

# Midlife Ankylosing Spondylitis Increases the Risk of Cardiovascular Diseases in Males 5 Years Later

## *A National Population-Based Study*

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**Abstract:** There are limited studies describing the association between ankylosing spondylitis (AS) and cardiovascular disease (CVD) in patients over 40 years old. We aimed to focus on the incident AS patients in those aged 40 years or older and to investigate whether events of CVD occurred more than the general population.

We conducted a nationwide cohort study between 2000 and 2005 using the Taiwan National Health Insurance Research Database. The risk of newly diagnosed CVD was compared between incident AS patients and matched age- and sex-matched subjects without AS. Events of CVDs were classified into 1 of 5 subcategories: hypertensive heart disease, coronary heart disease, congestive heart failure, cerebrovascular disease, or “other” CVD according to the ICD-9-CM codes. Cumulative incidences and hazard ratios (HRs) were calculated after adjusting for demographic and comorbid medical disorders. Multivariate analyses were performed using Cox proportional hazards model.

We compared 537 AS and 2685 non-AS patients and found that the cumulative incidence rate of CVD during follow-up period was higher in the AS cohort than the non-AS cohort. The crude HR of CVD for the AS group was 1.24 [95% confidence interval (95% CI), 1.05–1.46;  $P=0.01$ ] and the adjusted HR was 1.20 with 95% CI 1.02 to 1.42 ( $P=0.03$ ). When stratified by age, AS cohort at age 60 to 69 years exhibited a significantly higher HR for all CVD than the general population cohort (adjusted HR 1.48, 95% CI 1.06–2.08,  $P<0.05$ ). When stratified by gender, male AS group had a significantly higher HR for all CVD than the general population cohort with the adjusted HR 1.28 (95% CI 1.01–1.63,  $P<0.05$ ). There was no statistically significant difference for females.

Patients with AS, especially age 60 to 69 years male patients, had a higher risk of CVDs than non-AS controls.

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**Abbreviations:** 95% CI = 95% confidence interval, AS = Ankylosing spondylitis, COX-2 = cyclooxygenase-2 inhibitors, CVD = cardiovascular diseases, HR = hazard ratio, MRI = magnetic resonance imaging, NHIRD = National Health Insurance Research Database, NSAIDs = nonsteroidal anti-inflammatory drugs.

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JC-CW is the corresponding author and has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Y-MH, W-PC, JC-CW did the study conception and design. W-PC and JC-CW did the acquisition of data. Y-MH, W-PC, JC-CW, PC, and PY-PW did the analysis and interpretation of data. Y-MH, JC-CW, PY-PW wrote the paper. PY-PW gave the English edition.

The data source used for this study was the claims data of Taiwan's National Health Insurance Research Database (NHIRD). Taiwan's NHIRD is a publically released and de-identified research database that each researcher in Taiwan can apply, but should stick to the research guideline of Taiwan's NHIRD. In this data set, each patient's original identification number was encrypted to protect privacy.

All the authors have declared no competing interest.

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## INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disorder characterized by spondylitis, sacroiliitis, peripheral joints involvement, and enthesitis as a singular feature of AS different from other findings observed in other types of inflammatory arthritides such as rheumatoid arthritis. Besides affecting the musculoskeletal systems, AS can also exhibit a range of extra-articular manifestations, such as uveitis, inflammatory bowel disease, psoriasis, and cardiovascular diseases (CVDs).<sup>1–3</sup> The prevalence of AS varies widely in terms of country, age, sex, and background human leukocyte antigen-B27 prevalence.<sup>3</sup> In recent years, however, with the introduction of magnetic resonance imaging (MRI) in diagnosis and tumor necrosis factor inhibitors for treatment, the management of AS has undergone significant changes.<sup>4,5</sup> Very recently, studies have shown that relatively consistent prevalence rates and gender ratios within the continents studied, despite previous assumptions that these may vary.<sup>3,6</sup> Given the relatively low prevalence of AS, validated administrative databases represent a valuable resource for studying AS. In addition, population-based epidemiological study on the incidence of AS have the strength over of population-based prevalent AS patients.<sup>7</sup>

