Long-term outcomes of large artery thromboangiitis obliterans and comparison with small artery thromboangiitis obliterans

Sang Ah Lee, MD[a], Min-Jae Jeong, MD, PhD[b], Gi-Young Ko, MD, PhD[c], Hee Sang Hwang, MD, PhD[d], Dong Il Gwon, MD, PhD[c], Eol Choi, MD, PhD[a], Tae-Won Kwon, MD, PhD[a], Yong-Pil Cho, MD, PhD[a,*] iD

Abstract

Although the distribution of arterial involvement is still the subject of controversy for defining the diagnostic criteria for thromboangiitis obliterans (TAO), several reports have described TAO involving the more proximal arterial segment. This study aimed to investigate the clinical characteristics and outcomes of large artery TAO in comparison with those of small artery TAO.

Between January 2007 and July 2019, 83 consecutive symptomatic patients with a diagnosis of lower extremity TAO were stratified according to the most proximal arterial involvement, with the cutoff level of the adductor canal as a reference (large artery TAO versus small artery TAO), and analyzed retrospectively. The study outcomes included any amputations and major amputations.

The large artery TAO group consisted of 30 patients (36.1%), and the small artery TAO group consisted of 53 patients (63.9%). In terms of clinical symptoms and signs, the proportion of major tissue loss (Rutherford class 6) was significantly higher among patients with large artery TAO than among those with small artery TAO (13.3% versus 0%, $P = .02$). Any amputation rate was similar between the large and small artery TAO groups during the median follow-up period of 148 months (range, 0–376 months) (43.3% versus 28.3%, $P = .16$). However, the major amputation rate was significantly higher among patients with large artery TAO (13.3% versus 0%, $P = .02$). On Kaplan–Meier survival analysis of the cumulative event-free rates, although there was a similar 10-year amputation-free survival rate ($P = .24$) between the 2 groups, the large artery TAO group had a significantly lower 10-year major amputation-free survival rate ($P < .01$) than the small artery TAO group.

Large artery TAO is a limb-threatening condition and had a worse prognosis than small artery TAO.

Abbreviations: CTA = computed tomography angiography, TAO = thromboangiitis obliterans, WIQ = walking impairment questionnaire.

Keywords: artery, diagnosis, outcome, smoking, thromboangiitis obliterans

[a] Department of Surgery, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea, [b] Department of Surgery, GangNeung Asan Hospital, University of Ulsan College of Medicine, Gangneung, Republic of Korea, [c] Department of Radiology, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea, [d] Department of Pathology, University of Ulsan College of Medicine and Asan Medical Center, Seoul, Republic of Korea.

* Correspondence: Yong-Pil Cho, Division of Vascular Surgery, Department of Surgery, University of Ulsan College of Medicine and Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea (e-mail: ypcho@amc.seoul.kr).

1. Introduction

Conventionally, thromboangiitis obliterans (TAO) is known to be an unusual non-atherosclerotic inflammatory arteritis that is characterized by segmental thrombotic occlusions of small- and medium-sized arteries and veins of the extremities affecting younger smokers.[1–4] However, the clinical spectrum has changed over time, and this is partly explained by a lack of universally accepted and standardized diagnostic criteria.[2] Contrary to the previous TAO diagnostic criteria,[5] several studies have suggested that age alone should not exclude a diagnosis of TAO,[2,6] and, in some rare cases, TAO has been reported to involve the coronary, carotid, and other large arteries; it has also been associated with multisystem involvement with systemic manifestations.[6–16] Smoking is strongly associated with the occurrence of TAO, suggesting that smoking plays a role in the pathogenesis of the disease; however, the specific pathogenetic mechanisms underlying the disease are still unknown.[1]

Despite the high amputation rates (ranging from 26%–48%) among TAO patients,[1–4] their life expectancy is reported to be comparable with that of age-matched controls.[2,3] Furthermore, the fact that TAO more commonly affects younger patients could lead to a heavy social and economic impact associated with the disease. Therefore, for TAO patients in jeopardy of losing a foot or leg, aggressive therapeutic intervention is required not only to avoid major amputation (allowing a return to ambulation) but

also to avoid a socioeconomic catastrophe (allowing a return to work) among these younger patients.[17,18] This study aimed to investigate the clinical characteristics and outcomes of TAO involving large arteries in comparison with those of TAO involving small arteries.

