# Clinical features and survival in pulmonary Takayasu's arteritis-associated pulmonary hypertension: a national registry study

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## ABSTRACT

**Aims:** This study aimed to assess the clinical characteristics and long-term survival outcome in patients with pulmonary Takayasu's arteritis-associated pulmonary hypertension (PTA-PH).

**Methods and results:** We conducted a nationally representative cohort study of PTA-PH using data from the National Rare Diseases Registry System of China. Patients with pulmonary artery involvement who fulfilled the diagnostic criteria of Takayasu's arteritis and pulmonary hypertension were included. The primary outcome was the time from diagnosis of PTA-PH to the occurrence of all-cause death. Between Jan. 2007 and Jan. 2019, a total of 140 patients were included, with a mean age of 41.4 years at diagnosis, and a female predominance (81%). Patients with PTA-PH had severely hemodynamic and functional impairments at diagnosis. Significant improvements have been found in N-terminal pro-B type natriuretic peptide (NT-proBNP) and hemodynamic profiles in patients with PTA-PH received drugs approved for pulmonary arterial hypertension. The overall 1-year, 3-year, and 5-year survival rates in PTA-PH were 94.0%, 83.2%, and 77.2%, respectively. Predictors associated with an increased risk of all-cause death were syncope [adjusted hazard ratio (HR) 5.38 (1.77–16.34), $P = 0.003$], NT-proBNP level [adjusted HR 1.04 (1.03–1.06), $P < 0.001$], and mean right atrial pressure [adjusted HR 1.07 (1.01–1.13), $P = 0.015$].

**Conclusion:** Patients with PTA-PH were predominantly female and had severely compromised hemodynamics. More than 80% of patients in our cohort survived for at least three years. Medical treatment was based on investigators' personal opinion and no clear risk-to-benefit ratio can be derived from the presented data.



**Keywords:** Takayasu's arteritis • Pulmonary artery involvement • Pulmonary hypertension

1 • Clinical features • Survival

## Introduction

Takayasu's arteritis, which predominantly involves the aorta and its major branches, is a primary and granulomatous vasculitis of unknown origin.[1, 2] It is characterized by infiltrative inflammation in the vessel wall, resulting in varying lesions of wall thickening, stenosis, occlusion or aneurysms. The disorder is distributed worldwide, affecting both genders, but it disproportionally affects young women and the Asian population.[3] The clinical manifestations of Takayasu's arteritis are usually nonspecific and remarkably heterogeneous, depending on the affected vessels and the severity of disease progression.[4, 5]

In recent years, pulmonary Takayasu's arteritis has been recognized as pulmonary artery involvement in Takayasu's arteritis.[6, 7] The occurrence of pulmonary artery involvement was not rare in patients with Takayasu's arteritis.[4, 8-10] Approximately half of patients with pulmonary Takayasu's arteritis suffer from overt pulmonary hypertension (PH) during their courses, which is mostly secondary to pulmonary artery stenosis or occlusion.[11, 12] Furthermore, the systemic artery involvement could theoretically cause post-capillary PH in a subset of patients with pulmonary Takayasu's arteritis. Hemodynamic assessment based on right-heart catheterization was, therefore, essential for accurate diagnosis and subsequent classification of PH. In the real world, patients with pulmonary Takayasu's arteritis associated-PH (PTA-PH) always experience delayed diagnosis due to nonspecific clinical manifestations and lack of attention regarding early symptoms of impaired pulmonary circulation. Up to now, information on clinical characteristics and long-term outcomes of patients with PTA-PH are only from case-series and small cohort studies, with their determination of PH commonly dependent on echocardiography.[11-13] Clinical phenotyping, by invasive hemodynamics, of patients with PTA-

PH is still not well established. The huge knowledge gap in the current international guidelines and recommendations has largely impeded the clinical management of patients with PTA-PH.[14-16]

Therefore, this multi-center cohort study was conducted to assess the clinical features, especially the hemodynamics characteristics, of patients with PTA-PH, and evaluate their long-term survival outcomes and identify prognostic factors for all-cause death.

## Methods

### Study cohort

We conducted a multi-center cohort study using the clinical, functional, and hemodynamic data from the National Rare Diseases Registry System of China (https://nrdrs.org.cn). The system is a nationwide registration of rare diseases, created in 2016 at Peking Union Medical College Hospital with contributions from other academic institutions.[17] Patients with rare types of PH, including but not limited to, group one pulmonary arterial hypertension (PAH), chronic thromboembolic pulmonary hypertension (CTEPH), and arteritis-associated PH (NCT03169010), were routinely registered.

