

## Clinical Article

# Risk Factors for the Development and Progression of Atlantoaxial Subluxation in Surgically Treated Rheumatoid Arthritis Patients, Considering the Time Interval between Rheumatoid Arthritis Diagnosis and Surgery

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**Objective :** Rheumatoid arthritis (RA) is a systemic disease that can affect the cervical spine, especially the atlantoaxial region. The present study evaluated the risk factors for atlantoaxial subluxation (AAS) development and progression in patients who have undergone surgical treatment.

**Methods :** We retrospectively analyzed the data of 62 patients with RA and surgically treated AAS between 2002 and 2015. Additionally, we identified 62 patients as controls using propensity score matching of sex and age among 12667 RA patients from a rheumatology registry between 2007 and 2015. We extracted patient data, including sex, age at diagnosis, age at surgery, disease duration, radiographic hand joint changes, and history of methotrexate use, and laboratory data, including presence of rheumatoid factor and the C-reactive protein (CRP) level.

**Results :** The mean patient age at diagnosis was 38.0 years. The mean time interval between RA diagnosis and AAS surgery was 13.6±7.0 years. The risk factors for surgically treated AAS development were the serum CRP level ( $p=0.005$ ) and radiographic hand joint erosion ( $p=0.009$ ). The risk factors for AAS progression were a short time interval between RA diagnosis and radiographic hand joint erosion ( $p<0.001$ ) and young age at RA diagnosis ( $p=0.04$ ).

**Conclusion :** The CRP level at RA diagnosis and a short time interval between RA diagnosis and radiographic hand joint erosion might be risk factors for surgically treated AAS development in RA patients. Additionally, a short time interval between RA diagnosis and radiographic hand joint erosion and young age at RA diagnosis might be risk factors for AAS progression.

**Key Words :** Atlantoaxial subluxation · Rheumatoid arthritis · Posterior cervical fusion.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by poly-articular synovial inflammation and progressive joint destruction<sup>3,25</sup>, and it has been reported to affect approximately 0.5–1% of the adult population<sup>2</sup>. The cervical spine is commonly affected in patients with RA synovitis and enthesitis<sup>6,14,15</sup>, and shows atlantoaxial subluxation (AAS), vertical subluxation (VS) of the axis, and subaxial subluxation (SAS). AAS is the most common type of cervical involvement, and the prevalence ranges from 19% to 70% of RA patients<sup>14,15,17</sup>.

Chronic synovitis and erosive pannus formation at the joint may cause bony destruction and ligamentous laxity in the surrounding ligamentous complex, resulting in instability and subluxation<sup>12,18</sup>. The subluxation can be anterior, posterior, lateral, or rotatory. Anterior AAS is the most common subtype, with a prevalence of 10–55%<sup>7,8,17</sup>. Many studies have reported the prevalence of cervical spine involvement and the predictive risk factors for rheumatoid cervical spine involvement, such as erosion at the peripheral joints, corticosteroid administration, early diagnosis of RA at <45 years of age, and presence of rheumatoid factor (RF)<sup>1,10,23,24,26</sup>. Because subluxation could result in irre-

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versible neural impairment, non-ambulation, respiratory dysfunction, and consequent death<sup>5)</sup>, its early diagnosis and treatment should be a priority in patients with RA.

The present study aimed to evaluate the risk factors for the development and progression of AAS in RA patients who have undergone surgical treatment, considering the time interval between RA diagnosis and AAS surgery. To our knowledge, this is the first such study in RA patients.

## MATERIALS AND METHODS

### Patient data collection

We retrospectively collected the data of 62 patients with RA and AAS from our hospital records between November 1, 2002 and February 28, 2015. All patients met the revised American College of Rheumatology criteria for RA<sup>3)</sup> and had a known diagnosis of AAS [atlantodental interval (ADI) >3 mm]<sup>20)</sup>. The patients experienced severe nuchal pain with upper extremity radiating pain. The detailed chief complains before surgery are presented in Table 1. All patients underwent surgery for posterior fusion. Of the 62 patients, 14 underwent unilateral transarticular screw fixation, 17 underwent bilateral transarticular screw fixation, 15 underwent unilateral C1 lateral mass and C2 pedicle screw fixation, 15 underwent bilateral C1 lateral mass and C2 pedicle screw fixation, and 1 underwent occipitocervical screw fixation. Furthermore, 48 patients underwent additional fusion with a wire using Sonntag's modified Gallie fusion technique (Table 1).

