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ORIGINAL ARTICLE

Increased Risk of Acute Pancreatitis in Patients with Sjögren Syndrome: A Nationwide Population-Based Cohort Study

Ming-Tsung Chen[1], Chung-Kuang Yao[2], Chi-Hsiang Chung[3], Chih-Hao Shen[1], Sheng-Huei Wang[1], Chih-Hsin Wang[4], Wu-Chien Chien[5], Chung-Kan Peng[1]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, [2]Division of Pulmonary and Critical Care, Department of Internal Medicine, Zuoying Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung, [3]Department of Medical Research, Tri-Service General Hospital, School of Public Health, National Defense Medical Center, Taiwanese Injury Prevention and Safety Promotion Association, Taipei, [4]Division of Plastic and Reconstructive Surgery, Department of Surgery, Tri-Service General Hospital, [5]Department of Medical Research, Tri-Service General Hospital, School of Public Health, National Defense Medical Center, Taipei, Taiwan

Background: Sjögren's syndrome (SS) is a chronic autoimmune disease with lymphocytic exocrine gland infiltration causing dry mouth and eyes. The disease can develop alone (primary SS, PSS) or with other autoimmune diseases (secondary SS, SSS). PSS has been suggested to increase the acute pancreatitis risk. However, whether all patients with SS share this higher risk remains uncertain. This nationwide population-based cohort study aimed to detect associations between SS and acute pancreatitis. **Methods:** We identified 11,922 individuals with SS cohort and 47,688 individuals without SS (non-SS cohort) between 2000 and 2010 from the Taiwan National Health Insurance database. We matched the individuals between the SS and non-SS cohorts according to age, gender, and index year at a 1:4 ratio. We used a Cox multivariable proportional-hazards model to determine the effects of SS on the acute pancreatitis risk. **Results:** The SS cohort had a higher acute pancreatitis risk than the non-SS cohort after covariate adjustments (adjusted hazard ratio [HR], 3.374; 95% confidence interval [CI], 2.869–3.969). Patients with PSS exhibited a 2.872-fold risk (95% CI, 2.611–3.901) and patients with SSS a 4.121-fold risk (95% CI, 3.752–5.124) for acute pancreatitis. Our subgroup analyses revealed that patients with SS and systemic lupus erythematosus (adjusted HR, 3.85; 95% CI, 3.259–4.999), rheumatoid arthritis (adjusted HR, 4.298; 95% CI, 3.862–5.286), systemic sclerosis (adjusted HR, 2.765; 95% CI, 2.26–3.68), or polymyositis (adjusted HR, 2.641; 95% CI,1.847–3.101) and dermatomyositis (adjusted HR, 3.77; 95% CI, 2.894–4.502) had higher acute pancreatitis risk. **Conclusions:** Patients with SS presented increased acute pancreatitis risks than patients without SS, and patients with SSS had higher acute pancreatitis risks than patients with PSS. Physicians should be aware of this increased risk in patients with SS.

Key words: Sjögren syndrome, acute pancreatitis, autoimmune diseases

INTRODUCTION

Sjögren's syndrome (SS) is a systemic slowly progressing autoimmune disease commonly affecting lacrimal and salivary glands. Approximately 30%–40% of the patients with SS have systemic manifestations involving the lungs, skin, central nerve system, kidneys, or other organs. The pathogenesis of SS includes a genetic predisposition, innate and adaptive immunity abnormalities, and hormonal and environmental factors.[1-3] The American-European Consensus Classification

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Corresponding Author: Dr. Chung-Kan Peng, No. 325, Section 2, Chenggong Road, Neihu District, Taipei, Taiwan. Tel: 886-2-8792-3311; Fax: 886-2-8792-7245. E-mail: kanpeng1025@yahoo.com.tw
Dr. Wu-Chien Chien, No. 325, Section 2, Chenggong Road, Neihu District, Taipei, Taiwan. Tel: 886-2-8792-3311; Fax: 886-2-8792-7245. E-mail: chienwu@mail.ndmctsgh.edu.tw