2. Patients and methods

2.1. Study design and study sample

In this single-center, retrospective, case-control study, we analyzed the data extracted from the medical records of our hospital's database using an electronic search to identify the diagnosis of TAO. Approval for data collection and publication was obtained from the institutional review board at our hospital (IRB No. 2019-0947), which waived the requirement for written informed consent because of the study's retrospective design. All methods were performed in accordance with the relevant guidelines and regulations.

Between January 2007 and July 2019, 189 consecutive symptomatic patients with a diagnosis of TAO on the basis of medical records were screened for inclusion in this study. All medical records and imaging data were independently re-evaluated by 2 specialized vascular surgeons and 2 board-certified radiologists. The diagnosis of TAO in our series was made among younger smokers aged less than 50 years at symptom onset and based on strict criteria[2] as follows: typical computed tomography angiography (CTA) or arteriographic findings[1,2,19] with or without typical pathological findings,[2,7,19–21] the absence of connective tissue disorders and atherosclerotic risk factors other than smoking, and the presence of superficial or deep thrombophlebitis. We excluded patients with no smoking history (n=2), upper extremity TAO (n=4), connective tissue disorders (n=13), and atherosclerotic risk factors (n=23), as well as patients lost to follow-up (n=38). Based on our strict diagnostic criteria, patients with equivocal TAO diagnoses according to re-evaluated imaging reports (n=26) were also excluded. Among patients with bilateral involvement, only the limb with more severe (according to clinical symptoms and signs and CTA or arteriographic findings) was included in the analysis. We ultimately included 83 symptomatic lower extremity TAO patients stratified into 2 groups according to the most proximal arterial involvement at the cutoff level of the adductor canal as a reference: large artery TAO, defined as involvement of the aortoiliac or femoral arteries, and small artery TAO, defined as involvement of the popliteal or tibial arteries. Our management strategy for TAO was determined based on signs and symptoms of limb ischemia (Rutherford class) as previously detailed[18]; conservative treatment, including smoking cessation, was the first line of treatment for patients without critical limb ischemia (Rutherford class 1–3), whereas a more aggressive therapeutic approach, with either surgical or endovascular intervention, was performed for selected patients with critical limb ischemia (Rutherford class 4–6) or whose with local symptoms refractory to conservative treatment.

The demographics and other data for all consecutive patients, including age at diagnosis, symptom duration, clinical and anatomical characteristics, procedural details, smoking cessation, and follow-up data were recorded in an Excel (Microsoft Corp., Redmond, WA) database and analyzed retrospectively.

2.2. Definitions of study outcomes and follow-up

The study outcomes were any amputations during the study period. Amputations were classified as either major (above the ankle) or minor (below the ankle) of the index limb.[18,22] Long-term ambulatory limitations were also assessed using the walking impairment questionnaire (WIQ).[23,24] The WIQ is a disease-specific questionnaire validated for use among patients with intermittent claudication; it consists of 4 subcategories: pain, distance, walking speed, and stair climbing.[24,25] The WIQ, which was translated into Korean using standard translation/back-translation procedures, was modified to be self-administered or interviewer-administered by telephone. In the analysis, we did not include patency outcomes after surgical or endovascular procedures because of the small number of patients received intervention in the small artery TAO group.

Patients were followed up in the outpatient clinic according to each patient's clinical status. The latest follow-up data, including all treatments performed for TAO, the presence or absence of limb amputation, smoking cessation, and the WIQ data, were recorded and analyzed.

2.3. Statistical analyses

Statistical analysis was performed using SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Categorical variables are reported as frequencies or percentages and continuous variables as means and standard deviations or medians and ranges. Categorical variables were compared using the chi-square test or Fisher exact test when the chi-square test was not appropriate. Student t test was used for comparisons of normally distributed continuous variables, and the Mann–Whitney rank test was used for comparisons of non-normally distributed continuous variables. Cox proportional hazards regression modeling was used to identify possible significant variables associated with the aforementioned study outcomes in the entire study sample, and hazard ratios with 95% confidence intervals are reported. Variables with P values <.1 on univariable analysis were subjected to multivariable analysis. Long-term outcomes between patients with large artery and small artery TAO were analyzed using Kaplan–Meier survival curves, and the log-rank test was used to compare the occurrence of events. P values <.05 were considered statistically significant.

