

Increased risks of aortic regurgitation and atrial fibrillation in radiographic axial spondyloarthritis patients: a 10-year nationwide cohort study

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Abstract

Background: To compare the incidences of aortic regurgitation, atrial fibrillation (AF), and atrioventricular (AV) block II–III between radiographic axial spondyloarthritis (r-axSpA) patients and the general population (GP).

Methods: National Health Insurance Services data were used. R-axSpA patients ($N = 8877$) and the age- and sex-matched GP ($N = 26,631$) were followed from August 2006 to December 2019. Incidence rates and standardized incidence ratios (SIRs) of aortic regurgitation, AF, and AV block II–III were compared between these groups. Ten-year incidence rates and hazard ratios (HRs) were calculated by the Kaplan–Meier method and Cox regression analysis.

Results: Incidence rates of aortic regurgitation, AV block II–III, and AF in the r-axSpA group were 0.42, 0.21, and 4.0 per 1000 person-years (PYs), respectively. In the r-axSpA group, the SIR for aortic regurgitation was highest among 40- to 49-year-old men (4.11). Incidence rates of aortic regurgitation and AF were higher in the r-axSpA group than in the GP group (0.42 versus 0.18 per 1000 PYs 4.00 versus 3.13 per 1000 PYs, both $p < 0.001$, respectively), whereas the difference was insignificant for AV block II–III (0.21 versus 0.14 per 1000 PYs, $p = 0.222$). In multivariate analysis, r-axSpA was associated with a higher hazard (risk) for the development of aortic regurgitation and AF [HR (95% confidence interval) = 2.55 (1.49–4.37) and 1.20 (1.04–1.39), respectively], but the difference was insignificant for AV block II–III [HR (95% confidence interval) = 1.17 (0.59–2.31)].

Conclusions: Compared with the GP, r-axSpA patients are at increased risk of aortic regurgitation and AF, but not AV block II–III. These patients should be carefully monitored for occurrence of aortic regurgitation and AF.

Keywords: aortic regurgitation, atrial fibrillation, atrioventricular block, conduction disturbance, radiographic axial spondyloarthritis

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Introduction

Radiographic axial spondyloarthritis (r-axSpA), previously termed ankylosing spondylitis (AS),¹ is a systemic inflammatory arthritis and a type of spondyloarthritis.² Arthritis and morning stiffness of axial joints are the main manifestations of r-axSpA, and other extra-articular manifestations

can arise. Among extra-articular symptoms, cardiac manifestations are the most critical complication. Furthermore, cardiovascular diseases (CVDs) are more frequent in r-axSpA patients than in the general population (GP),³ and combined CVD increases the risk of mortality in r-axSpA patients.⁴ Therefore, the European

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Alliance of Associations for Rheumatology recommends proper screening and early management of CVD in patients with r-axSpA.⁵

The risk of conduction disturbances and aortic regurgitation, as well as CVD, may be increased in r-axSpA patients.^{6,7} Recent studies from the Swedish National Patient and Population Registry reported that r-axSpA patients had increased risks of aortic regurgitation, atrioventricular (AV) block II–III, atrial fibrillation (AF), and pacemaker implantation than the GP.⁸ However, other studies reported that AV block II–III was not observed in r-axSpA patients^{9,10} and that the prevalence of AF was low (1.0%) in these patients.¹⁰ In addition, a study reported that the prevalence of conduction disturbance was lower in r-axSpA patients than in the GP and that the prevalence of aortic regurgitation was comparable between these two groups.¹¹ These discordant results regarding the risks of aortic regurgitation, AF, and AV block II–III in r-axSpA patients may be due to differences in study design and a relatively small sample size. Therefore, a further study using more data, with a larger sample size and longer follow-up duration, should be conducted.

The National Health Insurance Services (NHIS) of Korea cover most of the Korean population. In addition, medical expenses of patients with rare intractable diseases (RID) are supported by the national insurance service of Korea, and r-axSpA fulfilling the modified New York criteria was selected as one such RID in February 2006. Diagnosis of r-axSpA is strictly monitored due to the aforementioned financial support. These unique characteristics of the NHIS of Korea enhance the diagnostic accuracy of r-axSpA.

