Primary Sjögren's Syndrome and the Risk of Acute Myocardial Infarction: A Nationwide Study

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Background: Patients with autoimmune diseases have a high cardiovascular risk. However, few data are available on the risk of acute myocardial infarction (AMI) in patients diagnosed with primary Sjögren's syndrome (PSS). We conducted a large nationwide cohort study to investigate the possible association between PSS and the risk of AMI.

Methods: Between the years 2000-2006, a total of 5205 patients with newly diagnosed PSS and no history of AMI were identified from the Registry of Catastrophic Illness, a sub-dataset of the National Health Insurance Research Database in Taiwan. The control group, which consisted of subjects without systemic autoimmune disease or previous AMI, was matched by the date of enrollment, age, gender, history of coronary artery disease, diabetes, hypertension, chronic kidney disease, and hyperlipidemia. The study endpoints were the occurrence of AMI.

Results: Of the 5205 subjects with PSS and 5205 controls included in the study, 77 (35 PSS patients and 42 controls) developed AMI during the mean 3.7-year (interquartile range, 2.1-5.1 years) follow-up period. The incidence of AMI was similar in PSS patients and controls (1.91/1000 versus 2.25/1000 person-years). Multivariate analysis adjusted for baseline covariates demonstrated an insignificant association between PSS and AMI [adjusted hazard ratio, 0.86; 95% confidence interval (CI), 0.55-1.35; p = 0.506], suggesting that PSS does not increase the risk of AMI.

Conclusions: PSS is not associated with a higher risk of subsequent AMI.

Key Words: Acute myocardial infarction • Atherosclerosis • Primary Sjögren's syndrome

INTRODUCTION

Primary Sjögren's syndrome (PSS) is a chronic systemic autoimmune disorder characterized by inflammation of the exocrine glands and functional impairment of the salivary and lachrymal glands.[1] It mainly presents with sicca symptomatology of the main mucosal surfaces, including xerostomia, keratoconjunctivitis sicca, and parotid gland enlargement. The histological hallmark of PSS is focal lymphocytic infiltration of the exocrine glands, determined by a biopsy of the minor labial salivary gland. The disease spectrum extends from organ-specific autoimmune disease (autoimmune exocrinopathy) to a systemic involvement with diverse extraglandular manifestations.[2] The prevalence of PSS ranges from 0.05% to 4.8% across international communities with a female preponderance,[3] and a prevalence

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of 0.77% has been reported in Asians.[4]

Growing evidence suggests that cardiovascular events are major causes of morbidity and mortality in patients with some autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[5-7] However, few reports investigating the association between acute myocardial infarction (AMI) and PSS are available. Previous studies have suggested that PSS patients have a higher percentage of metabolic abnormalities, including altered lipid profiles and hyperuricemia.[8,9] Recently, one study reported that PSS is associated with an increased prevalence of diabetes mellitus and hypertriglyceridemia,[10] suggesting that patients with PSS may have a greater cardiovascular risk than the general population.

Although it has been reported that patients with PSS have increased intimal medial thickness (IMT), an index of subclinical atherosclerosis,[11] few studies have evaluated the relationship between PSS and the risk of subsequent AMI. Furthermore, the relationship between PSS and AMI-related comorbidities remains undetermined. Therefore, we conducted a large-scale, population-based, nationwide case-cohort study using the Taiwan National Health Insurance database to investigate whether patients with PSS have a higher risk of AMI than controls matched on the basis of age, gender, and comorbid disorders.

