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Increased risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study

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Abstract

Objectives

Sjögren's syndrome (SS) is a systemic autoimmune disorder. Several molecular pathways and the activation of matrix metalloproteinases associated with the pathogenesis of SS participate in the initiation and progression of aortic aneurysm (AA) and aortic dissection (AD). In this study, we aimed to evaluate whether patients with SS exhibit an increased risk of AA and AD.

Methods

We conducted a retrospective cohort study using a database extracted from Taiwan's National Health Insurance Research Database (NHIRD). All medical conditions for each case and control were categorized using the International Classification of Diseases, 9th Revision (ICD-9). Odds ratios (ORs) and 95% confidence intervals (CIs) for associations between SS and AA/AD were estimated using Cox regression and adjusted for co-morbidities.

Results

Our analyses included 10,941 SS cases and 43,764 propensity score-matched controls. Compared with the controls, the patients with SS exhibited a significantly increased risk of developing an AA and AD (adjusted OR = 3.642, P<0.001). The subgroup analysis revealed that patients with primary and secondary SS both

exhibited a significantly increased risk of developing AA and AD compared with patients without SS (adjusted hazard ratio (HR) = 1.753, P = 0.042; adjusted HR = 3.693, P < 0.001).

Conclusion

Patients with SS exhibit increased risks of developing AA and AD, and healthcare professionals should be aware of this risk when treating patients with SS. Increased aortic surveillance may be required in patients with SS syndrome.

Keywords: Sjögren's syndrome, aortic dissection, aortic aneurysm

Strengths and limitations of this study

- The strength of our study is its population-based cohort design. We excluded confounding factors, including comorbidities, from our study.
- We intended to control for potential disease-associated confounders to the utmost extent possible, unmeasured or unknown confounders may have existed in our findings.
- This was a retrospective cohort study.
- NHIRD can not provide detailed information regarding the laboratory results or lifestyle factors of the patients.
- Our results are limited to human data. It required both mechanistic and animal studies for further clarification.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disorder commonly presenting with dry eyes and mouth. The prevalence of SS is between 0.1% and 4.8% in various populations when strictly defined according to the American-European Consensus Criteria, and it is one of the most common autoimmune diseases [1]. SS may affect patients at any age, but more cases occur in the fourth decade of life, and there is a female predominance. The female-male ratio is approximately 9:1 [2]. Aortic aneurysms (AAs) are often diagnosed inadvertently and are a common cause of sudden death. Enlarged aneurysms can result in rupture. Aortic dissection (AD) is one of the most deadly complications of thoracic aortic disease. The incidence of AD ranges from 6 cases per 100,000 to 9.1 per 100,000 in women and 16.3 per 100,000 in men annually based on studies in England and Sweden [3,4]. Regarding the Asian population, the average annual incidence of AD was 5.6 per 100,000 persons in Taiwan, and the prevalence was 19.9 per 100,000 persons, with a predominance noted among men 50 to 54 years of age (27.3 per 100,000 persons per year) [5].

Previous studies have demonstrated that AA is more prevalent in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared with the general population [6,7]. Compared with age- and sex-matched healthy controls, primary SS (PSS) patients exhibited a 2-fold increased prevalence of hypertension and hypertriglyceridemia. Furthermore, hypertension is underdiagnosed and suboptimally

treated in PSS [8]. SS with positive autoantibodies is associated with a low ankle-brachial index, which may indicate an increased risk of early atherosclerosis [9]. Nonetheless, previous population-based studies indicated that SS is not associated with an increased risk of subsequent acute myocardial infarction (AMI) and ischaemic stroke [10,11].

Several molecular mechanisms, including JNK, NF-κB and TGF-β signalling pathways, and matrix metalloproteinase (MMP) activation are associated with the pathogenesis of SS [12,13]. These molecular mechanisms also actively participate in the initiation and progression of AA and AD [14,15]. Taken together, we hypothesized that patients with SS may have an increased risk of AA and AD due to SS-related cardiovascular risks and shared molecular mechanisms. However, the association between SS and AA or AD has not been thoroughly evaluated in large-scale studies. Therefore, we aimed to determine whether SS patients exhibit an increased risk of AA and AD using a nationwide healthcare insurance claim database.

Methods

Data source

The data described herein were acquired from the Longitudinal Health Insurance Database 2005 (LHID 2005), a subgroup database of the Taiwan National Health

Insurance Research Database (NHIRD) used for the nationwide population-based retrospective cohort study. The National Health Insurance programme in Taiwan provides health care for 99% of the population (greater than 23 million people) and was implemented in 1995. The LHID 2005 provides information on medical service utilization using a randomly selected sample of approximately one million people receiving benefits, representing approximately 5% of Taiwan's population in 2005. The information was obtained from the NHIRD between 2000 and 2010. The accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases (e.g., acute coronary syndrome and stroke), has been corroborated [16 17]. The LHID is composed of "de-identified" secondary data that are available to the public via open access for research. ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to five each), genders, birthdays, patient identification numbers, dates of admission and discharge, and outcomes are coded. In addition, information regarding the medical institutions that served patients was obtained. Individual information was protected using encoded personal identification to prevent ethical violations related to the data. Our study conformed to the Declaration of Helsinki and relevant guidelines. This Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, permitted this study (TSGH IRB No.2-105-05-082).

Sampled patients

This study utilized study and comparison cohorts. Using the LHID 2005, we selected adult patients aged >20 years who were newly diagnosed with SS (ICD-9-CM 710.2) and were followed-up between 2000 and 2010. We excluded patients who were diagnosed with SS, AA and AD (ICD-9-CM 441.0-441.9); Turner syndrome (ICD-9-CM 758.6); aortic coarctation (ICD-9-CM 747.10); bicuspid aortic valve (ICD-9-CM 746.4); Marfan syndrome (ICD-9-CM 759.82); and Ehler-Danlos syndrome (ICD-9-CM 756.83). Patients had a tracking time < 6 months. The date of SS diagnosis was used as the index date. Control candidate sampling comparisons were selected from individuals in the LHID 2005 who lacked a history of SS. The patients and control cohorts were selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities, including hypertension (ICD-9-CM 401-405), diabetes mellitus (DM) (ICD-9-CM 250), hyperlipidaemia (ICD-9-CM 272.0-272.4), Behcet's disease (ICD-9-CM 136.1), giant cell arteritis (ICD-9-CM 446.5), RA and other inflammatory polyarthropathies (ICD-9-CM 714), relapsing polychondritis (ICD-9-CM 733.99), Takayasu's arteritis (ICD-9-CM 446.7) and chronic obstructive pulmonary disease (COPD) (ICD-9-CM 490-496); and medication history, including β-blocker, calcium channel blocker, angiotensin-converting enzyme

inhibitor, angiotensin receptor blocker, diuretic and steroid history. We also divided SS patients into primary SS and secondary SS (SSS) patients and performed a subgroup analysis. SS in patients was previously diagnosed as SLE (ICD-9-CM 710.0), RA (ICD-9-CM 714), systemic sclerosis (ICD-9-CM 701.1), or primary biliary cirrhosis (ICD-9-CM 571.6), which was defined as SSS. The index dates for control patients were the same as the corresponding dates for patients with AA/AD. The study outcome was a diagnosis of AA/AD during the 10-year follow-up period. AA/AD was identified using ICD-9 codes. The end point of the follow-up period was 2010-12-31 or the time at which AA/AD events occurred or the patient died.

Statistical analysis

Categorical variables, which are presented as percentages, were compared using the chi-square or Fisher's exact tests. Continuous variables, which are presented as the means and standard deviations, were compared using a t-test. The primary goal of the study was to determine whether SS patients exhibit an increased risk for developing AA/AD. The association between those outcomes (prognoses) and clinical characteristics was investigated using Cox regression. The results are presented as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). The threshold for statistical significance was $P < 0.05$. All data analyses were conducted

using SPSS software version 22 (SPSS Inc., Chicago, IL, USA).

Results

A flow diagram of our patient enrolment scheme is presented in Figure 1. A total of 10,941 patients diagnosed with SS were identified in the NHIRD, which contains a total of 986,713 individuals. An additional 43,764 age-, gender-, comorbidity-, and medication-matched patients were designated controls. As shown in Table 1, no significant differences in gender, age or co-morbidities, including DM, hypertension, hyperlipidaemia, Behcet's disease, giant cell arteritis, RA, relapsing polychondritis, Takayasu's arteritis, COPD, and medications, were noted between the two groups after matching. Patients with SS exhibited a significantly increased cumulative risk of developing AA/AD in subsequent years compared with patients without SS (log rank test < 0.001, Figure 2). Table 2 presents the incidences of AA and AD during the ten-year follow-up period. At the end of the follow-up period, SS patients exhibited significantly increased incidences of AA/AAD (0.43% vs. 0.37%, P = 0.045) but lower incidences of DM (7.73% vs. 15.44%, P < 0.001) and COPD (5.96% vs. 6.72%, P = 0.004). In addition, patients with SS were younger and exhibited an increased CCI compared with patients without SS. Regarding the use of Cox regression independent of the effects of gender, age, co-morbidities and medication, patients with SS also

exhibited a significantly increased risk of developing AA/AD compared with patients without SS (adjusted HR = 3.642, 95% CI = 2.527-5.250, P < 0.001, Table 3). The subgroup analysis revealed that patients with PSS or SSS both exhibited significantly increased risks for developing AA/AD compared with patients without SS (adjusted HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693, 95% CI = 2.520-5.411, P < 0.001, Table 4).

Discussion

Our study is a retrospective cohort study that enrolled 10,941 patients with SS and 43,764 patients without SS matched by age, sex, year of index date of SS diagnosis, co-morbidities and medication from a large-scale nationwide population-based database. During follow-up, SS was associated with an increased incidence of the development of AA/AD compared with the comparison cohort.

SS patients exhibit an increased prevalence of developing traditional cardiovascular risk factors, such as hypertension and dyslipidaemia, which predispose patients to endothelial dysfunction and premature atherosclerosis. However, the disease-specific mechanisms associated with premature atherosclerosis in SS are not fully understood [18]. In a recent review article, cardiovascular disease was reported to be one of the primary causes of mortality in SS patients [19]. Primary SS shares clinical

and serological features with RA and SLE, and these two diseases are associated with acceleration of atherosclerosis [20]. However, the pathophysiology between SS and AA/AD remains unclear, although several possible mechanisms have been proposed. Previous studies have demonstrated that both SS and AA/AD are induced by chronic inflammation.[21-24] Recent studies have provided convincing evidence indicating that several signalling pathways are involved in both AA and SS, including the MAPK, TGF-β, and MMP signalling pathways [12-15]. Activation of the innate immune system and the production of interferons (IFNs) could be the first stages of primary SS pathogenesis [25]. IFNs and IL-21 could induce B-cell-activating factor (BAFF) and further activate B cell activity. In human salivary gland cells, interferon-γ modulates and increases MMP-2 and MMP-9 expression [26]. The circulating levels of MMP-9 were increased in patients with definite SS compared with patients with possible SS [27]. Furthermore, MMP-2 and MMP-9 also display a critical role in AAA formation [28]. MMPs play roles in tissue destruction and the weakening of the matrix, as noted in liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, and multiple sclerosis [29].

