# Factors associated with radiographic progression in patients with Takayasu's arteritis

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## ABSTRACT

**Objective.** *To identify the factors related to radiographic progression in patients with Takayasu's arteritis (TAK).*

**Methods.** *A retrospective cohort study was conducted among patients with TAK who underwent computed tomography angiography (CTA) at least twice in a 2-5-year interval. Radiographic progression was defined as newly developed and/or aggravated (more than 20%) characteristic CTA findings. Correlation analysis was performed using a multivariate Cox regression model.*

**Results.** *The cohort included 153 TAK patients with a mean CTA interval of 3.53 years, and 24 (15.7%) showed radiographic progression. Those with progression showed higher acute-phase reactant levels (erythrocyte sedimentation rate [ESR], 26.06 vs. 35.72 mm/h, p=0.040; C-reactive protein [CRP], 0.45 vs. 1.13 mg/dL, p<0.001), were younger at the initial CTA (43.70 vs. 31.81 years, p<0.001), and were more likely to be receiving immunosuppressants (14 [10.9%] vs. 7 [29.2%] patients, p=0.038). Multivariate Cox regression analysis revealed age at the initial CTA (hazard ratio [HR]=0.945, confidence interval [CI]=0.898–0.995, p=0.030) and area under the curve (AUC) of CRP levels (HR=2.126, CI=1.046–4.319, p=0.037) as significant factors for radiographic progression. In a subgroup of patients with high CRP levels, 30.4% (14/24) showed progression; only age at the initial CTA was significantly different (37.03 vs. 27.10 years, p=0.012) between those with and without progression.*

**Conclusion.** *Higher CRP levels and younger age were risk factors of radiographic progression in patients with TAK. In the high CRP group, younger patients are more prone to progression and may need aggressive anti-inflammatory treatment.*

## Introduction

Takayasu's arteritis (TAK) is a chronic, idiopathic inflammatory disease that primarily affects large-vessels such as the aorta and its main branches (1, 2). Chronic inflammation in vessel walls may lead to stenosis and/or occlusion of the involved arteries and less frequently, aneurysm formation or dilatation (3-5). Disease extent can be evaluated by modalities such as computed tomography angiography (CTA) (6-8). Previous studies on TAK have described the characteristic patterns of radiographic involvement. However, data on clinical aspects affecting radiographic progression are scarce because of the lack of an appropriate definition of radiographic progression in patients with TAK.

A few cohort studies on patients with TAK (9-14) have described clinical outcomes and revealed the factors related to survival (12, 13), morbidities (10, 13, 14), and disease activity (9, 15). However, the association between any clinical factor and radiographic progression has not yet been validated. Patients with TAK frequently exhibit relatively obscure disease activity owing to the deep position of large-vessels. Understanding the factors affecting radiographic progression may allow us to identify specific patient populations that require more aggressive treatment than others.

Therefore, we assessed radiographic progression in patients with TAK and described the nature of progression. Furthermore, we analysed the factors related to radiographic progression.

## Materials and methods

*Study population*

We retrospectively reviewed the medical records of patients who visited Samsung Medical Center, a tertiary referral hospital in Seoul, South Korea, between March 2002 and December

2019. All patients fulfilled the 1990 American College of Rheumatology criteria (16) or Sharma criteria (17) (modified Ishikawa criteria) (18) for TAK. The patients included in this study had undergone CTA of the aorta and its major branches at least twice in a 2-5-year interval. Patients with other causes of large-vessel abnormalities, including inflammatory aortitis (giant cell arteritis, IgG4-related disease, spondyloarthropathies, systemic lupus erythematosus, rheumatoid arthritis, Buerger's disease, Behçet's disease, Cogan's disease, Kawasaki disease, and infectious aortitis), developmental anomalies (Ehlers-Danlos syndrome and Marfan syndrome), and other aortic abnormalities (neurofibromatosis, ergotism, and radiation fibrosis), were excluded. In addition, the following patients were excluded: those who had co-morbidities that could increase inflammatory marker levels, infection, malignancy, or rheumatologic diseases other than TAK; those who underwent operation in the CTA follow-up period; and those without sufficient baseline clinical data.

*Baseline and follow-up measurements*

Baseline data, including data on age at the initial CTA, sex, disease duration, height, body weight, hypertension (HTN), diabetes mellitus, dyslipidemia, chronic kidney disease, acute phase reactants, pattern of vascular involvement, immunosuppressant use, and steroid use, were obtained. Acute-phase reactants included erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] levels. In case of acute-phase reactants, we used data of the area under the curve (AUC) during the CTA follow-up rather than the baseline data. The pattern of vascular involvement was defined as per angiographic classification according to the International Takayasu arteritis Conference in Tokyo 1994 classification (19).