In this study, we compared the incidence rates of aortic regurgitation, AV block II–III, and AF between r-axSpA patients and the age- and sex-matched GP using nationwide health insurance data.

Methods

Data source

The database of NHIS, which is an obligatory universal health insurance system covering 97.2% of the Korean population, was used. The remaining 3% of the population represent the lower income class and are part of the Medical Aid program. The NHIS database includes

sociodemographic information, utilization of inpatient and outpatient services, medical dispensing claims, procedure records, and diagnoses according to International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

NHIS are administrated by the Korean government and operate the RID programs, which offer financial support to patients with certain rare or intractable diseases, including r-axSpA (V140). RID programs require the physician to complete the application for registration of patients who have been diagnosed with r-axSpA (ICD-10-CM code M45, AS) and fulfill the modified New York criteria.¹² The NHIS database is accessible to all researchers and holds anonymized patient information to protect the privacy of individuals.

In this study, the diagnosis of r-axSpA was confirmed in both the NHIS and the RID systems. The NHIS database can be accessed by any researchers whose study protocols have been approved by an official review committee. All data are provided to the researcher after erasing personal information to de-identify the detail of enrolled patients. This study was exempt from review by the Catholic University of Korea, Incheon Saint Mary's Hospital Institutional Review Board (IRB number: OC20ZISI0042, approval date: 27 March 2020). Informed consent from participants was omitted under approval from IRB. The reporting of this study conforms to the STROBE statement.

Study populations

This study included all 9154 patients who had been diagnosed with r-axSpA (ICD-10-CM code M45 and RID code V14.0) between February 2006 and December 2011. A 1:3 age- and sex-matched cohort study design was used to investigate the risks of aortic regurgitation, AV block II–III, and AF in r-axSpA patients. Subjects who had been diagnosed with r-axSpA during the follow-up were excluded from the matched control cohort. Subjects with a history of aortic regurgitation, AV block II–III, and AF prior to the start of follow-up were excluded from both cohorts. Subjects who had received an ICD code indicating rheumatoid arthritis, systemic lupus erythematosus, Behcet's disease, or Takayasu's arteritis were also excluded. Finally, 8877 subjects with r-axSpA and 26,631 age- and sex-matched subjects were followed until 31 December 2019.

Follow-up

Follow-up started on 1 August 2006 for subjects who received their first r-axSpA diagnosis in rheumatology or internal medicine outpatient care prior to 31 January 2006. Follow-up started 6 months after the date of first diagnosis for subjects with a first registered diagnosis after 1 February 2006. Follow-up was initiated 6 months after the first r-axSpA diagnosis to reduce the risk of detection bias in the r-axSpA cohort owing to increased surveillance relating to diagnosis of r-axSpA. For age- and sex-matched controls, follow-up began the date of their first visit to outpatient or inpatient care after 1 August 2006.

All subjects were followed until the first occurrence of an outcome, death, completion of 10 years of follow-up, or 31 December 2019, whichever occurred first.

Definitions of outcomes and comorbidities

The primary outcomes were the occurrence of aortic regurgitation, AV block II–III, and AF. Each outcome was analyzed separately.

1. First occurrence of isolated aortic regurgitation reported as a primary or secondary diagnosis in inpatient or outpatient care. Aortic regurgitation in combination with stenosis was excluded.
2. First occurrence of AV block II–III reported as a primary or secondary diagnosis in inpatient or outpatient care.
3. First occurrence of AF reported as a primary or secondary diagnosis in inpatient or outpatient care. AF with rheumatic mitral stenosis and mechanical heart valves was regarded as valvular AF and excluded.

Cardiovascular and r-axSpA-related comorbidities were regarded as prevalent at baseline if the ICD-10 codes are specified (online Supplementary Table S1).

Statistical analyses

Descriptive statistics are presented as number (percentage) or mean (standard deviation). Categorical variables were compared using the conditional logistic regression global test. Continuous variables were analyzed using Student's *t* test. Comparison of cumulative event (aortic regurgitation, AV block II–III, and AF) rates between the r-axSpA and GP groups was

based on Kaplan–Meier censoring estimates and performed with the log-rank test. These were also analyzed by separating AV block II–III into AV blocks II and III.