Patients with PTA-PH who were registered for this study were geographically located in 13 PH referral centers, situated in ten provinces or municipalities of China. All patients were included between Jan. 2007 and Jan. 2019, based on the following procedures. Firstly, the diagnosis of Takayasu's arteritis was completed according to the Ishikawa criteria modified by Sharma and/or the 1990 American College of Rheumatology criteria.[18, 19] Secondly, pulmonary artery involvement was determined by either of the two imaging modalities, i.e., computed

tomography pulmonary angiography or transcatheter pulmonary angiography. Typical pulmonary artery involvement included stenosis, occlusion, dilation, or aneurysm. Representative images of pulmonary artery involvement in patients with PTA-PH were presented in supplementary material online, *Figure S1*. We excluded patients with pulmonary artery involvement caused by non-Takayasu's arteritis, such as other types of vasculitis (e.g., Behcet's disease, giant cell arteritis and antineutrophil cytoplasmic antibody associated-vasculitis), CTEPH, pulmonary artery sarcoma, fibrosing mediastinitis, pulmonary sarcoidosis, or schistosomiasis. Finally, all patients received standard right-heart catheterization in accordance with current guideline.[16] The study was performed in accordance with the Declaration of Helsinki and approved by the local Ethics Committee of each participating institution. All patients gave their written informed consent.

**Data sources**

Data on patient characteristics at first admission for PTA-PH diagnosis were collected, including demographic information, clinical symptoms, medical history, World Health Organization (WHO) functional class, six-minute walking distance, serological testing, vascular involvement, echocardiographic findings, invasive hemodynamics, and treatments. An elevated inflammatory marker was defined as C-reactive protein (CRP) > 5 mg/L or erythrocyte sedimentation rate (ESR) > 20 mm/h at diagnosis of PTA-PH, after any causes other than arteritis were excluded. The presence of left heart disease in patients with PTA-PH was identified by the echocardiography measuring left atrial or ventricular enlargement, moderate or severe left heart valve disease, or a left ventricular ejection fraction of less than

50%. Multidisciplinary teams consisting of senior rheumatologists, cardiologists, and radiologists, were established to collectively make the decisions regarding Takayasu's arteritis related therapies, including the use, timing, and dosage of corticosteroids and immunosuppressants. Drugs approved for PAH (endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin derivatives) were given to patients according to the clinical judgment and discretion of the individual treating physicians.

**Clinical assessment and follow-up**

Follow-ups were conducted on all patients via clinic visits, phone calls or online interviews. The study's primary outcome was the time from diagnosis of PTA-PH to the occurrence of all-cause death. The data from the first clinical and hemodynamic assessments after enrollment were collected to analyze the therapeutic effects of drugs approved for PAH on patients with PTA-PH.

**Statistical analyses**

Continuous variables were presented as mean (standard deviation, SD) or median (interquartile range, IQR). Categorical variables were summarized by number (proportion). For the two-group comparisons of patients stratified by inflammatory markers, the unpaired t-test or the Mann-Whitney U test was used for continuous variables, and the Chi-square test or the Fisher exact test for categorical variables, as appropriate. To assess the therapeutic effects of drugs approved for PAH on clinical and hemodynamics measurements, generalized linear mixed models were used to estimate the mean changes or odds ratio between re-evaluation and

baseline with 95% confidence intervals in clinical and hemodynamics variables, with time as study variable, age and sex as covariates, and subject as random effect.

The survival time for each patient was calculated in months from the date of diagnosis until the date of death, or until the last visit if the patient was still alive. Survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test. A multivariable Cox proportional hazard model was used to evaluate potential factors associated with all-cause death. Variables that demonstrated an association with the outcome at a level of 0.05 or less in univariate analysis were candidates for further multivariate analysis. Variable selection in the final parsimonious multivariate model was based on a backward stepwise selection procedure. Multiple imputation method was used for imputing missing variables at baseline in multivariate Cox regression analysis. Sensitivity analysis will be performed on the complete cases. All statistical analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.6.0 (The R Foundation). A two-sided $P < 0.05$ was considered statistically significant.

## Results

### Patient selection

The screening and inclusion of patients with PTA-PH are presented in *Figure 1*. Initially, 168 patients suspected of having Takayasu's arteritis were screened. Among them, 6 patients were excluded due to having other etiologies of pulmonary artery stenosis (2 with Behcet's disease, two with CTEPH, 1 with pulmonary sarcoidosis, and 1 with schistosomiasis), and another 22 patients were further excluded due to the absence of invasive hemodynamic parameters ($N$ = 12), or baseline mean pulmonary artery pressure less than 25 mm Hg ($N$ = 10). Finally, a total

of 140 patients fulfilled the inclusion criteria of PTA-PH and were included in the analysis.

