Journal of Computers Vol. 30 No. 6, 2019, pp. 232-241
doi:10.3966/199115992019123006019

A Bidirectional Study between Rheumatoid Arthritis and Sjogren's Syndrome: A Population-based Cohort Study in Taiwan

Ming-Chien Chiang[1], Chia-Ru Chung[1], Jorng-Tzong Horng[1,2*], Chien-Lung Chen[3]

[1] Department of Computer Science and Information Engineering, National Central University, Taoyuan City 32001, Taiwan
107522045@cc.ncu.edu.tw, jjrchris@g.ncu.edu.tw

[2] Department of Bioinformatics and Medical Engineering, Asia University, Taichung City 41354, Taiwan
horng@db.csie.ncu.edu.tw

[3] Division of Nephrology, Department of Medicine, Taiwan Landseed Hospital, Taoyuan City 32449, Taiwan
chencl@landseed.com.tw, chencl4922@gmail.com

Received 15 March 2019; Revised 30 June 2019; Accepted 4 September 2019

Abstract. Both of rheumatoid arthritis (RA) and Sjogren's syndrome (SS) are long-term autoimmune disorders. Meanwhile, RA tends to be more complicated than SS. Although there have been lots of studies about RA and SS, less research focused on their bidirectional effects. The major purpose of this study is to evaluate the risks between RA and SS. We build two datasets collected from Longitudinal Health Insurance Database (LHID) during the periods between 2006 and 2013. One is about 8469 patients with RA and 42,345 (1:5) age group-, and sex-matched non-RA controls. The other is regarding 8229 patients with SS and 41,145 (1:5) age group-, and sex-matched non-SS controls. We estimated hazard ratios (HRs) using Cox proportional hazard models in both datasets. We found that the risk of suffering SS in patients with RA (HR 3.29) is higher than the risk of suffering RA in patients with SS (HR 1.64), compared to the corresponding control cohorts, respectively. Additionally, for the RA case cohort, if patients had suffered from comorbidities such as hyperlipidemia (HR 1.28), autoimmune disease (HR 4.83), and gout (HR 1.61) before suffering RA, they would further have had higher risk of suffering SS than patients without these comorbidities.

Keywords: autoimmune disease, rheumatoid arthritis, Sjogren's syndrome

1 Introduction

Rheumatoid arthritis (RA) is a major long-term persistent disease that affects the joints. It usually causes joint fever, swelling and pain. Pain and stiffness tend to worsen after a break. The most common is the wrist and hand involved in the same joints on both sides of the body. This disease may also affect other parts of the body, which can lead to low red blood cell, lung inflammation, and heart inflammation. Sjogren's syndrome (SS), also known as Sicca syndrome, is also an autoimmune disorder: a condition that develops when your body is attacked by its own immune system. It offers up its own list of symptoms, including a painful burning or gritty feeling in the eyes which can leave patients prone to eye infections. Patients with SS may also have a dry sensation in their mouth, which increases the chances of dental decay or gum inflammation. In more extreme instances, SS can affect other parts of the body, including skin and internal organs like the lungs, liver, and kidneys. In addition, SS can occur by itself (primary SS) or in conjunction with RA and other rheumatic conditions (secondary SS), explains Philip L.

* Corresponding Author

Cohen, MD, chief of rheumatology at Temple University Hospital. “Secondary SS usually occurs long after the diagnosis of RA and generally is less severe than primary SS [1].”

About the treatment of RA and SS, some doctors consider that strict adherence to medication is the best course of action for both RA and SS. The good news is that treatment might not require patients to do anything different. Owing to both are systemic diseases, so biologic therapy for the RA will also treat the SS. SS may require some local therapy for the dryness of the eyes and mouth [1]. Additionally, rheumatologists are the physicians most likely to be familiar with these conditions, although primary care doctors, ophthalmologists, orthopedists, dermatologists and other specialists have an important role to play [2].

There were a lot of research about RA and SS. For example, some examined the characteristics [3] and activities [4] between RA and SS, and some research took one of these two diseases as a comorbidity of another one since both of them were known as their strong relationship in autoimmune disease. Moreover, we thought about the comorbidities of RA and SS from some related studies [5-10].