3. Results

A total of 83 patients included in this study were diagnosed with symptomatic lower extremity TAO based on our diagnostic criteria. Eligible patients were stratified into 2 groups according to the most proximal arterial involvement at the cutoff level of adductor canal as a reference: the large artery TAO group (n=30, 36.1%) and the small artery TAO group (n=53, 63.9%). The distributions of arterial involvement of the study sample are shown in Figure 1.

The baseline characteristics of the patients are presented in Table 1. All patients were smokers without serious cardiopulmonary comorbidities at the time of the diagnosis of TAO. The initial TAO diagnosis was made based on the presence of typical CTA or arteriographic findings in addition to the clinical history and physical examination findings. Age at diagnosis, symptom duration, and smoking history were similar between the 2 groups. Fourteen patients (14/83, 16.9%) continued or
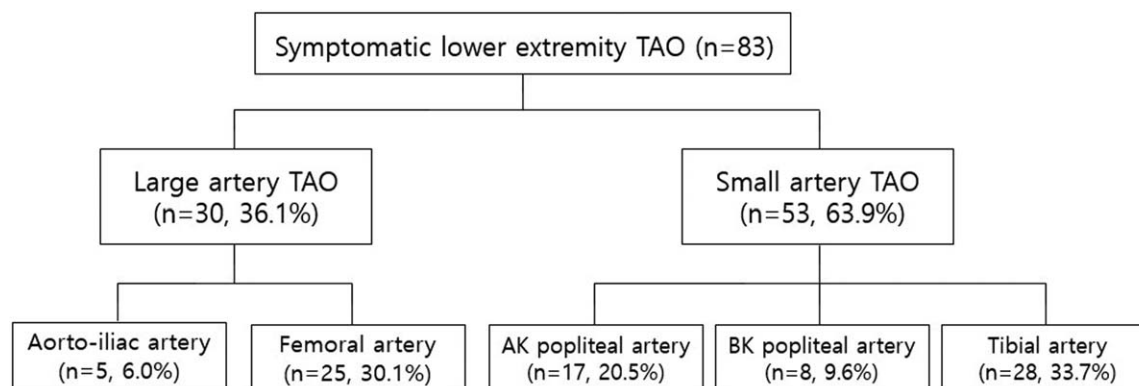
Figure 1. The distributions of arterial involvement of the study sample. A total of 83 symptomatic lower extremity TAO patients were stratified into 2 groups according to the most proximal arterial involvement at the cutoff level of the adductor canal as a reference: large artery TAO and small artery TAO. Values are presented as numbers of patients and percentages. AK=above knee, BK=below knee, TAO=thromboangiitis obliterans.

resumed smoking. In terms of clinical symptoms and signs, the proportion of patients with major tissue loss (Rutherford class 6) was significantly higher in the large artery TAO group than that in the small artery TAO group (13.3% versus 0%, $P=.02$). Among the patients with small artery TAO, 35 (35/53, 66.0%) received medical treatment, whereas 73.3% of patients with large artery TAO (22/30) underwent either surgical or endovascular interventions ($P<.01$). Among the patients who received surgical treatment, histopathological examination of the arterial segments was performed for 15 patients in the large artery TAO group (15/21, 71.4%) and 9 patients in the small artery TAO group (9/14, 64.3%). Among these patients, we confirmed the diagnosis of TAO based on typical histopathological findings [2, 7, 19–21] among 5 patients with large artery TAO (5/15, 33.3%) and 2 patients with small artery TAO (2/9, 22.2%). Figure 2

demonstrates the CTA and typical histopathological findings in a 45-year-old man with large artery TAO involving the aorta.

The study outcomes are summarized in Table 2. The overall rate of amputations was 33.7% (28/83) during the median follow-up period of 148 months (range, 0–376 months). There were similar overall amputation rates (43.3% versus 28.3%, $P=.16$) and minor amputation rates (30.0% versus 28.3%, $P=.87$) between the 2 groups; however, the major amputation rate was significantly higher among patients with large artery TAO than among those with small artery TAO (13.3% versus 0%, $P=.02$). Among the 53 patients in the small artery TAO group, 8 atherosclerosis risk factors (2 developed hypertension and 6 developed diabetes mellitus) during the follow-up period, and 5 of these patients, including 1 with hypertension and 2 with diabetes mellitus, exhibited radiological progression of proximal

Table 1

Baseline characteristics of the study population stratified into 2 groups according to the most proximal arterial involvement.

