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Primary Sjogren's Syndrome Increases the Risk of Acute Pancreatitis : A Nationwide Cohort Study

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Short Title: Primary Sjogren's Syndrome Increases the Risk of Acute Pancreatitis

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ABSTRACT

Objective: Studies on the risk of acute pancreatitis in primary Sjogren's syndrome (pSS) patients are limited. We evaluated the effects of pSS on the risk of acute pancreatitis in a nationwide, population-based cohort in Taiwan.

Study Design: Population-based retrospective cohort study.

Setting: We studied the claims data of the >97% Taiwan population from 2002 to 2012.

Participants: We identified 9,468 pSS patients by using the catastrophic illness registry of the National Health Insurance Database in Taiwan. We also selected 37,872 controls that were randomly frequency matched by age (in 5-year bands), sex, and index year from the general population.

Primary outcome measure: We analyzed the risk of acute pancreatitis by using Cox proportional hazards regression models including sex, age, and comorbidities.

Results: From 23.74 million people in the cohort, 9,468 pSS patients (87% women, mean age = 55.6 years) and 37,872 controls were followed-up for 4.64 and 4.74 years, respectively. A total of 44 cases of acute pancreatitis were identified in the pSS cohort versus 105 cases in the non-pSS cohort. Multivariate Cox regression analysis indicated that the incidence rate of acute pancreatitis was significantly higher in the pSS cohort than in the non-pSS cohort (adjusted hazard ratio [aHR] 1.48, 95%

confidence interval [CI] 1.03-2.12). Cyclophosphamide use increased the risk of acute pancreatitis (aHR 5.27, 95% CI 1.16-23.86). By contrast, hydroxychloroquine reduced the risk of acute pancreatitis (aHR 0.23, 95% CI 0.09-0.55).

Conclusion: This nationwide, retrospective cohort study demonstrated that the risk of acute pancreatitis was significantly higher in pSS patients than in the general population.

Keywords: primary Sjogren's syndrome, risk, acute pancreatitis

Strengths and limitations of this study

1. This is the first nationwide population-based cohort study that demonstrated the patients with Sjogren's syndrome increase the risk of acute pancreatitis.
2. Data on alcoholism and smoking, the major risk factors of acute pancreatitis, were unavailable in our study. However, no reports have mentioned the relationship between pSS and alcoholism.
3. Because of the lack of data on the severity of pSS, laboratory results, and indications for medication use, we could not determine the mechanism of pancreatitis.

INTRODUCTION

Sjogren's syndrome (SS) is a slowly progressive systemic autoimmune disease that may present either alone as primary SS (pSS) or, in association with an underlying autoimmune disease, as secondary SS. Systemic manifestations may result from cutaneous, respiratory, renal, hepatic, neurologic, and vascular involvement.[1] However, it mainly affects the salivary and lachrymal glands and leads to keratoconjunctivitis sicca and xerostomia because of focal inflammation.[2] The pancreas is, in part, an exocrine gland that is functionally and histologically comparable to the salivary glands. Involvement of pancreatic dysfunction in SS has been hypothesized.[3]

Acute pancreatitis, an inflammatory disorder of the pancreas, is the leading cause of admission for gastrointestinal disorders and may be fatal or lead to severe complications in certain cases. In addition to typical risk factors such as aging, alcoholism, smoking, gallstone, anatomic abnormalities, and metabolic factors, patients with autoimmune diseases have been shown to have a higher risk of autoimmune pancreatitis (AIP).[4] Many reports have mentioned the association between pSS and AIP.[5-7] In the largest series of pSS patients (1,010 patients), the prevalence of acute pancreatitis was 0.5%.[8] Despite these case reports and the case series of pSS-related acute pancreatitis[8,9], no cohort study has evaluated the risk of

acute pancreatitis in pSS patients. This risk should be assessed in a large population because of the low incidence rate.

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was began in 1995 and offers comprehensive medical care coverage almost all Taiwanese residents. The validity of the National Health Insurance Database in Taiwan has been evaluated, and research articles have been accepted worldwide for public access.[10-12] By using the National Health Insurance (NHI) dataset, we conducted a nationwide cohort study to investigate the risk of acute pancreatitis in pSS patients and related risk factors.

METHODS

Data source

The cohort from National Health Insurance (NHI) database was analyzed in this study. The bureau of NHI in Taiwan maintains a research-oriented database through the Health and Welfare Statistics Application Center (HWSAC) of the Ministry of Health and Welfare; this database includes all the original claims health care data of >97% of the entire Taiwanese population (23.74 million people). Comprehensive information on insurants, including demographic data, dates of clinical visits, and disease diagnoses, is included in the database. The diagnostic codes used were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We studied the data of the Taiwanese population from 2002 to 2012. The study was approved by the Institutional Review Board of Taipei Medical University (approval number: N201509007). As the datasets used in this study consist of de-identified secondary data released to the public for research purpose, no consent was needed for the review by the ethical review board.

Study population and design

In Taiwan, rheumatologists can apply for a catastrophic illness card for any SS patient who fulfills the criteria of the American–European Consensus Group (AECG) for SS.[3] The application of the catastrophic illness card is scrutinized in a peer review process. SS patients with the catastrophic illness card can be exempted from

copayment. We used the Registry for Catastrophic Illness Patients in NHI database to identify SS (ICD-9-CM Code 710.2) patients in the claims data, and the first-time SS diagnosis served as the index date from 2002 to 2012. In addition, we excluded patients with comorbidities such as systemic lupus erythematous, rheumatoid arthritis, scleroderma, polymyositis, and dermatomyositis to limit our study sample to pSS. pSS patients and comparison controls (non-pSS) were frequency matched at a 1:4 ratio by age (in 5-year bands), sex, and index year.

Outcome measures and case identification

The primary outcome was newly diagnosed acute pancreatitis from hospitalization records. All participants were followed-up from the index date to the date of the primary outcome, withdrawal from the NHI program, or the end of 2012, whichever came first. We identified patients with a discharge diagnosis of acute pancreatitis (ICD-9-CM Code 577.0 in any position of the five diagnosed codes). To overcome this misclassification bias, we included only patients who had been hospitalized to minimize false positive cases. In studies using the same database, the positive predictive value was high (90.0%) among randomly selected hospitalized patients coded with acute pancreatitis.[11,12] Patients who had been diagnosed with acute pancreatitis before the index date or chronic pancreatitis (ICD-9-CM Code 577.1) and those with incomplete age or sex information were excluded from this study. In Taiwan, the medical reimbursements and discharge notes of acute pancreatitis patients

are scrutinized in a peer review process.

Exposure variables

In addition to pSS, demographic characteristics such as sex, age, and comorbidities were analyzed. Preexisting comorbidities included diabetes mellitus (ICD-9-CM Code 220), hyperlipidemia (ICD-9-CM Codes 272.0-272.4), hypertriglyceridemia (ICD-9-CM Code 272.1), alcoholism (ICD-9-CM Codes 291, 303, 305.00-305.03, 571.0-571.3), gallstones (ICD-9-CM Codes 574.10 or 574.20), hepatitis B (ICD-9-CM Codes 070.2 or 070.3), and hepatitis C (ICD-9-CM Codes 070.4 or 070.5). Furthermore, we examined the potential effects of common therapies for pSS, including disease-modifying antirheumatic drugs (DMARDs; hydroxychloroquine, sulfasalazine, methotrexate, cyclophosphamide, cyclosporin, mycophenolate mofetil, and azathioprine) and steroids. Each medication was assessed as a time-dependent covariate constructed according to the prescription for each month. The drug exposure status was set to 0 if no prescription was filled during the period and set to 1 if at least one prescription was filled during the period. Steroids were analyzed as the average daily dose equivalent to prednisolone during the study period.

Statistical analysis

The SAS 9.3 statistical package (SAS Institute Inc., Cary, NC, USA) was used to

perform all analyses in this study. We examined differences in continuous variables between the two cohorts by using a Student *t* test, and we examined differences in dichromatic variables of the potential confounders between the two cohorts by using a Pearson χ^2 test.

The incidence rate is expressed per 100,000 person-years. The cumulative incidence of acute pancreatitis was assessed using the Kaplan–Meier estimator, with significance based on the log-rank test. The Cox proportional hazard regression model was used to analyze the risk of acute pancreatitis. Age, sex, and baseline comorbidities were adjusted in multivariate analysis. Crude and adjusted hazard ratios (HRs) are presented along with 95% confidence intervals (CIs). Each type of drug was separately analyzed as a time-dependent effect in the Cox proportional hazard regression model. The HRs of each type of drug could be explained as follows. In any given month, if a patient used the given type of drug, the risk of acute pancreatitis would averagely increase (HR > 1)/decrease (HR < 1) compared with a patient who did not use the given type of drug. The results of all statistical tests were considered significant if the two-sided *P* value was ≤0.05.

