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# Association of Congestive Heart Failure and Death with Ankylosing Spondylitis : A Nationwide Longitudinal Cohort Study in Korea

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**Objective :** We attempted to discover that Ankylosing spondylitis (AS) has a comprehensive relationship with congestive heart failure and death.

**Methods :** We used a nationwide database managed by the Korean National Health Insurance Service from 2010 to 2014. Twelve thousand nine hundred eighty-eight patients with a diagnosis of AS and 64940 age- and sex- stratified matching subjects without AS were enrolled in the AS and control groups. Incidence probabilities of 6 years congestive heart failure and death in each group were calculated. The Cox proportional hazard regression analysis was used to estimate the hazard ratio. We divided the AS and control groups into subgroups according to sex, age, income, and comorbidities.

**Results :** During the follow-up period, 102 patients (0.79%) in the AS group and 201 patients (0.32%) in the control group developed congestive heart failure ($p$<0.0001). In addition, 211 (1.62%) subjects in the AS group died during the follow-up period compared to 639 (0.98%) subjects in the control group ($p$<0.0001). The adjusted hazard ratio of congestive heart failure and death in the AS group was 2.28 (95% confidence interval [CI], 1.80–2.89) and 1.66 (95% CI, 1.42–1.95), respectively. The hazard ratios of congestive heart failure and death were significantly increased in all of the subgroups.

**Conclusion :** The incidence rates of congestive heart failure and death were increased in AS patients.

**Key Words :** Heart failure · Cardiovascular diseases · Death · Spondylitis, Ankylosing · Epidemiology.

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## INTRODUCTION

Congestive heart failure is a life-threatening disease affecting approximately 26 million people worldwide[25]. Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder that affects the axial skeleton[13]. Several case reports have focused on congestive heart failure in AS patients[1,2,27,29]. Studies have also been conducted to ascertain the incidence of congestive heart failure in AS patients[11,14,15,31]. However, large-scale studies are lacking[11,14,31]. Although one study did involve more than 10000 people[15], it was a cross-sectional study. One study included AS patients in only one city[31] and another study involved AS patients who were over 40 years old[14].

Several studies have reported death in AS patients[26,33], and there are controversies whether AS increases the death rate. A report showed that AS does not have an effect on death[6]. However, other studies suggested that AS patients are more likely to die[3,5,7,12,20]. Most studies about death rate in AS patients are limited by the small sample sizes[3,5-7,20]. Although one study investigated the relationship between AS and death in more than 10000 AS patients, it was only about vascular mortality[12].

The present study is a nationwide longitudinal cohort study to clarify the risk of congestive heart failure and all-cause death in an AS population.

## MATERIALS AND METHODS

### Data source

Data was acquired from the Korean National Health Insurance Service (NHIS) for 2010 to 2014. NHIS has information about people who have received health care. The NHIS database has extensive information and classifies diseases under the International Classification of Disease (ICD-10)[28]. Researchers who are approved by the official review committee can use this NHIS database, and we acquired the rights to use it from the institutional review board of the CHA Bundang Medical Center of CHA University (IRB No. 2017-08-015).

### Patient population

Initially, 15547 AS subjects were extracted from January 1, 2010 to December 31, 2014 among the total population of the Republic of Korea (50455745 people). Afterwards, 1400 subjects who had a previous history of ischemic stroke or acute myocardial infarction or congestive heart failure were excluded. Subsequently, 1159 people younger than 20 years old were excluded. Thus, 12988 subjects were established (Fig. 1). In the next step, 1 : 5 age- and sex- stratified matching was performed using a Greedy digit match algorithm. In this process, 12988 AS patients were matched with 64940 controls[17]. Both groups were followed up to December 31, 2015.

