

# Long-Term Outcomes and Prognostic Predictors of Takayasu Arteritis Patients With Pulmonary Artery Involvement

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## Research article

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# Abstract

**Objective:** This study aimed to investigate the clinical characteristics, long-term results, and prognostic predictors of Takayasu arteritis (TA) patients with pulmonary artery involvement (PAI).

**Methods:** A total of 806 TA patients admitted to Fuwai Hospital were screened for inclusion in this study. Clinical symptoms, imaging features, and prognosis were analyzed, and patients were categorized into those with and those without pulmonary hypertension (PH). Additionally, risk factors associated with cardiac death and repeated hospitalization were explored.

**Results:** Among 806 TA patients, a total of 142 patients with PAI were included, 90.8% (n = 129) of whom had PH (diagnosed by right heart catheterization) and 9.2% (n = 13) of whom did not have PH. The median follow-up time was 54 months (range, 29–83 months). Sixteen patients died from right heart failure caused by PH. Patients with PH were significantly more likely to have worse outcomes than patients without PH ( $P = 0.027$ ). The multivariate Cox proportional regression hazard model showed that 6-min walk distance (6MWD) and PH-targeted therapy were independent prognostic predictors of cardiac death and hospital readmissions.

**Conclusion:** This study found that a significant proportion of TA patients with PAI had PH. Patients with PH had a worse prognosis than patients without PH. Further 6MWD and PH-targeted therapy were independent prognostic predictors. In future, a multi-center clinical studies are needed to further clarify this issue prospectively.

## Highlights

1. The majority of previous studies on TA patients with PAI have focused on clinical symptoms and imaging characteristics. Data on the prognostic factors and long-term outcomes of these patients are scarce.
2. The most common misdiagnoses of TA patients with PAI were tuberculosis and pulmonary embolism.
3. Imaging Findings showed that patients with PH were significantly more likely to have aneurysms than patients without PH.
4. The PH was prevalent in 90.8% in our study and was diagnosed by RHC, and PH in TA patients with PAI is likely underestimated by echocardiography.
5. The multivariate Cox proportional regression hazard model showed that 6MWD and targeted therapy were independent predictors of cardiac death or repeated hospitalizations. The findings provided evidence for the TA patients with PH who received PH targeted treatment, which is ambiguous in the clinical practice at present.

## 1. Introduction

Takayasu arteritis (TA) is a rare large vasculitis that predominantly affects the aorta and its main branches, including the pulmonary and coronary arteries [1]. The exact etiology of this disease remains unknown. The most common demographic of affected individuals are women of childbearing age between 20 and 40 years. The clinical presentation varies greatly depending on the affected arteries, severity, and duration of the disease. Because of no specific symptoms and signs, early diagnosis of TA is still very challenging for clinicians.

It is not uncommon for TA patients to have pulmonary arterial involvement (PAI), although it is often overlooked in the clinical assessment. The prevalence of PAI in TA patients has been reported to range from 13.3–61.7% in different populations [2–4]. PAI may lead to pulmonary hypertension (PH), which can result in catastrophic consequences [5].

The majority of previous studies on TA patients with PAI have focused on clinical symptoms and imaging characteristics. Data on the prognostic factors and long-term outcomes of these patients are scarce. This study aimed to investigate the clinical manifestations, imaging features, and long-term prognosis of TA patients with PAI, focusing on the differences between patients with and without PH. Furthermore, the prognostic factors for the improvement of long-term outcomes were explored.

## **2. Materials And Methods**

### **2.1 Design and Setting**

This retrospective study was conducted by reviewing the electronic medical records of patients diagnosed with TA who were admitted to our hospital. The study protocol was approved by the Institutional Review Board of the Fuwai Hospital. Informed consent was waived because the study collected data retrospectively and all personal identifiers were removed. The data were not numbered in a way that was associated with personal identity. All collected data were password protected, and only the research personnel were given access to them.