Our ongoing RA registry (established in 2007), which was designed for the purpose of research, includes 12667 RA patients ( $\geq 18$  years of age at RA diagnosis). Among these patients, we identified 1840 patients who underwent cervical radiography, including full flexion/extension view. We then excluded patients diagnosed with AAS and identified 966 patients as possible controls

**Table 1.** Characteristics of the surgically treated patients

Cause and surgical technique	Total (n=62)
<b>Cause</b>	
Spontaneous	62 (100.0%)
Suboccipital headache	10 (16.1%)
Nuchal pain	27 (43.6%)
Upper extremity paresthesia	20 (32.3%)
Upper extremity hypoesthesia	3 (4.8%)
Upper extremity motor weakness	2 (3.2%)
Trauma	0 (0.0%)
<b>Surgical technique</b>	
Unilateral transarticular screw fixation	14 (22.6%)
Bilateral transarticular screw fixation	17 (27.4%)
Unilateral C1 lateral mass and C2 pedicle screw fixation	15 (24.2%)
Bilateral C1 lateral mass and C2 pedicle screw fixation	15 (24.2%)
Occipitocervical screw fixation	1 (1.6%)

Data are presented as number (percentage)

for the study. Among these patients, we finally identified 62 patients as controls, using propensity score matching of sex and age.

This study was approved by our institutional review board, and informed consent was not required owing to the retrospective nature of this study.

### Variables

We reviewed the medical charts of all 62 patients surgically treated for AAS (surgery group) and all 62 matched controls (control group). We extracted patient data, including sex, age at RA diagnosis, age at AAS surgery, disease duration, and history of methotrexate (MTX) use, and laboratory data, including presence of RF (assessed at baseline)<sup>13)</sup> and the C-reactive protein (CRP) level (measured at baseline).

### Image analysis

For radiological evaluation of the cervical spine, we followed the classification system of Yurube<sup>25)</sup>. Cervical spine radiographs were obtained in anteroposterior and lateral views during full flexion and extension. Hyperflexion lateral view radiographs were used for evaluation of AAS. Anterior AAS was measured by recording the shortest distance between the posterior surface of the anterior arch of the atlas and the anterior surface of the odontoid process. VS was diagnosed according to the Ranawat value. SAS was diagnosed if a vertebra had moved more than 2 mm in relation to the next vertebra, when measured from the posterior line of the vertebral bodies. Radiological cervical findings for diagnosis were as follows : 1) AAS : ADI >3 mm<sup>20,24)</sup>; 2) VS : Ranawat value <13 mm<sup>16)</sup>; and 3) SAS : irreducible translation  $\geq 2$  mm<sup>9)</sup>. Additionally, radiological cervical findings for the diagnosis of severe conditions were as follows : 1) severe AAS : ADI  $\geq 10$  mm<sup>15,24)</sup>; 2) severe VS : Ranawat value  $\leq 10$  mm<sup>16)</sup>; and 3) severe SAS : translation  $\geq 4$  mm or translation at multiple levels<sup>9)</sup>. The presence of erosion was investigated using radiographs of the hands and feet in all patients.

### Statistical analysis

Descriptive statistics were used to analyze the clinical information, demographic factors, and other data. Baseline characteristics of the patients are presented as mean $\pm$ standard deviation and number/percentage. The chi-square and Student's t-test were used to assess differences between the surgery and matched groups.

We used the univariate and multivariate logistic regression analyses to evaluate the risk factors for surgically treated AAS development. The covariates were sex, age at RA diagnosis, RF positivity, MTX use, CRP level, and time interval between RA diagnosis and radiographic hand joint erosion.

We used the univariate linear regression analysis to evaluate the potential associations of variables with the time interval between RA diagnosis and AAS surgery. We then entered covariates into the multivariate analysis to identify the independent association of each variable with the time interval between RA

diagnosis and AAS surgery.