MATERIALS AND METHODS

Data sources

Taiwan began the National Health Insurance (NHI) program in 1995 to provide comprehensive health care for all citizens. Enrollment in the program is mandatory, and its coverage extends to approximately 98% of the nation's population.[12] The program provides comprehensive medical care, including outpatient, inpatient, emergency, dental, and prescription drugs. Currently, the National Health Insurance Research Database (NHIRD) at the National Health Research Institutes (NHRI) in Taiwan is in charge of the complete National Health Insurance claims database and has published several dozen extracted datasets for research purposes. The Longitudinal Health Insurance Database (LHID2000) includes records of 1,000,000 randomly sampled people who were alive in 2000, and it contains the medical records of all these individuals from 1995 to 2006. It is one of the largest nationwide population-based datasets in the world, and it allows researchers to trace use of medical services by these 1,000,000 enrollees. These random samples have been confirmed to be representative of the Taiwanese population. The database contains all NHI enrollment files, claims data, and the registry for prescription drugs, which together provide comprehensive utilization information on subjects covered by the insurance program. In addition to the LHID2000 database of 1,000,000 sampled subjects representing the residents of Taiwan, an additional catastrophic illness database for rare and complicated illnesses was generated by the NHRI. In the NHI database, 31 medical conditions, including several cancers, hemophilia, PSS and other autoimmune diseases, and end-stage renal disease, that may lead to catastrophic financial burden and subsequent impoverishment are classified as "catastrophic illness." Both of the databases contain all patient all medical claim records, including coverage for outpatient, inpatient, emergency, dental, traditional Chinese medicine services, and prescription drugs. The National Health Research Institute released the two datasets with the same format, and the code and methods to collect data in these two dataset were similar. The attending physician of a patient whose diagnosed illness falls within one of the catastrophic illness categories under the Department of Health guidelines can submit related information in an application for a catastrophic illness certificate (CIC). Patients with catastrophic illnesses are examined by specialists that form part of a committee of the Bureau of National Insurance. If approved, the patients are exempted from copayment for catastrophic expenditures. PSS is listed as a catastrophic illness and all cases identified from the CIC database should be confirmed. To get a CIC for PSS, at least one rheumatologist (typically the patient's attending physician) is required to provide relevant clinical and laboratory information as part of the application for review; the review committee will assess applications according to the criteria of the American College of Rheumatology for PSS. Because the NHIRD and catastrophic illness database consist of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review

Board. The encrypting procedure is consistent between these 2 databases, and the linkage of claims belonging to the same patient is therefore feasible within these databases.

Study population

We conducted a retrospective cohort study using data from January 1, 2000, to December 31, 2006. The cohort of patients with PSS was confined to those who were 18 years of age or older and had been approved for the CIC because of their PSS.[13] All patients who had PSS and had been identified from the CIC database were reviewed by specialists from the committee of the Bureau of National Insurance, according to the criteria of the American-European Consensus Group for PSS.[14] To avoid selection bias, we excluded PSS patients with any other autoimmune diseases, such as SLE, RA, and other connective tissue diseases, who should instead be classified as having secondary Sjögren's syndrome. One previous study has used this methodology.[13] To investigate the causal relationships, patients who had a history of AMI before obtaining a CIC for PSS were also excluded. We identified 5025 PSS patients who were newly diagnosed between 2000 and 2006 as our final PSS cohort. Information on comorbidities was also collected for analysis.

Control cohort

Subjects without any record of autoimmune diseases were used as the matched control cohort and were randomly selected from the remaining NHI beneficiaries registered in the LHID2000. Each PSS patient was matched with 1 control by age, sex, date of enrollment, and presence of comorbid disorders, including hypertension, diabetes, coronary artery disease (CAD), hyperlipidemia, chronic kidney disease, atrial fibrillation, and chronic obstructive pulmonary disease, within the same follow-up period. The same exclusion criteria as those of the PSS group were applied. A total of 5025 subjects served as the matched control cohort.

Occurrence of acute myocardial infarction

The endpoint of the study was the occurrence of AMI, identified by an insurance claim [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 410 to 410.92] as the primary diagnosis during ambulatory care visits, emergency care visits, or hospitalization during the follow-up period. All study subjects were followed-up until AMI, death, or until December 31, 2006, whichever came first. The diagnosis of AMI was made according to the World Health Organization guidelines, which specify that at least 2 of the 3 following criteria should be met: prolonged ($\geq$ 30 minutes) anterior chest discomfort; abnormal electrocardiography readings (ST segment elevation or depression, evolving Q waves, symmetric inversion of T waves); and elevated levels of cardiac enzymes (CK-MB, troponin T, or troponin I).[15]