	Total (n=83)	Large artery TAO (n=30)	Small artery TAO (n=53)	P value
Age at diagnosis (yrs)	34.1±7.4	33.4±6.9	34.5±7.8	.52
Symptom duration (mos)[*]	14.8±24.3	15.1±22.0	14.6±25.8	.92
Male sex	82 (98.8)	30 (100)	52 (98.1)	>.99
BMI (kg/m^2)	24.0±3.7	23.6±3.8	24.3±3.7	.43
Smoking history				
Age at smoking initiation (yrs)	20.0±3.2	20.4±3.8	19.7±2.7	.35
Duration (pack-years)	15.1±10.5	14.2±9.3	15.7±11.3	.57
Current smoker	14 (16.9)	4 (13.3)	10 (18.9)	.52
Rutherford class				
1. Mild claudication	18 (21.7)	5 (16.7)	13 (24.5)	.40
2. Moderate claudication	7 (8.4)	3 (10.0)	4 (7.5)	.70
3. Severe claudication	7 (8.4)	3 (10.0)	4 (7.5)	.70
4. Ischemia rest pain	2 (2.4)	1 (3.3)	1 (1.9)	>.99
5. Minor tissue loss	45 (54.2)	14 (46.7)	31 (58.5)	.30
6. Major tissue loss	4 (4.8)	4 (13.3)	0 (0)	.02
Therapeutic modality				
Medical treatment	43 (51.8)	8 (26.7)	35 (66.0)	<.01
Intervention	40 (48.2)	22 (73.3)	18 (34.0)	<.01
Surgical treatment	35 (42.2)	21 (70.0)	14 (26.4)	<.01
Endovascular treatment	5 (6.0)	1 (3.3)	4 (7.5)	.65

Continuous data are presented as means±standard deviations; categorical data are given as number (%).

BMI=body mass index, TAO=thromboangiitis obliterans.

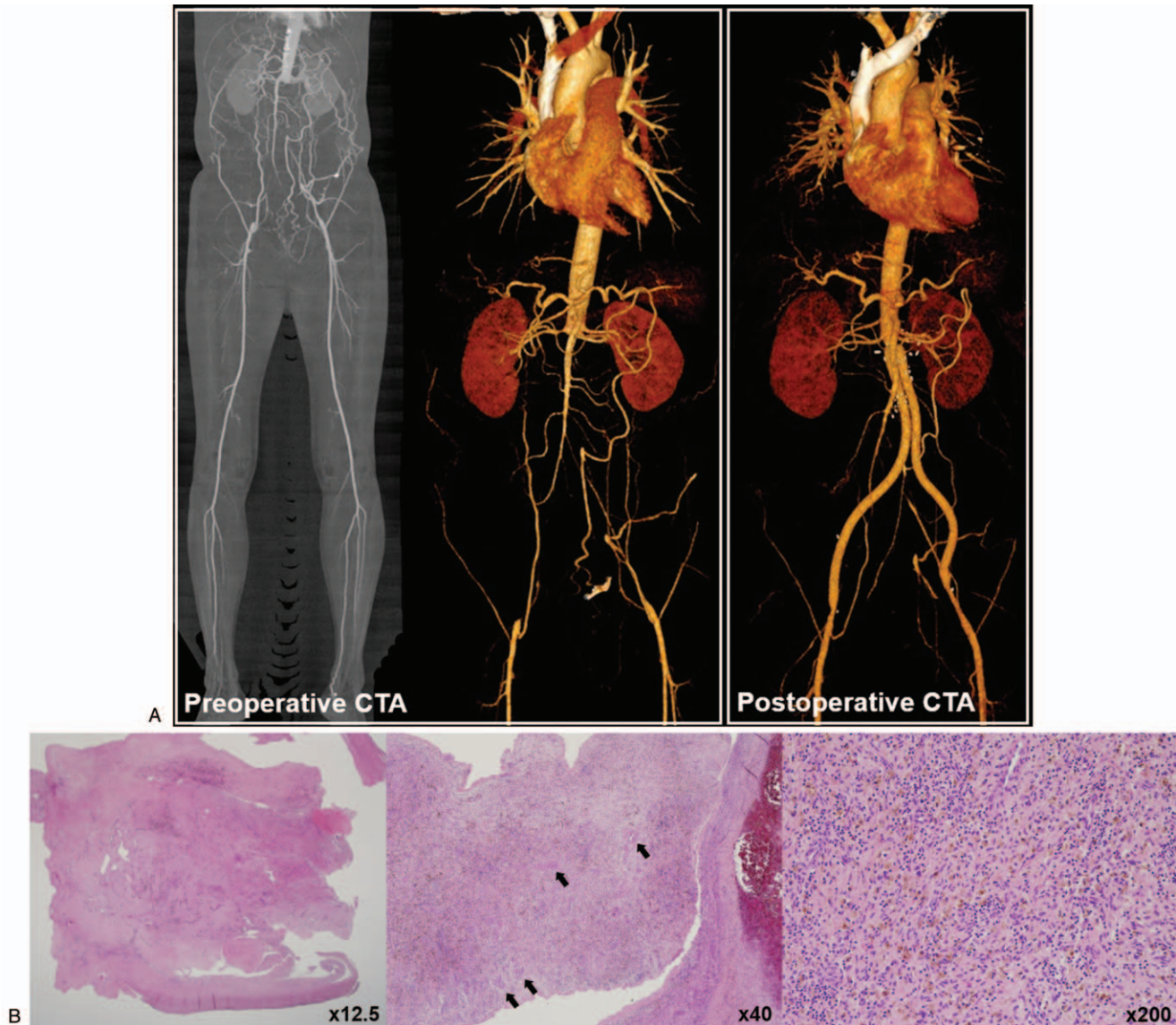[*] Duration from symptom onset to the diagnosis of TAO.

