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# Vascular Uptake on $^{18}$F-FDG PET/CT During the Clinically Inactive State of Takayasu Arteritis Is Associated with a Higher Risk of Relapse

Oh Chan Kwon[1], Tae Joo Jeon[2], and Min-Chan Park[1]

[1]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;
[2]Department of Nuclear Medicine, Yonsei University College of Medicine, Seoul, Korea.

**Purpose:** To evaluate whether vascular uptake on $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) during the clinically inactive state of Takayasu arteritis (TAK) is associated with disease relapse.

**Materials and Methods:** Patients with TAK who underwent $^{18}$F-FDG PET/CT during the clinically inactive state of the disease between 2006 and 2019 were included. Clinically inactive disease was defined as a status not fulfilling the National Institutes of Health (NIH) criteria for active disease in TAK. Relapse was defined as recurrence of clinically active disease after a clinically inactive period, requiring change in the treatment regimen. Vascular uptake on $^{18}$F-FDG PET/CT was assessed using target/background ratio (TBR), calculated as arterial maximum standardized uptake value (SUV)/mean SUV in venous blood pool. Multivariable Cox regression analysis was performed to identify factors associated with relapse.

**Results:** A total of 33 patients with clinically inactive TAK were included. During a median observation period of 4.5 (0.9–8.1) years, relapse occurred in 9 (27.3%) patients at median 1.3 (0.7–6.9) years. Notably, TBR [1.5 (1.3–1.8) vs. 1.3 (1.1–1.4), $p$=0.044] was significantly higher in patients who relapsed than in those who did not. On multivariable Cox regression analysis, the presence of NIH criterion 2 [adjusted hazard ratio (HR): 7.044 (1.424–34.855), $p$=0.017] and TBR [adjusted HR: 11.533 (1.053–126.282), $p$=0.045] were significantly associated with an increased risk of relapse.

**Conclusion:** Vascular uptake on $^{18}$F-FDG PET/CT and the presence of NIH criterion 2 are associated with future relapse in patients with clinically inactive TAK.

**Key Words:** PET/CT, inactive, relapse, Takayasu arteritis

## INTRODUCTION

Takayasu arteritis (TAK) is a large-vessel vasculitis characterized by inflammation of the aorta and its major branches.[1] For its treatment, it is important to detect active inflammation early in the disease and treat it accordingly before the occurrence of irreversible structural vessel damage, such as stenosis or aneurysmal change.[2] However, assessing the disease activity of TAK is challenging as clinical symptoms and laboratory data do not precisely reflect the actual inflammation of the arterial wall, which makes it difficult to effectively monitor and treat the disease.[2-4]

$^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT) has been suggested as a useful diagnostic tool for large vessel vasculitis.[5,6] Moreover, several studies have demonstrated the value of $^{18}$F-FDG PET/CT in assessing the disease activity of TAK.[7-12] The sensitivity and specificity of $^{18}$F-FDG PET/CT in detecting the clinically active state of the disease have been reported to be 75%–100% and 64.3%–88.9%, respectively.[7-9,11] Notably, the specificity was relatively low, implicating that a substantial proportion of patients with a clinically inactive state of the disease may have vascular up-

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**Corresponding author:** Min-Chan Park, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-gu, Seoul 06273, Korea.
Tel: 82-2-2019-3310, Fax: 82-2-3463-3882, E-mail: mcpark@yuhs.ac

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take on $^{18}$F-FDG PET/CT. Although previous studies have reported that clinically inactive patients with vascular uptake on $^{18}$F-FDG PET/CT exist,[7-10] the clinical significance of vascular uptake on $^{18}$F-FDG PET/CT in patients with clinically inactive TAK remains unclear. Given that TAK is an inflammatory disease that primarily affects vessels (large vessels in particular),[1] vascular uptake on $^{18}$F-FDG PET/CT during the clinically inactive state of the disease might be associated with future relapse. In this study, we aimed to evaluate whether vascular uptake on $^{18}$F-FDG PET/CT during clinically inactive disease in patients with TAK are associated with disease relapse.

## MATERIALS AND METHODS

### Patients

Patients with TAK who underwent an $^{18}$F-FDG PET/CT between 2006 and 2019 at two tertiary referral hospitals were retrospectively screened for inclusion. All patients fulfilled the American College of Rheumatology 1990 criteria for the classification of TAK.[13] Patients with clinically active disease at the time of $^{18}$F-FDG PET/CT were excluded, and the remaining patients who had clinically inactive disease at the time of $^{18}$F-FDG PET/CT were included for the analysis. All of the included patients underwent $^{18}$F-FDG PET/CT for further evaluation of disease activity, despite the clinically inactive disease state. The timing of $^{18}$F-FDG PET/CT was at the investigator's discretion. None of the patients had experienced relapse prior to the date of $^{18}$F-FDG PET/CT. The following data at the time of $^{18}$F-FDG PET/CT were reviewed: age, sex, disease duration, presence of hypertension, diabetes mellitus, and dyslipidemia, smoking status (current smoker or not), body mass index, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), vascular involvement pattern according to the Hata classification,[14] and current use of glucocorticoids and immunosuppressants (methotrexate or azathioprine).

