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The Association Between Sjögren Syndrome and Adverse Postoperative Outcomes: A Historical Cohort Study Using Administrative Health Data

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Abstract

BACKGROUND—Sjögren syndrome is a chronic autoimmune disorder of the exocrine glands associated with cardiovascular events. We aimed to evaluate postoperative complications in patients with Sjögren syndrome undergoing noncardiac surgery. Specifically, we tested the primary hypothesis that patients with Sjögren syndrome have a greater risk of postoperative cardiovascular complications than those without the disease. Our secondary hypotheses were that

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DISCLOSURES

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Attestation: Rovnat Babazade has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

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patients with Sjögren syndrome are at greater risk of thromboembolic complications, microcirculatory complications, and mortality.

METHODS—We obtained censuses of 2009 to 2010 inpatient hospital discharges across 7 states. Sjögren syndrome was identified by the present-on-admission diagnosis code 710.2. Each Sjögren syndrome discharge was propensity matched to 4 control discharges. A generalized linear model was used to compare matched Sjögren syndrome patients and controls on risk of in-hospital cardiovascular complications, thromboembolic complications, microcirculatory complications, and mortality.

RESULTS—Among 5.5 million qualifying discharges, our final matched sample contained 22,785 matched discharges, including 4557 with Sjögren syndrome. Sixty-six (1.45%) of the matched discharges with Sjögren syndrome and 213 (1.17%) of the matched controls had associated in-hospital cardiovascular complications. The adjusted odds ratio (99% confidence interval) was estimated at 1.14 (0.79–1.64), which was not statistically significant ($P = 0.35$). There were no significant differences in the odds of in-hospital thromboembolic complications (1.12 [0.82–1.53]; $P = 0.36$), in the odds of in-hospital microcirculatory complications (0.98 [0.77–1.26]; $P = 0.86$), or in the odds of in-hospital mortality (1.11 [0.76–1.61]; $P = 0.49$).

CONCLUSIONS—The presence of Sjögren syndrome does not place patients at an increased risk for postoperative complications or in-hospital mortality.

Sjögren syndrome is a chronic autoimmune disorder of the exocrine glands that also can affect other organs and provoke other complications, such as vasculitis, pericarditis, pulmonary hypertension, acceleration of atherosclerosis, and autonomic dysfunction.^{1–4} The overall prevalence of Sjögren syndrome is 0.1% to 0.4% of the general population, with a female to male ratio of 9:1.⁵ On the basis of prevalence data and population figures, researchers have suggested that 0.4 to 3.1 million people in the United States experience Sjögren syndrome.⁶ Patients diagnosed with this syndrome have a slightly increased mortality and morbidity rate in comparison with the remainder of the population.^{5,7,8} In a recent, large, retrospective cohort study, a greater prevalence of myocardial infarction and cerebrovascular events was observed in patients with Sjögren syndrome compared with general population.⁹ The pathogenesis of the syndrome leading to increased morbidity and mortality has not been fully elucidated, but susceptible triggers such as genetic background and environmental and hormonal factors are thought to contribute to this process. Subsequently, in nonoperative settings, patients with Sjögren syndrome have a greater prevalence of endothelial dysfunction,¹⁰ thromboembolism, early atherosclerosis,¹¹ vasculitis,¹² and intima-media thickening of the large vessels.^{2–4,13} Furthermore, deterioration in systolic and diastolic left ventricular dysfunction was found in patients with Sjögren syndrome¹⁴; autoimmune phenomena and small intramyocardial vessel or vasa vasorum vasculitis have been suggested as mechanisms for this left ventricular dysfunction.¹⁵

Thromboembolic and cardiovascular events are the main causes of postoperative morbidity and mortality. Anesthesia and surgery incite a substantial release of inflammatory mediators.¹⁶ Surgery increases the thrombotic risk because of increased inflammatory and hypercoagulable states, whereas the decrease of fibrinolysis can adversely affect underlying

cardiovascular disease.^{16,17} Inflammatory cytokines are contributors to postoperative organ dysfunction, including cardiovascular, lung, liver, kidney injury, and central nervous system disorders.^{1,16,18,19} The inflammatory response to surgical stimulus and anesthesia combined with Sjögren syndrome–related inflammation may thus be harmful. However, there are no large epidemiologic peri-operative studies on postoperative cardiovascular, micro-circulatory complications, and causes of death in Sjögren syndrome. The available literature does not address the relationship between Sjögren syndrome and postoperative complications and mortality.

