



Association of Uveitis with Radiographic Progression in Patients with Axial Spondyloarthritis: A Propensity Score Matching Analysis

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Objective. Acute anterior uveitis (AAU) is the most common extra-articular manifestation in patients with axial spondyloarthritis (axSpA). However, the relationship between AAU and radiographic progression in axSpA remains unclear. Hence, we investigated whether the presence of AAU is associated with radiographic structural damage in patients with axSpA. **Methods.** Clinical and radiographic data were obtained from 253 patients with axSpA. Radiographic progression over 2 years was assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Progression was defined as mSASSS worsening by \geq two units. Using propensity score (PS) matching, differences between patients with and without AAU were analyzed. **Results.** The proportion of progressors among patients with AAU was lower than that of patients without AAU (13.6% vs. 29.5%, $p=0.058$). The rate of increase in mSASSS and number of syndesmophytes were lower in patients with AAU than patients without AAU (0.57 ± 1.37 vs. 1.02 ± 1.79 , $p=0.085$ and 0.46 ± 1.45 vs. 0.83 ± 1.62 , $p=0.158$). In multivariate regression analysis, presence of AAU was independently associated with slowed radiographic progression (odds ratio [95% confidence interval] 0.21 [0.07, 0.67], $p=0.004$). **Conclusion.** PS-matched axSpA patients with AAU showed significantly less radiographic progression than those without AAU. (*J Rheum Dis* 2019;26:248-256)

Key Words. Axial spondyloarthritis, Radiographic progression, Uveitis, Propensity score matching

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic, progressive disease characterized by inflammation of entheses, leading to new bone formation and ankylosis of joints, primarily in the axial skeleton [1,2]. Functional disability resulting from progressive deformation and ankylosis of the spine leads to decreases in physical activity and quality of life. Because axSpA occurs more commonly in economically active, young males, it can lead to productivity losses that result in substantial economic burden to society [3,4].

axSpA is an interesting rheumatic disease due to close associations with acute anterior uveitis (AAU), psoriasis,

and inflammatory bowel disease, so-called extra-articular manifestations [5,6]. The presence of extra-articular manifestations not only plays a critical role in the diagnosis of axSpA [7], but also has an impact on health-related quality of life and treatment choice [8]. AAU is the most common extra-articular manifestation, with a prevalence of 20% ~ 30% [5,6,9]. Presence of AAU increases the probability of axSpA in patients presenting with chronic back pain [10] and is associated with higher disease activity, poor functional ability, and advanced physical impairment [11]. In axSpA patients with a history of AAU, infliximab and adalimumab are preferred over etanercept because of lower AAU flare rates [12].

Several parameters have been identified as risk factors

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for radiographic progression in patients with axSpA: male sex, smoking, syndesmophyte(s) at baseline, high degree of sacroiliitis on magnetic resonance images, and increased level of C-reactive protein (CRP) [1]. High body mass index (BMI) and peripheral arthritis were also suggested as potential clinical predictors of radiographic progression of the spine [13-17]. However, the relationship between AAU and radiographic progression in axSpA remains unclear. In a previous cohort study, history of AAU was associated with higher Bath Ankylosing Spondylitis Radiology Index (BASRI) score, but the association was found only in male patients and was not statistically significant [14].

The absence of randomization in observational studies can make inferences about factor or treatment effects susceptible to indication [18]. Propensity score (PS) matching is a statistical technique that matches patients in two groups using a factor to balance observed characteristics, achieve exchangeability, and produce groups that are functionally randomized [18,19]. Therefore, once patients have been matched based on PS, any observed difference in outcomes is assumed to be a direct result of the factor or treatment dividing the two groups. To properly investigate the relationship between AAU and radiographic progression in axSpA, we used PS matching to match axSpA patients with and without AAU and compared the radiographic progression between the two groups.