Cardiovascular involvement is one of the extra-articular manifestations or complications of AS. Of these, aortic disease, conduction disturbances of the atrioventricular node, and myocardial involvement are the most commonly associated cardiovascular disorders.<sup>8,9</sup> There is also a study showing an

increased risk of other CVDs in AS. In a cross-sectional study by Han et al,<sup>10</sup> patients with AS had a statistically significant higher prevalence rates of CVD, heart failure, and peripheral vascular disease than age, gender-matched controls. They found that the prevalence of hypertension and hyperlipidemia was higher among the patients with AS, which are possible contributing risk factors. A large population-based administrative data from Quebec also showed that compared with the general population, patients with AS are at an increased risk for many types of cardiovascular and cerebrovascular diseases. However, these studies evaluating cardiovascular risk in AS patients were carried out on prevalent cases, and the study design may be an overestimate of the risk of AS-related cardiovascular or cerebrovascular diseases.<sup>11</sup> A very recent study using newly diagnosed AS showed an increased risk of developing ischemic heart disease in young patients with AS (aged 18–45 years).<sup>7</sup> We aimed to focus on the incident AS patients in those age 40 years or older and to investigate whether types of cardiovascular and cerebrovascular diseases occurred more than the general population. Accordingly, we used a population-based administrative data to evaluate and estimate the hazard ratio (HR) of AS between 2000 and 2006.

## METHODS

### Data Source

The data source used for this study was the claims data of Taiwan's National Health Insurance Research Database (NHIRD), which contains health care data of virtually all residents in Taiwan. Taiwan's NHIRD is a publicly released and de-identified research database that virtually covers 99.6% of 2.3 million population in Taiwan. Within Taiwan's national health insurance (NHI) scheme, medical claims are sent to the Bureau of National Health Insurance (BNHI) of Taiwan for cross-checking and validation with the aim of ensuring the accuracy of diagnosis coding. A recent validation study supports the reliability of the NHIRD diagnostic codes.<sup>12</sup> The NHIRD contains all registration files, original claim data for reimbursement, and information regarding all types of visits, including outpatient, inpatients, emergency department, and includes all laboratory tests codes, prescription details, and diagnostic codes [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)] code. We used a subdataset composed of a 1 million insured population created by NHRI using a systematic random sampling method, with approximately 5% of the entire population. There were no statistically significant differences of distribution in age, gender, or health care costs between the patients of 1 million insured population and original NHIRD, as reported by the National Health Research Institute of Taiwan. In this data set, each patient's original identification number was encrypted to protect privacy. Our study has been approved by the institutional review board of Chung Shan Medical University Hospital, Taichung, Taiwan.

### Study Subjects

In Taiwan, patients who fulfill the 1984 modified New York criteria for AS are defined in NHI database as AS. Our study identified newly diagnosed patients with AS in the period of 2000 to 2005 from both ambulatory care and inpatient care as the exposure cohort (ICD-9-CM code 720 or 720.0). The index visit was defined as the first ambulatory visit during which the principal diagnosis of AS was made. To maximize case ascertainment, only patients with at least 1 inpatient admission or 2 ambulatory visits (including the index visit) with a principal

diagnosis of AS between January 1, 2001, and December 31, 2005, were considered for inclusion in the AS group. The exclusion criteria for the recruitment of subjects into the AS group were age less than 40 years to focus our research objective the older adult population; a previous diagnosis of AS during year 1998 to 1999 to increase the likelihood of identifying only newly diagnosed AS cases in 2000; a previous diagnosis of any type of CVDs (ICD-9-CM codes 401–405, 410–414, 428, 430–438, 390–400, 406–409, 415–427, 429, 439–459) before the index visit. Finally, a total of 537 subjects were therefore included in the final AS group on the basis of the above criteria. For the comparison cohort, we randomly selected 5 insured people without AS in the same period, frequency matched with the AS cohort on age and gender. The age of each study subject was measured by the difference in time between the index date and the date of birth. Subjects with the history of any type of CVDs diagnosed before index date were excluded. We finally included 2685 subjects as a comparison cohort (non-AS group) in this study.

### Outcome and Follow-Up

All the ambulatory medical care and inpatient records for each subject in the 2 groups were tracked from their index visit till the end of 2005. The date of the first principal diagnosis of CVD during the follow-up period was defined as the primary endpoint. The ICD-9-CM codes used in this study for CVD include hypertensive heart disease (ICD-9-CM code 401–405), coronary heart disease (410–414), heart failure (428), cerebrovascular disease (430–438), and other CVDs (390–400, 406–409, 415–427, 429, 439–459); All subjects were followed from the index visit to the first occurrence of CVD, or end of follow-up.

