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Ankylosing Spondylitis Is Associated with Risk of New Onset Obstructive Sleep Apnea: A Nationwide Population-Based Cohort Study

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Subtitle: AS and risk of OSA

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Abstract

Background: The aim of this study was to investigate the risk of obstructive sleep apnea (OSA) among ankylosing spondylitis (AS) patients in a nationwide population.

Methods: We conducted a nationwide cohort study between 2003 and 2013 using the Taiwan National Health Insurance Research Database. The AS cohort included 2,210 patients who were newly diagnosed between 2003 and 2013. Randomly selected non-AS controls were matched at a 1:4 ratio based on age, sex and index date. The endpoint of OSA was occurrence or the end of 2013. Cumulative incidences, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated after adjusting for age, gender, comorbidities and co-medications. Multivariate analyses were performed using Cox proportional hazards model. Due to violation of the proportionality assumption, landmark analysis was conducted to explore the risk of OSA during specific follow-up periods.

Results: The adjusted HR (aHR) of OSA for the AS group was 2.826 (95% C.I.= 1.727-4.625) compared to the control group. On landmark analysis, aHR was 7.919 (95% C.I.=3.169-19.792) for AS group 0-24 months from index date, and decreased to 1.816 (95% C.I.=0.944-3.494) at ≥ 24 months from index date. On subgroup analyses increased risks of OSA in AS group compared to the control group were found for both males and females (aHRs were 4.533 (95% C.I.=1.441-14.262) and 2.672 (95% C.I.=1.522-4.692) for females and males, respectively). On age stratified analysis, there was significant risk only for the 40-59 age group with aHR of 3.913 (95% C.I.=1.890-8.102)

Conclusions: A higher risk of developing OSA was found among newly diagnosed AS cohort during the 12-year follow-up period, especially within 2 years after AS index date and in the 40-59 age group.

Key Words: Ankylosing spondylitis, obstructive sleep apnea, population-based cohort study

Statement of Significance

This is the first study to harvest national population base and 10 years cohort with matching groups to describing the association between ankylosing spondylitis (AS) and obstructive sleep apnea (OSA).This study also showed the difference of medication among groups within 180 days before or after index date and the associated disease between OSA and non-OSA groups in asthma, esophageal disease, hepatitis B virus infection and administration of non-steroid anti-inflammatory drugs(NSAIDs). Compared with non-AS patients of the same age, AS patients have a significantly increased risk of developing OSA and age differences were obvious when people more than 40 years old.

Introduction

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Obstructive sleep apnea (OSA) is a common chronic disorder characterized by recurrent collapse of the upper airway during sleep, leading to sleep fragmentation and daytime sleepiness.[1-3] Individuals with OSA present with apneas, hypopneas or respiratory effort-related arousals, occurring at least five times/hour during sleep (apnea–hypopnea index, AHI ≥5).[2 3] The estimated prevalence in North America is about 20 to 30 percent in males and 10 to 15 percent in females when OSA is defined broadly as an AHI greater than five events per hour as measured on polysomnogram.[4 5] Even with the more stringent definition of AHI ≥15 events per hour, the estimated prevalence is around 15 percent in males and 5 percent in females.[5 6] A recent population-based study demonstrated a need to revise the definition of this disease and presented high prevalence rates for moderate to severe OSA (AHI≥15) (23.4% in women and 49.7% in men) .[7] Even though OSA is not an immediate life-threatening disease, it can lower quality of life and productivity, increase risk of hospitalization and elevate morbidity from cardiovascular diseases.[8-10] There have been several studies showing that patients with OSA have higher healthcare service utilization, including medical costs, medication usage, emergency department visits, and hospitalization compared to subjects without OSA in the US[11 12], Canada[13], Denmark[14] , Israel[15], and Taiwan[16].