For each outcome, incidence rates, overall and stratified by sex, were calculated from the number of incident events and person-years (PYs) at risk (the number of events per 1000 PYs). For risk assessment, hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated using Cox proportional hazard models to investigate the association between r-axSpA and each outcome, after adjusting for age, sex, diabetes, hypertension, dyslipidemia, chronic renal disease, and CVD (heart failure, ischemic heart disease, and cerebrovascular disease). All *p* values were two-sided, and a value less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics of enrolled patients with r-axSpA and the GP

The mean follow-up durations in the r-axSpA and GP groups were 9.04 and 9.35 years, respectively. In total, 73.5% of r-axSpA patients were male. The prevalence of extra-articular symptoms of r-axSpA such as uveitis, inflammatory bowel disease, and psoriasis at baseline was significantly higher in the r-axSpA group than in the GP group. Comorbidities were present significantly more in the r-axSpA group than in the GP group (Table 1).

Incidence rates of aortic regurgitation, AV block II–III, and AF

During follow-up, the total numbers of incident events of aortic regurgitation, AV block II–III, and AF were 34, 17, and 317 in the r-axSpA group, respectively. The overall incidence rates of aortic regurgitation, AV block II–III, and AF in the r-axSpA group were 0.42, 0.21, and 4.00 per 1000 PYs, respectively. The overall incidence rates of aortic regurgitation, AV block II–III, and AF in the GP group were 0.18, 0.14, and 3.13 per 1000 PYs, respectively (Table 2). In subgroup analysis by separating AV blocks II and III, the incidence rate for AV block II was 0.05 *versus* 0.04 per 1000 PYs, and for AV block III was 0.16 *versus* 0.10 per 1000 PYs in r-axSpA and GP groups, respectively

Table 1. Baseline characteristics of patients with r-axSpA and the age- and sex-matched general population at the start of follow-up.

	r-axSpA (n = 8877)	General population (n = 26,631)	p value
Sex			
Male	6522 (73.5)	19,566 (73.5)	
Female	2355 (26.5)	7065 (26.5)	
Age, years, mean (SD)			
	47 (18)	47 (18)	
Age, years			
18–29	1750 (19.7)	5250 (19.7)	
30–39	1993 (22.5)	5979 (22.5)	
40–49	1522 (17.1)	4566 (17.1)	
50–59	1103 (12.4)	3309 (12.4)	
60–69	1043 (11.7)	3129 (11.7)	
≥70	1466 (16.5)	4398 (16.5)	
Start of follow-up			
2006	2917 (32.9)		
2007	1620 (18.2)		
2008	1471 (16.6)		
2009	1482 (16.7)		
2010	718 (8.1)		
2011	669 (7.5)		
Uveitis	657 (7.4)	89 (0.3)	<0.001
Inflammatory bowel disease	106 (1.2)	139 (0.5)	<0.001
Psoriasis	91 (1.0)	35 (0.1)	<0.001
Comorbidity			
Hypertension	2245 (25.3)	4980 (18.7)	<0.001
DM	1176 (13.2)	2471 (9.3)	<0.001
Dyslipidemia	1326 (14.9)	2238 (8.4)	<0.001
CKD	80 (0.9)	102 (0.4)	<0.001
Ischemic heart disease	536 (6.0)	1075 (4.0)	<0.001
Heart failure	116 (1.3)	240 (0.9)	0.001
Cerebrovascular disease	351 (4.0)	650 (2.4)	<0.001
All data are presented as number (%).			
CKD, chronic kidney disease; DM, diabetes mellitus; r-axSpA, radiographic axial spondyloarthritis.			

Table 2. Incidence rates of aortic regurgitation, atrioventricular block, and atrial fibrillation in patients with r-axSpA and the age- and sex-matched general population.