**Clinical characteristics**

Most patients (81%) in the current study were female. The mean age of patients was 36.1 ± 14.3 years at initial PH-associated symptoms, and 41.4 ± 14.3 years at confirmed diagnosis of PTA-PH (see *Table 1*). The median diagnosis delay from symptoms onset to PH diagnosis was 2.0 (IQR 1.0–6.0) years. Hemoptysis was a common symptom, occurring in 50 (36%) patients with PTA-PH. Syncope episodes were observed in 14 (10%) patients. A history of tuberculosis infection was found in 27 (19%) patients; no patients had active tuberculosis.

Severely compromised hemodynamic profiles were identified in our patients, characterized by an elevated mean pulmonary artery pressure (50 ± 16 mm Hg) and pulmonary vascular resistance (10.8 ± 6.4 Wood U) (see *Table 1*). According to the classification of PH, 118 patients (85%) were diagnosed with pre-capillary PH. Fourteen (10%) patients were identified to have both elevated pulmonary artery wedge pressure (> 15 mm Hg) and elevated pulmonary vascular resistance (> 3 Wood U). Additionally, 8 patients were only diagnosed with PH due to the absence of pulmonary artery wedge pressure or pulmonary vascular resistance. Moreover, isolated post-capillary PH was not observed using available data.

In the present study, 81 (58%) patients had normalized inflammatory markers at diagnosis. Elevated CRP and ESR were separately recorded in 44 (31%) and 33 (24%) patients, with 20 (14%) patients recorded as having both CRP and ESR elevation. Compared to patients with elevated inflammatory markers, patients with a normal level exhibited a higher mean pulmonary artery pressure (54 ± 18 mm Hg versus 46 ± 13 mm Hg, $P = 0.004$). The details of

comparisons between the two groups are shown in the Supplementary material online, *Table S1*.

Regarding medical treatment, drugs approved for PAH were prescribed for 127 (91%) patients, of which 63 (45%) patients were administrated with combination therapy and 10 (7%) with triple-combination therapy. Eighty-six (62%) patients received corticosteroids and 28 (20%) received immunosuppressants for Takayasu's arteritis. Among them, 27 (19%) patients were treated using a combined strategy of corticosteroids and immunosuppressants.

**Treatment effects of drugs approved for PAH**

After a median follow-up time of 6 (IQR 3–15) months, 92 of 127 patients who received drugs approved for PAH completed first clinical assessments. Of these, data on hemodynamics at follow-up visits were available for 61 patients. A significant decrease was found in N-terminal pro-B type natriuretic peptide (NT-proBNP) [log-transformed -0.34 (95% confidence interval (CI) -0.62 – -0.05), $P = 0.022$)], mean pulmonary artery pressure [-3.36 mm Hg (95% CI -6.46 – -0.26), $P = 0.034$)], and pulmonary vascular resistance [-1.93 Wood U (95% CI -2.89 – -0.98), $P < 0.001$)] after treatment (see *Table 2*). The treatment of drugs approved for PAH was also associated with an increment in cardiac index [0.30 L/min per m² (95% CI 0.03 – 0.56), $P = 0.028$)]. However, numerical but non-significant improvements were observed in six-minute walking distance and WHO functional class.

**Long-term survival**

Eight out of the 140 patients (6%) were lost to follow-up. The median follow-up time was 24

(IQR 9–56) months. Death was recorded in 20 patients, with overall 1-year, 3-year, and 5-year survival rates of 94.0% (95% CI 90.0–98.4), 83.2% (95% CI 75.4–91.7), and 77.2% (95% CI 67.8–87.9), respectively (see *Figure 2*). The causes of death were right heart failure ($N = 17$), sudden cardiac death ($N = 1$), massive hemoptysis ($N = 1$), and lung infection ($N = 1$). We did not observe any significant differences in survival rates between patients with normal and elevated inflammation markers (log-rank $P = 0.310$).

**Risk factors for all-cause death**

In univariate analyses, 12 baseline variables were associated with all-cause death (see *Table 3*). Three significant predictors were retained, following backward-stepwise variable selection, in the final multivariate Cox regression model (see *Table 3*). The factors associated with an increased risk of all-cause death were the presence of syncope [adjusted hazard ratio (HR) 5.38, 95% CI 1.77–16.34, $P = 0.003$), increased NT-proBNP level (adjusted HR per 100 pg/mL 1.04, 95% CI 1.02–1.06, $P < 0.001$) and elevated mean right atrial pressure (adjusted HR per 1 mm Hg 1.07, 95% CI 1.02–1.13, $P = 0.015$). The Cox model, with the three significant predictors, was also estimated as a sensitivity analysis, based on the complete cases, and similar results were observed (see Supplementary material online, *Table S2*).