Regression lines with 95% confidence intervals (CIs) and box plots were used to graphically present the associations of sex, time interval between RA diagnosis and hand joint erosion, age at surgery, and time interval between RA diagnosis and MTX initiation with the time interval between RA diagnosis and AAS surgery.

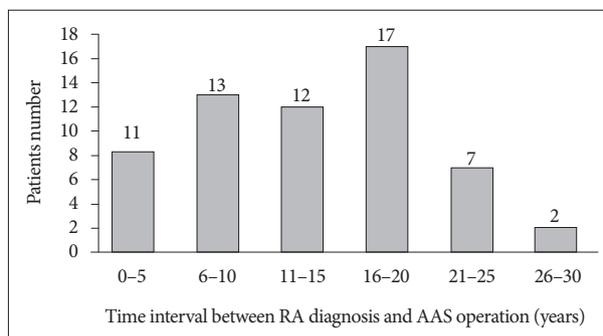
All statistical analyses were performed using R software (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria) and SPSS software for Windows (version 22.0; IBM Corp., Armonk, NY, USA). A *p*-value <0.05 was considered statistically significant.

## RESULTS

The characteristics of the 124 study patients are presented in Table 2. The time interval between RA diagnosis and radiographic hand joint erosion was lower in the surgery group than in the matched group (2.9±2.9 years vs. 4.0±3.3 years, *p*=0.042). Additionally, the CRP level at RA diagnosis was higher in the surgery group than in the matched group (4.0±3.7 vs. 1.9±2.3, *p*<0.001). However, there were no significant differences in RF positivity and MTX use between the 2 groups. In the surgery group, the mean age of the patients at surgery was 52.1 years, and the mean

time interval between RA diagnosis and AAS surgery was 13.6 years. Fig. 1 shows the number of surgically treated patients stratified into 6 categories based on a 5-year time interval between RA diagnosis and AAS surgery. Additionally, the mean time interval between RA diagnosis and radiographic hand joint erosion was 2.5 years.

To evaluate the total incidence of cervical spine subluxation, we assessed the patients according to “mild” and “severe” condi-



**Fig. 1.** The number of surgically treated patients stratified into 6 categories based on a 5-year time interval between RA diagnosis and AAS surgery. A total of 53 (85.4%) patients underwent surgical treatment less than 20 years after RA diagnosis. RA : rheumatoid arthritis, AAS : atlantoaxial subluxation.

