Relationship of chronic rhinosinusitis with Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis*

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Rhinology 61: 2, 124 - 131, 2023

https://doi.org/10.4193/Rhin22.300

***Received for publication:**

July 29, 2022

Accepted: November 28, 2022

Abstract

Background: Several studies have demonstrated the association between chronic rhinosinusitis (CRS) and autoimmune diseases. However, there are few long-term longitudinal studies on this relationship. Therefore, we investigated the association between CRS and the risk of a subgroup of autoimmune disease using a representative nationwide cohort sample.

Methodology: We investigated the association between CRS and autoimmune diseases, including Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis. A total of 15,130 CRS patients and 30,260 patients without CRS were enrolled after 1:2 propensity score matching. A Cox proportional hazards model was used to analyse the hazard ratio (HR) of CRS for autoimmune disease.

Results: The incidence of Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis was 0.55, 0.10, and 0.48 per 1000 person-years, respectively. Among autoimmune diseases, the risk of Sjögren's syndrome in CRS patients was significantly increased to an adjusted HR (aHR) of 1.70, whereas we could not detect any significant risk of developing systemic lupus erythematosus or ankylosing spondylitis. In the subgroup analysis according to CRS phenotype, the adjusted HR of developing Sjögren's syndrome was greater in CRS patients without nasal polyps) than in CRS patients with nasal polyps.

Conclusions: Our study suggests that CRS without nasal polyps is associated with an increased incidence of Sjögren's syndrome diagnosis compared to CRS without nasal polyps. Additionally, there was no association between CRS and systemic lupus erythematosus or ankylosing spondylitis, regardless of CRS phenotype.

Key words: rhinosinusitis, sinusitis, Sjögren's syndrome, systemic lupus erythematosus, ankylosing spondylitis

Introduction

Chronic rhinosinusitis (CRS) is one of the most common chronic diseases with a prevalence of 2–16% worldwide [(1)]. Its symptoms, such as nasal obstruction, mucus accumulation, and anosmia, reduce the health-related quality of life of patients, as well as imposing a high socioeconomic burden due to direct and indirect costs. Clinically, CRS is classified into two phenotypes based on the presence of nasal polyps: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [(2)]. In terms of immunologic characteristics, CRSwNP is skewed with a type II immune response with eosinophil infiltration, whereas CRSsNP is associated with neutrophilic inflammation and a mixed immune response, mainly type I and III [(3-5)]. CRS is a multifactorial disease that is affected by various factors and several prior studies have reported various comorbidities, including airway diseases, gastroesophageal reflux disease, and other inflammatory diseases [(6-9)].

To date, several prior studies have focused on the relationship between autoimmune diseases and CRS because these diseases share a similar immunologic background. One cross-sectional study reported a 1.4–5.9% prevalence of CRS in patients with autoimmune disease, especially in patients with rheumatoid arthritis who show a higher frequency of CRS than patients with systemic lupus erythematosus [(10)]. Another cross-sectional study