**Discussion**

As far as we know, this is the first multi-center cohort study with a large enough sample size to establish clinical features and long-term prognosis of patients with PTA-PH, based on diagnostic right-heart catheterization. We found that patients with PTA-PH presented with a

severely compromised function status and hemodynamics at diagnosis. In a subset of 92 patients who completed the first clinical assessments, significant improvements were found in NT-proBNP, mean pulmonary artery pressure, cardiac index, and pulmonary vascular resistance after treatment of PAH medications. Patients with PTA-PH had an estimated 3-year survival rate of 83.2%, and most of them died owing to right heart failure. Furthermore, the syncope symptom, NT-proBNP, and mean right atrial pressure were found to be significantly associated with all-cause death.

Takayasu's arteritis has been known to mainly affect young females at their second and third decades of life. In our cohort, female predominance in patients with PTA-PH was consistent with that in Takayasu's arteritis populations.[2, 5] However, the onset time of first PH-associated symptom seems 5-10 years later than the occurrence of Takayasu's arteritis.[20, 21] Given the symptoms of patients with PTA-PH are usually insidious and nonspecific, diagnosis delay was common, with a median of 2 years in our study.[8] Tuberculosis infection was found in 19% of patients with PTA-PH, which was largely in parallel with a previous study.[22] Observational data has found that tuberculosis is related to more frequent pulmonary artery involvement and more chest discomfort in patients with Takayasu's arteritis,[23] but there is still little known about the role of tuberculosis infection in the development and progression of Takayasu's arteritis and PTA-PH.

The prevalence of hemoptysis in patients with PTA-PH (36%) is pretty high, and in accordance with a previous report.[13] The suspected causes for hemoptysis are inconclusive, including the rupture of collateral vessels or micro-aneurysms, hypertensive response, or pulmonary infarction.[24] Moreover, frequent anticoagulants using in this study may have

facilitated the high rate of hemoptysis. In clinical practice, anticoagulants have been empirically used for the prophylaxis of *in situ* thrombosis, which was not rare in patients with PTA-PH.[12] However, the risk-benefit for anticoagulation treatment should be further investigated.

Despite notable divergences in underlying causes of pulmonary vascular obstruction, PTA-PH and CTEPH might share similar pathophysiological mechanisms of the pre-capillary PH development, such as pulmonary vascular bed loss by mechanical obstruction and secondary remodeling of unobstructed vessels.[25] Additionally, elevated pulmonary artery wedge pressure was also identified in some patients with PTA-PH, which could possibly be attributed to the impairments of systolic or diastolic left ventricular function due to hypertension secondary to the extensive systemic artery stenosis or severely aortic valve involvement. However, in view of the fact that left heart disease only existed in a fraction of patients with elevated pulmonary artery wedge pressure, most if not all patients of elevated pulmonary artery wedge pressure were probably due to false measurement caused by central pulmonary artery involvement.

Moreover, elevated CRP and ESR levels were observed separately in 31% and 24% of patients with PTA-PH. We also found that patients with normal level of inflammatory makers had a higher mean pulmonary artery pressure. The active inflammation was commonly seen at the early stage of Takayasu's arteritis and tapered with frequent relapse at the late stage. Patients with PTA but not PH have been indicated at the early and active inflammatory stage with the suggesting of a shorter disease course, a higher level of ESR, and a higher incidence of subpleural wedge-shaped shadows, comparing to those with PTA-PH.[8] We hence assumed that patients with normal inflammatory markers might have a longer clinical course of

Takayasu's arteritis and present with more severe pulmonary vascular remodeling in comparison to those with elevated inflammatory markers.

Despite data are limited, a number of "real-world" patients with pre-capillary PH have been prescribed with drugs approved for PAH. In the current study, we found significant post-treatment improvements in NT-proBNP level and pulmonary hemodynamics among patients with PTA-PH receiving drugs approved for PAH. Nevertheless, these finding should be interpreted with caution especially considering that the study design and sample size could not provide sufficient evidence. The dispensing of drugs approved for PAH based on investigators' personal opinion also made the interpretation of results difficult. Future prospective, controlled trials were warrant to identify the risk-to-benefit of drugs approved for PAH in patients with PTA-PH. Additionally, as the established treatment strategies for CTEPH, pulmonary endarterectomy and balloon pulmonary angioplasty also might be the treatment options that need to be further explored in patients with PTA-PH.