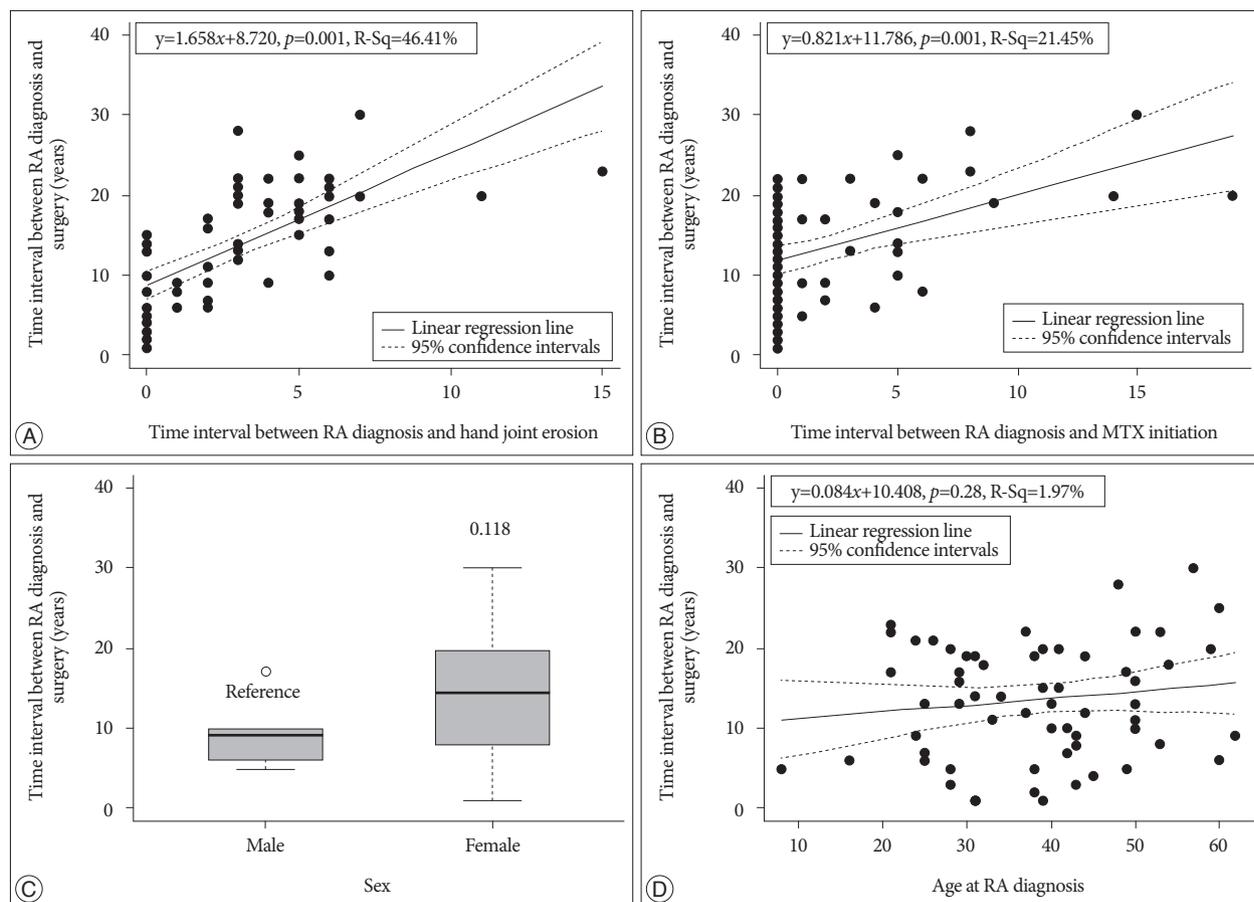
**Table 2.** Characteristics of the study patients

Variables	Total (n=124)	Surgery group (n=62)	Matched group (n=62)	<i>p</i> -value
Sex				1.000
Female	113 (91.1%)	56 (90.3%)	57 (91.9%)	
Male	11 (8.9%)	6 (9.7%)	5 (8.1%)	
Age at RA diagnosis, y	39.8±12.2	38.0±11.9	41.6±12.4	0.098
Age at surgery, y	-	52.1±12.6	-	-
RF				0.685
Negative	33 (26.6%)	18 (29.0%)	15 (24.2%)	
Positive	91 (73.4%)	44 (71.0%)	47 (75.8%)	
MTX				0.680
No	6 (4.8%)	2 (3.2%)	4 (6.5%)	
Yes	118 (95.2%)	60 (96.8%)	58 (93.5%)	
Time interval between RA diagnosis and radiographic hand joint erosion, y	3.5±3.1	2.9±2.9	4.0±3.3	0.042
aADI, mm	4.4±3.2	7.1±2.4	1.7±0.8	0.000
aADI classification				
0.0-2.9	62 (50.0%)	-	62 (100.0%)	
3.0-5.0	12 (9.7%)	12 (19.4%)	-	
5.1-7.5	27 (21.8%)	27 (43.5%)	-	
7.6-10.0	15 (12.1%)	15 (24.2%)	-	
>10.0	8 (6.4%)	8 (12.9%)	-	
CRP level, mg/dL	2.9±3.2	4.0±3.7	1.9±2.3	0.000
Time interval between RA diagnosis and AAS surgery, y	-	13.6±7.0	-	-
Time interval between RA diagnosis and AAS diagnosis, y	-	11.0±6.9	-	-
Time interval between AAS diagnosis and AAS surgery, y	-	2.5±2.7	-	-

Data are presented as mean±standard deviation or number (percentage). RF : rheumatoid factor, RA : rheumatoid arthritis, MTX : methotrexate, aADI : anterior atlantodental interval, CRP : C-reactive protein, AAS : atlantoaxial subluxation

tions. We found that 100% of the patients had AAS, 17.8% had VS, 29.1% had SAS, and 40.3% had basilar invagination, with some overlap. There was no evidence of severity associations among instabilities, and we found that all severe SAS patients had mild AAS (Table 3).