MATERIALS AND METHODS

Patients

A total of 412 axSpA patients who fulfilled the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axSpA [7] and had received care at St. Vincent's Hospital, The Catholic University of Korea (Suwon, Korea) between 2008 and 2017 was identified. Clinical and laboratory data and radiographic images were retrieved from medical records. At baseline, sex, age at diagnosis, time since diagnosis, HLA-B27 status, smoking status, and history of extra-articular manifestations (uveitis, psoriasis, inflammatory bowel disease, peripheral arthritis, and enthesitis) were recorded. Disease activity was assessed using the Ankylosing Spondylitis Disease Activity Score (ASDAS) according to CRP level [20]. Of the total sample, 253 patients who were followed for 2 years were assessed for radiographic progression. The study was carried out in ac-

cordance with the Helsinki Declaration and approved by the institutional review board of St. Vincent's Hospital, The Catholic University of Korea (no. VC19RESI0090).

Radiographs and scoring

Radiographs of the sacroiliac joints and the cervical and lumbar spine were obtained by the local investigator at baseline and after 2 years of follow-up. All available radiographs for each patient were independently scored at the same time by two experienced readers who were blinded to all other data except radiograph chronology according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [21]. Spinal radiographic progression was defined as worsening of the mean mSASSS by more than two units over 2 years, in conformity with previous studies [22-24], and axSpA patients were categorized into two subgroups, progressors, and non-progressors. Radiographic sacroiliitis (SI) was scored according to the modified New York criteria [25], and radiological hip involvement was graded using the BASRI-hip scoring system [26]. Interobserver reliability was assessed by calculating the interclass correlation coefficient, which was 0.946 (95% confidence interval [CI] 0.940 to 0.952).

Propensity score matching

Because we expected systematic differences in the baseline characteristics of subjects with or without AAU, we performed PS matching to adjust for these potential imbalances [18,19]. We used logistic regression to obtain the PS [27], and the variables included in PS estimation were sex, age at diagnosis, disease duration, BMI, HLA-B27 positivity, smoking status, history of peripheral arthritis, enthesitis, psoriasis, inflammatory bowel disease, erythrocyte sedimentation rate at baseline, CRP level at baseline, ASDAS-CRP at baseline, use of tumor necrosis factor (TNF) inhibitors, mSASSS, presence of syndesmophyte(s), SI score, BASRI-hip score, and z-scores of bone mineral density at the lumbar spine and femur neck. Patients without AAU were matched based on PS using the nearest-neighbor matching algorithm without replacement and with a 1:3 ratio within 0.05 of the estimated PS [27].

Statistical analyses

For continuously distributed data, the results are shown as mean with standard deviation (SD); between-group comparisons were performed using Student's t-test. Categorical and dichotomous variables are expressed as

Table 1. Baseline characteristics of axSpA patients with and without AAU after propensity score matching

