

# Pulmonary Artery Involvement in Patients with Takayasu Arteritis

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**ABSTRACT. Objective.** This study was performed to explore the clinical manifestations and longterm prognosis in patients with Takayasu arteritis (TA) with pulmonary artery involvement (PAI).

**Methods.** The medical records of 194 patients with TA who underwent traditional catheter angiography or computed tomography of pulmonary artery from 2009 to 2016 were retrospectively reviewed. The clinical manifestations, angiographic features, and mortality of 128 patients with TA with PAI were further analyzed.

**Results.** Patients with TA with PAI had a higher risk of pulmonary hypertension (PH) than patients with TA alone (61.7% vs 7.6%,  $p < 0.001$ ). Patients with PAI and PH more frequently developed dyspnea, hemoptysis, and lower limbs edema (all  $p < 0.05$ ) than those without PH. Patients with PH also had a higher incidence of bilateral PAI (84.8% vs 34.7%,  $p < 0.001$ ) and a higher pulmonary artery obstruction index [23 (interquartile range 20–27) vs 10 (6–15),  $p < 0.001$ ]. Left heart disease was presented in 39 (30.5%) patients with TA with PAI. During the median followup of 38 (21–58) months, 19 and 2 deaths occurred among patients with and without PH, respectively. Among patients with PAI, the mortality rate was 7 times higher in patients with than without PH ( $p = 0.009$ ). Independent predictors of mortality were the disease duration ( $p = 0.047$ ), New York Heart Association class III/IV ( $p = 0.019$ ), right ventricular systolic dysfunction ( $p = 0.019$ ), and respiratory failure ( $p = 0.007$ ).

**Conclusion.** Patients with TA with PAI have a higher risk of developing PH than patients with TA alone. The presence of PH in patients with PAI increases the risk of early mortality. (J Rheumatol First Release October 15 2019; doi:10.3899/jrheum.190045)

## Key Indexing Terms:

TAKAYASU ARTERITIS  
PULMONARY HYPERTENSION

PULMONARY ARTERY  
PROGNOSIS

Takayasu arteritis (TA) is a chronic granulomatous vasculitis that primarily affects the aorta and its main branches, including the pulmonary artery (PA)<sup>1,2,3</sup>. The profound inflammatory process in the affected arteries can lead to stenosis, occlusion, aneurysms, and end-organ ischemia, thereby increasing the risk of cardiovascular morbidity and mortality.

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PA involvement (PAI) is frequent, occurring in 20–56% of patients with TA, according to autopsy reports<sup>4,5</sup>. However, the pulmonary circulation is often overlooked in the initial assessment of patients with TA. Pulmonary hypertension (PH) is a major complication in the course of TA-associated PAI<sup>6–12</sup>. The diagnosis of PH carries a 7-fold higher risk of early mortality in many different clinical conditions<sup>13</sup>. Because of the rarity of the disease, few studies have comprehensively investigated the clinical manifestations and longterm outcomes of TA with PAI.

In our present study, we explored the clinical manifestations and longterm prognosis of a relatively large cohort of patients with TA with PAI. The aim of our study was to help clinicians systematically recognize PAI in patients with TA.

## MATERIALS AND METHODS

**Patients.** The medical records of 598 consecutive inpatients diagnosed with TA from January 2009 to December 2016 were retrospectively reviewed. Of 194 patients who underwent traditional catheter angiography or computed tomography (CT) of PA, 128 had PAI. The patients' medical records were retrospectively reviewed for demographic data, clinical symptoms and signs, comorbidities, laboratory test results, echocardiographic variables, and imaging findings. This research conformed to the ethical guidelines of the 1975 Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Fuwai Hospital (2010-246).

**Diagnosis and classification.** TA was classified in accordance with the 1990 American College of Rheumatology criteria<sup>14</sup>. All patients fulfilled at least 3 of the following 6 criteria: age of < 40 years at onset, claudication of the extremities, a decreased brachial artery pulse, a blood pressure difference of > 10 mmHg, bruit over the subclavian arteries or aorta, and arteriogram abnormalities<sup>14</sup>. The subtypes of systemic artery involvement were classified into 5 types (I, IIa, IIb, III, IV, and V) based on the classification proposed by Hata, *et al*<sup>15</sup>.