We aimed to evaluate cardiac and thromboembolic postoperative complications in patients with Sjögren syndrome undergoing noncardiac surgery. Specifically, we tested the primary hypothesis that patients with Sjögren syndrome have a greater risk of postoperative cardiovascular complications than patients without the disease. Our secondary hypothesis was that patients with Sjögren syndrome have a greater risk of thromboembolic complications, microcirculatory complications, and mortality.²⁰

METHODS

IRB approval and waiver of consent were obtained. We designed a historical cohort study by using administrative health data of State Inpatient Databases authorized by US Agency for Healthcare Research and Quality. Censuses of 2009 to 2010 inpatient hospital discharge data were obtained^a for across the following 7 states: Arizona, California, Florida, Iowa, Maryland, Michigan, and New Jersey. Seven states were chosen as a convenience sample and chosen to provide a representative spectrum of a geographic locales and socioeconomic characteristics. The years 2009 and 2010 were used because only these data were purchased by the Cleveland Clinic from the US Agency for Healthcare Research and Quality. All patients were admitted within 2009 to 2010 calendar years and followed up until discharge from the hospital. Discharge data included all inpatient care records for selected states and are composed of basic demographic characteristics, such as age and gender, emergency admission, diagnosis codes with present-on-admission (POA) indicators, and procedure codes. All diagnosis and procedure codes were based on the International Classification of Diseases and Injuries, version 9, Clinical Modification coding system (ICD-9-CM codes).^b

We excluded medical visits (as defined by zero procedures performed) and visits associated with patients younger than 18 and older than 80 years of age on admission. We excluded visits comprising minor procedures and kept only inpatient visits with surgical procedures^c recorded as POA. In-hospital mortality was available as a binary indicator variable in the discharge record.

^aState Inpatient Databases (SID). Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/sidoverview.jsp. Accessed February 2013.

^bHCUP CCS. Healthcare Cost and Utilization Project (HCUP). Agency for Healthcare Research and Quality, Rockville, MD. Available at: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed February 2013.

^cSurgical procedures were defined through Surgery Flag Software by US Healthcare Cost and Utilization Project (HCUP). Department of Health and Human Services, Agency for Healthcare Research and Quality (AHRQ). Available at: <http://www.hcup-us.ahrq.gov/toolssoftware/surgflags/surgeryflags.jsp#download>. Accessed November 2014.

We considered state of discharge, gender, age, emergency admission, year of discharge, principal procedure code, and all POA diagnosis codes (excluding that specified earlier for Sjögren syndrome) as potential confounding variables. Sjögren syndrome was identified using the POA diagnosis code 710.2.

Primary procedures and diagnosis ICD-9-CM codes are hierarchical and were aggregated for the purpose of the analysis. Each diagnosis code is represented by a maximum of 5 digits, and each procedure code is represented by a maximum of 4 digits. The diagnosis (procedure) codes represented by <5000 (10,000) patients were aggregated to a more general diagnosis (procedure) class (for explanation for the aggregation of diagnostic codes see Appendix 1). Coupled with an assumed Sjögren syndrome incidence of approximately 1%, this implied a minimal cell size of about 50 discharges for any predictor in our propensity model. The diagnosis (procedure) codes were aggregated up to 4 digits (3 digits); aggregated diagnosis (procedure) codes still not meeting 5000 (10,000) patient criterion were removed.

Statistical Analysis

To account for potential confounding because of systematic differences between study groups, we matched each Sjögren syndrome discharge to four control discharges.

For the matching, we used a hybrid approach which enforced exact matches on certain variables and allowed approximate matches on other variables (via propensity scores).