We evaluated the effect of AS on CVD-free survival, adjusting for demographic features (age and sex) and the preexisting cardiovascular comorbidities of hypertension (ICD-9-CM code 401–405), diabetes (ICD-9-CM code 250), and hyperlipidemia (ICD-9-CM code 272). Information on comorbid medical disorders was obtained by tracing all the ambulatory medical care and inpatients records in the NHI database in the year before the index visit.

### Statistical Analysis

The sociodemographic data, distributions of categorical age, gender, occupation, urbanization level, living region, and income level between patients with qualified AS group and non-AS group patients were analyzed using Chi-square tests. We also calculated the incidence density with person-years by these variables in both cohorts.

The Cox's proportion hazard regression analysis was conducted to measure the effects of AS on the risk of CVD. HR and 95% confidence interval (95% CI) were calculated in the model. All data measurements were performed by SPSS statistical software (Version 17; SPSS Inc., Chicago, IL), and the significance level was set to be 0.05.

## RESULTS

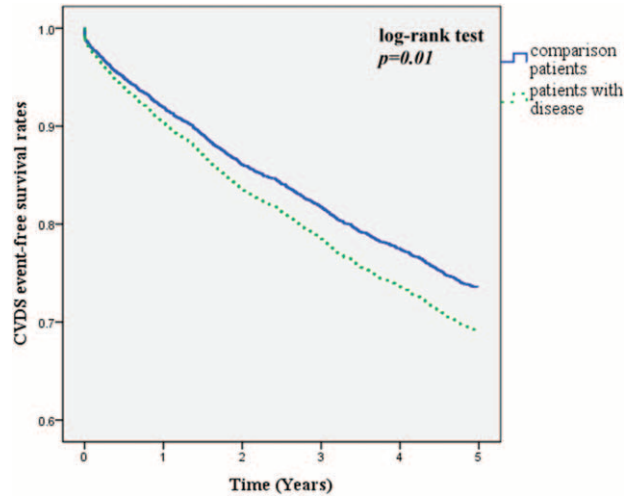
Our study included 537 AS and 2685 non-AS patients totaling 3222, among whom 51.9% were female. Among all cases, those ages 41 to 50 years comprised half of the study population (49.2%). The median follow-up time was 3 to 4 years. Table 1 compares distributions of demographic characteristics between the AS cohort and the comparison cohort. There was more follow-up time (4.12 vs. 3.71) in the non-AS group. Patients in the AS group had less urbanization level and had higher percentages of diabetes (29.6 vs. 25.0%) ( $P = 0.024$ ).

**TABLE 1.** Demographic Characteristics for the Selected Patients, Stratified by Presence/Absence of Ankylosing Spondylitis Disease From 2000 to 2005 (n = 3222)

	Patients With Ankylosing Spondylitis Disease (n = 537)		Patients Without Ankylosing Spondylitis Disease (n = 2685)		P
	n	%	n	%	
Gender					1
Male	259	48.2	1295	48.2	
Female	278	51.8	1390	51.8	
Age (y)					1
40–49	264	49.2	1320	49.2	
50–59	135	25.1	675	25.1	
60–69	98	18.2	490	18.2	
70–	40	7.4	200	7.4	
Follow-up, y, mean (SD)	3.71	1.92	4.12	1.59	<0.001
Urbanization level					0.004
1 (most urbanized)	156	29.1	884	32.9	
2	128	23.8	752	28.0	
3	97	18.1	437	16.3	
4 (least urbanized)	156	29.1	612	22.8	
Monthly income					0.359
0	99	18.4	544	20.3	
NT\$ 1–15,840	45	8.4	256	9.5	
NT\$ 15,841–25,000	270	50.3	1240	46.2	
25,001	123	22.9	645	24.0	
Geographic region					<0.001
North	191	35.6	1204	44.8	
Central	117	21.8	662	24.7	
South	220	41.0	691	25.7	
Eastern	9	1.7	128	4.8	
Hyperlipidemia					<0.001
Yes	260	48.4	1059	39.4	
No	277	51.6	1626	60.6	
Diabetes					0.024
Yes	159	29.6	670	25.0	
No	378	70.4	2015	75.0	

and hyperlipidemia (48.4% vs. 39.4%) than non-AS group men ( $P < 0.001$ ). Figure 1 shows the CVD-free survival rates for patient with AS disease patients and the comparison groups. Log-rank test revealed  $P$  value equal to 0.01. There is statistically significant difference of CVD-free survival rates between the 2 groups. AS patients tend to have more CVDs.