We further browsed through some studies based on population-based cohort about RA. In 2015, Chang et al. [11] considered the RA cohort comprised patients ages 20 years and older who were newly diagnosed with RA between 2000 and 2011. They selected patients without RA as their control cohort matched with the RA cohort in 1:1 according to age, sex, and year of RA diagnosis. They wanted to figure out whether peripheral neuropathy and inflammatory reactions of the central nervous system may accompany RA. In 2018, Chen et al. [12] wanted to know the effect of RA on the risk of cerebrovascular disease and coronary artery disease in young adults. They analyzed data regarding 52,840 subjects who were 18-45 years old (10,568 patients with RA and 42,272 age-, sex-, urbanization-, and income-matched non-RA controls) were collected from the National Health Insurance Research Database (NHIRD) in 2006. Moreover, another research made by Mirouse et al. [13] described the characteristics and the outcome of primary SS (pSS) associated arthritis and to compare the efficacy of different therapeutic regimen in France.

In 2019, Lee et al. [14] explored the prescribing trend of anti-rheumatic drugs in Taiwan and risk of cardiovascular Disease in patients with RA. Their study subjects were 15,366 new RA patients from 2003 to 2010 and 76,830 control cohorts matched in 1:5 based on gender, age, premium-based monthly income, and urbanization. In their study, the Cox proportional hazard model was used to evaluate the risk of cardiovascular disease in patients with RA. Thus, we can know the relationship between RA and other diseases by these references, and we want to figure out the relationship between RA and SS in Taiwan.

2 Materials and Methods

2.1 Data Sources

The data sources are from the Longitudinal Health Insurance Database (LHID), which is originated from National Health Insurance Research Database (NHIRD) [17], released and maintained by the Taiwan Bureau of National Health Insurance (NHI). The LHID contains the entire original claims data for 1,000,000 beneficiaries randomly sampled from the entire population of NHI beneficiaries. The identification numbers of all patients are encrypted in order to protect their privacy, and the other information is de-identified and anonymized. All the codes of diseases in the LHID are following the rules that formulated in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). In addition, this study has been reviewed and accepted by the institutional review board of Landseed International Hospital (No. 19-032-C0).

2.2 The RA Case Cohort and the SS Case Cohort

The flow charts of process for the RA case cohort and the SS case cohort are shown in Fig. 1 and Figure 2, respectively. Between January 1, 2005, and December 31, 2013, we identified all patients diagnosed with RA (ICD-9-CM code 714) in the RA case cohort and patients diagnosed with SS (ICD-9-CM code 710.2) in the SS case cohort. In both case cohorts, we excluded patients who might affect our results. Firstly, we considered some literatures about RA, and found that some focused on adults [11-12] whose immune system might start to decline after 20 years olds [15], so patients younger than 20 years old were excluded in our study. Secondly, pre-existing RA before 2006 in the RA case cohort and pre-existing SS

before 2006 in the SS case cohort were excluded, respectively. Thirdly, clinical visits of case diseases less than 2 times were also excluded.

Furthermore, both of RA and SS were autoimmune diseases so patients with other autoimmune diseases before enrollment might affect our results of analysis. Therefore, we wanted to exclude this factor in both case cohorts and considered the following 16 kinds of autoimmune diseases, including celiac disease (ICD-9-CM code 579.0), type 1 diabetes mellitus (ICD-9-CM code 250_1, 250_3), system lupus erythematosus (ICD-9-CM code 695.4), multiple sclerosis (ICD-9-CM code 340), Hashimoto's thyroiditis (ICD-9-CM code 245.2), Graves' disease (ICD-9-CM code 242.0), primary thrombocytopenia (ICD-9-CM code 287.3), aplastic anemia (ICD-9-CM code 284), psoriasis (ICD-9-CM code 696), Behcet's disease (ICD-9-CM code 136.1, 711.2), Addison's disease (ICD-9-CM code 255.4), autoimmune hemolytic anemias (ICD-9-CM code 283.0), Goodpasture's syndrome (ICD-9-CM code 446.21), Myasthenia gravis (ICD-9-CM code 358.0), autoimmune hepatitis (ICD-9-CM code 571.42), and Ankylosing spondylitis (ICD-9-CM code 720.0). Finally, there were 8,469 patients in the RA case cohort and 8,229 patients in the SS case cohort.