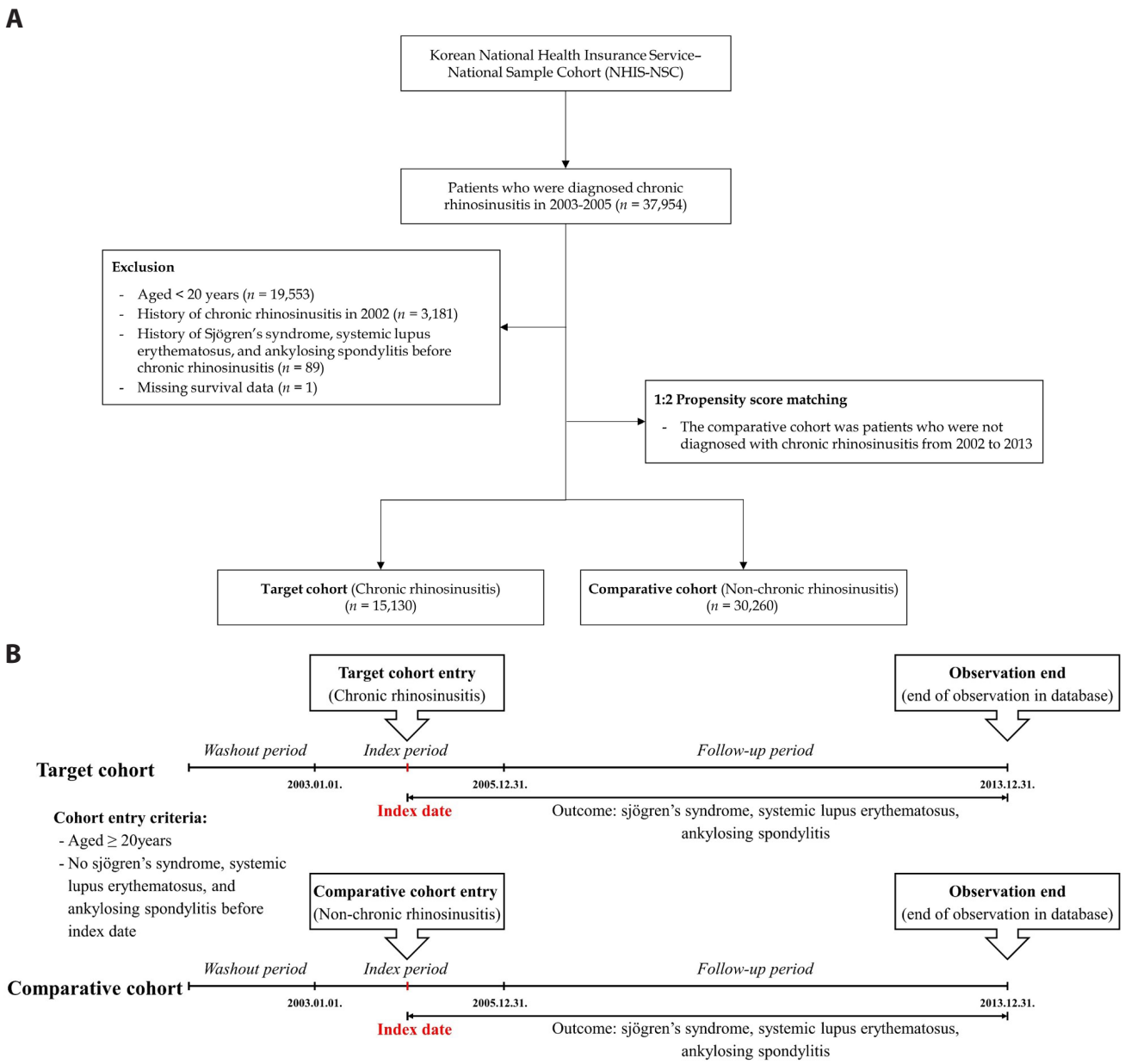

Figure 1. (A) Description of the schematic flow of participant's enrollment and (B) study design in this cohort study.

also described a significantly increased prevalence of some autoimmune diseases, such as rheumatoid arthritis and ankylosing spondylitis, in patients with CRS compared to controls [11]. Recently, one cohort study from Taiwan reported that CRS had a higher significant association with premorbid autoimmune diseases, specifically in polymyositis, psoriasis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, and Sjögren's syndrome [12]. Additionally, autoimmune disease has been considered a risk factor for CRS and a contributor to poor CRS prognosis [13,14]. However, the causal relationship between CRS and autoimmune disease is not yet fully understood.

Therefore, we investigated the association of CRS (and its subtypes) with autoimmune diseases using socio-demographically matched individuals extracted from a nationwide 11-year longitudinal cohort database of 1,025,340 South Korean patients. In this study, we particularly focused on Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis because they have a relatively higher prevalence in South Korea than other autoimmune diseases.

Methods

Ethical approval and data availability

This retrospective, nationwide propensity score-matched cohort study used data from the national health claims database collected by the Korean National Health Insurance Service (KNHIS). The present study was approved by the Institutional Review Board (IRB) of Hallym Medical University, Chuncheon Sacred

Hospital (No. 2021-08-006), and the study adhered to the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived by the IRB because the KNHIS database used in the study comprises de-identified secondary data. The datasets generated and/or analysed in the present study are not publicly available because of the Korea National Health Insurance Service policies but are available from the corresponding author upon reasonable request.

Study participants and design

The schematic flow of the study is shown in Figure 1. We collected CRS patients using the diagnostic code (International Classification of Diseases-10 [ICD-10], J32X for CRSsNP and J33 for CRSwNP) among the 1,025,340 representative sample subjects obtained from the KNHIS. In this study cohort, we identified the incident CRS diagnosis during the index period (1 January 2003 to 31 December 2005). We also had a washout period of 1 year (2002) to remove the risk of Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis diagnosed before enrolment. To avoid misdiagnosis error, we defined the diagnosis of CRS as when patients obtained independently established the diagnosis of CRS more than twice at intervals of 3 months or more and were conducted by the head and neck computed tomography (one time). Then, we excluded patients aged <20 years or patients who were diagnosed with Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis before the first diagnosis of CRS during the index period. To comprise the comparison group (non-CRS), we randomly selected propensity score-matched participants from the remaining cohort registered in the database. We selected two participants without CRS for each CRS patient. These patients were matched with patients with CRS for age, sex, residential area, household income, comorbidities, and the year of enrolment (CRS diagnosis). Specifically, we analysed comorbidities using the Charlson comorbidity index (CCI). Eventually, a total of 30,260 subjects in the comparison group and 15,130 eligible patients with CRS were enrolled in this study.