Well-defined risk factors for OSA include age, male gender, obesity, orthopedic pathology and upper airway soft tissue abnormalities. Potential risk factors include smoking, nasal congestion, and family history.[17-19] Systemic autoimmune diseases are characterized by dysregulation of the immune system, which in turn activates the immune cells to attack autoantigens resulting in inappropriate inflammation and multi-tissue damage. ,OSA has been linked to inflammation, coagulation and endothelial dysfunction.[20.] Therefore, the correlation between autoimmune diseases and OSA deserves attention. The results of a previous study have shown an association between rheumatoid arthritis (RA) and subsequent OSA.[21]

Ankylosing spondylitis (AS) is a type of spondyloarthritis characterized by spondylitis, sacroilitis, peripheral joint involvement, and enthesitis.[22] In addition to affecting the musculoskeletal system, AS exhibits a range of extra-articular manifestations, such as inflammatory bowel disease, psoriasis, and cardiovascular diseases.[22 23] The prevalence of OSA in AS patients is higher than that reported in the general population, but it is not easy to identify without detailed testing.[24 25] Most of the previous studies have been performed

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with small study populations. Or, they have been cross sectional studies without long term follow up. Therefore, they cannot be used to explain the temporal relationship between AS and OSA. Due to a lack of research on the epidemiological relationship between AS and the subsequent development of OSA, this longitudinal nationwide cohort study was conducted to explore whether patients with newly diagnosed AS are prone to the subsequent development of OSA.

Materials and methods

Data source

The Longitudinal Health Insurance Research Datasets (LHIRD) were collected from the National Health Insurance (NHI) program, which is a single-payer, social insurance system, covering 94% of the population in 2000. The randomly sampled beneficiaries (n= 1 million) of LHIRD were registered in the NHI program in 2000. The 1997-2013 claim datasets, including outpatient visits, discharge records, and prescription data of LHIRD were retrieved for analysis. Identifiers were scrambled to protect the privacy of subjects. This study was approved by the Institutional Review Board of Chung Shan Medical University in Taiwan (IRB permit number CS15134), which waived the requirement for informed consent due to the anonymous use of data with subjects unidentifiable before analysis.

Patients with ankylosing spondylitis (AS)

This retrospective cohort study was conducted using administrative claims records. Patients with AS (ICD-9 code: 720.0), as defined by the 1984 modified New York criteria, were identified based on at least 2 outpatient visits or 1 admission within 1 year by rheumatologist, orthopedist or rehabilitation physician. There were 4,990 AS patients and 917,042 non-AS individuals from 1997-2013 included in the LHIRD. In order to observe the risk of OSA from new-onset AS, we excluded cases with AS before 2003 (n=2,086). Furthermore, we excluded AS patients who did not receive spinal X-ray within 6 months before or after AS diagnosis (n=672), or with OSA event before AS diagnosis (n=22). Finally, there were 2,210 AS patients newly diagnosed with AS from 2003 to 2013, and the index date was the first date of AS diagnosis.

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The 1:4 age-sex individual matched controls were randomly sampled from among the non-AS individuals. The index date for the controls corresponded to the date of matched AS case. All study participants met the inclusion criteria and were at risk at index date.

Identified events of obstructive sleep apnea (OSA)

Newly diagnosed OSA (ICD-9 code: 327.23, 780.51, 780.53 and 780.57) was identified from index date to the end of the study (Dec 2013) or withdrawal from the NHI program. We only considered OSA diagnoses made by otolaryngologist, neurologist, or chest physician. For more accurate OSA diagnosis, we referred to specific examinations (eg polysomnography) and specialist knowledge . There were 30 (1.36 %) and 40 (0.45%) OSA cases diagnosed by otolaryngologist, neurologist, or chest physician in AS and non-AS groups, respectively. There were 8 (0.36%) and 22 (0.25%) OSA cases diagnosed by other specialist in AS and non-AS groups, respectively.