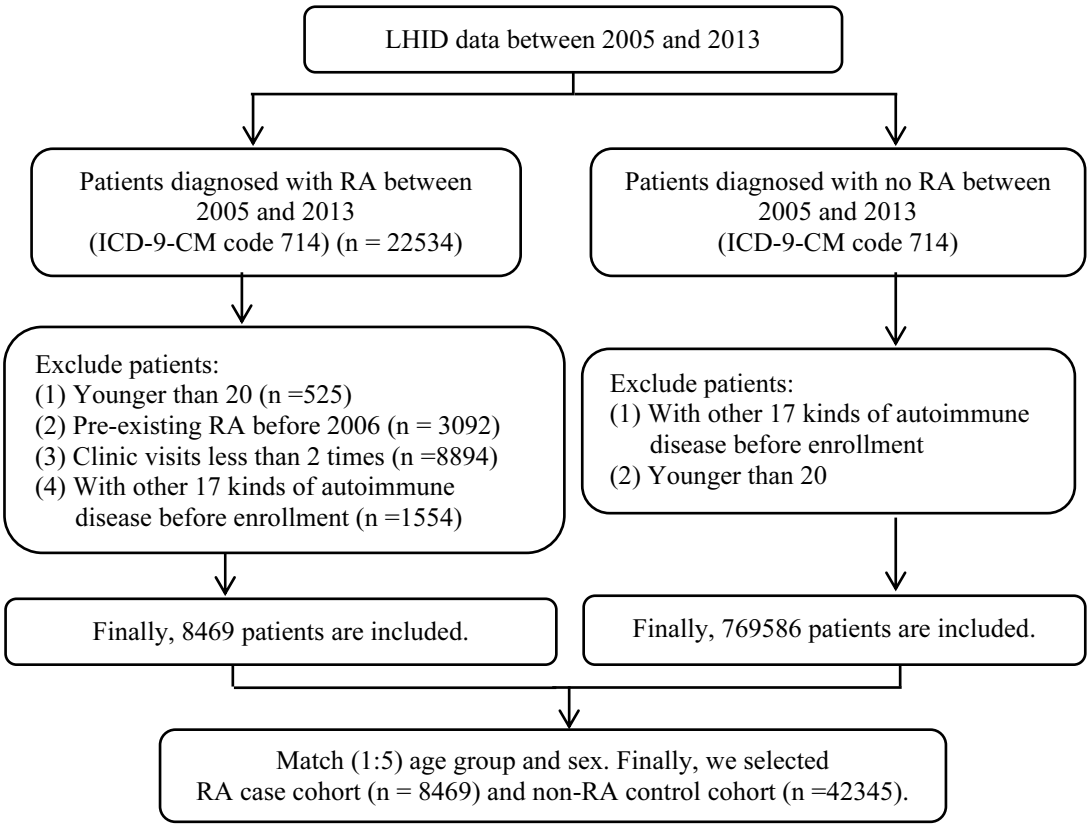

Fig. 1. Flow chart of forming RA case and non-RA control cohorts

2.3 The Non-RA Control Cohort and the Non-SS Control Cohort

The flow charts of process for the non-RA control cohort and the non-SS control cohort were shown in Fig. 1 and Fig. 2, respectively. Between January 1, 2005, and December 31, 2013, we identified patients with no RA in the non-RA control cohort and patients with no SS in the non-SS control cohort. We also excluded patients younger than 20 years old and other 17 kinds of autoimmune disease and before enrollment. Besides, we found age and sex were also the general and basic control variables from other medical literature. Thus, in our sampling method, we used propensity score matching to select the control cohort in the ratio 1:5 (case: control) with age group-, sex matched, and then used Logistic regression to calculate propensity scores based on the following variables: age group and sex. For each patient in case cohort, we randomly selected five patients from the control cohort whose propensity score is equal to the corresponding case patient's score. Finally, there were 42,345 patients in the non-RA control cohort and 41,145 patients in the non-SS control cohort.