Table 2 summarizes the adjusted HR for all CVDs and according to the types of CVD. During the 5-year follow-up period from the index ambulatory visits or inpatient care, AS cohort exhibited a significantly higher HR for all CVDs (HR, 1.20; 95% CI, 1.02–1.42,  $P = 0.03$ ) than the non-AS group. Among each type of CVD, AS cohort and the general population cohort showed no significant differences in hypertensive heart disease, ischemic heart disease, or heart failure. The crude HR (95% CI) of developing cerebrovascular disease was 1.55 (1.13–2.13) ( $P = 0.007$ ); however, after adjustments were made for patients' sex, age, urbanization level, geographic region,



**FIGURE 1.** CVD (cardiovascular diseases)-free survival rates for patient with ankylosing spondylitis disease patients and comparison groups from 2000 to 2005.

hypertension, hyperlipidemia, and diabetes, the adjusted HR (95% CI) was lower at 1.38 (0.99–1.92) ( $P = 0.06$ ). In “other” CVD category, even adjusted HR (95% CI) was 1.28 (1.02–1.61) ( $P = 0.03$ ).

Table 3 summarizes the HR of CVD between 2 groups of patients during the 1-, 3-, and 5-year follow-up period from the index visits. Only until at 5-year follow-up period did the AS cohort showed crude HR of 1.24 (95% CI 1.05–1.46,  $P = 0.01$ ) and adjusted HR of 1.20 (1.02–1.42,  $P = 0.03$ ) for all CVDs.

Table 4 summarizes the HR of CVD between 2 groups of patients when stratified by age or sex. When stratified by age (40–49, 50–59, 60–69, and  $\geq 70$  years), the HR was different in each stratified group. From age 40 to 69 years, the HR of AS group showed higher than non-AS group, but only at age group 60 to 69 years did it reach a statistical significant difference (adjusted HR 1.48, 95% CI, 1.06–2.08,  $P < 0.05$ ); For age 70 years or older, the development of new CVD number in AS group was 16 (40%), whereas in non-AS group, it was higher (117; 58.5%), but the HR of AS group has not reached a statistically significant difference (adjusted HR 0.67, 95% CI, 0.39–1.16).

When stratified by gender, male AS group had a significantly higher HR for all CVDs than the general population cohort with an adjusted HR of 1.28 (95% CI, 1.01–1.63).

## DISCUSSION

The present population-based follow-up study showed that male of age greater than 40 years (especially age group of 60–69 years) with newly diagnosed AS were at a higher risk of developing CVDS. Their risk increased to the significant level after 5-year follow-up period. In this population-based observational study of a Taiwan-based cohort of relatively older AS patients, we collected 537 incident cases with AS from the NHRI of Taiwan. It may sound strange to see more women than men in the group of AS patients. We only included newly diagnosis AS patients over the age of 40. All patients under age of 40 were actually excluded in order to power the effect of CVD, which is a disease usually in aged population. For this group of AS patients, gender ratio is different from young AS patients.

**TABLE 2.** Hazard Ratios (HRs) of CVDS Among Ankylosing Spondylitis Disease Patients During the 5-Year Follow-Up Period From the Index Ambulatory Visits or Inpatient Care From 2000 to 2005

5-y Follow-up Period	Total		Patients With Ankylosing Spondylitis Disease		Patients Without Ankylosing Spondylitis Disease		P
	No.	(%)	No.	(%)	No.	(%)	
Development of CVD							
Yes	956	29.7	176	32.8	780	29.1	
Crude HR (95% CI)				1.24 (1.05–1.46)*	1		0.01
Adjusted HR (95% CI)				1.20 (1.02–1.42)*	1		0.03
Development of CHD							
Yes	335	10.4	57	10.6	278	10.4	
Crude HR (95% CI)				1.03 (0.78–1.38)	1		0.82
Adjusted HR (95% CI)				0.94 (0.70–1.26)	1		0.66
Development of hypertensive heart disease							
Yes	423	13.1	75	14.0	348	13.0	
Crude HR (95% CI)				1.09 (0.85–1.40)	1		0.49
Adjusted HR (95% CI)				1.03 (0.80–1.33)	1		0.82
Development of heart failure							
Yes	69	2.1	11	2.0	58	2.2	
Crude HR (95% CI)				0.95 (0.50–1.81)	1		0.88
Adjusted HR (95% CI)				1.09 (0.56–2.14)	1		0.79
Development of cerebrovascular disease							
Yes	213	6.6	49	9.1	164	6.1	
Crude HR (95% CI)				1.55 (1.13–2.13)†	1		0.007
Adjusted HR (95% CI)				1.38 (0.99–1.92)	1		0.06
Development of other CVD							
Yes	487	15.1	96	17.9	391	14.6	
Crude HR (95% CI)				1.29 (1.04–1.62)*	1		0.02
Adjusted HR (95% CI)				1.28 (1.02–1.61)*	1		0.03