	r-axSpA (n = 8877)	General population (n = 26,631)
Aortic regurgitation		
Incident events, n (male/female)	34 (13/21)	45 (21/24)
PYs	80,148	248,879
Overall incidence (n/1000 PYs)	0.42 (0.30–0.59)	0.18 (0.13–0.24)
Male incidence (n/1000 PYs)	0.22 (0.13–0.38)	0.11 (0.07–0.17)
Female incidence (n/1000 PYs)	1.02 (0.66–1.56)	0.37 (0.25–0.56)
Atrioventricular block II–III		
Incident events, n (male/female)	17 (13/4)	34 (22/12)
PYs	80,178	248,940
Overall incidence (n/1000 PYs)	0.21 (0.13–0.34)	0.14 (0.10–0.19)
Male incidence (n/1000 PYs)	0.22 (0.13–0.38)	0.12 (0.08–0.18)
Female incidence (n/1000 PYs)	0.19 (0.07–0.51)	0.19 (0.11–0.33)
Atrial fibrillation		
Incident events, n (male/female)	317 (213/104)	772 (524/248)
PYs	79,160	246,280
Overall incidence (n/1000 PYs)	4.00 (3.59–4.47)	3.13 (2.92–3.36)
Male incidence (n/1000 PYs)	3.62 (3.17–4.41)	2.86 (2.63–3.12)
Female incidence (n/1000 PYs)	5.11 (4.21–6.19)	3.92 (3.46–4.44)
Rates are presented as number of events per 1000 PYs at risk. All rates were calculated with a Poisson distribution when estimating 95% confidence intervals. PYs, person-years; r-axSpA, radiographic axial spondyloarthritis.		

(Supplementary Table S2). A pacemaker was implanted in 8 and 10 cases during 80,178 and 248,940 PYs in the r-axSpA and GP groups, respectively (data not shown). The 10 years of incidence rates of aortic regurgitation and AF was significantly higher in the r-axSpA group than in the GP group (Figure 1(a) and (e)). The differences in the incidence rates of aortic regurgitation and AF between the r-axSpA and GP groups were more prominent in subjects aged ≥ 40 years (Figure 1(b) and (f)). By contrast, the incidence rates of AV block II–III did not significantly differ between the r-axSpA and GP groups (Figure 1(c) and (d)), and these were also insignificant in subgroup analysis of AV blocks II and III ($p = 0.544$ for AV block II, $p = 0.286$ for AV block III). Standardized incidence ratios (SIRs) of aortic

regurgitation were higher than 1.0 for both men and women and were highest in subjects aged 40–49 years for men (4.11) and those aged 50–59 years for women (3.08) in the r-axSpA group. SIRs of AF in the r-axSpA group were all higher than 1.0, except for men aged 18–29 years and women aged 60–69 years. For AV block II–III, men aged 18–29, 30–39, and 60–69 years and women aged 50–59 and 60–69 years had higher SIRs when comparing the incidence rates between the r-axSpA and GP groups (Table 3). In subgroup analysis, men aged 18–29, 30–39 years, and women aged over 70 years had higher SIRs for AV block II. In addition, men aged 60–69, over 70 years, and women aged 50–59, 60–69 years had higher SIRs for AV block III (Supplementary Table 3).

