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Risk of Chronic Obstructive Pulmonary Disease in Female Adults With Primary Sjögren Syndrome

A Nationwide Population-Based Cohort Study

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Abstract: No large-scale population-based cohort study has ever investigated the risk of developing chronic obstructive pulmonary disease (COPD) in patients with Sjögren syndrome (SS). This study evaluated the risk of COPD in women with primary SS (pSS) in a nationwide population.

We used the data of the National Health Insurance Research Database of Taiwan to establish a pSS group consisting of 3013 female adults diagnosed between 2000 and 2005, and a non-SS group consisting of 12,052 women without SS matched by a propensity score. Incident COPD cases were identified to the end of 2011. The pSS group to non-SS group adjusted hazard ratios (aHRs) of COPD were estimated using multivariable Cox proportional hazards regression analysis.

After a mean follow-up period of 7.99 years, the incidence of COPD was 1.4-fold greater in the pSS group than in the non-SS group (3.87 vs 2.77 per 1000 person-years) with an aHR of 1.39 (95% confidence interval [CI] = 1.10–1.75, $P = 0.007$). The COPD incidence was 7-fold greater for women aged 50 years and above than women aged 20 to 49, with the aHR of 4.24 (95% CI = 3.06–5.88, $P < 0.001$). Comorbidity increased the COPD risk further for women with pSS. Women with both pSS and comorbidity had an aHR of 3.11 (95% CI = 2.23–4.33, $P < 0.001$) for COPD, compared to those free of both pSS and comorbidity.

Women with pSS are at a greater risk of developing COPD than those without SS. Patients with SS require close monitoring to prevent COPD development, particularly for those with comorbidity.

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Abbreviations: CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, FEV1 = forced expiratory volume in first second, FVC = forced vital capacity, HR = hazard ratio, ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, SD = standard deviation, SLE = systemic lupus erythematosus, SMD = standardized mean difference, SS = Sjögren syndrome.

INTRODUCTION

Sjögren syndrome (SS) is an autoimmune condition in which the immune system reacts abnormally and attacks healthy cells and tissue. The typical symptom in patients with SS is dryness, which mainly attacks the eyes and mouth. In addition to affecting the tear and saliva glands, the immune system also attacks other secretary glands in the body. More than 90% of patients with SS are women.[1] The etiology of SS remains largely unknown, but it is likely triggered by a combination of genetic, environmental, and hormonal factors.[2] When the syndrome develops without a known cause, it is defined as primary SS (pSS); when the syndrome develops in association with other autoimmune disorder such as lupus or rheumatoid arthritis, it is known as secondary SS.

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory response in the airways and the lungs. Patients suffer from persistent airflow obstruction which is usually progressive. Spirometry is usually required to diagnose the disease in clinics. The postbronchodilator ratio of forced expiratory volume in 1 second (FEV1) and forced vital capacity

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(FVC) were generally measured. A FEV1 to FVC ratio of <0.70 was considered as having persistent airflow limitation.[3] Cigarette smoking is a known risk factor in the development of COPD; however, a substantial number of COPD patients have never smoked.[4,5] Other contributing factors must therefore exist, one of which could be autoimmunity. Indeed, studies have reported that autoimmune pathology plays a role in the development and progression of COPD.[6–12]

Among studies for the association between autoimmune diseases and COPD, some evidences suggest that SS has the pulmonary involvement.[13–15] Mandl et al recently reported that pSS patients showed deterioration in FEV1 and in the ratio of FEV1 to FVC after a mean follow-up time of 11 years.[16] In addition, they found that 37% of the pSS patients developed COPD during the follow-up. However, their study lacked a comparison group and included only a small number of cases; therefore, the relationship between pSS and COPD deserves more studies.

The National Health Insurance (NHI) database of Taiwan is a nationwide database with the longitudinal medical data of ~23 million people. The claims data are reliable and have been used for various studies, including those on SS or COPD.[17–20] The present study attempts to use the data to determine if there is a higher risk of COPD in adult women with pSS.

MATERIALS AND METHODS

Data Sources

Taiwan's NHI program has offered a universal health insurance coverage to >99% of all residents of Taiwan since 1995. Taiwan's National Health Research Institute (NHRI) has been responsible to manage the claims data and to establish the National Health Insurance Research Database (NHIRD) containing medical claims from 1996 to 2011 for public uses. To protect all individuals' privacy, identifications of insured individuals had been encrypted before the data files were released. The NHIRD contains outpatient and inpatient information on demographic status, dates of cares, diagnostic codes, and details of prescriptions. The diseases were coded using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) in the NHIRD. In the present study, the diagnosis of SS was defined according to the American-European Consensus Group diagnostic criteria[21] and was confirmed by experts specialized in the disease field. This study was approved by the Research Ethic Review committee of China Medical University and Hospital (CMUH104-REC2-115).