The primary endpoints of the study were the event (Sjögren's syndrome [M350], systemic lupus erythematosus [M32], and ankylosing spondylitis [M45]) or all-cause mortality. However, if patients had no events and were alive on 31 December 2013 (the final following period of this database), they were censored after this time point (Supplementary Table 1).

Statistical analyses

The risks of autoimmune diseases were compared between the CRS and non-CRS groups by using person-years at risk, which were defined as the duration between either the date of CRS diagnosis or 1 January 2003 (for the comparison group), and the patient's respective endpoint. To identify whether CRS increased the risk of occurrence of specific diseases, we used Cox proportional hazard regression analyses to calculate the hazard ratio (HR) and 95% confidence intervals (CI), adjusted for the other independent variables. During the follow-up period, the Kaplan–Meier method was used to calculate autoimmune disease-free survival among CRS patients. All statistical analyses were performed using R version 4.0.0 software with a significance level of $p<0.05$.

Table 1. Profile of cohort sample between comparison (non-CRS) and CRS group.

Variables	Comparison (n = 30,260)	Chronic rhinosinusitis (n = 15,130)	P value
Sex			1.000
Male	12214 (40.4%)	6107 (40.4%)	
Female	18046 (59.6%)	9023 (59.6%)	
Ages (years)			1.000
<45	18488 (61.1%)	9244 (61.1%)	
45-64	9288 (30.7%)	4644 (30.7%)	
>64	2484 (8.2%)	1242 (8.2%)	
Residence			1.000
Seoul	8086 (26.7%)	4043 (26.7%)	
Second area	7976 (26.4%)	3988 (26.4%)	
Third area	14198 (46.9%)	7099 (46.9%)	
Household income			1.000
Low (0–30%)	5598 (18.5%)	2799 (18.5%)	
Middle (30–70%)	11270 (37.2%)	5635 (37.2%)	
High (70–100%)	13392 (44.3%)	6696 (44.3%)	
CCI			1.000
0	19436 (64.2%)	9718 (64.2%)	
1	6672 (22.0%)	3336 (22.0%)	
≥2	4152 (13.7%)	2076 (13.7%)	

CCI, Charlson comorbidity index.

Results

The CRS group and non-CRS group were similarly distributed in terms of sex, age, residential area, household income, and comorbidities which were the variables used for sample matching (Table 1). We also analysed the balance plot test to confirm the matching and it revealed that group matching was performed appropriately (Supplementary Figure 1).

For analysis of incidence, we detected that the incidence of Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis was at 0.55, 0.10, and 0.48, respectively per 1000 person-years for the CRS group, compared to 0.32, 0.09, and 0.45, respectively per 1000 person-years for the comparison group (Table 2). We also analysed the HR for the development of Sjögren's syndrome, systemic lupus erythematosus, and ankylo-

Table 2. Incidence rate (1000 person-years) and HR (95% CI) of autoimmune disease between comparison (non-CRS) and CRS group.

Variables	N	Case	Incidence rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Sjögren's syndrome					
Comparison	30260	96	0.32	1.00 (ref)	1.00 (ref)
CRS	15130	79	0.55	1.69 (1.25-2.28)***	1.70 (1.26-2.29)***
Systemic lupus erythematosus					
Comparison	30260	27	0.09	1.00 (ref)	1.00 (ref)
CRS	15130	15	0.10	1.14 (0.61-2.16)	1.15 (0.61-2.17)
Ankylosing spondylitis					
Comparison	30260	134	0.45	1.00 (ref)	1.00 (ref)
CRS	15130	69	0.48	1.06 (0.79-1.42)	1.04 (0.78-1.40)

CRS, chronic rhinosinusitis; HR, hazard ratio; CI, confidence interval *** P<0.001.

Table 3. Incidence rate (1000 person-years) and HR (95% CI) of incident autoimmune disease according to the phenotype of CRS.

