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CLINICAL RESEARCH
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Clinical features and survival in Takayasu's arteritis-associated pulmonary hypertension: a nationwide study

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See page 4306 for the editorial comment for this article 'Takayasu arteritis-associated pulmonary hypertension', by Y. Fukumoto, https://doi.org/10.1093/eurheartj/ehab688.

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

Methods and results We conducted a nationally representative cohort study of TA-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 TA-PH to the occurrence of all-cause death. Between January 2007 and January 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 TA-PH had severely haemodynamic and functional impairments at diagnosis. Significant improvements have been found in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and haemodynamic profiles in patients with TA-PH receiving drugs approved for pulmonary arterial hypertension. The overall 1-, 3-, and 5-year survival rates in TA-PH

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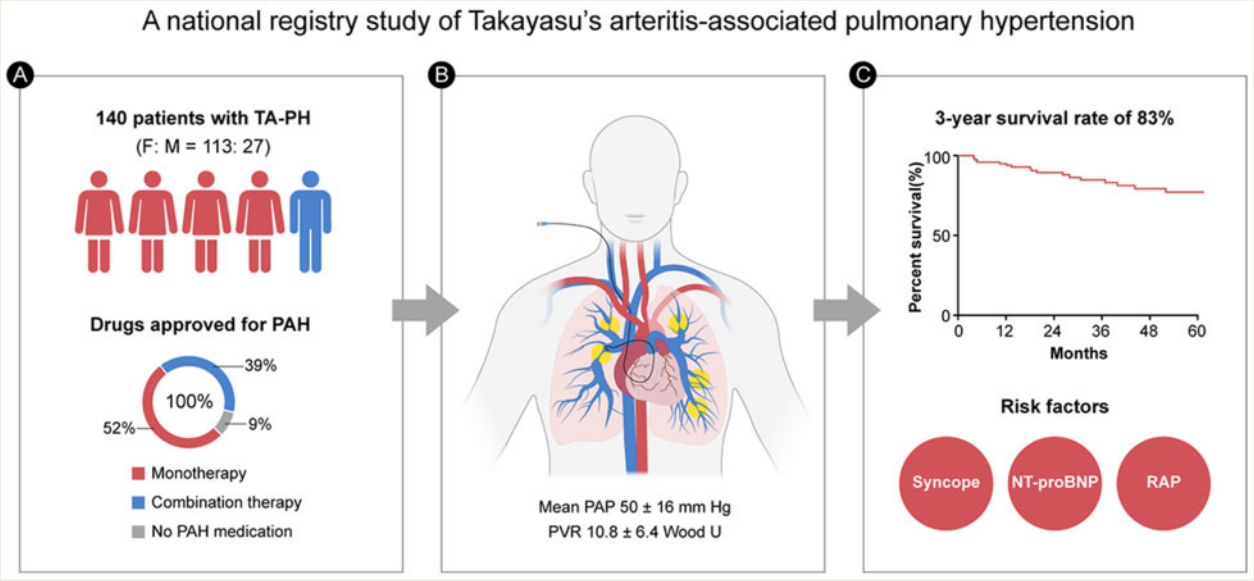
were 94.0%, 83.2%, and 77.2%, respectively. Predictors associated with an increased risk of all-cause death were syncope [adjusted hazard ratio (HR) 5.38 (95% confidence interval 1.77–16.34), $P = 0.003$], NT-proBNP level [adjusted HR 1.04 (1.03–1.06), $P < 0.001$], and mean right atrial pressure [adjusted HR 1.07 (1.01–1.13), $P = 0.015$].

Conclusion Patients with TA-PH were predominantly female and had severely compromised haemodynamics. More than 80% of patients in our cohort survived for at least 3 years. Medical treatment was based on investigators' personal opinions, and no clear risk-to-benefit ratio can be derived from the presented data.