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Criteria are available to diagnose SS based on symptoms, signs, histopathology from salivary gland biopsy, and autoantibodies such as Anti-SSA (Ro) or Anti-SSB (La).[4]

SS is most common in middle-aged women but can occur in men and at any age. SS incidence and prevalence rates vary widely around the world.[5] The disease can present alone (primary SS, PSS) or with other autoimmune diseases (secondary SS, SSS). About 30% of patients with autoimmune rheumatic disease have SSS.[6] SSS can coexist with systemic lupus erythematosus (SLE) (15%–36%), rheumatoid arthritis (RA) (20%–32%), systemic sclerosis (SSc) (11%–24%), or polymyositis (9%–18%).[7] Some studies have focused on differences between PSS and SSS, and patients with PSS have predominantly B lymphocyte infiltration in the lip biopsy and a higher frequency of parotid enlargement, oral symptoms, and titers of anti-Ro/La autoantibodies than patients with SSS.[8]

The pancreas exerts both exocrine and endocrine functions, and secreted pancreatic juice contains bicarbonate and digestive enzymes that assist digestion and the absorption of nutrients in the small intestine. Acute pancreatitis is an acute inflammatory process of the pancreas and is also a public health issue associated with severe morbidity and mortality. The global incidence of acute pancreatitis is 33.74/100,000 person-years, and the mortality is 1.16/100,000 person-years.[9] Many factors can induce acute pancreatitis, gallstone and alcohol abuse being the most common (about 70%). The frequency of acute pancreatitis associated with another autoimmune disease is <1%.[10]

SS is an autoimmune disease involving exocrine glands. Chronic pancreatitis has been found in association with other autoimmune diseases such as SS, primary biliary cirrhosis, and sclerosing cholangitis.[11-13] A study on the association between PSS and acute pancreatitis showed that PSS may increase the acute pancreatitis risk, but the study population excluded individuals with coexisting autoimmune diseases.[14] Since SS may concur with other autoimmune diseases, the association between SS and acute pancreatitis remains unclear. We conducted a nationwide population-based cohort study to assess whether SS increases the acute pancreatitis risk.

METHODS

Data source

We used data from the National Health Insurance Research Database (NHIRD). The NHIRD contains health insurance claim data from the Taiwan NHI program. The Taiwanese government established the NHI in 1995 as a single-payer, compulsory program for all 23 million Taiwanese citizens. The database from the NHIRD contains comprehensive information including a beneficiary registry, demographic data, diagnostic codes, and prescription codes. The diagnostic codes are recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). To protect patient privacy, the NHIRD removes identifying information and assigns an anonymous number before releasing patient records for research. We used the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD, for establishing our study. The Institutional Review Board of Tri-Service General Hospital approved this study.

Sampled patients

We conducted a nationwide population-based cohort study to investigate the association between SS and acute pancreatitis risk. The LHID included patients older than 20 years and diagnosed as having SS (ICD-9-CM code 710.2) between 2000 and 2010 [Figure 1]. Physicians confirmed the diagnoses according to the American-European Consensus Group diagnostic criteria.[4] We excluded any patients with a history of acute pancreatitis (ICD-9-CM code 577.0), chronic pancreatitis (ICD-9-CM code 577.1), or a malignant neoplasm in the pancreas (ICD-9-CM code 157) before the index date, patients younger than 20 years, and those with incomplete medical information. We randomly chose the SS and non-SS cohorts from the LHID and matched them by frequency according to their age, gender, and index year at a 1:4 ratio. The exclusion criteria for the non-SS cohort were the same as those for the SS cohort. We also divided patients with SS into those with PSS and those with SSS for subgroup analyzes. We defined SSS as syndrome including SS accompanying another rheumatic disease such as SLE (ICD-9-CM code 710.0), RA (ICD-9-CM code 714.0), SSc (ICD-9-CM code 710.1), polymyositis (ICD-9-CM code 710.4), or dermatomyositis ((ICD-9-CM code 710.3).

