Comparison of clinical features between patients with young-onset and late-onset Takayasu's arteritis

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Abstract

Objective

This study included patients diagnosed with Takayasu's arteritis (TAK) according to the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for TAK and compared the frequencies of items satisfied in the 2022 criteria between patients with young-onset TAK (YOTAK) and those with late-onset TAK (LOTAK).

Methods

The medical records of 138 patients with TAK were retrospectively reviewed. YOTAK was arbitrarily defined as TAK diagnosed at 20–40 years of age, whereas LOTAK was defined as TAK classified at 41-60 years of age. The analyses were conducted by assessing and comparing the frequencies of items that fulfilled the 2022 criteria for TAK.

Results

The median age of the 138 patients diagnosed with TAK was 45.0 years, and 89.1% of the patients were female. Of the 138 patients, 47 and 91 were allocated to the YOTAK and LOTAK groups. Patients with LOTAK exhibited significantly higher frequencies of the items of vascular bruit (85.7% vs. 70.2%, OR 2.55 (95% CI 1.08–6.00), p=0.030), reduced pulse in upper extremities (73.6% vs. 42.6%, OR 3.77 (95% CI 1.79–7.92), p<0.001), and systolic blood pressure difference in arms (96.7% vs. 87.2%, OR 4.29 (95% CI 1.02–18.02), p=0.033) than those with YOTAK. Conversely, the involvement of the ascending aorta was significantly more frequently found in patients with YOTAK than those with LOTAK (19.1% vs. 7.7%, OR 0.35 (95% CI 0.12–0.99), p=0.046).

Conclusion

Results of this study revealed that patients with LOTAK exhibited higher frequencies of vascular bruit, reduced brachial arterial pulse, and systolic blood pressure differences in arms, but a lower frequency of ascending aorta involvement than those with YOTAK.

Key words

Takayasu's arteritis, early-onset, late-onset, comparison, criteria

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Received on September 17, 2025; accepted in revised form on December 12, 2025.

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Funding: this study was funded by Eisai Korea Inc. Seoul, Republic of Korea (4-2024-0700), Yuhan Corporation, Seoul, Republic of Korea, as part of their "2024 Investigator Initiated Translation Research Program" (4-2025-0044), and Samsung Bioepis Co., Ltd., Incheon, Republic of Korea (4-2025-1066). The funder was not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication. Therefore, we disclose that these analyses were pre-specified and conducted independently.

Competing interests: none declared.

Introduction

According to the revised Chapel Hill Consensus Conference nomenclature of systemic vasculitides proposed in 2012, Takayasu's arteritis (TAK) is a granulomatous large-vessel vasculitis that primarily affects the aorta and its major branches (1, 2). TAK mainly occurs in females ≤50 years of age, which is known to be a critical clinical feature that distinguishes it from giant cell arteritis (GCA), another type of large-vessel vasculitis (3, 4). The classification criteria for TAK proposed by the American College of Rheumatology (ACR) in 1990 ('the 1990 criteria') defined age ≤40 years as one of the five items, and TAK can be classified when ≥3 items are fulfilled (3). Meanwhile, the classification criteria recently proposed by the ACR and the European Alliance of Associations for Rheumatology (EULAR) in 2022 ("the 2022 criteria") proposed age ≤60 years as an absolute requirement along with evidence of vasculitis on imaging (5). However, the 2022 criteria for GCA still determined age ≥50 years, which is consistent with the 1990 criteria for GCA, as an absolute requirement (6). Given that the two classification criteria for TAK suggest different age cut-offs for TAK diagnosis, it can be reasonably inferred that there must be subtle yet substantial differences in clinical features between patients diagnosed with TAK at ≤40 years of age (young-onset TAK (YOTAK)), and those diagnosed with TAK at 41-60 years of age (late-onset TAK (LOTAK)) (7, 8). Accordingly, this study included patients classified as having TAK according to the 2022 criteria for TAK and compared the frequencies of items satisfied in the 2022 criteria between patients with YOTAK and those with LOTAK (5).