| Variable | Patients with AAU (n=44) | Patients without AAU | | | |
|------------------------------|-----------------------------|------------------------------|----------------------|-------------------------------|----------------------|
| | | After PS matching (n=132) | p-value [†] | Before PS matching (n=209) | p-value [†] |
| Male | 34 (77.3) | 107 (81.1) | 0.744 | 153 (73.2) | 0.712 |
| Age at diagnosis (yr) | 34.2±12.6 | 33.3±12.4 | 0.672 | 32.7±12.1 | 0.190 |
| Disease duration (yr) | 4.48±4.96 | 4.61±5.46 | 0.878 | 3.88±5.18 | 0.227 |
| BMI (kg/m ²) | | | 0.794 | | |
| Underweight, <18.5 | 0 (0.0) | 1 (0.8) | | 9 (4.3) | |
| Normal, 18.5~25 | 24 (54.5) | 80 (60.6) | | 133 (63.6) | |
| Overweight, 25~30 | 16 (36.4) | 39 (29.5) | | 52 (24.9) | |
| Obese, >30 | 4 (9.1) | 12 (9.1) | | 15 (7.2) | |
| HLA-B27 | 42 (95.5) | 126 (95.5) | 1.000 | 175 (83.7) | 0.074 |
| Smoking | | | 0.861 | | 0.578 |
| Non-smoker | 25 (56.8) | 71 (53.8) | | 131 (62.7) | |
| Smoker | 19 (43.2) | 61 (46.2) | | 78 (37.3) | |
| Peripheral arthritis | 8 (18.2) | 27 (20.5) | 0.913 | 77 (36.8) | 0.027 |
| Enthesitis | 0 (0.0) | 0 (0.0) | 1.000 | 13 (6.2) | 0.186 |
| Psoriasis | 1 (2.3) | 3 (2.3) | 1.000 | 3 (1.4) | 1.000 |
| Inflammatory bowel disease | 1 (2.3) | 1 (1.5) | 1.000 | 5 (2.4) | 1.000 |
| ESR (mm/h) | 30.2±21.4 | 31.5±25.1 | 0.768 | 36.1±27.6 | 0.122 |
| CRP (mg/dL) | 2.1±3.8 | 1.8±2.9 | 0.616 | 1.8±2.7 | 0.542 |
| ASDAS-CRP | 3.0±1.0 | 3.0±0.9 | 0.974 | 3.1±0.9 | 0.650 |
| Use of TNF inhibitor* | 25 (56.8) | 76 (57.6) | 1.000 | 114 (54.5) | 0.913 |
| Continuous use of NSAIDs | 17 (61.4) | 89 (67.4) | 0.582 | 140 (67.0) | 0.589 |
| mSASSS, units | 8.3±13.0 | 8.7±13.1 | 0.891 | 8.4±13.9 | 0.962 |
| Presence of syndesmophyte(s) | 19 (43.2) | 52 (39.4) | 0.790 | 82 (39.2) | 0.751 |
| Number of syndesmophyte(s) | 2.3±4.5 | 2.5±4.3 | 0.835 | 2.6±4.8 | 0.781 |
| Sacroiliac joint | | | 0.859/0.746 | | 0.552/0.560 |
| Grade 0 (right/left) | 7 (15.9)/7 (15.9) | 16 (12.1)/18 (13.6) | | 39 (18.7)/46 (22.0) | |
| Grade 1 (right/left) | 6 (13.6)/6 (13.6) | 24 (18.2)/25 (18.9) | | 45 (21.5)/38 (18.2) | |
| Grade 2 (right/left) | 12 (27.3)/13 (29.3) | 42 (31.8)/35 (26.5) | | 59 (28.2)/53 (25.4) | |
| Grade 3 (right/left) | 8 (18.2)/7 (15.9) | 23 (17.4)/29 (22.0) | | 32 (15.3)/38 (18.2) | |
| Grade 4 (right/left) | 11 (25.0)/11 (25.0) | 27 (20.5)/25 (18.9) | | 34 (16.3)/34 (16.3) | |
| Hip involvement | | | 0.056/0.793 | | 0.036/0.469 |
| Grade 0 (right/left) | 39 (88.6)/40 (90.9) | 121 (91.7)/123 (93.2) | | 192 (91.9)/192 (91.9) | |
| Grade 1 (right/left) | 2 (4.5)/1 (2.3) | 3 (2.3)/4 (3.0) | | 7 (3.3)/9 (4.3) | |
| Grade 2 (right/left) | 1 (2.3)/2 (4.5) | 8 (6.1)/3 (2.3) | | 9 (4.3)/4 (1.9) | |
| Grade 3 (right/left) | 0 (0.0)/0 (0.0) | 0 (0.0)/1 (0.8) | | 1 (0.5)/3 (1.4) | |
| Grade 4 (right/left) | 2 (4.5)/1 (2.3) | 0 (0.0)/1 (0.8) | | 0 (0.0)/1 (0.5) | |
| BMD (g/cm ²) | | | | | |
| Lumbar spine | 1.050±0.136 | 1.060±0.168 | 0.932 | 1.060±0.157 | 0.802 |
| Femoral neck | 0.862±0.096 | 0.856±0.131 | 0.733 | 0.847±0.117 | 0.384 |
| Total hip | 0.942±0.104 | 0.924±0.119 | 0.337 | 0.907±0.107 | 0.047 |
| Z score | | | | | |
| Lumbar spine | -0.173±0.917 | -0.227±1.210 | 0.754 | -0.220±1.130 | 0.768 |
| Femoral neck | -0.118±0.900 | -0.264±0.852 | 0.350 | -0.386±0.804 | 0.073 |
| Total hip | -0.207±0.793 | -0.304±0.817 | 0.488 | -0.434±0.726 | 0.085 |