Outcome and comorbidities

All the patients were followed up from the index date until the time of a diagnosis of acute pancreatitis, withdrawal from the NHI program, or December 31, 2010. Baseline comorbidities, such as diabetes mellitus (DM) (ICD-9-CM code 250), hypertriglyceridemia (ICD-9-CM code 272.1), biliary stones (ICD-9-CM code 574), alcohol-related diseases (ARD) (ICD-9-CM codes 291, 303, 305.00–305.03, 790.3, and V11.3), hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, and V02.62), hepatitis B (ICD-9-CM codes 070.20, 070.22, 070.30, 070.32, and V02.61), cardiovascular disease (CVD) (ICD-9-CM codes 410–414, 428, 430–438, and 440–448), chronic kidney disease (CKD) (ICD-9-CM codes 585–586 and 588.8–588.9), and chronic obstructive

pulmonary disease (COPD) (ICD-9-CM codes 491–493 and 496) were also included in our analyses.

Statistical analysis

We compared the distributions of categorical characteristics and baseline comorbidities between patients with or without SS using the Chi-square test. In addition, we compared continuous variables between the cohorts using Student's *t*-tests. We plotted the cumulative incidence of acute pancreatitis for each cohort based on the Kaplan–Meier method and used the log-rank test to analyze differences between the survival curves. The univariate and multivariate Cox proportion hazards regression models were used to analyze the incidence densities (per 10^5 person-years) of acute pancreatitis in each cohort, and we obtained hazard ratios (HRs) categorized by gender, age, and comorbidities such as DM, hypertriglyceridemia, biliary stones, ARD, hepatitis C, hepatitis B, CVD, CKD, and COPD. We performed all analyzes using the SAS 9.4 software (SPSS, Chicago, IL, USA) and considered 2-side tests' $P < 0.05$ as statistically significant.

RESULTS

We included 11,922 patients in the SS cohort and 47,688 patients in the comparison (non-SS) cohort. The age and gender distributions between both cohorts were similar. The patients were predominantly women (81.26%), and most ages ranged between 45 and 69 years (51.35%). Patients with SS had a higher prevalence of hepatitis C and hepatitis B and a lower prevalence of DM, hypertriglyceridemia, biliary stones, ARD, CVD, and COPD than patients without SS [Table 1]. The mean follow-up years for SS and non-SS cohorts were 6.89 ert. 51 and 7.12 ert. 67 years, respectively.

Patients with SS had a higher acute pancreatitis risk than patients without SS (adjusted HR, 3.374; 95% confidence interval [CI], 2.869–3.969; $P < 0.001$) in the multivariate Cox model [Table 2]. The acute pancreatitis risk was higher in men, in patients aged from 45 to 69 years, and in those with DM, hypertriglyceridemia, biliary stones, ARD, or CKD. The cumulative incidence for acute pancreatitis in subsequent years was higher in the SS cohort than in the comparison cohort (log-rank test, $P < 0.001$) [Figure 2].

Table 3 shows the stratified analysis based on gender, age, and comorbidities. The gender-specific relative acute pancreatitis risk in patients with SS was higher than that in patients without SS regardless of gender (adjusted HR, 3.971; 95% CI, 3.305–4.722; adjusted HR, 2.013; 95% CI, 1.410–2.873). The age-specific relative acute pancreatitis risk in patients with SS was higher than in those without SS regardless of the age group. The adjusted HR for acute pancreatitis was higher in patients with SS than in those without it, regardless of the presence of DM (adjusted HR, 3.179; 95% CI, 2.094–4.826), biliary stones (adjusted HR, 3.781; 95% CI, 3.164–4.525), HCV (adjusted HR, 6.545; 95% CI, 2.064–20.750), HBV (adjusted HR, 10.934; 95% CI, 2.044–58.491), CVD (adjusted HR, 3.377; 95% CI, 1.966–5.662), CKD (adjusted HR, 2.499; 95% CI, 1.131–5.523), or COPD (adjusted HR, 4.740; 95% CI, 2.146–10.471).