In this study, we observed that the 3-year survival rate of PTA-PH was 83.2%, which was poorer than overall survival in Takayasu's arteritis cohort.[26] PH-associated right heart failure was the main cause of death in patients with PTA-PH, differing from the left heart failure and vascular complications, which substantially contributed to death in patients with Takayasu's arteritis. In the multivariate Cox model, we identified syncope symptoms, NT-proBNP and mean right atrial pressure as factors independently associated with all-cause death in patients with PTA-PH. These markers presented a strong relationship with PH phenotype, and the prognostic value of them had been reported in current PH guidelines.[16] Furthermore, these findings also suggest that the PH per se, instead of Takayasu's arteritis related factors like

systemic artery involvement or inflammatory markers, was the decisive factor of long-term prognosis of PTA-PH.

## Limitations

Some limitations in our study need to be acknowledged. Firstly, this study was limited by its small number of patients. Given the sample size and number of events, the study may fail to reach statistical power, therefore, the findings should be considered hypothesis-generating rather than definitive evidence. However, patient recruitment for such rare disease is difficult and the current study performed in 13 referral centers of China represents the largest cohort of PTA-PH to date. Secondly, we included patients with well-defined pulmonary Takayasu's arteritis and PH phenotypes, therefore, the generalization of our findings to patients only with pulmonary Takayasu's arteritis should be cautious. Thirdly, it should be noted that the overestimated pulmonary artery wedge pressure in some patients was still possible due to the presence of stenosis/obstructions in proximal pulmonary arteries. Last but not least, limited by study design and treatment heterogeneity of drugs approved for PAH, this study could not provide sufficient information on the risk-to-benefit ratio of drugs approved for PAH in patients with PTA-PH.

## Conclusions

In this first multi-center cohort study of PTA-PH with invasive hemodynamic diagnoses, we found that patients with PTA-PH were predominantly female and had severely compromised hemodynamics. We further found that more than 80% of patients could survive for three years

from diagnosis. Medical treatment was based on investigators' personal opinion and no clear risk-to-benefit ratio can be derived from the presented data. These findings provide new insights into this specific PH entity, and call for future therapeutic trials to improve the prognosis of patients with PTA-PH.

## Data sharing statement

The data underlying this article will be shared on reasonable request to the corresponding author.


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## Figure legends

**Figure 1** Flowchart of the study patient selection. PTA, pulmonary Takayasu's arteritis; CTEPH, chronic thromboembolic pulmonary hypertension; RHC, right-heart catheterization; mPAP, mean pulmonary artery pressure.

**Figure 2** Kaplan-Meier plot for survival rate in patients with pulmonary Takayasu's arteritis-associated pulmonary hypertension. The overall 1-year, 3-year, and 5-year survival rates were 94.0% (95% CI 90.0-98.4), 83.2% (95% CI 75.4-91.7), and 77.2% (95% CI 67.8-87.9), respectively.

**Table 1 Baseline characteristics of patients with pulmonary Takayasu's arteritis-associated pulmonary hypertension[a]**

| Characteristics | All patients (*N* = 140) |
|---|---|
| Age at initial symptoms (years) | 36.1 ± 14.3 |
| Age at diagnosis of PH (years) | 41.4 ± 14.3 |
| Diagnosis delay (years) | 2.0 (1.0–6.0) |
| Female sex | 113 (81) |
| Hemoptysis | 50 (36) |
| Syncope | 14 (10) |
| Hypertension | 37 (26) |
| History of tuberculosis infection | 27 (19) |
| NT-proBNP (pg/mL) | 127, 752 (173–2040) |
| C-reactive protein (mg/L) | 138, 3.3 (2.0–6.9) |
| Erythrocyte sedimentation rate (mm/h) | 133, 8.0 (4.0–20.0) |
| WHO functional class III-IV | 73 (52) |
| Six-minute walking distance (m) | 115, 373 ± 132 |
| Hemodynamics | |
| Mean right atrial pressure (mm Hg) | 137, 9 ± 6 |
| Mean pulmonary artery pressure (mm Hg) | 50 ± 16 |
| Pulmonary artery wedge pressure (mm Hg) | 137, 11 ± 5 |
| Cardiac index (L/min per $m^2$) | 136, 2.7 ± 0.8 |
| Pulmonary vascular resistance (Wood U) | 137, 10.8 ± 6.4 |

| | |
|---|---|
| Arterial oxygen saturation (%) | 130, 92 ± 6 |
| Mixed venous oxygen saturation (%) | 133, 63 ± 12 |
| Stroke volume index (mL/m$^2$) | 138, 31 ± 10 |
| Pulmonary arterial compliance (mL/mm Hg) | 138, 0.95 ± 0.66 |
| Medications | |
| Corticosteroid | 86 (61) |
| Immunosuppressant | 29 (21) |
| Anticoagulation | 87 (62) |
| Drugs approved for PAH | 127 (91) |
| ERA | 73 (52) |
| PDE5 inhibitor | 98 (70) |
| Oral beraprost | 8 (6) |
| Subcutaneous treprostinil | 2 (1) |
| None/Mono/Dual/Triple drugs therapy[b] | 13/53/63/10 |