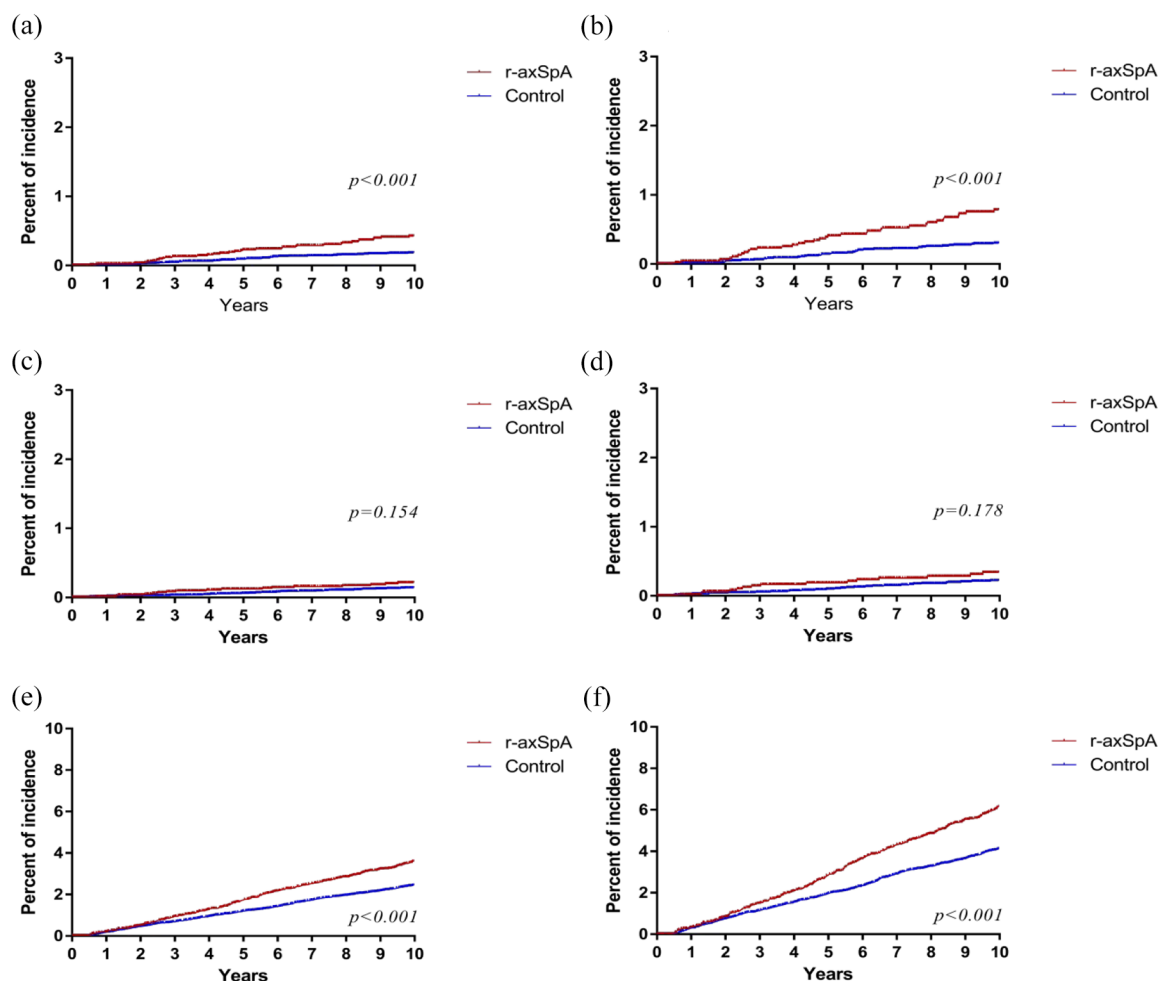


Figure 1. Ten-year incidence rates among patients with r-axSpA and matched controls.

Ten-year incidence rates among r-axSpA patients and the age- and sex-matched GP. (a) Incidence rate of aortic regurgitation in subjects of all ages. (b) Incidence rate of aortic regurgitation in subjects aged ≥ 40 years. (c) Incidence rate of atrioventricular block (II and III) in subjects of all ages. (d) Incidence rate of atrioventricular block (II and III) in subjects aged ≥ 40 years. (e) Incidence rate of atrial fibrillation in subjects of all ages. (f) Incidence rate of atrial fibrillation in subjects aged ≥ 40 years.

Risks of aortic regurgitation, AV block II–III, and AF

In univariate Cox regression analysis, the r-axSpA group had an increased HR for aortic regurgitation, and this was also found in subgroup analysis of subjects aged ≥ 40 years and divided into each gender (Figure 2(a) and (b)). The risk of AV block II–III was not increased in the r-axSpA group. In univariate Cox regression analysis, r-axSpA patients had an increased risk of AF. However, the HR was only increased for men, and similar results were obtained in subgroup analysis of subjects aged ≥ 40 years. HRs for other baseline characteristics were also calculated for the r-axSpA group. Older age significantly increased the risks of aortic

regurgitation, AV block II–III, and AF. Subjects with combined dyslipidemia had a significantly higher HR for AV block II–III. Baseline hypertension and CVD increased the risk of AF, whereas female gender lowered the risk, in the r-axSpA group (Supplementary Table 4). In multivariate Cox proportional regression analysis, the age-, sex-, comorbidities (hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and CVD)-adjusted HR for aortic regurgitation was significantly increased in the r-axSpA group (HR: 2.55, 95% CI: 1.49–4.37). Subgroup analysis of men and women also detected an increased HR for aortic regurgitation in the r-axSpA group. These increased HRs were also detected in

Table 3. Standardized incidence ratios according to age and sex.