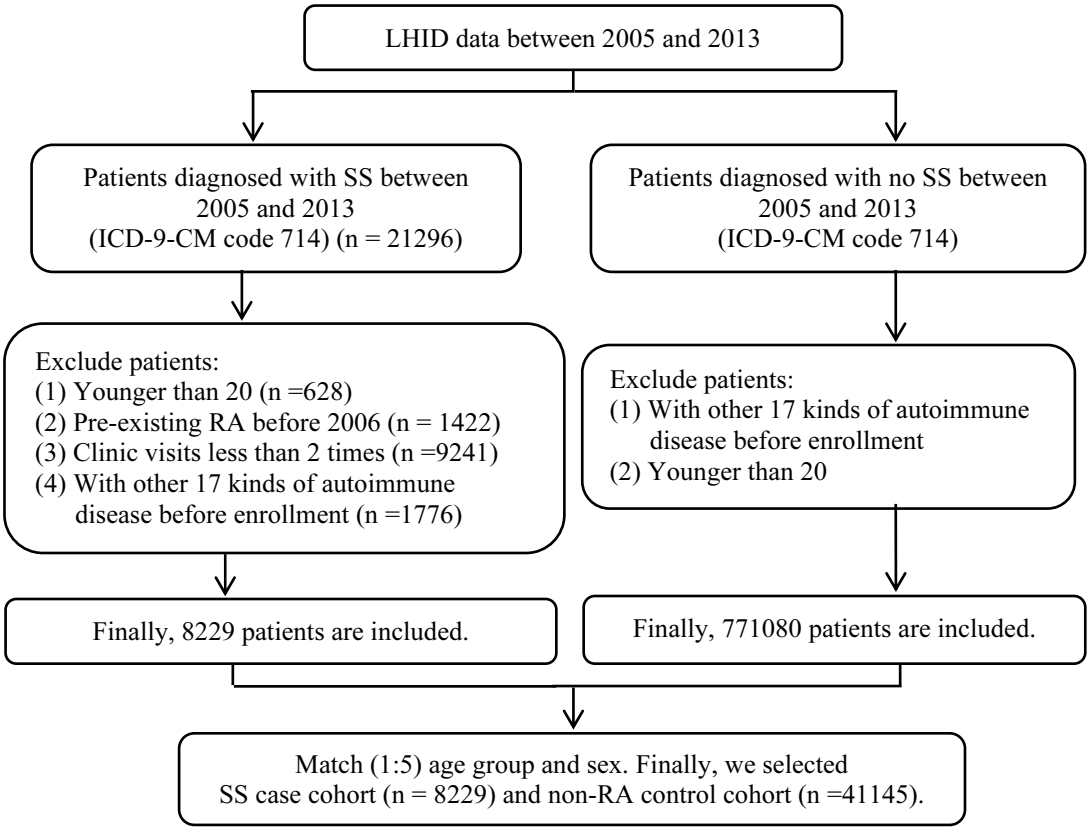

Fig. 2. Flow chart of forming SS case and non-SS control cohorts

2.4 Statistical Analysis

Pearson chi-squared test was employed on categorical data to observed difference between the sets arose by chance, where a 2-tailed P value of <.05 is considered statistically significant difference. The Kaplan-Meier method was applied to estimate the SS-free survival probability (in the RA case cohort and the non-RA control cohort) and the RA-free survival probability (in SS case cohort and non-SS control cohort), where the log-rank test was adopted here to compare whether the difference in survival probability was significant between the case cohort and the control cohort. The survival time (follow-up years) was defined from the enrollment day to the day when patients suffered SS or died in the RA case cohort and the non-RA control cohort, and to the day when patients suffered RA or died in the SS case cohort and the non-SS control cohort.

However, the above mentioned methods - Kaplan-Meier method and the log-rank test - are the univariate analysis. They describe the survival probability according to one factor under investigation, but ignore the impact of any others. It doesn't work properly for quantitative predictors such as age, comorbidities, etc. Therefore, according to some medical research, most of them used Cox proportional hazard model to investigate the associated risk between the survival time of patients and one or more predictor variables. The Cox proportional hazard model was developed by Cox in 1972 [16]. This model is expressed by the hazard function denoted by $h(t)$. In brief, the hazard function can be viewed as the risk of dying at time t. It can be shown as below.

$$h(t) = h_0(t) \times \exp(c_1 x_1 + c_2 x_2 + \cdots + c_p x_p) \quad \textbf{(1)}$$

Where t represents the survival time (follow-up years); $h(t)$ is determined by a set of p covariates $(x_1, x_2, ..., x_p)$; the coefficients $(c_1, c_2, ..., c_p)$ measure the effect on these covariates; the term h_0 is called the baseline hazard, which corresponds to the value of the hazard if all the x_1 are equal to zero; the $h(t)$ means that the hazard may vary over time. If the number of hazard ratio (HR) of factors is more than 1, it means that those factors might increase in hazard, and vice versa.

Therefore, we used this model by the follow-up years to calculated HR and 95% confidence interval

(CI). Firstly, we evaluated the risk of suffering SS in the RA case cohort and the risk of suffering RA in the SS case cohort corresponding to the non-RA control cohort and the non-SS control cohort, respectively. Secondly, we further focused on the RA case cohort and the SS case cohort, and then determined if the comorbidities were also the possible risk factors. Thus, we calculate the crude HR and adjusted HR after adjusting age, sex, and other comorbidities: hypertension (ICD-9-CM code 401-405), hyperlipidemia (ICD-9-CM code 272.2-272.4), diabetes (ICD-9-CM code 250), kidney disease (ICD-9-CM code 403-404, 580-587), cerebral vascular disease (ICD-9-CM code 430-438), autoimmune disease (ICD-9-CM code 279.4), gout (ICD-9-CM code 274.0), and osteoporosis (ICD-9-CM code 733.0) in the RA case cohort, as well as hypertension, hyperlipidemia, diabetes, kidney disease, thyroid disease (ICD-9-CM code 240-242, 244-246), lymphoma (ICD-9-CM code 200-208), autoimmune disease in the SS case cohort. In addition, SAS 9.4 software is used to analyze the data in this study.