Variables	N	Case	Incidence rate	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	P value
Sjögren's syndrome						
Comparison	30260	96	0.32	1.00 (ref)	1.00 (ref)	
CRSsNP	14113	78	0.58	1.80 (1.33-2.42)***	1.78 (1.32-2.41)***	<0.001
CRSwNP	1017	1	0.10	0.32 (0.04-2.28)	0.37 (0.05-2.69)	0.329
Systemic lupus erythematosus						
Comparison	30260	27	0.09	1.00 (ref)	1.00 (ref)	
CRSsNP	14113	14	0.10	1.15 (0.60-2.20)	1.14 (0.60-2.17)	0.694
CRSwNP	1017	1	0.10	1.15 (0.16-8.48)	1.33 (0.18-9.83)	0.783
Ankylosing spondylitis						
Comparison	30260	134	0.45	1.00 (ref)	1.00 (ref)	
CRSsNP	14113	64	0.48	1.05 (0.78-1.42)	1.05 (0.78-1.42)	0.743
CRSwNP	1017	5	0.52	1.14 (0.47-2.78)	0.97 (0.40-2.38)	0.954

CRSsNP, chronic rhinosinusitis without nasal polyp; CRSwNP, chronic rhinosinusitis with nasal polyp; HR, hazard ratio; CI, confidence interval.
*** P<0.001.

sing spondylitis using univariate and multivariate Cox regression models. After adjusting for sex, age, residence, income level, and comorbidities, we found that CRS was significantly associated with the development of Sjögren's syndrome (adjusted HR = 1.70, 95% CI 1.26–2.29) but there was no significant relationship between CRS and developing systemic lupus erythematosus or ankylosing spondylitis (adjusted HR = 1.15 or 1.04, 95% CI 0.61–2.17 or CI 0.78–1.40, respectively; Figure 2). The reverse Kaplan-Meier survival curves with log-rank tests are presented in Figure 3, which depict the cumulative incidences of Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis in the two groups. These log-rank tests indicated that subjects with CRS developed Sjögren's syndrome more frequently than those in the comparison group, whereas there was no significant between-group difference in the risk of developing systemic lupus erythematosus or ankylosing spondylitis.

We further analysed the risk of incident Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis according to the phenotype of CRS (Table 3). We found that CRSsNP patients had a significantly higher likelihood of developing Sjögren's syndrome (adjusted HR = 1.78 [95% CI, 1.32–2.41]); whereas CRSwNP patients showed no significant association with Sjögren's syndrome (adjusted HR = 0.37 [95% CI, 0.05–2.69]). However, we could not detect any difference in adjusted HR for developing systemic lupus erythematosus and ankylosing spondylitis according to the phenotype of CRS. Specifically, we detected that the relatively lower risk ratio for developing Sjögren's syndrome after CRSsNP diagnosis was observed within

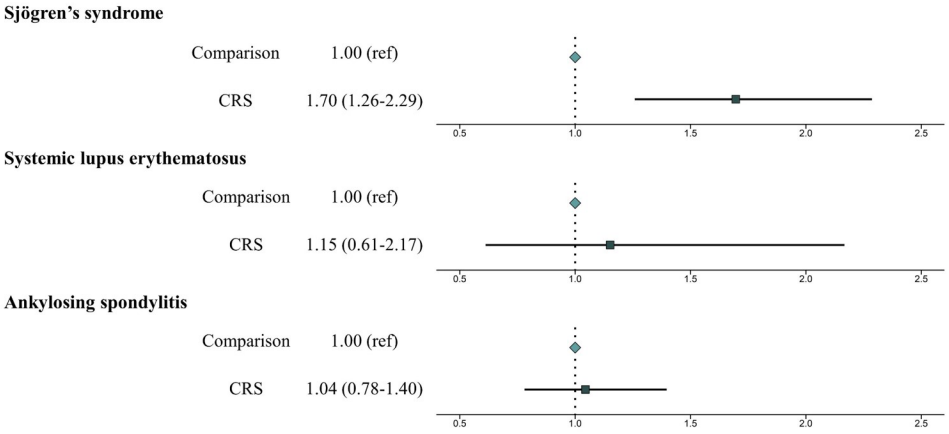

Figure 2. Hazard ratio (95% confidence interval) of autoimmune disease between comparison (non-CRS) and CRS group.