Patients and methods

Patients

The medical records of 138 patients diagnosed with TAK between 2000 and 2022 were retrospectively reviewed. Data were collected and analysed in 2024. The inclusion criteria were as follows: i) patients who had been diagnosed with TAK according to the 1990 criteria before 2023 and who were reclassified as having TAK according to the 2022 criteria -in 2023, and those who were diagnosed with TAK according to the 2022 criteria after 2023 (3, 5); ii) patients who were first diagnosed with TAK in this tertiary university hospital by vasculitis-specific rheumatologists; iii) patients who were aged between 20 and 60 years at the time of diagnosis (5); iv) patients who had sufficient medical records for collecting clinical data at diagnosis; v) patients who underwent at least one of the four imaging modalities performed at TAK diagnosis, as it was described in our previous study (7); vi) patients who had no concurrent serious medical conditions mimicking TAK, including malignancies and severe infections, at diagnosis (5); vii) patients who were not exposed to immunosuppressive drugs for TAK treatment within 4 weeks before diagnosis.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Severance Hospital (Seoul, Korea, IRB No. 4-2022-1075) and was conducted in accordance with the Declaration of Helsinki. Given the retrospective design of the study and the use of anonymised patient data, the requirement for written informed consent was waived by the IRB.

Clinical data at diagnosis

In this study, the analyses were conducted by assessing and comparing the frequencies of items satisfied in the 2022 criteria for TAK. Absolute requirements include i) age ≤60 years, and ii) evidence of vasculitis on imaging. Additional clinical criteria include i) female sex; ii) angina or ischaemic cardiac pain; iii) arm or leg claudication; iv) vascular bruit (abbreviated as bruit); v) reduced pulse in upper extremities (abbreviated as reduced pulse); vi) carotid artery abnormality; and vii) systolic blood pressure difference in arms more than 20 mmHg (abbreviated as systolic BP difference). Additional imaging criteria include i) number of affected arteries (one, two, and three or more), ii) symmetric involvement of paired arteries, and iii) abdominal aorta

involvement with renal or mesenteric involvement. A total score of ≥5 points is required for classifying TAK (5).

Groups

In this study, YOTAK was arbitrarily defined as TAK diagnosed at 20-40 years of age, whereas LOTAK was defined as TAK classified at 41-60 years of age. The reason for dividing patients into two groups based on the age of 40 was due to the apparent gap in the age criterion between the 1990 criteria and the 2022 criteria.

Imaging modalities

Imaging modalities approved in this study included the following methods: conventional angiography, computed tomography (CT) angiography, F-18 fluorodeoxyglucose-positron emission tomography (FDG-PET), and magnetic resonance (MR) angiography at diagnosis (7). Among some patients, only one imaging method was used for TAK diagnosis, whereas in others, several imaging methods were employed. To avoid duplication, the investigation on the imaging modality for TAK diagnosis was conducted in the following order: conventional angiography, CT angiography, FDG-PET, and MR angiography. When an imaging test provided decisive information for the classification of TAK, the next imaging modality was not investigated. The corresponding description was shown in Supplementary Table S1. The radiology reports were collected, reviewed, and interpreted retrospectively.

Statistical analyses

All statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA). Continuous and categorical variables were expressed as medians (interquartile ranges (IQR)), and numbers (percentages). Significant differences between two categorical variables were analysed using the Chi-square and Fisher's exact tests. The Mann-Whitney U test was used to compare significant differences between two continuous variables. The odds ratio (OR) with 95% confidence interval (CI) comparing LOTAK (*vs*. YOTAK) for fulfilling each criterion was estimated using logistic regression analysis. As a hypothesis-driven exploratory study, multiplicity correction was not applied. All *p*-values were tow-sided, and a *p*-value <0.05 was considered to be statistically significant.

Table I. Frequencies of the satisfied items of the 2022 ACR/EULAR classification criteria for TAK (n=138).

At classification	Score	values
Absolute requirements		
Age ≤60 years		138 (100)
Age (years)		45.0 (16.0)
Evidence of vasculitis on imaging		138 (100)
Additional clinical criteria		
Female sex	**1**	123 (89.1)
Angina or ischaemic cardiac pain	**2**	14 (10.1)
Arm or leg claudication	**2**	40 (29.0)
Vascular bruit	**2**	111 (80.4)
Reduced pulse in upper extremities	**2**	87 (63.0)
Carotid artery abnormality	**2**	82 (59.4)
Systolic blood pressure difference in arms ≥20mmHg	**1**	129 (93.5)
Additional imaging criteria		
Number of affected arteries (aorta or its primary branches)		
One artery	**1**	28 (20.3)
Two arteries	**2**	48 (34.8)
Three or more arteries	**3**	62 (44.9)
Symmetric involvement of paired arteries	**1**	59 (42.8)
Abdominal aorta involvement with renal or mesenteric involvement	**3**	15 (10.9)
Total score		10.0 (11.0)
Patients with a total score ≥5 points (n (%))		138 (100)

Values are expressed as number (percentage) or median (interquartile range).
ACR: the American College of Rheumatology; EULAR: the European Alliance of Associations for Rheumatology; TAK: Takayasu's arteritis.