Confounding comorbidities and co-medications

The comorbidities analyzed in this study were hypertension (ICD-9-CM codes 401-405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, 496), asthma (ICD-9-CM code 493), cancer (ICD-9-CM codes 140-208), chronic liver diseases (ICD-9-CM code 571.4), hepatitis B (ICD-9-CM codes 070.2, 070.3, V02.61), hepatitis C (ICD-9-CM codes 070.41, 070.44, 070.51, 070.54, V02.62), coronary artery disease (CAD) (ICD-9-CM codes 410–414), dysrhythmia (ICD-9-CM code 427), congestive heart failure (CHF) (ICD-9-CM code 428), stroke (ICD-9-CM codes 430 −438), chronic kidney disease (CKD) (ICD-9-CM code 585), asthma (ICD-9-CM codes 493), thyroid disorders (ICD-9: 240, 241, 242, 244.9, 245.0, 245.1, 245.2), other rheumatic diseases (ICD-9: 714, 710, 696.0, 696.1), RA (ICD-9 code: 714.0), systemic lupus erythematosus (SLE) (ICD-9 code: 710.0), Sjögren's syndrome (ICD-9 code: 710.2) and psoriasis (ICD-9 code: 696.0, 696.1), Information on comorbid medical disorders was obtained by tracing all ambulatory medical care and inpatient records in the NHI database within 2 years of the index visit. The medication confounders in this study were corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), H_2 receptor antagonists, aspirin, oral antihypertensive drugs (including alpha-

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blockers, beta- blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs), oral antihypoglycemic agents (including biguanides, sulfonylureas, alpha glucosidase inhibitors, thiazolidinediones), and statins. Drug use was defined as usage of that drug for ≥ 30 days within 180 days before and after index date.

Statistical analysis

The chi-square test was used to test the homogeneity of category variables between AS and control groups. After examining the proportional hazard assumption, the risk of OSA from AS exposure was found to be time dependent. Therefore, landmark analysis was performed to analyze the OSA risk during 2 specific time intervals (index date to 24 months and ≥24 months after index date). Univariate and multivariate Cox regression models were used to estimate the crude and adjusted hazard ratios (HRs, 95% confidence interval, 95% C.I.). Furthermore, subgroup analysis was used to explore the interaction factors. All statistical analyses were performed with SAS software (version 9.4; SAS Institute, Cary, NC, USA). A p value less than 0.05 indicated statistical significance.

Results

After applying the inclusion and exclusion criteria and carrying out age-sex matching, 2,210 AS patients and 8,840 controls were enrolled (Figure 1). Table 1 provides the baseline characteristics of the study groups. Among AS patients, 79.14% were 20-59 years old and 64.62% were male. There were significantly lower proportions of low-income households, longer hospital stays, higher proportions of co-morbidities (such as other rheumatic diseases, thyroid disorders, asthma, COPD, hypertension, hyperlipidemia, coronary artery disease, dysrhythmia, esophageal disease, peptic ulcer, hepatitis B virus infection, chronic liver disease, and chronic kidney disease), and higher proportions of medication usage (including NSAIDs, DMARDs, corticosteroids, PPIs, H2 receptor antagonists, aspirin, and oral antihypertensive drugs) when compared with non-AS group. (Table 2)

Table 3 shows the HRs of OSA. On univariate modeling, the crude HR was 3.031 (95% C.I.= 1.888-4.865) in patients with AS. On multivariate modeling, the adjusted HR (aHR) was 2.826 (95% C.I.= 1.727-4.625) in

patients with AS. The significantly associated risk factors were male gender (aHR=2.144, 95% C.I.= 1.190-3.862), asthma (aHR=2.381, 95% C.I.= 1.036-5.475), esophageal disease (aHR=2.544, 95% C.I.= 1.230-5.259), and hepatitis B viral infection (aHR=3.551, 95% C.I.= 1.419-8.889). NSAIDs use (aHR=1.954, 95% C.I.= 0.965-3.954) was borderline significantly associated with OSA.

The incidence rates (per 100000 person months) of OSA were 7.54 (95% C.I.=5.53-10.28) and 22.84 (95% C.I.= 15.97-32.68) for control and AS groups, respectively. We conducted 4 different proportional hazard models to examine the stability of aHR. The aHRs did not show large variance with a range from 2.718 (95% C.I.=1.670-4.423) to 3.036 (95% C.I.=1.891-4.875). (Table 4)

Figure 2 indicates the cumulative proportions of OSA in both AS and non-AS groups. Higher cumulative proportion in AS group was observed and the log-rank test p was less than 0.0001. According to the slope of Kaplan-Meier curves and test for proportional assumption, the risk of OSA in AS is time dependent. Therefore, landmark analysis (Table 5) was conducted to explore the risk of OSA during specific follow-up periods. The aHR was 7.919 (95% C.I.=3.169-19.792) in AS group at 0-24 months from index date and decreased to 1.816 (95% C.I.=0.944-3.494) at ≥ 24 months from index date.