As a downstream effector molecule of CD40, the JNK cascade is activated in salivary infiltrating T cells and mononucleated cells in patients with SS [12 13]. JNK plays a pivotal role in IL-1β-mediated inhibition of lacrimal gland secretion and

subsequent dry eye [30]. JNK is not only involved in T cell infiltration in salivary glands but is also associated with subsequent NF-κB activation, MMP activation and reactive oxygen species (ROS) production [21 31]. Increased TGF-β signalling was observed in salivary glands with increased Smad2 phosphorylation and concomitant increases in extracellular matrix deposition. In a mouse study of SS, aberrant TGF-β overexpression caused salivary gland hypofunction [32]. In addition, TGFBR1 and TGFBR2 mutations result in up-regulation of TGF-β signalling and lead to extracellular matrix deposition and matrix degradation, which represent critical steps in AA or AD [33].

Low-dose steroids, such as prednisone, may be used to treat SS-induced joint and muscle pain. Prolonged or high-dose corticosteroid treatment likely causes disintegration of connective tissue of the media possibly together with primary aortic wall involvement and/or vascular damage in patients with autoimmune disorders, which can result in aortic aneurysmal enlargement and AD [29 34]. In this study, the medical condition of steroids was matched. Therefore, the effect of steroids was mitigated.The strength of our study involves its population-based database design. We accounted for several aneurysm-related confounding factors. Although we adjusted the results extensively using multivariate logistic regression models, there were several limitations and unmeasured confounders in our study. The NHIRD registry is

not able to provide detailed information on laboratory results, family histories and health-related lifestyle factors, such as alcohol consumption and tobacco use, which can increase the risk of AA/AD and were potential confounding factors in this study. In our study, we also considered COPD incidence as a proxy variable for tobacco use to eliminate its potential confounding effect [35]. Although our study identified the association between SS and AA/AD, the cohort study design did not enable determination of the cause-effect relationship. Further prospective follow-up studies, mechanistic studies and animal experiments should be performed.

Conclusion

Patients with SS exhibit an increased risk for developing AA and AD, and healthcare professionals should be aware of this risk when treating patients with SS. Increased aortic surveillance may be required in patients with SS.

Author contributions

Y-DT, J-CW, and S-HT conceived and designed the study.

W-CC provided the materials for the study. C-HC and S-JC analysed the data. C-JY and M-TL contributed reagents, materials and analysis tools. Y-DT, J-CW, W-IL and S-HT wrote the manuscript. All the authors approved the manuscript.

Competing interests

None declared.

Data sharing statement

No additional data sharing available.

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Legends to tables and figures

Table 1. Characteristics of the study participants at baseline

Table 2. Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Table 3. Factors associated with aortic aneurysm and dissection according to Cox regression

Table 4. Factors associated with aortic aneurysm and dissection stratified by primary/secondary SS using Cox regression

Figure 1. Patient selection flowchart

Figure 2. Kaplan-Meier curve of the cumulative risk of aortic aneurysm and dissection due to Sjögren's syndrome

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Table 1 Characteristics of the study participants at baseline

Sjögren's syndrome	Total	With	Without	P-value
	N (%)	N (%)	N (%)	
Total	54,705	10,941 (20.00%)	43,764(80.00%)	
Gender				0.999
Male	10,187 (18.63%)	2,011 (18.44%)	8,176 (18.68%)	
Female	44,485 (81.37%)	8,897 (81.56%)	35,588 (81.32%)	
Age (years)	55.78±17.09	55.80±16.65	55.77±17.20	0.897
DM	3,553 (6.49%)	724 (6.62%)	2,829 (6.46%)	0.558
Hypertension	8,091 (14.79%)	1,578 (14.42%)	6,513 (14.88%)	0.228
Hyperlipidaemia	1,145 (2.09%)	234 (2.14%)	911 (2.08%)	0.709
Behcet's disease	321 (0.59%)	62 (0.57%)	259 (0.59%)	0.834
Giant cell arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
Rheumatoid arthritis	8,907 (16.28%)	1,784 (16.31%)	7,123 (16.28)	0.942
Relapsing polychondritis	71 (0.13%)	14 (0.13%)	57 (0.13%)	0.953
Takayasu's arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
COPD	2,931 (5.36%)	581 (5.3%)	2,350 (5.37%)	0.831
Steroid	16,799 (30.71%)	3,345 (30.57%)	13,454 (30.74%)	0.737
β blocker	12,588 (23.01%)	2,513 (22.97%)	10,075 (23.02%)	0.919
CCB	11,553 (21.12%)	2,342 (21.41%)	9,211 (21.05%)	0.409
ACEI	13,586 (24.84%)	2,711 (24.78%)	10,875 (24.85%)	0.878
ARB	12,718 (23.25%)	2,620 (23.95%)	10,098 (23.07%)	0.054
Diuretic	12,440 (22.74%)	2,429 (22.20%)	10,011 (22.87%)	0.136
Statin	13,922 (25.45%)	2,811 (25.69%)	11,111 (25.39%)	0.516

P-value (categorical variable: chi-square/Fisher's exact test; continuous variable: t-test)

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 2 Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Sjögren's syndrome	Total N (%)	With N (%)	Without N (%)	P-value
Total	54,705	10,941(20.00%)	43,764(80.00%)	
Aortic aneurysm and dissection	207 (0.38%)	47(0.43%)	160(0.37%)	0.045
Gender				0.999
Male	10,187 (18.63%)	2,011(18.44%)	8,176(18.68%)	
Female	44,485 (81.37%)	8,897(81.56%)	35,588(81.32%)	
Age (years)	61.36±5.41	60.90±4.98	61.47±5.51	<0.001
DM	7,603 (13.90%)	846(7.73%)	6,757(15.44%)	<0.001
Hypertension	8,821 (16.12%)	1,708(15.61%)	7,113(16.25%)	0.102
Hyperlipidaemia	1,128 (2.06%)	240(2.19%)	888(2.03%)	0.279
Behcet's disease	324 (0.59%)	63(0.58%)	261(0.60%)	0.802
Giant cell arteritis	16 (0.03%)	3(0.03%)	13(0.03%)	0.901
Rheumatoid arthritis	9,033 (16.51%)	1,774(16.21%)	7,259(16.59%)	0.348
Relapsing polychondritis	80 (0.15%)	19 (0.17%)	61 (0.14%)	0.401
Takayasu's arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
COPD	3,593 (6.57%)	652 (5.96%)	2,941 (6.72%)	0.004
CCI_R	0.78±1.53	0.83±1.39	0.77±1.56	<0.001
Steroid	17,112 (31.28%)	3,511 (32.09%)	13,601 (31.08%)	0.041
β blockers	13,750 (25.13%)	2,674 (24.44%)	11,076 (25.31%)	0.061
CCB	11,833 (21.63%)	2,397 (21.91%)	9,436 (21.56%)	0.430
ACEI	13,793 (25.21%)	2,784 (25.45%)	11,009 (25.16%)	0.532
ARB	12,976 (23.72%)	2,681 (24.50%)	10,295 (23.52%)	0.031
Diuretic	12,692 (23.20%)	2,507 (22.91%)	10,185 (23.27%)	0.427
Statin	14,123 (25.82%)	2,828 (25.85%)	11,295 (25.81%)	0.934

P-value (categorical variable: chi-square/Fisher's exact test; continuous variable: t-test)

CCI_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 3 Factors associated with aortic aneurysm and dissection according to Cox regression

Variables	Crude HR	95% CI	P	Adjusted HR	95% CI	P
Sjögren's syndrome	3.205	2.254-3.565	<0.001	3.642	2.527-5.250	<0.001
Gender (male)	2.645	1.974-3.597	<0.001	2.035	1.534-2.700	<0.001
Age (years)	1.049	1.032-1.057	<0.001	1.043	1.032-1.055	<0.001
DM	1.704	1.389-1.944	0.024	1.674	1.065-1.976	0.037
Hypertension	1.165	1.022-1.454	0.038	1.305	0.973-1.751	0.075
Hyperlipidaemia	1.211	0.594-2.436	0.618	1.343	0.656-2.751	0.420
Rheumatoid arthritis	1.645	0.774-3.496	0.196	0.801	0.362 -1.769	0.583
COPD	1.838	1.256-2.691	0.002	1.170	0.790-1.735	0.433
CCI_R	1.036	0.945-1.087	0.074	1.016	0.968-1.065	0.527
Steroid	1.497	0.598-2.976	0.495	1.501	0.339-3.298	0.617
β blockers	1.468	0.453-2.772	0.862	1.398	0.401-2.895	0.803
CCB	1.345	0.343-2.901	0.372	1.402	0.452-2.806	0.280
ACEI	1.298	0.426-3.041	0.601	1.288	0.395-2.845	0.334
ARB	1.346	0.379-1.986	0.711	1.345	0.343-1.886	0.682
Diuretic	1.198	0.598-2.511	0.652	1.201	0.490-2.907	0.703
Statin	1.364	0.667-4.972	0.798	1.335	0.679-4.787	0.897

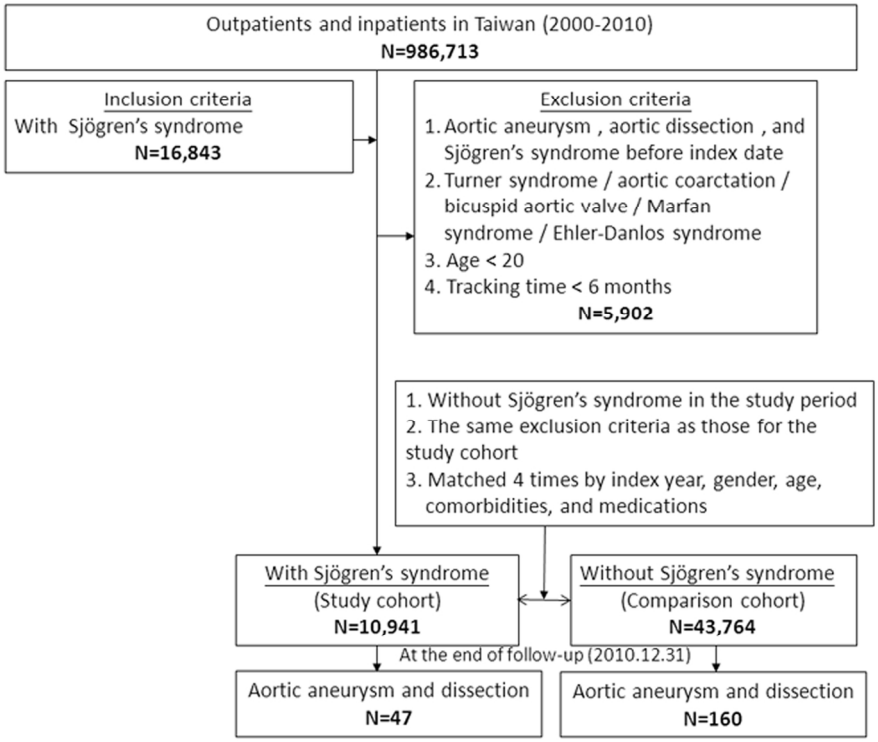
HR= hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table; CCI_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 4. Factors associated with aortic aneurysm and dissection stratified by primary/secondary Sjögren's syndrome using Cox regression

	Patients with Sjögren's syndrome			Patients without Sjögren's syndrome			Ratio	Adjusted HR*	95% CI	P-value
	Events	PY	Incidence rate (per 10^5 PY)	Events	PY	Incidence rate (per 10^5 PY)				
Total	47	55,860.08	84.14	160	253,779.88	63.05	1.335	3.642	2.527-5.250	<0.001
Without RA / SLE / SS /PBC	30	36,607.55	81.95	158	248,694.36	63.53	1.290	1.753	1.108-9.382	0.042
With RA / SLE / SS /PBC	17	19,252.53	88.30	2	5,085.52	39.33	2.245	3.693	2.520-5.411	<0.001

