism, uncomplicated diabetes, and depression.

Comparisons of SS patients and controls on demographic variables revealed equal distributions for age and gender. On the other hand, there were significantly more admissions for Hispanics among the control group. The control group also had more admissions to hospitals in rural locations.

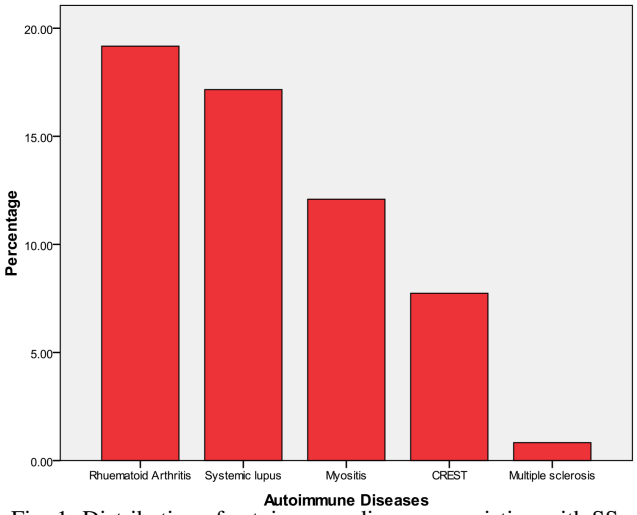

Fig. 1: Distribution of autoimmune diseases coexisting with SS.

There were a significantly higher percentage of SS patients with the following comorbidities compared to the controls: Lymphoma, valvular disease, congestive heart failure, hypothyroidism, paralysis, deficiency anemia, depression, neurological disorders, chronic pulmonary disease, and hypertension (table 3).

There was a significantly lower percentage of SS patients with the following comorbidities compared to the controls: metastatic cancer (OR 0.56; 95% CI, 0.48-0.66), alcohol abuse (OR 0.64; 95% CI, 0.57-0.72), weight loss (OR 0.80; 95% CI 0.68-0.94), fluid and electrolytes disorders (OR 0.82; 95% CI, 0.78-0.86), obesity (OR 0.88; 95% CI 0.82-0.95), coagulopathy (OR 0.89; 95% CI 0.81-0.97), and uncomplicated diabetes (OR 0.92; 95% CI 0.87-0.97).

Discussion

This study aimed to examine the prevalence of comorbidities among SS patients based on hospital admissions data. The results of data analyses suggest that the most common comorbid condition, beside hypertension, was rheumatoid arthritis with a prevalence of 40.84%, which is in agreement to those reported in other studies reporting a prevalence rate of 39.0% for arthralgias/arthritis (14). Sjö-

gren's syndrome is frequently associated with rheumatoid arthritis and systemic lupus erythematosus. It has been estimated that 18-30% of rheumatoid arthritis patients have secondary SS (15). Moreover, rheumatoid factors appear to play an important role in the pathogenesis of SS as it has been suggested to be an indicator of the severity of salivary gland damage (16).

Table 2: Frequencies of comorbidities in patients with SS.

Comorbidity	Number	%
Hypertension	7900	42.14
Fluid and Electrolytes Disorders	3931	20.97
Chronic Pulmonary Disease	3303	17.62
Deficiency Anemia	3131	16.70
Hypothyroidism	2807	14.97
Diabetes, uncomplicated	2594	13.84
Depression	2132	11.37
Renal Failure	1652	8.81
Obesity	1373	7.32
Congestive Heart Failure	1340	7.15
Neurological Disorders	1192	6.36
Valvular Disease	769	4.10
Peripheral Vascular Disorders	746	3.98
Weight Loss	731	3.90
Coagulopathy	719	3.83
Psychosis	707	3.77
Diabetes with chronic complications	581	3.10
Liver Disease	510	2.72
Alcohol Abuse	469	2.50
Drug Abuse	446	2.38
Pulmonary Circulation Disorders	429	2.29
Paralysis	350	1.87
Chronic Blood Loss	323	1.72
Solid Tumor without Metastasis	321	1.71
Metastatic Cancer	253	1.35
Lymphoma	201	1.07

Anemia occurred in 16.7% of SS patients and this was significantly higher than that for the control population (p=0.0001). The prevalence of anemia was reported to be 34.1% in previous studies (17). Kang et al. reported an odds ratio (OR) of 1.33 (95% CI 1.01-1.77) for anemia (6) which is similar to the OR of 1.16 (95% CI 1.11-1.22) found in this study, however, the prevalence was only 3.4%, much lower than our results and that of previous studies (17).

Table 3: Elevated comorbidities in patients with SS compared to controls.