Total sample number = 3222; Both crude and adjusted HRs were calculated by Cox proportional hazard regressions, and stratified by age and sex. Adjustments were made for patients' sex, age, urbanization level, geographic region, hypertension, hyperlipidemia, and diabetes.

\*P < 0.05.

†P < 0.01.

**TABLE 3.** Hazard Ratios (HRs) of CVD Among Ankylosing Spondylitis Disease Patients During the 1-, 3-, and 5-year Follow-Up Period From The Index Ambulatory Visits or Inpatient Care From 2000 to 2005

Development of CVD	1-y Follow-Up Period			3-y Follow-Up Period			5-y Follow-Up Period		
	Patients With Ankylosing Spondylitis Disease	Comparison	P	Patients With Ankylosing Spondylitis Disease	Comparison	P	Patients With Ankylosing Spondylitis Disease	Comparison	P
Yes (%)	57 (10.6)	259 (9.6)		120 (22.3)	564 (21.0)		176 (32.8)	780 (29.1)	
No (%)	480 (89.4)	2426 (90.4)		417 (77.7)	2121 (79.0)		361 (67.2)	1905 (70.9)	
Crude HR (95% CI)	1.19 (0.89–1.58)	1	0.24	1.16 (0.95–1.41)	1	0.15	1.24 (1.05–1.46)*	1	0.01
Adjusted HR (95% CI)	1.26 (0.94–1.68)	1	0.13	1.14 (0.93–1.40)	1	0.20	1.20 (1.02–1.42)*	1	0.03

Total sample number = 3222.

Both crude and adjusted HRs were calculated by Cox proportional hazard regressions, and stratified by age and sex.

Adjustments were made for patients' sex, age, urbanization level, geographic region, hypertension, hyperlipidemia, and diabetes.

\*P < 0.05.



**TABLE 4.** Hazard Ratios for CVDs Among Patients With Ankylosing Spondylitis Disease and the Comparison Cohort by Age or Gender Group

Variable	Patients With Ankylosing Spondylitis Disease			Comparison Cohort			HR	Adjusted HR <sup>†</sup>
	Incident Cases	Person-year	ID per 1000 Patient-years	Incident cases	Person-year	ID per 1000 Patient-years		
Age <sup>‡</sup>								
40–49	60	1117.72	53.68 (40.47–66.89)	244	5916.55	41.24 (36.17–46.31)	1.30 (0.98–1.72)	1.25 (0.94–1.66)
50–59	50	474.52	105.37 (77.74–132.00)	215	2742.80	78.39 (68.33–88.45)	1.33 (0.98–1.81)	1.23 (0.90–1.69)
60–69	50	294.21	169.95 (127.03–212.86)	204	1781.98	114.48 (99.70–129.26)	1.44 (1.06–1.96)*	1.48 (1.06–2.08)*
≥70	16	106.40	150.38 (82.46–218.29)	117	624.92	187.22 (156.64–217.80)	0.80 (0.47–1.34)	0.67 (0.39–1.16)
Sex <sup>‡</sup>								
Male	83	952.79	87.11 (69.21–105.02)	355	5410.46	65.61 (59.02–72.21)	1.31 (1.03–1.66)*	1.28 (1.01–1.63)*
Female	93	1040.06	89.42 (72.08–106.75)	425	5655.78	75.14 (68.27–82.01)	1.18 (0.94–1.48)	1.13 (0.90–1.43)
Follow-up period								
Within 1 y	57	454.93	125.29 (94.87–155.72)	259	2530.51	102.35 (90.54–114.16)	1.19 (0.89–1.58)	1.26 (0.94–1.68)
Within 3 y	120	1285.01	93.38 (77.48–109.29)	564	7054.63	79.95 (73.62–86.28)	1.16 (0.95–1.41)	1.14 (0.93–1.40)
Within 5 y	176	1992.85	88.32 (75.86–100.77)	780	11066.24	70.48 (65.72–75.25)	1.24 (1.05–1.46)*	1.20 (1.02–1.42)*

ID = incidence density.