Table 6 shows the results of subgroup analyses. On sex stratified analysis (p for interaction was 0.5428), aHRs were 4.533 (95% C.I.=1.441-14.262) for females and 2.672 (95% C.I.=1.522-4.692) for males. On age stratified analysis (p for interaction was 0.7562), aHRs were 0.719 (95% C.I.=0.015-35.162) for those <20, 1.847 (95% C.I.=0.830-4.108) for those 20-39, 3.913 (95% C.I.=1.890-8.102) for those 40-59, and 3.930 (95% C.I.=0.665-23.234) for those ≥60.

DISCUSSION

To the best of our knowledge, this is the first retrospective cohort study using nationwide population-based data to investigate the OSA risk associated with AS. The results of this study showed a 2.826-fold greater risk of subsequent development of OSA among AS patients than the general population. Furthermore, stratified analyses revealed significant effects for both genders and the 40-59 age group. Although the AS group had a significantly higher rate of comorbid diseases compared to the non-AS group, AS remained an

independent risk factor for developing OSA after adjusting for gender, age, comorbidities and co-medications.

There are four significant findings of this study. First, it is currently the only large cohort study to investigate the association between AS and the subsequent development of OSA. The Taiwan NHI Research Database is one of the largest nationwide population databases in the world, covering approximately 23 million residents in Taiwan. [26 27] Large population-based studies can inform on the incidences, treatments, correlates, and associations of disease, as well as on the patterns of health care utilization. The major advantages include enormous sample size and lack of selection or participation bias. [27] The study cohorts were large enough to observe the risk variations among subgroups. Second, we performed concise subgroup analyses to illustrate the interrelationships of gender, age, comorbidities and medications. This can help to identify and appropriately monitor the high-risk groups of AS patients, such as male subjects and those aged 40-59. Third, the validity of the findings was enhanced by unbiased subject selection and strict criteria for the diagnosis of OSA. Fourth, significant risk of developing OSA (aHR was 7.919 with 95% C.I.=3.169-19.792) was noted in the first 2 years after diagnosis of AS. We speculated that the disease activity of AS is controlled by medications and physical therapy, leading to a decrease in the associated risk of OSA.
The underlying mechanism of the relationship between AS and OSA remains largely unclear. The possible mechanisms of OSA in AS patients include restriction of the oropharyngeal airway due to temporomandibular joint involvement, pharyngeal and tracheal compression by cervical spine disease, and restrictive pulmonary disease.[24 25] There is a possible role for cytokines in the regulation of sleep in patients with systemic inflammatory disorders.[28 29]

Several limitations should be considered when interpreting the findings of this study. First, information on potential confounding factors, such as body mass index, family history and drinking and smoking habits was unavailable. Smoking increases the risk of OSA or at least aggravates preexisting symptoms. However, we used COPD as a proxy variable for cigarette smoking, based on the accepted methodology of several previous studies.[30-32] Second, NHIRD did not provide detailed information on the severity of RA or OSA, and it was therefore not possible to demonstrate the dose–response relationship between AS and OSA.

Third, relevant clinical variables such as imaging reports, serum laboratory data and polysomnography results were unavailable, making it difficult to understand whether clinical characteristics are associated with the risk of developing OSA. Our findings, therefore, should be interpreted with caution given the absence of data on important OSA risk factors and AS disease severity.

Conclusion

This 12-year population-based cohort study demonstrated a higher risk of OSA in patients with AS, among both genders and those aged 40-59. The risk was highest within the first 2 years of diagnosis of AS. Further studies are recommended to clarify the underlying biological mechanisms of these associations. It is important to evaluate sleep quality and quantity for patients with AS to detect the occurrence of OSA and to reduce further complications.