PAI was defined as the presence of vascular involvement manifested as stenosis, occlusion, dilation, or aneurysm formation in either PA. For patients who underwent CT pulmonary angiography, we used the PA Obstruction Index (PAOI) to quantify the degree of PA obstruction<sup>16</sup>. The PAOI can be expressed as  $\Sigma (n \times d) / 40 \times 100$ , where *n* is the value of the proximal obstruction in the PA tree equal to the number of segmental branches arising distally (minimum, 1; maximum, 20), and *d* is the degree of obstruction (minimum, 0; maximum, 2)<sup>16</sup>. According to routine clinical practice at Fuwai Hospital, each PA imaging examination was systematically assessed by qualified chest radiologists. The results were further reviewed by senior chest radiologists.

All the 194 patients with TA in our study underwent echocardiography by certified echocardiologists. The result of each echocardiographic examination was also systematically reviewed by a senior echocardiologist. According to the European Society of Cardiology/European Respiratory Society guidelines for PH, patients with PAI were considered to have a high probability of PH if their peak tricuspid regurgitation velocity (TRV) was 3.4 m/s with or without the presence of other echo "PH signs"<sup>17</sup>. Patients with a peak TRV of 2.9–3.4 m/s and additional echo signs suggestive of PH were also considered to have a high probability of PH<sup>17</sup>. The PA systemic pressure is estimated based on the peak TRV, taking the right atrial pressure into account according to the simplified Bernoulli equation<sup>17</sup>. Based on the echocardiographic measurements, left heart disease (LHD) was considered to be present in patients with left atrial or left ventricular enlargement, left ventricular hypertrophy, moderate or severe left heart valve disease, and a left ventricular ejection fraction of < 50%.

**Outcome and followup.** The major outcome was all-cause mortality. Patients were followed up by consulting the hospital records or performing the clinic interviews or telephone surveys. The followup duration was defined as the length of time from the first admission to March 2018. For the patients who died during followup, the followup duration was defined as the length of time in months from the first admission to the time of death. Patients who were lost to followup were censored at their last available followup visit.

**Statistical analysis.** Continuous variables with a normal distribution are presented as mean and SD. The differences between groups were analyzed by Student *t* test. Continuous variables with a non-normal distribution are expressed as median and interquartile range. Comparisons between groups were performed using the Mann–Whitney *U* test. Qualitative variables are presented as number (percentage). The chi-square test or Fisher's exact test was used to compare the differences. Survival rates were estimated by the Kaplan–Meier method, and differences between groups were assessed by the log-rank test. Univariate and multivariate Cox proportional hazard regressions were used to detect factors independently associated with mortality. The data analysis was conducted using the SPSS 21.0 statistical package (IBM Corp.). Figures were presented by GraphPad Prism 6.01 (GraphPad Software).

## RESULTS

**Demographic data and clinical characteristics between patients with TA with and without PAI.** The demographic and clinical characteristics of patients with and without PAI are presented in Table 1. Among the 194 patients included in the current study (185 patients had CT and 54 patients had traditional PA angiography), 65% (120/185) of the patients were confirmed to have PAI by CT, and 98% (53/54) were

confirmed to have PAI by traditional PA angiography. In total, 66% (128/194) patients were diagnosed as PAI by CT or PA angiography. The mean age and disease duration of TA in the patients with PAI was  $39.2 \pm 12.3$  years and 60 (24–156) months, respectively, with no significant difference compared to patients without PAI. Patients with PAI more frequently developed dyspnea (74.2% vs 22.7%,  $p < 0.001$ ), hemoptysis (20.3% vs 3.0%,  $p = 0.001$ ), and leg edema (20.3% vs 3.0%,  $p = 0.001$ ). Patients with PAI also had an increased risk of developing PH (61.7% vs 7.6%,  $p < 0.001$ ) and were more often classified into New York Heart Association (NYHA) class III/IV (40.6% vs 19.7%,  $p = 0.003$ ). The patients with PAI had fewer systemic ischemia-related symptoms and comorbidities such as dizziness (18.0% vs 34.8%,  $p = 0.009$ ), limb claudication (19.5% vs 39.4%,  $p = 0.003$ ), hypertension (47.7% vs 77.3%,  $p < 0.001$ ), and stroke (3.9% vs 15.2%,  $p = 0.005$ ).

Detailed information regarding systemic artery involvement is shown in Figure 1. Patients with PAI had a lower tendency to have involvement of the renal artery (30.5% vs 42.4%,  $p = 0.097$ ), iliofemoral artery (9.4% vs 18.2%,  $p = 0.078$ ), and coronary artery (6.3% vs 13.6%,  $p = 0.085$ ). Patients with PAI had a higher tendency to be classified as having angiographic type IIa systemic artery involvement (8.6% vs 1.5%,  $p = 0.062$ ; Table 1). However, the differences in the distribution of the involved systemic arteries and angiographic classification were not statistically significant between the 2 groups (all  $p > 0.05$ ).