PYs = person-years; Ratio = incidence of patients with AA/AD divided by the incidence of patients without AA/AD; *Adjusted HR = adjusted hazard ratio: adjusted for age, sex, comorbidities, and medications, as listed in Table 3, using Cox regression; CI = confidence interval; RA = rheumatoid arthritis ; SLE = systemic lupus erythematosus ; SS = systemic sclerosis ; PBC = primary biliary cirrhosis

Primary Sjögren's syndrome: Sjögren's syndrome without systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or primary biliary cirrhosis; Secondary Sjögren's syndrome: Sjögren's syndrome with systemic lupus erythematosus, rheumatoid arthritis , systemic sclerosis, or primary biliary cirrhosis



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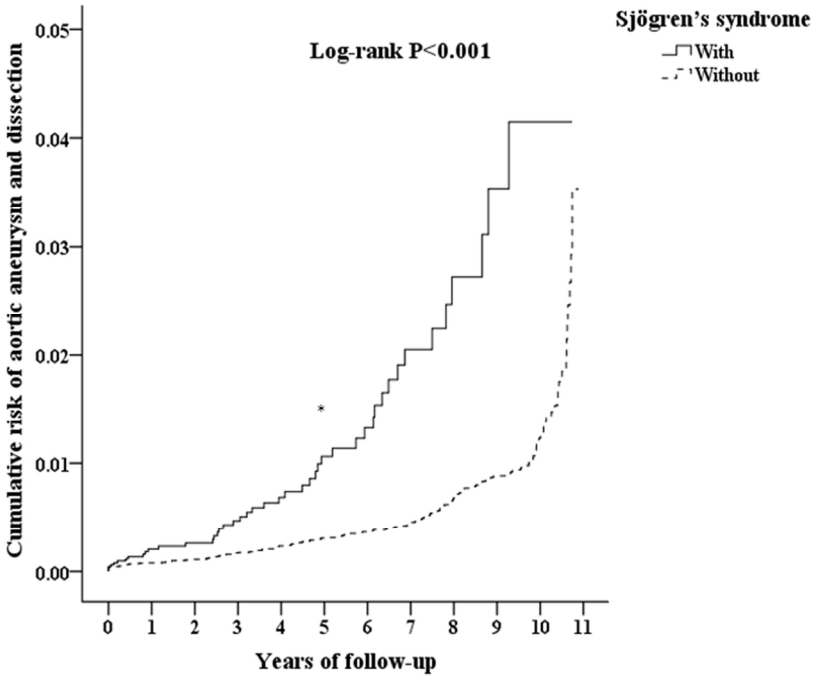

With Sjögren's syndrome (N=10,941)	13	15	21	26	32	35	41	44	46	47	47
Without Sjögren's syndrome (N=43,764)	27	36	49	63	77	81	94	113	130	146	160
P value	0.897	0.513	0.275	0.102	0.036	0.015	0.001	<0.001	<0.001	<0.001	<0.001

*:P<0.05 is considered statistically significant

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Risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan

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Increased risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan

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ABSTRACT

Objectives: Sjögren's syndrome (SS) is a systemic autoimmune disorder. Several molecular pathways and the activation of matrix metalloproteinases associated with the pathogenesis of SS participate in the initiation and progression of aortic aneurysm (AA) and aortic dissection (AD). In this study, we aimed to evaluate whether patients with SS exhibit an increased risk of AA or AD.

Methods: We conducted a retrospective cohort study using a database extracted from Taiwan's National Health Insurance Research Database (NHIRD). All medical conditions for each case and control were categorized using the International Classification of Diseases, 9th Revision (ICD-9). Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between SS and AA/AD were estimated using Cox regression and adjusted for co-morbidities.

Results: Our analyses included 10,941 SS cases and 43,764 propensity score-matched controls. Compared with the controls, the patients with SS exhibited a significantly increased risk of developing an AA or AD (adjusted HR = 3.642, P < 0.001). Subgroup analysis revealed that compared with patients without SS, patients with primary and secondary SS both exhibited a significantly increased risk of developing AA or AD (adjusted HR = 1.753, P = 0.042; adjusted HR = 3.693, P < 0.001).

Conclusion: Patients with SS exhibit increased risks of developing AA or AD, and

healthcare professionals should be aware of this risk when treating patients with SS.

Increased aortic surveillance may be required for patients with SS syndrome.

Keywords: Sjögren's syndrome, aortic dissection, aortic aneurysm

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strength of our study is its population-based cohort design with a large sample size.
- The patients and controls were selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities; and medications used. This population-based cohort study was adjusted for potential risk factors to minimize study bias.
- This was a retrospective cohort study.
- NHIRD cannot provide detailed information regarding the laboratory results or lifestyle factors of the patients.
- Our results are limited to human data. Both mechanistic and animal studies are required for further clarification.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disorder commonly presenting with dry eyes and mouth. The prevalence of SS is between 0.1% and 4.8% in various populations when strictly defined according to the American-European Consensus Criteria, and it is one of the most common autoimmune diseases.[1] SS may affect patients at any age, but more cases occur in the fourth decade of life, and there is a female predominance. The female-male ratio is approximately 9:1.[2] Aortic aneurysms (AAs) are often diagnosed inadvertently and are a common cause of sudden death. Enlarged aneurysms can result in rupture. Aortic dissection (AD) is one of the deadliest complications of thoracic aortic disease. Estimates of the incidence of AD range from 6 cases per 100,000 to 16.3 per 100,000 in England and Sweden, respectively.[3,4] Regarding the Asian population, the average annual incidence of AD is 5.6 per 100,000 persons in Taiwan and the prevalence is 19.9 per 100,000 persons, with a predominance noted among men 50 to 54 years of age (27.3 per 100,000 persons per year).[5]

Previous studies have demonstrated that AA is more prevalent in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared with the general population.[6,7] Compared with age- and sex-matched healthy controls, primary SS (PSS) patients exhibited a 2-fold increased prevalence of hypertension

and hypertriglyceridemia. Furthermore, hypertension is underdiagnosed and suboptimally treated in PSS.[8] SS with positive autoantibodies is associated with a low ankle-brachial index, which may indicate an increased risk of early atherosclerosis.[9] Nonetheless, previous population-based studies indicated that SS is not associated with an increased risk of subsequent acute myocardial infarction (AMI) and ischaemic stroke.[10,11]

Several molecular mechanisms, including JNK, NF-κB and TGF-β signalling pathways, and matrix metalloproteinase (MMP) activation are associated with the pathogenesis of SS.[12,13] These molecular mechanisms also actively participate in the initiation and progression of AA or AD.[14,15] Based on these findings, we hypothesized that patients with SS may have an increased risk of AA or AD due to SS-related cardiovascular risks and shared molecular mechanisms. However, the association between SS and AA or AD has not been thoroughly evaluated in large-scale studies. Therefore, we aimed to determine whether SS patients exhibited an increased risk of AA or AD using a nationwide healthcare insurance claim database.

METHODS

Data source

The data described herein were acquired from the Longitudinal Health Insurance Database 2005 (LHID 2005), a subgroup database of the Taiwan National Health Insurance Research Database (NHIRD) used for the nationwide population-based retrospective cohort study. The National Health Insurance programme in Taiwan provides health care for 99% of the population (greater than 23 million people) and was implemented in 1995. The LHID 2005 provides information on medical service utilization using a randomly selected sample of approximately one million people receiving benefits, representing approximately 5% of Taiwan's population in 2005. The information was obtained from the NHIRD between 2000 and 2010. The accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases (e.g., acute coronary syndrome and stroke), has been corroborated.[16,17] The LHID is composed of "de-identified" secondary data that are available to the public via open access for research. ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to five each), sex, birthdays, patient identification numbers, dates of admission and discharge, and outcomes are coded. In addition, information regarding the medical institutions that served patients was obtained. Individual information was protected using encoded personal identification to prevent ethical violations related to the data. Our study conformed to the Declaration of Helsinki and relevant guidelines. This Institutional

Review Board of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, permitted this study (TSGH IRB No.2-105-05-082).

Patient and public involvement

This is a database study using NHIRD. No patients or public were involved in setting out the research question or developing the outcome measures. No patients or public involved in developing plans for design or implementation of the study. No patients or public were asked to advise on interpretation or writing up of results. No patients or public were the burden of the interventions on patients assessed. The results of the research were not disseminated to those study patients.

Sampled patients

We utilized study and comparison cohorts. Using the LHID 2005, we selected adult patients aged > 20 years who were newly diagnosed with SS (recorded from both the LHID 2005 and the Registry of Catastrophic Illness Patient Database) after 2000 and who were followed-up between 2000 and 2010. We excluded patients who were diagnosed with SS before 2000 and AA or AD, Turner syndrome, aortic coarctation, bicuspid aortic valve, Marfan syndrome, or Ehler-Danlos syndrome. Patients had a tracking time < 6 months. The date of SS diagnosis was used as the index date. Control candidate sampling comparisons were selected from individuals in the LHID 2005 who lacked a history of SS. The patient and control cohorts were

selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities, including hypertension, diabetes mellitus (DM), hyperlipidaemia, Behcet's disease, giant cell arteritis, RA and other inflammatory polyarthropathies, relapsing polychondritis, Takayasu's arteritis, and chronic obstructive pulmonary disease (COPD); and medication history, including β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and steroid history. We used COPD as a proxy variable for tobacco use to eliminate its potential confounding effect as previously described.[18] The SS patient and control cohorts were matched 1:4 based on their propensity score matching, for which the matching tolerance was 0.15 with the nearest neighbour method. The independent variables were demographics, co-morbidities, medications, and SS. The propensity matching analysis was performed in the logistic regression model. We also divided SS patients into PSS and secondary SS (SSS) patients and performed a subgroup analysis. SS previously diagnosed as SLE, RA, systemic sclerosis, or primary biliary cirrhosis were defined as SSS. We integrated the ICD-9-CM codes of the above diseases into a table in the supplementary materials (Supplement Table 1). The index dates for control patients were the same as the corresponding dates for patients with AA/AD. The study outcome was a diagnosis of AA/AD during the 10-year follow-up period. AA/AD was identified using ICD-9 codes. The end point of

the follow-up period was 2010-12-31 or the time at which AA/AD events occurred or the patient died or was lost to follow-up. We integrated the median follow-up time and follow-up year with AA/AD events in the supplementary materials (Supplement Tables 2 and 3).