Graphical Abstract



Keywords Takayasu's arteritis • Pulmonary artery involvement • Pulmonary hypertension • 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 aneurysm. 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 Takayasu's arteritis-associated pulmonary artery involvement suffer from overt pulmonary hypertension (PH) during their courses, which is mostly secondary to pulmonary artery stenosis or occlusion.[11,12] Furthermore, the concomitant systemic artery involvement could theoretically cause post-capillary PH in a subset of patients with Takayasu's arteritis-associated pulmonary artery involvement. Haemodynamic assessment based on right heart catheterization was, therefore, essential for accurate diagnosis and subsequent classification of PH. In the real world, patients with Takayasu's arteritis-associated PH (TA-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 TA-PH is only from case series and small cohort studies, with their determination of PH commonly dependent on echocardiography.[11–13] Clinical phenotyping, by invasive haemodynamics, of patients with TA-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 TA-PH.[14–16]

Therefore, this multicentre cohort study was conducted to assess the clinical features, especially the haemodynamic characteristics, of patients with TA-PH, as well as to evaluate their long-term survival outcomes and identify prognostic factors for all-cause death.

Methods

Study cohort

We conducted a multicentre cohort study using the clinical, functional, and haemodynamic 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, were routinely registered (NCT03169010).

Patients with TA-PH who were registered for this study were geographically located in 13 PH referral centres and situated in 10 provinces or municipalities of China. All patients were included between January 2007 and January 2019, based on the following procedures. First, 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] Second, 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 TA-PH are 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 guidelines.[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 TA-PH diagnosis were collected, including demographic information, clinical symptoms, medical history, World Health Organization (WHO) functional class, 6-min walking distance, serological testing, vascular involvement, echocardiographic findings, invasive haemodynamics, 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 the diagnosis of TA-PH, after any causes other than arteritis were excluded. The presence of left heart disease in patients with TA-PH was identified by echocardiography measuring left atrial or ventricular enlargement, moderate or severe left heart valve disease, or a left ventricular ejection fraction of <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 judgement 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 primary outcome was the time from the diagnosis of TA-PH to the occurrence of all-cause death. The data from the first clinical and haemodynamic assessments after enrolment were collected to analyse the therapeutic effects of drugs approved for PAH on patients with TA-PH.

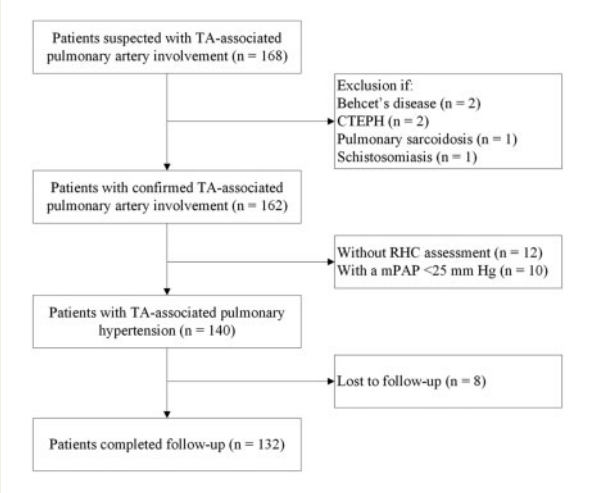


Figure 1 Flowchart of patient selection for the study. CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; TA, Takayasu's arteritis; RHC, right heart catheterization.

Statistical analyses

Continuous variables were presented as mean (± standard deviation) or median [with interquartile range (IQR)]. Categorical variables were summarized by number (with percentage). 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 haemodynamic measurements, generalized linear mixed models were used to estimate the mean changes or odds ratios between measurements at baseline and re-evaluation with 95% confidence intervals (CIs), with time as a study variable, age and sex as covariates, and subject as a 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. A 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 TA-PH are presented in *Figure 1*. Initially, 168 patients suspected of having Takayasu's arteritis-associated pulmonary artery involvement were screened. Among them, 6 patients were excluded due to having other aetiologies of

Table 1 Baseline characteristics of patients with Takayasu's arteritis-associated pulmonary hypertension[a] (*n* = 140)