**Angiography features of PA lesion.** Most patients with PAI (84, 65.6%) had bilateral involvement. Among the other 44 (34.4%) patients with unilateral involvement, right and left PAI were present in 32 (25.0%) and 12 (9.4%) patients, respectively. The PA trunk was compensatorily enlarged in the patients with PH. The lobar PA (97, 75.8%) was the most commonly involved artery, followed by the main PA (63, 49.2%) and segmental PA (62, 48.4%). The distribution of the involved PA is shown in Table 2. The right upper lobar branches (72, 56.3%) were the most frequently involved regions. Multibranch PAI was more common than single-branch involvement (89.1% vs 10.9%). Stenosis and occlusion were the most frequent type of lesions. Aneurysm formation and *in situ* thrombosis in the PA were detected in 4 (3.1%) and 5 (3.9%) patients, respectively.

**Differences between patients with PAI with and without PH.** The comparisons between patients with PAI, with and without PH, are displayed in Table 3. Respiratory symptoms were the initial chief complaints in 68 patients (60 in the PH group vs 8 in the non-PH group,  $p < 0.001$ ). Among the other 60 patients without respiratory symptoms as the initial symptom, 27 patients were diagnosed with PAI within the first year of diagnosis of TA (10 in the PH group vs 17 in the non-PH group,  $p = 0.419$ ), 7 in the second to third year (0 in the PH group vs 7 in the non-PH group,  $p = 0.086$ ), and 26 patients after the third year (17 in the PH group vs 9 in the

Table 1. Demographic and clinical characteristics between patients with TA with and without PAI.

Characteristics	TA with PAI, n = 128	TA without PAI, n = 66	p
Age, yrs	39.2 ± 12.3	37.7 ± 14.8	0.493
Female	111 (86.7)	59 (89.4)	0.592
Disease duration of TA, mos	60 (24–156)	66 (7–216)	0.757
Hypertension	61 (47.7)	51 (77.3)	< 0.001
Hyperlipidemia	27 (21.1)	25 (37.9)	0.012
Diabetes	6 (4.7)	3 (4.5)	> 0.999
Stroke	5 (3.9)	10 (15.2)	0.005
Symptoms and signs			
Fever	14 (10.9)	6 (9.1)	0.689
Fatigue	38 (29.7)	22 (33.3)	0.603
Dizziness	23 (18.0)	23 (34.8)	0.009
Blurred vision	7 (5.5)	5 (7.6)	0.564
Limb claudication	25 (19.5)	26 (39.4)	0.003
Cough	26 (20.3)	8 (12.1)	0.155
Dyspnea on exertion	95 (74.2)	15 (22.7)	< 0.001
Chest pain	22 (17.2)	10 (15.2)	0.717
Hemoptysis	26 (20.3)	2 (3.0)	0.001
Syncope	11 (8.6)	6 (9.1)	0.908
Pulselessness	65 (50.8)	36 (54.5)	0.619
Asymmetric blood pressure	90 (70.3)	47 (71.2)	0.896
Subclavian arteries or aorta bruits	78 (60.9)	37 (56.1)	0.521
Lower limbs edema	26 (20.3)	2 (3.0)	0.001
Type of vascular involvement			
I	29 (22.7)	18 (27.3)	0.477
IIa	11 (8.6)	1 (1.5)	0.062
IIb	11 (8.6)	5 (7.6)	0.807
III	6 (4.7)	1 (1.5)	0.426
IV	9 (7.0)	10 (15.2)	0.071
V	62 (48.4)	31 (47.0)	0.846
NYHA III/IV	52 (40.6)	13 (19.7)	0.003
ESR > 20 mm/h	39 (30.5)	25 (37.9)	0.298
CRP > 8 mg/l	40 (31.3)	19 (28.8)	0.724
High probability of PH	79 (61.7)	5 (7.6)	< 0.001

Data are presented as mean ± SD, median (interquartile range), or number (percentage). TA: Takayasu arteritis; PAI: pulmonary artery involvement; NYHA: New York Heart Association; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PH: pulmonary hypertension.

non-PH group,  $p = 0.668$ ). Unsurprisingly, clinical manifestations such as dyspnea (94.9% vs 40.8%,  $p < 0.001$ ), hemoptysis (26.2% vs 10.2%,  $p = 0.025$ ), leg edema (26.6% vs 10.2%,  $p = 0.025$ ), respiratory failure ( $\text{PaO}_2 < 60$  mmHg, 29.1% vs 6.1%,  $p = 0.001$ ), and NYHA class III/IV (59.5% vs 10.2%,  $p < 0.001$ ) were more common among patients with than without PH. In addition, patients with PH less frequently had an elevated C-reactive protein concentration (reference value, 0–8 mg/l; 22.8% vs 44.9%,  $p = 0.009$ ) and erythrocyte sedimentation rate (reference value, < 20 mm/h; 24.1% vs 40.8%,  $p = 0.045$ ).