RESULTS

Baseline characteristics of the study population

During the study period, a total of 13,673 SS patients were identified. We excluded 3,911 secondary SS patients, 38 patients with incomplete age or sex information, 59 patients aged <18 years, 139 patients with a history of acute pancreatitis, and 58 with CP before the enrollment date. In total, 9,468 pSS patients were enrolled. We randomly selected and studied age- and sex-matched non-pSS controls with the same exclusion criteria, who were four times the number of pSS patients (**Table 1**). The mean age of pSS patients was 55.6 years, and the majority (87.23%) was female. The mean follow-up period of pSS and matched cohorts was 4.64 and 4.73 years, respectively. In the pSS cohort, hyperlipidemia, gallstones, and viral hepatitis (B or C) at baseline were more prevalent ($P < 0.001$). During the follow-up period, the pSS cohort had a significantly higher incidence of acute pancreatitis (0.46% versus 0.28%; $P = 0.005$) and a higher incidence rate of acute pancreatitis (100.0 versus 58.6 per 100,000 person-years) than the control cohort. **Figure 1** shows the Kaplan–Meier analysis, which also revealed a significantly higher cumulative incidence of acute pancreatitis in pSS patients compared with that in matched controls (log rank test $P = 0.0025$)

<Table 1 inserted here>

<Figure 1 inserted here>

Comorbidities and acute pancreatitis based on univariate and multivariate Cox proportional hazard analyses

The HR of developing acute pancreatitis during the follow-up period was 1.71 (95% CI 1.20-2.43) in pSS patients compared with that in non-pSS patients (**Table 2**). After adjustment for patients' sex, age, and other comorbidities, the hazard of developing acute pancreatitis during the follow-up period was 1.48 (95% CI 1.07-2.193) times greater in pSS patients compared with that in non-pSS patients. This finding suggests that pSS is an independent risk factor for acute pancreatitis. In addition, older age, DM, and gallstones increased the risk of acute pancreatitis (aHR 1.61, 2.39, and 5.49, respectively).

<Table 2 inserted here>

Risk factors for acute pancreatitis in pSS patients

In pSS patients, the univariate Cox regression model revealed that male sex, age more than 65 years, DM, gallstone, daily steroids over 5-mg prednisolone equivalent, and time-dependent DMARDs of hydroxychloroquine and cyclophosphamide were significant factors associated with acute pancreatitis (**Table 3**). The multivariate Cox regression model indicated that statistically significant risk factors for acute pancreatitis included age more than 65 years (aHR 2.92, 95% CI 1.27-6.75), gallstones (aHR 5.05, 95% CI 2.10-12.16), daily steroids over 5-mg prednisolone equivalent (aHR 7.66, 95% CI 3.71-15.84), and cyclophosphamide use (aHR 5.27,

95% CI 1.16-23.86), whereas hydroxychloroquine use reduced the risk (aHR 0.23, 95% CI 0.09-0.55).

<Table 3 inserted here>

DISCUSSION

This nationwide, population-based study in Taiwan demonstrated that 9,468 pSS patients had a significantly higher risk of acute pancreatitis compared with the risk in 37,872 matched controls, with an aHR of 1.48 after adjustment for age, sex, and comorbidities. The incidence rate of acute pancreatitis in pSS patients was 100.05 per 100,000 person-years. The risk factors for acute pancreatitis included age more than 65 years, gallstones, daily steroids over 5-mg prednisolone equivalent, cyclophosphamide use, and no hydroxychloroquine use.

To the best of our knowledge, this is the first cohort study to prove that pSS patients have a higher risk of acute pancreatitis. The validity of this study is supported by the stringent study design. First, patients with catastrophic illness certification for pSS can be exempted from copayment in the NHI system. The verification requires fulfillment of the AECG criteria after peer review. We also excluded patients diagnosed with other autoimmune diseases. Thus, we believe that our pSS cohort is exhaustive and reliable. Second, this national large cohort was less vulnerable to selection bias and was suitable for studying rare complications and related risk factors.

The prevalence rate of acute pancreatitis in our pSS cohort was 0.46%, which is similar to the result obtained in a cohort study in Spain.[8] The largest case series reported five cases of pSS-related acute pancreatitis among 1,010 pSS patients (0.5%).

Furthermore, our study revealed that the pSS cohort had a significantly higher risk of acute pancreatitis than age- and sex-matched controls. Comorbidities such as alcoholism, DM, hepatitis B, hepatitis C, and hyperlipidemia had significantly higher prevalence rates in our pSS cohort. However, we believe the higher rates of these comorbidities might due to the characteristics associated with pSS patients or, more likely, a higher diagnosis rate caused by the higher medical usage rate in the pSS cohort. Moreover, our conservative analysis revealed pSS to be a significant independent risk factor for acute pancreatitis after correcting for these comorbidities.

The risk factors of older age and gallstone were common between our pSS cohort and the general population. In addition, we found that medication use was associated with acute pancreatitis in pSS patients. Limited studies have examined the association between steroids or DMARDs and acute pancreatitis. Immunosuppressants such as azathioprine and cyclosporin have been implicated as causes of pancreatitis in several case reports. Badalov et al. found that cyclophosphamide use was associated with acute pancreatitis, which was also observed in our pSS cohort.[13] In this claims-data-based study, it was unclear whether cyclophosphamide increased the risk through drug toxicity or was a marker of systemic manifestations in the pSS cohort. However, autoimmune-related inflammation was suspected on the basis of the association with higher daily steroid

use and no HCQ use. A similar finding was obtained for SLE-related acute pancreatitis and AIP.[14,15] AIP was found to be associated with autoimmune diseases (SS, rheumatoid arthritis, primary sclerosing cholangitis, and inflammatory bowel disease).[16] Vascular damage, including vasculitis, intimal thickening, immune complex deposition, and occlusion of arteries and arterioles); autoantibody production; and abnormal cellular immune response may be responsible for the development of pancreatitis.[17] Patients with a higher daily steroid dose and cyclophosphamide therapy and without HCQ use might have a higher risk of autoimmune-related pancreatitis.

Our study has clinical implications. First, acute pancreatitis is a rare complication among pSS patients and should be considered one of the differential diagnoses of abdominal pain. Second, judicious hydroxychloroquine might be considered as a risk factor, particularly among those with higher daily steroid use or cyclophosphamide treatment. Administrative databases enable population-based epidemiologic studies; however, limitations exist. First, some data are unavailable in this claims-based data set. Data on alcoholism and smoking, the major risk factors of acute pancreatitis, were unavailable in our study. However, no reports have mentioned the relationship between pSS and alcoholism. The defected oral mucosa of pSS patients might be susceptible to stimulation by alcohol. Furthermore, because of the lack of data on the severity of pSS, laboratory results, and indications for medication use, we could not

determine the mechanism of pancreatitis. Second, IgG4-related disease may involve salivary and lacrimal glands and AIP.[18] However, in the NHIRD, the certification of pSS requires a positive anti-Ro or/and anti-La antibodies or a positive lip biopsy. In addition, the observed lower risk in those using HCQ, which is not beneficial to IgG4-related disease, also implied the limited effect of IgG4-related disease in our study.

In conclusion, we demonstrated that pSS patients had a higher risk of acute pancreatitis, and the magnitude of hazard in the pSS-affected population was 48% higher than that in the non-pSS population. On the basis of these findings, pSS patients should be carefully monitored for acute pancreatitis.

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Chi-Ching Chang contributed to the conception and design of the work, drafting of the article, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Yu-Sheng Chang** contributed to interpretation of data, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Shu-HungWang and Shyr-Yi Lin** contributed to the analysis of data, revision of the article critically for crucial

intellectual content, and final approval of the version to be published. **Yi-Hsuan Chen** contributed to the analysis of the data, drafting of the article, and final approval of the version to be published. **Jin-Hua Chen** designed the study and conceived the work, completed the analysis, revised the article critically for crucial intellectual content, and corresponded for final approval of the version to be published. All authors have disclosed any potential competing financial interests regarding the submitted article.

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Table 1. Baseline characteristics and follow-up status of the primary Sjogren's syndrome (pSS) cohort and the age- and sex-matched comparison cohort

Group	Comparison cohort (N = 37,872)	pSS cohort (N = 9,468)	
Variable	n(%)	n(%)	*P* value*
Sex			1.00
Male	4,836(12.77)	1,209(12.77)	
Female	33,036(87.23)	8,259(87.23)	
Age, mean (SD)	55.61(14.33)	55.64(14.26)	0.863
Age groups			0.996
≤50	12,945(34.18)	3,241(34.23)	
51-65	14,643(38.66)	3,658(38.64)	
>65	10,284(27.15)	2,569(27.13)	
Baseline comorbidity			
Alcoholism	73(0.19)	36(0.38)	<0.001
Diabetes mellitus	4,327(11.43)	1,095(11.57)	0.702
Gallstone	423(1.12)	272(2.87)	<0.001
Hepatitis B	501(1.32)	321(3.39)	<0.001
Hepatitis C	324(0.86)	367(3.88)	<0.001
Hyperlipidemia	4,716(12.45)	1,498(15.82)	<0.001
Hypertriglyceridemia	187(0.49)	59(0.62)	0.117
No. of comorbidities§			<0.001
0	30,028(79.29)	6,674(70.49)	
1	5,512(14.55)	2,108(22.26)	
2	2,217(5.85)	616(6.51)	
≥3	115(0.30)	70(0.74)	
Follow-up duration, mean (SD)	4.73(2.78)	4.64(2.78)	0.005
No. of acute pancreatitis (AP)	105(0.28)	44(0.46)	0.005
AP incidence per 100,000 person-years	58.56	100.05	0.004

**P* values were calculated using the chi-square test for categorical variables or the *t* test for continuous variables; the *P* value for incidence was calculated using the exact Poisson test.

§The No. of comorbidity was counted from the predescribed baseline comorbidity, except hypertriglyceridemia (a subgroup of hyperlipidemia).