This study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Review Board of Gangnam Severance Hospital (approval no. 3-2019-0423). The requirement for informed consent was waived owing to the retrospective nature of this study.

### Definition of clinically inactive disease and relapse

Clinically inactive disease was defined as a status not meeting the National Institutes of Health (NIH) criteria for active disease in TAK.[2] According to the NIH criteria, new onset or worsening of two or more of the following criteria indicates active disease: criterion 1, systemic features such as fever or arthralgia; criterion 2, elevated ESR; criterion 3, features of vascular ischemia or inflammation; and criterion 4, typical angiographic features.[2] The NIH criterion 4 was assessed based on CT or magnetic resonance angiography that was performed at the closest date (within 1 month in all cases) to the date $^{18}$F-FDG PET/CT was performed. Due to the heterogeneity of angiographic modalities, worsening of angiographic features was confined to worsening of luminal changes in the affected vessels. The fulfillment of each criterion at the time of $^{18}$F-FDG PET/CT was retrospectively reviewed. Relapse was defined as a recurrence of clinically active disease (based on the NIH criteria) after a period of clinically inactive disease, necessitating an increase in the prednisone dose of ≥10 mg/day from the basal dose and/or the addition of glucocorticoid-sparing therapy. The retrospective observation period was from the time of $^{18}$F-FDG PET/CT to the last follow-up date or the occurrence of relapse, whichever came first.

### $^{18}$F-FDG PET/CT

$^{18}$F-FDG PET/CT scans were obtained using a dedicated PET/CT scanner [Discovery STE (GE Healthcare, Chicago, IL, USA) or Biograph 40 TruePoint (Siemens Medical Systems, Erlangen, Germany)], as previously described.[15] The dose of $^{18}$F-FDG was 5.5 MBq/kg. The images were interpreted by a nuclear physician who was blinded to the clinical data. As used in previous studies,[16,17] the target/background ratio (TBR) was assessed as a parameter of vascular uptake. TBR was calculated as arterial maximum standardized uptake value (max SUV)/mean SUV in background reference tissue. The arterial max SUV was defined as the highest value in a slice-by-slice analysis of the entire aorta and its major branches. The mean SUV in background reference tissue was measured in venous blood pool.

### Statistical analysis

The patient characteristics are summarized as median (interquartile range) for continuous variables and as number (%) for categorical variables. For comparison between patients who did and did not experience relapse, the Mann-Whitney U-test was performed for continuous variables and Fisher's exact test was used for categorical variables. Multivariable Cox proportional hazard regression analysis with a stepwise backward elimination procedure was used to identify factors associated with relapse. The proportional hazard assumption was confirmed by examination of log [-log (survival)] curves and by testing Schoenfeld partial residuals, which revealed no relevant violation. Factors with a $p$ value of <0.05 in univariable analysis were included in multivariable analysis. To assess the predictive accuracy and determine the cut-off value of TBR that best predicts relapse, we performed a receiver-operating characteristic (ROC) analysis. Relapse-free survival rates were analyzed using the Kaplan-Meier survival analysis and were compared using the log-rank test. All analyses were performed using the SPSS software (version 25.0; IBM Corp., Armonk, NY, USA).

## RESULTS

### Patient characteristics

A total of 33 patients with TAK who underwent $^{18}$F-FDG PET/

CT during the clinically inactive state of the disease were identified. The characteristics of patients at the time of $^{18}$F-FDG PET/CT are summarized in Table 1. The median patient age was 49.0 (38.0–55.0) years, and majority of the patients were female (30 of 33, 90.9%). The median disease duration of TAK at the time of $^{18}$F-FDG PET/CT was 4.0 (1.0–10.0) years. During a median observation period of 4.5 (0.9–8.1) years, relapse occurred in 9 (27.3%) patients at a median of 1.3 (0.7–6.9) years. The median values of arterial max SUV, mean SUV in blood pool, and TBR were 2.3 (1.9–2.9) g/mL, 1.7 (1.5–2.3) g/mL, and 1.4 (1.2–1.6), respectively.