Characteristics	
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)
Haemoptysis	50 (36)
Syncope	14 (10)
Hypertension	37 (26)
History of tuberculosis infection	27 (19)
NT-proBNP (pg/mL)	752 (173–2040) (*n* = 127)
C-reactive protein (mg/L)	3.3 (2.0–6.9) (*n* = 138)
Erythrocyte sedimentation rate (mm/h)	8.0 (4.0–20.0) (*n* = 133)
WHO functional class III–IV	73 (52)
Six-minute walking distance (m)	373 ± 132 (*n* = 115)
Haemodynamics	
Mean right atrial pressure (mmHg)	137.9 ± 6
Mean pulmonary artery pressure (mmHg)	50 ± 16
Pulmonary artery wedge pressure (mmHg)	11 ± 5 (*n* = 137)
Cardiac index (L/min/m^2)	2.7 ± 0.8 (*n* = 136)
Pulmonary vascular resistance (Wood U)	10.8 ± 6.4 (*n* = 137)
Arterial oxygen saturation (%)	92 ± 6 (*n* = 130)
Mixed venous oxygen saturation (%)	63 ± 12 (*n* = 133)
Stroke volume index (mL/m^2)	31 ± 10 (*n* = 138)
Pulmonary arterial compliance (mL/mmHg)	0.95 ± 0.66 (*n* = 138)
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 drug therapy[b]	13/53/63/10

Data are presented as mean (± standard deviation), or median (with interquartile range), or number (with percentage), unless otherwise stated.
ERA, endothelin receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; PH, pulmonary hypertension; WHO, World Health Organization.
[a]Number of recorded observations is provided if a variable has missing data.
[b]Data are presented as count (*N*).

pulmonary artery stenosis (2 with Behcet's disease, 2 with CTEPH, 1 with pulmonary sarcoidosis, and 1 with schistosomiasis) and another 22 patients were further excluded due to the absence of invasive haemodynamic parameters (*n* = 12), or a baseline mean pulmonary artery pressure of <25 mmHg (*n* = 10). Finally, a total of 140 patients fulfilled the inclusion criteria of TA-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 TA-PH (*Table 1*). The median diagnosis delay from symptom onset to PH diagnosis was 2.0 (IQR 1.0–6.0) years. Haemoptysis was a common symptom, occurring in 50 (36%) patients with TA-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 haemodynamic profiles were identified in our patients, characterized by an elevated mean pulmonary artery pressure (50 ± 16 mmHg) and pulmonary vascular resistance (10.8 ± 6.4 Wood U) (*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). In addition, 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, respectively, 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 vs. 46 ± 13 mmHg, $P = 0.004$). The details of comparisons between the two groups are shown in Supplementary material online, *Table S1*.

Regarding medical treatment, drugs approved for PAH were prescribed for 127 (91%) patients, of whom 63 (45%) patients were administered with combination therapy and 10 (7%) with triple-combination therapy. Eighty-six (61%) patients received corticosteroids and 29 (21%) 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 pulmonary arterial hypertension

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 haemodynamics 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% CI -0.62 to -0.05), $P = 0.022$], mean pulmonary artery pressure [-3.36 mmHg (95% CI -6.46 to -0.26), $P = 0.034$], and pulmonary vascular resistance [-1.93 Wood U (95% CI -2.89 to -0.98), $P < 0.001$] after treatment (*Table 2*). The treatment of drugs approved for PAH was also associated with an increment in cardiac index [0.30 L/min/m^2 (95% CI 0.03–0.56), $P = 0.028$]. However, numerical but non-significant improvements were observed in 6-min walking distance and WHO functional class.

Table 2 Clinical and haemodynamic assessments of drugs approved for pulmonary arterial hypertension in patients with Takayasu's arteritis-associated pulmonary hypertension

Characteristics	Baseline	Second assessment	Difference (95% CI)c	*P*-value
Follow-up time (months)[a]		6 (3–15)		
Clinical assessments (*n* = 92)				
NT-proBNP[b]	6.4 ± 1.6	6.0 ± 1.7	-0.34 (-0.62 to -0.05)	0.022
Six-minute walking distance (m)	378 ± 130	400 ± 128	12.46 (-14.35 to 39.26)	0.362
WHO functional class III–IV	46 (50)	40 (44)	0.51 (0.20 to 1.33)[d]	0.171
Haemodynamics assessments (*n* = 61)				
Mean pulmonary artery pressure (mmHg)	50 ± 16	47 ± 16	-3.36 (-6.46 to -0.26)	0.034
Cardiac index (L/min/m^2)	2.7 ± 0.8	3.0 ± 1.1	0.30 (0.03 to 0.56)	0.028
Pulmonary vascular resistance (Wood U)	10.4 ± 6.7	8.6 ± 5.4	-1.93 (-2.89 to -0.98)	<0.001

Data are presented as mean (± standard deviation), or number (with percentage), unless otherwise state.
CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHO, World Health Organization.
[a]The follow-up time is summarized as median (with interquartile range).
[b]NT-proBNP is log-transformed.
[c]Generalized linear mixed models are used to estimate the mean changes with 95% CIs for continuous variables and odds ratio with 95% CI for binary variable between baseline and re-evaluation, with time as a study variable, age and sex as covariates, and subject as a random effect.
[d]Odds ratio with 95% CI.