Table 2. Cox regression analysis for the risk of acute pancreatitis

	Univariate Analysis		Multivariate Analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary Sjogren's syndrome	1.71 (1.20-2.43)	0.003	1.48 (1.03-2.12)	0.034
Sex (male)	1.78 (1.21-2.63)	0.004	1.42 (0.96-2.12)	0.083
Age groups (reference: age≤50)				
51-65	1.93 (1.20-3.12)	0.007	1.61 (0.99-2.12)	0.055
>65	4.01 (2.54-6.31)	<0.001	2.90 (1.81-4.67)	<0.001
Baseline comorbidity				
Diabetes mellitus	3.30 (2.30-4.73)	<0.001	2.39 (1.65-3.46)	<0.001
Gallstone	7.78 (4.56-13.27)	<0.001	5.49 (3.19-9.46)	<0.001
Hepatitis B	2.27 (0.93-5.53)	0.072	1.84 (0.74-4.54)	0.189
Hepatitis C	3.39 (1.59-7.25)	0.002	2.06 (0.95-4.51)	0.069
Hyperlipidemia	1.83 (1.22-2.75)	0.004	--	
Hypertriglyceridemia	1.34 (0.19-9.56)	0.085	--	
No. of comorbidities				
0	1.00			
1	2.51 (1.72-3.68)			
≥2	4.97 (3.24-7.65)			

HR: hazard ratio; CI: confidence interval

*All variables, except No. of comorbidities, were selected using stepwise Cox regression analysis with entry and retention criteria at $P \leq 0.2$ in multivariate analysis

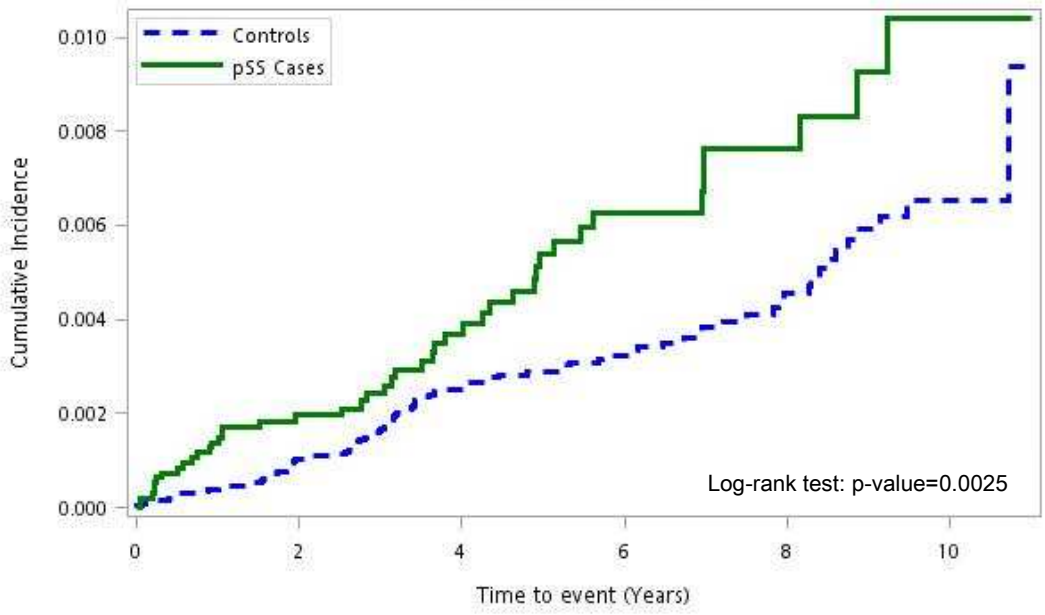
Table 3. Cox regression analysis for the risk of acute pancreatitis among pSS patients

	Univariate Analysis		Multivariate Analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	2.44 (1.26-4.74)	0.009	1.64 (0.82-3.26)	0.161
Age groups (reference: age≤50)				
51-65	1.42 (0.58-3.48)	0.441	1.17 (0.47-2.90)	0.739
>65	4.22 (1.89-9.39)	<0.001	2.92 (1.27-6.75)	0.012
Baseline comorbidity				
Diabetes mellitus	2.10 (1.01-4.37)	0.047	1.47 (0.70-3.12)	0.313
Gallstone	5.60 (2.37-13.24)	<0.001	5.05 (2.10-12.16)	<0.001
Hepatitis B	2.28 (0.71-7.37)	0.168	--	--
Hepatitis C	2.21 (0.79-6.20)	0.130	--	--
Hyperlipidemia	1.10 (0.49-2.47)	0.817	--	--
Hypertriglyceridemia	NA	NA	--	--
Steroid PO dose>5 mg (equal to prednisolone)	6.99 (3.53-13.88)	<0.001	7.66 (3.71-15.84)	<0.001
Time-dependent drug effect				
Hydroxychloroquine	0.26 (0.11-0.62)	0.002	0.23 (0.09-0.55)	0.001
Cyclophosphamide	9.61 (2.26-39.27)	0.002	5.27 (1.16-23.86)	0.031
Azathioprine	1.88 (0.45-7.78)	0.384	--	--
Cyclosporin	NA	NA	--	--
Sulfasalazine	NA	NA	--	--
Methotrexate	NA	NA	--	--
Mycophenolate mofetil	NA	NA	--	--

HR: hazard ratio; CI: confidence interval; NA: not available (did not converge)

*Age groups, sex, and other variables with $P < 0.05$ were selected in multivariate analysis

Figure 1. Cumulative incidence of acute pancreatitis in the primary Sjogren's syndrome cohort and the comparison cohort



STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8,9
		(*e*) Describe any sensitivity analyses	8,9

Section/Topic	Item No	Recommendation	Reported on Page No
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	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11,12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11,12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11,12
		Cross-sectional study—Report numbers of outcome events or summary measures	11,12
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	11,12
		(*b*) Report category boundaries when continuous variables were categorized	11,12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11,12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13,14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	1

**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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Primary Sjogren's Syndrome Increases the Risk of Acute Pancreatitis : A Nationwide Cohort Study

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Primary Sjogren's Syndrome Increases the Risk of Acute Pancreatitis : A Nationwide Cohort Study

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Short Title: Primary Sjogren's Syndrome Increases the Risk of Acute Pancreatitis

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Declaration of interests : All authors declare no conflicts of interest for this work

ABSTRACT

Objective: Studies on the risk of acute pancreatitis in primary Sjogren's syndrome (pSS) patients are limited. We evaluated the effects of pSS on the risk of acute pancreatitis in a nationwide, population-based cohort in Taiwan.

Study Design: Population-based retrospective cohort study.

Setting: We studied the claims data of the >97% Taiwan population from 2002 to 2012.

Participants: We identified 9,468 pSS patients by using the catastrophic illness registry of the National Health Insurance Database in Taiwan. We also selected 37,872 controls that were randomly frequency matched by age (in 5-year bands), sex, and index year from the general population.

Primary outcome measure: We analyzed the risk of acute pancreatitis by using Cox proportional hazards regression models including sex, age, and comorbidities.

Results: From 23.74 million people in the cohort, 9,468 pSS patients (87% women, mean age = 55.6 years) and 37,872 controls were followed-up for 4.64 and 4.74 years, respectively. A total of 44 cases of acute pancreatitis were identified in the pSS cohort versus 105 cases in the non-pSS cohort. Multivariate Cox regression analysis indicated that the incidence rate of acute pancreatitis was significantly higher in the pSS cohort than in the non-pSS cohort (adjusted hazard ratio [aHR] 1.48, 95%

confidence interval [CI] 1.03-2.12). Cyclophosphamide use increased the risk of acute pancreatitis (aHR 5.27, 95% CI 1.16-23.86). By contrast, hydroxychloroquine reduced the risk of acute pancreatitis (aHR 0.23, 95% CI 0.09-0.55).

Conclusion: This nationwide, retrospective cohort study demonstrated that the risk of acute pancreatitis was significantly higher in pSS patients than in the general population.

Keywords: primary Sjogren's syndrome, risk, acute pancreatitis

Strengths and limitations of this study

1. This is the first nationwide population-based cohort study that demonstrated the patients with Sjogren's syndrome increase the risk of acute pancreatitis.
2. Data on alcoholism and smoking, the major risk factors of acute pancreatitis, were unavailable in our study. However, no reports have mentioned the relationship between pSS and alcoholism.
3. Because of the lack of data on the severity of pSS, laboratory results, and indications for medication use, we could not determine the mechanism of pancreatitis.

INTRODUCTION

Sjogren's syndrome (SS) is a slowly progressive systemic autoimmune disease that may present either alone as primary SS (pSS) or, in association with an underlying autoimmune disease, as secondary SS. Systemic manifestations may result from cutaneous, respiratory, renal, hepatic, neurologic, and vascular involvement.[1] However, it mainly affects the salivary and lachrymal glands and leads to keratoconjunctivitis sicca and xerostomia because of focal inflammation.[2] The pancreas is, in part, an exocrine gland that is functionally and histologically comparable to the salivary glands. Involvement of pancreatic dysfunction in SS has been hypothesized.[3]

Acute pancreatitis, an inflammatory disorder of the pancreas, is the leading cause of admission for gastrointestinal disorders and may be fatal or lead to severe complications in certain cases. In addition to typical risk factors such as aging, alcoholism, smoking, gallstone, anatomic abnormalities, and metabolic factors, patients with autoimmune diseases have been shown to have a higher risk of autoimmune pancreatitis (AIP).[4] Many reports have mentioned the association between pSS and AIP.[5-7] In the largest series of pSS patients (1,010 patients), the prevalence of acute pancreatitis was 0.5%.[8] Despite these case reports and the case series of pSS-related acute pancreatitis[8,9], no cohort study has evaluated the risk of

acute pancreatitis in pSS patients. This risk should be assessed in a large population because of the low incidence rate.

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was began in 1995 and offers comprehensive medical care coverage almost all Taiwanese residents. The validity of the National Health Insurance Database in Taiwan has been evaluated, and research articles have been accepted worldwide for public access.[10-12] By using the National Health Insurance (NHI) dataset, we conducted a nationwide cohort study to investigate the risk of acute pancreatitis in pSS patients and related risk factors.