Statistical analysis

Categorical variables, which are presented as percentages, were compared using the chi-square or Fisher's exact tests. Continuous variables, which are presented as the means and standard deviations, were compared using a t-test. The primary goal of the study was to determine whether SS patients exhibit an increased risk for developing AA/AD. The associations between those outcomes (prognoses) and clinical characteristics were investigated using Cox regression. The results are presented as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Kaplan-Meier curves with the log-rank test were used to compare patients with and without SS in terms of the cumulative risk of AA or AD. The threshold for statistical significance was $P < 0.05$. All data analyses were conducted using SPSS software version 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

A flow diagram of our patient enrolment scheme is presented in Figure 1. A total of 10,941 patients diagnosed with SS were identified in the NHIRD, which contains a

total of 986,713 individuals. An additional 43,764 age-, sex-, comorbidity-, and medication-matched patients were designated controls. As shown in Table 1, no significant differences in sex, age, co-morbidities, including DM, hypertension, hyperlipidaemia, Behcet's disease, giant cell arteritis, RA, relapsing polychondritis, Takayasu's arteritis, and COPD, or medications were noted between the two groups after matching. Patients with SS exhibited a significantly increased cumulative risk of developing AA/AD in subsequent years compared with patients without SS (log- rank test < 0.001, Figure 2). Table 2 presents the incidences of AA or AD during the ten-year follow-up period. At the end of the follow-up period, SS patients exhibited significantly increased incidences of AA or AD (0.43% vs. 0.37%, P = 0.045) but lower incidences of DM (7.73% vs. 15.44%, P < 0.001) and COPD (5.96% vs. 6.72%, P = 0.004). In addition, patients with SS were younger and exhibited higher Charlson comorbidity index (CCI) than patients without SS. The incidence for AA or AD was higher in males and older patients regardless of whether patients had SS or not (Supplement Figures 1 and 2). Regarding the use of Cox regression independent of the effects of sex, age, co-morbidities, and medication, compared with patients without SS, patients with SS also exhibited a significantly increased risk of developing AA or AD (adjusted HR = 3.642, 95% CI = 2.527-5.250, P < 0.001, Table 3). The subgroup analysis revealed that patients with PSS or SSS both exhibited

significantly increased risks for developing AA/AD compared with patients without SS (adjusted HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693, 95% CI = 2.520-5.411, P < 0.001, Table 4). We also integrated the first event of AA/AD coding into the distribution analysis in the supplemental material (Supplement Table 4). All patients were coded with AA/AD for the first time in the Inpatient and ER sections.

Table 1 Characteristics of the study participants at baseline

Sjögren's syndrome	Total N (%)	With N (%)	Without N (%)	P-value
Total	54,705	10,941 (20.00%)	43,764 (80.00%)	
Sex				0.999
Male	10,187 (18.63%)	2,011 (18.44%)	8,176 (18.68%)	
Female	44,485 (81.37%)	8,897 (81.56%)	35,588 (81.32%)	
Age (years)	55.78 ± 17.09	55.80 ± 16.65	55.77 ± 17.20	0.897
DM	3,553 (6.49%)	724 (6.62%)	2,829 (6.46%)	0.558
Hypertension	8,091 (14.79%)	1,578 (14.42%)	6,513 (14.88%)	0.228
Hyperlipidaemia	1,145 (2.09%)	234 (2.14%)	911 (2.08%)	0.709
Behcet's disease	321 (0.59%)	62 (0.57%)	259 (0.59%)	0.834
Giant cell arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
Rheumatoid arthritis	8,907 (16.28%)	1,784 (16.31%)	7,123 (16.28%)	0.942
Relapsing polychondritis	71 (0.13%)	14 (0.13%)	57 (0.13%)	0.953
Takayasu's arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
COPD	2,931 (5.36%)	581 (5.3%)	2,350 (5.37%)	0.831
Steroid	16,799 (30.71%)	3,345 (30.57%)	13,454 (30.74%)	0.737
β blocker	12,588 (23.01%)	2,513 (22.97%)	10,075 (23.02%)	0.919
CCB	11,553 (21.12%)	2,342 (21.41%)	9,211 (21.05%)	0.409
ACEI	13,586 (24.84%)	2,711 (24.78%)	10,875 (24.85%)	0.878
ARB	12,718 (23.25%)	2,620 (23.95%)	10,098 (23.07%)	0.054
Diuretic	12,440 (22.74%)	2,429 (22.20%)	10,011 (22.87%)	0.136
Statin	13,922 (25.45%)	2,811 (25.69%)	11,111 (25.39%)	0.516

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 2 Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Sjögren's syndrome	Total N (%)	With N (%)	Without N (%)	P-value
Total	54,705	10,941 (20.00%)	43,764 (80.00%)	
Aortic aneurysm and dissection	207 (0.38%)	47 (0.43%)	160 (0.37%)	0.045
Sex				0.999
Male	10,187 (18.63%)	2,011 (18.44%)	8,176 (18.68%)	
Female	44,485 (81.37%)	8,897 (81.56%)	35,588 (81.32%)	
Age (years)	61.36 ± 5.41	60.90 ± 4.98	61.47 ± 5.51	<0.001
DM	7,603 (13.90%)	846 (7.73%)	6,757 (15.44%)	<0.001
Hypertension	8,821 (16.12%)	1,708 (15.61%)	7,113 (16.25%)	0.102
Hyperlipidaemia	1,128 (2.06%)	240 (2.19%)	888 (2.03%)	0.279
Behcet's disease	324 (0.59%)	63 (0.58%)	261 (0.60%)	0.802
Giant cell arteritis	16 (0.03%)	3 (0.03%)	13 (0.03%)	0.901
Rheumatoid arthritis	9,033 (16.51%)	1,774 (16.21%)	7,259 (16.59%)	0.348
Relapsing polychondritis	80 (0.15%)	19 (0.17%)	61 (0.14%)	0.401
Takayasu's arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
COPD	3,593 (6.57%)	652 (5.96%)	2,941 (6.72%)	0.004
CCI_R	0.78 ± 1.53	0.83 ± 1.39	0.77 ± 1.56	<0.001
Steroid	17,112 (31.28%)	3,511 (32.09%)	13,601 (31.08%)	0.041
β blockers	13,750 (25.13%)	2,674 (24.44%)	11,076 (25.31%)	0.061
CCB	11,833 (21.63%)	2,397 (21.91%)	9,436 (21.56%)	0.430
ACEI	13,793 (25.21%)	2,784 (25.45%)	11,009 (25.16%)	0.532
ARB	12,976 (23.72%)	2,681 (24.50%)	10,295 (23.52%)	0.031
Diuretic	12,692 (23.20%)	2,507 (22.91%)	10,185 (23.27%)	0.427
Statin	14,123 (25.82%)	2,828 (25.85%)	11,295 (25.81%)	0.934

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

CCI_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 3 Factors associated with aortic aneurysm and dissection according to Cox regression

Variables	Crude HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Sjögren's syndrome	3.205	2.254-3.565	< 0.001	3.642	2.527-5.250	< 0.001
Sex (male)	2.645	1.974-3.597	< 0.001	2.035	1.534-2.700	< 0.001
Age (years)	1.049	1.032-1.057	< 0.001	1.043	1.032-1.055	< 0.001
DM	1.704	1.389-1.944	0.024	1.674	1.065-1.976	0.037
Hypertension	1.165	1.022-1.454	0.038	1.305	0.973-1.751	0.075
Hyperlipidaemia	1.211	0.594-2.436	0.618	1.343	0.656-2.751	0.420
Rheumatoid arthritis	1.645	0.774-3.496	0.196	0.801	0.362 -1.769	0.583
COPD	1.838	1.256-2.691	0.002	1.170	0.790-1.735	0.433
CCI_R	1.036	0.945-1.087	0.074	1.016	0.968-1.065	0.527
Steroid	1.497	0.598-2.976	0.495	1.501	0.339-3.298	0.617
β blockers	1.468	0.453-2.772	0.862	1.398	0.401-2.895	0.803
CCB	1.345	0.343-2.901	0.372	1.402	0.452-2.806	0.280
ACEI	1.298	0.426-3.041	0.601	1.288	0.395-2.845	0.334
ARB	1.346	0.379-1.986	0.711	1.345	0.343-1.886	0.682
Diuretic	1.198	0.598-2.511	0.652	1.201	0.490-2.907	0.703
Statin	1.364	0.667-4.972	0.798	1.335	0.679-4.787	0.897

HR= hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table; CCI_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 4 Factors associated with aortic aneurysm and dissection stratified by primary/secondary Sjögren's syndrome using Cox regression

	Patients with Sjögren's syndrome			Patients without Sjögren's syndrome			Ratio	Adjusted HR*	95% CI	P-value
	Events	PY	Incidence rate (per 10^5 PY)	Events	PY	Incidence rate (per 10^5 PY)				
Total	47	55,860.08	84.14	160	253,779.88	63.05	1.335	3.642	2.527-5.250	< 0.001
Without RA/SLE/SS/PBC	30	36,607.55	81.95	158	248,694.36	63.53	1.290	1.753	1.108-9.382	0.042
With RA/SLE/SS/PBC	17	19,252.53	88.30	2	5,085.52	39.33	2.245	3.693	2.520-5.411	< 0.001

PYs = person-years; Ratio = incidence of patients with AA/AD divided by the incidence of patients without AA/AD; *Adjusted HR = adjusted hazard ratio: adjusted for age, sex, co-morbidities, and medications, as listed in Table 3, using Cox regression; CI = confidence interval; RA = rheumatoid arthritis ; SLE = systemic lupus erythematosus ; SS = systemic sclerosis ; PBC = primary biliary cirrhosis

Primary Sjögren's syndrome: Sjögren's syndrome without systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or primary biliary cirrhosis; Secondary Sjögren's syndrome: Sjögren's syndrome with systemic lupus erythematosus, rheumatoid arthritis , systemic sclerosis, or primary biliary cirrhosis

DISCUSSION

This is a retrospective cohort study including 10,941 patients with SS and 43,764 patients without SS matched by age, sex, year of index date of the SS diagnosis, co-morbidities, and medication use from a large-scale nationwide population-based database. During follow-up, SS was associated with an increased incidence of the development of AA/AD compared with the comparison cohort.

Our research findings should remind healthcare providers of new information that SS patients exhibit an increased risk for AA or AD. Healthcare professionals should be aware of these life-threatening aortic events and aim to make early diagnosis of AA or AD. When SS patients present with chest, back, or abdominal symptoms, the possibility of AA or AD should be considered, with a specific and rapid examination.

SS patients exhibit an increased prevalence of developing traditional cardiovascular risk factors, such as hypertension and dyslipidaemia, which predispose patients to endothelial dysfunction and premature atherosclerosis. However, the disease-specific mechanisms associated with premature atherosclerosis in SS are not fully understood.[19] In a recent review article, cardiovascular disease was reported to be one of the primary causes of mortality in SS patients.[20] PSS shares clinical and serological features with RA and SLE, and these two diseases are associated with

acceleration of atherosclerosis.[21] However, the pathophysiology between SS and AA or AD remains unclear, although several possible mechanisms have been proposed. Previous studies have demonstrated that both SS and AA/AD are induced by chronic inflammation.[22-25] Recent studies have provided convincing evidence indicating that several signalling pathways are involved in both AA and SS, including the MAPK, TGF-β, and MMP signalling pathways.[12-15] Activation of the innate immune system and the production of interferons (IFNs) could be the first stages of PSS pathogenesis.[26] IFNs and IL-21 could induce B-cell-activating factor (BAFF) and further activate B cell activity. In human salivary gland cells, interferon-γ modulates and increases MMP-2 and MMP-9 expression.[27] The circulating levels of MMP-9 were increased in patients with definite SS compared with patients with possible SS.[28] Furthermore, MMP-2 and MMP-9 also display a critical role in AAA formation.[29] MMPs play roles in tissue destruction and the weakening of the matrix, as noted in liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, and multiple sclerosis.[30] Several molecules that are activated in the salivary glands, including JNK, NF-κB, and TGF-β, also lead to inflammation and reactive oxygen species (ROS) production in the aortic matrix. This process may be a possible mechanistic pathway by which SS aggravates AA or AD.[12,13,22,31-34]

Low-dose steroids, such as prednisone, may be used to treat SS-induced

joint and muscle pain. Prolonged or high-dose corticosteroid treatment likely causes disintegration of connective tissue of the media possibly together with primary aortic wall involvement and/or vascular damage in patients with autoimmune disorders, which can result in aortic aneurysmal enlargement and AD.[30,35] In this study, the medical condition of steroids was matched. Therefore, the effect of steroids was mitigated. The strength of our study involves its population-based database design. We accounted for several aneurysm-related confounding factors. Although we adjusted the results extensively using Cox regression models, our study had several limitations and unmeasured confounders. The NHIRD registry is not able to provide detailed information on laboratory results, family histories and health-related lifestyle factors, such as alcohol consumption and tobacco use, which can increase the risk of AA/AD and were potential confounding factors in this study. In our study, we also considered COPD incidence as a proxy variable for tobacco use to eliminate its potential confounding effect.[18] The limitation is that not all smokers develop disease. Although our study identified the association between SS and AA/AD, the cohort study design did not enable determination of the cause-effect relationship. Further prospective follow-up studies, mechanistic studies and animal experiments should be performed.