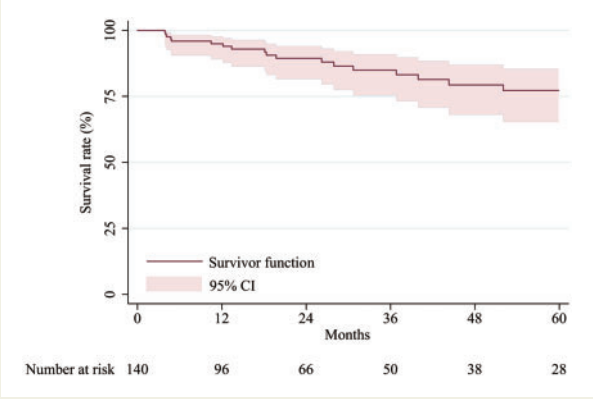


Figure 2 Kaplan–Meier plot for survival rate in patients with Takayasu's arteritis-associated pulmonary hypertension. The overall 1-, 3-, and 5-year survival rates were 94.0% (95% confidence interval 90.0–98.4), 83.2% (95% confidence interval 75.4–91.7), and 77.2% (95% confidence interval 67.8–87.9),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

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-, 3-, 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 (*Figure 2*). The causes of death were right heart failure (*n* = 17), sudden cardiac death (*n* = 1), massive haemoptysis (*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 (*Table 3*). Three significant predictors were retained, following backward-stepwise variable selection, in the final multivariate Cox regression model (*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 1.03–1.06, *P* < 0.001), and elevated mean right atrial pressure (adjusted HR per 1 mm Hg 1.07, 95% CI 1.01–1.13, *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 multicentre cohort study with a large enough sample size to establish clinical features and long-term prognosis of patients with TA-PH, based on diagnostic right heart catheterization. We found that patients with TA-PH presented with a severely compromised function status and haemodynamics 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 TA-PH had an estimated 3-year survival rate of 83.2%, and most of them died due 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 (*Graphical Abstract*).

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 TA-PH was consistent with that in Takayasu's arteritis populations.[2,5] However, the onset time of first PH-associated symptom seems to be 5–10 years later than the occurrence of Takayasu's arteritis.[20,21] Given that the symptoms of patients with TA-PH are usually insidious and nonspecific, diagnosis delay was common, with a median of 2 years in our study.[8] Tuberculosis

Table 3 Predictors of all-cause death in patients with Takayasu's arteritis-associated pulmonary hypertension: univariate and multivariate Cox regression analyses

Characteristics	Univariate analyses[a]		Multivariate analyses[b]	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Syncope	3.57 (1.28–9.94)	0.015	5.38 (1.77–16.34)	0.003
NT-proBNP, per 100 pg/mL	1.04 (1.02–1.06)	<0.001	1.04 (1.03–1.06)	<0.001
WHO functional class, III–IV vs. I–II	4.98 (1.66–14.97)	0.004		
Six-minute walking distance, per 50 m	0.56 (0.44–0.71)	<0.001		
Mean right atrial pressure, mmHg	1.07 (1.02–1.12)	0.007	1.07 (1.01–1.13)	0.015
Mean pulmonary artery pressure, mmHg	1.02 (1.00–1.05)	0.035		
Cardiac index, L/min/m^2	0.34 (0.17–0.70)	0.003		
Pulmonary vascular resistance, Wood U	1.12 (1.06–1.17)	<0.001		
Arterial oxygen saturation, %	0.92 (0.87–0.98)	0.009		
Mixed venous oxygen saturation, %	0.93 (0.90–0.96)	<0.001		
Stroke volume index (mL/m^2)	0.90 (0.85–0.95)	<0.001		
Pulmonary arterial compliance (mL/mmHg)	0.11 (0.02–0.53)	0.006		

CI, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; WHO, World Health Organization.
[a]Univariate analyses are based on the complete cases without missing value.
[b]Multivariate analyses are based on imputed values in predictors. The final variables included were chosen by backward-stepwise selection procedure.

infection was found in 19% of patients with TA-PH, which was largely in parallel with a previous study.[22] Observational data have shown 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 TA-PH.