Values are presented as number (%) or mean±standard deviation. axSpA: axial spondyloarthritis, AAU: acute anterior uveitis, PS: propensity score, BMI: body mass index, ESR, erythrocyte sedimentation rate, CRP: c-reactive protein, ASDAS: Ankylosing Spondylitis Disease Activity Score, TNF: tumor necrosis factor, NSAIDs: non-steroidal anti-inflammatory drugs, mSASSS: modified Stoke Ankylosing Spondylitis Spine Score, BMD: bone mineral density. *Counted if ever used. TNF inhibitors include etanercept, adalimumab, infliximab, and golimumab. [†] Comparison between patients with AAU and the matched patients without AAU.

[†] Comparison between patients with AAU and the unmatched patients without AAU.

frequency and percentage and were compared using the chi-square test or Fisher's exact test. Multivariable logistic regression analysis was performed to identify independent predictors associated with radiographic progression. The effect size was computed by Cohen's *d* method [28]. In our analysis, α was set at 5%, and a two-sided p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using R (version 3.5.3, The R Project for Statistical Computing; www.r-project.org).

RESULTS

Characteristics of the study sample

A total of 44 axSpA patients was identified to have a history of AAU from the original sample of 253 patients who were followed for 2 years and assessed for radiographic progression. Through PS matching, 44 patients with AAU were matched to 209 patients without AAU at a 1:3 ratio and a comparator group of 132 patients without AAU was created. The baseline characteristics of the axSpA patients with AAU ($n=44$) and without AAU ($n=132$) did not differ and were well-balanced (Table 1).