Study Population

We conducted a population-based retrospective cohort study with 2 cohorts: the pSS group and the non-SS group. Using the NHIRD, females newly diagnosed with SS (ICD9-CM 710.2) during 2000 to 2005 were identified (n = 4475) for the potential study cohort of pSS. Those with a secondary SS (n = 335) at the baseline were excluded. We further excluded patients <20 years of age (n = 39) and with the history of COPD (ICD-9-CM 491, 492, and 496) (n = 1088) from the pSS cohort. A secondary SS was defined as a diagnosis of SS in patients with a previous history of rheumatoid arthritis (ICD-9-CM 714), systemic lupus erythematosus (SLE; ICD-9-CM 710.0), systemic sclerosis (ICD-9-CM 701.1), or primary biliary cirrhosis (ICD-9-CM 571.6). The date with pSS diagnosed was defined as the index date. From the same period of 2000 to 2005, we randomly selected 4-fold of women without the history of SS and COPD from the NHIRD as the non-SS group, matched by the propensity score to increase their comparability between the 2 groups. Subjects <20 years of age were also excluded for the non-SS group. We used a logistic regression model, including year of index date, age, and comorbidities of hypertension, diabetes, hyperlipidemia, coronary artery disease (CAD), stroke and chronic kidney disease (CKD), to estimate the probability of assigning a women to the study cohorts.

Covariates and Outcome

The medical records of comorbidities were obtained before the index date; these comorbidities included hypertension (ICD-9-CM 401–405), diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), CAD (ICD-9-CM 410–414), stroke (ICD-9-CM 430–438), and CKD (ICD-9-CM 585). The primary outcome was COPD, which was determined by linking outpatient and/or inpatient care data from the NHIRD. To increase the validity of COPD diagnoses, we included only those patients who had been diagnosed with COPD and treated with relevant medication. Both groups were followed from the index date to the date of COPD diagnosis, withdrawal from the NHI system, or the end of 2011.

Statistical Analysis

Data were expressed as frequencies and percentages for categorical data and as means and standard deviations (SD) calculated for continuous variables. We compared the distributions of age and comorbidity between the pSS group and the non-SS group. The standardized mean difference (SMD) was calculated by the pooled value to determine whether the difference between the 2 group significant. A value of 0.1 or less was considered as a negligible difference between 2 groups.[22] Incidence density rates of COPD were calculated for both groups (per 1000 person-years) stratified by age and comorbidity. The Kaplan–Meier method was used to plot the cumulative incidences of COPD during the follow-up period, and the log-rank test was used to assess the differences between the survival

TABLE 1. Age and Comorbidities in Cohorts With and Without Primary Sjögren Syndrome

	Primary SS				
	No N = 12,052		Yes N = 3013		Standardized Mean Difference
Variables	n	%	n	%	
Age, y					0.01
20–49	6098	50.6	1515	50.3	
≥ 50	5954	49.4	1498	49.7	
Mean (SD)	51.0	(15.0)	50.5	(13.0)	0.04
Comorbidity					
Hypertension	2853	23.7	761	25.3	0.04
Diabetes	983	8.16	283	9.39	0.07
Hyperlipidemia	2163	18.0	619	20.5	0.04
CAD	1473	12.2	455	15.1	0.08
Stroke	197	1.63	58	1.92	0.02
CKD	42	0.34	12	0.40	0.08*

CAD = coronary artery disease, CKD = chronic kidney disease, SD = standard deviation, SS = Sjögren syndrome.
* Fisher exact test.

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curves. Univariate and multivariate Cox proportion hazards regression models were used to examine the hazard ratios (HRs) and 95% confidence intervals (CIs) of incident COPD and COPD-associated risk factors. HRs between age groups and between groups with and without comorbidity were calculated. We also performed age- and comorbidity-specific stratified analyses to measure the pSS group to the non-SS group HRs of developing COPD. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC), and a 2-sided $P < 0.05$ was considered statistically significant.

RESULTS

The pSS group consisted of 3013 female adults diagnosed with pSS from 2000 to 2005, and the non-SS group comprised 12,052 women without SS. Table 1 compares the distributions of age and comorbidities between the pSS and non-SS groups. There were no significant differences between the pSS group and non-SS group in the distributions of age and comorbidity.