3 Results

3.1 The Risk of Suffering SS in the RA Case Cohort and the Non-RA Control Cohort

In the RA case cohort and the non-RA control cohort, we show demographic characteristics in Table 1, including information about age, age group, sex, and comorbidities. Pearson chi-squared test was employed to observe the difference between two cohorts. Since we selected age group and sex as our matching standard, we could find out there was no significant difference in age group and sex. A total of 8,469 RA case patients were identified in this study, including 5,826 (68.8%) females and 2,643 (31.2%) at the mean age 56.05 ± 15.11. Patients were the most in the 50 to 59 age group but the least in more than 90 years old in both cohorts. In addition, if we observed patients with some comorbidities, we could find that the number of patients was the most with hypertension but the least with the autoimmune disease in both cohorts.

Table 1. Characteristics for RA case and non-RA control cohorts

Characteristic	Rheumatoid arthritis		Control		*P*-value
N	8469		42345		
Variables	N	%	N	%	
Age (Mean ± SD)	56.05 ± 15.11		55.80 ± 15.35		<.0001
Age Group					1.0000
20-29	387	4.6%	1935	4.6%	
30-39	828	9.8%	4140	9.8%	
40-49	1555	18.4%	7775	18.4%	
50-59	2339	27.6%	11695	27.6%	
60-69	1600	18.9%	8000	18.9%	
70-79	1220	14.4%	6100	14.4%	
80-89	497	5.9%	2485	5.9%	
≥90	43	0.5%	215	0.5%	
Sex					1.0000
Male	2643	31.2%	13215	31.2%	
Female	5826	68.8%	29130	68.8%	
Comorbidities					
Hypertension	3140	37.1%	12969	30.6%	<.0001
Hyperlipidemia	1308	15.4%	4497	10.6%	<.0001
Diabetes	1350	15.9%	5935	14.0%	<.0001
Kidney disease	511	6.0%	1578	3.7%	<.0001
Cerebral vascular disease	721	8.5%	2987	7.1%	<.0001
Autoimmune disease	132	1.6%	45	0.1%	<.0001
Gout	1776	21.0%	2641	6.2%	<.0001
Osteoporosis	915	10.8%	2365	5.6%	<.0001

In Table 2, we further examine the follow-up years about incidence of SS, and find out the decreasing trend in the occurrence of SS. A total of 457 events of SS occurred in the RA case cohort and 706 events of SS occurred in the non-RA control cohort. After adjusting for age, sex, and other comorbidities in the

Cox proportional hazard model, the adjusted HR for suffering SS in the RA case cohort was 3.29 (95%CI 2.91-3.72) compared to the non-RA control cohort. In addition, we also show the SS-free survival probability curve about the RA case cohort and the non-RA control cohort in Fig. 3. We can easily observe the more decreasing decline of SS-free survival probability in the RA case cohort, which means that the RA case cohort tends to suffer SS during the follow-up years, where the log-rank test also shows the significant difference between their SS-free survival probabilities ($p < .0001$).

Table 2. The HR and incidence of SS and its follow-up period in RA case and non-RA control cohorts

Characteristic	Rheumatoid arthritis		Control	
N	8469		42345	
Sjogren's syndrome occurrence	No.	%	No.	%
follow-up, years				
> 0 and ≤ 1	230	2.72%	282	0.67%
> 1 and ≤ 2	65	0.77%	122	0.29%
> 2 and ≤ 3	40	0.47%	101	0.24%
> 3 and ≤ 4	31	0.37%	78	0.18%
> 4 and ≤ 5	40	0.47%	44	0.10%
> 5 and ≤ 6	26	0.31%	33	0.08%
> 6 and ≤ 7	20	0.24%	27	0.06%
> 7 and ≤ 8	5	0.06%	19	0.04%
Total	457	5.40%	706	1.67%
Crude HR (95%CI)	3.34 (2.96-3.75)		1.000	
Adjusted* HR (95%CI)	3.29 (2.91-3.72)		1.000	

Note. *Cox proportional hazard model was performed to adjust for age, sex, and other comorbidities.