Statistical analyses

Extraction and computation of data were performed using the Perl programming language (version 5.12.2), and Microsoft SQL Server 2005 (Microsoft Corp., Redmond, WA, USA) was used for data management and computing. Statistical analysis was performed using the SPSS software (version 17.0, SPSS Inc., Chicago, Illinois, USA). All data were expressed as the frequency (percentage) for ordinal and categorical data or as mean $\pm$ standard deviation (SD) for continuous data. Continuous data for the study group and comparison group were compared by the Student's *t*-test. Categorical data were compared with the chi-square test and Yates' correction or Fisher's exact test, as appropriate. To assess the risk of developing AMI during the follow-up period of up to 7 years, the Kaplan-Meier method was used. Multivariate regression analysis was performed using the Cox proportional hazards model with adjustment for confounding factors such as age, sex, and comorbid disorders. Variables of comorbidities were treated as time-varying covariates in the Cox model. $p < 0.05$ was considered statistically significant.

RESULTS

The data of 5025 PSS patients and 5025 controls were analyzed. The mean $\pm$ SD age of the study subjects was 53.2 $\pm$ 14.1 years, and the median follow-up duration was 3.7 years (interquartile range, 2.1-5.1 years), with a maximum follow-up period of 7 years. During 37,185 patient-years of follow-up, 77 patients (0.77%) were diagnosed with AMI, of which 35 were PSS pa-

tients (0.70%) and 42 were controls (0.83%). Table 1 shows the baseline characteristics of the PSS patients and controls. The mean follow-up duration and baseline comorbidities were similar between the PSS patients and the controls. The prevalence of previous stroke, peripheral artery disease, and valvular heart disease was higher among PSS patients than controls. Table 2 shows the baseline characteristics of patients with and without AMI development during follow-up. Older patients and men had a higher incidence of AMI. Patients who developed AMI also had more comorbid disorders, including hypertension, diabetes, CAD, hyperlipidemia, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and previous stroke.

Figure 1 shows the results of the log-rank test and Kaplan-Meier survival analysis. During the maximum 7-year follow-up period, AMI-free survival rate was similar between PSS patients and controls (p = 0.470 by log-rank test). Table 3 shows the association between PSS and the risk of subsequent AMI. The crude hazards

Table 1. Baseline characteristics and medication use of the study population

	Primary Sjögren's syndrome		p value
	No (n = 5,025)	Yes (n = 5,025)	
Age, years	53.2 ± 14.1	53.0 ± 14.1	NS
Follow-up duration, years	3.7 ± 1.8	3.7 ± 1.9	NS
Male, n (%)	651 (13.0)	651 (13.0)	NS
Hypertension, n (%)	1,633 (32.5)	1,614 (32.1)	NS
Diabetes, n (%)	1,056 (21.0)	1,050 (20.9)	NS
CAD, n (%)	1,202 (23.9)	1,189 (23.7)	NS
Hyperlipidemia, n (%)	1,421 (28.3)	1,378 (27.4)	NS
Chronic kidney disease, n (%)	692 (13.8)	692 (13.8)	NS
Atrial fibrillation, n (%)	67 (1.3)	65 (1.3)	NS
COPD, n (%)	1,356 (27.0)	1,349 (26.8)	NS
Previous stroke, n (%)	324 (6.4)	465 (9.3)	< 0.001
PAD, n (%)	224 (4.5)	324 (6.4)	< 0.001
Valvular heart disease, n (%)	285 (5.7)	530 (10.5)	< 0.001

Data are mean ± SD or median (interquartile range) values; t test and chi-square test were used for evaluating continuous and categorical variables, respectively.
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NS, non-significant; PAD, peripheral artery disease.