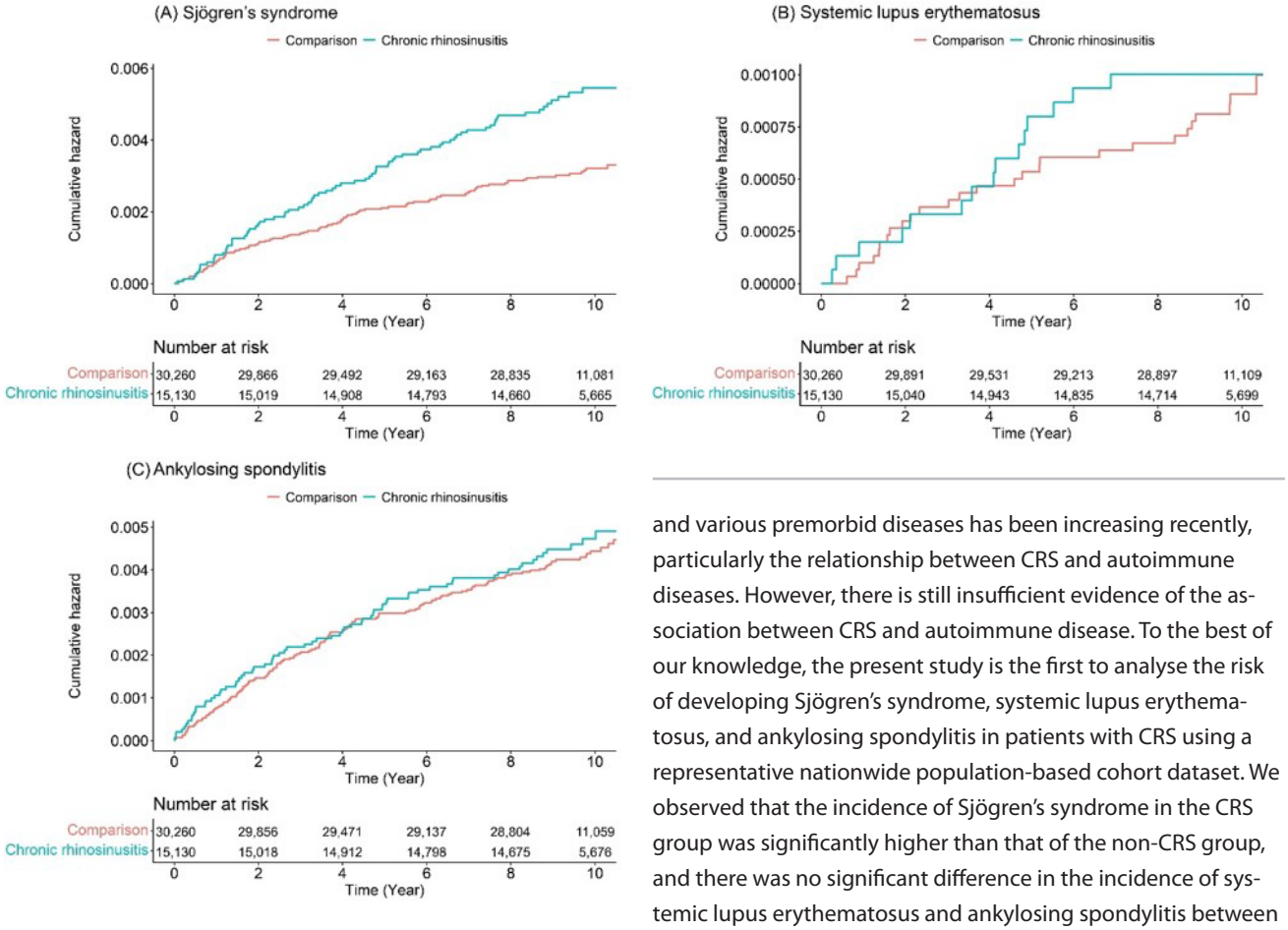

Figure 3. Cumulative hazard plot of autoimmune disease between comparison (non-CRS) and CRS group: (A) Sjögren's syndrome; (B) systemic lupus erythematosus; (C) ankylosing spondylitis.

the first 2 years. From there, the HR increased slowly and gradually throughout the duration of follow-up (Figure 4).