Figure 2. Representative figure of CTA and typical histopathological findings in a 45-year-old man with large artery TAO involving the aorta. (A) Pre-operative CTA shows total occlusion of the infrarenal aorta to both iliac arteries. Note the patent lower extremity arteries from the abdominal wall collateral arteries without abnormal findings (left and middle panels). After aorto-biiliac bypass surgery, postoperative CTA showed a well-placed Y-graft with patent distal arterial flow (right panel). (B) Photomicrography of the transverse section of the resected aorta showing occlusion of the aortic lumen by an irregular-shaped, fibro-inflammatory thrombus (H & E, ×12.5, left panel). The thrombus has exuberant cellular components with multifocal neovascularization (arrows) (H & E, ×40, middle panel). The cellular components are composed of the mixed inflammatory cells, many stromal fibroblasts, and hemosiderin-laden macrophages (H & E, ×200, right panel). CTA = computed tomography angiography, TAO = thromboangiitis obliterans.

arterial involvement. However, none of these patients underwent additional amputations or interventions.

Univariable and multivariable Cox proportional hazards regression analyses were performed to identify clinical variables associated with long-term outcomes. After adjustment for potential confounding variables, multivariable analysis of the association between clinical variables and the 10-year amputation rate indicated that the Rutherford classification at the time of TAO diagnosis was the only independent predictor of an increased risk of any amputations during the 10-year follow-up period (hazard ratio, 2.05; 95% confidence interval, 1.20–3.48; $P < .01$) (Table 3). The low number of major amputations (n = 4) limited our ability to assess the correlation between clinical variables and the 10-year major amputation rate with a Cox proportional hazards regression model.

On Kaplan–Meier survival analyses of the cumulative event-free rates, although there was a similar 10-year amputation-free survival rate ($P = .24$) between the 2 groups, the large artery TAO group had a significantly lower 10-year major amputation-free survival rate ($P < .01$) than the small artery TAO group (Fig. 3).

The long-term ambulatory limitations of TAO patients were investigated using the WIQ. The response rate was 68.7% (57/83): 56.7% in the large artery group (17/30) and 75.4% in the small artery group (40/53). The mean time interval between TAO diagnosis and questionnaire completion was 140.8 ± 94.4 months. The mean WIQ score was 32.8 ± 17.5, and there was

Table 2

Study outcomes of the study population stratified into 2 groups according to the most proximal arterial involvement.

	Total (n=83)	Large artery TAO (n=30)	Small artery TAO (n=53)	P value
Any amputation	28 (33.7)	13 (43.3)	15 (28.3)	.16
Major amputation	4 (4.8)	4 (13.3)	0 (0)	.02
Above-knee amputation	1 (1.2)	1 (3.3)	0 (0)	.36
Below-knee amputation	3 (3.6)	3 (10.0)	0 (0)	.04
Minor amputation	24 (28.9)	9 (30.0)	15 (28.3)	.87

Values in parentheses are percentages.
TAO = thromboangiitis obliterans.

Table 3

Factors associated with an increased risk of any amputations during the 10-year follow-up period.