Specifically, we used POA diagnosis codes to estimate propensity scores for Sjögren syndrome and matched each patient with Sjögren syndrome to 4 patients without Sjögren syndrome based on the logit of propensity score (within ± 0.2 of SDs of the logit propensity score),²¹ restricting successful matches to those with common gender, common state of discharge, status on emergency admission, common primary procedure, and difference in age of <5 years. The greedy distance-based algorithm was used for the matching.²² Propensity scores (i.e., the estimated probability of having Sjögren syndrome as a function of the patients' other POA diagnoses) were estimated with the use of elastic net logistic regression^{23,24}; the R statistical software (The R Foundation for Statistical Computing, Vienna, Austria) package "glmnet" was used to fit the propensity model from the aggregated POA diagnosis-related predictors.²⁵

After matching, the balance between Sjögren syndrome and normal controls on the aforementioned baseline variables (including major diagnosis-related predictors) was assessed by the use standard univariate summary statistics (means and SDs, medians and quartiles, or proportions, as appropriate) and standardized difference scores (defined as the difference in means, mean rankings, or proportions divided by a combined estimate of SD). Any baseline variable exhibiting a standardized difference score >0.04 in absolute value was used for adjustment within our final models comparing matched patients on outcomes.²⁶

For the final models, a generalized linear model with logit link function for binary data was used to compare matched Sjögren syndrome patients and controls on risk of in-hospital cardiovascular complications, thromboembolic complications, microcirculatory complications, and mortality (after adjustment for any imbalanced baseline variables

according to the aforementioned definition). This model allowed adjustment for possible dependence among discharges within the same matched sample.²⁷ To perform this adjustment, we used the method of generalized estimating equations with unstructured correlation among outcomes of patients within a given matched sample. Adjusted odds ratios and 99% confidence intervals (CIs) for each outcome were derived from these models. Respective hypotheses of independent association between Sjögren syndrome and each outcome were evaluated using model-based Wald tests with type I error rate (α) conservatively fixed at 0.01.

In a sensitivity analysis, we assessed the degree to which risk adjustment based on comorbidities modified the adjusted measures of association. To do this, we matched patients only on age (<5 years difference), gender, state, emergency admission, and principal procedure code and excluded comorbidities from matching. Another sensitivity analysis allowed for the possibility that chronic heart disease might be a mechanism by which Sjögren syndrome affects the risk of cardiovascular complications (i.e., a mediator rather than a confounder). For this analysis, chronic heart disease was excluded from the estimation of propensity scores. A list of POA ICD-9-CM codes we used to define chronic heart disease is given in Table 1.

RESULTS

Of the 21.78 million discharges included in the statewide censuses, 5.54 million met study inclusion criteria (Fig. 1). There were a total of 37.5 million POA diagnosis codes in the data set, for an average of 7 per discharge. Overall, 5463 discharges (0.10%) contained a POA diagnosis code for Sjögren syndrome. By gender, this incidence was estimated at 431 of 2.05 million (0.02%) for males and at 5030 of 3.45 million (0.15%) for females. Among patients discharged in 2009, the incidence was 2595 of 2.80 million (0.09%), similarly in 2010 it was 2868 of 2.74 million (0.10%). State-level discharge summaries are given in Table 2.

Our aggregation of the POA diagnosis codes resulted in 1061 distinct diagnosis-related covariates (each with >5000 discharges represented [for the list of baseline diagnosis-related covariates, please see Supplemental Digital Content, Appendix 2, <http://links.lww.com/AA/B207>]). Among the 37.5 million total POA diagnosis codes, 34.16 million (91.2%) were successfully mapped. The propensity score model based on these diagnosis-related covariates discriminated between normal and Sjögren syndrome discharges moderately well, with a C-statistic (area under the receiver operating characteristic curve) of 0.88.

Before matching, 37,255 discharges (0.56%) were removed because of lack of gender information (2 of which had a POA Sjögren syndrome code); there were no other missing data. The matching procedure yielded 18,228 successful controls for 4557 Sjögren syndrome discharges (84% of total 5461 Sjögren syndrome discharges). Therefore, our final matched sample contained 22,785 discharges. Assessing balance between groups after matching, imbalance on Charlson comorbidity index, diabetes without chronic complications, and hypertension were identified (Table 3) and included for adjustment in our multivariable models. The top 20 procedures included in the study for matched patients and pre-matched patients are reported in Table 4.