Discussion

The number of studies regarding the association between CRS and various premorbid diseases has been increasing recently, particularly the relationship between CRS and autoimmune diseases. However, there is still insufficient evidence of the association between CRS and autoimmune disease. To the best of our knowledge, the present study is the first to analyse the risk of developing Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis in patients with CRS using a representative nationwide population-based cohort dataset. We observed that the incidence of Sjögren's syndrome in the CRS group was significantly higher than that of the non-CRS group, and there was no significant difference in the incidence of systemic lupus erythematosus and ankylosing spondylitis between the two groups (p<0.001, p=0.661, and p=0.769, respectively). Additionally, the HR of Sjögren's syndrome after adjusting for sex, age, residence, income level, and comorbidities was significantly higher in the CRS group than in the non-CRS group. However, we could not detect any significant difference in the risk of developing systemic lupus erythematosus and ankylosing between the two groups. Interestingly, we also found that CRSsNP patients showed an increased risk of development of subsequent Sjögren's syndrome, but this was not found in CRSwNP patients. Additionally, the risk of systemic lupus erythematosus

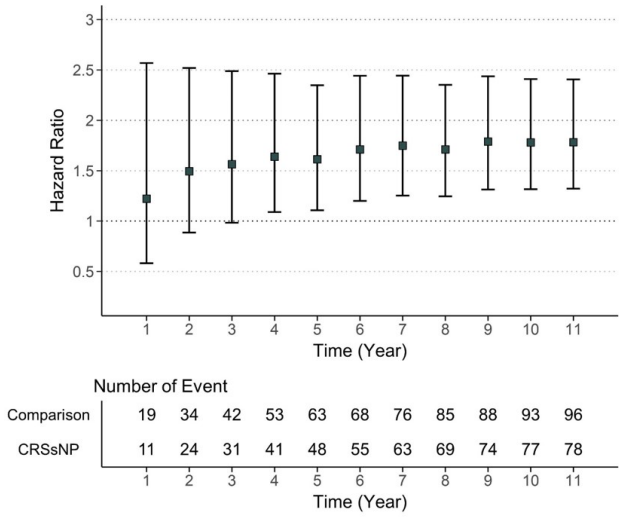

Figure 4. Hazard ratios for incident Sjögren's syndrome associated with CRSsNP by time since CRSsNP diagnosis.

and ankylosing spondylitis were not significantly different according to the phenotype of CRS.

Previously, Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis have been reported to be associated with CRS in some studies using population-based datasets, but they have shown various results and are still controversial [10-12]. One age- and gender-matched cohort study revealed that the prevalence of ankylosing spondylitis was significantly higher in patients with CRS compared to a control group, but not significantly higher for systemic lupus erythematosus [11], whereas another socio-demographically matched study showed an increased odds ratio for Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis in a CRS group [12]. However, that cohort study was not controlled for any other comorbidities which could have influenced immunologic statuses in the CRS and non-CRS groups. The follow-up period was also relatively short. Thus, that cohort study showed that CRS patients had a significantly increased OR for most types of autoimmune disease (Sjögren's syndrome, systemic lupus erythematosus, ankylosing spondylitis, polymyositis, psoriasis, and rheumatoid arthritis). In contrast with that study, we adjusted comorbidities using the Charlson comorbidity index and had a relatively long follow-up period (10 years). Additionally, to avoid small-sample error, we investigated only Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis because other diseases showed quite a small incidence in South Korea. Although rheumatoid arthritis is common enough in South Korea, it is one of the most commonly over-diagnosed diseases due to medical insurance coverage issues. Thus, to avoid inaccurate diagnosis issues, we did not include it in our analysis.

Sjögren's syndrome is a chronic autoimmune disease characterised by lymphocytic infiltration of the exocrine glands, mainly the salivary and lacrimal glands, causing symptoms of xerostomia and keratoconjunctivitis sicca [15,16]. Its global prevalence is about 0.1–4.6% and it causes dry mouth and eyes as well as nasal symptoms such as nasal crusting, epistaxis, and nasal stuffiness [17,18]. Some studies have reported the occurrence of nasal symptoms, such as nasal crusting and epistaxis in patients with Sjögren's syndrome [17,19,20]. Nasal mucosal dryness and thickened secretions caused by Sjögren's syndrome are also known to be conditions leading to the development of CRS, and one study showed that sicca symptoms had strong association with CRS (OR = 2.5 [95% CI, 1.9–3.4]) [21]. Moreover, one recent study reported that the prevalence of CRS in patients with SS was significantly higher than that of the control group, and SS could be a risk factor for development of CRS (adjusted HR=2.51) [22]. Consistent with those studies, we found that the risk of SS development was significantly higher in CRS patients, specifically in CRSsNP, not CRSwNP.