**Table 1.** Characteristics of the 33 Patients with Clinically Inactive TAK

| | |
|---|---|
| Age at $^{18}$F-FDG PET/CT, yr | 49.0 (38.0–55.0) |
| Female sex | 30 (90.9) |
| Disease duration, yr | 4.0 (1.0–10.0) |
| Hypertension | 16 (48.5) |
| Diabetes mellitus | 2 (6.1) |
| Dyslipidemia | 14 (42.4) |
| Smoking | 3 (9.1) |
| BMI, kg/m$^2$ | 22.2 (21.6–24.8) |
| ESR, mm/h | 19.0 (11.5–24.0) |
| CRP, mg/L | 1.0 (0.6–2.8) |
| Type of vascular involvement | |
| I | 8 (24.2) |
| IIA | 4 (12.1) |
| IIB | 8 (24.2) |
| III | 1 (3.0) |
| IV | 0 (0.0) |
| V | 12 (36.4) |
| NIH criterion 1 | 2 (6.1) |
| NIH criterion 2 | 11 (33.3) |
| NIH criterion 3 | 2 (6.1) |
| NIH criterion 4 | 12 (36.4) |
| Fulfillment of no NIH criteria | 6 (18.2) |
| Fulfillment of one NIH criterion | 27 (81.8) |
| Arterial max SUV, g/mL | 2.3 (1.9–2.9) |
| Mean SUV in blood pool, g/mL | 1.7 (1.5–2.3) |
| TBR | 1.4 (1.2–1.6) |
| Medications at $^{18}$F-FDG PET/CT | |
| Glucocorticoid | 13 (39.4) |
| Glucocorticoid dose*, mg/d | 0.0 (0.0–5.0) |
| Methotrexate | 7[†] (21.2) |
| Azathioprine | 2[‡] (6.1) |

TAK, Takayasu arteritis; $^{18}$F-FDG PET/CT, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography; IQR, interquartile range; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NIH, National Institutes of Health; SUV, standardized uptake value; TBR, target/background ratio.
Data are presented as median (IQR) or n (%).
*Equivalent to prednisolone, [†]Median dose: 10.0 (IQR 7.5–15.0) mg/week, [‡]Both patients received 100 mg/d.

## Comparison between patients who did and did not experience relapse

Patients who experienced relapse had longer disease duration [10.0 (3.5–16.5) years vs. 3.5 (0.8–5.8) years, $p$=0.029], higher ESR [26.0 (19.0–32.5) mm/h vs. 18.0 (10.8–20.0) mm/h, $p$=0.010] and CRP [3.2 (0.8–4.3) mg/L vs. 1.0 (0.6–1.3) mg/L, $p$=0.049), more commonly fulfilled NIH criterion 2 (77.8% vs. 16.7%, $p$=0.002), and less commonly fulfilled NIH criterion 4 (0.0% vs. 50.0%, $p$=0.012), compared to patients who did not experience relapse. Notably, the TBR [1.5 (1.3–1.8) vs. 1.3 (1.1–1.4), $p$=0.044] was significantly higher in patients who experienced relapse than in those who did not (Fig. 1). On the other hand, there was no significant difference in age ($p$=0.766), sex distribution ($p$>0.999), BMI ($p$=0.453), type of vascular involvement (type I, $p$=0.394; type IIA, $p$=0.555; type IIB, $p$=0.651; type III, $p$=0.273; and type V, $p$=0.690), fulfillment of NIH criterion 1 ($p$=0.477) and NIH criterion 3 ($p$=0.477), arterial max SUV ($p$=0.486), mean SUV in IVC ($p$=0.166), use and dose of glucocorticoids ($p$>0.999 and $p$=0.648, respectively), and use of methotrexate ($p$>0.999) and azathioprine ($p$=0.477) between the two groups (Table 2).

Among the total 33 patients with clinically inactive TAK, one patient with a TBR of 1.6 was newly administered prednisolone at a dose of 10 mg/day based on the $^{18}$F-FDG PET/CT result. No disease relapse was noted in this patient during the observation period.

## Factors associated with relapse

On univariable analysis, ESR [unadjusted hazard ratio (HR): 1.112, 95% confidence interval (CI): 1.035–1.195, $p$=0.004], CRP (unadjusted HR: 1.573, 95% CI: 1.005–2.460, $p$=0.047), presence of NIH criterion 2 (comparison with absence of NIH criterion 2) (unadjusted HR: 8.210, 95% CI: 1.688–39.927, $p$=0.009), and TBR (unadjusted HR: 14.751, 95% CI: 1.484–146.663, $p$=0.022) had a $p$ value of <0.05. Among these variables, ESR and CRP were not included in the multivariable analysis owing to multicollinearity with NIH criterion 2. On multivariable analysis,

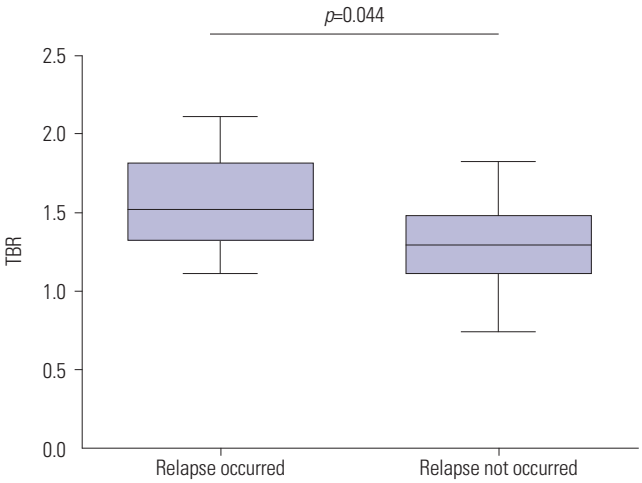


**Fig. 1.** Comparison of TBR in patients who did and did not relapse. The whiskers represent 10–90 percentile range. TBR, target/background ratio.