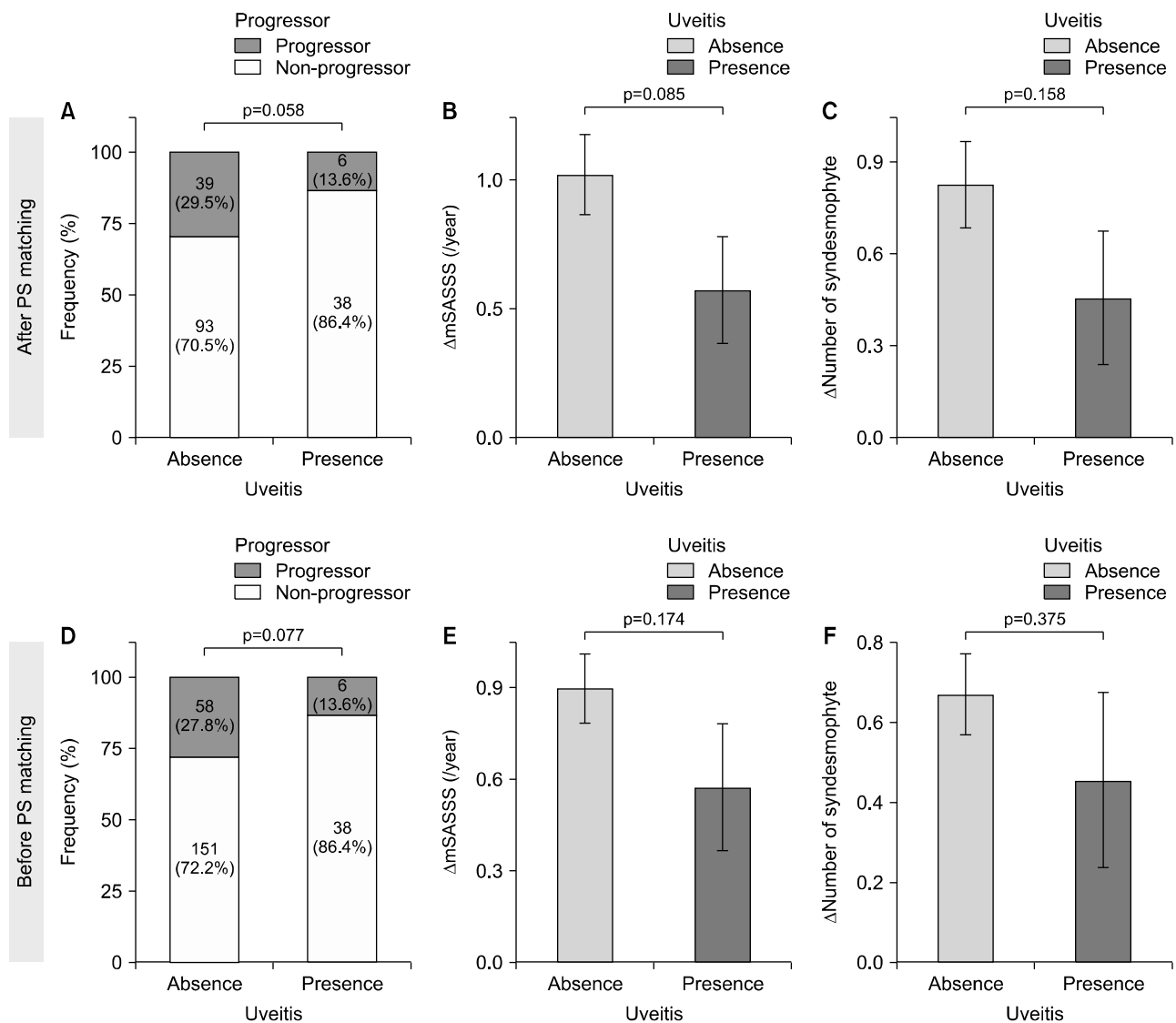


Figure 1. Radiographic progression over 2 years in axSpA patients with AAU and those without AAU. Upper panel indicates the result after PS matching and lower panel before PS matching. (A, D) Proportion of progressors. Comparison by chi-square test. (B, E) Change in mSASSS. Comparison by t-test. (C, F) Change in number of syndesmophytes. Comparison by t-test. axSpA: axial spondyloarthritis, AAU: acute anterior uveitis, PS: propensity score, mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

Before PS matching, in patients without AAU, HLA-B27 positivity was less frequent, peripheral arthritis was more common, and bone mineral density of total hip was lower compared with those with AAU.

Radiographic progression

We examined radiographic progression over 2 years in axSpA patients with AAU and those without AAU. The proportion of progressors among patients with AAU was lower than that among patients without AAU (13.6% vs. 29.5%, $p=0.058$; Figure 1A). The rate of increase in mSASSS was lower in patients with AAU compared with patients without AAU (0.57 ± 1.37 vs. 1.02 ± 1.79 , $p=0.085$; Figure 1B). The number of syndesmophytes showed a smaller increase among patients with AAU than patients without AAU (0.46 ± 1.45 vs. 0.83 ± 1.62 , $p=0.158$; Figure 1C). Before PS matching, differences in the indices of radiographic progression (the proportion of progressors, the rate of increase in mSASSS, and change

in the number of syndesmophytes) were weak and not clear (Figure 1D~F).