### **2.2 Study Population**

Patients with TA who were admitted to Fuwai Hospital between January 2008 and December 2019 were identified from the electronic medical records system. A total of 806 TA patients were hospitalized during the study period. Patients with TA fulfilling PAI criteria were eligible for inclusion. The modified Ishikawa criteria, created by Sharma et al. for diagnosing TA, were used because it included pulmonary artery lesions as one of the diagnostic criteria [6]. Although the 1990 American College of Rheumatology (ACR) diagnostic criteria for TA are commonly used in clinical practice, they emphasize aortic involvement more than other arteries, which limits its clinical applicability in our study. PAI was determined by computed tomography pulmonary angiography (CTPA). The estimation of the pulmonary arterial systolic pressure (PASP) was based on the simplified Bernoulli equation, using the peak tricuspid regurgitation velocity (TRV) and taking into account the right atrial pressure. The lack of PH was defined as an estimated PASP of < 35 mmHg and a peak TRV of < 2.8 m/s. In the event of PASP and TRV values above these limits, right

heart catheterization (RHC) was performed to confirm the diagnosis of PH as per the European Society of Cardiology Guidelines [7]. PH related to TA patients with PAI was defined as mean pulmonary arterial pressure of  $\geq 25$  mmHg, pulmonary artery wedge pressure of  $\leq 15$  mmHg, and pulmonary vascular resistance of  $> 3$  Wood Units at rest, as assessed by RHC. Patients with PH associated with left-sided heart failure were excluded. (Fig. 1)

## 2.3 Data Collection

The patients' medical records and imaging findings were collected, included patient age, sex, medical history, current medications, symptoms, physical signs, laboratory tests, echocardiogram, CTPA results, and so on. Coronary artery disease was defined as a  $> 50\%$  reduction in the diameter of more than one major coronary artery. CTPA results were interpreted by a radiologist who was blinded to the patients' status. All patient data used in this study were mutually checked by two researchers to guarantee their accuracy and comprehensiveness.

## 2.4 Treatment and Follow-up

The treatment plan was decided by the physicians in charge of the patients. Clinical symptoms coupled with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as radiological imaging (CT angiography, magnetic resonance angiography, and  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography) were used to assess disease activity [8, 9]. Follow-up visits were scheduled at 6 and 12 months and each year following discharge. To minimize the rate of loss to follow-up, patients living in remote areas were followed-up by phone or mail. Routine blood tests, liver function, renal function, CRP level, ESR, electrocardiogram, and echocardiogram were monitored. Primary endpoints were defined as death from cardiovascular causes and repeater hospitalization for heart failure (major cardiovascular adverse events, MACEs).

## 2.5 Statistical Analyses

Continuous variables with normal distribution were reported as means  $\pm$  standard deviations, and continuous variables without normal distribution were presented as medians (interquartile ranges). Categorical variables were presented as absolute numbers and percentages. Continuous variables were tested using the independent t-test or Mann–Whitney U test. Categorical variables were analyzed using the Fisher exact test. Survival curves were analyzed using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. Univariate and multivariate Cox proportional regression hazard models were used to analyze the independent risk factors related to MACEs. A  $P$  value of  $< 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS software (version 21; SPSS, Chicago, IL, USA).

## 3. Results

### 3.1 Patient Demographics

A total of 142 TA patients with PAI were included in this study, comprising 110 women and 32 men with a female: male ratio of 3.4:1. The median follow-up time was 54 months (range, 29–83 months). The mean age was  $40.3 \pm 13.0$  years. PH was diagnosed by RHC in 90.8% ( $n = 129$ ) of the patients; 140 patients completed follow-up. The median disease duration was 48 months (range, 18–120 months). Patients with PH were significantly more likely to have a longer disease duration ( $P = 0.031$ ) and a more severe cardiac function at baseline ( $P = 0.003$ ) than patients without PH. Patients without PH had higher CRP levels and ESR, implying that they had higher disease activity than patients with PH (all  $P < 0.05$ ). Patients with PH had worse outcomes if they had shorter 6-min walk distance (6MWD), and higher total bilirubin (TBIL) and NTpro-BNP (all  $P < 0.05$ ). There were no significant differences in age, sex, renal function, and comorbidities between the two groups. (Table 1)

## 3.2 Clinical Manifestations

The most common symptom of TA with PAI was exertional dyspnea (81.0%,  $n = 115$ ), followed by chest tightness (71.1%,  $n = 101$ ), hemoptysis (15.5%,  $n = 22$ ), cough (9.9%,  $n = 14$ ), fatigue (9.9%,  $n = 14$ ), chest pain (6.3%,  $n = 9$ ), and fever (0.7%,  $n = 1$ ). There were no reports of syncope. (Table 1)