It is well known that changes in mucociliary clearance, abnormality of the sinonasal epithelial cell barrier, tissue remodeling, and innate and adaptive immune responses contribute to the pathogenesis of CRS [23]. However, the mechanism of Sjögren's syndrome on the development of CRS has not yet been clarified. Some prior studies have investigated possible mechanism by which Sjögren's syndrome can influence the pathophysiology of CRS [24,25]. They reported that Sjögren's syndrome affects the meibomian gland, increasing the evaporation rate of the tears and reducing the number of natural tears entering the nasal cavity through the nasolacrimal duct. In addition, it was reported that Sjögren's syndrome had mild nasal glandular involvement, which can reduce nasal secretion [17]. The decrease in nasal secretions caused by the aforementioned factors could lead to a dry nasal cavity and an increase in nasal mucus viscosity. Thus, this nasal condition could induce changes in nasal clearance, and several studies which support this hypothesis also showed an increase in the nasal saccharin clearance time in patients with Sjögren's syndrome compared to the controls [17,20,26]. Moreover, mucus with increased viscosity could lead to poor sinus drainage, which causes bacterial overgrowth, creating an environment favourable for developing CRS. Sjögren's syndrome can also impair natural innate immunity by reducing mucosal secretions containing secretary IgA and effector molecules, which contribute to immune defence at the mucosal surface and reduce amylase and carbonic anhydrase secreted by the salivary glands [27-30]. Collectively, these findings imply that Sjögren's syndrome may affect the nasal susceptibility to infection.

In this study, we performed subgroup analyses to confirm the association between CRS and autoimmune disease according to the phenotype of CRS. It revealed that patients with CRSsNP had a significantly higher likelihood of developing Sjögren's syndrome, but not systemic lupus erythematosus and ankylosing spondylitis. Whereas, in CRSwNP patients, there was no signifi-

cant association between CRS and Sjögren's syndrome, systemic lupus erythematosus, or ankylosing spondylitis. It has been well-known that CRSwNP is characterised by increased Th2 cytokine expression, high eosinophilic infiltration, oedematous stromal tissue, frequent epithelial damage, and a thickened basement membrane. On the other hand, CRSsNP shows increased Th1 cytokine expression and less eosinophilic infiltration compared to CRSwNP [31-33]. The presence of one Th1 pathology is often associated with the presence or occurrence of other comorbid Th1 pathology [34]. Some prior studies have suggested that autoimmune disease may skew airway inflammatory disease away from Th2 pathways [35,36]. Therefore, underlying Th1 status due to Sjögren's syndrome is most likely a factor influencing the phenotypic expression with CRSsNP. Additionally, it is considered that the increase in infection susceptibility due to Sjögren's syndrome may have increased the incidence of CRSsNP, which is mainly caused by various types of infection, more than CRSwNP.

Our study had several strengths. First, to the best of our knowledge, this is the first cohort study to use nationwide population-based data to evaluate the incidence of autoimmune disease in Korean patients with CRS. Second, our study included a large number of patients and had a relatively long observation period of 10 years. Finally, a prior study for validation of KNHIS-NSC data reported a similar prevalence of major diseases every year, and these findings indicate that the KNHIS-NSC data is highly reliable. However, this study also had certain limitations. First, patients with CRS and autoimmune disease were identified based on ICD-10 diagnostic codes, not on detailed medical records that include information on medical history and pathologic reports. Therefore, this study may have a misclassification bias. To overcome this issue, we included patients with CRS who underwent head and neck computed tomography for CRS diagnosis and patients with the autoimmune disease diagnosed by rheumatologists. However, in this situation, it is only likely to enroll mainly severe-form CRS patients. Second, information about disease duration (onset history) and severity of CRS (Lund-Mackay or Lund-Kennedy score) could not be assessed. Thus, we were not able to investigate whether the duration or severity of CRS could influence autoimmune disease. Finally, because this was a retrospective cohort study, the pathological mechanisms of CRS and autoimmune diseases could not be directly investigated and analysed. In order to elucidate the underlying pathophysiological mechanisms, clinical studies including a wider range of factors are needed in the future.

Conclusions

The present study examined the association between CRS and risk of autoimmune diseases events including Sjögren's syndrome, systemic lupus erythematosus, and ankylosing spondylitis while adjusting for clinical and demographic factors. We found an increased risk of Sjögren's syndrome events in patients with CRS compared to those with non-CRS, specifically in CRSsNP. Therefore, clinicians should be aware of the potential for Sjögren's syndrome development in patients with CRS and be ready to make appropriate referrals to rheumatologic health professionals.

Authorship contribution

D-KK had the research idea and conceived the study design; IHL and D-KK performed data acquisition; IHL and D-KK performed data analysis/interpretation; D-KK performed the statistical analysis; IHL and D-KK prepared the original draft; D-KK was responsible for funding acquisition. The review and editing of the manuscript were supervised by all authors, under the mentorship of D-KK. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Both authors declare that they have no conflicts of interest relevant to the work presented in this article.