METHODS

Data source

The cohort from National Health Insurance (NHI) database was analyzed in this study. The bureau of NHI in Taiwan maintains a research-oriented database through the Health and Welfare Statistics Application Center (HWSAC) of the Ministry of Health and Welfare; this database includes all the original claims health care data of >97% of the entire Taiwanese population (23.74 million people). Comprehensive information on insurants, including demographic data, dates of clinical visits, and disease diagnoses, is included in the database. The diagnostic codes used were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We studied the data of the Taiwanese population from 2002 to 2012. The study was approved by the Institutional Review Board of Taipei Medical University (approval number: N201509007). As the datasets used in this study consist of de-identified secondary data released to the public for research purpose, no consent was needed for the review by the ethical review board.

Study population and design

In Taiwan, rheumatologists can apply for a catastrophic illness card for any SS patient who fulfills the criteria of the American–European Consensus Group (AECG) for SS.[3] The application of the catastrophic illness card is scrutinized in a peer review process. SS patients with the catastrophic illness card can be exempted from

copayment. We used the Registry for Catastrophic Illness Patients in NHI database to identify SS (ICD-9-CM Code 710.2) patients in the claims data, and the first-time SS diagnosis served as the index date from 2002 to 2012. In addition, we excluded patients with comorbidities such as systemic lupus erythematous, rheumatoid arthritis, scleroderma, polymyositis, and dermatomyositis to limit our study sample to pSS. pSS patients and comparison controls (non-pSS) were frequency matched at a 1:4 ratio by age (in 5-year bands), sex, and index year.

Outcome measures and case identification

The primary outcome was newly diagnosed acute pancreatitis from hospitalization records. All participants were followed-up from the index date to the date of the primary outcome, withdrawal from the NHI program, or the end of 2012, whichever came first. We identified patients with a discharge diagnosis of acute pancreatitis (ICD-9-CM Code 577.0 in any position of the five diagnosed codes). To overcome this misclassification bias, we included only patients who had been hospitalized to minimize false positive cases. In studies using the same database, the positive predictive value was high (90.0%) among randomly selected hospitalized patients coded with acute pancreatitis.[11,12] Patients who had been diagnosed with acute pancreatitis before the index date or chronic pancreatitis (ICD-9-CM Code 577.1) and those with incomplete age or sex information were excluded from this study. In Taiwan, the medical reimbursements and discharge notes of acute pancreatitis patients

are scrutinized in a peer review process.

Exposure variables

In addition to pSS, demographic characteristics such as sex, age, and comorbidities were analyzed. Preexisting comorbidities included diabetes mellitus (ICD-9-CM Code 220), hyperlipidemia (ICD-9-CM Codes 272.0-272.4), hypertriglyceridemia (ICD-9-CM Code 272.1), alcoholism (ICD-9-CM Codes 291, 303, 305.00-305.03, 571.0-571.3), gallstones (ICD-9-CM Codes 574.10 or 574.20), hepatitis B (ICD-9-CM Codes 070.2 or 070.3), and hepatitis C (ICD-9-CM Codes 070.4 or 070.5). Furthermore, we examined the potential effects of common therapies for pSS, including disease-modifying antirheumatic drugs (DMARDs; hydroxychloroquine, sulfasalazine, methotrexate, cyclophosphamide, cyclosporin, mycophenolate mofetil, and azathioprine) and steroids. Each medication was assessed as a time-dependent covariate constructed according to the prescription for each month. The drug exposure status was set to 0 if no prescription was filled during the period and set to 1 if at least one prescription was filled during the period. Steroids were analyzed as the average daily dose equivalent to prednisolone during the study period.

Statistical analysis

The SAS 9.3 statistical package (SAS Institute Inc., Cary, NC, USA) was used to

perform all analyses in this study. We examined differences in continuous variables between the two cohorts by using a Student *t* test, and we examined differences in dichromatic variables of the potential confounders between the two cohorts by using a Pearson χ^2 test.

The incidence rate is expressed per 100,000 person-years. The cumulative incidence of acute pancreatitis was assessed using the Kaplan–Meier estimator, with significance based on the log-rank test. The Cox proportional hazard regression model was used to analyze the risk of acute pancreatitis. Age, sex, and baseline comorbidities were adjusted in multivariate analysis. Crude and adjusted hazard ratios (HRs) are presented along with 95% confidence intervals (CIs). Each type of drug was separately analyzed as a time-dependent effect in the Cox proportional hazard regression model. The HRs of each type of drug could be explained as follows. In any given month, if a patient used the given type of drug, the risk of acute pancreatitis would averagely increase (HR > 1)/decrease (HR < 1) compared with a patient who did not use the given type of drug. The results of all statistical tests were considered significant if the two-sided *P* value was ≤0.05.

RESULTS

Baseline characteristics of the study population

During the study period, a total of 13,673 SS patients were identified. We excluded 3,911 secondary SS patients, 38 patients with incomplete age or sex information, 59 patients aged <18 years, 139 patients with a history of acute pancreatitis, and 58 with CP before the enrollment date. In total, 9,468 pSS patients were enrolled. We randomly selected and studied age- and sex-matched non-pSS controls with the same exclusion criteria, who were four times the number of pSS patients (**Table 1**). The mean age of pSS patients was 55.6 years, and the majority (87.23%) was female. The mean follow-up period of pSS and matched cohorts was 4.64 and 4.73 years, respectively. In the pSS cohort, hyperlipidemia, gallstones, and viral hepatitis (B or C) at baseline were more prevalent ($P < 0.001$). During the follow-up period, the pSS cohort had a significantly higher incidence of acute pancreatitis (0.46% versus 0.28%; $P = 0.005$) and a higher incidence rate of acute pancreatitis (100.0 versus 58.6 per 100,000 person-years) than the control cohort. **Figure 1** shows the Kaplan–Meier analysis, which also revealed a significantly higher cumulative incidence of acute pancreatitis in pSS patients compared with that in matched controls (log rank test $P = 0.0025$)

<Table 1 inserted here>

<Figure 1 inserted here>

Comorbidities and acute pancreatitis based on univariate and multivariate Cox proportional hazard analyses

The HR of developing acute pancreatitis during the follow-up period was 1.71 (95% CI 1.20-2.43) in pSS patients compared with that in non-pSS patients (**Table 2**). After adjustment for patients' sex, age, and other comorbidities, the hazard of developing acute pancreatitis during the follow-up period was 1.48 (95% CI 1.07-2.193) times greater in pSS patients compared with that in non-pSS patients. This finding suggests that pSS is an independent risk factor for acute pancreatitis. In addition, older age, DM, and gallstones increased the risk of acute pancreatitis (aHR 1.61, 2.39, and 5.49, respectively).

<Table 2 inserted here>

Risk factors for acute pancreatitis in pSS patients

In pSS patients, the univariate Cox regression model revealed that male sex, age more than 65 years, DM, gallstone, daily steroids over 5-mg prednisolone equivalent, and time-dependent DMARDs of hydroxychloroquine and cyclophosphamide were significant factors associated with acute pancreatitis (**Table 3**). The multivariate Cox regression model indicated that statistically significant risk factors for acute pancreatitis included age more than 65 years (aHR 2.92, 95% CI 1.27-6.75), gallstones (aHR 5.05, 95% CI 2.10-12.16), daily steroids over 5-mg prednisolone equivalent (aHR 7.66, 95% CI 3.71-15.84), and cyclophosphamide use (aHR 5.27,

95% CI 1.16-23.86), whereas hydroxychloroquine use reduced the risk (aHR 0.23, 95% CI 0.09-0.55).

<Table 3 inserted here>

DISCUSSION

This nationwide, population-based study in Taiwan demonstrated that 9,468 pSS patients had a significantly higher risk of acute pancreatitis compared with the risk in 37,872 matched controls, with an aHR of 1.48 after adjustment for age, sex, and comorbidities. The incidence rate of acute pancreatitis in pSS patients was 100.05 per 100,000 person-years. The risk factors for acute pancreatitis included age more than 65 years, gallstones, daily steroids over 5-mg prednisolone equivalent, cyclophosphamide use, and no hydroxychloroquine use.

To the best of our knowledge, this is the first cohort study to demonstrate that pSS patients have a higher risk of acute pancreatitis. The validity of this study is supported by the stringent study design. First, patients with catastrophic illness certification for pSS can be exempted from copayment in the NHI system. The verification requires fulfillment of the AECG criteria after peer review. We also excluded patients diagnosed with other autoimmune diseases. Thus, we believe that our pSS cohort is exhaustive and reliable. Second, this national large cohort was less vulnerable to selection bias and was suitable for studying rare complications and related risk factors.

The prevalence rate of acute pancreatitis in our pSS cohort was 0.46%, which is similar to the result obtained in a cohort study in Spain.[8] The largest case series reported five cases of pSS-related acute pancreatitis among 1,010 pSS patients (0.5%).

Furthermore, our study revealed that the pSS cohort had a significantly higher risk of acute pancreatitis than age- and sex-matched controls. Comorbidities such as alcoholism, DM, hepatitis B, hepatitis C, and hyperlipidemia had significantly higher prevalence rates in our pSS cohort. However, we believe the higher rates of these comorbidities might due to the characteristics associated with pSS patients or, more likely, a higher diagnosis rate caused by the higher medical usage rate in the pSS cohort. Moreover, our conservative analysis revealed pSS to be a significant independent risk factor for acute pancreatitis after correcting for these comorbidities.