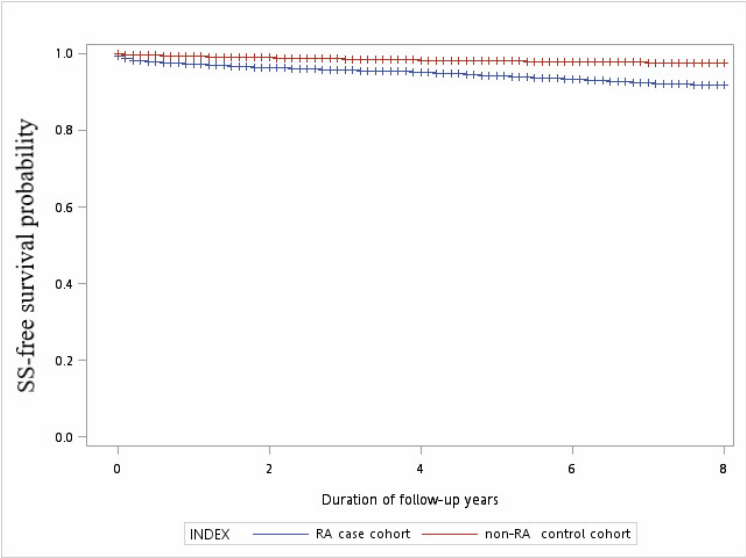

Fig. 3. SS-free survival curves of RA case and non-RA control cohorts, log-rank test $p < .0001$

Furthermore, we further focus on the RA case cohort, and then determine if the comorbidities are possible risk factors which may cause the higher or lower risk of suffering SS in Table 3. If we first analyze male patients, we could observe that autoimmune disease (HR 8.69; 95%CI 2.76-27.34) and gout (HR 1.61; 95%CI 1.12-2.33) might cause higher risk of suffering SS 2222 if they had suffered from RA and these comorbidities, compared to those male patients only with RA. For all RA patients, the hypertension (HR 0.76; 95%CI 0.65-0.88) would cause lower risk of suffering SS. However, hyperlipidemia (HR 1.29; 95%CI 1.07-1.56), autoimmune disease (HR 4.84; 95%CI 2.95-7.93), and gout (HR 1.60; 95%CI 1.31-1.95) would cause higher risk of suffering SS. While other predictors, such as diabetes (HR 0.86; 95%CI 0.72-1.04), kidney disease (HR 1.19; 95%CI 0.90-1.59), cerebral vascular disease (HR 0.95; 95%CI 0.75-1.22), and osteoporosis (HR 1.05; 95%CI 0.84-1.31) were not significantly related to the risk of suffering SS if they had suffered RA and these comorbidities.

Table 3. Evaluate HR of SS in the RA case cohort with comorbidities by Cox proportional hazard model

Comorbidities	Male		Female		All	
	Crude HR (95%CI)	Adjusted HR* (95%CI)	Crude HR (95%CI)	Adjusted HR* (95%CI)	Crude HR (95%CI)	Adjusted HR^ (95%CI)
Hypertension	0.56 (0.33-0.97)	0.77 (0.54-1.10)	0.66 (0.53-0.83)	**0.76 (0.64-0.90)**	0.62 (0.50-0.77)	**0.76 (0.65-0.88)**
Hyperlipidemia	1.13 (0.56-2.28)	1.22 (0.76-1.98)	0.88 (0.66-1.19)	**1.31 (1.07-1.61)**	0.94 (0.72-1.23)	**1.29 (1.07-1.56)**
Diabetes	0.45 (0.18-1.11)	0.90 (0.58-1.38)	0.66 (0.48-0.91)	0.86 (0.70-1.06)	0.63 (0.46-0.85)	0.86 (0.72-1.04)
Kidney disease	0.81 (0.29-2.22)	1.25 (0.70-2.25)	0.83 (0.51-1.37)	1.16 (0.84-1.61)	0.76 (0.48-1.19)	1.19 (0.90-1.59)
Cerebral vascular disease	1.86 (0.95-3.65)	0.84 (0.49-1.43)	0.96 (0.66-1.41)	0.98 (0.74-1.29)	1.07 (0.77-1.48)	0.95 (0.75-1.22)
Autoimmune disease	3.19 (0.78-13.01)	**8.69 (2.76-27.34)**	2.29 (1.29-4.07)	**4.34 (2.51-7.51)**	2.51 (1.48-4.28)	**4.84 (2.95-7.93)**
Gout	0.79 (0.47-1.33)	**1.61 (1.12-2.33)**	1.06 (0.79-1.42)	**1.59 (1.25-2.02)**	0.75 (0.59-0.97)	**1.60 (1.31-1.95)**
Osteoporosis	0.28 (0.04-2.03)	0.72 (0.29-1.77)	0.70 (0.50-0.99)	1.10 (0.87-1.34)	0.77 (0.55-1.08)	1.05 (0.84-1.31)

Note. *Cox proportional hazard model was performed to adjust for age, and other comorbidities.
^Cox proportional hazard model was performed to adjust for age, sex, and other comorbidities.