Both crude and adjusted measures of association are provided in Table 5. Sixty-six (1.45%) of the matched Sjögren syndrome discharges and 213 (1.17%) of the matched controls had associated in-hospital cardiovascular complications (Table 5). On the basis of the generalized linear model, the adjusted odds ratio (99% CI) for postoperative cardiovascular complications was estimated at 1.14 (0.79–1.64), which was not statistically significant ($P=0.35$, Wald test). For the secondary outcomes, we found no difference in the odds of in-hospital thromboembolic complications (adjusted odds ratio [99% CI] of 1.12 [0.82–1.53]; $P=0.36$), in the odds of in-hospital microcirculatory complications (0.98 [0.77–1.26]; $P=0.86$), or in the odds of in-hospital mortality (1.11 [0.76–1.61]; $P=0.49$; Table 5).

The simpler analysis that considered age, gender, state, emergency admission, and principal procedure and that disregarded baseline comorbidities resulted in odds ratio [99% CI] estimates for cardiovascular complications of 1.12 [0.80–1.55] ($P=0.39$); for thromboembolic, microcirculatory, and in-hospital mortality odds ratios of 1.34 [1.02–1.75] ($P=0.005$), 1.23 [0.99–1.52] ($P=0.01$), and 1.49 [1.13–1.96] ($P=0.0002$), respectively. Excluding chronic heart diseases from the adjustment, results change slightly (although still insignificant) from those obtained in our primary analysis. In particular, adjusted odds ratio (99% CI) estimates for cardiovascular complications were 1.01 [0.70–1.44] ($P=0.97$); for thromboembolic, microcirculatory, and in-hospital mortality, odds ratios were 1.20 [0.88–1.65] ($P=0.13$), 1.05 [0.82–1.35] ($P=0.62$), and 1.06 [0.74–1.53] ($P=0.66$), respectively.

DISCUSSION

Our results did not support our hypothesis. We found no significant difference between rates of cardiovascular complications between the patients with Sjögren syndrome and control patients. Although previous studies showed a significant increase in mortality and morbidity in the general nonsurgical population, we found no difference in mortality or thromboembolic complications between the 2 groups of patients.^{13,15}

These outcomes may have resulted from multiple factors. The effect of therapeutic strategies for the treatment of Sjögren syndrome on cardiovascular complications is not clear, although treatment is known to prevent the complications related to inflammation, which may have limited us from seeing a difference. The database used in the analysis provided us with the ability to differentiate patients with Sjögren syndrome from non-Sjögren syndrome patients, as well as to account for varying comorbidities using the same method. The database, however, did not provide us with patient medications, nor was it able to describe the level of severity of Sjögren syndrome in each patient. These factors could have played a role, as corticosteroid therapy (one of the most preferred) in patients with Sjögren syndrome has been associated with increased levels of complications when compared with patients not receiving corticosteroids.²⁸ With varying levels of severity, one could hypothesize that less-controlled or more severe Sjögren syndrome symptoms may correlate with greater levels of cardiovascular complications and mortality as well. Most importantly, surgery causes significant inflammation and complications, which may have screened a possible difference between Sjögren syndrome and others. Further exploration is required to determine long-term mortality rates secondary to silent cardiac complications, which may not have been documented as well.

In 2012, the Sjögren's International Collaborative Clinical Alliance Research Groups released new guidelines meant to establish a new criterion standard for the diagnosis of Sjögren syndrome.²⁹ Given that our data were taken from 2009 to 2010, patients in the study may have misrepresented the groups they were sorted into on the basis of outdated diagnostic criteria used for Sjögren syndrome in the past. New criteria were established after we obtained patient information. Thus, some of our diagnosis may not be accurate according to new guidelines in some patients diagnosed with Sjögren syndrome or vice versa. However, it will be many years before we can determine whether new criteria are better than previous ones and perform a similar study. In addition, given the constantly evolving nature of understanding the distinctions and overlapping qualities of each unique connective tissue disorder, we must consider that cardiovascular complications with increased mortality may occur in only a certain subset of patients with Sjögren syndrome that would be impossible to isolate as a group, given historical data.