The risk factors of older age and gallstone were common between our pSS cohort and the general population. In addition, we found that medication use was associated with acute pancreatitis in pSS patients. Limited studies have examined the association between steroids or DMARDs and acute pancreatitis. Immunosuppressants such as azathioprine and cyclosporin have been implicated as causes of pancreatitis in several case reports. Badalov et al. found that cyclophosphamide use was associated with acute pancreatitis, which was also observed in our pSS cohort.[13] In this claims-data-based study, it was unclear whether cyclophosphamide increased the risk through drug toxicity or was a marker of systemic manifestations in the pSS cohort. However, autoimmune-related inflammation was suspected on the basis of the association with higher daily steroid

use and no HCQ use. A similar finding was obtained for SLE-related acute pancreatitis and AIP.[14,15] AIP was found to be associated with autoimmune diseases (SS, rheumatoid arthritis, primary sclerosing cholangitis, and inflammatory bowel disease).[16] Vascular damage, including vasculitis, intimal thickening, immune complex deposition, and occlusion of arteries and arterioles); autoantibody production; and abnormal cellular immune response may be responsible for the development of pancreatitis.[17] Patients with a higher daily steroid dose and cyclophosphamide therapy and without HCQ use might have a higher risk of autoimmune-related pancreatitis.

HCV is associated with both Sjogren's syndrome and acute pancreatitis and might be an important confounder in our study. Furthermore, patients with HCV should be excluded according to the 2002 AECG criteria. However, the pathogenesis of the association between Sjogren's syndrome and HCV were not fully known and the sicca syndrome in HCV patients is pSS, secondary Sjogren's syndrome or only SS-like symptoms remains controversial.[18] Moreover, neither correcting HCV in the multivariate Cox model nor the analysis after excluding pSS patients with prior HCV and their matched controls resulted in different outcome. Thus, the initial study design was not altered and HCV was not excluded.

Our study has clinical implications. First, acute pancreatitis is a rare complication among pSS patients and should be considered one of the differential

diagnoses of abdominal pain. Second, without using hydroxychloroquine might be considered as a risk factor, particularly among those with higher daily steroid use or cyclophosphamide treatment. Administrative databases enable population-based epidemiologic studies; however, limitations exist. First, some data are unavailable in this claims-based data set. Data on alcohol consumption and smoking, the major risk factors of acute pancreatitis, were unavailable in our study. We still included "alcoholism" in our study, which was defined as the presence of related ICD-9CM codes prior to the diagnosis of pSS. Unlike other comorbidities, alcoholism was easily underestimated because that we could only identify those went to a doctor. Thus, we believed the coding of alcoholism was influenced by the medical utilization, which resulted in a significant lower rate of alcoholism in the control cohort. Moreover, no reports have mentioned the relationship between pSS and alcoholism. The defected oral mucosa of pSS patients might be susceptible to stimulation by alcohol. However, we could not know whether the alcohol consumption decreased after dry mouth aggravated as our inference. Furthermore, because of the lack of data on the severity of pSS, laboratory results, and indications for medication use, we could not determine the mechanism of pancreatitis. Second, IgG4-related disease may involve salivary and lacrimal glands and AIP.[19] However, in the NHIRD, the certification of pSS requires a positive anti-Ro or/and anti-La antibodies or a positive lip biopsy. In addition, the observed

lower risk in those using HCQ, which is not beneficial to IgG4-related disease, also implied the limited effect of IgG4-related disease in our study.

In conclusion, we demonstrated that pSS patients had a higher risk of acute pancreatitis, and the magnitude of hazard in the pSS-affected population was 48% higher than that in the non-pSS population. On the basis of these findings, acute pancratitis should be considered one of the differential diagnoses when related symtptoms present.

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Chi-Ching Chang contributed to the conception and design of the work, drafting of the article, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Yu-Sheng Chang** contributed to interpretation of data, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Shu-HungWang and Shyr-Yi Lin** contributed to the analysis of data, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Yi-Hsuan Chen** contributed to the analysis of the data, drafting of the article, and final approval of the version to be published. **Jin-Hua Chen** designed the study and conceived the

work, completed the analysis, revised the article critically for crucial intellectual content, and corresponded for final approval of the version to be published. All authors have disclosed any potential competing financial interests regarding the submitted article.

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Table 1. Baseline characteristics and follow-up status of the primary Sjogren's syndrome (pSS) cohort and the age- and sex-matched comparison cohort

Group	Comparison cohort (N = 37,872)	pSS cohort (N = 9,468)	
Variable	n(%)	n(%)	*P* value*
Sex			1.00
Male	4,836(12.77)	1,209(12.77)	
Female	33,036(87.23)	8,259(87.23)	
Age, mean (SD)	55.61(14.33)	55.64(14.26)	0.863
Age groups			0.996
≤50	12,945(34.18)	3,241(34.23)	
51-65	14,643(38.66)	3,658(38.64)	
>65	10,284(27.15)	2,569(27.13)	
Baseline comorbidity			
Alcoholism	73(0.19)	36(0.38)	<0.001
Diabetes mellitus	4,327(11.43)	1,095(11.57)	0.702
Gallstone	423(1.12)	272(2.87)	<0.001
Hepatitis B	501(1.32)	321(3.39)	<0.001
Hepatitis C	324(0.86)	367(3.88)	<0.001
Hyperlipidemia	4,716(12.45)	1,498(15.82)	<0.001
Hypertriglyceridemia	187(0.49)	59(0.62)	0.117
No. of comorbidities§			<0.001
0	30,028(79.29)	6,674(70.49)	
1	5,512(14.55)	2,108(22.26)	
2	2,217(5.85)	616(6.51)	
≥3	115(0.30)	70(0.74)	
Follow-up duration, mean (SD)	4.73(2.78)	4.64(2.78)	0.005
No. of acute pancreatitis (AP)	105(0.28)	44(0.46)	0.005
AP incidence per 100,000 person-years	58.56	100.05	0.004

**P* values were calculated using the chi-square test for categorical variables or the *t* test for continuous variables; the *P* value for incidence was calculated using the exact Poisson test.

§The No. of comorbidity was counted from the predescribed baseline comorbidity, except hypertriglyceridemia (a subgroup of hyperlipidemia).

Table 2. Cox regression analysis for the risk of acute pancreatitis

	Univariate Analysis		Multivariate Analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary Sjogren's syndrome	1.71 (1.20-2.43)	0.003	1.48 (1.03-2.12)	0.034
Sex (male)	1.78 (1.21-2.63)	0.004	1.42 (0.96-2.12)	0.083
Age groups (reference: age≤50)				
51-65	1.93 (1.20-3.12)	0.007	1.61 (0.99-2.12)	0.055
>65	4.01 (2.54-6.31)	<0.001	2.90 (1.81-4.67)	<0.001
Baseline comorbidity				
Diabetes mellitus	3.30 (2.30-4.73)	<0.001	2.39 (1.65-3.46)	<0.001
Gallstone	7.78 (4.56-13.27)	<0.001	5.49 (3.19-9.46)	<0.001
Hepatitis B	2.27 (0.93-5.53)	0.072	1.84 (0.74-4.54)	0.189
Hepatitis C	3.39 (1.59-7.25)	0.002	2.06 (0.95-4.51)	0.069
Hyperlipidemia	1.83 (1.22-2.75)	0.004	--	
Hypertriglyceridemia	1.34 (0.19-9.56)	0.085	--	
No. of comorbidities				
0	1.00			
1	2.51 (1.72-3.68)			
≥2	4.97 (3.24-7.65)			

HR: hazard ratio; CI: confidence interval

*All variables, except No. of comorbidities, were selected using stepwise Cox regression analysis with entry and retention criteria at $P \leq 0.2$ in multivariate analysis

Table 3. Cox regression analysis for the risk of acute pancreatitis among pSS patients

	Univariate Analysis		Multivariate Analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	2.44 (1.26-4.74)	0.009	1.64 (0.82-3.26)	0.161
Age groups (reference: age≤50)				
51-65	1.42 (0.58-3.48)	0.441	1.17 (0.47-2.90)	0.739
>65	4.22 (1.89-9.39)	<0.001	2.92 (1.27-6.75)	0.012
Baseline comorbidity				
Diabetes mellitus	2.10 (1.01-4.37)	0.047	1.47 (0.70-3.12)	0.313
Gallstone	5.60 (2.37-13.24)	<0.001	5.05 (2.10-12.16)	<0.001
Hepatitis B	2.28 (0.71-7.37)	0.168	--	--
Hepatitis C	2.21 (0.79-6.20)	0.130	--	--
Hyperlipidemia	1.10 (0.49-2.47)	0.817	--	--
Hypertriglyceridemia	NA	NA	--	--
Steroid PO dose>5 mg (equal to prednisolone)	6.99 (3.53-13.88)	<0.001	7.66 (3.71-15.84)	<0.001
Time-dependent drug effect				
Hydroxychloroquine	0.26 (0.11-0.62)	0.002	0.23 (0.09-0.55)	0.001
Cyclophosphamide	9.61 (2.26-39.27)	0.002	5.27 (1.16-23.86)	0.031
Azathioprine	1.88 (0.45-7.78)	0.384	--	--
Cyclosporin	NA	NA	--	--
Sulfasalazine	NA	NA	--	--
Methotrexate	NA	NA	--	--
Mycophenolate mofetil	NA	NA	--	--

HR: hazard ratio; CI: confidence interval; NA: not available (did not converge)

*Age groups, sex, and other variables with $P < 0.05$ were selected in multivariate analysis

Figure 1. Cumulative incidence of acute pancreatitis in the primary Sjogren's syndrome cohort and the comparison cohort