### Definitions of cardiovascular events and comorbidities

AS was diagnosed according to the Reduction of Medical Expenses for Rare Complaints Code, V14.0, between January 1, 2010 and December 31, 2014. Cardiovascular events were defined as a new occurrence of myocardial infarction or ischemic stroke or congestive heart failure during the follow-up period. An acute myocardial infarction diagnosis was defined by ICD-10 (I21 and I22) and hospitalization ≥1. The ischemic stroke patients had ICD-10 codes of I63, I64 and hospitalization ≥1 with imaging studies (brain computed tomography or magnetic resonance imaging). A congestive heart failure diagnosis was defined by ICD-10 codes (I50) and hospitalization ≥1[17,24,28]. Comorbidities such as diabetes mellitus (E11–E14), hypertension (I10–I13, I15), and dyslipidemia (E78) were de-

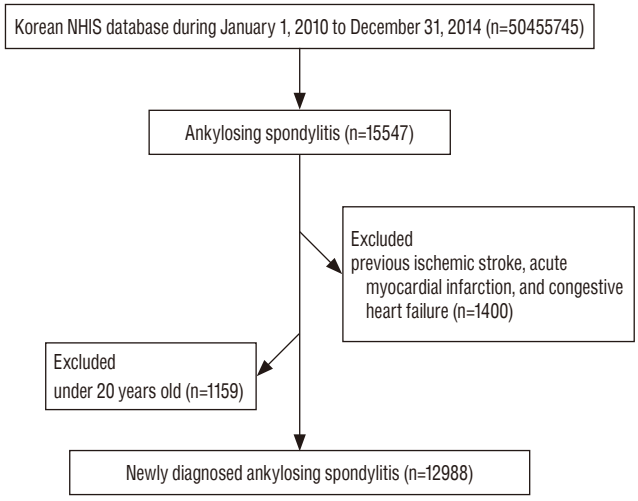


**Fig. 1.** Procedure for establishment of the study cohort. Among the total population of the Republic of Korea (50455745 people), 15547 Ankylosing spondylitis (AS) subjects were extracted for the period, January 1, 2010 to December 31, 2014. One thousand four hundred subjects who had a previous history of ischemic stroke or acute myocardial infarction or congestive heart failure were excluded. Subsequently, 1159 people younger than 20 years old were also excluded. Eventually, 12988 subjects constituted the base cohort. NHIS : National Health Insurance Service.

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fined by ICD-10 codes with additional information described previously[18,19,24].

## Statistical analysis

We used the Chi-square test and Student's t-test to compare the mean differences in the demographic characteristics and comorbidities between the AS and the control groups. Cumulative incidence probabilities of congestive heart failure and death in the AS and control groups were estimated using the Kaplan-Meier method. Differences in survival rates between the two groups were measured using the Wilcoxon's log-rank test. Multivariate analyses of the Cox proportional hazard regression model were conducted to estimate the effects of AS on congestive heart failure and death. The incidence rate was calculated as the number of events per 1000 person-years. Two Cox proportional hazard regression models were applied to estimate the hazard ratio and the corresponding 95% confidence intervals (CIs). Age and sex were adjusted in model 1. In addition to age and sex, other comorbidities were adjusted in model 2. We organized subgroups in the AS and control group according to sex, age, income, and comorbidities. Age was divided into two groups; those over 65 and under 65 years old. Income was divided into upper/middle and lowest categories. Comorbidities included diabetes mellitus, hypertension, and dyslipidemia. Data measurements were analyzed using SAS version 9.2 software (for Windows; SAS Institute, Cary, NC, USA).

**Table 1.** Characteristics of the AS and control group

| Variable | AS (n=12988) | Control (n=64940) | *p*-value |
|---|---|---|---|
| Female | 3566 (27.46) | 17830 (27.46) | |
| Age | 40.186±14.195 | 40.186±14.194 | |
| Age ≥40 | 5,915 (45.54) | 29575 (45.54) | |
| Age ≥65 | 864 (6.65) | 4320 (6.65) | |
| Diabetes mellitus | 623 (4.80) | 2447 (3.77) | <0.0001 |
| Hypertension | 1710 (13.17) | 6199 (9.55) | <0.0001 |
| Dyslipidemia | 1135 (8.74) | 3763 (5.79) | <0.0001 |
| Congestive heart failure | 102 (0.79) | 210 (0.32) | <0.0001 |
| Death | 211 (1.62) | 639 (0.98) | <0.0001 |

Values are presented as mean±standard deviation or number (%). AS : ankylosing spondylitis

# RESULTS

## Characteristics of the AS and control group

Table 1 showed the baseline characteristics about sex, age, comorbidities, congestive heart failure, and death. There were 12988 subjects in the AS group and 64940 subjects in the control group during the study period. Males (72.54%) outnumbered females (27.46%). The mean age of the subjects was 40.19±14.20 years. There were significant differences between the two groups in the prevalence rates of diabetes mellitus ($p$<0.0001), hypertension ($p$<0.0001), dyslipidemia ($p$<0.0001), congestive heart failure ($p$<0.0001), and death ($p$<0.0001). The incidence rates of congestive heart failure and death were significantly higher in the AS group than those in the control group ($p$<0.0001 and $p$<0.0001, respectively). The other comorbidities of diabetes mellitus, hypertension, and dyslipidemia were significantly higher in the AS group than in the control group ($p$<0.0001, $p$<0.0001, $p$<0.0001, respectively, Table 1).