Results

Frequencies of items satisfied in the 2022 ACR/EULAR classification criteria for TAK

The median age of the 138 patients with TAK was 45.0 years (Supplementary Fig. S1), and 89.1% of the patients were female. In terms of absolute requirements, all patients were ≤60 years of age and exhibited evidence of vasculitis on imaging. Among additional clinical criteria, the most frequently satisfied item was systolic BP difference (93.5%), followed by female sex (89.1%) and bruit (80.4%). In terms of additional imaging criteria, 62 (44.9%) patients exhibited three or more arteries affected. Moreover, 59 (42.8%) and 15 (10.9%) patients presented with symmetric involvement of paired arteries and abdominal aorta involvement with renal or mesenteric involvement, respectively (Table I).

Comparison between patients with YOTAK and those with LOTAK

Of the 138 patients, 47 and 91 were allocated to the YOTAK and LOTAK groups, respectively. Patients with LOTAK exhibited significantly higher frequencies of the items of bruit (85.7% *vs*. 70.2%, OR 2.55 (95% CI 1.08–6.00), *p*=0.030), reduced pulse (73.6% *vs*. 42.6%, OR 3.77 (95% CI 1.79–7.92), *p*<0.001), and systolic BP difference (96.7% *vs*. 87.2%, OR 4.29 (95% CI 1.02–18.02), *p*=0.033) than those with YOTAK. Conversely, patients with LOTAK tended to exhibit a lower frequency of the item of abdominal aorta involvement with renal or mesenteric involvement than those with YOTAK (7.7% *vs*. 17.0%, *p*=0.095), although the difference was not statistically significant. No significant differences in the item of number of affected arteries (aorta or its primary branches) were observed between the two groups (Table II).

Comparison of vascular sites affected between patients with YOTAK and those with LOTAK

Among vascular sites affected by TAK, the involvement of the ascending aorta was significantly more fre-

Table II. Comparison of the frequency of the satisfied items of the 2022 criteria between patients with YOTAK and those with LOTAK.

At classification	YOTAK (n=47)	LOTAK (n=91)	OR (95% CI)	*p*-value
Absolute requirements				
Age ≤60 years	47 (100)	91 (100)		1.000
Age (years)	30.0 (11.0)	49.0 (10.0)		<0.001
Evidence of vasculitis on imaging	47 (100)	91 (100)		1.000
Additional clinical criteria				
Female sex	42 (89.4)	81 (89.0)	0.96 (0.31–3.00)	0.950
Angina or ischaemic cardiac pain	3 (6.4)	11 (12.1)	2.02 (0.53–7.61)	0.381
Arm or leg claudication	11 (23.4)	29 (31.9)	1.53 (0.68–3.43)	0.299
Vascular bruit	33 (70.2)	78 (85.7)	2.55 (1.08–6.00)	0.030
Reduced pulse in upper extremities	20 (42.6)	67 (73.6)	3.77 (1.79–7.92)	<0.001
Carotid artery abnormality	28 (59.6)	54 (59.3)	0.98 (0.48–2.03)	0.979
Systolic blood pressure difference in arms ≥20 mmHg	41 (87.2)	88 (96.7)	4.29 (1.02–18.02)	0.033
Additional imaging criteria				
Number of affected arteries (aorta or its primary branches)				0.791
One artery	9 (19.1)	19 (20.9)	1.11 (0.46–2.70)	
Two arteries	15 (31.9)	33 (36.3)	1.21 (0.58–2.56)	
Three or more arteries	23 (48.9)	39 (42.9)	0.78 (0.39–1.59)	
Symmetric involvement of paired arteries	24 (51.1)	35 (38.5)	0.60 (0.29–1.22)	0.156
Abdominal aorta involvement with renal or mesenteric involvement	8 (17.0)	7 (7.7)	0.41 (0.14–1.20)	0.095

Values are expressed as number (percentage) or median (quartile).
TAK: Takayasu's arteritis; YOTAK: young-onset TAK; LOTAK: late-onset TAK.

Table III. Comparison of vascular sites affected by TAK between patients with YOTAK and those with LOTAK.