## 3.3 Distribution of Misdiagnoses

The median time from the initial symptoms to definitive diagnosis was 15.5 months (range, 2–247 months). The most common misdiagnoses of TA patients with PAI were tuberculosis (9.9%,  $n = 14$ ) and pulmonary embolism (8.5%,  $n = 12$ ). Other misdiagnoses were chronic thromboembolic pulmonary hypertension (CTEPH) (5.6%,  $n = 8$ ), congenital malformations (4.9%,  $n = 7$ ), asthma (2.8%,  $n = 4$ ), and idiopathic pulmonary artery hypertension (IPAH) (0.7%,  $n = 1$ ). (Table 2)

## 3.4 Imaging Findings

Eleven patients (7.7%) had  $PASP < 35$  mmHg and  $TRV < 2.8$  m/s by echocardiogram. Two patients with  $PASP \geq 35$  mmHg underwent RHC but did not fulfill the criteria for PH diagnosis. Seventy-three (51.4%) patients only had PAI involvement and no other arterial involvement. Pulmonary artery stenosis was the most common pulmonary artery lesion (88.0%,  $n = 125$ ), followed by pulmonary artery occlusion (82.4%,  $n = 117$ ). Vascular wall thickening was more common in patients without PH, although the difference was not statistically significant ( $P = 0.081$ ). Patients with PH were significantly more likely to have aneurysms than patients without PH (39.5% vs. 7.7%,  $P = 0.049$ ). The rate of in situ thrombosis was similar between the two groups. The characteristics of pulmonary artery lesions in TA patients with PAI are summarized in Table 3.

## 3.5 Treatment and Prognosis

The majority of patients (67.6%,  $n = 96$ ) received prednisone treatment. Additionally, some patients received immunosuppressive agents based on hormone therapy for poor disease control (7%,  $n = 10$ ). Among patients with PH, 82.9% ( $n = 107$ ) received targeted therapy, including sildenafil, tadalafil, anrisentan, bosentan and treprostinil. The follow-up time was not significantly different between both

groups. Sixteen patients died from right heart failure caused by PH associated with PAI of TA. In terms of a single endpoint event, there was no significant difference between the two groups. (Table 4)

The Kaplan-Meier survival analysis (combined endpoint events) indicated that PAI patients with PH had a worse prognosis compared with PAI patients without PH ( $P = 0.027$ ). (Fig. 2)

The univariate regression analysis illustrated that the World Health Organization functional class, 6MWD, TBIL, tricuspid annular plane systolic excursion, the right ventricle/left ventricle ratio, and targeted treatment were all related to composite endpoint events. The multivariate Cox proportional regression hazard model showed that 6MWD and targeted therapy were independent predictors of cardiac death or repeated hospitalizations. (Table 5)

## 4. Discussion

The long-term outcomes and prognostic factors of TA patients with PAI were investigated in this study. Of these patients, 90.8% were diagnosed with PH by RHC. Patients with PH were found to have a worse prognosis than patients without PH. Furthermore, 6MWD and PH-targeted therapy were independent predictors of cardiac death and repeated hospitalizations.

Pulmonary vascular damage caused by TA has not received sufficient attention in the clinical setting, apparent by the ACR diagnostic criteria for TA, where the role of pulmonary lesions has been ignored [10]. The prevalence of PAI among TA patients is still unclear, with varying percentages (13.3–61.7%) across different studies depending on disease duration, diagnostic criteria, and study populations [2–4, 11]. During our study period, from the 806 patients with TA, PAI was diagnosed by CTPA in 17.6%. Among TA patients with PAI, more attention should be paid to the diagnosis of PH. Previous studies have indicated that PH is associated with a poor prognosis. Toledano et al. reported a mortality rate of 20.5% in patients with PAI and 33.3% among patients with PH [12]. Yang et al. reported that 58.8% of TA patients with PAI had PH on echocardiography [13]. In their study, PH was defined as an estimated PASP of  $> 50$  mmHg and TRV of  $> 3.4$  m/s, which suggests a high probability of PH according to the European Society of Cardiology/European Respiratory Society guidelines [7]. In contrast, the PH was prevalent in 90.8% in our study and was diagnosed by RHC, which is considered the gold standard. It is important to note that nine patients had an estimated PASP of  $< 50$  mmHg but showed signs of PH on RHC, suggesting that PH in TA patients with PAI is likely underestimated by echocardiography. Another reason for this difference could be related to the duration of the disease, which was longer in the patients of our study than in previous reports [7, 14].