**Table 2.** Adjusted hazard ratio for cardiovascular events and death in the AS and control group

| Group | N | Event | Duration (hours) | Incidence rate (%) | Hazard ratio (95% CI) | |
|---|---|---|---|---|---|---|
| | | | | | Model 1 | Model 2 |
| Congestive heart failure | | | | | | |
| Control | 64940 | 210 | 227134.68 | 0.92 | 1 | 1 |
| AS | 12988 | 102 | 45307.12 | 2.25 | 2.46 (1.94–3.11) | 2.28 (1.80–2.89) |
| Death | | | | | | |
| Control | 64940 | 639 | 226338.94 | 2.82 | 1 | 1 |
| AS | 12988 | 211 | 45095.12 | 4.68 | 1.71 (1.46–2.00) | 1.66 (1.42–1.95) |

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, income, diabetes mellitus, hypertension, and dyslipidemia. AS : ankylosing spondylitis, CI : confidence interval

## Congestive heart failure in the AS and control group

Of the 12988 subjects in the AS group, 102 (0.79%) developed congestive heart failure during the follow-up period compared to 210 (0.32%) out of the 64940 subjects in the control group ($p$<0.0001, Table 1). In a multivariate analysis of Cox proportional hazards regression model 1, the hazard ratio of congestive heart failure in the AS group was 2.46 compared to that in the control group (95% CI, 1.94–3.11; Table 2). In a multivariate analysis of model 2, the hazard ratio of congestive heart failure in the AS group was 2.28 compared to that in the control group (95% CI, 1.80–2.89; Table 2, Fig. 2).

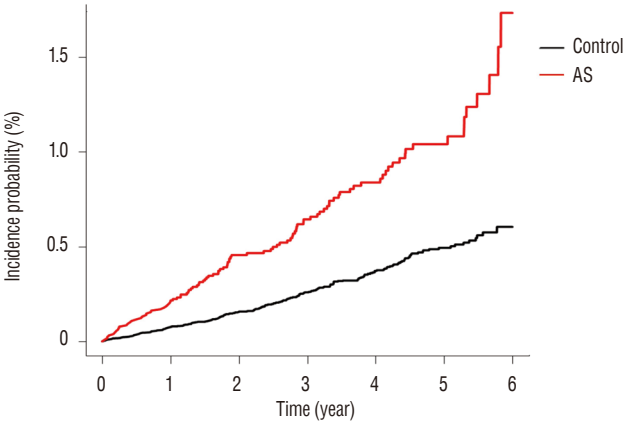


**Fig. 2.** Comparison of the incidence probability of congestive heart failure between the Ankylosing spondylitis (AS) and control groups during the follow-up period. Kaplan-Meier curves with cumulative hazards of congestive heart failure were used in the AS and control groups. The incidence probability of congestive heart failure in the AS group was significantly higher than that in the control group ($p$<0.0001).

In both male and female subgroup, congestive heart failure incidence rate was significantly different between AS and control group (95% CI, 1.61–2.93; 1.71–3.76; respectively; Table 3). In both age group (<65 and ≥65), congestive heart failure incidence rate was significantly different between AS and control group (95% CI, 1.59–3.09; 1.67–3.30; respectively; Table 3). In both upper/middle and lowest income subgroup, congestive heart failure incidence rate was significantly different between AS and control group (95% CI, 1.94–3.46; 1.19–2.75; respectively; Table 3). In both non-diabetes and diabetes subgroup, congestive heart failure incidence rate was significantly different between AS and control group (95% CI, 1.74–2.98; 1.27–3.62; respectively; Table 3). In both non-hypertension and hyperten-