At classification	YOTAK (n=47)	LOTAK (n=91)	OR (95% CI)	*p*-value
Vascular sites affected (n, (%))				
Ascending aorta	9 (19.1)	7 (7.7)	0.35 (0.12–0.99)	0.046
Aortic arch	16 (34.0)	32 (35.2)	1.05 (0.50–2.21)	0.896
Descending aorta	13 (27.7)	27 (29.7)	1.10 (0.51–2.41)	0.805
Right subclavian artery	17 (36.2)	27 (29.7)	0.74 (0.35–1.57)	0.437
Right common carotid artery	16 (34.0)	35 (38.5)	1.21 (0.58–2.53)	0.610
Left common carotid artery	22 (46.8)	45 (49.5)	1.11 (0.55–2.25)	0.769
Left subclavian artery	27 (57.4)	43 (47.3)	0.66 (0.33–1.35)	0.256
Celiac trunk	0 (0)	3 (3.3)	55073006.12 (N/A)	0.551
Superior mesenteric artery	3 (6.4)	5 (5.5)	0.85 (0.20–3.73)	1.000
Inferior mesenteric artery	0 (0)	1 (1.1)	17949720.44 (N/A)	1.000
Renal arteries	9 (19.1)	15 (16.5)	0.83 (0.33–2.08)	0.695

Values are expressed as number (percentage).
TAK: Takayasu's arteritis; YOTAK: young-onset TAK; LOTAK: late-onset TAK.

quently found in patients with YOTAK than those with LOTAK (19.1% *vs*. 7.7%, OR 0.35 (95% CI 0.12–0.99), *p*=0.046). No significant differences in the remaining vascular sites affected were observed between the two groups (Table III).

Discussion

Compared to the 1990 criteria, the 2022 criteria for TAK include two items of absolute entry requirements and are divided into two categories of additional clinical and imaging criteria. A critically notable change between the two criteria can be considered the improved scoring system of the new criteria, which assigns differently weighted points to each item and calculates a total score. When a total score is more than 5 points, TAK could be classified. Another important difference between the two criteria is the cut-off for TAK onset age: age ≤40 years in the 1990 criteria and age ≤60 years in the 2022 criteria. Also, age ≤40 years is not a mandatory provision as it is one of the five items, but age ≤60 years is a mandatory provision that must be absolutely observed (3, 5, 7). Given this gap between the two different cut-offs for TAK onset age, this study divided patients into the YOTAK and LOTAK groups and compared the frequencies of items satisfied in the 2022 criteria between patients with YOTAK and those with LOTAK. Results of this study revealed that bruit, reduced brachial arterial pulse, and systolic BP difference in arms were more frequently found in patients with LOTAK than those with YOTAK. Conversely, this study revealed that patients with YOTAK were more vulnerable to ascending aorta involvement than those with LOTAK.

The TAK-related clinical features of LOTAK, which are one axis of the results of this study, are summarised as bruit, decreased blood pressure in the arms and systolic BP difference be-

Table IV. Comparison of LOTAK-predominant variables among the three groups.

At classification	YOTAK (n=47)	First half of LOTAK (n=52)	Second half of LOTAK (n=39)	*p*-value
Additional clinical criteria				
Vascular bruit	33 (70.2)	46 (88.5)	32 (82.1)	0.070
Reduced pulse in upper extremities	20 (42.6)	43 (82.7)	24 (61.5)	<0.001
Systolic blood pressure difference in arms ≥20mmHg	41 (87.2)	49 (94.2)	39 (100)	0.060

Values are expressed as number (percentage).
LOTAK: late-onset Takayasu's arteritis; YOTAK: young-onset Takayasu's arteritis.

tween the two arms. Based on these results, the following theoretical inferences were made. In terms of structural alterations, the first theoretical inference is that patients with LOTAK may have a higher frequency of TAK involvement in common carotid arteries, subclavian arteries, and descending aorta with major branches in terms of bruit. This is because, in real clinical practice, the major arteries commonly affected by TAK provoking bruit are the common carotid arteries, subclavian arteries, and descending aorta with major branches (9, 10). However, the frequencies of TAK involvement in common carotid arteries, subclavian arteries, and descending aorta with major branches did not significantly differ between patients with YOTAK and those with LOTAK (Table III). Therefore, we tentatively conclude that the first theoretical inference may not be sufficiently valid.

The second theoretical inference is that patients with LOTAK may have a higher incidence of the subclavian artery with/without axillary and brachial artery involvement in terms of reduced pulse and systolic BP difference in arms (11). However, in Table III no significant differences in TAK-involvement in bilateral or unilateral subclavian arteries between patients with YOTAK and those with LOTAK were found. Additionally, even when each TAK-involvement in unilateral left/right or bilateral subclavian arteries was merged into one subclavian artery involvement and compared, no differences between patients with YOTAK and those with LOTAK were observed (63.8% *vs*. 58.2%, p=0.525) at all. Therefore, we tentatively conclude that the second theoretical inference may not be sufficiently valid. Nonetheless, we believe that the possibility of subclinical stenosis, which may result in TAK-related clinical manifestations but may not be easily detected by imaging modalities, cannot be ruled out (12), and thus, we insist that these two theoretical inferences shall not be totally considered invalid until further studies clarify these issues.