Risk factors for radiographic progression

To determine the relationship between presence of AAU and radiographic progression, we performed multivariable logistic regression analysis including known risk factors (Table 2). The presence of syndesmophyte(s) at baseline, male sex, and BMI had significant association with rapid radiographic progression (odds ratio [OR] [95% confidence interval, 95% CI] 1.16 [1.05, 1.28], 4.65 [1.02, 21.25], and 2.89 [1.46, 5.72], respectively, all $p < 0.05$). This agrees well with previous results [15,23,29]. The presence of AAU was independently associated with slowed radiographic progression (OR [95% CI] 0.23 [0.07, 0.75], $p=0.015$). Cumulative probability plots of spinal progression after stratification by AAU status at the onset of the next radiographic interval are presented in Figure 2. Difference of change in mSASSS between the

Table 2. Multivariable logistic regression analysis for radiographic progression in patients with axial spondyloarthritis

| Variables | Crude OR (95% CI) | Adjusted OR (95% CI) | p-value |
|--|-------------------|----------------------|---------|
| After PS matching | | | |
| Male sex | 3.18 (1.05, 9.57) | 4.65 (1.02, 21.25) | 0.047 |
| Age at diagnosis | 1.04 (1.01, 1.07) | 1.04 (0.99, 1.09) | 0.097 |
| Disease duration | 1.01 (0.96, 1.06) | 1.06 (0.98, 1.14) | 0.141 |
| BMI | 2.02 (1.23, 3.31) | 2.89 (1.46, 5.72) | 0.002 |
| HLA-B27 | 0.56 (0.13, 2.42) | 0.20 (0.03, 1.53) | 0.122 |
| Smoking | 1.73 (0.87, 3.42) | 1.31 (0.51, 3.34) | 0.576 |
| CRP | 1.04 (0.94, 1.15) | 0.93 (0.76, 1.13) | 0.454 |
| ASDAS-CRP | 1.30 (0.90, 1.88) | 0.91 (0.47, 1.76) | 0.790 |
| Presence of syndesmophyte(s) at baseline | 1.21 (1.11, 1.32) | 1.16 (1.05, 1.28) | 0.004 |
| Use of TNF inhibitor | 0.63 (0.32, 1.24) | 0.39 (0.15, 1.01) | 0.052 |
| Continuous use of NSAIDs | 1.85 (0.86, 3.97) | 1.86 (0.70, 4.94) | 0.211 |
| Uveitis | 0.38 (0.15, 0.96) | 0.23 (0.07, 0.75) | 0.015 |
| Before PS matching | | | |
| Male sex | 5.62 (1.01, 1.06) | 6.94 (2.08, 23.13) | 0.002 |
| Age at diagnosis | 1.04 (1.01, 1.06) | 1.04 (1.00, 1.08) | 0.040 |
| Disease duration | 1.03 (0.99, 1.07) | 1.06 (0.99, 1.13) | 0.086 |
| BMI | 1.88 (1.25, 2.84) | 2.44 (1.43, 4.18) | 0.001 |
| HLA-B27 | 1.02 (0.45, 2.30) | 0.72 (0.24, 2.12) | 0.549 |
| Smoking | 2.27 (1.27, 4.03) | 1.62 (0.76, 3.47) | 0.210 |
| CRP | 1.07 (0.98, 1.18) | 0.97 (0.53, 1.56) | 0.725 |
| ASDAS-CRP | 1.35 (0.99, 1.84) | 0.91 (0.53, 1.56) | 0.719 |
| Presence of syndesmophyte(s) at baseline | 1.19 (1.11, 1.27) | 1.22 (1.02, 1.20) | 0.011 |
| Use of TNF inhibitor | 0.70 (0.40, 1.24) | 0.56 (0.27, 1.29) | 0.134 |
| Continuous use of NSAIDs | 2.47 (1.26, 4.85) | 2.14 (0.94, 4.91) | 0.072 |
| Uveitis | 0.41 (0.17, 1.02) | 0.23 (0.07, 0.69) | 0.009 |

OR: odds ratio, CI: confidence interval, PS: propensity score, BMI: body mass index, CRP: c-reactive protein, ASDAS: Ankylosing Spondylitis Disease Activity Score, TNF: tumor necrosis factor, NSAIDs: non-steroidal anti-inflammatory drugs.