Figure 1 shows that the cumulative incidence of COPD was significantly higher in the pSS group than in the non-SS group during the follow-up period ($P < 0.001$) in the log-rank test. After an average follow-up period of 7.99 years, the incidence density rate of COPD was greater in the pSS group than in the non-SS groups (3.87 vs 2.77 per 1000 person-years, respectively) (Table 2). Women with pSS had an aHR of 1.39 to develop COPD (95% CI = 1.10–1.75, $P = 0.007$) compared

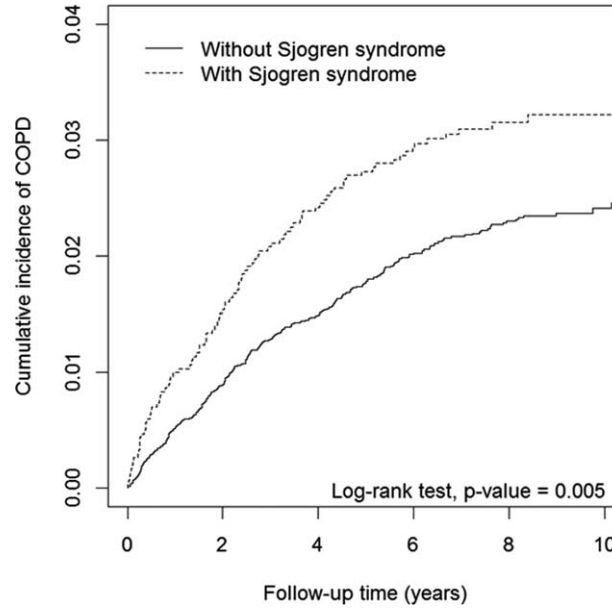

FIGURE 1. Cumulative incidence of chronic obstructive pulmonary disease in female adults with and without primary Sjogren syndrome.

TABLE 2. Cox Model Measured Hazard Ratios and 95% Confidence Intervals of Chronic Obstructive Pulmonary Disease Associated With Primary Sjögren Syndrome and Covariates

				HR (95% CI)			
Variables	**Events**	**Person-years**	**IR**	**Univariate**	***P* Value**	**Multivariate***	***P* Value**
Primary SS							
No	266	96020	2.77	1.00		1.00	
Yes	94	24314	3.87	1.40 (1.11–1.78)	0.005	1.39 (1.10–1.75)	0.007
Age, y							
20–49	49	62983	0.78	1.00		1.00	
≥ 50	311	57352	5.42	6.82 (5.05–9.22)	<0.001	4.24 (3.06–5.88)	<0.001
Comorbidity							
Hypertension							
No	153	93392	1.64	1.00		1.00	
Yes	207	26943	7.68	4.56 (3.70–5.62)	<0.001	2.12 (1.65–2.72)	<0.001
Diabetes							
No	291	111242	2.62	1.00		1.00	
Yes	69	9093	7.59	2.78 (2.14–3.61)	<0.001	1.29 (0.97–1.70)	0.08
Hyperlipidemia							
No	236	98573	2.39	1.00		1.00	
Yes	124	21761	5.70	2.35 (1.89–2.93)	<0.001	1.00 (0.79–1.28)	0.97
CAD							
No	242	105855	2.29	1.00		1.00	
Yes	118	14479	8.15	3.51 (2.82–4.37)	<0.001	1.50 (1.18–1.91)	0.001
Stroke							
No	341	118711	2.87	1.00		1.00	
Yes	19	1624	11.7	3.75 (2.36–5.95)	<0.001	1.40 (0.88–2.25)	0.16
CKD							
No	359	120025	2.99	1.00		1.00	
Yes	1	310	3.23	0.98 (0.14–6.96)	0.98	0.48 (0.07–3.43)	0.46

CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, IR = incidence rate, per 1000 person-years, SS = Sjögren syndrome.

* Adjusted for age and comorbidities in Cox proportional hazards regression.

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with those without SS after adjusting for age and comorbidities. The risk of developing COPD appears to increase with age. Individuals aged >50 had an aHR of 4.24 (95% CI = 3.06–5.88, $P < 0.001$) compared with individuals aged 20 to 49. The incidence of COPD was higher for individuals with hypertension (HR = 2.12, 95% CI = 1.65–2.72, $P < 0.001$) and CAD (HR = 1.50, 95% CI = 1.18–1.91, $P = 0.001$).