Our secondary hypothesis was that patients with Sjögren syndrome have a greater risk of thromboembolic, microcirculatory complications, and mortality. Patients with this syndrome have vascular complications such as increased intima-media thickness potentially creating an environment predisposed to inflammatory vascular changes, as well as complications related to skin vasculitis.^{1,13} Our results, however, did not show any significant difference in the rates of thromboembolic events between the Sjögren syndrome group and the control group. The use of prophylactic anticoagulation in the postoperative setting, however, may have nullified any prothrombotic-related events secondary specifically to Sjögren syndrome.³⁰ Patients in both groups, for which confounding comorbidities were accounted for in the statistical analysis, would have received similar prophylactic anticoagulation.

As in all retrospective studies, our ability to adjust for potential confounding is limited to available data. Although we accounted for hundreds of POA diagnosis, age, location, and performed procedure, residual bias because of uncontrolled confounding variables may remain. For example, race, body mass index, medication history, and secondary procedures were among unreported factors and could possibly have affected the results of this study. Diagnosis codes were dichotomous variables; therefore, we could adjust only for the presence of a disease and not its severity. Another potential limitation of our study is that, in theory, discharges from the states included in our study may not fully represent the general US surgical inpatient population. However, we feel that the risk of such lack of representativeness is low, as we have included states that exhibit a spectrum of a geographic locales and socioeconomic characteristics. Another limitation of the study is that our data set does not contain unique patient identifiers; therefore, we were not able to adjust for possible correlated multiple outcomes per patient. We also recognize that excluded rare baseline conditions might be associated with both Sjögren syndrome and cardiovascular outcomes and, therefore, might confound the results. There have been patients in the control group who would have the disease if examined and tested but who had not sought treatment may be present in the control group, which is another drawback of the database. The limitations of administrative data sets have been well described and include errors in the abstraction, undercoding,³¹ and lack of precise definitions for ICD-9-CM codes,³² underreporting of "complication" codes,³³ and "overcoding" of patient diagnoses to maximize reimbursements.³² Clinical data sets also have problems. Despite the limitations of

administrative data, research questions related to rare diseases still need to be investigated in these data sets because of their size.

In summary, we expected to find an increased risk of cardiovascular, thromboembolic, and microcirculatory complications in patients with Sjögren syndrome; our results did not support this association. In addition, we did not find any association between the presence of Sjögren syndrome and the risk of in-hospital complications and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX 1

Explanation For the Aggregation of Diagnostic (Procedure) Codes

The International Classification of Diseases and Injuries, version 9, Clinical Modification (ICD-9-CM) has been the official system used in the United States to classify and assign codes to diagnoses and procedures since 1979. It is extension of the ICD-9, which the World Health Organization established to track mortality statistics across the world. The National Center for Health Statistics and the Centers for Medicare and Medicaid Services (<http://www.cms.gov>) are the US governmental agencies responsible for overseeing all changes and modifications to the ICD-9-CM.

Diagnosis and procedure codes are hierarchical in nature. Each diagnosis code is represented by a maximum of 5 digits, and each procedure code is represented by a maximum of 4 digits.

Truncating trailing digits will result in an aggregation of detailed diagnoses (procedure) to a more general diagnosis (procedure) class. For example, the diagnosis code 550.03 represents bilateral, recurrent inguinal hernia with gangrene, whereas 550.0 represents all inguinal hernias with gangrene (unilateral, bilateral, or unspecified) and 550 represents all inguinal hernias. Five-digit diagnosis codes are thus more sparsely represented than 3-digit codes—some to the extent that they pose model stability issues relating to small cell sizes while running a statistical model on the data. Therefore, in encoding baseline diagnosis-related (procedure) predictors for analysis, we may want to use hierarchical nature of codes and aggregate present-on-admission diagnoses into more general diagnosis if they were represented by little patients.

In our study, we aggregated 4-digit procedure codes into more general 3-digit procedure codes if they were represented by <10,000 patients. We aggregated 5-digit diagnosis codes into more general 4-digit diagnosis codes if they were represented by <5000 patients. For example, we aggregated the following rare 5-digit ICD-9-CM diagnoses (<5000 cases among 5.5 million patients) into “733.1 Pathologic Fracture; Spontaneous Fracture; Chronic fracture” diagnosis class:

- 733.10 Pathologic fracture, unspecified site
- 733.11 Pathologic fracture of humerus
- 733.12 Pathologic fracture of distal radius and ulna
- 733.14 Pathologic fracture of neck of femur
- 733.15 Pathologic fracture of other specified part of femur
- 733.16 Pathologic fracture of tibia and fibula
- 733.19 Pathologic fracture of other specified site

We kept “733.13 Pathologic fractures of vertebrae” ICD-9-CM code separate because there were >5000 diagnoses in the data set.