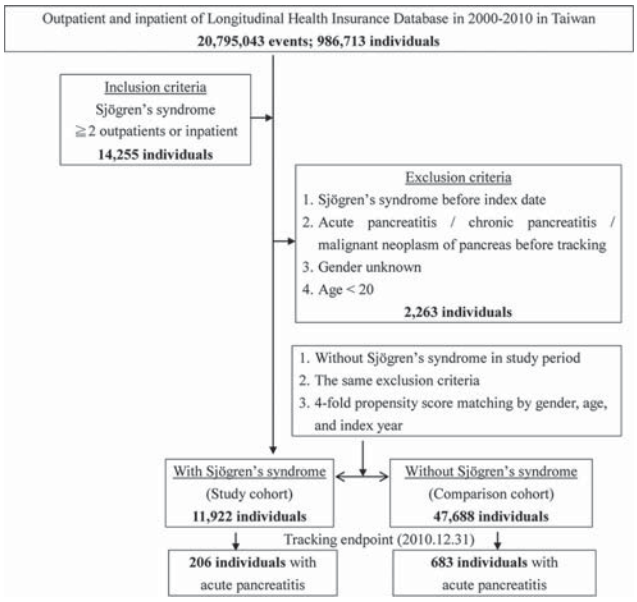

Figure 1: Flow chart of the process used to select the study partcipants from the National Health Insurance Research Database in Taiwan

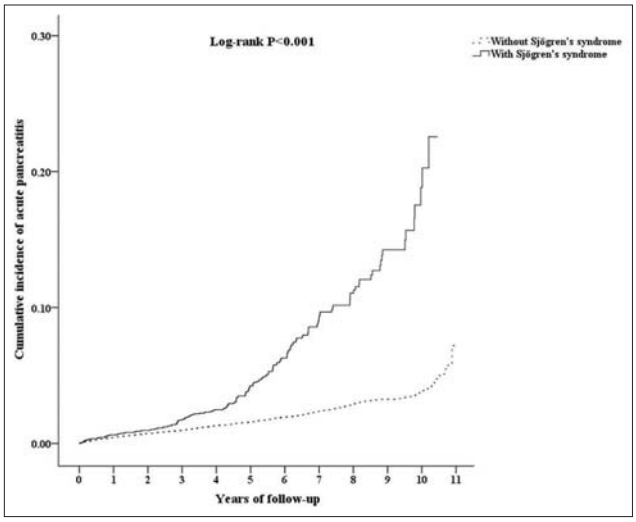

Figure 2: Kaplan–Meier analysis of the cumulative incidence of acute pancreatitis between the Sjögren's syndrome and non-Sjögren's syndrome cohorts (log-rank $P < 0.001$)

Table 1: Comparison of the demographics, characteristics, and comorbidities of the Sjögren's syndrome and non-Sjögren's syndrome cohorts