Table 3 shows incidences and hazard ratios of COPD for the pSS group compared with non-SS group by age and comorbidities. The impact of pSS on developing COPD was greater for younger pSS subgroup (aged 20–49 years) than for older pSS subgroup (aged ≥ 50 years) and slightly greater for pSS subjects without comorbidity than for those with comorbidities. The hazards of COPD for the pSS group compared with non-SS group were also significant for individuals with hyperlipidemia (aHR = 1.66, 95 % CI = 1.13–2.45, $P = 0.01$), hypertension (aHR = 1.56, 95% CI = 1.12–2.16, $P = 0.008$), and CAD (aHR = 1.52, 95% CI = 1.01–2.30, $P = 0.04$).

However, Table 4 shows that the risk of COPD had a stronger association with comorbidity than with pSS. Women with both pSS and comorbidity had an aHR of 3.11 (95% CI = 2.23–4.33, $P < 0.001$) for COPD, compared with those free of both pSS and comorbidity.

DISCUSSION

To the best of our knowledge, this is the first nationwide population-based cohort study evaluating patients with pSS for their subsequent risk of developing COPD. The study demonstrates that female adults with pSS have an increased risk of developing COPD, compared with female adults without SS. Furthermore, we found that incidence of COPD was substantially higher in older people (aged ≥ 50 years) in both the pSS and non-SS groups. However, the aHR of COPD for the pSS group compared with non-SS group was greater in younger patients (aged 20–49 years) than in the older patients (aged ≥ 50 years), indicating that SS alone has a greater impact for younger patients to develop COPD, whereas the overall hazard was greater for older women. A possible explanation for this might be that older people, whether affected by pSS or not, tend to have prolonged and sufficient exposure to risk factors and be affected by more comorbid diseases than younger people, and these are risk factors of COPD. Another possibility is that using a fixed ratio (FEV1/FVC = 70%) to define obstructive ventilation defeat often causes an overestimation of COPD prevalence in the elderly population.

Several hypotheses can be postulated on the relationship between SS and COPD. Mandl et al have suggested that the

TABLE 3. Incidences and Hazard Ratios of Chronic Obstructive Pulmonary Disease for Primary Sjögren Syndrome Group Compared With Non-Sjögren Syndrome Group by Age and Comorbidities

	Primary SS									
	No			Yes			HR (95% CI)			
Variables	Events	Person-year	IR	Events	Person-year	IR	Crude	*P* Value	Adjusted*	*P* Value
Age, y										
20–49	30	50131	0.60	19	12852	1.48	2.55 (1.43–4.53)	0.001	2.41 (1.35–4.30)	0.003
≥ 50	236	45889	5.14	75	11463	6.54	1.26 (0.97–1.63)	0.08	1.26 (0.97–1.63)	0.09
Comorbidity status†										
No	74	64345	1.15	25	14463	1.73	1.53 (0.97–2.40)	0.07	1.72 (1.09–2.72)	0.02
Yes	192	31675	6.06	69	9851	7.00	1.16 (0.8–1.52)	0.30	1.56 (1.18–2.06)	0.002
Comorbidity										
Hypertension										
No	108	74826	1.44	45	18566	2.42	1.70 (1.20–2.40)	0.003	1.65 (1.16–2.35)	0.005
Yes	158	21194	7.45	49	5748	8.52	1.15 (0.83–1.58)	0.41	1.56 (1.12–2.16)	0.008
Diabetes										
No	209	89070	2.35	82	22172	3.70	1.58 (1.23–2.05)	<0.001	1.80 (1.39–2.33)	<0.001
Yes	57	6950	8.20	12	2142	5.60	0.70 (0.38–1.30)	0.26	0.99 (0.53–1.86)	0.97
Hyperlipidemia										
No	179	79020	2.27	57	19553	2.92	1.30 (0.97–1.76)	0.08	1.59 (1.17–2.15)	0.003
Yes	87	17000	5.12	37	4762	7.77	1.50 (1.02–2.20)	0.04	1.66 (1.13–2.45)	0.01
CAD										
No	180	84973	2.12	62	20883	2.97	1.41 (1.06–1.88)	0.02	1.62 (1.21–2.17)	0.001
Yes	86	11047	7.78	32	3432	9.32	1.19 (0.80–1.79)	0.39	1.52 (1.01–2.30)	0.04
Stroke										
No	248	94817	2.62	93	23894	3.89	1.50 (1.18–1.90)	<0.001	1.72 (1.35–2.19)	<0.001
Yes	18	1203	15.0	1	421	2.38	0.16 (0.02–1.23)	0.08	0.39 (0.05–2.99)	0.36
CKD										
No	266	95789	2.78	93	24235	3.84	1.39 (1.10–1.76)	0.006	1.62 (1.28–2.06)	<0.001
Yes	0	231	0.00	1	79	12.7	–	–	–	–

CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, HR = hazard ratio, IR = incidence rate, per 1000 person-years, SS = Sjögren syndrome.