	Men			Women		
	r-axSpA (n/1000 PYs)	Control (n/1000 PYs)	SIR	r-axSpA (n/1000 PYs)	Control (n/1000 PYs)	SIR
Aortic regurgitation (years)						
18–29	0.00	0.05	0.00	0.00	0.00	
30–39	0.00	0.04	0.00	0.00	0.00	
40–49	0.34	0.08	4.11	0.00	0.00	
50–59	0.13	0.04	3.14	0.77	0.25	3.08
60–69	0.37	0.23	1.60	0.83	0.35	2.35
≥70	1.48	0.66	2.26	2.68	0.96	2.77
AV block II–III (years)						
18–29	0.07	0.05	1.53	0.00	0.00	
30–39	0.06	0.04	1.53	0.00	0.00	
40–49	0.08	0.00		0.00	0.00	
50–59	0.13	0.21	0.63	0.39	0.38	1.03
60–69	1.29	0.29	4.50	0.28	0.18	1.56
≥70	0.49	0.58	0.84	0.33	0.37	0.89
Atrial fibrillation (years)						
18–29	0.42	0.49	0.87	0.34	0.34	1.02
30–39	1.23	0.84	1.46	1.37	0.33	4.15
40–49	2.12	1.32	1.61	1.91	0.62	3.08
50–59	5.24	3.53	1.48	3.92	2.53	1.55
60–69	11.28	8.58	1.31	3.37	4.41	0.76
≥70	16.33	13.99	1.17	12.36	9.22	1.34
AV, atrioventricular; PYs, person-years; r-axSpA, radiographic axial spondyloarthritis; SIR, standardized incidence ratio.						

subgroup analysis of subjects aged ≥ 40 years. However, the HR for AV block II–III was not significantly altered in the r-axSpA group, and also insignificant when HR was evaluated after separating AV block II–III into AV blocks II and III (Supplementary Table 5). The HR for AF was significantly higher in the r-axSpA group overall and in the subgroup of r-axSpA patients aged ≥ 40 years (HR: 1.20, 95% CI: 1.04–1.39, and HR: 1.18, 95% CI: 1.02–1.38, respectively). The HR for AF was significantly increased in men, but not women (Table 4).

Discussion

In this study using NHIS data, we demonstrated that aortic regurgitation and AF occurred more frequently in r-axSpA patients than in the GP. R-axSpA increased the risks of aortic regurgitation and AF. Furthermore, the risk of aortic regurgitation was consistently increased in all subgroups (men, women, and subjects aged ≥ 40 years) of r-axSpA patients, whereas the risk of AF was only increased in men. The incidence rate and HR of AV block II–III were not higher in the r-axSpA group than in the GP group.

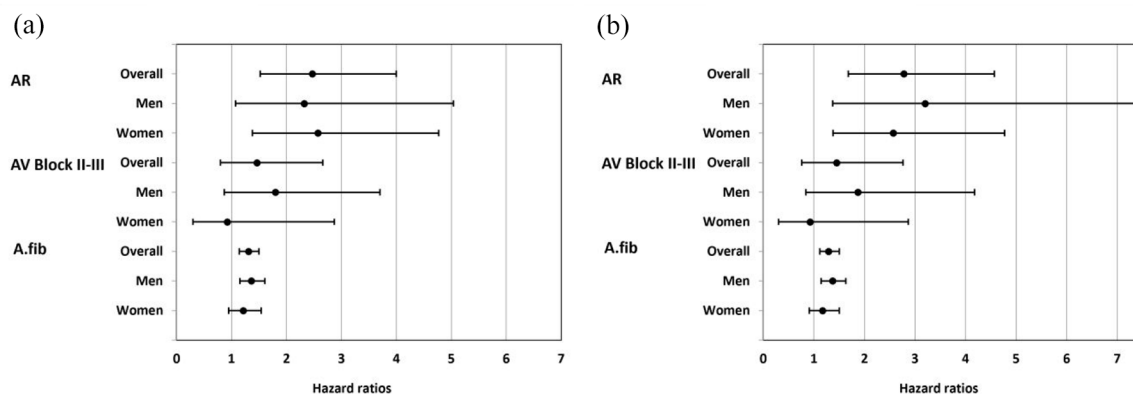


Figure 2. HRs for aortic regurgitation, atrioventricular block II–III, and atrial fibrillation in all r-axSpA patients and those aged ≥ 40 years stratified by sex. (a) HRs calculated by univariate Cox proportional regression analysis for aortic regurgitation, AV block II–III, and atrial fibrillation in all r-axSpA patients. (b) HRs for aortic regurgitation, AV block II–III, and atrial fibrillation in r-axSpA patients aged ≥ 40 years.