Table 2. Demographic data of the study population with or without acute myocardial infarction

	Acute Myocardial Infarction		p value
	No (n = 9,973)	Yes (n = 77)	
Age, years	53.1 ± 14.1	68.5 ± 10.8	< 0.001
Male, n (%)	1,275 (12.8)	27 (35.1)	< 0.001
Hypertension, n (%)	3,186 (31.9)	61 (79.2)	< 0.001
Diabetes, n (%)	2,067 (20.7)	39 (50.6)	< 0.001
CAD, n (%)	2,346 (23.5)	45 (58.4)	< 0.001
Hyperlipidemia, n (%)	2,762 (27.7)	37 (48.1)	< 0.001
Chronic kidney disease, n (%)	1,366 (13.7)	18 (23.4)	0.019
Atrial fibrillation, n (%)	129 (1.3)	3 (3.9)	NS
COPD, n (%)	2,661 (26.7)	44 (57.1)	< 0.001
Previous stroke, n (%)	773 (7.8)	16 (20.8)	< 0.001
PAD, n (%)	540 (5.4)	8 (10.4)	NS
Valvular heart disease, n (%)	806 (8.1)	9 (11.7)	NS

Data are mean ± SD values; t test and chi-square test were used for evaluating continuous and categorical variables, respectively.
CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NS, non-significant; PAD, peripheral artery disease.

ratio (HR) for AMI in PSS patients was 0.85 [95% confidence interval (CI), 0.54-1.33; p = 0.470]. After adjustment for other confounders such as age, sex, and comorbid disorders, the risk of AMI remained similar between PSS patients and controls (HR, 0.86; 95% CI, 0.55-1.35; p = 0.506). Figure 2 shows a stratified analysis of PSS and AMI risk among variable subgroups. Patients with PSS did not have a higher risk of AMI in different subgroups.

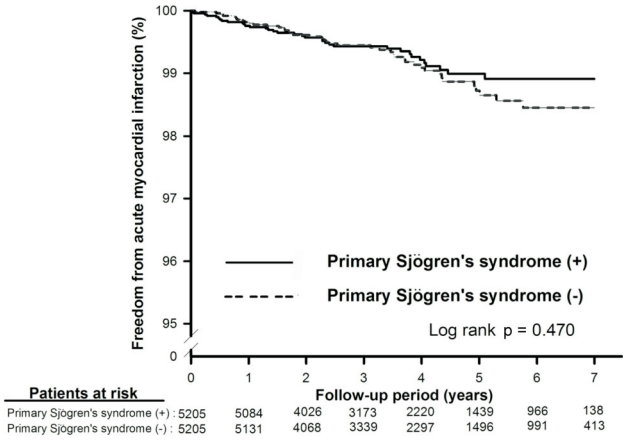

Figure 1. *Kaplan-Meier estimates of AMI-free survival rates of acute myocardial infarction (AMI) in primary Sjögren's syndrome (PSS) patients and controls. The AMI-free survival rates were similar between the 2 groups (p = 0.470 by log-rank test).*

DISCUSSION

There is convincing evidence that autoimmune rheumatic diseases such as SLE and RA are associated with increased rates of cardiovascular morbidity and mortality.[5-7,16] PSS is a connective tissue disease that mainly affects the exocrine glands. It shares several clinical manifestations and laboratory features typical of SLE and RA, such as polyclonal hypergammaglobuli-

Table 3. Association between primary Sjögren's syndrome (PSS) and acute myocardial infarction (AMI)

	AMI, n (%)		Incidence	Hazard ratio (95% CI)			
				Unadjusted HR	Adjusted HR		
Patient groups	Yes	No	(per 1000 person-years)		Model 1*	Model 2†	Model 3‡
Controls (n = 5,025)	42 (0.8)	4,983 (99.2)	2.25	1.00	1.00	1.00	1.00
PSS (n = 5,025)	35 (0.7)	4,990 (99.3)	1.91	0.85 (0.54-1.33)	0.86 (0.55-1.35)	0.84 (0.54-1.32)	0.86 (0.55-1.35)

AMI, acute myocardial infarction; PSS, primary Sjögren's syndrome.
*Model 1: Adjusted for age and gender; †Model 2: Adjusted for age, gender, hypertension, diabetes, coronary artery disease, hyperlipidemia, and ischemic stroke; ‡Model 3: Adjusted for age, gender, hypertension, diabetes, coronary artery disease, hyperlipidemia, ischemic stroke, chronic kidney disease, atrial fibrillation, chronic obstructive pulmonary disease, peripheral artery disease, and valvular heart disease.