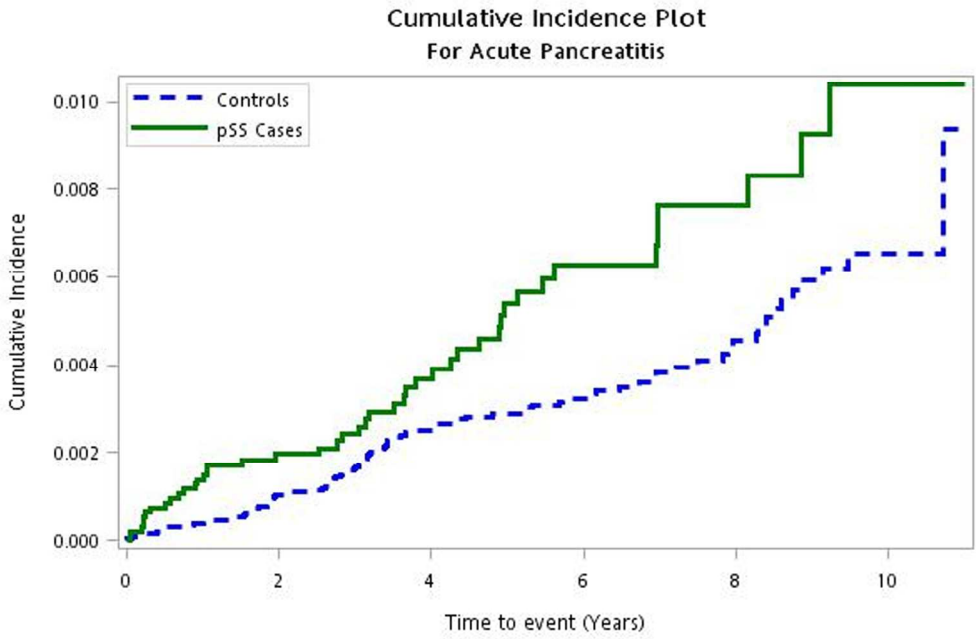

Figure 1. Cumulative incidence of acute pancreatitis in the primary Sjogren's syndrome cohort and the comparison cohort

158x105mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8,9
		(*e*) Describe any sensitivity analyses	8,9

Section/Topic	Item No	Recommendation	Reported on Page No
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	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11,12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11,12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11,12
		Cross-sectional study—Report numbers of outcome events or summary measures	11,12
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	11,12
		(*b*) Report category boundaries when continuous variables were categorized	11,12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11,12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13,14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	1

**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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Primary Sjogren's Syndrome and the Risk of Acute Pancreatitis : A Nationwide Cohort Study

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Primary Sjogren's Syndrome and the Risk of Acute Pancreatitis : A Nationwide Cohort Study

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Short Title: Primary Sjogren's Syndrome Increases the Risk of Acute Pancreatitis

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ABSTRACT

Objective: Studies on the risk of acute pancreatitis in primary Sjogren's syndrome (pSS) patients are limited. We evaluated the effects of pSS on the risk of acute pancreatitis in a nationwide, population-based cohort in Taiwan.

Study Design: Population-based retrospective cohort study.

Setting: We studied the claims data of the >97% Taiwan population from 2002 to 2012.

Participants: We identified 9,468 pSS patients by using the catastrophic illness registry of the National Health Insurance Database in Taiwan. We also selected 37,872 controls that were randomly frequency matched by age (in 5-year bands), sex, and index year from the general population.

Primary outcome measure: We analyzed the risk of acute pancreatitis by using Cox proportional hazards regression models including sex, age, and comorbidities.

Results: From 23.74 million people in the cohort, 9,468 pSS patients (87% women, mean age = 55.6 years) and 37,872 controls were followed-up for 4.64 and 4.74 years, respectively. A total of 44 cases of acute pancreatitis were identified in the pSS cohort versus 105 cases in the non-pSS cohort. Multivariate Cox regression analysis indicated that the incidence rate of acute pancreatitis was significantly higher in the pSS cohort than in the non-pSS cohort (adjusted hazard ratio [aHR] 1.48, 95%

confidence interval [CI] 1.03-2.12). Cyclophosphamide use increased the risk of acute pancreatitis (aHR 5.27, 95% CI 1.16-23.86). By contrast, hydroxychloroquine reduced the risk of acute pancreatitis (aHR 0.23, 95% CI 0.09-0.55).

Conclusion: This nationwide, retrospective cohort study demonstrated that the risk of acute pancreatitis was significantly higher in pSS patients than in the general population.

Keywords: primary Sjogren's syndrome, risk, acute pancreatitis

Strengths and limitations of this study

1. This is the first nationwide population-based cohort study that demonstrated the patients with Sjogren's syndrome increase the risk of acute pancreatitis.
2. Data on alcoholism and smoking, the major risk factors of acute pancreatitis, were unavailable in our study. However, no reports have mentioned the relationship between pSS and alcoholism.
3. Because of the lack of data on the severity of pSS, laboratory results, and indications for medication use, we could not determine the mechanism of pancreatitis.

INTRODUCTION

Sjogren's syndrome (SS) is a slowly progressive systemic autoimmune disease that may present either alone as primary SS (pSS) or, in association with an underlying autoimmune disease, as secondary SS. Systemic manifestations may result from cutaneous, respiratory, renal, hepatic, neurologic, and vascular involvement.[1] However, it mainly affects the salivary and lachrymal glands and leads to keratoconjunctivitis sicca and xerostomia because of focal inflammation.[2] The pancreas is, in part, an exocrine gland that is functionally and histologically comparable to the salivary glands. Involvement of pancreatic dysfunction in SS has been hypothesized.[3]

Acute pancreatitis, an inflammatory disorder of the pancreas, is the leading cause of admission for gastrointestinal disorders and may be fatal or lead to severe complications in certain cases. In addition to typical risk factors such as aging, alcoholism, smoking, gallstone, anatomic abnormalities, and metabolic factors, patients with autoimmune diseases have been shown to have a higher risk of autoimmune pancreatitis (AIP).[4] Many reports have mentioned the association between pSS and AIP.[5-7] In the largest series of pSS patients (1,010 patients), the prevalence of acute pancreatitis was 0.5%.[8] Despite these case reports and the case series of pSS-related acute pancreatitis[8,9], no cohort study has evaluated the risk of

acute pancreatitis in pSS patients. This risk should be assessed in a large population because of the low incidence rate.

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was began in 1995 and offers comprehensive medical care coverage almost all Taiwanese residents. The validity of the National Health Insurance Database in Taiwan has been evaluated, and research articles have been accepted worldwide for public access.[10-12] By using the National Health Insurance (NHI) dataset, we conducted a nationwide cohort study to investigate the risk of acute pancreatitis in pSS patients and related risk factors.

METHODS

Data source

The cohort from National Health Insurance (NHI) database was analyzed in this study. The bureau of NHI in Taiwan maintains a research-oriented database through the Health and Welfare Statistics Application Center (HWSAC) of the Ministry of Health and Welfare; this database includes all the original claims health care data of >97% of the entire Taiwanese population (23.74 million people). Comprehensive information on insurants, including demographic data, dates of clinical visits, and disease diagnoses, is included in the database. The diagnostic codes used were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). We studied the data of the Taiwanese population from 2002 to 2012. The study was approved by the Institutional Review Board of Taipei Medical University (approval number: N201509007). As the datasets used in this study consist of de-identified secondary data released to the public for research purpose, no consent was needed for the review by the ethical review board.

Study population and design

In Taiwan, rheumatologists can apply for a catastrophic illness card for any SS patient who fulfills the criteria of the American–European Consensus Group (AECG) for SS.[3] The application of the catastrophic illness card is scrutinized in a peer review process. SS patients with the catastrophic illness card can be exempted from

copayment. We used the Registry for Catastrophic Illness Patients in NHI database to identify SS (ICD-9-CM Code 710.2) patients in the claims data, and the first-time SS diagnosis served as the index date from 2002 to 2012. In addition, we excluded patients with comorbidities such as systemic lupus erythematous, rheumatoid arthritis, scleroderma, polymyositis, and dermatomyositis to limit our study sample to pSS. pSS patients and comparison controls (non-pSS) were frequency matched at a 1:4 ratio by age (in 5-year bands), sex, and index year.

Outcome measures and case identification

The primary outcome was newly diagnosed acute pancreatitis from hospitalization records. All participants were followed-up from the index date to the date of the primary outcome, withdrawal from the NHI program, or the end of 2012, whichever came first. We identified patients with a discharge diagnosis of acute pancreatitis (ICD-9-CM Code 577.0 in any position of the five diagnosed codes). To overcome this misclassification bias, we included only patients who had been hospitalized to minimize false positive cases. In studies using the same database, the positive predictive value was high (90.0%) among randomly selected hospitalized patients coded with acute pancreatitis.[11,12] Patients who had been diagnosed with acute pancreatitis before the index date or chronic pancreatitis (ICD-9-CM Code 577.1) and those with incomplete age or sex information were excluded from this study. In Taiwan, the medical reimbursements and discharge notes of acute pancreatitis patients

are scrutinized in a peer review process.