The diagnosis of PAI in patients with TA is often delayed or misdiagnosed because of nonspecific respiratory manifestations and a lack of symptoms of systemic vessel involvement [15]. The main clinical manifestations in our study were dyspnea, chest tightness, hemoptysis, cough, fatigue, and chest pain, which were related to disease duration, severity, and the study population. TA patients with PAI were often misdiagnosed with lung disease in our study, including tuberculosis, pulmonary embolism, CTEPH, congenital malformations, asthma, and IPAH. Previous studies have indicated that diagnosis and

treatment delays range from 3 to 72 months in these patients [15–17]. In our study, the median time from the initial symptoms to definitive diagnosis was 15.5 months (range, 2–247 months). Interestingly, one patient with a ventricular septal defect in our study was admitted to several hospitals and was misdiagnosed with both PH associated with congenital heart diseases and IPAH. This indicates the need for adherence to current guidelines, as well as screening for all possible causes of PH before making a final diagnosis.

In our study, 16 patients died from right heart failure caused by PH, which was associated with the PAI of TA. However, the risk factors affecting the prognosis of these patients remain unclear. The univariate regression analysis illustrated that the World Health Organization functional class, 6MWD, TBIL, tricuspid annular plane systolic excursion, the right ventricle/left ventricle ratio, and targeted treatment were all related to composite endpoint events. After adjusting for confounders, 6MWD and targeted therapy were independent predictors of cardiac death and repeated hospital admissions. The first-line treatment of active inflammation is corticosteroids, with suggested initial dosages of 0.5–1 mg/kg/day according to our experience. For the conventional treatment of TA patients with PAI and PH, PH-targeted therapy is necessary to improve the prognosis of these patients. Yang et al. found that the risk of death or readmission significantly increased if PASP was  $\geq 100$  mmHg in TA patients with PAI [13]. However, our results did not support this finding. This could be due to a PASP value that is lower than baseline in patients with severe right heart failure that significantly decreased the cardiac output at the end-stage. Interestingly, their study demonstrated that patients with an ESR  $\geq 20$  mm/h had a lower risk of death after repeated hospital admissions. Our findings were somewhat consistent with these results, as patients with PH were found to have lower ESR levels than those without PH. The reason for this phenomenon is unclear. This could be related to the decline of the body's inflammatory response in TA patients with PAI and PH at the end-stage.

A previous study found that both the initial and any changes in the 6MWD are predictive of morbidity and mortality in patients with PH, highlighting its use in clinical management and trials [18–20]. Our results suggest that the baseline 6MWD significantly worsens prognosis, where a lower value indicates a higher risk of death or readmission. Investigations focusing on the efficiency of targeted treatment of PH associated with TA patients are very limited, even in small samples. Sari et al. reported that only one patient with PAI and PH was treated with PH-specific agents, and a decrease in brain natriuretic peptide levels and an improvement in the 6MWD were observed with an 8-year follow-up [21]. Wang et al. found that PH-targeted therapy was useful in a small sample of TA patients with PAI and PH [22]. Our study indicates that PH targeted treatment is related to prognosis, lowering the risk of death and readmission. Additionally, in contrast to the results of Lee et al. [23], we did not find a relationship between PAI and disease activity. This is in accordance with a report from China [24]. The discrepancy between these results could be due to differences in the disease stage of TA because of its gradual onset.

This study has some limitations related to its retrospective cohort design, in addition to being conducted in a single center. Two patients were lost to follow-up, which may have led to an underestimation of mortality. However, as a national research center for TA, our center is a referral region from over the

country, including cities, rural, and remote areas. Therefore, these TA patients with PAI are representative of other patients. Moreover, a long-term follow-up was conducted for these patients.

## **5. Conclusions**

This study found that a high proportion of TA patients with PAI had PH. Compared with TA patients with PAI but without PH, patients with PH had a worse prognosis. Moreover, 6MWD and PH-targeted therapy were found to be independently associated with the risk of cardiac death or repeated hospital admissions. In future, a multi-center clinical studies are needed to further clarify this issue prospectively.