Comparing with the patients without PH, patients with PH more frequently had bilateral PAI (84.8% vs 34.7%,  $p < 0.001$ ) and a higher PAOI [23 (20–27) vs 10 (6–15),  $p < 0.001$ ]. The PAOI was strongly correlated with PA systemic pressure ( $r = 0.570$ ,  $p < 0.001$ ) as estimated by echocardiography. The numbers of patients in the PH group with abnormal right cardiac structure and function were as

follows: 57 (72.2%) had right atrial enlargement, 56 (70.9%) had right ventricular enlargement, and 29 (36.7%) had right ventricular systolic dysfunction. Patients with PH less frequently had left ventricular enlargement (8.9% vs 34.7%,  $p < 0.001$ ) and significant aortic regurgitation (5.1% vs 26.5%,  $p = 0.001$ ) than patients without PH.

When we divided all patients with TA with PAI according to the presence of PH and LHD, 21 patients were assigned to the non-PH and non-LHD group (Group 1), 28 to the non-PH and LHD group (Group 2), 68 to the PH and non-LHD group (Group 3), and 11 to the PH and LHD group (Group 4).

**Treatment.** Corticosteroids were administered to 61 (77.2%) and 42 (85.7%) patients with PAI among those with and without PH ( $p = 0.238$ ). Immunosuppressants were additionally prescribed to 14 patients with no significant differences between patients with and without PH (13.9% vs 6.1%,  $p = 0.169$ ). No patients in our cohort were treated with biologics. Twenty-five patients (19.5%) did not receive

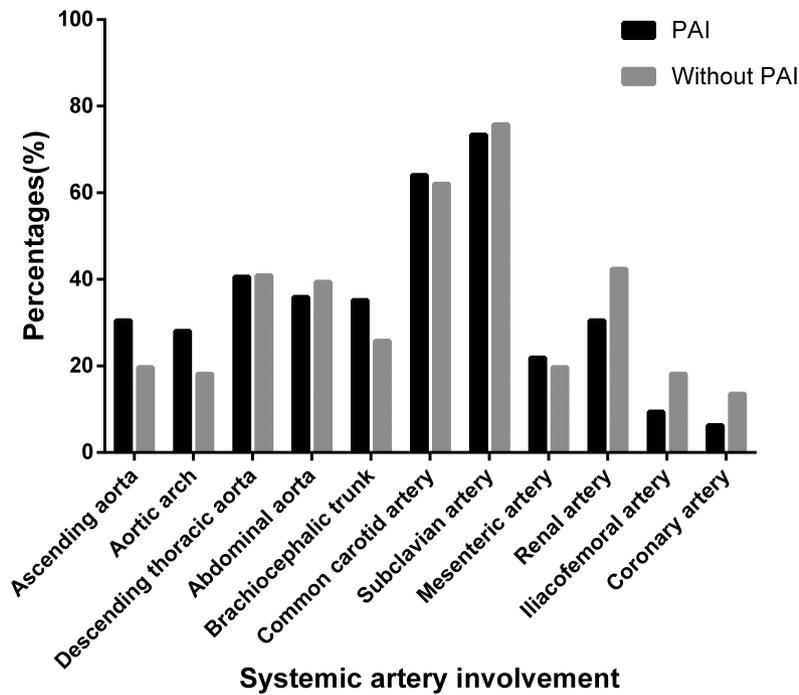


Figure 1. No significant differences in systemic artery involvement were found between patients with and without PAI (all  $p > 0.05$ ). PAI: pulmonary artery involvement.

Table 2. Angiographic features of PA lesion in 128 TA patients with PAI.

Characteristics	Stenosis	Occlusion	Poststenotic Dilatation	Aneurysm Formation	<i>In situ</i> Thrombosis	Total No. Patients
Right main PA	28 (21.9)	20 (15.6)	8 (6.3)	0 (0)	1 (0.8)	48 (37.5)
Left main PA	15 (11.7)	5 (3.9)	1 (0.8)	0 (0)	0 (0)	20 (15.6)
Right upper lobar PA or its segment	31 (24.2)	44 (34.4)	5 (3.9)	0 (0)	0 (0)	72 (56.3)
Left upper lobar PA or its segment	31 (24.2)	25 (19.5)	8 (6.3)	0 (0)	0 (0)	49 (38.3)
Right middle lobar PA or its segment	22 (17.2)	37 (28.9)	2 (1.6)	1 (0.8)	2 (1.6)	57 (44.5)
Left lingular lobar PA or its segment	20 (15.6)	24 (18.8)	5 (3.9)	1 (0.8)	0 (0)	44 (34.4)
Right lower lobar PA or its segment	34 (26.6)	35 (27.3)	10 (7.8)	1 (0.8)	1 (0.8)	62 (48.4)
Left lower lobar PA or its segment	41 (32.0)	37 (28.9)	9 (7.0)	1 (0.8)	1 (0.8)	68 (53.1)