Conflict of interest: All of the authors have declared that they have no competing interests.

Contributors: All authors were involved in drafting and/or revising this manuscript and all authors have approved the final version for publication.

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Acquisition of data. Huang JY, Wei.

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Writing of the paper: Tsao Hung, Wei,

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Figure 1. Flow chart of subjects selection

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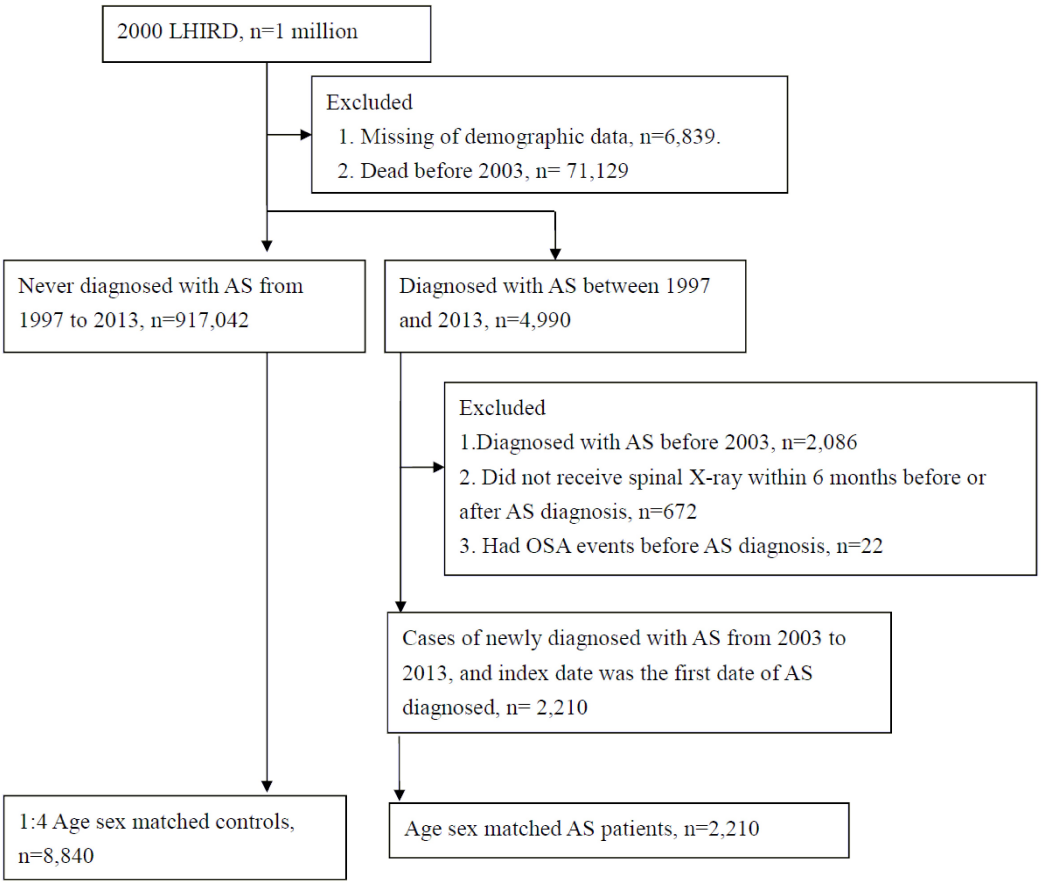