CONCLUSION

Patients with SS exhibit an increased risk for developing AA or AD, and healthcare professionals should be aware of this risk when treating patients with SS. Increased aortic surveillance may be required in patients with SS.

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COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

Y-DT, J-CW, and S-HT conceived and designed the study.

W-CC provided the materials for the study. C-HC and S-JC analysed the data. C-JY and M-TL contributed reagents, materials, and analysis tools. Y-DT, J-CW, W-IL, and S-HT wrote the manuscript. All the authors approved the manuscript.

DATA SHARING STATEMENT

No additional data sharing available.

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FIGURE LEGENDS

Figure 1. Patient selection flowchart

Figure 2. Kaplan-Meier curve of the cumulative risk of aortic aneurysm or dissection due to Sjögren's syndrome

TABLE LEGENDS

Table 1. Characteristics of the study participants at baseline

Table 2. Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Table 3. Factors associated with aortic aneurysm and dissection according to Cox regression

Table 4. Factors associated with aortic aneurysm or dissection stratified by primary/secondary SS using Cox regression

SUPPLEMENTARY MATERIAL

Supplement Table 1 ICD-9-CM coding of diseases in the manuscript

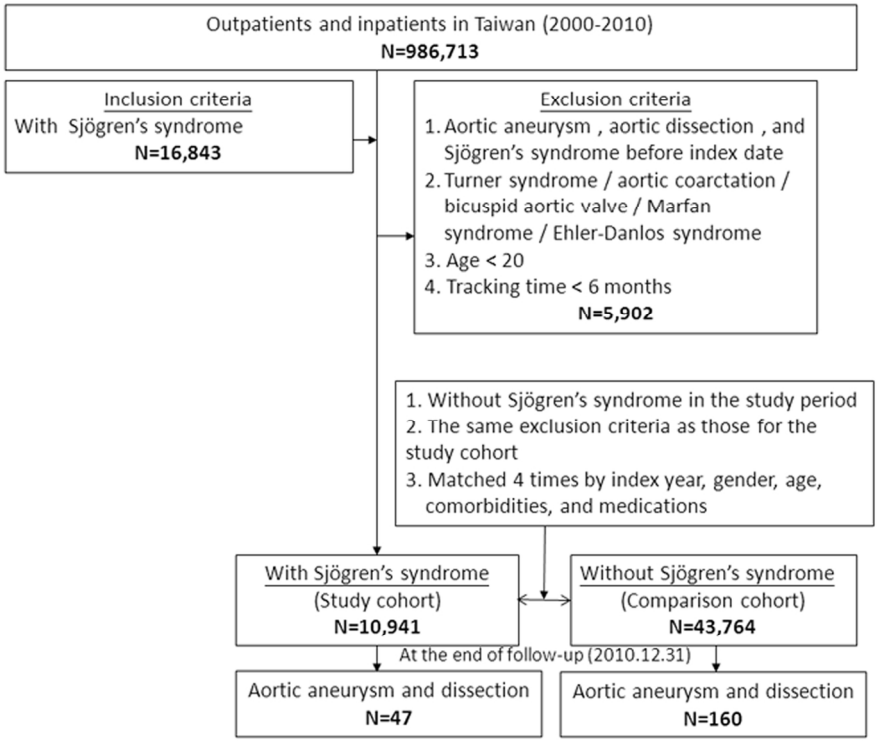
Supplement Table 2 Years of follow-up

Supplement Table 3 Years to AA /AD

Supplement Table 4 First event of the (AA/AD) coding distribution

Supplement Figure 1. Sex-specific incidence of AA or AD in the study cohort, control cohort, and general population.

Supplement Figure 2. Age-specific incidence of AA or AD in the study cohort, control cohort, and general population.



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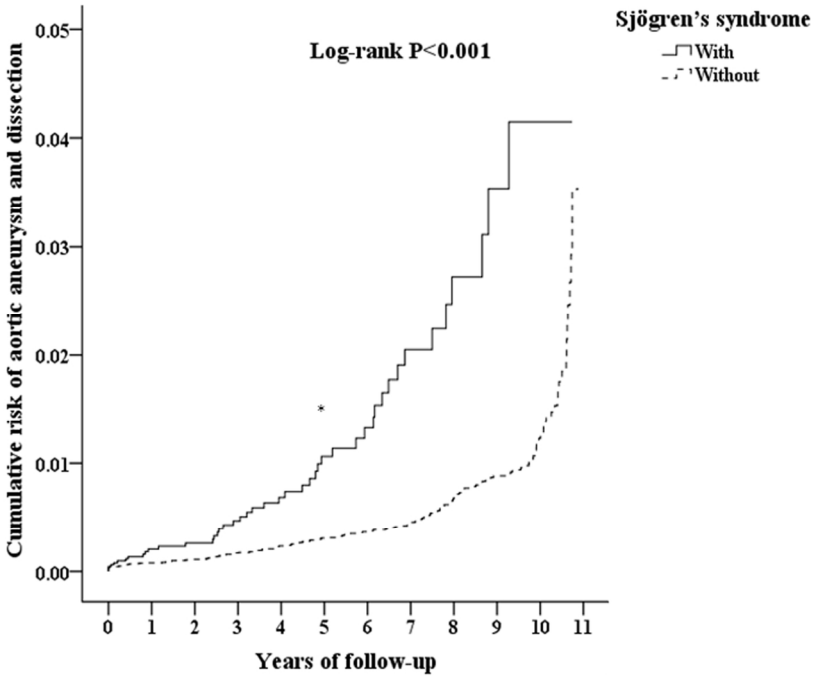

With Sjögren's syndrome (N=10,941)	13	15	21	26	32	35	41	44	46	47	47
Without Sjögren's syndrome (N=43,764)	27	36	49	63	77	81	94	113	130	146	160
P value	0.897	0.513	0.275	0.102	0.036	0.015	0.001	<0.001	<0.001	<0.001	<0.001

*:P<0.05 is considered statistically significant

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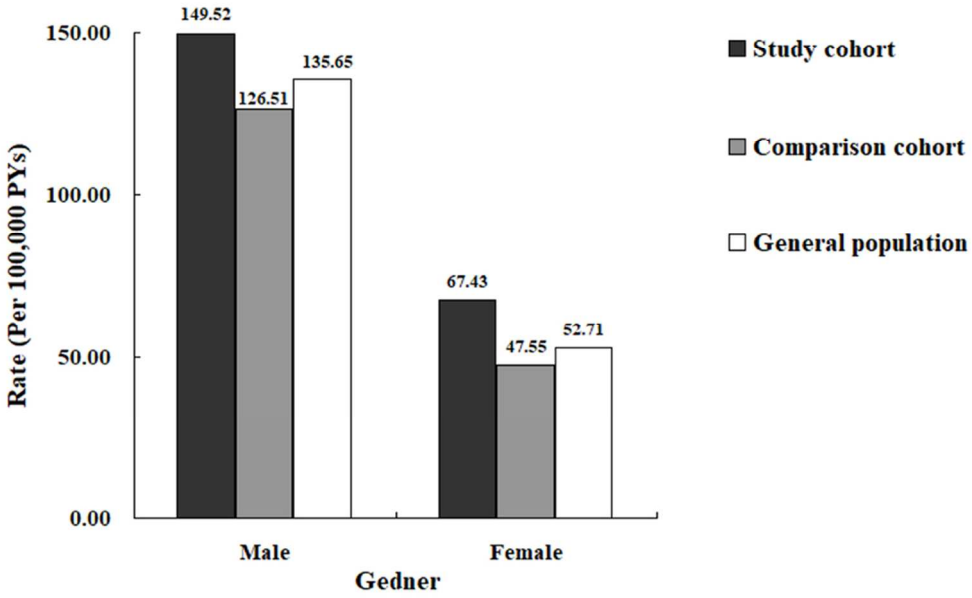

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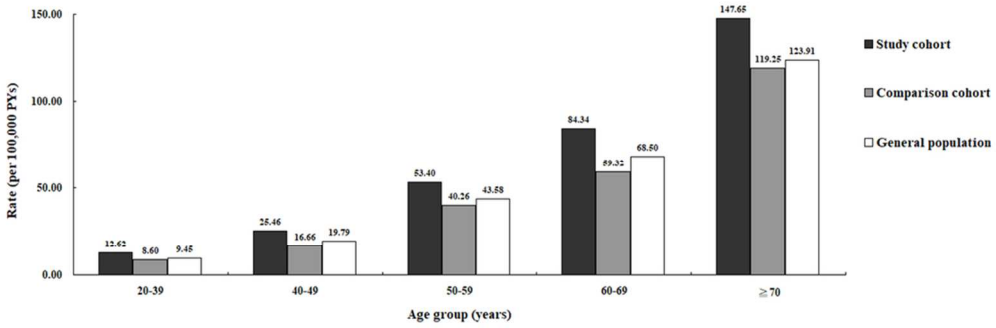

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Supplement Table 1 ICD-9-CM coding of diseases in the manuscript

Disease	ICD-9-CM	Disease	ICD-9-CM
Aortic aneurysm and dissection	441.0-441.9	Behcet's disease	136.1
Sjögren's syndrome	710.2	Giant cell arteritis	446.5
Turner syndrome	758.6	RA	714
Aortic coarctation	747.10	Relapsing polychondritis	733.99
Bicuspid aortic valve	746.4	Takayasu's arteritis	446.7
Marfan syndrome	759.82	COPD	490-496
Ehler-Danlos syndrome	756.83	SLE	710.0
Diabetes mellitus	250	Systemic sclerosis	701.1
Hypertension	401-405	Primary biliary cirrhosis	571.6
Hyperlipidaemia	272.0-272.4		

RA = rheumatoid arthritis and other inflammatory polyarthropathies; COPD = chronic obstructive pulmonary disease; SLE = systemic lupus erythematosus

Supplement Table 2 Years of follow-up

Sjögren's syndrome	Min	Middle	Max	Mean ± SD
With	0.50	3.26	10.91	5.11 ± 7.52
Without	0.50	4.57	10.98	5.80 ± 5.53
Total	0.50	3.69	10.98	5.66 ± 5.99

Supplement Table 3 Years to AA/AD

Sjögren's syndrome	Min	Middle	Max	Mean ± SD
With	0.51	3.32	9.27	4.67 ± 3.82
Without	0.52	5.07	10.87	5.53 ± 3.65
Total	0.51	4.93	10.87	5.12 ± 3.49

Supplement Table 4 First event of the (AA/AD) coding distribution

Sjögren's syndrome	Inpatient		Emergency Room	
	N	%	N	%
With	40	85.11	7	14.89
Without	141	88.12	19	11.88
Total	181	87.44	26	12.56

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10*
Bias	9	Describe any efforts to address potential sources of bias	19
Study size	10	Explain how the study size was arrived at	17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	8-9
		(c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Sjögren's syndrome, aortic dissection, aortic aneurysm

Increased risk of aortic aneurysm and dissection in patients with Sjögren's syndrome: a nationwide population-based cohort study in Taiwan

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ABSTRACT

Objectives: Sjögren's syndrome (SS) is a systemic autoimmune disorder. Several molecular pathways and the activation of matrix metalloproteinases associated with the pathogenesis of SS participate in the initiation and progression of aortic aneurysm (AA) and aortic dissection (AD). In this study, we aimed to evaluate whether patients with SS exhibit an increased risk of AA or AD.