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Figure 1.

Study flow diagram and inclusion criteria. Data only for years 2009 and 2010 were purchased by the Cleveland Clinic from the US Agency for Healthcare Research and Quality. Seven states were chosen as a convenience sample. SS = Sjögren syndrome.

Table 1

Description of Chronic Heart Disease

Chronic heart conditions at admission	Description	ICD-9-CM
Chronic rheumatic pericarditis	Adherent pericardium, rheumatic	393
	Chronic rheumatic	
Disease of mitral valve	Mitral stenosis/insufficiency	394
Disease of aortic valve	Aortic stenosis/insufficiency	395
Disease of mitral and aortic valve	Mitral stenosis/insufficiency combined with aortic stenosis/insufficiency	396
Diseases of other endocardial structures	Diseases of tricuspid valve	397
	Rheumatic diseases of pulmonary valve	
	Rheumatic diseases of endocardium and valve unspecified	
Other rheumatic heart disease	Rheumatic myocarditis	398
	Other and unspecified rheumatic heart diseases	
Hypertensive heart disease	Hypertensive: cardiomegaly, cardiomyopathy, cardiovascular disease, heart failure	402
	Any condition classifiable due to hypertension	
Ischemic heart disease	Old myocardial infarction	412
	Angina decubitus	413
	Coronary atherosclerosis	414
Cardiac dysrhythmias	Paroxysmal supraventricular tachycardia	427
	Paroxysmal ventricular tachycardia	
	Paroxysmal tachycardia, unspecified	
	Atrial fibrillation and flutter	
	Ventricular fibrillation and flutter	
	Cardiac arrest	
	Premature beats	
	Other specified cardiac dysrhythmias	
	Cardiac dysrhythmia, unspecified	
Heart failure	Congestive heart failure, unspecified	428
	Left heart failure	
	Systolic heart failure	
	Diastolic heart failure	
	Combined systolic and diastolic heart failure	

ICD-9-CM = *International Classification of Diseases and Injuries*, version 9, Clinical Modification.

Table 2

Summary of Discharges Meeting Study Inclusion/Exclusion Criteria by State of Discharge

State	Number meeting inclusion criteria	Percentage of sample	Number (percentage within state) with SS	Percentage of all SS patients
Arizona	467,189	8.43	636 (0.14)	11.6
California	1,952,193	35.24	1,807 (0.09)	33.1
Florida	1,314,672	23.73	1,248 (0.09)	22.8
Iowa	180,658	3.26	148 (0.08)	2.7
Maryland	366,721	6.62	534 (0.15)	9.8
Michigan	722,059	13.03	689 (0.10)	12.6
New Jersey	536,383	9.68	401 (0.07)	7.4
Total	5,539,875	100	5,463 (0.10)	100

SS = Sjögren syndrome.

Table 3

Balance of Select Preoperative Characteristics Among Matched Sjögren Syndrome and Control (Normal) Discharges

Demographic and surgical characteristics	Before matching		After matching		ASD ^a
	SS (n = 5463)	Normal (n = 5.53 millions)	SS (n = 4557)	Normal (n = 18,228)	
Age (y)	60 ± 13	50 ± 18	61 ± 13	61 ± 13	0.01
Female gender (%)	92	63	92	92	0.00
Surgery in 2010 (vs 2009) (%)	53	50	50	52	0.04
Emergency admission (%)	30	30	3	3	0.00
State (%)					
AZ	12	8	11	11	0.00
CA	33	35	34	34	
FL	23	24	24	24	
IA	3	3	3	3	
MD	10	7	9	9	
MI	12	13	13	13	
NJ	7	10	7	7	
Charlson comorbidity index	2.2 ± 1.7	1.1 ± 1.8	2.2 ± 1.6	1.6 ± 1.8	0.34 ^a
Chronic heart condition ^b (%)	4	5	4	4	0.01
Diabetes without chronic complications ^c (%)	12	14	12	15	0.10 ^a
Diabetes with chronic complications ^c (%)	3	4	4	4	0.03
Renal failure ^c (%)	8	7	8	7	0.01
Hypertension ^c (%)	43	33	43	47	0.08 ^b
Peripheral vascular disease ^c (%)	5	6	5	6	0.03
Chronic pulmonary disease ^c (%)	23	13	22	23	0.02
Pulmonary circulation disease ^c (%)	5	2	4	3	0.04

SS = Sjögren syndrome; ICD-9-CM = *International Classification of Diseases and Injuries*, version 9, Clinical Modification.