Values are n (%). PA: pulmonary artery; TA: Takayasu arteritis; PAI: PA involvement.

corticosteroids or immunosuppressive agents because their condition was judged inactive. Among the 79 patients with PH, 46 patients (58.2%) were prescribed PH-targeted agents. There were 9 patients with PH-targeted agents and 10 patients without PH-targeted agents who died during followup, and their survival was not significantly improved by the PH-targeted agents ( $p = 0.414$ ).

Percutaneous transluminal pulmonary angioplasty (PTPA) was performed in 28 patients at the first admission or during followup. The main indication for PTPA was severe PA

stenosis combined with severe PH. One patient with occlusion in the right main PA and stenosis of 90% in the left lower lobar PA died of reperfusion pulmonary edema after PTPA. Among the other 27 patients, the mean PA pressure was decreased from  $53 \pm 17$  to  $41 \pm 13$  mmHg ( $p < 0.001$ ), and 6 of these patients had a mean PA pressure of  $< 30$  mmHg after PTPA procedure.

*Longterm survival and its predictors.* During the median followup of 38 (21–58) months, 12 patients were lost to followup and 21 of the remaining 116 patients died. The

Table 3. Demographic, clinical characteristics, echocardiography, and therapy between patients with PAI with and without PH.

Variables	PAI with PH, n = 79	PAI without PH, n = 49	p
Age, yrs	42 (30–48)	34 (28–44)	0.076
Female	65 (82.3)	46 (93.9)	0.067
Onset with respiratory symptoms	60 (75.9)	8 (16.3)	< 0.001
Disease duration, mos	72 (24–156)	48 (12–162)	0.351
Hypertension	27 (34.2)	34 (69.4)	< 0.001
Hyperlipidemia	13 (16.5)	14 (28.6)	0.102
Diabetes	4 (5.1)	2 (4.1)	> 0.999
Stroke	2 (2.5)	3 (6.1)	0.370
Symptoms and signs			
Fever	7 (8.9)	7 (14.3)	0.339
Fatigue	20 (25.3)	18 (36.7)	0.169
Dizziness	8 (10.1)	15 (30.6)	0.003
Blurred vision	3 (3.8)	4 (8.2)	0.427
Cough	20 (25.3)	6 (12.2)	0.074
Dyspnea on exertion	75 (94.9)	20 (40.8)	< 0.001
Chest pain	13 (16.5)	9 (18.4)	0.781
Hemoptysis	21 (26.6)	5 (10.2)	0.025
Syncope	6 (7.6)	5 (10.2)	0.609
Claudication	9 (11.4)	16 (32.7)	0.003
Pulselessness	34 (43.0)	31 (63.3)	0.026
Asymmetric blood pressure	51 (64.6)	39 (79.6)	0.070
Subclavian arteries or aorta bruits	41 (51.9)	37 (75.5)	0.008
Lower limbs edema	21 (26.6)	5 (10.2)	0.025
NYHA III/IV	47 (59.5)	5 (10.2)	< 0.001
Bilateral PA involvement	67 (84.8)	17 (34.7)	< 0.001
PAOI	23 (20–27)	10 (6–15)	< 0.001
PaO <sub>2</sub> < 60 mmHg	23 (29.1)	3 (6.1)	0.001
ESR > 20 mm/h	19 (24.1)	20 (40.8)	0.045
CRP > 8 mg/l	18 (22.8)	22 (44.9)	0.009
Echocardiography			
Enlargement of LA	8 (10.1)	9 (18.4)	0.182
Enlargement of LV	7 (8.9)	17 (34.7)	< 0.001
Enlargement of RA	57 (72.2)	0	< 0.001
Enlargement of RV	56 (70.9)	0	< 0.001
LV hypertrophy	7 (8.9)	12 (24.5)	0.016
Moderate or severe AR	4 (5.1)	13 (26.5)	0.001
Moderate or severe MR	2 (2.5)	2 (4.1)	0.637
TRV, m/s	4.4 ± 0.6	2.7 ± 0.4	< 0.001
PASPe, mmHg	89.2 ± 24.5	34.8 ± 9.9	< 0.001
LVEF < 50%	4 (5.1)	7 (14.3)	0.103
RVSD	29 (36.7)	0	< 0.001
PE	11 (13.9)	3 (6.1)	0.246
Therapy			
Corticosteroids	61 (77.2)	42 (85.7)	0.238
Immunosuppressants	11 (13.9)	3 (6.1)	0.169
PH-targeted agents	46 (58.2)	0	< 0.001
PTPA	28 (35.4)	0	< 0.001