Methods: We conducted a retrospective cohort study using a database extracted from Taiwan's National Health Insurance Research Database (NHIRD). All medical conditions for each case and control were categorised using the International Classification of Diseases, 9th Revision (ICD-9). Hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between SS and AA/AD were estimated using Cox regression and adjusted for co-morbidities.

Results: Our analyses included 10,941 SS cases and 43,764 propensity score-matched controls. Compared with the controls, the patients with SS exhibited a significantly increased risk of developing an AA or AD (adjusted HR = 3.642, P < 0.001). Subgroup analysis revealed that compared with patients without SS, patients with primary and secondary SS both exhibited a significantly increased risk of developing AA or AD (adjusted HR = 1.753, P = 0.042; adjusted HR = 3.693, P < 0.001).

Conclusion: Patients with SS exhibit increased risks of developing AA or AD, and

healthcare professionals should be aware of this risk when treating patients with SS.

Increased aortic surveillance may be required for patients with SS syndrome.

Keywords: Sjögren's syndrome, aortic dissection, aortic aneurysm

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The strength of our study is its population-based cohort design with a large sample size.
- The patients and controls were selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities; and medications used. This population-based cohort study was adjusted for potential risk factors to minimize study bias.
- This was a retrospective cohort study.
- NHIRD cannot provide detailed information regarding the laboratory results or lifestyle factors of the patients.
- Our results are limited to human data. Both mechanistic and animal studies are required for further clarification.

INTRODUCTION

Sjögren's syndrome (SS) is a systemic autoimmune disorder commonly presenting with dry eyes and mouth. The prevalence of SS is between 0.1% and 4.8% in various populations when strictly defined according to the American-European Consensus Criteria, and it is one of the most common autoimmune diseases.[1] SS may affect patients at any age, but more cases occur in the fourth decade of life, and there is a female predominance. The female-male ratio is approximately 9:1.[2] Aortic aneurysms (AAs) are often diagnosed inadvertently and are a common cause of sudden death. Enlarged aneurysms can result in rupture. Aortic dissection (AD) is one of the deadliest complications of thoracic aortic disease. Estimates of the incidence of AD range from 6 cases per 100,000 to 16.3 per 100,000 in England and Sweden, respectively.[3,4] Regarding the Asian population, the average annual incidence of AD is 5.6 per 100,000 persons in Taiwan and the prevalence is 19.9 per 100,000 persons, with a predominance noted among men 50 to 54 years of age (27.3 per 100,000 persons per year).[5]

Previous studies have demonstrated that AA is more prevalent in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared with the general population.[6,7] Compared with age- and sex-matched healthy controls, primary SS (PSS) patients exhibited a 2-fold increased prevalence of hypertension

and hypertriglyceridemia. Furthermore, hypertension is underdiagnosed and suboptimally treated in PSS.[8] SS with positive autoantibodies is associated with a low ankle-brachial index, which may indicate an increased risk of early atherosclerosis.[9] Nonetheless, previous population-based studies indicated that SS is not associated with an increased risk of subsequent acute myocardial infarction (AMI) and ischaemic stroke.[10,11]

Several molecular mechanisms, including JNK, NF-κB and TGF-β signalling pathways, and matrix metalloproteinase (MMP) activation are associated with the pathogenesis of SS.[12,13] These molecular mechanisms also actively participate in the initiation and progression of AA or AD.[14,15] Based on these findings, we hypothesized that patients with SS may have an increased risk of AA or AD due to SS-related cardiovascular risks and shared molecular mechanisms. However, the association between SS and AA or AD has not been thoroughly evaluated in large-scale studies. Therefore, we aimed to determine whether SS patients exhibited an increased risk of AA or AD using a nationwide healthcare insurance claim database.

METHODS

Data source

The data described herein were acquired from the Longitudinal Health Insurance Database 2005 (LHID 2005), a subgroup database of the Taiwan National Health Insurance Research Database (NHIRD) used for the nationwide population-based retrospective cohort study. The National Health Insurance programme in Taiwan provides health care for 99% of the population (greater than 23 million people) and was implemented in 1995. The LHID 2005 provides information on medical service utilization using a randomly selected sample of approximately one million people receiving benefits, representing approximately 5% of Taiwan's population in 2005. The information was obtained from the NHIRD between 2000 and 2010. The accuracy of the diagnoses in the NHIRD, particularly the diagnoses of major diseases (e.g., acute coronary syndrome and stroke), has been corroborated.[16,17] The LHID is composed of "de-identified" secondary data that are available to the public via open access for research. ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to five each), sex, birthdays, patient identification numbers, dates of admission and discharge, and outcomes are coded. In addition, information regarding the medical institutions that served patients was obtained. Individual information was protected using encoded personal identification to prevent ethical violations related to the data. Our study conformed to the Declaration of Helsinki and relevant guidelines. This Institutional

Review Board of the Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, permitted this study (TSGH IRB No.2-105-05-082).

Patient and public involvement

This is a database study using NHIRD. No patients or public were involved in setting out the research question or developing the outcome measures. No patients or public involved in developing plans for design or implementation of the study. No patients or public were asked to advise on interpretation or writing up of results. No patients or public were the burden of the interventions on patients assessed. The results of the research were not disseminated to those study patients.

Sampled patients

We utilized study and comparison cohorts. Using the LHID 2005, we selected adult patients aged > 20 years who were newly diagnosed with SS (recorded from both the LHID 2005 and the Registry of Catastrophic Illness Patient Database) after 2000 and who were followed-up between 2000 and 2010. We excluded patients who were diagnosed with SS before 2000 and had AA or AD, Turner syndrome, aortic coarctation, bicuspid aortic valve, Marfan syndrome, or Ehler-Danlos syndrome. Patients who had a tracking time < 6 months were also excluded in order to decrease the probability of including AA/AD cases that went undiagnosed before SS diagnosis. The date of SS diagnosis was used as the index date. Control candidate sampling

comparisons were selected from individuals in the LHID 2005 who lacked a history of SS. The patient and control cohorts were selected by 1:4 matching according to the following baseline variables: age; sex; co-morbidities, including hypertension, diabetes mellitus (DM), hyperlipidaemia, Behcet's disease, giant cell arteritis, RA and other inflammatory polyarthropathies, relapsing polychondritis, Takayasu's arteritis, and chronic obstructive pulmonary disease (COPD); and medication history, including β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and steroid history. We used COPD as a proxy variable for tobacco use to eliminate its potential confounding effect as previously described.[18] The SS patient and control cohorts were matched 1:4 based on their propensity score matching, for which the matching tolerance was 0.15 with the nearest neighbour method. The independent variables were demographics, co-morbidities, medications, and SS. The dependent variables were AA and AD. We also divided SS patients into PSS and secondary SS (SSS) patients and performed a subgroup analysis. SS previously diagnosed as SLE, RA, systemic sclerosis, or primary biliary cirrhosis were defined as SSS. We integrated the ICD-9-CM codes of the above diseases into a table in the supplementary materials (Supplement Table 1). The index dates for control patients were the same as the corresponding dates for patients with AA/AD. The study outcome was a diagnosis of AA/AD during the

10-year follow-up period. AA/AD was identified using ICD-9 codes. The end point of the follow-up period was 2010-12-31 or the time at which AA/AD events occurred or the patient died or was lost to follow-up. We integrated the median follow-up time and follow-up year with AA/AD events in the supplementary materials (Supplement Tables 2 and 3).

Statistical analysis

Propensity matching analysis was performed in the logistic regression model. The potential confounders were index year, gender, age, comorbidities, and medications. The match tolerance was 0.15 with the nearest neighbour method. The study comparison cohort-matching ratio was 4-fold (study: comparison = 1:4). Categorical variables, which are presented as percentages, were compared using the chi-square or Fisher's exact tests. Continuous variables, which are presented as the means and standard deviations, were compared using a t-test. The primary goal of the study was to determine whether SS patients exhibit an increased risk for developing AA/AD. The associations between those outcomes (prognoses) and clinical characteristics were investigated using Cox regression. As shown in Supplement Tables 4, all explanatory variables in the fully adjusted model were retained. The results are presented as adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Kaplan-Meier curves with the log-rank test were used to

compare patients with and without SS in terms of the cumulative risk of AA or AD. The threshold for statistical significance was $P < 0.05$. All data analyses were conducted using SPSS software version 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

A flow diagram of our patient enrolment scheme is presented in Figure 1. A total of 10,941 patients diagnosed with SS were identified in the NHIRD, which contains a total of 986,713 individuals. An additional 43,764 age-, sex-, comorbidity-, and medication-matched patients were designated controls. As shown in Table 1, no significant differences in sex, age, co-morbidities, including DM, hypertension, hyperlipidaemia, Behcet's disease, giant cell arteritis, RA, relapsing polychondritis, Takayasu's arteritis, and COPD, or medications were noted between the two groups after matching. Patients with SS exhibited a significantly increased cumulative risk of developing AA/AD in subsequent years compared with patients without SS (log- rank test < 0.001, Figure 2). Table 2 presents the incidences of AA or AD during the ten-year follow-up period. At the end of the follow-up period, SS patients exhibited significantly increased incidences of AA or AD (0.43% vs. 0.37%, $P = 0.045$) but lower incidences of DM (7.73% vs. 15.44%, $P < 0.001$) and COPD (5.96% vs. 6.72%, $P = 0.004$). In addition, patients with SS were younger and exhibited higher Charlson comorbidity index (CCI) than patients without SS. The incidence for AA or AD was

higher in males and older patients regardless of whether patients had SS or not (Supplement Figures 1 and 2). Regarding the use of Cox regression independent of the effects of sex, age, co-morbidities, and medication, compared with patients without SS, patients with SS also exhibited a significantly increased risk of developing AA or AD (adjusted HR = 3.642, 95% CI = 2.527-5.250, P < 0.001, Table 3). The subgroup analysis revealed that patients with PSS or SSS both exhibited significantly increased risks for developing AA/AD compared to patients without SS (adjusted HR = 1.753, 95% CI = 1.108-9.382, P = 0.042; adjusted HR = 3.693, 95% CI = 2.520-5.411, P < 0.001, Table 4). We also have included the first event of AA/AD coding into the distribution analysis in the supplemental material (Supplement Table 5). All patients were coded with AA/AD for the first time in the Inpatient and ER sections.