In multivariate logistic regression analysis, age at RA diagnosis [odds ratio (OR), 0.97; 95% CI, 0.94–1.00;  $p=0.049$ ], CRP level (OR, 3.21; 95% CI, 1.41–7.30;  $p=0.005$ ), and time interval between RA diagnosis and radiographic hand joint erosion (OR, 0.83; 95% CI, 0.72–0.96;  $p=0.009$ ) were identified as risk factors



**Fig. 2.** A : In scatterplot graph, the linear regression line shows a statistically significant overall gradual upward slope, which means the time to surgery reduces by 1.658 years when the time to radiographic hand joint erosion reduces by 1 year. B : In scatterplot graph, the linear regression line shows a statistically significant overall gradual upward slope, indicating that patients who started MTX early required early surgery. C : The boxplot graph shows the mean time interval between RA diagnosis and AAS surgery was 4.7 years greater in female patients than in male patients. D : In scatterplot graph, the linear regression line shows an upward trend, indicating that patients who are diagnosed with RA at a young age might require early AAS surgery. RA : rheumatoid arthritis, AAS : atlantoaxial subluxation.

**Table 3.** Descriptive statistics according to the atlantoaxial subluxation subgroups

Atlantoaxial subluxation	Total (n=62)	Mild (aADI ≤10 mm) (n=54)	Severe (aADI >10 mm) (n=8)	p-value
Vertical subluxation	11 (17.8%)			0.838
No	51 (82.2%)	44 (81.5%)	7 (87.5%)	
Mild (10<ranawat value ≤13)	9 (14.5%)	8 (14.8%)	1 (12.5%)	
Severe (ranawat value ≤10)	2 (3.3%)	2 (3.7%)	0 (0.0%)	
Subaxial subluxation	18 (29.1%)			0.153
No	44 (70.9%)	36 (66.7%)	8 (100.0%)	
Mild (2 ≤ irreducible translation <4)	14 (22.6%)	14 (25.9%)	0 (0.0%)	
Severe (irreducible translation ≥4)	4 (6.5%)	4 (7.4%)	0 (0.0%)	
Basilar invagination	25 (40.3%)			0.575
No	37 (59.7%)	31 (57.4%)	6 (75.0%)	
Yes	25 (40.3%)	23 (42.6%)	2 (25.0%)	

Data are presented as number (percentage). aADI : anterior atlantodental interval

**Table 4.** Risk factors to predict surgically treated AAS development in patients with rheumatoid arthritis

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Sex (reference=male)	0.82 (0.24–2.84)	0.752	0.91 (0.24–3.45)	0.888
Age at RA diagnosis (per 1-year increase)*	0.98 (0.95–1.01)	0.099	0.97 (0.94–1.00)	0.049
RF positivity	0.78 (0.35–1.74)	0.543	0.67 (0.27–1.65)	0.382
MTX use	2.07 (0.37–11.73)	0.412	2.86 (0.43–19.18)	0.280
CRP level (>0.8 mg/dL)	2.70 (1.27–5.74)	0.010	3.21 (1.41–7.30)	0.005
Time interval (per 1-year increase)*	0.88 (0.78–0.99)	0.047	0.83 (0.72–0.96)	0.009

\*Time interval between RA diagnosis and radiographic hand joint erosion. RA : rheumatoid arthritis, AAS : atlantoaxial subluxation, OR : odds ratio, CI : confidence interval, RF : rheumatoid factor, MTX : methotrexate, CRP : C-reactive protein

**Table 5.** Univariate and multivariate linear regression analyses of the associations of various patient factors with the time interval between RA diagnosis and AAS surgery

Variable	Univariate linear regression			Multivariate linear regression				
	$\beta$	SE	<i>p</i>	Intercept	$\beta$	SE	<i>p</i>	R <sup>2</sup>
Sex (reference=male)	4.738	2.988	0.118		4.634	2.287	0.048	
Age at RA diagnosis	0.084	0.076	0.277		0.125	0.060	0.044	
RF	1.725	1.974	0.386		2.384	1.487	0.115	
Time interval between RA diagnosis and MTX initiation	0.821	0.203	<0.001		0.276	0.199	0.172	
Time interval between RA diagnosis and radiographic hand joint erosion	1.658	0.230	<0.001	0.498	1.470	0.270	<0.001	0.568
aADI	-0.289	0.383	0.454		-0.282	0.278	0.314	
CRP level	0.328	0.242	0.180		-0.121	0.194	0.534	

RA : rheumatoid arthritis, AAS : atlantoaxial subluxation, SE : standard error, R<sup>2</sup> : coefficient of determination, RF : rheumatoid factor, MTX : methotrexate, aADI : anterior atlantodental interval, CRP : C-reactive protein

for surgically treated AAS development in RA patients (Table 4).