* Adjusted for age and comorbidities in Cox proportional hazards regression.

† Patients with any comorbidity of hypertension, diabetes, hyperlipidemia, CAD, stroke, and CKD were classified as the comorbidity group.

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TABLE 4. Joint Effect Between Primary Sjögren Syndrome and Comorbidity in Association With Chronic Obstructive Pulmonary Disease in Study Population

					HR (95% CI)			
Primary SS	**Comorbidity***	**N**	**Events**	**IR**	**Crude**	***P* Value**	**Adjusted†**	***P* Value**
No	No	7890	74	1.15	1.00		1.00	
No	Yes	4162	192	6.06	5.16 (3.95–6.75)	<0.001	2.01 (1.51–2.67)	<0.001
Yes	No	1733	25	1.73	1.52 (0.97–2.39)	0.07	1.73 (1.10–2.73)	0.02
Yes	Yes	1280	69	7.00	5.97 (4.30–8.29)	<0.001	3.11 (2.23–4.33)	<0.001

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 person-years, SS = Sjögren syndrome.
* Model was adjusted for age.
† Patients with any comorbidity of hypertension, diabetes, hyperlipidemia, coronary artery disease, stroke, and chronic kidney disease were classified as the comorbidity group.

inflammation of exocrine glands and mucosal dryness in the airways, dysfunction of mucociliary clearance, and interaction between sicca and smoking may increase the risk of developing COPD.[16] In addition, some other theories support autoimmune pathogenesis of COPD.[23,24] Consistent with the results of the present study, Hemminki et al reported that the risk of COPD increased in patients with several autoimmune diseases, including SS with an observed to expected incidence ratio of 1.89 (95 % CI = 1.12–2.99).[25]

Tobacco smoking may be the most important potential confounding factor in the present study because the NHIRD does not contain data on personal smoking habits. However, Karabulut et al reported a weak association between cigarette smoking and the development of pSS.[26] In addition, most studies reported no significant difference in smoking between pSS patients and controls[27–29] or even significantly fewer smokers in SS patient groups.[30,31] Therefore, patients with SS do not necessarily have a significantly higher smoking rate than those without SS.

In the present study, we also evaluated the risk of COPD in association with several cardiovascular-related diseases. We found that HRs of COPD were significant for hypertension, diabetes, hyperlipidemia, CAD, and stroke in our univariate analysis. But the HRs of COPD remained significant only for hypertension and CAD in the multivariate analysis. These data are valuable for further studies because the incidence of COPD has risen in women in recent years.[32]

The strength of this study comes from providing a longitudinal population-based evaluation of pSS patients and their risk of developing COPD. It is generally costly to conduct a population-based prospective cohort study. On the other hand, a retrospective cohort study, using the existing data, is a suitable alternative that is economical and meets the necessary follow-up requirements. However, several limitations of the study must be considered when interpreting the study findings. First, this study used the ICD-9-CM algorithm to define SS, COPD, and comorbidities. The diagnosis depends on the performance of clinical physicians. However, an ad hoc committee established by the insurance authority has been responsible to monitor the claims data to prevent errors and violations. In addition, SS is categorized as a ''catastrophic illness'' in the insurance system and patients diagnosed with SS are entitled to receive the ''catastrophic illness certification'' issued by the insurance authority. The certification process requires the confirmation from experts specialized in the disease field based on medical records including serological and/or pathological evidences. The diagnosis of SS is likely correct, regardless that data of pathological reports were unavailable in the claims data. Second, the NHIRD does not provide detailed information on socioeconomic status, environmental factors, smoking habits, alcohol consumption, diet preference, or family history, but these are all potential confounding factors for this study. In addition, this study followed the 2 study cohorts for 6 to 11 years, which might be not long enough to observe the development of all COPD cases, particularly our study groups were relatively young. Therefore, we might underestimate the risk of COPD for patients with SS.

CONCLUSION

Our study suggests that women with pSS apparently have a greater risk of developing COPD than women without SS. This finding may lead to develop monitor strategy for patients with SS more emphasis on COPD screening, particularly for SS patients with comorbidity.

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