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**Table 2.** Comparison of Patients according to the Occurrence of Relapse

| | Relapse occurred (n=9) | Relapse did not occur (n=24) | *p* value |
|---|---|---|---|
| Age at $^{18}$F-FDG PET/CT, yr | 50.0 (26.5–57.0) | 49.5 (45.0–55.0) | 0.766 |
| Female sex | 8 (88.9) | 22 (91.7) | >0.999 |
| Disease duration, yr | 10.0 (3.5–16.5) | 3.5 (0.8–5.8) | 0.029 |
| Hypertension | 5 (55.6) | 11 (45.8) | 0.708 |
| Diabetes mellitus | 1 (11.1) | 1 (4.2) | 0.477 |
| Dyslipidemia | 3 (33.3) | 11 (45.8) | 0.698 |
| Smoking | 1 (11.1) | 2 (8.3) | >0.999 |
| BMI, kg/m$^2$ | 22.1 (21.7–24.1) | 22.4 (21.3–25.1) | 0.453 |
| ESR, mm/h | 26.0 (19.0–32.5) | 18.0 (10.8–20.0) | 0.010 |
| CRP, mg/L | 3.2 (0.8–4.3) | 1.0 (0.6–1.3) | 0.049 |
| Type of vascular involvement | | | |
| I | 1 (11.1) | 7 (29.2) | 0.394 |
| IIA | 0 (0.0) | 4 (16.7) | 0.555 |
| IIB | 3 (33.3) | 5 (20.8) | 0.651 |
| III | 1 (11.1) | 0 (0.0) | 0.273 |
| IV | 0 (0.0) | 0 (0.0) | N/A |
| V | 4 (44.4) | 8 (33.3) | 0.690 |
| NIH criterion 1 | 1 (11.1) | 1 (4.2) | 0.477 |
| NIH criterion 2 | 7 (77.8) | 4 (16.7) | 0.002 |
| NIH criterion 3 | 1 (11.1) | 1 (4.2) | 0.477 |
| NIH criterion 4 | 0 (0.0) | 12 (50.0) | 0.012 |
| Fulfillment of no NIH criteria | 1 (11.1) | 5 (20.8) | >0.999 |
| Fulfillment of one NIH criterion | 8 (88.9) | 19 (79.2) | >0.999 |
| Arterial max SUV, g/mL | 2.3 (1.9–3.4) | 2.3 (1.8–2.9) | 0.486 |
| Mean SUV in blood pool, g/mL | 1.5 (1.4–1.8) | 1.8 (1.7–2.4) | 0.166 |
| TBR | 1.5 (1.3–1.8) | 1.3 (1.1–1.4) | 0.044 |
| Medications at $^{18}$F-FDG PET/CT | | | |
| Glucocorticoid | 4 (44.4) | 9 (37.5) | >0.999 |
| Glucocorticoid dose*, mg/d | 0.0 (0.0–7.5) | 0.0 (0.0–4.4) | 0.648 |
| Methotrexate | 2 (22.2) | 5 (20.8) | >0.999 |
| Azathioprine | 1 (11.1) | 1 (4.2) | 0.477 |

$^{18}$F-FDG PET/CT, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography; IQR, interquartile range; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NIH, National Institutes of Health; SUV, standardized uptake value; TBR, target/background ratio.
Data are presented as median (IQR) or n (%).
*Equivalent to prednisolone.

the presence of NIH criterion 2 (comparison with absence of NIH criterion 2) (adjusted HR: 7.044, 95% CI: 1.424–34.855, $p$=0.017) and TBR (adjusted HR: 11.533, 95% CI: 1.053–126.282, $p$=0.045) were significantly associated with an increased risk of relapse (Table 3).

### Predictive accuracy and cut-off value of TBR and relapse-free survival according to TBR

The ROC curve assessing the predictive accuracy of TBR for relapse is shown in Fig. 2A. The area under the curve (AUC) of TBR was 0.731, and the cut-off value of TBR that best predicted relapse was 1.46. When TBR was used in combination with NIH criterion 2 as a composite parameter, the AUC was higher (Fig. 2B, AUC=0.903). Using the TBR cut-off value of 1.46, we divided the patients into high TBR (n=13) and low TBR (n=20) groups. The high TBR group had a significantly lower relapse-free survival compared to the low TBR group ($p$=0.019) (Fig. 3).

## DISCUSSION

In this study, we demonstrated that the vascular uptake on $^{18}$F-FDG PET/CT, as assessed by TBR, and the presence of NIH criterion 2 during the clinically inactive state of the disease in TAK are associated with an increased risk of relapse. This finding has an important clinical implication, as it may aid in identifying patients with inactive disease who are at a higher risk of relapse.