Data are presented as mean (standard deviation), or median (interquartile range), or number (proportion), unless otherwise stated. PH, pulmonary hypertension; NT-proBNP, N-terminal pro-B type natriuretic peptide; WHO, World Health Organization; PAH, pulmonary arterial hypertension; ERA, endothelin receptor antagonist; PDE5, phosphodiesterase type 5.

[a]Number of nonmissing observations is provided if a variable has missing data.

[b]Data were presented as count (N).

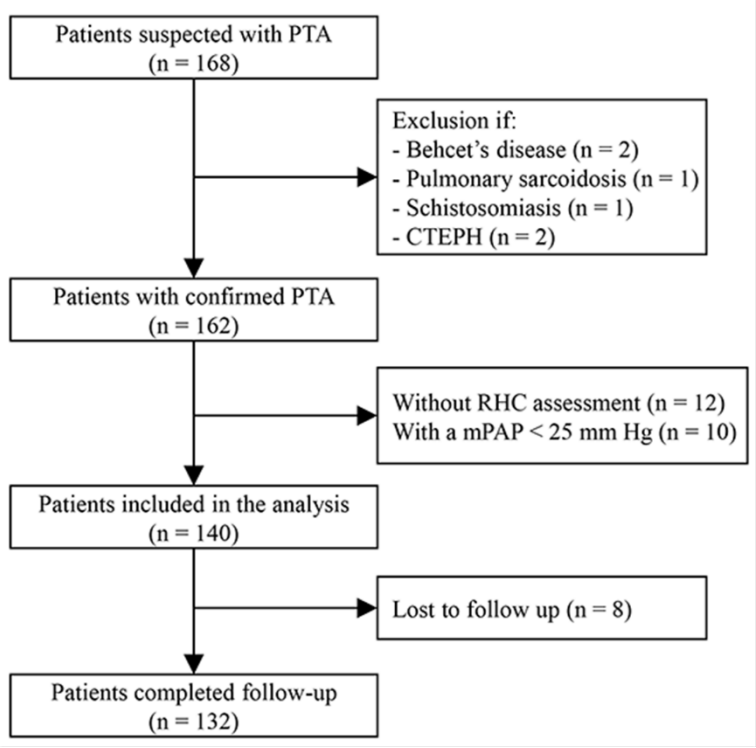



**Figure 1** Flowchart of the study patient selection. PTA, pulmonary Takayasu's arteritis; CTEPH, chronic thromboembolic pulmonary hypertension; RHC, right-heart catheterization; mPAP, mean pulmonary artery pressure.