Exposure variables

In addition to pSS, demographic characteristics such as sex, age, and comorbidities were analyzed. Preexisting comorbidities included diabetes mellitus (ICD-9-CM Code 220), hyperlipidemia (ICD-9-CM Codes 272.0-272.4), hypertriglyceridemia (ICD-9-CM Code 272.1), alcoholism (ICD-9-CM Codes 291, 303, 305.00-305.03, 571.0-571.3), gallstones (ICD-9-CM Codes 574.10 or 574.20), hepatitis B (ICD-9-CM Codes 070.2 or 070.3), and hepatitis C (ICD-9-CM Codes 070.4 or 070.5). Furthermore, we examined the potential effects of common therapies for pSS, including disease-modifying antirheumatic drugs (DMARDs; hydroxychloroquine, sulfasalazine, methotrexate, cyclophosphamide, cyclosporin, mycophenolate mofetil, and azathioprine) and steroids. Each medication was assessed as a time-dependent covariate constructed according to the prescription for each month. The drug exposure status was set to 0 if no prescription was filled during the period and set to 1 if at least one prescription was filled during the period. Steroids were analyzed as the average daily dose equivalent to prednisolone during the study period.

Statistical analysis

The SAS 9.3 statistical package (SAS Institute Inc., Cary, NC, USA) was used to

perform all analyses in this study. We examined differences in continuous variables between the two cohorts by using a Student *t* test, and we examined differences in dichromatic variables of the potential confounders between the two cohorts by using a Pearson χ^2 test.

The incidence rate is expressed per 100,000 person-years. The cumulative incidence of acute pancreatitis was assessed using the Kaplan–Meier estimator, with significance based on the log-rank test. The Cox proportional hazard regression model was used to analyze the risk of acute pancreatitis. Age, sex, and baseline comorbidities were adjusted in multivariate analysis. Crude and adjusted hazard ratios (HRs) are presented along with 95% confidence intervals (CIs). Each type of drug was separately analyzed as a time-dependent effect in the Cox proportional hazard regression model. The HRs of each type of drug could be explained as follows. In any given month, if a patient used the given type of drug, the risk of acute pancreatitis would averagely increase (HR > 1)/decrease (HR < 1) compared with a patient who did not use the given type of drug. The results of all statistical tests were considered significant if the two-sided *P* value was ≤0.05.

RESULTS

Baseline characteristics of the study population

During the study period, a total of 13,673 SS patients were identified. We excluded 3,911 secondary SS patients, 38 patients with incomplete age or sex information, 59 patients aged <18 years, 139 patients with a history of acute pancreatitis, and 58 with CP before the enrollment date. In total, 9,468 pSS patients were enrolled. We randomly selected and studied age- and sex-matched non-pSS controls with the same exclusion criteria, who were four times the number of pSS patients (**Table 1**). The mean age of pSS patients was 55.6 years, and the majority (87.23%) was female. The mean follow-up period of pSS and matched cohorts was 4.64 and 4.73 years, respectively. In the pSS cohort, hyperlipidemia, gallstones, and viral hepatitis (B or C) at baseline were more prevalent ($P < 0.001$). During the follow-up period, the pSS cohort had a significantly higher incidence of acute pancreatitis (0.46% versus 0.28%; $P = 0.005$) and a higher incidence rate of acute pancreatitis (100.0 versus 58.6 per 100,000 person-years) than the control cohort. **Figure 1** shows the Kaplan–Meier analysis, which also revealed a significantly higher cumulative incidence of acute pancreatitis in pSS patients compared with that in matched controls (log rank test $P = 0.0025$)

<Table 1 inserted here>

<Figure 1 inserted here>

Comorbidities and acute pancreatitis based on univariate and multivariate Cox proportional hazard analyses

The HR of developing acute pancreatitis during the follow-up period was 1.71 (95% CI 1.20-2.43) in pSS patients compared with that in non-pSS patients (**Table 2**). After adjustment for patients' sex, age, and other comorbidities, the hazard of developing acute pancreatitis during the follow-up period was 1.48 (95% CI 1.07-2.193) times greater in pSS patients compared with that in non-pSS patients. This finding suggests that pSS is an independent risk factor for acute pancreatitis. In addition, older age, DM, and gallstones increased the risk of acute pancreatitis (aHR 1.61, 2.39, and 5.49, respectively).

<Table 2 inserted here>

Risk factors for acute pancreatitis in pSS patients

In pSS patients, the univariate Cox regression model revealed that male sex, age more than 65 years, DM, gallstone, daily steroids over 5-mg prednisolone equivalent, and time-dependent DMARDs of hydroxychloroquine and cyclophosphamide were significant factors associated with acute pancreatitis (**Table 3**). The multivariate Cox regression model indicated that statistically significant risk factors for acute pancreatitis included age more than 65 years (aHR 2.92, 95% CI 1.27-6.75), gallstones (aHR 5.05, 95% CI 2.10-12.16), daily steroids over 5-mg prednisolone equivalent (aHR 7.66, 95% CI 3.71-15.84), and cyclophosphamide use (aHR 5.27,

95% CI 1.16-23.86), whereas hydroxychloroquine use reduced the risk (aHR 0.23, 95% CI 0.09-0.55).

<Table 3 inserted here>

DISCUSSION

This nationwide, population-based study in Taiwan demonstrated that 9,468 pSS patients had a significantly higher risk of acute pancreatitis compared with the risk in 37,872 matched controls, with an aHR of 1.48 after adjustment for age, sex, and comorbidities. The incidence rate of acute pancreatitis in pSS patients was 100.05 per 100,000 person-years. The risk factors for acute pancreatitis included age more than 65 years, gallstones, daily steroids over 5-mg prednisolone equivalent, cyclophosphamide use, and no hydroxychloroquine use.

To the best of our knowledge, this is the first nationwide population-based cohort study that has demonstrated that patients with Sjögren's syndrome have an increased risk of acute pancreatitis. The validity of this study is supported by the stringent study design. First, patients with catastrophic illness certification for pSS can be exempted from copayment in the NHI system. The verification requires fulfillment of the AECG criteria after peer review. We also excluded patients diagnosed with other autoimmune diseases. Thus, we believe that our pSS cohort is exhaustive and reliable. Second, this national large cohort was less vulnerable to selection bias and was suitable for studying rare complications and related risk factors.

The prevalence rate of acute pancreatitis in our pSS cohort was 0.46%, which is similar to the result obtained in a cohort study in Spain.[8] The largest case series reported five cases of pSS-related acute pancreatitis among 1,010 pSS patients (0.5%).

Furthermore, our study revealed that the pSS cohort had a significantly higher risk of acute pancreatitis than age- and sex-matched controls. Comorbidities such as alcoholism, DM, hepatitis B, hepatitis C, and hyperlipidemia had significantly higher prevalence rates in our pSS cohort. However, we believe the higher rates of these comorbidities might due to the characteristics associated with pSS patients or, more likely, a higher diagnosis rate caused by the higher medical usage rate in the pSS cohort. Moreover, our conservative analysis revealed pSS to be a significant independent risk factor for acute pancreatitis after correcting for these comorbidities. The risk factors of older age and gallstone were common between our pSS cohort and the general population. In addition, we found that medication use was associated with acute pancreatitis in pSS patients. Limited studies have examined the association between steroids or DMARDs and acute pancreatitis. Immunosuppressants such as azathioprine and cyclosporin have been implicated as causes of pancreatitis in several case reports. Badalov et al. found that cyclophosphamide use was associated with acute pancreatitis, which was also observed in our pSS cohort.[13] In this claims-data-based study, it was unclear whether cyclophosphamide increased the risk through drug toxicity or was a marker of systemic manifestations in the pSS cohort. However, autoimmune-related inflammation was suspected on the basis of the association with higher daily steroid use and no HCQ use. A similar finding was

obtained for SLE-related acute pancreatitis and AIP.[14,15] AIP was found to be associated with autoimmune diseases (SS, rheumatoid arthritis, primary sclerosing cholangitis, and inflammatory bowel disease).[16] Vascular damage, including vasculitis, intimal thickening, immune complex deposition, and occlusion of arteries and arterioles); autoantibody production; and abnormal cellular immune response may be responsible for the development of pancreatitis.[17] Patients with a higher daily steroid dose and cyclophosphamide therapy and without HCQ use might have a higher risk of autoimmune-related pancreatitis.

HCV is associated with both Sjogren's syndrome and acute pancreatitis and might be an important confounder in our study. Furthermore, patients with HCV should be excluded according to the 2002 AECG criteria. However, the pathogenesis of the association between Sjögren's syndrome and HCV is not fully known and whether the sicca syndrome in HCV patients is due to pSS, secondary Sjögren's syndrome or only SS-like symptoms remains controversial.[18] Moreover, neither correcting HCV in the multivariate Cox model nor the analysis after excluding pSS patients with prior HCV and their matched controls resulted in different outcome. Thus, the initial study design was not altered and HCV was not excluded.

Our study has clinical implications. First, acute pancreatitis is a rare complication among pSS patients and should be considered one of the differential diagnoses of

abdominal pain. Second, without using hydroxychloroquine might be considered as a risk factor, particularly among those with higher daily steroid use or cyclophosphamide treatment. Administrative databases enable population-based epidemiologic studies; however, limitations exist. First, some data are unavailable in this claims-based data set. Data on alcohol intake and smoking, the major risk factors of acute pancreatitis, were unavailable in our study. We still included "alcoholism" in our study, which was defined as the presence of related ICD-9CM codes prior to the diagnosis of pSS. Unlike other comorbidities, alcoholism was easily underestimated because that we could only identify those went to a doctor. Thus, we believed the coding of alcoholism was influenced by the medical utilization, which resulted in a significant lower rate of alcoholism in the control cohort. Moreover, no reports have mentioned the relationship between pSS and alcoholism. Dryness of the oral mucosa in pSS can result in alcohol intolerance. However, we do not know whether average alcohol consumption decreased after the onset of dry mouth. Furthermore, because of the lack of data on the severity of pSS, laboratory results, and indications for medication use, we could not determine the mechanism of pancreatitis. Second, IgG4-related disease may involve salivary and lacrimal glands and AIP.[19] However, in the NHIRD, the certification of pSS requires a positive anti-Ro or/and anti-La antibodies or a positive lip biopsy. In addition, the observed lower risk in those using

HCQ, which is not beneficial to IgG4-related disease, also implied the limited effect of IgG4-related disease in our study.