Data are presented as mean ± SD, median (IQR), or as number (percentage). PAI: pulmonary artery involvement; PH: pulmonary hypertension; NYHA: New York Heart Association; PA: pulmonary artery; PAOI: Pulmonary Artery Obstruction Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PaO<sub>2</sub>: arterial oxygen pressure; LA: left atrium; LV: left ventricular; RA: right atrium; RV: right ventricular; AR: aortic regurgitation; MR: mitral regurgitation; TRV: tricuspid regurgitant velocity; PASPe: estimated pulmonary artery systolic pressure; LVEF: LV ejection fraction; RVSD: RV systolic dysfunction; PE: pericardial effusion; PTPA: percutaneous transluminal pulmonary angioplasty; IQR: interquartile range.

causes of death among the 19 patients with PH were as follows: heart failure in 15, sudden cardiac death in 2, massive cerebral infarction in 1, and post-PTPA reperfusion

lung injury in 1 patient. The causes of death in the 2 patients without PH were severe aortic regurgitation in 1 and severe mitral-aortic regurgitation in 1.

The 1-, 3-, and 5-year survival rates in patients with PAI with and without PH were 93.3% vs 98.0%, 82.3% vs 98.0%, and 69.0% vs 92.5%, respectively. Kaplan–Meier analysis showed that patients with PAI with PH had a higher probability of mortality during followup (log-rank test:  $p = 0.002$ ; Figure 2A). The patients in the non-PH and non-LHD group (Group 1) had a much better prognosis than the patients with PH (Group 1 vs Group 3,  $p = 0.012$ ; Group 1 vs Group 4,  $p = 0.002$ ; Figure 2B). Among the 39 patients with LHD, those with PH (Group 4) had a significantly higher mortality rate than those without PH (Group 2,  $p = 0.029$ ; Figure 2B). Among the 79 patients with PH, no differences were found in mortality between patients with LHD (Group 4) and without LHD (Group 3,  $p = 0.406$ ; Figure 2B).

In the univariate Cox analyses, the mortality rate was 7-times higher in the patients with PH than without PH (HR 7.003, 95% CI 1.637–30.218,  $p = 0.009$ ). The multivariate analyses, which included variables associated with mortality in the univariate analysis, showed that the disease duration (HR 1.004, 95% CI 1.001–1.007,  $p = 0.047$ ), NYHA class III/IV (HR 4.201, 95% CI 1.269–13.911,  $p = 0.019$ ), right ventricular systolic dysfunction (HR 3.189, 95% CI 1.207–8.428,  $p = 0.019$ ), and respiratory failure (HR 3.601, 95% CI 1.416–9.154,  $p = 0.007$ ) were independently associated with mortality in patients with TA with PAI (Table 4).

## DISCUSSION

PAI is not rare but the pulmonary circulation is often overlooked in the clinical assessment of TA. According to previous research, when including only patients with TA who have undergone imaging of the PA, the incidence of PAI varied from 33% to 86%<sup>3,6,18,19,20,21</sup>. In the present study, the ratio of PAI was 66% among the patients who underwent PA angiography and 21.4% among all patients with TA, which is consistent with previous studies.

Patients with PAI are more prone to develop PH than those without PAI. Sari, *et al*<sup>12</sup> reported that PH was present in 25.0% of patients with PAI and 7.7% without PAI. In a case review conducted by Toledano, *et al*<sup>7</sup>, 42.2% of patients with PAI also had PH. In the present study, patients with PAI also had a higher risk of developing PH than those without PAI (61.7% vs 7.6%). Mechanical obstruction of the pulmonary vasculature is the leading mechanism underlying the development of PH in TA-associated PAI. Similar to the findings reported by Wang, *et al*<sup>22</sup>, the PA pressure was significantly correlated with the extent of PAI in the present study. Additionally, marked reduction in blood flow of the PA leads to hypoxemia because of ventilation–perfusion mismatch. Wang, *et al*<sup>22</sup> also reported that patients with PH due to PAI were more prone to respond to vasoreactivity testing. This suggests that increased vascular tone in the PA may contribute to increases in the PA pressure. Moreover, the coexistence of LHD might contribute to the development of PH<sup>12,22</sup>, which occurred in 11 of 79 patients with PAI and PH in our study.