	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis	1.01 (0.95–1.06)	.87	NA	NA
Symptom duration	1.00 (0.98–1.01)	.82	NA	NA
Male gender	20.61 (0.00–NA)	.67	NA	NA
BMI	0.85 (0.75–0.96)	<.01	0.89 (0.79–1.01)	.08
Age at smoking	1.02 (0.90–1.15)	.79	NA	NA
Duration of smoking	0.99 (0.96–1.03)	.65	NA	NA
Current smoker	0.68 (0.84–1.95)	.47	NA	NA
Rutherford classification	2.32 (1.35–4.01)	<.01	2.05 (1.20–3.48)	<.01
Small artery TAO	0.64 (0.29–1.38)	.25	NA	NA
Medical treatment	0.46 (0.21–1.04)	.06	0.70 (0.15–3.24)	.65
Surgical treatment	1.96 (0.90–4.27)	.09	1.29 (0.29–5.68)	.74
Endovascular treatment	1.38 (0.33–5.87)	.66	NA	NA

BMI = body mass index, CI = confidence interval, HR = hazard ratio, NA = not applicable, TAO = thromboangiitis obliterans.
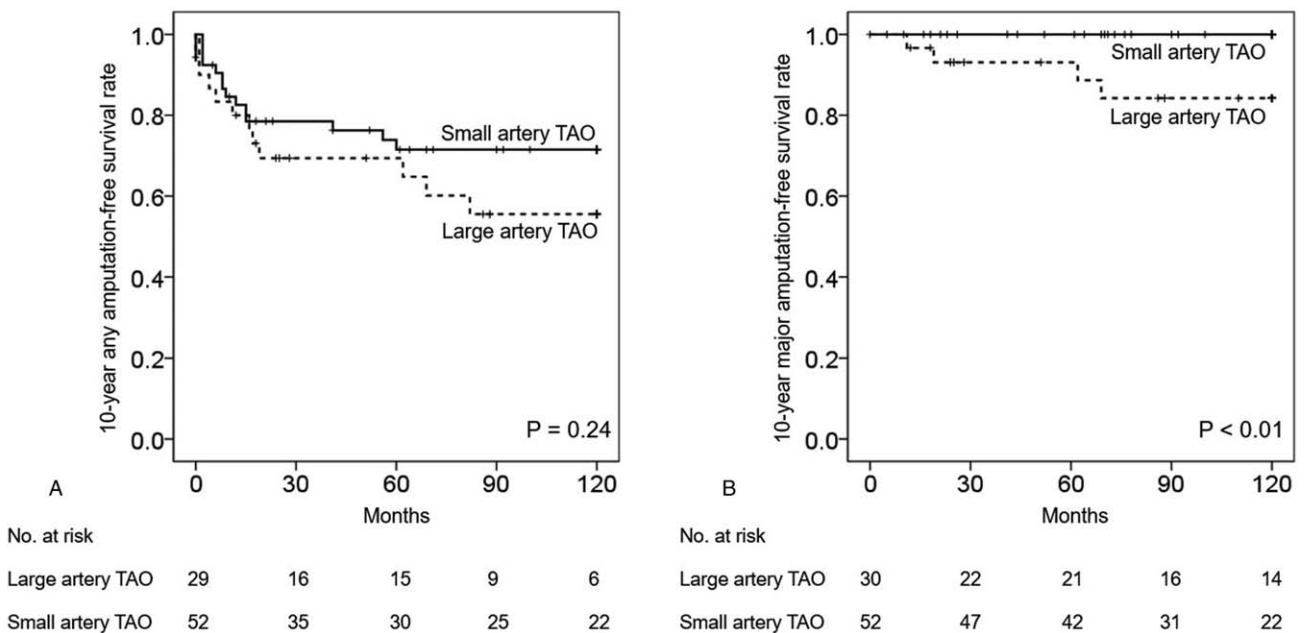

Figure 3. Kaplan–Meier analyses of cumulative event-free rates. (A) Ten-year any amputation-free and (B) major amputation-free survival rates among patients in the large artery and small artery TAO groups. TAO = thromboangiitis obliterans.

Table 4

Comparison of WIQ scores between patients with large artery and small artery TAO.