Tezuka, et al.[16] compared $^{18}$F-FDG uptake between patients with relapsed TAK (defined as active disease while receiving immunosuppressants) and patients with inactive TAK who were

**Table 3.** Factors Associated with Relapse

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| Age at $^{18}$F-FDG PET/CT, yr | 0.957 (0.903–1.014) | 0.134 | | |
| Female (vs. male) sex | 1.067 (0.131–8.695) | 0.952 | | |
| Disease duration, yr | 1.056 (0.997–1.119) | 0.062 | | |
| Hypertension | 1.512 (0.400–5.714) | 0.542 | | |
| Diabetes mellitus | 2.262 (0.271–18.858) | 0.451 | | |
| Dyslipidemia | 1.038 (0.256–4.212) | 0.958 | | |
| Smoking | 1.278 (0.159–10.296) | 0.818 | | |
| BMI, kg/m$^2$ | 0.897 (0.688–1.170) | 0.423 | | |
| ESR, mm/h | 1.112 (1.035–1.195) | 0.004* | | |
| CRP, mg/L | 1.573 (1.005–2.460) | 0.047* | | |
| Type I (vs. non-type I) | 0.265 (0.033–2.137) | 0.213 | | |
| Type IIA (vs. non-type IIA) | 0.042 (0.000–24640.130) | 0.641 | | |
| Type IIB (vs. non-type IIB) | 1.289 (0.321–5.174) | 0.720 | | |
| Type III (vs. non-type III) | 9.155 (0.952–88.046) | 0.055 | | |
| Type IV (vs. non-type IV) | N/A | N/A | | |
| Type V (vs. non-type V) | 1.588 (0.424–5.938) | 0.492 | | |
| Presence of NIH criterion 1 (vs. absence of NIH criterion 1) | 1.682 (0.206–13.710) | 0.627 | | |
| Presence of NIH criterion 2 (vs. absence of NIH criterion 2) | 8.210 (1.688–39.927) | 0.009 | 7.044 (1.424–34.855) | 0.017 |
| Presence of NIH criterion 3 (vs. absence of NIH criterion 3) | 1.521 (0.187–12.380) | 0.695 | | |
| Presence of NIH criterion 4 (vs. absence of NIH criterion 4) | 0.022 (0.000–5.447) | 0.174 | | |
| Fulfillment of one NIH criterion (vs. fulfillment of no NIH criteria) | 3.204 (0.393–26.104) | 0.277 | | |
| Use of glucocorticoid | 1.413 (0.376–5.316) | 0.609 | | |
| Dose of glucocorticoid | 0.993 (0.904–1.091) | 0.884 | | |
| Use of methotrexate | 0.797 (0.163–3.896) | 0.779 | | |
| Use of azathioprine | 3.116 (0.347–27.951) | 0.310 | | |
| Arterial max SUV, g/mL | 1.457 (0.999–2.124) | 0.050 | | |
| Mean SUV in blood pool, g/mL | 1.187 (0.545–2.583) | 0.666 | | |
| TBR | 14.751 (1.484–146.663) | 0.022 | 11.533 (1.053–126.282) | 0.045 |

HR, hazard ratio; CI, confidence interval; $^{18}$F-FDG PET/CT, $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NIH, National Institutes of Health; SUV, standardized uptake value; TBR, target/background ratio.
*ESR and CRP were not included in multivariable analysis.