Table 1 Characteristics of the study participants at baseline

Sjögren's syndrome	Total	With	Without	P-value
	N (%)	N (%)	N (%)	
Total	54,705	10,941 (20.00%)	43,764 (80.00%)	
Sex				0.999
Male	10,187 (18.63%)	2,011 (18.44%)	8,176 (18.68%)	
Female	44,485 (81.37%)	8,897 (81.56%)	35,588 (81.32%)	
Age (years)	55.78 ± 17.09	55.80 ± 16.65	55.77 ± 17.20	0.897
DM	3,553 (6.49%)	724 (6.62%)	2,829 (6.46%)	0.558
Hypertension	8,091 (14.79%)	1,578 (14.42%)	6,513 (14.88%)	0.228
Hyperlipidaemia	1,145 (2.09%)	234 (2.14%)	911 (2.08%)	0.709
Behcet's disease	321 (0.59%)	62 (0.57%)	259 (0.59%)	0.834
Giant cell arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
Rheumatoid arthritis	8,907 (16.28%)	1,784 (16.31%)	7,123 (16.28%)	0.942
Relapsing polychondritis	71 (0.13%)	14 (0.13%)	57 (0.13%)	0.953
Takayasu's arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
COPD	2,931 (5.36%)	581 (5.3%)	2,350 (5.37%)	0.831
Steroid	16,799 (30.71%)	3,345 (30.57%)	13,454 (30.74%)	0.737
β blocker	12,588 (23.01%)	2,513 (22.97%)	10,075 (23.02%)	0.919
CCB	11,553 (21.12%)	2,342 (21.41%)	9,211 (21.05%)	0.409
ACEI	13,586 (24.84%)	2,711 (24.78%)	10,875 (24.85%)	0.878
ARB	12,718 (23.25%)	2,620 (23.95%)	10,098 (23.07%)	0.054
Diuretic	12,440 (22.74%)	2,429 (22.20%)	10,011 (22.87%)	0.136
Statin	13,922 (25.45%)	2,811 (25.69%)	11,111 (25.39%)	0.516

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 2 Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Sjögren's syndrome	Total N (%)	With N (%)	Without N (%)	P-value
Total	54,705	10,941 (20.00%)	43,764 (80.00%)	
Aortic aneurysm and dissection	207 (0.38%)	47 (0.43%)	160 (0.37%)	0.045
Sex				0.999
Male	10,187 (18.63%)	2,011 (18.44%)	8,176 (18.68%)	
Female	44,485 (81.37%)	8,897 (81.56%)	35,588 (81.32%)	
Age (years)	61.36 ± 5.41	60.90 ± 4.98	61.47 ± 5.51	<0.001
DM	7,603 (13.90%)	846 (7.73%)	6,757 (15.44%)	<0.001
Hypertension	8,821 (16.12%)	1,708 (15.61%)	7,113 (16.25%)	0.102
Hyperlipidaemia	1,128 (2.06%)	240 (2.19%)	888 (2.03%)	0.279
Behcet's disease	324 (0.59%)	63 (0.58%)	261 (0.60%)	0.802
Giant cell arteritis	16 (0.03%)	3 (0.03%)	13 (0.03%)	0.901
Rheumatoid arthritis	9,033 (16.51%)	1,774 (16.21%)	7,259 (16.59%)	0.348
Relapsing polychondritis	80 (0.15%)	19 (0.17%)	61 (0.14%)	0.401
Takayasu's arteritis	15 (0.03%)	3 (0.03%)	12 (0.03%)	0.999
COPD	3,593 (6.57%)	652 (5.96%)	2,941 (6.72%)	0.004
CCI_R	0.78 ± 1.53	0.83 ± 1.39	0.77 ± 1.56	<0.001
Steroid	17,112 (31.28%)	3,511 (32.09%)	13,601 (31.08%)	0.041
β blockers	13,750 (25.13%)	2,674 (24.44%)	11,076 (25.31%)	0.061
CCB	11,833 (21.63%)	2,397 (21.91%)	9,436 (21.56%)	0.430
ACEI	13,793 (25.21%)	2,784 (25.45%)	11,009 (25.16%)	0.532
ARB	12,976 (23.72%)	2,681 (24.50%)	10,295 (23.52%)	0.031
Diuretic	12,692 (23.20%)	2,507 (22.91%)	10,185 (23.27%)	0.427
Statin	14,123 (25.82%)	2,828 (25.85%)	11,295 (25.81%)	0.934

P-value (categorical variable: Chi-square/Fisher's exact test; continuous variable: t-test)

CCI_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor

blocker

Table 3 Factors associated with aortic aneurysm and dissection according to Cox regression

Variables	Crude HR	95% CI	P-value	Adjusted HR	95% CI	P-value
Sjögren's syndrome	3.205	2.254-3.565	< 0.001	3.642	2.527-5.250	< 0.001
Sex (male)	2.645	1.974-3.597	< 0.001	2.035	1.534-2.700	< 0.001
Age (years)	1.049	1.032-1.057	< 0.001	1.043	1.032-1.055	< 0.001
DM	1.704	1.389-1.944	0.024	1.674	1.065-1.976	0.037
Hypertension	1.165	1.022-1.454	0.038	1.305	0.973-1.751	0.075
Hyperlipidaemia	1.211	0.594-2.436	0.618	1.343	0.656-2.751	0.420
Rheumatoid arthritis	1.645	0.774-3.496	0.196	0.801	0.362 -1.769	0.583
COPD	1.838	1.256-2.691	0.002	1.170	0.790-1.735	0.433
CCI_R	1.036	0.945-1.087	0.074	1.016	0.968-1.065	0.527
Steroid	1.497	0.598-2.976	0.495	1.501	0.339-3.298	0.617
β blockers	1.468	0.453-2.772	0.862	1.398	0.401-2.895	0.803
CCB	1.345	0.343-2.901	0.372	1.402	0.452-2.806	0.280
ACEI	1.298	0.426-3.041	0.601	1.288	0.395-2.845	0.334
ARB	1.346	0.379-1.986	0.711	1.345	0.343-1.886	0.682
Diuretic	1.198	0.598-2.511	0.652	1.201	0.490-2.907	0.703
Statin	1.364	0.667-4.972	0.798	1.335	0.679-4.787	0.897

HR= hazard ratio; CI = confidence interval; Adjusted HR: adjusted variables listed in the table; CCI_R = Charlson comorbidity index removed DM, COPD; DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Table 4 Factors associated with aortic aneurysm and dissection stratified by primary/secondary Sjögren's syndrome using Cox regression

	Patients with Sjögren's syndrome			Patients without Sjögren's syndrome			Ratio	Adjusted HR*	95% CI	P-value
	Events	PY	Incidence rate (per 10^5 PY)	Events	PY	Incidence rate (per 10^5 PY)				
Total	47	55,860.08	84.14	160	253,779.88	63.05	1.335	3.642	2.527-5.250	< 0.001
Without RA/SLE/SS/PBC	30	36,607.55	81.95	158	248,694.36	63.53	1.290	1.753	1.108-9.382	0.042
With RA/SLE/SS/PBC	17	19,252.53	88.30	2	5,085.52	39.33	2.245	3.693	2.520-5.411	< 0.001

PYs = person-years; Ratio = incidence of patients with AA/AD divided by the incidence of patients without AA/AD; *Adjusted HR = adjusted hazard ratio: adjusted for age, sex, co-morbidities, and medications, as listed in Table 3, using Cox regression; CI = confidence interval; RA = rheumatoid arthritis ; SLE = systemic lupus erythematosus ; SS = systemic sclerosis ; PBC = primary biliary cirrhosis

Primary Sjögren's syndrome: Sjögren's syndrome without systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, or primary biliary cirrhosis; Secondary Sjögren's syndrome: Sjögren's syndrome with systemic lupus erythematosus, rheumatoid arthritis , systemic sclerosis, or primary biliary cirrhosis

DISCUSSION

This is a retrospective cohort study including 10,941 patients with SS and 43,764 patients without SS matched by age, sex, year of index date of the SS diagnosis, co-morbidities, and medication use from a large-scale nationwide population-based database. During follow-up, SS was associated with an increased incidence of the development of AA/AD compared with the comparison cohort.

Our research findings should remind healthcare providers of new information that SS patients exhibit an increased risk for AA or AD. Healthcare professionals should be aware of these life-threatening aortic events and aim to make early diagnosis of AA or AD. When SS patients present with chest, back, or abdominal symptoms, the possibility of AA or AD should be considered, with a specific and rapid examination.

SS patients exhibit an increased prevalence of developing traditional cardiovascular risk factors, such as hypertension and dyslipidaemia, which predispose patients to endothelial dysfunction and premature atherosclerosis. However, the disease-specific mechanisms associated with premature atherosclerosis in SS are not fully understood.[19] In a recent review article, cardiovascular disease was reported to be one of the primary causes of mortality in SS patients.[20] PSS shares clinical and serological features with RA and SLE, and these two diseases are associated with

acceleration of atherosclerosis.[21] However, the pathophysiology between SS and AA or AD remains unclear, although several possible mechanisms have been proposed. Previous studies have demonstrated that both SS and AA/AD are induced by chronic inflammation.[22-25] Recent studies have provided convincing evidence indicating that several signalling pathways are involved in both AA and SS, including the MAPK, TGF-β, and MMP signalling pathways.[12-15] Activation of the innate immune system and the production of interferons (IFNs) could be the first stages of PSS pathogenesis.[26] IFNs and IL-21 could induce B-cell-activating factor (BAFF) and further activate B cell activity. In human salivary gland cells, interferon-γ modulates and increases MMP-2 and MMP-9 expression.[27] The circulating levels of MMP-9 were increased in patients with definite SS compared with patients with possible SS.[28] Furthermore, MMP-2 and MMP-9 also display a critical role in AAA formation.[29] MMPs play roles in tissue destruction and the weakening of the matrix, as noted in liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, and multiple sclerosis.[30] Several molecules that are activated in the salivary glands, including JNK, NF-κB, and TGF-β, also lead to inflammation and reactive oxygen species (ROS) production in the aortic matrix. This process may be a possible mechanistic pathway by which SS aggravates AA or AD.[12,13,22,31-34]

Low-dose steroids, such as prednisone, may be used to treat SS-induced joint and

muscle pain. Prolonged or high-dose corticosteroid treatment likely causes disintegration of connective tissue of the media possibly together with primary aortic wall involvement and/or vascular damage in patients with autoimmune disorders, which can result in aortic aneurysmal enlargement and AD.[30,35] In this study, the medical condition of steroids was matched. Therefore, the effect of steroids was mitigated. The strength of our study involves its population-based database design. We accounted for several aneurysm-related confounding factors. Although we adjusted the results extensively using Cox regression models, our study had several limitations and unmeasured confounders. The NHIRD registry is not able to provide detailed information on laboratory results, family histories and health-related lifestyle factors, such as alcohol consumption and tobacco use, which can increase the risk of AA/AD and were potential confounding factors in this study. This is a database study using NHIRD. All medical conditions for each case and the controls were categorized using the ICD-9-CM, in which diagnostic codes (up to five each) are coded. There may be a small number of coding errors or missing information when using this kind of administrative data, and limitations are bound to exist in any statistical method, even the propensity score matching. In our study, we also considered COPD incidence as a proxy variable for tobacco use to eliminate its potential confounding effect.[18] The limitation is that not all smokers develop disease. Although our study identified

the association between SS and AA/AD, the cohort study design did not enable determination of the cause-effect relationship. Further prospective follow-up studies, mechanistic studies and animal experiments should be performed.