Funding

This study was supported by a grant from the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (grant number NRF-2021R1C1C1005746).

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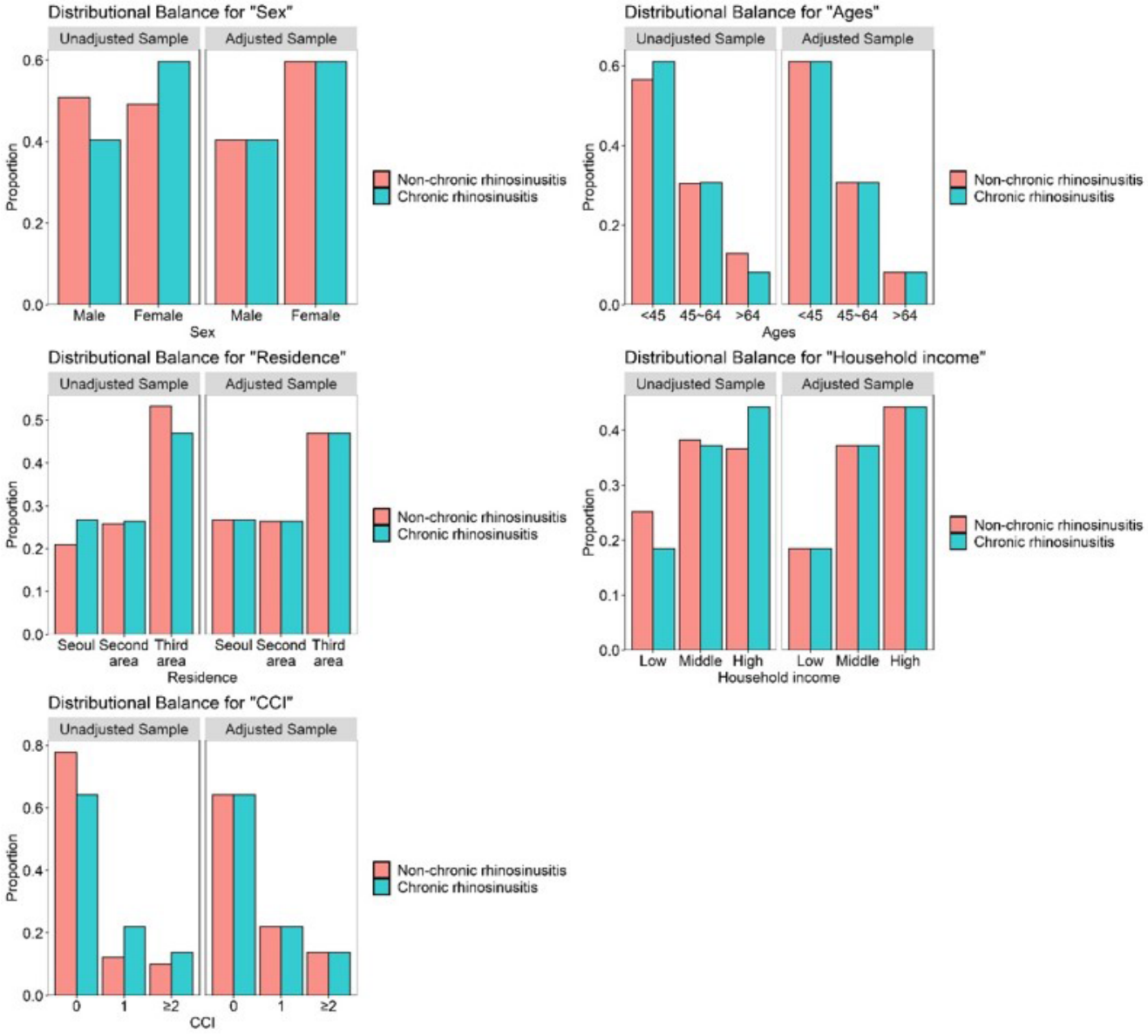
This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Balance plot for 5 variables before and after matching.

Supplementary Table 1. Description of time to event and censored data.

	Sjögren's syndrome event	Systemic lupus erythematosus event	Ankylosing spondylitis event
Event number	175	42	203
Comparison	96	27	134
CRS	79	15	69
Total censored (No event)	45215	45348	45187
Comparison	30164	30233	30126
CRS	15051	15115	15061
Termination of study	43034	43163	43012
Comparison	28473	28539	28436
CRS	14561	14624	14576
Loss to follow up / Drop-out	2181	2185	2175
Comparison	1691	1694	1690
CRS	490	491	485