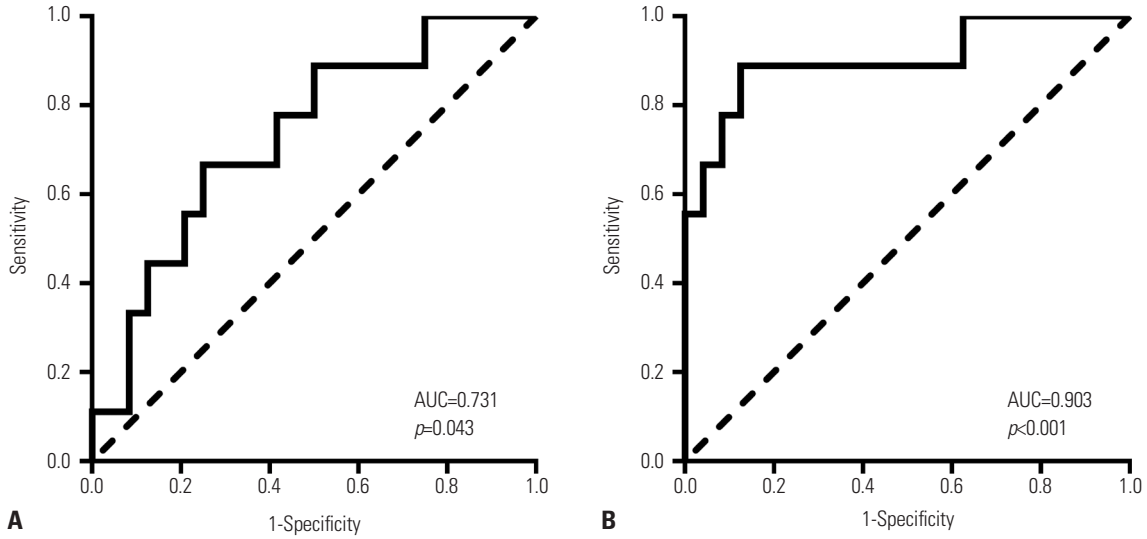


**Fig. 2.** Receiver-operating characteristic curves for (A) TBR and (B) combination of TBR and NIH criterion 2 in predicting relapse. TBR, target/background ratio; NIH, National Institutes of Health; AUC, area under the curve.



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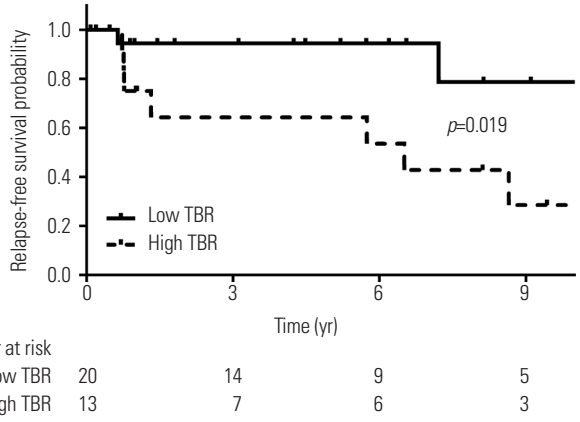


**Fig. 3.** Comparison of relapse-free survival between patients with high TBR and low TBR. TBR, target/background ratio.

receiving immunosuppressants, and showed that $^{18}$F-FDG uptake was higher in the former group than in the latter group, suggesting that $^{18}$F-FDG PET/CT is a useful tool in detecting active disease even during immunosuppressant treatment. Our data add to the previous finding that $^{18}$F-FDG PET/CT can be useful not only for detecting the occurrence of relapse but also for stratifying the risk of relapse in patients during clinically inactive disease. Similar to our present study, a previous prospective cohort study consisting of patients with large-vessel vasculitis showed that high $^{18}$F-FDG PET/CT activity during clinical remission is associated with a future clinical relapse.[18] However, both TAK and giant cell arteritis (GCA) were included in that study, and only one patient with TAK was included in the high $^{18}$F-FDG PET/CT activity group.[18] Therefore, it was unclear whether the previous finding still applies when confined to patients with TAK. Our study suggests that higher $^{18}$F-FDG PET/CT activity during remission is associated with future relapse, even when confined to patients with TAK.

While vascular uptake on $^{18}$F-FDG PET/CT during the clinically inactive state of the disease may indicate subclinical vasculitis, it may also represent atherosclerosis.[19] Due to the lack of histologic data in our study, it was difficult to determine whether the uptake in the vascular wall was due to subclinical vasculitis or atherosclerosis. With respect to atherosclerosis in inflammatory rheumatic diseases, ESR and CRP, as markers of systemic inflammation, are positively associated with atherosclerosis, suggesting that inflammation is a major contributor to accelerated atherosclerosis.[20,21] On the other hand, acute phase reactants poorly reflect the histologically-proven actual vascular wall inflammation.[22] Therefore, assessment of the correlation between TBR and acute phase reactants could aid in speculating the cause of vascular uptake. In the present study, there was no significant correlation between TBR and ESR ($\gamma$=0.055, $p$=0.762), as well as between TBR and CRP ($\gamma$=-0.167, $p$=0.353) (data not shown in the results). Given the lack of correlation of TBR with ESR and CRP, we presume that the vascular uptake observed in $^{18}$F-FDG PET/CT favors subclinical vasculitis, rather than atherosclerosis, attributed to the inflammation. In any case, it is important to perceive patients with vascular uptake on $^{18}$F-FDG PET/CT during the clinically inactive state of the disease as high-risk patients for disease relapse.

A previous study has shown that in some patients with GCA, which also is a large-vessel vasculitis, vascular uptake on $^{18}$F-FDG PET/CT does not completely resolve even after treatment.[23] Furthermore, a recent study consisting of patients with large vessel vasculitis showed that when treatment was reduced, $^{18}$F-FDG PET/CT activity worsened, despite no change in clinical and serologic disease activity.[24] Considering the association between vascular uptake on $^{18}$F-FDG PET/CT and the risk of relapse, as observed in our study, it could be helpful to perform $^{18}$F-FDG PET/CT in patients with clinically inactive disease and tailor treatment accordingly. In our study, although limited by the small number, one patient with a relatively high TBR (TBR=1.6, which corresponds to the upper quartile among the total population) on $^{18}$F-FDG PET/CT received increased medication despite clinically inactive disease state and remained relapse free, supporting the potential usefulness of adjusting treatment based on $^{18}$F-FDG PET/CT findings.