Variables	SS			*P*
	Total, *n* (%)	With, *n* (%)	Without, *n* (%)	
Total	59,610	11,922 (20.00)	47,688 (80.00)	
Gender				
Male	11,170 (18.74)	2234 (18.74)	8936 (18.74)	0.999
Female	48,440 (81.26)	9688 (81.26)	38,752 (81.26)	
Age (years)	56.25±17.26	56.30±16.03	56.24±17.55	0.734
Age group (years)				
20-44	15,135 (25.39)	3027 (25.39)	12,108 (25.39)	0.999
45-69	30,610 (51.35)	6122 (51.35)	24,488 (51.35)	
≧70	13,865 (23.26)	2773 (23.26)	11,092 (23.26)	
DM				
Without	52,433 (87.96)	11,086 (92.99)	41,347 (86.70)	<0.001
With	7177 (12.04)	836 (7.01)	6341 (13.30)	
Hypertriglyceridemia				
Without	59,420 (99.68)	11,905 (99.86)	47,515 (99.64)	<0.001
With	190 (0.32)	17 (0.14)	173 (0.36)	
Biliary stones				
Without	58,305 (97.81)	11,792 (98.91)	46,513 (97.54)	<0.001
With	1305 (2.19)	130 (1.09)	1175 (2.46)	
ARD				
Without	59,526 (99.86)	11,915 (99.94)	47,611 (99.84)	0.006
With	84 (0.14)	7 (0.06)	77 (0.16)	
HCV				
Without	58,963 (98.91)	11,570 (97.05)	47,393 (99.38)	<0.001
With	647 (1.09)	352 (2.95)	295 (0.62)	
HBV				
Without	59,205 (99.32)	11,728 (98.37)	47,477 (99.56)	<0.001
With	405 (0.68)	194 (1.63)	211 (0.44)	
CVD				
Without	50,403 (84.55)	10,297 (86.37)	40,106 (84.10)	<0.001
With	9,207 (15.45)	1,625 (13.63)	7582 (15.90)	
CKD				
Without	58,131 (97.52)	11,680 (97.97)	46,451 (97.41)	<0.001
With	1479 (2.48)	242 (2.03)	1237 (2.59)	
COPD				
Without	56,632 (95.00)	11,485 (96.33)	45,147 (94.67)	<0.001
With	2978 (5.00)	437 (3.67)	2541 (5.33)	

P (category variable: Chi-square/Fisher's exact test; continue variable: *t*-test). SS=Sjögren's syndrome; DM=diabetes mellitus; ARD=Alcohol-related diseases; HCV=Hepatitis C; HBV=Hepatitis B; CVD=Cardiovascular disease; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease

In Table 4, the subgroup analysis revealed that patients with PSS or SSS both had significantly increased acute pancreatitis risks than patients without SS (adjusted HR, 2.872; 95% CI, 2.611–3.901; and adjusted HR, 4.121; 95% CI, 3.752–5.124, respectively). Besides, patients with SS and SLE, RA, SSc, or polymyositis and dermatomyositis had higher acute

Table 2: Factors of acute pancreatitis by using cox regression

Variables	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
SS				
Without	Reference	<0.001	Reference	<0.001
With	3.058 (2.608-3.586)		3.374 (2.869-3.969)	
Gender				
Male	1.328 (1.139-1.549)	<0.001	1.427 (1.219-1.670)	<0.001
Female	Reference		Reference	
Age group (years)				
20-44	Reference		Reference	
45-69	1.539 (1.247-1.900)	<0.001	1.304 (1.051-1.618)	0.016
≧70	1.087 (0.875-1.351)	0.452	1.076 (0.856-1.353)	0.529
DM				
Without	Reference	0.034	Reference	<0.001
With	1.180 (1.012-1.376)		1.360 (1.161-1.594)	
Hypertriglyceridemia				
Without	Reference	<0.001	Reference	<0.001
With	6.124 (3.052-12.287)		5.269 (2.601-10.674)	
Biliary stones				
Without	Reference	<0.001	Reference	<0.001
With	14.013 (12.046-16.300)		13.909 (11.915-16.238)	
ARD				
Without	Reference	<0.001	Reference	<0.001
With	9.618 (5.562-16.632)		11.424 (6.537-19.964)	
HCV				
Without	Reference	0.960	Reference	0.120
With	1.013 (0.608-1.688)		0.652 (0.390-1.088)	
HBV				
Without	Reference	0.950	Reference	0.710
With	0.978 (0.488-1.962)		0.876 (0.436-1.759)	
CVD				
Without	Reference	<0.001	Reference	<0.001
With	0.444 (0.360-0.549)		0.526 (0.424-0.653)	
CKD				
Without	Reference	<0.001	Reference	<0.001
With	1.698 (1.304-2.211)		2.078 (1.592-2.712)	
COPD				
Without	Reference	<0.001	Reference	0.006
With	0.502 (0.352-0.714)		0.607 (0.425-0.867)	