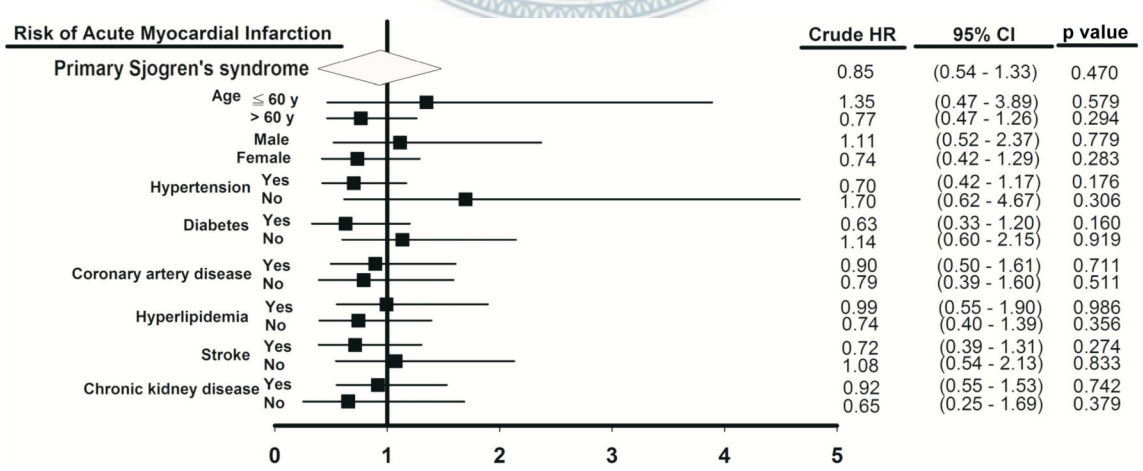

Figure 2. *Association between primary Sjögren's syndrome and acute myocardial infarction in specific subgroups, identified by Cox regression analysis. CI, confidence interval; HR, hazard ratio.*

nemia, circulating antibiotics, chronic inflammation of the exocrine glands, and frequent joint involvement during the course of the disease. However, there are few large epidemiologic studies on cardiovascular risk in PSS patients. In the present study, the risk of AMI was similar between PSS patients and age-, gender-, and comorbidity-matched controls. To the best of our knowledge, this is the largest study investigating the risk of AMI in PSS, especially in an Asian population.

Although several hypotheses have been proposed in support of a link between autoimmune diseases and atherosclerosis, the connection between these diseases remains unclear. SLE and RA are associated with endothelial dysfunction as detected by flow-mediated vasodilation (FMV) and accelerated atherosclerosis.[17,18] In addition, it is well-known that endothelial dysfunction can precede arterial wall thickening and predict future cardiovascular manifestations in the general population.[19] However, research on the link between PSS and cardiovascular disease has been limited. A recent study by Gerli et al. showed that there was no significant loss of FMV in 45 women with PSS, compared to that in matched controls.[20] These results suggest that PSS patients have normal endothelium-dependent vasodilatation, which may support our findings. Another possible explanation for our findings may be the disease duration. Rachapalli et al. demonstrated that ankle-brachial index, a simple method of identifying patients who are at high risk of premature death and vascular events,[21] was not significantly reduced in PSS patients, except in patients with disease duration of more than 10 years.[22] In the current study, we identified newly diagnosed PSS patients and followed them for up to 7 years. A longer follow-up duration may be necessary in future studies to accurately assess cardiovascular risk in PSS patients.

Two previous case-control studies attempted to link PSS with cardiovascular and metabolic abnormalities in a small series of PSS patients. Both of these studies excluded PSS patients with previous cardiovascular diseases. Lodde et al. found abnormalities of serum lipid profile in patients with PSS.[8] Vaudo et al., on the other hand, showed an increased rate of subclinical atherosclerosis in female PSS patients, as determined by femoral and carotid ultrasonography.[11] Another recent study that analyzed the main cardiovascular risk factors associated with PSS found an increased frequency of diabetes mellitus and hypertriglyceridemia and a decreased frequency of hypertension and smoking in 312 PSS patients compared to that in 312 age- and sex-matched controls.[10] Although these previous studies assessed the cardiovascular risk factors associated with PSS, whether PSS patients have higher incidence of major cardiovascular events and poorer cardiovascular outcomes remains undetermined. Our current study demonstrated that patients with PSS have a similar risk of AMI as controls, thus providing evidence linking the results of the previous case-control studies to clinical cardiovascular outcomes.