The presence of NIH criterion 2 (new or worsening elevation of ESR) during the clinically inactive state of the disease was also associated with the risk of relapse. The median value of ESR in patients fulfilling NIH criterion 2 was 26.0 (23.0–30.0) mm/h (data not shown in the results). Considering the normal range of ESR (0–15 mm/h for male and 0–20 mm/h for female), ESR was only modestly increased in patients who fulfilled NIH criterion 2. Our data suggest that ESR increments during the clinically inactive state of the disease, even in small amounts, might indicate an increased risk of future relapse. However, among the nine patients who relapsed, two patients did not fulfill NIH criterion 2 at the time of $^{18}$F-FDG PET/CT. One of these two patients had high TBR (TBR=2.1, which corresponds to the top 3.0% among the total population), suggesting that $^{18}$F-FDG PET/CT results can identify patients at higher risk of relapse who otherwise would have not been identified using NIH criterion 2 alone. Therefore, TBR can be used as a complementary parameter with NIH criterion 2 in predicting the risk of relapse. Notably, combination of TBR and NIH criterion 2 as a composite parameter had an excellent predictive accuracy (AUC=0.903).

New or worsening of angiographic feature (i.e. NIH criterion 4) during apparent clinical remission is common (up to 61%) in TAK.[2] We also observed that substantial proportion of patients (12 of 33, 36.4%) fulfilled NIH criterion 4 during the clinically inactive state of TAK. Interestingly, the presence of NIH criterion 4 was more common in patients who did not experience relapse compared to those who experienced relapse. Although an exact explanation for this observation remains unclear, it could be speculated that the presence of NIH criterion 4 indicates an end-stage sequelae, and therefore, is less likely to relapse. Similar observation has been reported in a prospective study consisting of 60 patients with TAK, in which a subgroup of patients who had new angiographic feature during clinical

remission had a lower relapse rate (27.3%) than the total study population (45%).[2] These suggest that the presence of NIH 4 criterion during clinically inactive state might be associated with a lower risk of relapse. However, the presence of NIH criterion 4 did not show a significant association with the risk of relapse in Cox regression analysis; therefore, it cannot be concluded that the presence of NIH criterion 4 is associated with a lower risk of relapse.

We defined clinically inactive disease as a status not meeting the NIH criteria for active disease in TAK,[2] as used in previous studies.[7-10] Therefore, patients who fulfilled none of the NIH criteria and those who fulfilled one NIH criterion were both included in our study population. An important question arises as to whether the risk of relapse is different between patients who fulfilled one NIH criterion and those who did not fulfill any of the NIH criteria. In the Cox regression analysis, no significant increase in the risk of relapse was observed in patients who fulfilled one NIH criterion compared to those who did not fulfill any of the NIH criteria (unadjusted HR: 3.204, 95% CI: 0.393–26.104, $p$=0.277). Furthermore, we conducted an additional Cox regression analysis including the TBR, number of NIH criterion fulfilled (none or one), and an interaction term TBR*number of NIH criterion fulfilled (none or one) in the model. The interaction effect was not significant ($p$=0.761, data not shown in the results), indicating that the number of NIH criterion fulfilled, either none or one, does not influence the association between TBR and risk of relapse.

This study has some limitations. First, due to the retrospective nature of the study, bias resulting from unmeasured confounding cannot be excluded. Second, the number of patients was relatively small. Due to the small number of patients and events in this study, we were unable to include more than two variables in the multivariable analysis. However, compared with previous studies,[7-10] this study included the largest number of patients with TAK who underwent an $^{18}$F-FDG PET/CT during the clinically inactive state of the disease. Third, the NIH criteria was used to define patients with clinically inactive disease. The NIH criteria are suboptimal as a tool for detecting pathologically proven active disease.[7] Nevertheless, owing to the lack of a gold standard for assessing disease activity in TAK,[25] several studies have similarly used the NIH criteria for defining active disease.[7-10]

In conclusion, we found that TBR on $^{18}$F-FDG PET/CT and the presence of NIH criterion 2 during the clinically inactive state of the disease could be associated with future relapse. These indicators may help clinicians in identifying patients who are at a higher risk of relapse during the clinically inactive state of the disease, leading to closer monitoring and earlier adjustment of treatment in patients with TAK.

## AUTHOR CONTRIBUTIONS

Conceptualization: Min-Chan Park. Data curation: all authors. Formal analysis: all authors. Investigation: Oh Chan Kwon and Min-Chan Park. Methodology: Oh Chan Kwon and Min-Chan Park. Project administration: all authors. Resources: all authors. Software: Oh Chan Kwon and Min-Chan Park. Supervision: Min-Chan Park. Validation: Oh Chan Kwon and Min-Chan Park. Visualization: Oh Chan Kwon and Min-Chan Park. Writing—original draft: Oh Chan Kwon and Min-Chan Park. Writing—review & editing: Oh Chan Kwon and Min-Chan Park. Approval of final manuscript: all authors.