Patients with PH due to TA-associated PAI have a poor prognosis. According to Toledano, *et al*<sup>7</sup>, the mortality rate was 20.5% in patients with PAI and 33.3% among patients with PH. In a recent Chinese study involving 57 patients with PAI (33 with PH and 24 without PH), all 3 patients who died had PH<sup>8</sup>. In the present study, the risk of mortality was 7 times higher among patients with PH than among those without PH during the 38-month followup. Additionally, severe complications of PH such as right heart failure, respiratory failure, a poor NYHA class, and a long disease duration were independent predictive factors for mortality among patients with TA-associated PAI.

Because of the poor prognosis of PH in the patients with PAI, pulmonary circulation must be routinely screened in patients with TA in the early stage. Traditional angiography

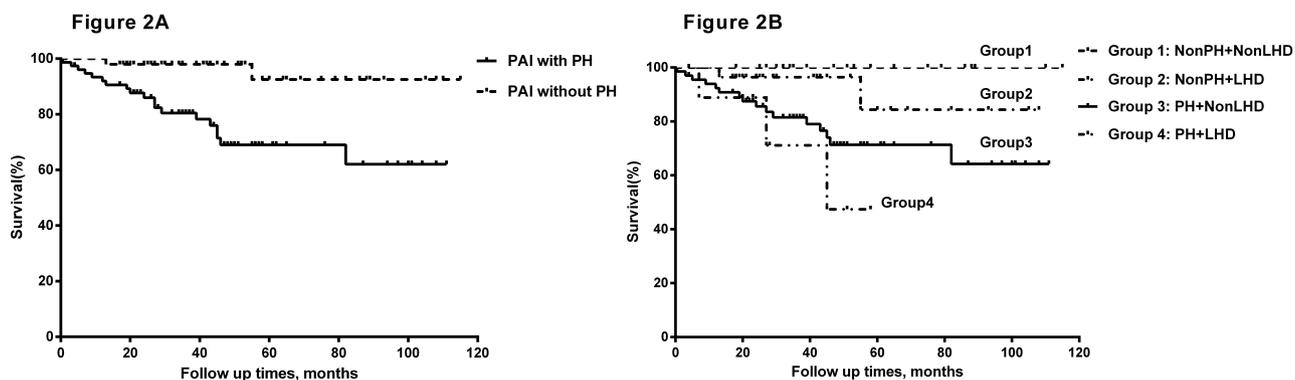


Figure 2. A. Comparison of survival rates between patients with PAI with and without PH. The risk of all-cause mortality was significantly higher in patients with PH ( $p = 0.002$ ). B. Comparison of survival rates of patients with PAI on the basis of PH and LHD. Group 1 versus Group 2 ( $p = 0.161$ ), Group 1 versus Group 3 ( $p = 0.012$ ), Group 1 versus Group 4 ( $p = 0.002$ ), Group 2 versus Group 4 ( $p = 0.029$ ), Group 3 versus Group 4 ( $p = 0.406$ ). Group 1: Non-PH and non-LHD; Group 2: Non-PH and LHD; Group 3: PH and non-LHD; Group 4: PH and LHD. PAI: pulmonary artery involvement; PH: pulmonary hypertension; LHD: left heart disease.

Table 4. Predictors of mortality in patients with TA with PAI.

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.046 (1.010–1.083)	0.011		
Female	3.036 (0.407–22.633)	0.279		
Disease duration	1.005 (1.002–1.008)	0.001	1.004 (1.000–1.007)	0.047
Hypertension	0.786 (0.331–1.866)	0.585		
Hyperlipidemia	0.907 (0.331–2.483)	0.849		
Diabetes	1.487 (0.342–6.459)	0.597		
NYHA class III/IV	8.072 (2.709–24.054)	<0.001	4.201 (1.269–13.911)	0.019
Respiratory failure	4.686 (1.939–11.324)	0.001	3.601 (1.416–9.154)	0.007
PH	7.003 (1.637–30.218)	0.009		
LHD	0.834 (0.305–2.283)	0.724		
RVSD	6.257 (2.630–14.885)	<0.001	3.189 (1.207–8.428)	0.019

TA: Takayasu arteritis; PAI: pulmonary artery involvement; NYHA: New York Heart Association; PH: pulmonary hypertension; LHD: left heart disease; RVSD: right ventricular systolic dysfunction.