Figure 2. The cumulative proportions of OSA in both AS and non-AS groups

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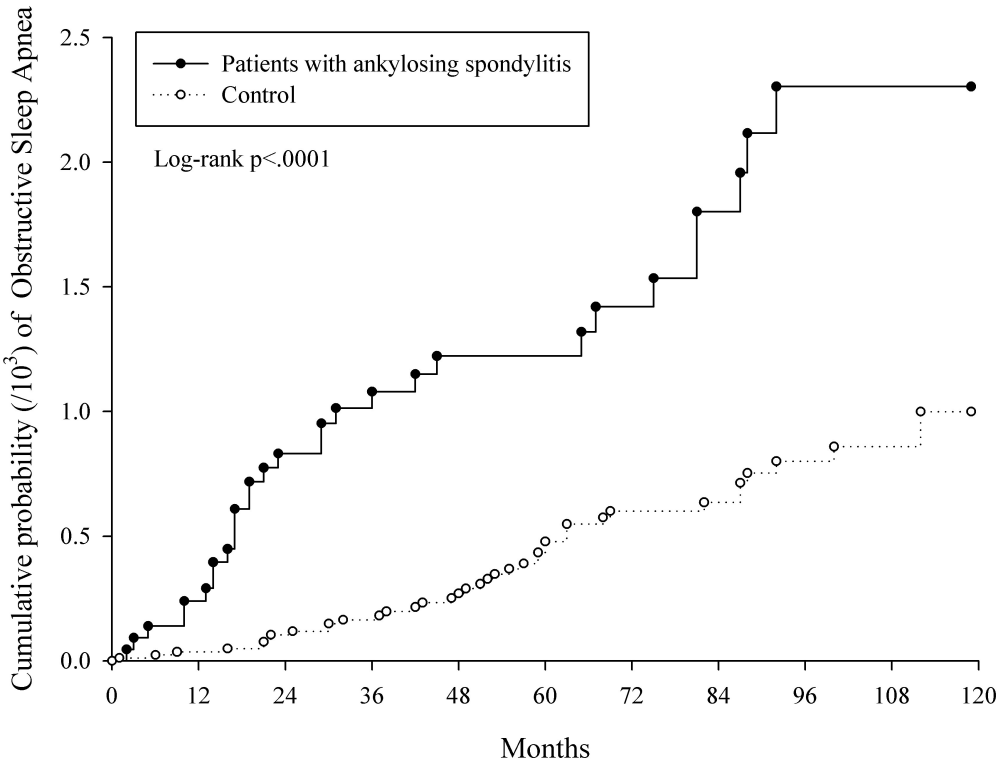

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Table 1 Characteristics among groups

	Control n=8,840	Patients with AS n=2,210	p value
Age at index date			1.0000
<20	524(5.93%)	131(5.93%)	
20-39	4,116(46.56%)	1,029(46.56%)	
40-59	2,880(32.58%)	720(32.58%)	
>=60	1,320(14.93%)	330(14.93%)	
Sex			1.0000
Female	3,128(35.38%)	782(35.38%)	
Male	5,712(64.62%)	1,428(64.62%)	
Urbanization			0.7017
Urban	5439(61.53%)	1356(61.36%)	
Sub-urban	2626(29.71%)	648(29.32%)	
Rural	775(8.77%)	206(9.32%)	
Low income	59(0.67%)	5(0.23%)	0.0145
Length of hospital stay			<.0001
0	7811(88.36%)	1855(83.94%)	
1-6	621(7.02%)	197(8.91%)	
7-13	211(2.39%)	96(4.34%)	
>=14	197(2.23%)	62(2.81%)	
Co-morbidities			
Other rheumatic diseases	159(1.80%)	202(9.14%)	<.0001
Thyroid disorders	152(1.72%)	81(3.67%)	<.0001
Asthma	329(3.72%)	119(5.38%)	0.0004
COPD	534(6.04%)	202(9.14%)	<.0001
Hypertension	1225(13.86%)	379(17.15%)	<.0001
Diabetes mellitus	613(6.93%)	171(7.74%)	0.1884

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Hyperlipidemia	821(9.29%)	285(12.90%)	<.0001
Coronary artery disease	442(5.00%)	171(7.74%)	<.0001
Dysrhythmia	237(2.68%)	108(4.89%)	<.0001
Heart failure	93(1.05%)	30(1.36%)	0.2209
Cerebrovascular accident	278(3.14%)	87(3.94%)	0.0625
Esophageal disease	396(4.48%)	226(10.23%)	<.0001
Peptic ulcer	724(8.19%)	357(16.15%)	<.0001
Hepatitis B virus infection	201(2.27%)	77(3.48%)	0.0012
Hepatitis C virus infection	61(0.69%)	22(1.00%)	0.1369
Chronic liver disease	621(7.02%)	265(11.99%)	<.0001
Chronic kidney disease	175(1.98%)	73(3.30%)	0.0002