The prevalence of haemoptysis in patients with TA-PH (36%) is relatively high, and in accordance with a previous report.[13] The suspected causes for haemoptysis are inconclusive, but potentially include the rupture of collateral vessels or micro-aneurysms, hypertensive response, or pulmonary infarction.[24] Moreover, frequent anticoagulant usage in this study may have facilitated the high rate of haemoptysis. In clinical practice, anticoagulants have been empirically used for the prophylaxis of *in situ* thrombosis, which was not rare in patients with TA-PH.[12] However, the risk–benefit analysis for anticoagulation treatment should be further investigated.

Despite notable divergences in underlying causes of pulmonary vascular obstruction, TA-PH, and CTEPH might share similar pathophysiological mechanisms in pre-capillary PH development, such as pulmonary vascular bed loss by mechanical obstruction and secondary remodelling of unobstructed vessels.[25] In addition, elevated pulmonary artery wedge pressure was also identified in some patients with TA-PH, which could possibly be attributed to the impairments of systolic or diastolic left ventricular function due to hypertension secondary to extensive systemic artery stenosis. 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 cases 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 TA-PH. We also found that patients with a normal level of inflammatory makers had a higher mean pulmonary artery pressure. The active inflammation was commonly seen in the early stages of Takayasu's arteritis and tapered with frequent relapse in the late stages. Patients with Takayasu's arteritis-associated pulmonary artery involvement but not PH were indicated at the early and active inflammatory stage, suggesting a shorter disease course, a higher level of ESR, and a higher incidence of subpleural wedge-shaped shadows, compared to those with TA-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 remodelling in comparison to those with elevated inflammatory markers.

Despite limited data, a number of "real-world" patients with pre-capillary PH have been prescribed drugs approved for PAH. In the current study, we found significant post-treatment improvements in NT-proBNP level and pulmonary haemodynamics in patients with TA-PH receiving drugs approved for PAH. Nevertheless, these findings 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 opinions also made the interpretation of results difficult. Future prospective, controlled trials are warranted to identify the risk-to-benefit ratio of drugs approved for PAH for patients with TA-PH. In addition, the established treatment strategies for CTEPH, i.e. pulmonary endarterectomy and balloon pulmonary angioplasty, might also be treatment options that need to be further explored for patients with TA-PH.

In this study, we observed that the 3-year survival rate of TA-PH was 83.2%, which was poorer than the overall survival rate in the Takayasu's arteritis cohort.[26] PH-associated right heart failure was the main cause of death in patients with TA-PH, differing from 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 TA-PH. These markers presented a strong relationship with PH phenotype, and their prognostic value has been reported in current PH guidelines.[16] Furthermore, these findings suggest that PH *per se*, instead of Takayasu's arteritis related factors like systemic artery involvement or inflammatory markers, was the key factor for long-term prognosis of TA-PH.

Limitations

Some limitations of our study need to be acknowledged. First, 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 as hypothesis-generating rather than as definitive evidence. However, patient recruitment for such rare diseases is difficult, and the current study performed in 13 referral centres of China represents the largest cohort of TA-PH to date. Second, we included Takayasu's arteritis patients with well-defined pulmonary artery involvement and PH phenotypes; therefore, the generalization of our findings to patients with only Takayasu's arteritis-associated pulmonary artery involvement should be considered with caution. Third, it should be noted that pulmonary artery wedge pressure in some patients was possibly overestimated due to the presence of stenosis/obstruction in the proximal pulmonary arteries. Last but not least, limited by treatment heterogeneity of drugs approved for PAH and potential confounding factors, this study could not provide sufficient information on the risk-to-benefit ratio of drugs approved for PAH in patients with TA-PH.

Conclusions

In this first multicentre cohort study of TA-PH with invasive haemodynamic diagnoses, we found that patients with TA-PH were predominantly female and had severely compromised haemodynamics. We further found that >80% of patients were able to survive for 3 years from diagnosis. Medical treatment was based on investigators' personal opinions 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 TA-PH.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

Data availability

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

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