## ORCID iDs

Oh Chan Kwon https://orcid.org/0000-0001-7962-3697
Tae Joo Jeon https://orcid.org/0000-0002-7574-6734
Min-Chan Park https://orcid.org/0000-0003-1189-7637

## REFERENCES

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
2. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med 1994;120:919-29.
3. Lagneau P, Michel JB, Vuong PN. Surgical treatment of Takayasu's disease. Ann Surg 1987;205:157-66.
4. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum 2007;56:1000-9.
5. Balink H, Bennink RJ, van Eck-Smit BL, Verberne HJ. The role of 18F-FDG PET/CT in large-vessel vasculitis: appropriateness of current classification criteria? Biomed Res Int 2014;2014:687608.
6. Chrapko BE, Chrapko M, Nocuń A, Stefaniak B, Zubilewicz T, Drop A. Role of 18F-FDG PET/CT in the diagnosis of inflammatory and infectious vascular disease. Nucl Med Rev Cent East Eur 2016;19:28-36.
7. Lee SG, Ryu JS, Kim HO, Oh JS, Kim YG, Lee CK, et al. Evaluation of disease activity using F-18 FDG PET-CT in patients with Takayasu arteritis. Clin Nucl Med 2009;34:749-52.
8. Lee KH, Cho A, Choi YJ, Lee SW, Ha YJ, Jung SJ, et al. The role of 18F-fluorodeoxyglucose-positron emission tomography in the assessment of disease activity in patients with Takayasu arteritis. Arthritis Rheum 2012;64:866-75.
9. Karapolat I, Kalfa M, Keser G, Yalçin M, Inal V, Kumanlioğlu K, et al. Comparison of F18-FDG PET/CT findings with current clinical disease status in patients with Takayasu's arteritis. Clin Exp Rheumatol 2013;31(1 Suppl 75):S15-21.
10. Han Q, Liang Q, Kang F, Wang J, Wu Z, Zhu P. An increased major vessel uptake by 18F-FDG-PET/CT in NIH criteria inactive patients with Takayasu's arteritis. Clin Exp Rheumatol 2018;36(2 Suppl 111):S88-92.
11. Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. Medicine (Baltimore) 2015;94:e622.
12. Incerti E, Tombetti E, Fallanca F, Baldissera EM, Alongi P, Tombolini E, et al. 18F-FDG PET reveals unique features of large vessel inflammation in patients with Takayasu's arteritis. Eur J Nucl Med Mol Imaging 2017;44:1109-18.
13. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990;33:1129-34.
14. Moriwaki R, Noda M, Yajima M, Sharma BK, Numano F. Clinical


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manifestations of Takayasu arteritis in India and Japan--new classification of angiographic findings. Angiology 1997;48:369-79.
15. Ahn SS, Hwang SH, Jung SM, Lee SW, Park YB, Yun M, et al. Evaluation of spleen glucose metabolism using 18F-FDG PET/CT in patients with febrile autoimmune disease. J Nucl Med 2017;58:507-13.
16. Tezuka D, Haraguchi G, Ishihara T, Ohigashi H, Inagaki H, Suzuki J, et al. Role of FDG PET-CT in Takayasu arteritis: sensitive detection of recurrences. JACC Cardiovasc Imaging 2012;5:422-9.
17. Rosenblum JS, Quinn KA, Rimland CA, Mehta NN, Ahlman MA, Grayson PC. Clinical factors associated with time-specific distribution of 18F-fluorodeoxyglucose in large-vessel vasculitis. Sci Rep 2019;9:15180.
18. Grayson PC, Alehashemi S, Bagheri AA, Civelek AC, Cupps TR, Kaplan MJ, et al. 18F-fluorodeoxyglucose-positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. Arthritis Rheumatol 2018;70:439-49.
19. Rosenbaum D, Millon A, Fayad ZA. Molecular imaging in atherosclerosis: FDG PET. Curr Atheroscler Rep 2012;14:429-37.
20. Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumatic diseases. Nat Rev Rheumatol 2015;11:693-704.
21. Del Rincón I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. Arthritis Rheum 2003;48:1833-40.
22. Hoffman GS. Takayasu arteritis: lessons from the American National Institutes of Health experience. Int J Cardiol 1996;54 Suppl:S99-102.
23. Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum 2006;55:131-7.
24. Banerjee S, Quinn KA, Gribbons KB, Rosenblum JS, Civelek AC, Novakovich E, et al. Effect of treatment on imaging, clinical, and serologic assessments of disease activity in large-vessel vasculitis. J Rheumatol 2020;47:99-107.
25. Direskeneli H, Aydin SZ, Kermani TA, Matteson EL, Boers M, Herlyn K, et al. Development of outcome measures for large-vessel vasculitis for use in clinical trials: opportunities, challenges, and research agenda. J Rheumatol 2011;38:1471-9.