On the other hand, the TAK-related imaging feature of YOTAK, which is one axis of the results of this study, is summarised as predominant TAK-involvement in the ascending aorta. It can be assumed that a certain contribution of atherosclerosis to TAK-related imaging features may be made in patients with LOTAK, because the progression of atherosclerosis generally begins after the age of 40 (13, 14). However, the ascending aorta is unlikely to have a haemodynamically significant overlap with atherosclerosis. Therefore, we believe that this phenomenon can be considered a unique clinical feature of TAK in patients with YOTAK. Returning to atherosclerosis, given that atherosclerosis generally begins after age 40 and accelerates between ages 50 and 60, we divided patients into three groups based on age: 47 patients YOTAK (20-40 years), 52 patients with the first half of LOTAK (41-50 years), and 39 patients with the second half of LOTAK (51-60 years). And we compared the frequencies of the following variables that were more commonly observed in patients with LOTAK among the three groups: i) bruit, ii) reduced pulse, and iii) systolic BP difference. First, patients with the first half of LOTAK exhibited the highest frequency of reduced pulse in arms among the three groups (p<0.001). Furthermore, patients with the first half of LOTAK tended to have higher incidences of bruit (p=0.070) than those with YOTAK and those with the second half of LOTAK, despite no statistical significance. Finally, although patients with the second half of LOTAK showed the highest systolic BP difference, no significant differences were observed between the first and second LOTAK groups (Table IV). Therefore, because patients with the first half of LOTAK showed a higher frequency of TAK-related clinical features than patients with the second half of LOTAK, we infer that the progression of atherosclerosis with age made no significant contribution to the results of this study (14).

Particularly, we focused on the discrepancies between the frequencies of items satisfied in the additional clinical criteria of the 2022 criteria and the frequencies of items satisfied in the distribution of affected vessels in the results of the comparative analysis between patients with YOTAK and those with LOTAK. In real clinical practice, the discrepancy between the clinical signal (or sign) and vascular abnormality may be observed in not a few patients. We inferred the reasons for these discrepancies as follows. In cases with clinical signs of vascular stenosis but without substantial vascular abnormalities on imaging tests, haemodynamic alterations or detection limits of imaging tests can be considered. Conversely, in cases with vascular stenosis on imaging tests but without corresponding clinical signs, subclinical stenosis may be considered. Therefore, it is believed that the advantage of the 2022 criteria is that they include both clinical and imaging criteria (3, 5), which could reduce the effect of such discrepancies and thus increase the sensitivity of TAK diagnosis.

The strength of this study is that it

demonstrated significant differences in TAK-related clinical and imaging features based on the 2022 criteria for TAK between patients with YOTAK and those with LOTAK. This study also has several limitations. First, because this study was conducted retrospectively on Korean patients with TAK, it was not possible to accurately identify, compare, or adjust for risk factors for arteriosclerosis among the groups, such as exact disease-exposure durations, cardiovascular risk profiles, obesity or metabolic syndrome. Moreover, since the radiology reports were collected, reviewed, and interpreted retrospectively, it was impossible to blind the clinical data to the image readers or to establish the standard operating definitions for site involvement in this study. We were also unable to comprehensively assess treatment response, treatment exposure, or the disease course after diagnosis. Second, because this study only included TAK patients from a single-centre cohort, the number of TAK patients was not sufficient to generalise the results of this study and apply them to Korean patients with TAK immediately. Additionally, we recognise the need for an external validation process to minimise the potential referral bias inherent in a single-centre study, and this should be incorporated into future research. Third, another critical limitation was that this study could not precisely identify the reasons for the discrepancy between clinical and imaging features based on the 2022 criteria for TAK but proposed only a few inferences. Finally, it was regrettable that this study could not include clinical evaluation items, such as the Takayasu Arteritis Integrated Disease Activity Index at diagnosis, or radiological assessment items, such as the Positron Emission Tomography Vascular Activity Score at diagnosis (15, 16). We believe that future prospective studies with more patients will provide more valuable, reliable, and dynamic information on age-dependent clinical features of patients with TAK.

In conclusion, results of this study revealed that patients with LOTAK exhibited higher frequencies of bruit, reduced brachial arterial pulse, and systolic BP difference in arms, but a lower frequency of ascending aorta involvement than those with YOTAK.

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