CONCLUSION

Patients with SS exhibit an increased risk for developing AA or AD, and healthcare professionals should be aware of this risk when treating patients with SS. Increased aortic surveillance may be required in patients with SS.

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COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

Y-DT, J-CW, and S-HT conceived and designed the study.

W-CC provided the materials for the study. C-HC and S-JC analysed the data. C-JY and M-TL contributed reagents, materials, and analysis tools. Y-DT, J-CW, W-IL, and S-HT wrote the manuscript. All the authors approved the manuscript.

DATA SHARING STATEMENT

No additional data sharing available.

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FIGURE LEGENDS

Figure 1. Patient selection flowchart

Figure 2. Kaplan-Meier curve of the cumulative risk of aortic aneurysm or dissection due to Sjögren's syndrome

TABLE LEGENDS

Table 1. Characteristics of the study participants at baseline

Table 2. Incidences of aortic aneurysm and dissection and other characteristics during the ten-year follow-up period

Table 3. Factors associated with aortic aneurysm and dissection according to Cox regression

Table 4. Factors associated with aortic aneurysm or dissection stratified by primary/secondary SS using Cox regression

SUPPLEMENTARY MATERIAL

Supplement Table 1 ICD-9-CM coding of diseases in the manuscript

Supplement Table 2 Years of follow-up

Supplement Table 3 Years to AA /AD

Supplement Table 4 Variables including in the Cox regression

1 Supplement Table 5 First event of the (AA/AD) coding distribution

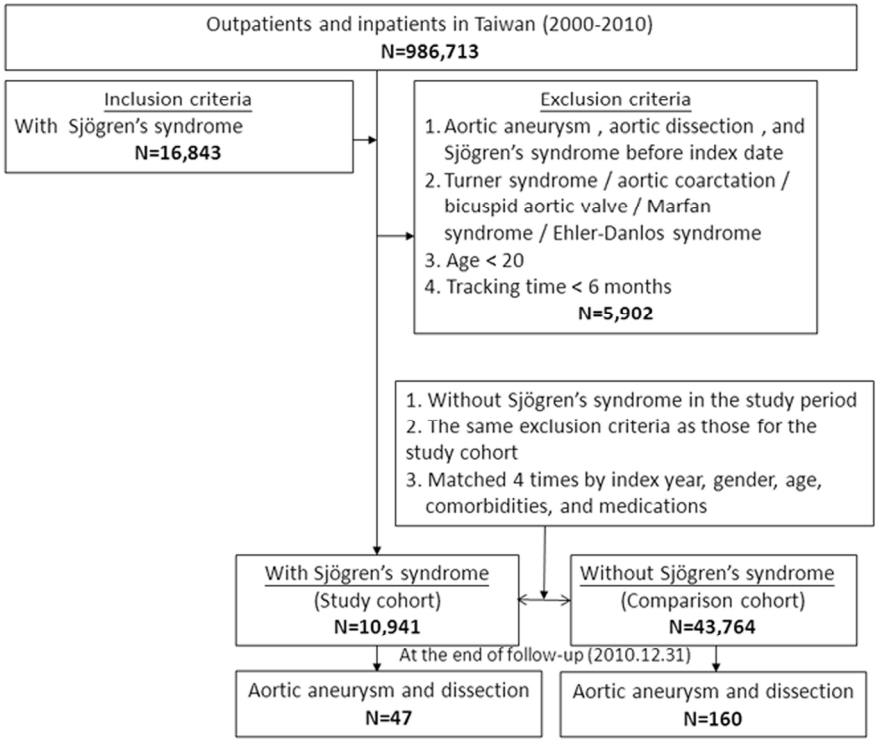
2 Supplement Figure 1. Sex-specific incidence of AA or AD in the study cohort, control

3 cohort, and general population.

4 Supplement Figure 2. Age-specific incidence of AA or AD in the study cohort, control

5 cohort, and general population.

6



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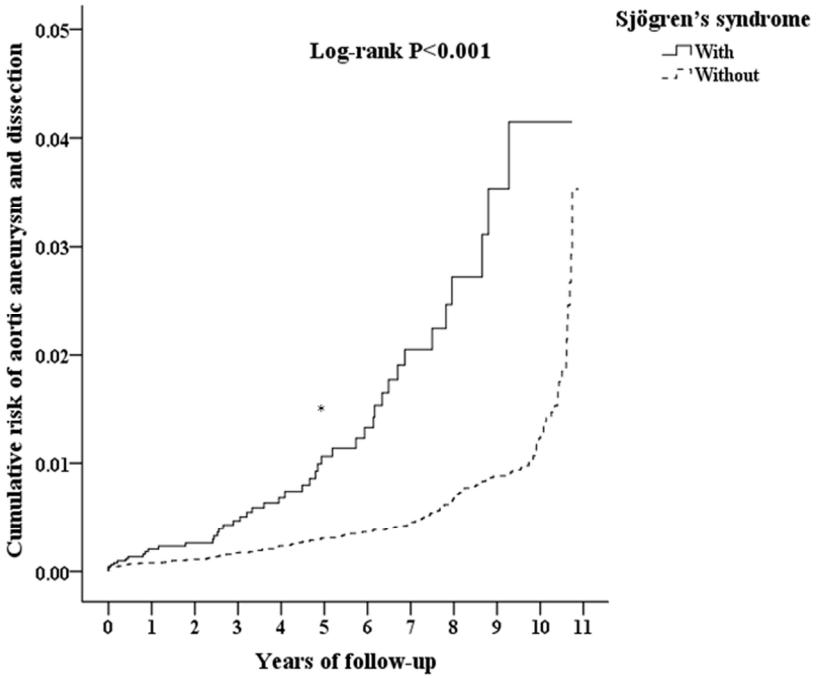

With Sjögren's syndrome (N=10,941)	13	15	21	26	32	35	41	44	46	47	47
Without Sjögren's syndrome (N=43,764)	27	36	49	63	77	81	94	113	130	146	160
P value	0.897	0.513	0.275	0.102	0.036	0.015	0.001	<0.001	<0.001	<0.001	<0.001

*:P<0.05 is considered statistically significant

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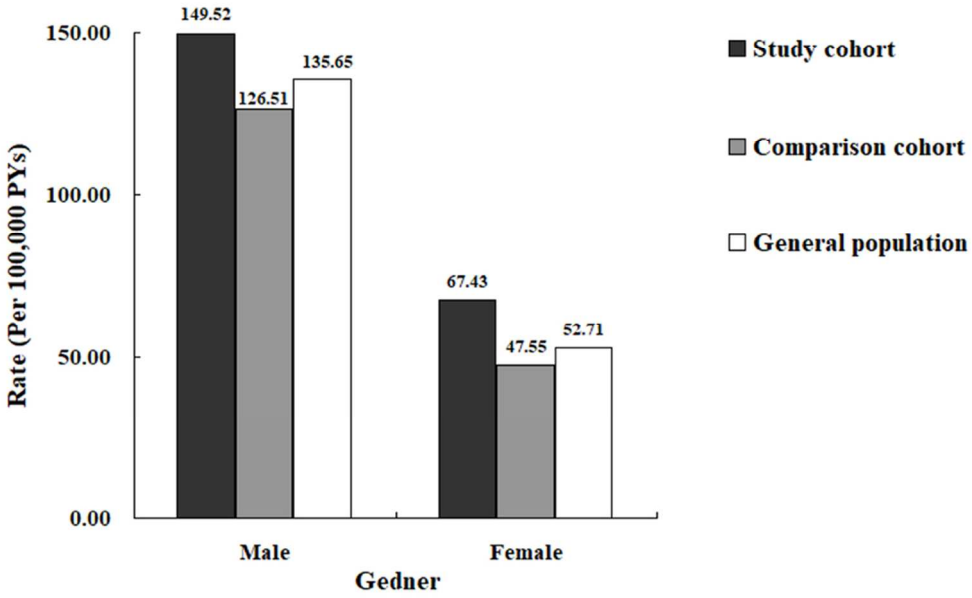

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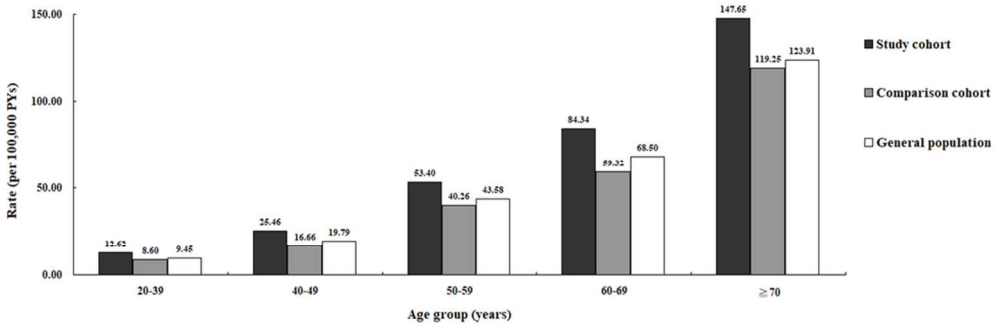

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Supplement Table 1 ICD-9-CM coding of diseases in manuscript

Disease	ICD-9-CM	Disease	ICD-9-CM
Aortic aneurysm and dissection	441.0-441.9	Behcet's disease	136.1
Sjögren's syndrome	710.2	Giant cell arteritis	446.5
Turner syndrome	758.6	RA	714
Aortic coarctation	747.10	Relapsing polychondritis	733.99
Bicuspid aortic valve	746.4	Takayasu's arteritis	446.7
Marfan syndrome	759.82	COPD	490-496
Ehler-Danlos syndrome	756.83	SLE	710.0
Diabetes mellitus	250	Systemic sclerosis	701.1
Hypertension	401-405	Primary biliary cirrhosis	571.6
Hyperlipidaemia	272.0-272.4		

RA = Rheumatoid arthritis and other inflammatory polyarthropathies; COPD = chronic obstructive pulmonary disease; SLE = systemic lupus erythematosus

Supplement Table 2 Years of follow-up

Sjögren's syndrome	Min	Middle	Max	Mean±SD
With	0.50	3.26	10.91	5.11±7.52
Without	0.50	4.57	10.98	5.80±5.53
Total	0.50	3.69	10.98	5.66±5.99

Supplement Table 3 Years to AA /AD

Sjögren's syndrome	Min	Middle	Max	Mean±SD
With	0.51	3.32	9.27	4.67±3.82
Without	0.52	5.07	10.87	5.53±3.65
Total	0.51	4.93	10.87	5.12±3.49

Supplement Table 4 Variables including in the Cox regression

Variables	Variables
Sjögren's syndrome	CCI_R
Sex (male)	Steroid
Age (years)	β blockers
DM	CCB
Hypertension	ACEI
Hyperlipidaemia	ARB
Rheumatoid arthritis	Diuretic
COPD	Statin

DM = diabetes mellitus; COPD = chronic obstructive pulmonary disease; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker

Supplement Table 5 First event of (AA / AD) coding distribution

Sjögren's syndrome	Inpatient		ER	
	N	%	N	%
With	40	85.11	7	14.89
Without	141	88.12	19	11.88
Total	181	87.44	26	12.56

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10*
Bias	9	Describe any efforts to address potential sources of bias	19
Study size	10	Explain how the study size was arrived at	17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	11
		(c) Explain how missing data were addressed	11
		(d) If applicable, explain how loss to follow-up was addressed	11
		(*e*) Describe any sensitivity analyses	11
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12-13
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	11
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.