*Definition of radiographic progression*

A few methods have been developed to measure the activity of large-vessel vasculitis. For example, the Birmingham Vasculitis Activity Score (BVAS) (20), the Disease Extent Index for TA (DEI-TaK) (21), and the Indian TAK Score (ITAS) 2010 (22) have been used in clinical research for TA. The OMERACT Vasculitis Working Group performed a Delphi exercise for the assessment of disease activity in TAK to develop a core set of validated outcome measures (23-25). However, the definition of radiographic progression in TAK is still lacking. Thus, we defined radiographic progression for CTA as one of the followings: 1) progression of existing stenotic lesions, vessel wall thickening, or aneurysmal changes; 2) newly developed stenotic lesions, vessel wall thickening, or aneurysmal changes; and 3) increased diameter of the aorta. This definition was based on the characteristic radiographic changes reported in previous studies (3-6). Progression of an existing stenotic lesion was defined as luminal narrowing of more than 20% as compared with the baseline value. Similarly, progression of existing vessel wall thickening and aneurysmal changes and increased diameter of the aorta were defined as a more than 1.2-fold increase compared with the baseline values. In case of vessel wall thickening, progression was determined only when the thickness increased by more than 1 mm while considering the CTA resolution.

*Statistical analysis*

Continuous variables were compared using the Student's *t*-test, and categorical variables were analysed by a chi-square test. Correlation analyses were performed by a multivariate Cox regression analysis. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). All statistical analyses were performed using R software (version 3.6.3). A value of $p<0.05$ (two-sided) indicated significant differences.

*Ethics*

Data was extracted from the Clinical Data Warehouse Darwin-C of Samsung Medical Center for this study. This study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, South Korea (IRB No.: 2019-04-001) and the informed consent requirement was waived by the IRB, because the study information was de-identified.

## Results

*Clinical characteristics of the study subjects*

In total, 153 patients with TAK met the inclusion criteria between 2002 and 2019. The clinical characteristics of these patients are shown in Table I. Mean age at the initial CTA was 41.84±12.98 years, and 134 (87.6%) patients were female. Type V (93 patients, 60.8%) was the most common pattern, followed by type IIb (15.7%) and type IIa (13.1%). Mean interval between the initial CTA and follow-up CTA was 3.53±0.89 years. The numbers of patients receiving immunosuppressants and steroids during follow-up were 21 (13.7%) and 53 (34.6%), respectively. The AUCs for ESR and CRP levels during follow-up were 28.23±19.54 mm/h and 0.56±0.86 mg/dL, respectively.

The clinical characteristics of patients according to radiographic progression are shown in Table I. Twenty-four patients (15.7%) showed radiographic progression between the initial and follow-up CTA. Patients with radiographically progressive disease had higher ESR (26.06 *vs*. 35.72 mm/h, $p=0.040$) and CRP levels (0.45 *vs*. 1.13 mg/dL, $p<0.001$), were younger at the initial CTA (43.70 *vs*. 31.81 years, $p<0.001$), and were more likely to be receiving immunosuppressants (14 [10.9%] *vs*. 7 [29.2%] patients, $p=0.038$) than those without. Steroid use showed a borderline difference (40 [31.0%] *vs*. 13 [54.2%] patients, $p=0.050$). Other clinical characteristics showed no significant differences between the two groups.

*Characteristics of radiographic progression in patients with TAK*

We categorised patients based on different types of radiographic progression. The numbers of patients with progression of a pre-existing lesion, newly developed lesions, increased diameter of the aorta, and progression of multiple lesions were 15, 4, 1, and 4, respectively (Supplementary Table

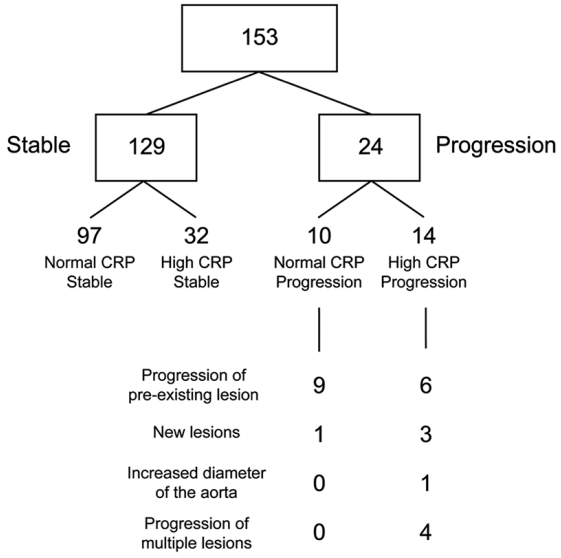
**Table I.** Clinical characteristics of the cohort and the comparison of characteristics according to radiographic progression.