is still the gold standard for detecting lesions in the PA<sup>6,19</sup>. However, angiography is an invasive procedure and is therefore frequently replaced by CT and magnetic resonance (MR) angiography, especially in the initial evaluation. CT and MR angiography of the PA can reveal not only stenosis, occlusion, or dilation of the vascular lumen but also thickening of the artery wall<sup>8,23,24</sup>. MR angiography can also disclose early mural inflammatory signs in the PA by late gadolinium enhancement<sup>25</sup>. A more sensitive modality is 18F-fluorodeoxyglucose positron emission tomography (FDG-PET); it can depict active inflammation of the aorta and PA even before any structural change<sup>26,27</sup>. The change in the standardized uptake value with FDG-PET can also help with early evaluation of the treatment response<sup>28</sup>. However, one study showed that FDG-PET may have low power to detect the lesions in small-diameter PA<sup>29</sup>. Thus, to clearly evaluate lesions and inflammatory activity in the PA, various imaging modalities may be needed to complement each other.

Echocardiography is a simple and noninvasive imaging modality with which to evaluate the structure and function of the heart and estimate the PA pressure. Echocardiography can also provide information on lesions in the right and left main PA<sup>30</sup>. In the present study, the prognosis of patients with PAI was also well stratified based on the echocardiography assessment. Therefore, echocardiography should be routinely performed for all patients with TA at the time of the initial evaluation, and subsequent assessment is advocated for patients with a high probability of PH or new-onset symptoms suggesting PH. For patients with a high probability of PH as evaluated by echocardiography, right heart catheterization is necessary to further assess the hemodynamics and confirm the diagnosis of PH<sup>17</sup>.

Aggressive stabilization of the disease activity plays a key role in the progression and prognosis of TA-associated PAI and PH. In our cohort, patients with a history of corticosteroid therapy tended to have a lower incidence of PH than those without history of corticosteroid (50% vs 67%,  $p = 0.066$ ).

Immunosuppressants were less frequently prescribed in our study; thus it was difficult to evaluate their effect on patients with PAI by such limited samples. However, according to Lee, *et al*<sup>31</sup>, patients with active disease were at high risk of developing PAI and PH. Sari, *et al*<sup>12</sup> also reported that patients with severe or treatment-resistant TA had a high risk of PH. Therefore, more widespread use of immunosuppressive agents and biologics might improve the poor prognosis of patients with PAI and PH. PH-targeted drugs were also used but not associated with improvement of survival in our study. However, the therapeutic effect of PH-targeted agents should be further evaluated by a well-designed prospective randomized study and the endpoint should include not only survival but also change in the exercise capacity.

Established PH and stenosis of the PA cannot usually be reversed by medical treatment alone. Pulmonary revascularization is a complementary strategy to restore pulmonary blood flow and should be performed during the inactive disease stage<sup>10</sup>. Surgical treatments seemed to effectively recover the cardiopulmonary function but preclude widespread application because of high operational difficulty and surgery-related complications<sup>32</sup>. Inspired by developments in the treatment of chronic thromboembolic PH<sup>33</sup>, PTPA has also reportedly been applied in single cases and small series of patients with TA-associated PAI. In the present study, the PA pressure decreased after PTPA, but 1 patient who underwent the procedure died of PTPA-associated reperfusion pulmonary edema. Similarly, according to previous studies conducted by Dong, *et al*<sup>10</sup> and Yanagisawa, *et al*<sup>34</sup>, although the therapeutic effect of PTPA on TA-associated PAI and PH was smaller than the effect on chronic thromboembolic PH, the symptoms and hemodynamics were still markedly improved by PTPA. Procedure-related complications such as pulmonary artery injury or reperfusion pulmonary edema were also acceptable<sup>10,34</sup>. Therefore, PTPA is a potential useful therapeutic strategy for patients with PH

because of TA-associated PAI, but it should be performed cautiously. Future case-control studies are required to evaluate the longterm clinical efficacy of PTPA in patients with PAI-associated PH.

The major limitation of our study is that the diagnosis of PH was mainly dependent upon echocardiography. According to current guidelines, right heart catheterization is required to confirm the diagnosis of PH and identify pre- or postcapillary PH. However, right heart catheterization was difficult to perform on every patient with TA with PAI. Second, the study was conducted in a single institution specializing in cardiovascular disease, and only inpatients who underwent PA angiography were included; this might have resulted in selection bias. Finally, the retrospective study design had the limitations inherent to all retrospective studies. A prospective study is needed to investigate the clinical features and prognosis of patients with TA with PAI.

PAI is not rare in patients with TA. PAI is associated with PH in patients with TA and increases the risk of mortality. Early detection and aggressive treatment of PAI among patients with TA may improve the poor prognosis.

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