Diabetes without chronic complications included ICD-9-CM codes: 250.00-250.33, 648.00-648.04, and 249.00-249.31.

Diabetes with chronic complications included ICD-9-CM codes: 250.40-250.93, 775.1, and 249.40-249.91.

Renal failure included following ICD-9-CM codes: 585.3, 585.4, 585.5, 585.6, 585.9, 586, V42.0, V45.1, V56.0-V56.32, V56.8, and V45.11-V45.12.

Hypertension included ICD-9-CM codes: 401.1, 401.9, 642.00-642.04.

Peripheral vascular disorder included ICD-9-CM codes: 440.0-440.441.00-41.9, 442.0-42.9, 443.1-443.9, 444.21-44.22, 447.1, 449, 557.1, 557.9, V43.4.

Chronic pulmonary disease included ICD-9-CM codes: 490-492.8, 493.00-493.92, 494-494.1, 495.0-505, 506.4.

Pulmonary circulation disorder included ICD-9-CM codes: 415.11-415.19, 416.0-416.9, 417.9.

^a ASD = absolute standardized difference score for matched groups. The ASD is equal to the absolute difference in means, mean rankings, or proportions divided by a combined estimate of SD. Any baseline variable exhibiting an ASD score >0.04 was considered to be imbalanced and included for adjustment within our final models comparing matched patients on outcomes.

^bChronic heart condition description presented in Table 1.

^cDefined by the Comorbidity Software, which identifies comorbidities, using the diagnosis coding of ICD-9-CM (<http://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp>):

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Table 4

Top 20 Procedures of the Study (Cover 69% of Matched Cases) Among Prematched Patients and Matched Patients Ordered by the Latter One

Procedure ICD-9-CM code	Procedure description	Percentage of all patients (<i>n</i> = 5.5 million)	Percentage of matched patients (<i>n</i> = 22,785)
86.69	Other skin graft to other sites	0.2	26
81.52	Partial hip replacement	0.4	10.3
81.3	Refusion of spine	0.2	4.5
00.66	Percutaneous transluminal coronary angioplasty or coronary atherectomy	5	3.5
51.23	Laparoscopic cholecystectomy	3.5	3.4
73.6	Episiotomy	1.6	3
81.07	Lumbar and lumbosacral fusion, lateral transverse process technique	0.2	2.5
81.0	Spinal fusion	0.3	2.1
68.41	Laparoscopic total abdominal hysterectomy	0.3	1.6
79.32	Open reduction of fracture with internal fixation. Radius and ulna, arm NOS	0.3	1.4
03.09	Other exploration and decompression of spinal canal	0.8	1.3
38.7	Interruption of the vena cava	0.7	1.3
86.07	86.07 Insertion of totally implantable vascular access device	0.3	1.3
68.51	Laparoscopically assisted vaginal hysterectomy	0.6	1.1
79.35	Open reduction of fracture with internal fixation. Femur	0.7	1.1
85.43	Unilateral extended simple mastectomy	0.2	1.1
32.20	Thoracoscopic excision of lesion or tissue of lung	0.2	1
33.27	Closed endoscopic biopsy of lung	0.3	1
00.7	Other hip procedures	0.3	0.9
79.36	Open reduction of fracture with internal fixation. Tibia and fibula, leg NOS	1.1	0.9

ICD-9-CM = *International Classification of Diseases and Injuries*, version 9, Clinical Modification; NOS = not otherwise specified.