Fig. 2A presents a scatterplot for the time interval between RA diagnosis and hand joint erosion and the time interval between RA diagnosis and AAS surgery for all patients, with a linear regression line with 95% CIs. The linear regression line shows a statistically significant overall gradual upward slope ( $\beta=1.658$ ,  $SE=0.230$ ,  $p<0.001$ ), and the time to surgery reduces by 1.658 years when the time to radiographic hand joint erosion reduces by 1 year, indicating that patients with early hand joint erosion required early surgery. Fig. 2B presents a scatterplot for the time interval between RA diagnosis and MTX initiation and the time interval between RA diagnosis and AAS surgery for all patients, with a linear regression line with 95% CIs. The linear regression line shows a statistically significant overall gradual upward slope ( $\beta=0.821$ ,  $SE=0.203$ ,  $p<0.001$ ), indicating that patients who started MTX early required early surgery.

In multivariate linear regression analysis, after complete adjustment, the time interval between RA diagnosis and radiographic hand joint erosion ( $\beta=1.470$ ,  $SE=0.270$ ,  $p<0.001$ ), age at RA diagnosis ( $\beta=0.125$ ,  $SE=0.060$ ,  $p=0.044$ ), and sex ( $\beta=4.634$ ,  $SE=2.287$ ,  $p=0.048$ ) were identified as risk factors for AAS progression (Table 5). However, the time interval between RA diagnosis and MTX initiation ( $p=0.172$ ), RF seropositivity ( $p=0.115$ ), the serum level of CRP ( $p=0.534$ ), and the anterior ADI ( $p=0.314$ ) were not significantly associated with disease progression (Table 5). Fig. 2C presents a boxplot for sex and the time interval between RA diagnosis and AAS surgery. We found that the mean

time interval between RA diagnosis and AAS surgery was 4.7 years greater in female patients than in male patients. Fig. 2D presents a scatterplot for age at RA diagnosis and the time interval between RA diagnosis and AAS surgery. The linear regression line shows an upward trend ( $\beta=0.084$ ,  $SE=0.076$ ,  $p=0.277$ ), indicating that patients who are diagnosed with RA at a young age might require early AAS surgery.

## DISCUSSION

RA is a chronic systemic inflammatory disease, and cervical spine involvement may cause severe complications, such as headache, neck pain, upper extremity paresthesia, and death<sup>7,19</sup>. The prevalence of cervical spine involvement has been shown to range from 16% to 70.4%, and AAS has been reported to be the most common abnormal finding<sup>1,4,24</sup>. The risk factors for cervical involvement have been shown to be peripheral hand or foot joint erosion<sup>1,4,24</sup>, disease-modifying antirheumatic drug (DMARD) failure<sup>4</sup>, corticosteroid use<sup>24</sup>, and age at RA diagnosis<sup>1</sup>. Additionally, our study found that the CRP level and time interval between RA diagnosis and radiographic hand joint erosion were risk factors for surgically treated AAS development.

The natural course of conservatively treated rheumatoid patients with myelopathy is poor<sup>15,21</sup>, and surgical decompression with fusion should be considered in such patients. Our study identified a short time interval between RA diagnosis and radiographic hand joint erosion and young age at RA diagnosis as

risk factors for early surgical treatment. We believe that this is the first study to evaluate the risk factors for AAS progression in surgically treated RA patients, considering the time interval between RA diagnosis and AAS surgery.