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Table 2 Medication among groups within 180 days before or after index date

	Control	Patients with AS	p value
NSAIDs	**4111(46.50%)**	**2032(91.95%)**	**<.0001**
Indomethacin	161(1.82%)	177(8.01%)	<.0001
Piroxicam	298(3.37%)	293(13.26%)	<.0001
Diclofenac	2224(25.16%)	1365(61.76%)	<.0001
Nabumetone	20(0.23%)	57(2.58%)	<.0001
Naproxen	267(3.02%)	228(10.32%)	<.0001
Sulindac	133(1.5%)	308(13.94%)	<.0001
Tiaprofenic acid	81(0.92%)	143(6.47%)	<.0001
Tenoxicam	46(0.52%)	56(2.53%)	<.0001
Ibuprofen	1204(13.62%)	502(22.71%)	<.0001
Celecoxib	76(0.86%)	463(20.95%)	<.0001
Mefenamic acid	1495(16.91%)	560(25.34%)	<.0001
Ketorolac	283(3.2%)	274(12.4%)	<.0001
Meloxicam	107(1.21%)	410(18.55%)	<.0001
DMARDs	**112(1.27%)**	**752(34.03%)**	**<.0001**
Hydroxychloroquine	17(0.19%)	89(4.03%)	<.0001
Leflunomide	0(0.00%)	2(0.09%)	0.0047
Methotrexate	10(0.11%)	41(1.86%)	<.0001
Azathioprine	5(0.06%)	9(0.41%)	<.0001
Ciclosporin	2(0.02%)	5(0.23%)	0.0007
Sulfasalazine	9(0.10%)	680(30.77%)	<.0001
Minocycline	81(0.92%)	29(1.31%)	0.0936
Corticosteroids	**1147(12.98%)**	**632(28.60%)**	**<.0001**
PPI	**169(1.91%)**	**109(4.93%)**	**<.0001**
H2 receptor antagonist	**1063(12.02%)**	**475(21.49%)**	**<.0001**
Aspirin	**522(5.90%)**	**188(8.51%)**	**<.0001**

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Oral antihypertensive drugs	**1263(14.29%)**	**461(20.86%)**	**<.0001**
Oral antihyperglycemic agents	**387(4.38%)**	**97(4.39%)**	**0.9815**
Statin	**325(3.68%)**	**97(4.39%)**	**0.1179**

Oral antihypertensive drugs, including Alpha-blockers, Beta- blockers, CCBs, ACEI, ARBs

Oral antihyperglycemic agents, including Biguanides, Sulfonylureas, Alpha glucosidase inhibitors, Thiazolidinediones

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Table 3 Estimation the hazard ratio of OSA by using Cox proportional hazard regression

	Univariate modeling		Multivariate modeling	
	HR	95% C.I.	aHR	95% C.I.
Exposure of AS (ref: non AS)				
AS patient	**3.031**	**1.888-4.865**	**2.826**	**1.727-4.625**
Age at index date (ref: 20-39)				
<20	0.559	0.134-2.345	0.600	0.143-2.525
40-59	1.751	1.063-2.884	1.636	0.948-2.824
>=60	0.754	0.313-1.817	0.583	0.208-1.636
Sex (ref: Female)				
Male	**1.957**	**1.106-3.464**	**2.144**	**1.190-3.862**
Urbanization (ref: Urban)				
Sub-urban	1.224	0.746-2.008	1.207	0.732-1.988
Rural	0.495	0.153-1.597	0.429	0.131-1.408
Length of hospital stay (ref: 0)				
1-6	1.618	0.773-3.389	1.174	0.540-2.553
7-13	0.573	0.079-4.137	0.457	0.060-3.466
>=14	2.414	0.756-7.709	2.009	0.593-6.804
Co-morbidities				
Other rheumatic diseases	0.438	0.061-3.153	0.242	0.032-1.824
Thyroid disorders	1.568	0.384-6.398	0.891	0.182-4.370
Asthma	**2.810**	**1.287-6.135**	**2.381**	**1.036-5.475**
COPD	2.089	1.038-4.206	1.506	0.698-3.250
Hypertension	1.708	0.951-3.069	1.753	0.842-3.649
Diabetes mellitus	1.438	0.622-3.321	1.245	0.481-3.222
Hyperlipidemia	1.507	0.749-3.036	0.858	0.370-1.990
Coronary artery disease	2.120	0.971-4.628	1.943	0.771-4.898
Dysrhythmia	1.523	0.479-4.842	0.905	0.263-3.121