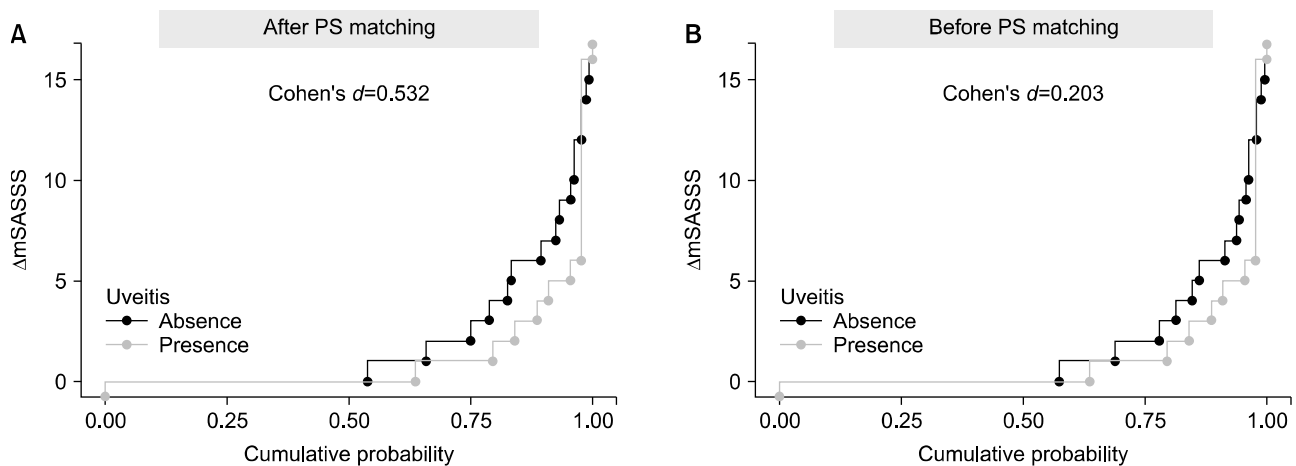


Figure 2. Cumulative probability plot of 2-year progression in the modified Stoke Ankylosing Spine Score (mSASSS), illustrating the change (Δ) in mSASSS values from baseline of each individual radiographic interval to 2 years in patients with acute anterior uveitis (AAU) and those without AAU. Radiographic progression was defined as an increase in mSASSS ≥ 2 in 2 years. The effect size was computed by Cohen's d method. (A) After propensity score (PS) matching, (B) Before PS matching.

patients with AAU and without AAU were more evident and the effect size was moderate (Cohen's $d=0.532$). Before PS matching, the presence of AAU held the independent association with retarded radiographic progression (OR [95% CI] 0.23 [0.07, 0.69], $p=0.009$), but the effect size was small (Cohen's $d=0.203$) (Table 2).

DISCUSSION

Our PS matching analysis matched axSpA patients with AAU with those having similar characteristics without AAU at a 1:3 ratio. This enabled the results from the two groups to be effectively and credibly compared in terms of radiographic progression (proportion of progressors, rate of mSASSS, and development of new syndesmophytes). We confirmed a significant association between presence of AAU and delayed radiographic progression in axSpA patients in multivariable regression analysis.

Given the irreversibility of structural damage to the axial skeleton, the ability to effect early prediction of radiographic progression and aggressive treatment would be of great benefit for rheumatologists who wish to monitor patient risk [30]. The inverse association between AAU and radiographic progression is a novel finding and probably was not captured in previous studies because of the wide phenotypic diversity and heterogeneity of patients with axSpA [31]. We addressed this limitation by PS matching [18,19,27].