Table 4. Multivariate Cox proportional regression analysis of the risks of aortic regurgitation, atrioventricular block, and atrial fibrillation.

	Total		Age ≥ 40 years	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Aortic regurgitation				
Overall ^a	2.55 (1.49–4.37)	<0.001	2.95 (1.68–5.18)	<0.001
Men ^b	2.58 (1.05–6.33)	0.038	4.87 (1.62–14.61)	0.005
Women ^b	2.44 (1.15–5.16)	0.020	2.44 (1.15–5.16)	0.020
AV block II–III				
Overall ^a	1.17 (0.59–2.31)	0.653	1.18 (0.56–2.45)	0.664
Men ^b	0.88 (0.36–2.17)	0.785	0.91 (0.33–2.47)	0.849
Women ^b	2.44 (0.46–12.91)	0.296	2.44 (0.46–12.91)	0.296
Atrial fibrillation				
Overall ^a	1.20 (1.04–1.39)	0.011	1.18 (1.02–1.38)	0.029
Men ^b	1.27 (1.07–1.51)	0.007	1.26 (1.05–1.52)	0.015
Women ^b	1.09 (0.84–1.41)	0.511	1.06 (0.82–1.38)	0.640

AV, atrioventricular; CI, confidence interval.

^aMultivariate analysis was adjusted for baseline age, sex, hypertension, diabetes, dyslipidemia and chronic renal disease, and cardiovascular disease.

^bMultivariate analysis was adjusted for baseline age, hypertension, diabetes, dyslipidemia and chronic renal disease, and cardiovascular disease.

The structure of the aortic valve is similar to that of the main pathologic site of r-axSpA, the enthesis,¹³ and the pathophysiology of aortic regurgitation in r-axSpA patients was hypothesized to involve inflammation and subsequent damage of

the Valsalva sinuses by pathologic cells.¹⁴ Interleukin-23-dependent and interleukin-17-producing T cells infiltrate the aortic root and valve in an animal model of r-axSpA, confirming the aforementioned hypothesis in a preclinical

animal model.^{15,16} The incidence of cardiac valve regurgitation was reported to be significantly higher in r-axSpA patients than in healthy controls (45% *versus* 3%, $p < 0.001$).¹⁷ A more recent study reported that echocardiography-proven aortic regurgitation was present in 18% of r-axSpA patients, whereas the prevalence of aortic regurgitation was 2–8% in the GP.¹⁸ In a Swedish nationwide registry, r-axSpA patients had an increased HR for aortic regurgitation (HR: 1.93, 95% CI: 1.28–2.91), consistent with this study.⁸ Valvular heart disease usually occurs at an older age.¹⁹ This study demonstrated that the risk of aortic regurgitation was increased in the r-axSpA group overall and in a subgroup of r-axSpA patients aged ≥ 40 years. Furthermore, the HR for aortic regurgitation was higher in the subgroup of r-axSpA patients aged ≥ 40 years than in the r-axSpA group overall (HR: 2.95 *versus* 2.55). Taking the findings of previous studies^{8,17,18} and this study together, the risk of aortic regurgitation is increased in r-axSpA patients.