	Total	Large artery TAO	Small artery TAO	*P* value
No. of patients[*]	57 (68.7)	17 (56.7)	40 (75.4)	.08
Follow up duration (mos)				
Mean ± SD	140.8 ± 94.4	151.2 ± 101.9	134.9 ± 90.4	.45
Median (ranges)	148.0 (0–376)	163.5 (12–376)	137.0 (0–339)	.45
WIQ scores				
Mean ± SD	32.8 ± 17.5	38.4 ± 18.6	30.4 ± 16.5	.11
Median (ranges)	25 (19–90)	33 (21–90)	23 (19–85)	.11

Continuous data are presented as means ± standard deviations; categorical data are given as number (%).
SD = standard deviations, TAO = thromboangiitis obliterans, WIQ = walking impairment questionnaire.
[*] Patients responded to WIQ.

no significant difference in WIQ scores between the 2 groups (38.4 ± 18.6 versus 30.4 ± 16.5, *P* = .11) (Table 4).

4. Discussion

Since Buerger reported detailed the pathologic characteristics of TAO in 11 amputated limbs,[20] its clinical spectrum has been changing—the male-to-female ratio is decreasing, more elderly patients are being affected, and upper extremity involvement is commonly seen.[2,6] In some rare cases, TAO may involve large arteries, or it may manifest with multisystem involvement and systemic features.[6–14] Therefore, there have been varied definitions and diagnostic criteria for TAO between different studies,[1–5,17,26] and consequently, the prevalence is not clearly known.[2] Despite the lack of a unified method for establishing the diagnosis, several studies with relatively larger cohorts have reported on long-term clinical and social consequences of TAO based on the varying diagnostic criteria.[1–4,17]

Most recently, Le Joncour et al[1] reported a nationwide study of 224 patients with TAO fulfilling Papa's criteria[26] and showed that 34% of TAO patients will experience an amputation within 15 years from the diagnosis; ethnic group (non-white) and limb infection at diagnosis were significantly associated with vascular events, and limb infection was an independent risk factor for limb amputation. Olin et al[2] reported 112 patients with TAO from 1970 to 1987, based on their diagnostic criteria, with a 27% amputation rate, and showed that the clinical spectrum changed over time, with an increase in prevalence among women, and that patients who stopped smoking had a lower amputation rate. With similar clinical criteria to those of Shionoya,[5] Cooper et al[4] reported 111 patients from 1976 to 1999 at the Mayo Clinic with a time-dependent amputation rate of 48% at 10 years.

Although medical treatment and smoking cessation are sometimes sufficient to induce a remission of the ischemic symptoms, TAO demonstrates an intimate relationship of remission and relapse with cessation and resumption of smoking,[26] respectively, and the resulting ischemia may lead to severe chronic symptoms, such as non-healing ulceration and gangrene, and even major amputation.[18,27] Successful arterial bypass surgery dramatically improves the signs and symptoms of ischemia; however, bypass surgery is not always feasible for TAO involving small- and medium-sized arteries with poor distal runoff.[18] Recently advanced less-invasive endovascular treatment is a technically feasible and potentially effective treatment modality for TAO.[22,28–30] However, despite more aggressive and advanced therapeutic options, there remains a high rate of amputations associated with TAO.[1–4]

TAO has been considered to be limited to the small- and medium-sized arteries of the distal extremities affecting younger smokers. However, recently, age and the distribution of arterial involvement have been the subjects of controversy for defining diagnostic criteria. Several studies have suggested that age alone should not exclude a diagnosis of TAO, and studies have reported 16%[6] and 29%[2] of TAO patients as aged 50 years and older when first diagnosed. Olin et al[2] suggested that large artery involvement may be due to increased thrombosis secondary to extremely poor distal runoff, whereas several reports have described patients with TAO in more proximal arterial segments, such as the iliac or femoral arteries.[6,13–16] Based on the Nationwide Survey of Intractable Vasculitis database in Japan, Sasaki et al[6] reported the distribution of arterial involvement in TAO. In this series, based on the strict diagnostic criteria established by the Ministry of Health and Welfare in Japan, large artery involvement was common, affecting the iliac artery in 5.3% and the femoral artery in 12.3% of the lower extremity arteries.[6] Although they did not report the pathological findings of patients with large artery involvement, TAO seems to not be limited to the infrapopliteal small- and medium-sized distal arteries. Despite a great number of publications, there are still no universally accepted and standardized diagnostic criteria for defining TAO and the extent of arterial involvement.[26]

In the present study with specified age criteria (<50 years at symptom onset), we found 30 TAO patients with involvement of large arteries (the aortoiliac and femoral arteries). The initial diagnosis of TAO was according to imaging findings in addition to the clinical history and physical examination findings. Among patients with large artery TAO, the histopathological confirmation of the diagnosis[2,7,19–21] was obtained for only 5 patients (5/30, 16.7%). Therefore, we could not completely rule out the possibility of increased thrombosis in the more proximal artery secondary to the poor distal runoff in the remaining patients with large artery TAO. However, in our series, the diagnosis of TAO was made based on strict criteria in all patients to confirm a definitive diagnosis, and patients with an equivocal diagnosis were excluded. Thus, the diagnosis of TAO was not in doubt in any of the patients analyzed.