\*p<0.05

<sup>†</sup>Adjustments were made for patients' sex, age, urbanization level, geographic region, hypertension, hyperlipidemia, and diabetes.

<sup>‡</sup>Adjusted for patients' age, urbanization level, geographic region, hypertension, hyperlipidemia, and diabetes.

It is well known that rheumatoid arthritis is associated with an increased cardiovascular risk.<sup>13</sup> Similarly, a number of studies including meta-analysis have shown that patients with AS have an increased risk of myocardial infarction and stroke.<sup>14</sup> A recent study by Haroon et al<sup>15</sup> involving 21,473 patients and 86,606 comparators has demonstrated that AS is associated with an increased risk for vascular mortality. In this study, HRs for vascular death were adjusted for history of cancer, diabetes, dementia, inflammatory bowel disease, hypertension, chronic kidney disease, peripheral vascular disease, and, among those aged 66 years or older, relevant drug therapies. The relevance of our study relies on the confirmation of the increased burden of CVD among Asian individuals with AS.

Our present study is unique for several reasons. First, our cases of AS are newly diagnosed. Most previous studies were either cross-sectional studies<sup>10</sup> or AS patients were carried out on prevalent cases.<sup>11</sup> Because of the nature of the study design, these prevalence estimates may be an overestimate of the risk of AS-related cardiovascular or cerebrovascular disease, as some diagnoses could have preceded the AS diagnosis.<sup>11</sup> To the best of knowledge, only 2 previous studies<sup>7,16</sup> utilized similar study design of incident AS cohort as the case group. However, the study by Huang et al<sup>7</sup> enrolled a total of 4794 persons aged 18 to 45 years and the research focus on risk of developing ischemic heart disease. Lin et al<sup>16</sup> studied the rates of ischemic stroke on young AS patients. Our study focused on the relatively older patient group (>40 years of age) and all types of CVD. Second, our study stratified the different age group and found that age could modify the effect of AS on development of CVD. Third, our cases included only one single race without the confounding factor of ethnicity. Fourth, due to 99.6% coverage of insurance population in Taiwan, all our patients were followed up comprehensively with all kinds of medical services.

Some of our findings deserved attention. Comparing with similar study designs, our study showed no increased risk of developing coronary heart disease, hypertensive heart disease, or heart failure. This differs from the study by Huang et al,<sup>7</sup>

which showed that young subjects with newly diagnosed AS were at a higher risk of developing coronary heart disease (adjusted HRs 1.47). In that study, there was no significant difference in the prevalence of diabetes or hypertension between the AS and non-AS groups.<sup>7</sup> The author explained their difference suggesting that AS independently contributes to an increased cardiovascular risk in the young.<sup>7</sup> Why did our relatively older population not show even a stronger relationship? We speculated that our older population may have less activity of inflammation due to natural course of the disease. Several previous studies have proposed that the role of chronic systemic inflammation in endothelial dysfunction and the pathogenesis of atherosclerosis and growing evidence suggest that elevated levels of inflammatory markers are correlated with an increased risk of coronary heart disease.<sup>7,17–20</sup> Increased prevalence of subclinical atherosclerosis, manifested by higher frequency of carotid plaques that reflects the presence of advanced atherosclerosis and associates closely with coronary heart disease, has been reported both in AS patients without previous history of CVD, who fulfilled the modified New York diagnostic criteria for AS,<sup>7,21</sup> and in patients with no history of CVD that fulfilled the Assessment of Spondyloarthritis International Society classification criteria for axial spondyloarthritis.<sup>22</sup> In addition, the best predictors of carotid plaques in patients with AS were the erythrocyte sedimentation rate at the time of disease diagnosis and the duration of disease from onset of symptoms.<sup>21</sup> Therefore, the duration of a persistent chronic inflammation may be of major importance to explain the accelerated atherogenesis observed in patients with AS.<sup>7</sup>