| | | Overall | Radiographic progression | | *p*-value |
|---|---|---|---|---|---|
| | | (n=153) | Stable (n=129, 84.3%) | Progression (n=24, 15.7%) | |
| Sex (female, %) | | 134 (87.6) | 112 (86.8) | 22 (91.7) | 0.746 |
| Age at the initial CTA (year) | | 41.84 (12.98) | 43.70 (12.22) | 31.81 (12.57) | < 0.001 |
| Disease duration (year) | | 4.03 (6.28) | 4.24 (6.59) | 2.90 (4.16) | 0.337 |
| Height (cm) | | 160.14 (7.11) | 159.94 (7.01) | 161.21 (7.71) | 0.434 |
| Body weight (kg) | | 57.44 (9.42) | 57.60 (9.72) | 56.56 (7.66) | 0.629 |
| HTN (%) | | 97 (63.4) | 85 (65.9) | 12 (50.0) | 0.210 |
| DM (%) | | 6 (3.9) | 5 (3.9) | 1 (4.2) | > 0.999 |
| Dyslipidemia (%) | | 69 (45.1) | 62 (48.1) | 7 (29.2) | 0.138 |
| CKD (%) | | 5 (3.4) | 4 (3.2) | 1 (4.3) | > 0.999 |
| AUC of CRP (mg/dL) | | 0.56 (0.86) | 0.45 (0.68) | 1.13 (1.36) | < 0.001 |
| AUC of ESR (mm/h) | | 28.23 (19.54) | 26.80 (17.80) | 35.72 (26.06) | 0.040 |
| Type of vascular involvement (%) | | | | | 0.294 |
| | I | 9 (5.9) | 9 (7.0) | 0 (0.0) | |
| | IIa | 20 (13.1) | 14 (10.9) | 6 (25.0) | |
| | IIb | 24 (15.7) | 21 (16.3) | 3 (12.5) | |
| | III | 4 (2.6) | 3 (2.3) | 1 (4.2) | |
| | IV | 3 (2.0) | 2 (1.6) | 1 (4.2) | |
| | V | 93 (60.8) | 80 (62.0) | 13 (54.2) | |
| Azathioprine (%) | | 5 (3.3) | 4 (3.1) | 1 (4.2) | > 0.999 |
| Methotrexate (%) | | 17 (11.1) | 10 (7.8) | 7 (29.2) | 0.007 |
| Tacrolimus (%) | | 1 (0.7) | 1 (0.8) | 0 (0.0) | > 0.999 |
| Leflunomide (%) | | 2 (1.3) | 1 (0.8) | 1 (4.2) | 0.715 |
| Infliximab (%) | | 1 (0.7) | 1 (0.8) | 0 (0.0) | > 0.999 |
| Cyclophosphamide (%) | | 1 (0.7) | 1 (0.8) | 0 (0.0) | > 0.999 |
| Immunosuppressant use (%) | | 21 (13.7) | 14 (10.9) | 7 (29.2) | 0.038 |
| Steroid use (%) | | 53 (34.6) | 40 (31.0) | 13 (54.2) | 0.050 |
| CTA interval (year) | Mean (SD) | 3.53 (0.89) | 3.56 (0.90) | 3.35 (0.85) | 0.281 |
| | Median (Q1-3) | 3.66 (2.81–4.27) | 3.70 (2.98–4.32) | 3.00 (2.74–4.15) | 0.213 |

Values are expressed as n (%) or mean (SD), unless specified otherwise.
CTA: computed tomography angiography; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; AUC: area under the curve; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SD: standard deviation.

S1). As shown in Figure 1, patients with new lesions, increased diameter of the ascending aorta, and progression of multiple lesions tended to show high CRP levels. Therefore, we divided the radiographic progression group into two groups and compared their characteristics: progression of pre-existing lesions and others. Only the levels of acute-phase reactants (AUC of ESR and CRP levels) were significantly different between the two groups (ESR, 27.16 *vs*. 49.99 mm/h, $p$=0.034; CRP levels, 0.69 *vs*. 1.85 mg/dL, $p$=0.040; Supplementary Table S2). The high acute-phase reactant group presented new lesions or the progression of multiple lesions more frequently than the low acute-phase reactant group.