## **Declarations**

### **Ethics approval and consent to participate**

The present study was approved by the ethics committee of Fuwai Hospital.

### **Consent for publication**

All authors have participated in the work and have reviewed and agree with the content of the article to publication.

### **Availability of data and material**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors report no conflicts of interest.

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### **Authors' contributions**

Professor Yan Liang, Xiaoming Liu and Zhiwei Huang are responsible for the design of the manuscript and responsible for quality of whole work. Dongfang Gao supervised the conduct of the study and data collection. Zhiwei Huang drafted the manuscript, and all authors contributed substantially to its revision.

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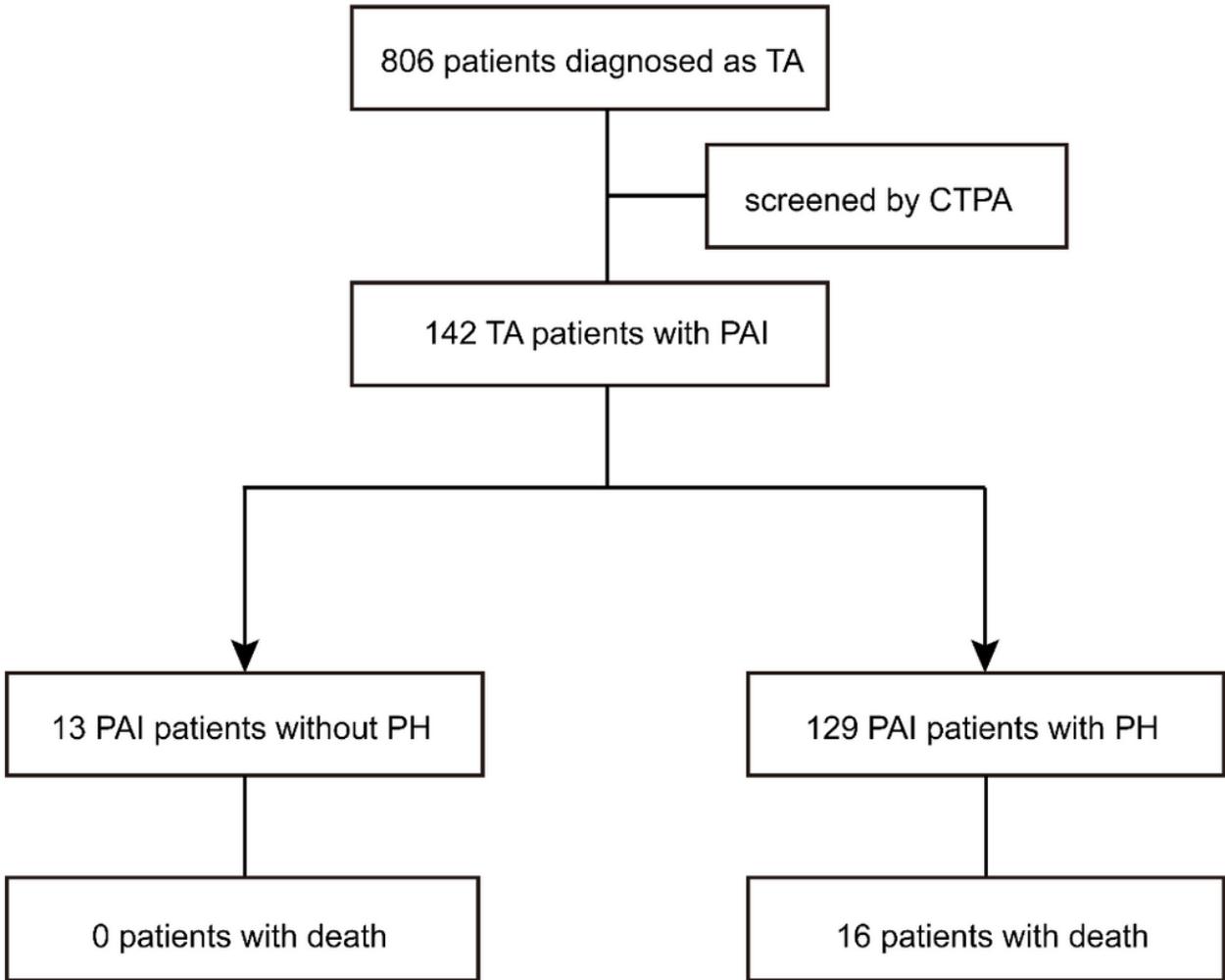
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## Tables

Due to technical limitations, table 1-5 is only available as a download in the Supplemental Files section.