Several studies evaluated the risk of cardiac conduction disorders in r-axSpA patients; however, most of them did not include proper healthy controls.^{9–11,20} The nationwide registry study from Sweden incorporated an appropriate GP group and reported that the HR for AF was increased in r-axSpA patients (HR: 1.35, 95% CI: 1.16–1.57) and the standardized incidence rate of AF was 7.1 per 1000 PYs.⁸ This study reported similar results (i.e. increased HR for AF in the r-axSpA group), but the incidence rate of AF was 4.0 per 1000 PYs in this study, which is lower than in the Swedish study.⁸ The incidence rates of AF differ between ethnicities.^{21,22} The difference in enrolled patients between the Swedish study⁸ and this study may underlie the lower incidence rate of AF in this study. In sex-stratified analyses, the risk of AF was elevated in male patients, but not female patients, r-axSpA patients compared with the GP. Another study of Korean health insurance data demonstrated that only men showed an increased HR for AF in sex-stratified analysis.²³ The severity of radiographic structural damage and the levels of an inflammatory marker and pro-inflammatory cytokines are higher in male than in female r-axSpA patients.^{24–27} Increased levels of inflammatory markers are associated with the initiation and continuation of AF.^{28,29} Although the analysis duration differs between the previous study²³ and this study, the HR for AF in r-axSpA patients was uniformly increased only in men. These findings imply that the increased risk of AF in male r-axSpA

patients may be attributable to their increased inflammatory status.

Another critical cardiac conduction disorder is AV block, and AV block II–III can result in sudden cardiac death. Therefore, implantation of a pacemaker is essential in patients with symptomatic AV blocks II and III.³⁰ There is debate about whether the risk of AV block II–III is increased in r-axSpA patients. Earlier studies claimed that the occurrence of AV block II–III was not increased in r-axSpA patients.^{9–11} However, a recent study from Sweden demonstrated that the risks of AV block II–III and pacemaker implantation were higher in r-axSpA patients than in the GP (HR: 2.27, 95% CI: 1.59–3.26; and HR: 2.14, 95% CI: 1.62–2.81, respectively).⁸ The SIR of AV block II–III was 0.9 per 1000 PYs in the Swedish study,⁸ and the incidence rate of AV block II–III was 0.21 per 1000 PYs in this study. Although the incidence rate of pacemaker implantation was low in this study, it was higher in the r-axSpA group than in the GP group (0.10 *versus* 0.04 per 1000 PYs, data not shown). The percentage of r-axSpA patients younger than 50 years was higher in this study than in the Swedish study (59.3% *versus* 47.5%). The rate of implantation of cardiac devices in patients with heart failure is lower in non-white subjects than in white subjects.³¹ Differences in age and ethnicity between the Swedish study⁸ and this study may underlie the discordant results regarding the risks of AV block II–III and pacemaker implantation. The clinical impact of AV block II–III and pacemaker implantation in r-axSpA patients may be less important than other cardiac manifestations because both studies showed that the incidence rates of AV block II–III and pacemaker implantation were relatively low in the r-axSpA group.

Klingberg *et al.* claimed routine monitoring for echocardiography. In this study, the SIR for aortic regurgitation was highest in men aged 40–49 years, and the HR for aortic regurgitation was 4.87 (95% CI: 1.62–14.61) in male r-axSpA patients aged ≥ 40 years. Valvular heart disease can be diagnosed by echocardiography, which is relatively expensive. Therefore, regular echocardiography may not be required in all r-axSpA patients, but required in a specific subgroup of these patients such as those who are male and older.

This study has several limitations. First and most importantly, diagnosis was judged by ICD-10-CM codes in NHIS data, and the diagnostic

accuracy may be limited. However, the Korean NHIS and RID programs strictly monitor the diagnosis of r-axSpA because patients who receive such a diagnosis are eligible for financial support. Second, we only included r-axSpA. Undifferentiated spondyloarthritis is not one of the rare diseases included in the Korean RID programs and consequently its diagnosis may be less accurate than that of r-axSpA. Therefore, we did not include non-r-axSpA in this study. Third, laboratory data and r-axSpA-associated parameters were not included in the analysis. These are intrinsic limitations of insurance data. Fourth, the influence of medications such as biologics on the occurrence of cardiac manifestations was not considered because complete information about medications was not provided by the NHIS.

In conclusion, the incidence rates of aortic regurgitation and AF were higher in r-axSpA patients than in the GP. Furthermore, the risks of these cardiac disorders were significantly increased in r-axSpA patients. Regular echocardiography in a specific subgroup of r-axSpA patients, such as those who are older and male, may increase the early detection of aortic regurgitation.

Author contributions

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Data availability statement

The data underlying this article are available in the article.

Supplemental material

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