**Fig. 1.** Radiographic progression and the levels of acute-phase reactants (high CRP: AUC of CRP levels ≥ 0.5 mg/dL).




*Factors related to radiographic progression in patients with TAK*

We aimed to identify the factors associated with radiographic outcomes in patients with TAK. Patients were divided into two groups: those with radiographic progression and those with radiographically stable disease. A multivariate Cox regression analysis was conducted using all clinical variables. Age at the initial CTA (HR = 0.945, CI = 0.898–0.995, $p$=0.030) and AUC of CRP levels (HR = 2.126, CI = 1.046–4.319, $p$=0.037) were identified as independent significant factors for radiographic progression in patients with TAK (Table II). The AUC of ESR and

**Table II.** Cox regression analysis to predict radiographic progression in patients with Takayasu's arteritis.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | *p* | HR | 95% CI | *p* |
| Sex | 0.673 | 0.156–2.906 | 0.596 | 0.259 | 0.034–1.963 | 0.191 |
| Age at the initial CTA | 0.946 | 0.915–0.978 | 0.001 | 0.945 | 0.898–0.995 | 0.030 |
| Disease duration | 0.966 | 0.889–1.048 | 0.403 | 0.971 | 0.874–1.079 | 0.589 |
| Height | 1.014 | 0.958–1.073 | 0.630 | 1.034 | 0.930–1.149 | 0.541 |
| Body weight | 0.989 | 0.946–1.035 | 0.632 | 0.996 | 0.034–1.061 | 0.890 |
| HTN | 0.747 | 0.333–1.674 | 0.479 | 2.077 | 0.711–6.063 | 0.181 |
| DM | 1.796 | 0.241–13.370 | 0.567 | 2.174 | 0.160–29.524 | 0.560 |
| Dyslipidemia | 0.591 | 0.245–1.430 | 0.244 | 2.183 | 0.606–7.868 | 0.233 |
| CKD | 1.053 | 0.141–7.856 | 0.960 | 0.801 | 0.088–7.277 | 0.844 |
| AUC of CRP | 1.852 | 1.384–2.478 | <0.001 | 2.126 | 1.046–4.319 | 0.037 |
| AUC of ESR | 1.021 | 1.004–1.038 | 0.015 | 0.987 | 0.954–1.021 | 0.454 |
| Type of vascular involvement | 0.842 | 0.647–1.096 | 0.202 | 0.877 | 0.627–1.228 | 0.445 |
| Immunosuppressant use | 3.204 | 1.304–7.873 | 0.011 | 1.150 | 0.275–4.809 | 0.848 |
| Steroid use | 2.583 | 1.129–5.908 | 0.025 | 0.801 | 0.231–2.776 | 0.726 |

HR: hazard ratio; CI: confidence interval; CTA: computed tomography angiography; HTN: hypertension; DM: diabetes mellitus; CKD: chronic kidney disease; AUC: area under the curve; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

immunosuppressant use, the clinical variables showing significant differences between those with and without progression, were not found to be significant factors in multivariate analysis.

### *Clinical characteristics of patients according to acute-phase reactant levels*

We divided the patients into two groups based on the level of CRP: the high CRP group (defined as a CRP AUC value equal to or greater than 0.5 mg/dL) and low CRP group (defined as a CRP AUC value lower than 0.5 mg/dL). Fourteen (30.4%) and 10 (9.3%) patients in the high CRP and low CRP groups showed radiographic progression, respectively. We compared the clinical characteristics of patients according to radiographic progression in each group. In the high CRP group, only age at the initial CTA (37.03 *vs*. 27.10 years, $p$=0.012) was significantly different (Supplementary Table S3). The AUC of CRP levels lost its significance in this subgroup analysis (1.38 *vs*. 1.80 mg/dL, $p$=0.219), and no significant difference according to radiographic progression was observed among patients in the low CRP group (Supplementary Table S4).

## Discussion

TAK is a chronic, autoimmune, systemic vasculitis of unknown aetiology. Vascular inflammation can lead to stenosis and/or occlusion of the involved arteries and less frequently, aneurysm formation or dilatation (3-5). In patients with active inflammation, the affected vessels may show wall thickening (6). TAK mainly involves the aorta and its branches, which are located deep inside the body; thereby non-invasive radiographic modalities such as CTA or magnetic resonance angiography are the key techniques for evaluating disease extent (7, 8, 26). In practice, radiographic modalities have been frequently used not only for diagnosis but also to assess disease progression and activity (27-29). However, no study has identified the clinical factors that could affect radiographic progression, probably owing to the absence of a validated definition of radiographic progression. Therefore, in this study, we defined radiographic progression based on the characteristic radiographic changes reported in previous studies. As previously mentioned, vascular stenosis, occlusion, aneurysmal change, and luminal dilatation may be observed in patients with TAK. Therefore, we defined new and/or aggravated existing stenotic lesions, vessel wall thickening, aneurysmal changes, and dilatation of the aorta as radiographic progression.