HR=Hazard ratio; CI=Confidence interval; DM=Diabetes mellitus; ARD=Alcohol-related diseases; HCV=Hepatitis C; HBV=Hepatitis B; CVD=Cardiovascular disease; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; SS=Sjögren's syndrome

pancreatitis risks (adjusted HR, 3.85; 95% CI, 3.259–4.999; adjusted HR, 4.298; 95% CI, 3.862–5.286; adjusted HR, 2.765; 95% CI, 2.26–3.68; adjusted HR, 2.641; 95% CI, 1.847–3.101; and adjusted HR, 3.77; 95% CI, 2.894–4.502) than the patients in the non-SS cohort. Patient with PSS and SSS exhibited a significantly increased cumulative acute pancreatitis risk in subsequent years than the patients without SS (log-rank test, $P < 0.001$) [Figure 3].

Table 3: Incidence and adjusted hazard ratio for acute pancreatitis in the Sjögren's syndrome and non-Sjögren's syndrome cohorts stratified by sex age and comorbidities

Variables	SS					
	With		Without		With versus without (reference)	
	Event	Rate (per 10^5 PYs)	Event	Rate (per 10^5 PYs)	Adjusted HR (95% CI)	*P*
Total	206	1011.69	683	730.34	3.374 (2.869-3.969)	<0.001
Gender						
Male	39	943.67	175	626.50	3.971 (3.305-4.722)	<0.001
Female	167	1029.01	508	774.56	2.013 (1.410-2.873)	<0.001
Age group (years)						
20-44	33	851.89	75	516.78	3.355 (2.203-5.109)	<0.001
45-69	113	1148.39	330	882.40	3.239 (2.592-4.046)	<0.001
≧70	60	902.48	278	668.15	3.436 (2.572-4.591)	<0.001
DM						
Without	178	981.63	494	677.49	3.439 (2.799-3.984)	<0.001
With	28	1256.22	189	917.37	3.179 (2.094-4.826)	<0.001
Hypertriglyceridemia						
Without	204	1002.81	677	725.05	3.371 (2.864-3.968)	<0.001
With	2	10,454.78	6	4118.90	4.401 (0.414-13.907)	0.329
Biliary stones						
Without	176	879.88	488	541.26	2.108 (1.414-3.141)	<0.001
With	30	8353.99	195	4578.97	3.781 (3.164-4.525)	<0.001
ARD						
Without	206	1012.86	670	717.55	3.436 (2.920-4.043)	<0.001
With	0	0.00	13	8966.75	0.000	0.985
HCV						
Without	199	1001.39	675	732.93	3.322 (2.818-3.916)	<0.001
With	7	1429.88	8	562.56	6.545 (2.064-20.750)	0.001
HBV						
Without	202	1003.52	679	732.41	3.325 (2.823-3.916)	<0.001
With	4	1718.95	4	493.37	10.934 (2.044-58.491)	0.005
CVD						
Without	186	1106.62	606	829.46	3.355 (2.828-3.981)	<0.001
With	20	562.76	77	376.37	3.377 (1.966-5.662)	<0.001
CKD						
Without	197	995.66	633	706.67	3.396 (2.875-4.011)	<0.001
With	9	1562.17	50	1268.02	2.499 (1.131-5.523)	0.024
COPD						
Without	197	1032.21	660	758.20	3.344 (2.833-3.948)	<0.001
With	9	704.95	23	355.47	4.740 (2.146-10.471)	<0.001

PYs=Person-years; HR=Hazard ratio; CI=Confidence interval; DM=Diabetes mellitus; ARD=Alcohol-related diseases; HCV=Hepatitis C; HBV=Hepatitis B; CVD=Cardiovascular disease; CKD=Chronic kidney disease; COPD=Chronic obstructive pulmonary disease; SS=Sjögren's syndrome