In the previous reports, an association of AAU with radiographic progression in axSpA was not significant

[13,32]. Essers et al. [32] investigated whether the presence of extra-articular manifestations is associated with more radiographic damage. In a multivariable model, AAU was not associated with mSASSS over time. However, baseline mSASSS was much higher and peripheral arthritis was more severe in the patients with AAU. Baseline radiographic damage such as syndesmophyte(s) is well-known as the strongest predictor for further radiographic progression [30], which might countervail the effect of uveitis. In addition, disease duration and age were longer and higher in patients with AAU and a long-term observation over 12 years was also a distinct difference from our study. Deminger et al. [13] investigated the predictors of radiographic progression overall and by sex in the 166 patients with axSpA who were followed up over 5 years. Radiographic progression (either as an increase in mSASSS by ≥ 2 points or as development of new syndesmophyte[s]) in this study was defined over the 5 years, which is quite different from the standard time frame, 2 years, to assess the radiographic progression [22-24]. In addition, the frequency of AAU (51%) was abnormally high compared with the general prevalence (20% ~ 30%).

Smoking and CRP level was not captured as having a significant association with radiographic progression in our study, and it depends partly on the multivariable models, design of studies and/or cohorts [23,33]. Influence of smoking on radiographic progression was further determined by its dose and the interaction with baseline syndesmophyte(s) and inflammation [23,34]. Use of

TNF inhibitors can effectively suppress the inflammation, leading to the decrease in the radiographic progression regardless of baseline CRP level [33,35]. In this study, over a half of the patients (n=101, 57.4%) received TNF inhibitors and use of TNF inhibitors was marginally associated with the slowed progression (OR [95% CI] 0.39 [0.15, 1.01], p=0.052; Table 2). The robust use of TNF inhibitors could mitigate against the effects of smoking and CRP in multivariable analysis.

Uveitis is the most common, clinically apparent, extra-articular manifestation of axSpA, and one-third of axSpA patients experience uveitis at some point in the course of their disease [5,6]. From a clinical standpoint, uveitis usually presents as sudden onset episodes affecting only one eye at a time, but sacroiliitis and new bone formation insidiously progress at multiple levels [36]. This observation led us to hypothesize that there is an opposing interaction between uveitis and radiographic progression. The uvea is the vascular middle layer of the eye, composed of the iris, ciliary body, and choroid [37]. The ciliary body includes the ciliary muscle and is connected to the lens through the zonular fiber, which is the suspensory ligament of the lens [38]. At a glance, the structure of the ciliary body looks like enthesitis. This might be a clue to the intriguing association between uveitis and axSpA. However, to the best of our knowledge, there have been no studies addressing this potential relationship. Unraveling the intriguing coupling between uveitis and radiographic progression could help us better understand the etiopathogenesis of axSpA.

There are some limitations to be addressed in this study. First, the study sample was relatively small and from a single center. Second, radiographic image evaluations were prospectively executed, but the data were retrospectively collected. Retrospective data collection is inherently susceptible to bias, including misclassification, information, and selection bias. Third, we cannot exclude the possibility of index event bias. When multiple risk factors contribute to the risk of an outcome, conditioning on the outcome induces dependence between the risk factors, even when these risk factors are independently distributed in the general population. This effect creates a spurious association among these risk factors with an index event [39,40].

CONCLUSION

In the present study, we demonstrate that the presence

of AAU has not only a role in diagnosis and treatment choice, but also an association with radiographic outcome in axSpA. The association between AAU and radiographic progression in axSpA should be validated through further large, multi-center studies. Unraveling the mystery of this association could help us better understand the pathoetiology of axSpA.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

K.J.K. designed the study, and K.J.K. and Y.B.J. carried out data collection. K.J.K. performed statistical analysis and drafted the paper, and all authors (K.J.K., Y.B.J., Y.J.P., and K.S.P.) were involved in critically revising the final preparation. All authors approved the final version to be published.

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