3.2 The Risk of Suffering RA in the SS Case Cohort and the Non-SS Control Cohort

In the SS case cohort and the non-SS control cohort, the demographic characteristics are shown in Table 4. The total of 8,229 SS case patients was identified in this study, inclusive of 6,102 (74.2%) females and 2,127 (25.8%) males at the mean age 53.17 ± 16.61. Patients were the most in the 50 to 59 age group but the least in more than 90 years old in both cohorts. In addition, if we observed patients with some comorbidities, we could find that the number of patients was the most with hypertension in both cohorts.

Table 4. Characteristics for SS case and non-SS control cohorts

Characteristic	Sjogren's syndrome		Control		*P*-value
N	8229		41145		
Variables	N	%	N	%	
Age (Mean ± SD)	53.17 ± 16.61		52.98 ± 16.85		<.0001
Age Group					1.0000
20-29	854	10.4%	4270	10.4%	
30-39	1058	12.9%	5290	12.9%	
40-49	1415	17.2%	7075	17.2%	
50-59	1863	22.6%	9315	22.6%	
60-69	1529	18.6%	7645	18.6%	
70-79	1053	12.8%	5265	12.8%	
80-89	425	5.2%	2125	5.2%	
≥90	32	0.4%	160	0.4%	
Sex					1.0000
Male	2127	25.8%	10635	25.8%	
emale	6102	74.2%	30510	74.2%	
Comorbidities					
Hypertension	2485	30.2%	11260	27.4%	<.0001
Hyperlipidemia	1203	14.6%	3869	9.4%	<.0001
Diabetes	1131	13.7%	5228	12.7%	0.0103
Kidney disease	412	5.0%	1431	3.5%	<.0001
Thyroid disease	365	4.4%	897	2.2%	<.0001
Lymphoma	30	0.4%	64	0.2%	<.0001
Autoimmune disease	148	1.8%	30	0.1%	<.0001

In Table 5, we further examine the follow-up years about incidence of RA, and find out the decreasing trend in the occurrence of RA. A total of 255 events of RA occurred in the SS case cohort and 858 events of RA occurred in the non-SS control cohort. After adjusting for age, sex, and other comorbidities in the Cox proportional hazard model, the adjusted HR for suffering SS in the SS case cohort was 1.64 (95%CI 1.42-1.89) compared to the non-SS control cohort. Moreover, we also show the RA-free survival probability curve about the SS case cohort and the non-SS control cohort in Fig. 4. We can easily see the more decreasing decline of RA-free survival probability in the SS case cohort than in the non-SS control cohort, which means that the SS case cohort tends to suffer RA during the follow-up years, where the

log-rank test also shows the significant difference between their RA-free survival probabilities ($p < .0001$).

Table 5. The HR and incidence of RA and its follow-up period in SS case and non-SS control cohorts

Characteristic	Sjogren's syndrome		Control	
N	8229		41145	
Rheumatoid arthritis occurrence	No.	%	No.	%
follow-up, years				
> 0 and ≤ 1	110	1.34%	423	1.03%
> 1 and ≤ 2	46	0.56%	145	0.35%
> 2 and ≤ 3	32	0.39%	85	0.21%
> 3 and ≤ 4	26	0.32%	80	0.19%
> 4 and ≤ 5	20	0.24%	52	0.13%
> 5 and ≤ 6	12	0.15%	37	0.09%
> 6 and ≤ 7	9	0.11%	23	0.06%
> 7 and ≤ 8	0	0.00%	13	0.03%
Total	255	3.10%	858	2.09%
Crude HR (95%CI)	1.63 (1.42-1.88)		1.000	
Adjusted* HR (95%CI)	1.64 (1.42-1.89)		1.000	

Note. *Cox proportional hazard model was performed to adjust for age, and other comorbidities.

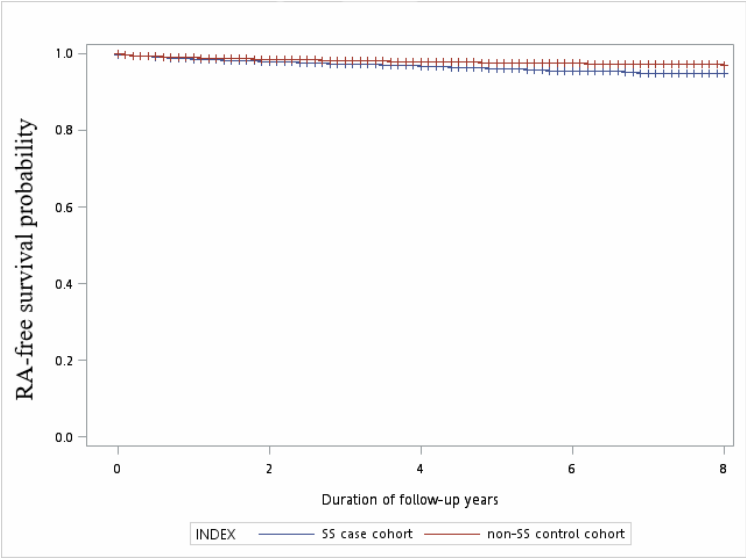

Fig. 4. RA-free survival curves of SS case and non-SS control cohorts, log-rank test p < .0001