Another finding of the present study showed an increased risk of developing ischemic stroke in young patients with AS. Although the crude HR (95% CI) of developing cerebrovascular disease is 1.55 (1.13–2.13) (P = 0.007), however, after adjustments for patients' sex, age, urbanization level, geographic region, hyperlipidemia, and diabetes, the adjusted HR (95% CI) became lower 1.38 (0.99–1.92) (P = 0.06). This finding can be explained by the relatively small sample size. A previous

study in young patients with AS showed a 1.9-fold increased risk of ischemic stroke. This association was still seen after controlling for common vascular risk factors.<sup>13</sup> The mechanism responsible for the association between AS and ischemic stroke remains unclear; however, Lin et al<sup>16</sup> proposed that accelerated atherosclerosis caused by systemic inflammation, AS-related aortic insufficiency, mitral valve disease, and cardiomyopathy may also contribute to a higher risk of ischemic stroke in AS.<sup>23,24</sup> Similarly, our study lacked some important variables supposed to be risk factors of ischemic stroke, such as patients' behaviors of smoking and exercise. AS patients are at a greater risk owing to the higher prevalence of smoking and a higher atherogenic index.<sup>25</sup>

In our subgroup analysis, we found that age and gender are important effect modifiers in developing CVDs in AS patients. There was a predominance of AS in younger males, but the gender's effect was not significant when the patients were younger. However, at age of 60 to 69 years was when significantly statistical difference emerged. Due to relatively small sample size, we did not evaluate the interaction between age and gender and the follow-up period also allowed for 5 years at most.

The use of cyclooxygenase-2 inhibitors (COX-2) and traditional nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with an increased risk of CVD.<sup>26</sup> These 2 groups of drugs are commonly used among AS patients, which may interfere with their cardiovascular risk.<sup>7</sup> However, we did not evaluate the risk factors of these 2 groups of drugs causing CVD due to the following 2 reasons.<sup>7</sup> In observational studies, AS patients with higher severity are more likely to receive higher doses of NSAID/COX-2 and are also likely at higher disease-related risk of CVD.<sup>7,16</sup> The other reason is that these drugs are widely available over the counter and cannot be correctly tracked in the current insurance database.<sup>7,16</sup> Therefore, it may be hard to differentiate the possible effects of NSAIDs/COX-2 from the biological impacts resulting from AS itself.<sup>7</sup> Further studies designs considering exposure of these 2 groups of drugs are required to investigate this specific issue.<sup>7</sup>

As the present study focused on a single ethnicity with comprehensively covered population insurance-based follow-ups and the temporal sequence between AS and CVD events was intact, the observed significant association seems unlikely to be due to selection bias or information bias. Nevertheless, several limitations in this study must be noted. First, an important limitation of the study is that no information is provided on disease activity, such as clinical activity index and no information is available on the degree of systemic inflammation that may have an impact on coagulation activation and endothelial dysfunction. These were not available in the current administrative databases. Second, another important limitation of the study is that no information is provided on the treatments administered to the patients with AS, namely no information is provided on the administration of NSAID and tumor necrosis factor alpha inhibitors, which may interfere with the cardiovascular risk. In patients with rheumatoid arthritis, the use of biological agents exerting a potent anti-inflammatory effect has been shown to reduce prothrombotic markers.<sup>27</sup> In addition, it has been suggested that the long-term frequent use of NSAID might protect patients with AS from CVDs, whereas NSAIDs apparently increase short-term risk in the non-frequent users.<sup>28</sup> All these aspects should be considered in the further studies designs. Third, the diagnosis of AS, CVD, and medical comorbidities was determined by the ICD codes from the NHI claim database, and information about diagnosis of AS was not from

medical chart review; The diagnosis of CVD was not obtained using standardized protocols as well. However, the NHI claim database is an established research database and there have been some independent studies demonstrating the validity of the NHIRD data.<sup>12,29–31</sup>

## CONCLUSIONS

In this population-based follow-up study, we found that male age greater than 40 years (particularly age group of 60–69 years) with newly diagnosed AS were at a higher risk of developing CVD. Their risk increased to the significant level after 5-year follow-up period. This finding suggests that we should evaluate the CVDs function in the elderly periodically and more vigilantly to help detect those high-risk patients with occult cardiovascular disorder. In addition, more studies should be done in the future in elderly AS patients with more clinical index and inflammatory biomarkers, or drugs that may be associated with different kinds of CVD.

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