In conclusion, we demonstrated that pSS patients had a higher risk of acute pancreatitis, and the magnitude of hazard in the pSS-affected population was 48% higher than that in the non-pSS population. On the basis of these findings, acute pancratitis should be considered one of the differential diagnoses when related symtptoms present.

Declaration of interest: This study had no specific funding source. All authors declare no conflicts of interest for this work.

Chi-Ching Chang contributed to the conception and design of the work, drafting of the article, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Yu-Sheng Chang** contributed to interpretation of data, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Shu-Hung Wang and Shyr-Yi Lin** contributed to the analysis of data, revision of the article critically for crucial intellectual content, and final approval of the version to be published. **Yi-Hsuan Chen** contributed to the analysis of the data, drafting of the article, and final approval of the version to be published. **Jin-Hua Chen** designed the study and conceived the work, completed the analysis, revised the article critically for crucial intellectual

content, and corresponded for final approval of the version to be published. All authors have disclosed any potential competing financial interests regarding the submitted article.

Data sharing: Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.22h7c

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Table 1. Baseline characteristics and follow-up status of the primary Sjogren's syndrome (pSS) cohort and the age- and sex-matched comparison cohort

Group	Comparison cohort (N = 37,872)	pSS cohort (N = 9,468)	
Variable	n(%)	n(%)	*P* value*
Sex			1.00
Male	4,836(12.77)	1,209(12.77)	
Female	33,036(87.23)	8,259(87.23)	
Age, mean (SD)	55.61(14.33)	55.64(14.26)	0.863
Age groups			0.996
≤50	12,945(34.18)	3,241(34.23)	
51-65	14,643(38.66)	3,658(38.64)	
>65	10,284(27.15)	2,569(27.13)	
Baseline comorbidity			
Alcoholism	73(0.19)	36(0.38)	<0.001
Diabetes mellitus	4,327(11.43)	1,095(11.57)	0.702
Gallstone	423(1.12)	272(2.87)	<0.001
Hepatitis B	501(1.32)	321(3.39)	<0.001
Hepatitis C	324(0.86)	367(3.88)	<0.001
Hyperlipidemia	4,716(12.45)	1,498(15.82)	<0.001
Hypertriglyceridemia	187(0.49)	59(0.62)	0.117
No. of comorbidities§			<0.001
0	30,028(79.29)	6,674(70.49)	
1	5,512(14.55)	2,108(22.26)	
2	2,217(5.85)	616(6.51)	
≥3	115(0.30)	70(0.74)	
Follow-up duration, mean (SD)	4.73(2.78)	4.64(2.78)	0.005
No. of acute pancreatitis (AP)	105(0.28)	44(0.46)	0.005
AP incidence per 100,000 person-years	58.56	100.05	0.004

**P* values were calculated using the chi-square test for categorical variables or the *t* test for continuous variables; the *P* value for incidence was calculated using the exact Poisson test.

§The No. of comorbidity was counted from the predescribed baseline comorbidity, except hypertriglyceridemia (a subgroup of hyperlipidemia).

Table 2. Cox regression analysis for the risk of acute pancreatitis

	Univariate Analysis		Multivariate Analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary Sjogren's syndrome	1.71 (1.20-2.43)	0.003	1.48 (1.03-2.12)	0.034
Sex (male)	1.78 (1.21-2.63)	0.004	1.42 (0.96-2.12)	0.083
Age groups (reference: age≤50)				
51-65	1.93 (1.20-3.12)	0.007	1.61 (0.99-2.12)	0.055
>65	4.01 (2.54-6.31)	<0.001	2.90 (1.81-4.67)	<0.001
Baseline comorbidity				
Diabetes mellitus	3.30 (2.30-4.73)	<0.001	2.39 (1.65-3.46)	<0.001
Gallstone	7.78 (4.56-13.27)	<0.001	5.49 (3.19-9.46)	<0.001
Hepatitis B	2.27 (0.93-5.53)	0.072	1.84 (0.74-4.54)	0.189
Hepatitis C	3.39 (1.59-7.25)	0.002	2.06 (0.95-4.51)	0.069
Hyperlipidemia	1.83 (1.22-2.75)	0.004	--	
Hypertriglyceridemia	1.34 (0.19-9.56)	0.085	--	
No. of comorbidities				
0	1.00			
1	2.51 (1.72-3.68)			
≥2	4.97 (3.24-7.65)			

HR: hazard ratio; CI: confidence interval

*All variables, except No. of comorbidities, were selected using stepwise Cox regression analysis with entry and retention criteria at $P \leq 0.2$ in multivariate analysis

Table 3. Cox regression analysis for the risk of acute pancreatitis among pSS patients

	Univariate Analysis		Multivariate Analysis*	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (male)	2.44 (1.26-4.74)	0.009	1.64 (0.82-3.26)	0.161
Age groups (reference: age≤50)				
51-65	1.42 (0.58-3.48)	0.441	1.17 (0.47-2.90)	0.739
>65	4.22 (1.89-9.39)	<0.001	2.92 (1.27-6.75)	0.012
Baseline comorbidity				
Diabetes mellitus	2.10 (1.01-4.37)	0.047	1.47 (0.70-3.12)	0.313
Gallstone	5.60 (2.37-13.24)	<0.001	5.05 (2.10-12.16)	<0.001
Hepatitis B	2.28 (0.71-7.37)	0.168	--	--
Hepatitis C	2.21 (0.79-6.20)	0.130	--	--
Hyperlipidemia	1.10 (0.49-2.47)	0.817	--	--
Hypertriglyceridemia	NA	NA	--	--
Steroid PO dose>5 mg (equal to prednisolone)	6.99 (3.53-13.88)	<0.001	7.66 (3.71-15.84)	<0.001
Time-dependent drug effect				
Hydroxychloroquine	0.26 (0.11-0.62)	0.002	0.23 (0.09-0.55)	0.001
Cyclophosphamide	9.61 (2.26-39.27)	0.002	5.27 (1.16-23.86)	0.031
Azathioprine	1.88 (0.45-7.78)	0.384	--	--
Cyclosporin	NA	NA	--	--
Sulfasalazine	NA	NA	--	--
Methotrexate	NA	NA	--	--
Mycophenolate mofetil	NA	NA	--	--

HR: hazard ratio; CI: confidence interval; NA: not available (did not converge)

*Age groups, sex, and other variables with $P < 0.05$ were selected in multivariate analysis

Figure 1. Cumulative incidence of acute pancreatitis in the primary Sjogren's syndrome cohort and the comparison cohort

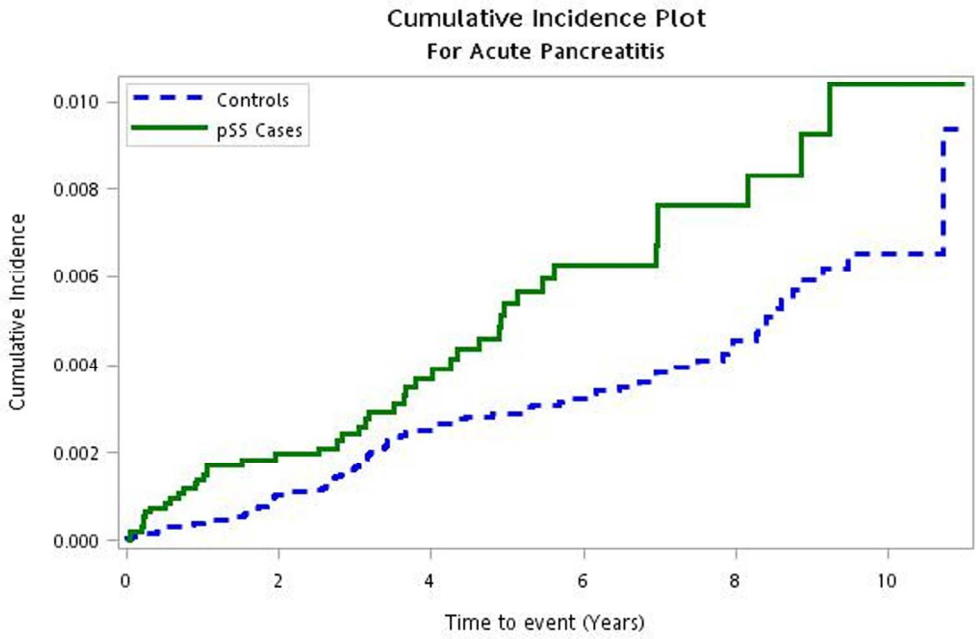

Figure 1. Cumulative incidence of acute pancreatitis in the primary Sjogren's syndrome cohort and the comparison cohort

158x105mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2,3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4,5
Objectives	3	State specific objectives, including any prespecified hypotheses	4,5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6,7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	6,7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
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	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	8,9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8,9
		(*e*) Describe any sensitivity analyses	8,9

Section/Topic	Item No	Recommendation	Reported on Page No
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	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11,12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	11,12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	11,12
		Cross-sectional study—Report numbers of outcome events or summary measures	11,12
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	11,12
		(*b*) Report category boundaries when continuous variables were categorized	11,12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11,12
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11,12
Discussion			
Key results	18	Summarise key results with reference to study objectives	13,14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
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	1

**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.