A short time interval between RA diagnosis and radiographic hand joint erosion was associated with surgically treated AAS development ( $p=0.009$ ) in RA patients and progression ( $p<0.001$ ) in patients with surgically treated AAS. Previous studies have shown that radiographic hand and foot joint erosion in radiographs was the most common risk factor for cervical involvement in RA patients<sup>1,4,10,24</sup>. Proliferative and erosive synovitis progresses to destruction of the articular cartilage, especially in metatarsophalangeal joints, which are the most commonly involved joints<sup>10</sup>, and the cervical spine is the second most commonly involved region. The same pathophysiology affects the hand joints and upper cervical region, and patients with hand joint erosion tend to have cervical involvement and early progression of subluxation.

We noted a significant association between young age at RA diagnosis and early AAS surgery ( $p=0.044$ ). A previous study showed that RA diagnosis at  $\leq 45$  years of age was a risk factor for cervical involvement<sup>1</sup>. Although patients with RA diagnosis at a young age received conservative treatment, including combination therapy of DMARDs and corticosteroids, this treatment could not protect against the progression of the disease after the start of erosive changes.

The time interval between RA diagnosis and AAS surgery was lower in male patients than in female patients ( $p=0.048$ ), although the number of female patients was significantly greater than the number of male patients. However, the small number of male patients in the study might lower the statistical power, and there is a possibility that these findings are incidental owing to the small sample size.

In univariate analysis, the time interval between RA diagnosis and MTX initiation was associated with the time interval between RA diagnosis and AAS surgery ( $p<0.001$ ); however, in multivariate analysis, it was not a significant risk factor for early surgery ( $p=0.172$ ). The time interval between RA diagnosis and hand joint erosion and the time interval between RA diagnosis and MTX initiation were associated, indicating that patients with early hand joint erosion received MTX early ( $R=0.44$ ,  $p=0.00$ , Pearson correlation analysis). Therefore, if a patient has a severe condition at RA diagnosis, combination medication, including MTX, is initiated. A previous study reported that adequate treatment with DMARDs and biological agents (BAs) prevented the development of cervical spine disease, but probably did not prevent the progression of pre-existing injury<sup>10</sup>. Additionally, another study reported that among patients who were administered MTX, only 8.3% without baseline instability developed instability, while 80% with baseline instability showed progression of instability<sup>11,24</sup>. Therefore, MTX can protect against the new onset of erosive synovitis; however, MTX cannot delay the progression of instability once destruction has started.

We found that the RF seropositivity was not a potential risk factor for surgically treated AAS development ( $p=0.382$ ) in RA patients and early surgical treatment ( $p=0.115$ ) in patients with surgically treated AAS. However, a previous study has noted RF positivity as a risk factor for disease progression<sup>7</sup>. The serum CRP level was a significant risk factor for surgically treated AAS development ( $p=0.005$ ) in RA patients, while it was not associated with disease progression in surgically treated AAS patients. Previous studies have identified a high serum CRP level as a risk factor for disease progression, and the CRP level was previously found to be very sensitive to changes in disease activity<sup>7,22</sup>.

The present study has several limitations. As this was a retrospective study, the findings may not be as accurate as the findings of a prospective study. In addition, owing to the small number of patients in our study and the data heterogeneity between the surgery group and control group because of data extraction from different databases at different periods, there might be low statistical power. All age ranges were included in the surgery group and patients aged  $\geq 18$  years were included in the control group. Moreover, this study focused on MTX, and other treatments, such as other DMARDs, BA, and corticosteroids, were not assessed. In future studies, larger number of patients should be included to confirm the risk factors for the prevalence of cervical involvement and progression of subluxation. Additionally, other medications should be assessed to determine their effects on disease progression.

## CONCLUSION

The CRP level at RA diagnosis and a short time interval between RA diagnosis and radiographic hand joint erosion might be risk factors for surgically treated AAS development in RA patients. Additionally, a short time interval between RA diagnosis and radiographic hand joint erosion and young age at RA diagnosis might be risk factors for rapid progression of AAS. Immediately after RA diagnosis, patients should be treated with DMARDs and corticosteroids before radiographic changes are noted in the hand joints and cervical spine, especially at a young age. Examinations, such as radiographic evaluation of the peripheral joints and cervical spine and evaluation of inflammatory markers, should be performed annually in patients with RA to assess the development of cervical spine instability, which will help in treatment.

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