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Heart failure	-	-	-	-
Cerebrovascular accident	0.483	0.067-3.476	0.285	0.037-2.187
Esophageal disease	**4.243**	**2.226-8.089**	**2.544**	**1.230-5.259**
Peptic ulcer	2.121	1.161-3.874	1.210	0.602-2.432
Hepatitis B virus infection	**3.907**	**1.692-9.025**	**3.551**	**1.419-8.889**
Hepatitis C virus infection	-	-	-	-
Chronic liver disease	2.218	1.191-4.130	1.220	0.601-2.480
Chronic kidney disease	-	-	-	-
Medications				
NSAIDs	**1.625**	**0.918-2.877**	**1.954**	**0.965-3.954**
DMARDs	-	-	-	-
Corticosteroids	1.416	0.516-3.886	0.740	0.231-2.374
PPI	4.403	1.079-17.967	2.267	0.417-12.321
H2 Receptor	2.367	0.953-5.880	1.408	0.456-4.343
Aspirin	0.877	0.122-6.312	0.715	0.088-5.833
Antihypertensive drugs	0.742	0.182-3.027	0.311	0.060-1.607
Antihyperglycemic agents	1.555	0.216-11.196	1.121	0.123-10.262
Statin	1.662	0.231-11.971	1.613	0.176-14.803

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Table 4 Time to event analysis

	Control	Patients with AS	p value
N	8,840	2,210	
Follow up person months	530518	131318	
Event of OSA	40	30	
Incidence rate* (95% C.I.)	7.54(5.53-10.28)	22.84(15.97-32.68)	
Model 1: Crude hazard ratio (95% C.I.)	Reference	3.031(1.888-4.865)	<.0001
Model 2: aHR (95% C.I.)	Reference	3.036(1.891-4.875)	<.0001
Model 3: aHR (95% C.I.)	Reference	2.718(1.670-4.423)	<.0001
Model 4: aHR (95% C.I.)	Reference	2.826(1.727-4.625)	<.0001

* per 100000 person months

Model 2: adjusted for demographic variables, including sex, age, and urbanization at baseline.

Model 3: adjusted for demographic variables, length of hospital stay, and co-morbidities at baseline

Model 4: adjusted for demographic variables, length of hospital stay, co-morbidities, and co-medications at baseline

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Table 5 Landmark analysis

	Control			
	Person months	Event	Incidence* (95% C.I.)	Person months
Follow up time interval				
Index date to 24 months	188613	8	4.24(2.12-8.48)	46810
>24 months	341905	32	9.36(6.62-13.23)	84508
p for interaction				

Table 6 Subgroup analysis

	Control			
	Person months	Event	Incidence* (95% C.I.)	Person months
Sex subgroups				
Female	184568	8	4.33(2.17-8.67)	46172
Male	345950	32	9.25(6.54-13.08)	85146
p for interaction				
Age subgroups				
<20	31924	1	3.13(0.44-22.24)	8016
20-39	258338	19	7.35(4.69-11.53)	64600
40-59	168657	17	10.08(6.27-16.21)	41679
>=60	71599	3	4.19(1.35-12.99)	17023
p for interaction				

* per 100000 person months

‡ Adjust for variables, including age, gender, residential urbanization, length of hospital stay, comorbidity, and drug use at baseline.