Comorbidity	OR*	95% CI	*p*-value
Lymphoma	1.60	1.32-1.93	0.0001
Vascular Disease	1.42	1.29-1.56	0.0001
Congestive Heart Failure	1.28	1.19-1.38	0.0001
Hypothyroidism	1.24	1.18-1.31	0.0001
Paralysis	1.24	1.08-1.42	0.0024
Deficiency Anemia	1.16	1.11-1.22	0.0001
Depression	1.18	1.11-1.25	0.0001
Neurological Disorders	1.17	1.09-1.27	0.0001
Chronic Pulmonary Disease	1.07	1.02-1.12	0.0076
Hypertension	1.04	1.01-1.08	0.0294
Psychosis	1.10	1.00-1.21	0.0578
Pulmonary Circulation Disorders	1.12	0.99-1.26	0.0716
Renal Failure	1.01	0.95-1.08	0.6725

*Adjusted for race and hospital location

Lymphoma risk was increased by 60% over the control group in this study. Several recent large cohort studies and a meta-analysis have estimated the lymphoma risk in patients with SS. A cohort study that included 507 incident patients with SS showed that the risk of developing lymphoma was about 16-fold higher in patients who did compared to those that did not fulfill the diagnostic American-European Consensus Criteria (18). Similar results were observed in a more recent cohort study, which estimated that the relative risk of developing lymphoma was about 16-fold higher in SS patients than general population and that this risk increased over time and remained high, even 15 years after SS diagnosis (19). Factors such as cytokine stimulation, environmental factors, viral infection and genetic events as well as vitamin deficiency may also contribute to the development of lymphoma (20).

Both congestive heart failure and valvular diseases were significantly increased among SS patients. Valvular regurgitation, pericardial effusion, pulmonary hypertension, and increased left ventricular mass index were reported to occur with disproportionately high frequency in patients with SS with no clinically apparent heart disease (21).

Hypothyroidism occurred in almost 15% of the SS patients. Moreover, there was a 24% increase in the risk of hypothyroidism among SS patients as compared to the controls. This increase is less than that reported in previous studies (OR 2.37; 95% CI 1.92-2.93) (6). Recent studies suggest thyroid gland dysfunction as a main endocrine abnormality occurring in the context of SS. Previous studies have shown that approximately one third of SS had thyroid disorders (22). Shared genetic and immunopathological findings such as common HLA antigens, periepithelial lymphocytic infiltration and oligoclonal B-cell expansion strongly support the presence of common pathophysiological operating mechanisms between the two entities (23).

More than 11% of SS patients in this study suffered from depression. Moreover, there was an 18% increase in the risk over the controls. Other studies in the literature report higher prevalence of depression among SS patients (24, 25).

Almost 4% of SS patients in this study were diagnosed with psychosis; there was a 10% increase in the risk over the controls. Other studies looking only at primary SS have reported a higher risk of psychoses (OR 2.15; 95% CI, 1.65-2.80) (6). Psychiatric or cognitive impairment, usually mild or moderate, was reported in over 80% highly selected population of SS patients, and more than 60% of these patients had both (26). Associations between autonomic symptoms and fatigue and symptoms of depression in patients with primary SS have also been reported (27).

Pulmonary manifestations were among the most prevalent complications, with reported prevalence varying widely (9-75%), depending on the methods of detection and patient selection (22, 28-30). About 17.6% of SS patients in this study were diagnosed with chronic pulmonary disease and this was significantly different from that for the controls. Similarly, a marginally significant difference was found for pulmonary circulation disorders. Another study did report a significant difference between patients and controls for pulmonary circulation disorders (OR 1.42, 95% CI 1.21-1.68) (14). Other risk factors besides SS such as smoking, environmental pollution, and infections play a major role in determining the risk of pulmonary diseases. However our data is not suitable to address this issue.

Our study has several important strengths. We used a national database representing 96% of the U.S. population with over 32 million patient records utilized in analysis, enabling a clearer picture of the prevalence of comorbidities among SS patients on a country-wide basis. Furthermore, the comorbidities identified in this study are based on doctor-diagnosed diseases, and not self-reporting by patients. In the case of autoimmune diseases, which include rare diseases and diseases with considerable clinical heterogeneity and complex case definitions, the collection of data through self reporting involves a high probability of referral bias (31).

There are also several potential weaknesses in the design of this study. First, the data are limited to hospitalized patients, and there-

fore not all patients suffering from Sjögren's syndrome were investigated. Second, we do not know if the diagnosis of SS was well established according to accepted criteria or was merely based on physicians' impression of dryness symptoms. Moreover, the extent to which the primary diagnosis (only 1.3% of patients had SS as the primary diagnosis for admission) contributes to the comorbidity cannot be estimated. Therefore, the HCUP data may not reflect the true prevalence of comorbidities. Third, the group included in this study was sicker and possibly showing higher prevalence of certain comorbidities. Fourth, we were unable to adjust for significant covariates such as smoking. Finally, multiple admissions for the same patient might be problematic. However, there is no reason to believe that the pattern of admission is different between SS patients and the controls.

In conclusion, comorbidities are common among patients with SS, with a preponderance of certain comorbidities such as lymphoma, pulmonary disease, deficiency anemia, hypothyroidism, congestive heart failure, and valvular diseases.

ACKNOWLEDGMENTS. The authors would like to acknowledge the contributions of Sreekiran Thotakura to analysis of the data.

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