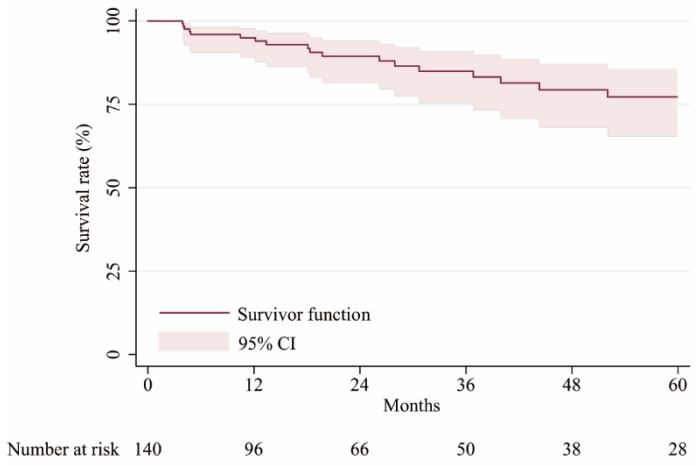
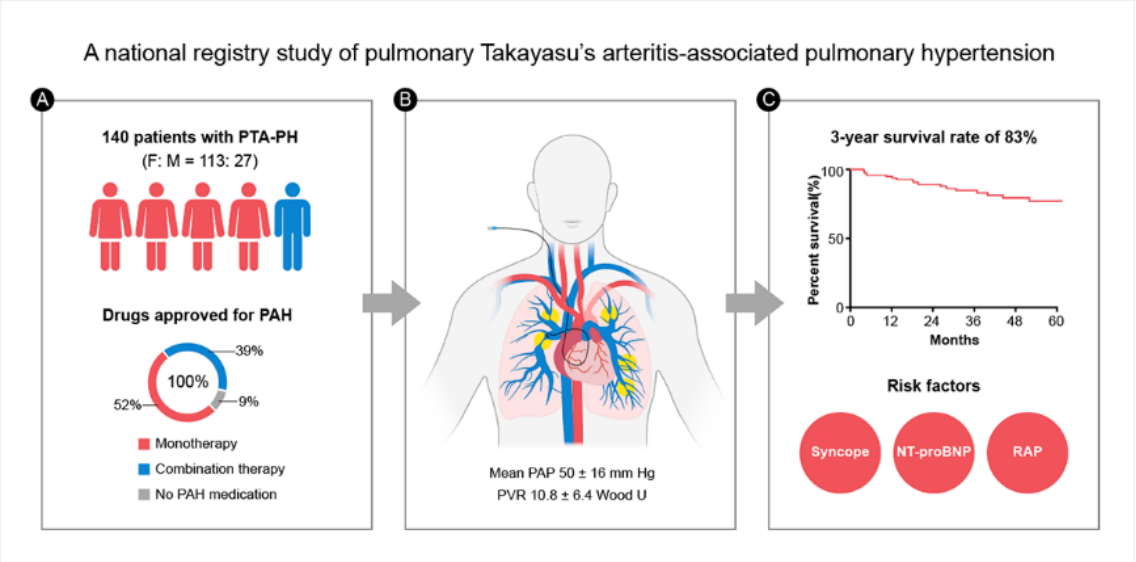



**Figure 2** Kaplan-Meier plot for survival rate in patients with pulmonary Takayasu's arteritis-associated pulmonary hypertension. The overall 1-year, 3-year, and 5-year survival rates were 94.0% (95% CI 90.0-98.4), 83.2% (95% CI 75.4-91.7), and 77.2% (95% CI 67.8-87.9),

respectively.




**Graphical abstract**

**Supplementary material online**

**Table S1.** Differences between patients with normal and elevated inflammatory markers.

| **Characteristics** | **Normal (*N* = 81)** | **Elevated (*N* = 57)[a]** | ***P*-value** |
|---|---|---|---|
| Age at initial symptoms (years) | 37.4 ± 15.0 | 35.0 ± 13.8 | 0.330 |
| Age at diagnosis of PH (years) | 40.8 ± 15.1 | 41.7 ± 14.0 | 0.726 |
| Diagnosis delay (years) | 3.0 (1.0-10.0) | 2.0 (1.0-5.0) | 0.132 |
| Female sex | 64 (77) | 47 (85) | 0.226 |
| Hemoptysis | 29 (35) | 19 (35) | 0.962 |
| Syncope | 9 (11) | 5 (9) | 0.739 |
| Hypertension | 27 (33) | 10 (18) | 0.062 |
| History of tuberculosis infection | 19 (23) | 6 (11) | 0.074 |
| NT-proBNP (pg/mL) | 630 (186-1820) | 830 (170-2891) | 0.272 |
| WHO functional class III-IV | 40 (48) | 32 (58) | 0.250 |
| Six-minute walking distance (m) | 376 ± 126 | 366 ± 142 | 0.705 |
| Hemodynamics | | | |
| Mean right atrial pressure (mm Hg) | 9 ± 6 | 8 ± 6 | 0.503 |
| Mean pulmonary artery pressure (mm Hg) | 54 ± 18 | 46 ± 13 | 0.004 |

| | | | |
|---|---|---|---|
| Pulmonary artery wedge pressure (mm Hg) | 11 ± 5 | 11 ± 6 | 0.957 |
| Cardiac index (L/min per $m^2$) | 2.7 ± 0.7 | 2.7 ± 0.8 | 0.998 |
| Pulmonary vascular resistance (Wood U) | 11.6 ± 6.5 | 9.9 ± 6.3 | 0.135 |
| Arterial oxygen saturation (%) | 91 ± 7 | 93 ± 5 | 0.096 |
| Mixed venous oxygen saturation (%) | 62 ± 12 | 63 ± 11 | 0.900 |
| Stroke volume index (mL/$m^2$) | 31 ± 10 | 31 ± 10 | 0.805 |
| Pulmonary arterial compliance (mL/mm Hg) | 0.90 ± 0.58 | 1.02 ± 0.76 | 0.296 |

Data are presented as mean (standard deviation), or median (interquartile range), or number (proportion). PH, pulmonary hypertension; NT-proBNP, N-terminal pro-B type natriuretic peptide; WHO, World Health Organization.