**Table 3.** Subgroup analysis of congestive heart failure in the AS and control group

| Variable | AS | | Control | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| | N | Incidence rate (%) | N | Incidence rate (%) | |
| Sex | | | | | |
| Male | 63 | 1.91 | 135 | 0.82 | 2.18 (1.61–2.93) |
| Female | 39 | 3.16 | 75 | 1.21 | 2.55 (1.71–3.76) |
| Age | | | | | |
| <65 | 53 | 1.25 | 107 | 0.50 | 2.23 (1.59–3.09) |
| ≥65 | 49 | 16.68 | 103 | 6.87 | 2.36 (1.67–3.30) |
| Income | | | | | |
| Upper/middle | 69 | 2.01 | 143 | 0.81 | 2.60 (1.94–3.46) |
| Lowest | 33 | 3.00 | 67 | 1.35 | 1.83 (1.19–2.75) |
| Diabetes mellitus | | | | | |
| No | 80 | 1.86 | 169 | 0.77 | 2.29 (1.74–2.98) |
| Yes | 22 | 10.07 | 41 | 4.84 | 2.17 (1.27–3.62) |
| Hypertension | | | | | |
| No | 48 | 1.22 | 125 | 0.61 | 1.96 (1.39–2.72) |
| Yes | 54 | 9.11 | 85 | 3.93 | 2.64 (1.87–3.71) |
| Dyslipidemia | | | | | |
| No | 70 | 1.69 | 171 | 0.80 | 2.06 (1.54–2.71) |
| Yes | 32 | 8.23 | 39 | 3.08 | 3.05 (1.89–4.87) |

AS : ankylosing spondylitis, CI : confidence interval


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sion subgroup, congestive heart failure incidence rate was significantly different between AS and control group (95% CI, 1.39–2.72; 1.87–3.71; respectively; Table 3). In both non-dyslipidemia and dyslipidemia subgroup, congestive heart failure incidence rate was significantly different between AS and control group (95% CI, 1.54–2.71; 1.89–4.87; respectively; Table 3).

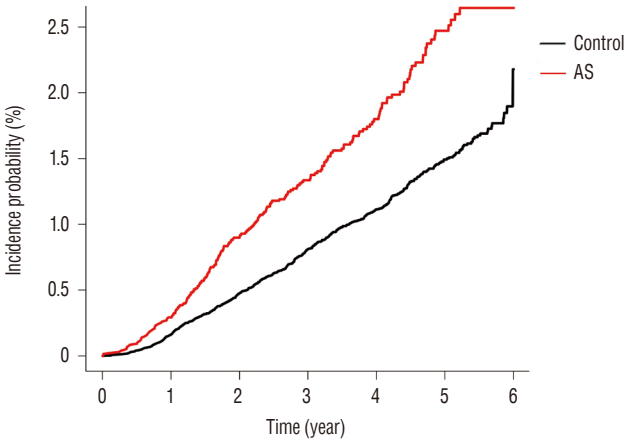


**Fig. 3.** Comparison of the incidence probability of death between the Ankylosing spondylitis (AS) and control groups during the follow-up period. Kaplan-Meier curves with cumulative hazards of death were used in the AS and control groups. The incidence probability of death in the AS group was significantly higher than that in the control group ($p$<0.0001).

## Death in the AS and control group

Of the 12988 subjects in the AS group, 211 (1.62%) subjects died during the follow-up period compared to 639 (0.98%) subjects in the control group ($p$<0.0001, Table 1). In a multivariate analysis of Cox proportional hazards regression model 1, the hazard ratio of death in the AS group was 1.71 compared to that in the control group (95% CI, 1.46–2.00; Table 2). In a multivariate analysis of model 2, the hazard ratio of death in the AS group was 1.66 compared to that in the control group (95% CI, 1.42–1.95; Table 2, Fig. 3).