DISCUSSION

We conducted a nationwide population-based cohort study to investigate the acute pancreatitis risk in patients with SS after subgroup analyses. After adjusting for gender, age, and comorbidities, the multivariate Cox model showed that patients with SS had a 3.374-fold higher acute pancreatitis risk than those without SS. This study also showed that

Table 4: Incidence and adjusted hazard ratio for acute pancreatitis in different models stratified by Sjögren's syndrome and other autoimmune diseases

Model	SS subgroup	Events	Rate (per 10^5 PYs)	Adjusted HR (95% CI)	*P*
Model 1	Without	683	730.34	Reference	
	With	206	1011.69	3.374 (2.869-3.969)	<0.001
Model 2	Without	683	730.34	Reference	
	Primary SS	92	958.50	2.872 (2.611-3.901)	<0.001
	Secondary SS	114	1,059.12	4.121 (3.752-5.124)	<0.001
Model 3	Without	683	730.34	Reference	
	SS only	92	958.50	2.872 (2.611-3.90) 1	<0.001
	SS + SLE	43	1029.98	3.850 (3.259-4.999)	<0.001
	SS + RA	57	1145.87	4.298 (3.862-5.286)	<0.001
	SS + SCc	8	839.80	2.765 (2.260-3.680)	0.001
	SS + polymyositis	2	777.63	2.641 (1.847-3.101)	0.007
	SS + dermatomyositis	4	988.63	3.770 (2.894-4.502)	<0.001

PYs=Person-years; HR=Hazard ratio; CI=Confidence interval; SLE=Systemic lupus erythematosus; RA=Rheumatoid arthritis; SSc=Systemic sclerosis

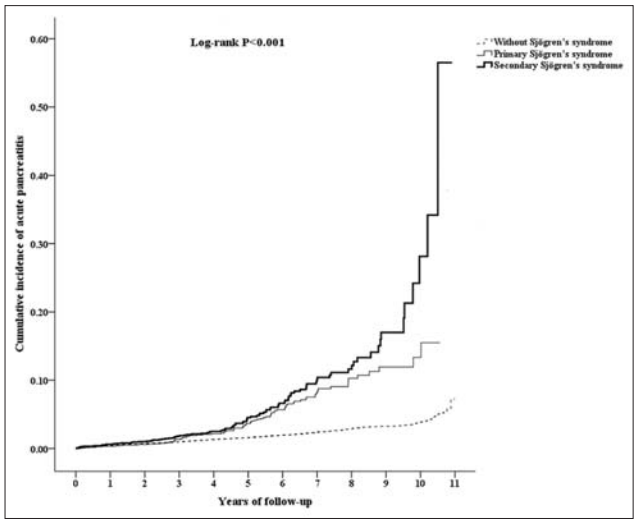

Figure 3: Kaplan–Meier analysis of the cumulative incidence of acute pancreatitis in primary, secondary Sjögren's syndrome, and non-Sjögren's syndrome cohorts (log-rank $P < 0.001$)

patients with SSS (including SLE, RA, SSc, polymyositis, and dermatomyositis) had higher acute pancreatitis risks than patients in the non-SS cohort (adjusted HR, 4.121; 95% CI, 3.752–5.124).

We observed that patients with SS had a significantly higher acute pancreatitis incidence than the comparison cohort, regardless of gender, age, and comorbidities such as DM, biliary stones, HCV, HBV, CVD, CKD, and COPD [Table 3]. Like other studies, ours indicated that middle-aged men, the presence of DM, hypertriglyceridemia, biliary stones, ARD, or CKD are independent risk factors for acute pancreatitis [Table 2].[10,15,16] These findings strengthen the finding of SS being an independent factor for acute pancreatitis.