[a]Elevated inflammatory markers were defined as any of elevated C-reactive protein or erythrocyte sedimentation rate.

**Table S2.** Predictors of all-cause death in patients with pulmonary Takayasu's arteritis-associated pulmonary hypertension from multivariate Cox model based on the complete cases ($N$ = 117): sensitivity analyses.

| Variables | Multivariate analyses | |
|---|---|---|
| | **HR (95% CI)** | ***P*-value** |
| Syncope | 6.74 (2.06-22.12) | 0.002 |
| NT-proBNP, per 100 pg/mL | 1.04 (1.02-1.06) | <0.001 |
| Mean right atrial pressure, mm Hg | 1.06 (0.99-1.12) | 0.096 |

HR, hazard ratio; CI, confidence interval; NT-proBNP, N-terminal pro-B type natriuretic peptide.

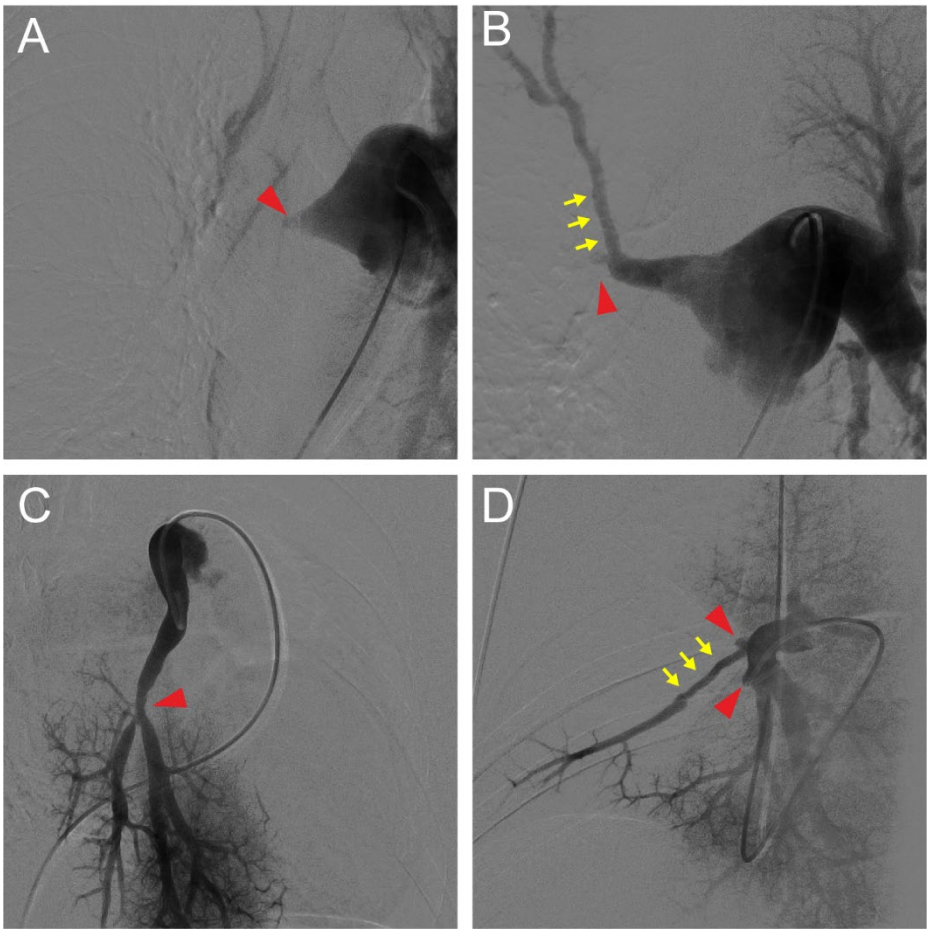



**Figure S1** Typical pulmonary angiographic images of pulmonary artery involvement in patients with pulmonary Takayasu's arteritis-associated pulmonary hypertension. (A) A total occluded lesion with tapered stump of right pulmonary artery (indicated by red triangle). (B) The diffuse stenotic lesion in right upper pulmonary artery (indicated by yellow arrows) and total occlusion of right lower-lobe and middle-lobe pulmonary artery (indicated by red triangle). (C) A bifurcation lesion of segmental pulmonary arteries (A10) in left lower-lobe (indicated by red triangle) and all other segmental pulmonary arteries were completely occluded. (D) A diffuse stenotic lesion of segmental pulmonary artery in right middle-lobe (A5) (indicated by yellow arrows) and totally occluded lesions in right middle-lobe (A4) and lower-lobe (A8) (indicated by red triangles).