Similarly, we further focus on the SS case cohort, and then determine if the comorbidities are the risk factors which may cause the higher or lower risk of suffering RA in Table 6. If we analyze female patients in Table 6, we can observe that hypertension (HR 0.83; 95%CI 0.70-0.98) and diabetes (HR 0.72; 95%CI 0.58-0.90) would cause lower risk of suffering RA if they had suffered from SS and these comorbidities, compared to those female patients only with SS. For all SS patients in Table 6, hypertension (HR 0.85; 95%CI 0.73-0.99) and diabetes (HR 0.70; 95%CI 0.57-0.85) would also cause lower risk of suffering RA if they had suffered from SS and these comorbidities.

Table 6. Evaluate HR of RA in the SS case cohort with comorbidities by Cox proportional hazard model

Comorbidities	Male		Female		All	
	Crude HR (95%CI)	Adjusted HR* (95%CI)	Crude HR (95%CI)	Adjusted HR* (95%CI)	Crude HR (95%CI)	Adjusted HR^ (95%CI)
Hypertension	2.09 (1.09-3.99)	0.98 (0.68-1.41)	1.01 (0.75-1.37)	**0.83 (0.70-0.98)**	1.09 (0.83-1.42)	**0.85 (0.73-0.99)**
Hyperlipidemia	0.57 (0.17-1.85)	0.54 (0.26-1.13)	1.30 (0.90-1.87)	1.03 (0.82-1.28)	1.16 (0.82-1.65)	0.96 (0.77-1.18)
Diabetes	1.29 (0.57-2.94)	0.58 (0.33-1.01)	1.02 (0.68-1.54)	**0.72 (0.58-0.90)**	1.03 (0.71-1.48)	**0.70 (0.57-0.85)**
Kidney disease	1.67 (0.59-4.70)	0.66 (0.29-1.51)	1.61 (0.92-2.82)	1.07 (0.76-1.51)	1.50 (0.92-2.45)	0.98 (0.72-1.35)
Thyroid disease	-	-	1.96 (1.23-3.14)	1.37 (0.98-1.91)	2.07 (1.30-3.30)	1.32 (0.95-1.85)
Lymphoma	-	-	-	-	-	-
Autoimmune disease	-	-	1.60 (0.71-3.59)	2.05 (0.97-4.31)	1.49 (0.66-3.35)	1.88 (0.90-3.97)

Note. *Cox proportional hazard model was performed to adjust for age, and other comorbidities.
^Cox proportional hazard model was performed to adjust for age, sex, and other comorbidities.

4 Discussions and Conclusions

Both of RA and SS are long-term autoimmune disorders. Owing to their similarity, there have been lots of studies about RA and SS, but less research focused on their bidirectional effects. In this work, we investigate the risks between RA and SS. We concluded our works. Firstly, from the analysis on the RA case cohort and the non-RA control cohort, the risk of suffering SS is more in the RA case cohort (HR 3.29) than in the non-RA control cohort. The SS-free survival probability curve reveals the more decreasing trend in the RA case cohort, which means that patients with RA tend to suffer SS than patients without RA. Additionally, for the RA case cohort, if they had suffered from comorbidities such as hyperlipidemia (HR 1.28), autoimmune disease (HR 4.83), gout (HR 1.61) before enrollment, they would have had higher risk of suffering SS than patients without these comorbidities. Secondly, from the analysis on the SS case cohort and the non-SS control cohort, the risk of suffering RA is more in the SS case cohort (HR 1.64) than in the non-SS control cohort. The RA-free survival probability curve reveals the more decreasing trend in the SS case cohort, which means that patients with SS tend to suffer RA than patients without SS. In summary, there is more risk of suffering SS in patients with RA (HR 3.29) than the risk of suffering RA in patients with SS (HR 1.64), compared to their corresponding control cohorts, respectively. If patients suffer RA with comorbidities, such as hyperlipidemia, autoimmune disease, and gout, at the same time, they should especially notice the risk of suffering SS.

Acknowledgements

This research was funded by the Ministry of Science and Technology, Taiwan (108-2221-E-008s-043-MY3). This manuscript was accepted to present at TANET2018 [18]. Then, this manuscript was recommended to Journal of Computers.

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