Our study showed a 2.872-fold higher acute pancreatitis risk in patients with PSS and a 4.121-fold higher risk in patients with SSS than the risk in the non-SS cohort. The exact mechanism of PSS-induced acute pancreatitis remains unknown. The activation of the innate immune system and production of interferons (IFNs) could represent the first PSS pathogenesis stages. Dendritic cell-secreted interleukin (IL)-12 leads to the activation of natural killer cells and type-1 Thelper cells that increase IFN-γ production and mediate tissue damage. Besides, IFN-α and IFN-γ enhance Bcellactivating factor (BAFF) secretion, creating a bridge between innate immunity and autoimmune Bcell activation in patients with PSS.[17,18] One study showed serum BAFF levels increasing significantly in patients with acute pancreatitis due to an acute phase reaction, and the levels reflected the disease severity.[19] The immune cells and cytokine interaction may play a crucial role in PSS-induced acute pancreatitis.

Our study showed patients with SS and other autoimmune diseases had higher acute pancreatitis risks than patients with PSS. Another study had shown that patients with overlapping SS and RA had a higher prevalence of arthritis, interstitial lung disease, and anemia, with elevated erythrocyte sedimentation rate, and high C-reactive protein levels than patients with PSS.[20] A possible mechanism by which RA increases the acute pancreatitis risk may involve a vasculitis that causes pancreatic ischemia.[21,22] On the other hand, patients with SLE and SS display a higher frequency of Raynaud's phenomenon, arthritis, central nervous system involvement, serositis, and perivascular infiltrates in the salivary glands than patients with PSS.[23] In a Chinese population study, 27 of 4053 patients with SLE had acute pancreatitis with

a high mortality rate (37.04%) due to severe SLE activity and multiple organ involvement.[24] The mechanism of SLE-related acute pancreatitis is multifactorial and includes vascular damage, drug toxicity, autoantibody reactions, or abnormal cellular immune responses.[25,26] Few case reports have presented juvenile dermatomyositis with pancreatitis; in those cases, vasculitis was the possible cause for the SLE-related pancreatitis.[27] However, no study has examined the association between acute pancreatitis and either scleroderma or polymyositis. We hypothesize that the presence of multiple autoimmune diseases may worsen the inflammation process and vasculitis, thereby increasing the acute pancreatitis risk in patients with SS.

Autoimmune pancreatitis (AIP) was first described by Yoshida *et al*. in 1995,[28] and the term was adopted for pancreatic disease of an autoimmune origin. The diagnostic AIP criteria proposed by the Mayo Clinic (the "HISORt" criteria) include 5 items: histology, imaging, serum immunoglobulin G4 (IgG4) level, other organ involvement, and response to therapy.[29] AIP is classified into two subtypes. Type 1 AIP is a systemic disease affecting the pancreas, salivary glands, and kidneys, while type 2 AIP affects only the pancreas.[10,30,31] A serum IgG4 concentration ≥2 times the upper normal limit is highly suggestive of AIP.[32] Some studies have shown raised IgG4 serum levels and IgG4-positive plasma cell infiltration in labial salivary glands of patients with SS.[33,34] Because we could not record the IgG4 level in this retrospective cohort study, the role of IgG4 in AIP and SS needs to be further studied.

We are aware of the limitations of our study. First, the NHIRD lacks information on patient behaviors, physical examinations, and crucial acute pancreatitis risk factors, such as smoking, obesity or BMI, dietary habits, and alcohol consumption. Second, relevant clinical variables including laboratory data, imaging results, and lip biopsy results were unavailable in the database. Third, due to the retrospective nature of our cohort study, bias from unknown confounders may have affected our results, and a well-designed randomized prospective control study is still necessary to help establish a causal relationship.

CONCLUSIONS

This study demonstrated that patients with SS exhibited a 3.374-fold higher acute pancreatitis risk than individuals in the general population. Both PSS and SSS increased the acute pancreatitis risk. Physicians should be aware of the possibility of acute pancreatitis when caring for patients with SS, particularly also having other autoimmune diseases.

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Conflicts of interest

There are no conflicts of interest.

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