Our findings are partially consistent with those of previous studies. Theander et al. followed 484 patients with a median follow-up period of 7 years and demonstrated that the overall mortality of PSS patients was not related to cardiovascular disease.[23] Another study enrolled 312 PSS patients and showed no differences in the prevalence of cardiovascular events between PSS patients and age- and sex-matched controls.[10] In concurring with this study, we found that nearly one-quarter of PSS patients had at least 3 cardiovascular risk factors. Age and male gender are well-recognized risk factors for AMI and our results corroborate these findings in PSS patients. Furthermore, after considering conventional cardiovascular risk factors, the risk of AMI remained similar in PSS and controls.

There is currently no consensus on the management of cardiovascular risk in PSS patients. Our findings suggest that traditional cardiovascular risk factors such as age, male gender, hypertension, diabetes, coronary artery disease, hyperlipidemia, chronic kidney disease, and previous stroke may have a higher impact on future AMI risk than PSS. However, the incidence of cardiovascular risk factors in PSS patients is high, making the control of traditional cardiovascular risk factors such as blood pressure, fasting sugar, and lipid profiles mandatory during the routine clinical follow-up of PSS patients.

Although previous studies have shown evidence of cardiovascular and metabolic abnormalities in PSS patients, these studies were limited by the low number of cases included. The strength of our study was the use of a population-based dataset and the enrollment of a large number of subjects, which enabled us to prospectively examine the differences between the 2 groups analyzed. Furthermore, certification of PSS as a cata-

strophic illness is strict and exempts patients from related medical expenses in the NHI system in Taiwan. The verification of PSS status must be supported by medical records, examination reports, and a diagnosis made by at least 1 rheumatologist. There are, however, some limitations to our study. First, certain patient data that may influence the risk of AMI, such as smoking status, body mass index, dietary habits, alcohol consumption, and family history of cardiovascular disease, were not available for analysis. Second, autoantibody data are not available in the NHI dataset, and we could not evaluate the severity of PSS. Third, the diagnosis of AMI was based on the administrative claim data reported by physicians or hospitals.[15] There is no information regarding the severity and extent of AMI, both from a clinical and also radiological point of view. Previous epidemiological studies conducted using the LHID showed results consistent with population-based surveys for several conditions.[24] Furthermore, to maximize the accuracy of diagnostic coding in medical claims, the NHI has extensive and systemic quality assurance processes, including routine crosschecking of chart reviews by clinical specialists. Because cardiovascular events such as myocardial infarction and stroke are critical illnesses causing severe disability, almost all such patients require medical treatment.[15] A previous validation study comparing ICD coding and hospital record reviews in Taiwan showed that the sensitivity and specificity for major cardiovascular events such as stroke were 100% and 95%, respectively, suggesting a high positive predictive value for major cardiovascular events requiring hospitalization.[25] Another study also demonstrated a high positive predictive value of up to 95% for the diagnosis of AMI after comparing ICD coding data from Medicare claims to diagnosis based on a structured review of hospital records,[26] further supporting the accuracy of AMI diagnosis in our study. Finally, the current study did not investigate whether the use of medications for PSS, such as steroids, antimalarials, immunosuppressive agents, anti-platelet agents, or lipid-lower agents further reduces AMI risk in PSS patients.

CONCLUSIONS

Our results show that PSS is not associated with an increased risk of subsequent AMI in Taiwan. Larger prospective epidemiological studies with longer follow-up duration are required to clarify our findings. Future studies should determine whether medical treatment of PSS further reduces cardiovascular risk.

DISCLOSURE

All authors state that they have no conflicts of interest.

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AUTHORS' ROLES

All the authors participated in the conception, design, drafting, and revision of the manuscript and in data interpretation.

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