To the best of our knowledge, this is the first study to analyse the factors associated with radiographic progression in patients with TAK. We assessed the radiographic outcomes of 153 patients. At a mean CTA interval of 3.5 years, 24 of 153 (15.7%) patients showed radiographic progression. Ten of these 24 patients had normal CRP levels throughout follow-up but showed radiographic progression. Among 46 patients who had high CRP levels (defined as a CRP AUC value higher than or equal to 0.5 mg/dL during follow-up), only 14 (30.4%) patients showed radiographic progression. Although the use of acute-phase reactants is frequently advocated in TA disease assessment, acute-phase reactants alone were found to be neither sensitive nor specific enough for monitoring disease activity (14, 30). One study has shown that TA can progress even in individuals with normal levels of inflammatory markers (31) and that acute-phase reactants alone cannot be used to measure disease activity.

Vascular stenosis and vessel wall thickening have been reported not only in inflammatory diseases such as TAK but also in degenerative disorders such as atherosclerosis (32). Several distinguishing points (8, 33) need to be noted. First, atherosclerotic plaques are usually not associated with long segment luminal stenosis and tend to be common in older patients. Second, calcification in the ascending aorta can be observed in some patients with TAK but is rare in patients with atherosclerosis. However, degenerative changes are difficult to differentiate in some cases and may be a confounding factor of association. In the present study, the clinical variables

associated with degenerative changes, such as HTN and dyslipidemia, were more frequent in patients with radiographically stable disease. Moreover, patients who had progressive disease were significantly younger at the initial CTA. Thus, degenerative changes may not be likely to affect the results of correlation analysis.

We divided radiographic progression into four categories as follows: progression of pre-existing lesions, new lesions, increased diameter of the aorta, and progression of multiple lesions. All four categories of radiographic progression were reported in patients with high CRP levels. However, only one individual with a normal CRP level showed progression in a form other than the progression of pre-existing lesions (a new lesion). Thus, the lesions tend to be more severe when the level of CRP is high.

The comparison of clinical features based on radiographic progression revealed acute-phase reactant levels (AUC of CRP levels and AUC of ESR), age at the initial CTA, and immunosuppressant use to be significantly different between the two groups. Among these clinical variables, the AUC of CRP levels and age at the initial CTA were related to radiographic progression in the multivariate Cox regression analysis. The AUC of CRP levels was correlated with increased radiographic progression (HR = 2.126) as expected, but no prior study has analysed this association. In contrast, age at the initial CTA was found to be correlated with decreased radiographic progression (HR = 0.945), showing that younger patients were more likely to show progression. We also compared clinical features according to radiographic progression in subgroups based on acute-phase reactant levels (cut-off value of the AUC of CRP levels was 0.5 mg/dL). Among patients with high CRP levels, only age at the initial CTA was significantly different ($p$=0.012) between the two radiographic groups. Conversely, some important factors such as AUC of ESR, immunosuppressant use, and steroid use that presumably affect radiographic progression were significantly different between the stable and progression groups, as analysed by the $t$-test (borderline $p$-value in steroid use), and showed a relationship in the univariate regression analysis. However, these factors were not significant in the multiple regression analysis. This observation suggests that these factors may be only predictive, given their associations with other predictors. Interestingly, the statistical significance for the AUCs of CRP levels and ESR was lost in this subgroup analysis. As mentioned earlier, only 30% of patients with high CRP levels showed radiographic progression. Therefore, with respect to radiographic changes, younger patients with high acute-phase reactant levels can be a good target for aggressive treatment.

This study has a few limitations. First, considering its retrospective design, we could not include a few interesting clinical factors such as carotidynia, fever, and smoking status in our analysis. Thus, we could not exclude the potential bias caused by unmeasured confounders. Second, the definition of radiographic progression of TAK had not been validated in previous studies. However, because there was no previously validated definition of radiographic progression of TAK, setting our own definition was inevitable.

In conclusion, the present study shows that patients with radiographically progressed TAK had higher acute-phase reactant levels, were younger at the initial CTA, and were more likely to be receiving immunosuppressants than those without. Multivariate Cox regression analysis revealed the AUC of CRP levels and age at the initial CTA as significant factors for radiographic progression. Among patients who had high CRP levels, age at the initial CTA was the only clinical variable significantly different between patients with and without progression. Therefore, younger patients may need more aggressive anti-inflammatory treatment.

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