Despite the small sample size and its retrospective design, the strengths of this study included its comparison of outcomes between the 2 groups—large artery and small artery TAO— according to the most proximal arterial involvement at the cutoff level of the adductor canal as a reference, and its suggestion of the new disease entity TAO with large artery involvement resulting in a higher major amputation rate. We achieved a median follow-up

period of 148 months, which allowed us to capture the effect of TAO on long-term rates of amputations and ambulatory limitations. Our findings have provided more insight into the clinical and social outcomes of large artery TAO over time.

This study did have its limitations. Similar to other previous studies, it was a retrospective analysis of single-center registry data from a relatively small number of patients and thus was subject to selection and information biases. Patients with upper extremity TAO were excluded to ensure that the impact of lower extremity TAO involving larger arteries on long-term clinical outcomes was specifically analyzed. A set of strict and well-defined clinical diagnostic criteria is essential for any study of TAO to ensure the homogeneity of the selected patient population for valid comparisons.[5] Therefore, we excluded patients with an equivocal diagnosis of TAO, and the number of the excluded patients was considerable. Although the diagnosis of TAO in our series was based on strict criteria, including the specified age criteria, supported by imaging findings independently re-evaluated by 2 board-certified radiologists in all patients to confirm a definitive diagnosis, a small number of patients with large artery TAO had their diagnoses confirmed based on the typical histopathological findings. We calculated patient age at baseline by using the patient self-reported age at symptom onset, which may have been inaccurate owing to the lag between the times of symptom and disease onset. A comparison of clinical manifestations evaluated by Rutherford classification was made in this study; the Rutherford classification may not be the best way to evaluate the clinical manifestations of TAO. The ascertainment of smoking cessation by chart review and survey might not have accurately reflected actual smoking cessation; a substantial number of TAO patients who reported smoking cessation may have continued to smoke. Our study cohort comprised only subjects of Asian descent; thus, because there may be racial/ethnic differences in the prevalence and clinical characteristics of TAO, our findings should be interpreted with caution with respect to different racial and ethnic groups. Based on the small sample size, this study was likely underpowered to provide robust evidence. Future multicenter studies with larger sample sizes should lead to a better understanding of the effects of TAO on clinical and social outcomes, as well as the natural history and outcomes among patients with large artery TAO.

In conclusion, although there were important limitations, and although our analysis involved only a small number of patients, it revealed that large artery TAO is a relatively common limb-threatening condition with a worse prognosis than small artery TAO. Therefore, young smokers without any connective tissue disorders and atherosclerotic risk factors other than smoking should be carefully evaluated with a high index of suspicion of TAO, even if the more proximal arterial segments are involved.

Author contributions

Conceptualization: Yong-Pil Cho.
Data curation: Sang Ah Lee, Min-Jae Jeong, Eol Choi, Tae-Won Kwon, Yong-Pil Cho.
Formal analysis: Sang Ah Lee, Min-Jae Jeong, Gi-Young Ko, Hee Sang Hwang, Dong Il Gwon, Eol Choi, Yong-Pil Cho.
Investigation: Sang Ah Lee, Min-Jae Jeong, Gi-Young Ko, Hee Sang Hwang, Dong Il Gwon, Eol Choi, Tae-Won Kwon, Yong-Pil Cho.
Methodology: Sang Ah Lee, Min-Jae Jeong, Gi-Young Ko, Hee Sang Hwang, Dong Il Gwon, Yong-Pil Cho.
Project administration: Yong-Pil Cho.
Supervision: Hee Sang Hwang, Dong Il Gwon, Tae-Won Kwon.
Validation: Sang Ah Lee, Min-Jae Jeong, Tae-Won Kwon.
Visualization: Sang Ah Lee, Min-Jae Jeong, Tae-Won Kwon.
Writing – original draft: Sang Ah Lee, Gi-Young Ko, Hee Sang Hwang, Yong-Pil Cho.
Writing – review & editing: Yong-Pil Cho.

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