In both male and female subgroup, death rate was significantly different between AS and control group (95% CI, 1.34–1.92; 1.40–2.61; respectively; Table 4). In both age group (<65 and ≥65), death rate was significantly different between AS and control group (95% CI, 1.09–1.74; 1.62–2.48; respectively; Table 4). In both upper/middle and lowest income subgroup, death rate was significantly different between AS and control group (95% CI, 1.48–

**Table 4.** Subgroup analysis of death in the AS and control group

| Variable | AS | | Control | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| | N | Incidence rate (%) | N | Incidence rate (%) | |
| Sex | | | | | |
| Male | 155 | 4.73 | 487 | 2.96 | 1.61 (1.34–1.92) |
| Female | 56 | 4.55 | 152 | 2.46 | 1.93 (1.40–2.61) |
| Age | | | | | |
| <65 | 90 | 2.13 | 318 | 1.50 | 1.39 (1.09–1.74) |
| ≥65 | 121 | 42.87 | 321 | 22.00 | 2.01 (1.62–2.48) |
| Income | | | | | |
| Upper/middle | 134 | 3.92 | 437 | 2.47 | 1.80 (1.48–2.18) |
| Lowest | 77 | 7.06 | 202 | 4.08 | 1.51 (1.15–1.95) |
| Diabetes mellitus | | | | | |
| No | 168 | 3.91 | 530 | 2.43 | 1.67 (1.40–1.98) |
| Yes | 43 | 19.87 | 109 | 13.07 | 1.68 (1.17–2.38) |
| Hypertension | | | | | |
| No | 138 | 3.52 | 444 | 2.17 | 1.69 (1.39–2.04) |
| Yes | 73 | 12.33 | 195 | 9.11 | 1.64 (1.24–2.14) |
| Dyslipidemia | | | | | |
| No | 176 | 4.27 | 576 | 2.70 | 1.62 (1.36–1.91) |
| Yes | 35 | 9.02 | 63 | 5.00 | 2.07 (1.35–3.12) |

AS : ankylosing spondylitis, CI : confidence interval

2.18; 1.15–1.95; respectively; Table 4). In both non-diabetes and diabetes subgroup, death rate was significantly different between AS and control group (95% CI, 1.40–1.98; 1.17–2.38; respectively; Table 4). In both non-hypertension and hypertension subgroup, death rate was significantly different between AS and control group (95% CI, 1.39–2.04; 1.24–2.14; respectively; Table 4). In both non-dyslipidemia and dyslipidemia subgroup, death rate was significantly different between AS and control group (95% CI, 1.36–1.91; 1.35–3.12; respectively; Table 4).

## DISCUSSION

Our study showed that the incidence of AS was 12988 during the study period and that AS increased the risk of congestive heart failure by 2.28 times and the risk of death by 1.66 times. These associations were constant after adjusting for demographics and comorbidities. In addition, the risk of congestive heart failure and death increased in all of the subgroups.

The present study was a nationwide longitudinal study using the NHIS database. NHIS was implemented in 1989[34], and the NHIS database covers 97% of people in the Republic of Korea[16,28]. Nearly all of the incident cases of vascular events would be identified. We analyzed 6 year follow-up data, covering all age groups over 20. This study also used a clear definition of AS using the Reduction of Medical Expenses for Rare Complaints Code.

The mechanism of which congestive heart failure increased in AS patients is unclear. However, there have been case reports which suggested amyloidosis in patients with both congestive heart failure and AS[8,10]. Amyloidosis may cause increase in the myocardial extracellular volume[4]. Therefore, the increased myocardial extracellular volume can cause heart failure. Inflammation in AS also can cause fibrosis in the aortic root and thickening in the adjacent ventricular septum[13]. These also may cause congestive heart failure.

The causes of increased death rate in AS are not clear yet as well. AS can produce a restrictive lung function and can cause bilateral apical pulmonary fibrobullous disease[13]. AS induces inflammatory bowel disease as well[13]. AS patients have weaker spines. Therefore, they are more vulnerable to trauma and fractures[9,23,32]. Further studies are warranted to elucidate the causes of increased congestive heart failure incidence rate and increased death rates.

Several limitations in this study should be noted. Due to the basic limit of the NHIS database, this study lacks information related to life habits such as smoking, alcohol consumption, physical activity, and eating patterns. Such factors may affect the cardiac function[22,30] and death rate[21]. Moreover, because vascular risk factors such as diabetes and hypertension and dyslipidemia are insidious disorders, they may not be identified in the NHIS database. Even with this limitation in mind, this is the largest nationwide longitudinal study to show an increased risk of congestive heart failure and death in AS patients.

## CONCLUSION

This nationwide longitudinal cohort study shows an increased risk of congestive heart failure and death in AS patients.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## INFORMED CONSENT

This type of study does not require informed consent.

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