Table 5

Summary of Outcomes Among Unmatched $n = 5.5$ million and $n = 22,785$ Matched Discharges ($n = 4557$ in Sjögren Syndrome Group and $n = 18,228$ in Normal Control Group)

	Before matching			After matching		
	SS ($n = 5463$)	Normal ($n = 5.53$ million)	Unadjusted OR (99% CI) ^a	SS ($n = 4557$)	Normal ($n = 18,228$)	Adjusted OR (99% CI) ^{b,c}
Cardiovascular outcomes						
997.1 Cardiac arrest/insufficiency during or resulting from a procedure	50 (0.92)	45,197 (0.82)		43 (0.94)	158 (0.87)	
410 Myocardial infarction	30 (0.55)	19,981 (0.36)		26 (0.57)	69 (0.38)	
518.4 Pulmonary edema, postoperative	5 (0.09)	4175 (0.08)		4 (0.09)	9 (0.05)	
411.81 Acute coronary occlusion without myocardial infarction	0(0)	213 (0)		0 (0)	0 (0)	
<i>Any of the above cardiovascular complications</i>	78 (1.43)	63,846 (1.15)	1.24 (0.93-1.67)	66 (1.45)	213 (1.17)	1.14 (0.79-1.64)
Thromboembolic outcomes						
453.4 Venous embolism and thrombosis of unspecified deep vessels of lower extremity	25 (0.46)	15,576 (0.28)		22 (0.48)	67 (0.37)	
451.83 Venous embolism and thrombosis of unspecified deep vessels of upper extremities	0 (0)	238 (0)		0 (0)	1 (0.01)	
453 Other venous embolism and thrombosis	56 (1.03)	29,882 (0.54)		42 (0.92)	125 (0.69)	
V12.51 Pulmonary embolism	22 (0.4)	11,760 (0.21)		15 (0.33)	55 (0.3)	
415.1 Pulmonary embolism and infarction	17 (0.31)	12,414 (0.22)		13 (0.29)	69 (0.38)	
997.02 Postoperative stroke	9 (0.16)	5657 (0.1)		9 (0.2)	21 (0.12)	
435 TIA	3 (0.05)	2428 (0.04)		2 (0.04)	5 (0.03)	
434 Occlusion of cerebral arteries	17 (0.31)	11,667 (0.21)		15 (0.33)	42 (0.23)	
997.2 Phlebitis or thrombophlebitis during or resulting from a procedure	10 (0.18)	5952 (0.11)		10 (0.22)	26 (0.14)	
997.7 Vascular complication of surgical and medical care	2 (0.04)	1115 (0.02)		1 (0.02)	6 (0.03)	
<i>Any of the above thromboembolic complications</i>	118 (2.16)	69,575 (1.26)	1.73 (1.36-2.20)	91 (2)	295 (1.62)	1.12 (0.82-1.53)
Microcirculatory outcomes						
998.3 Dehiscence of operation wound	16 (0.29)	11,113 (0.2)		15 (0.33)	48 (0.26)	
997.5 Renal insufficiency/failure (acute) specified as due to procedure	34 (0.62)	21,580 (0.39)		31 (0.68)	77 (0.42)	
584.9 Acute kidney injury	132 (2.42)	92,093 (1.66)		101 (2.22)	382 (2.1)	
						0.36

	Before matching		After matching		P value ^c
	SS (n = 5463)	Normal (n = 5.53 million)	SS (n = 4557)	Normal (n = 18,228)	
593.9 Acute renal disease	12 (0.22)	12,988 (0.23)	8 (0.18)	43 (0.24)	
Any of the above microcirculatory complications	185 (3.39)	131,404 (2.37)	146 (3.2)	528 (2.9)	0.86
In-hospital mortality	78 (1.43)	59,057 (1.07)	62 (1.36)	193 (1.06)	0.49
Length of hospital stay (d)	5 ± 8	6 ± 9	6 ± 9	6 ± 8	

SS = Sjögren syndrome; TIA = Transient ischemic attack.

Summary presented as n (%).

^aUnadjusted odds ratios (OR) with 99% confidence interval is a crude measure of SS effect and based on raw unmatched data; unadjusted OR do not take into account difference in SS and normal groups on any of the potential confounders.

^bOR adjusted for 3 imbalanced diagnosis-related potential confounders: Charlson comorbidity index, diabetes without chronic complications, and hypertension.

^cThe type I error rate (α) for all tests and confidence intervals (CIs) was 0.01. Significance criterion of 0.01 was used for P-values.