## Figures



**Figure 1**

Flow diagram of the study. Abbreviations: TA, takayasu's; CTPA, computed tomographic pulmonary angiography, PAI, pulmonary artery involvement; PH, pulmonary hypertension.

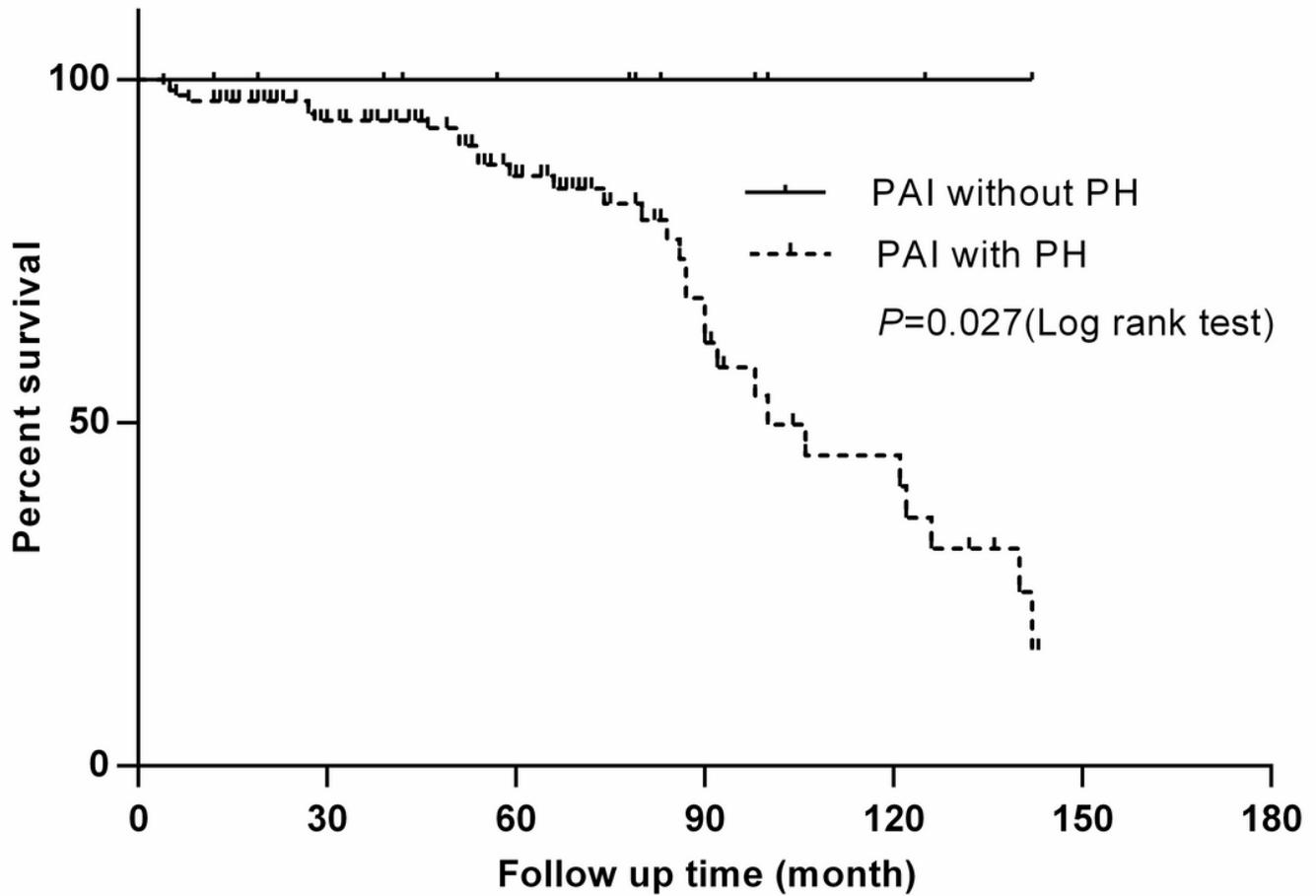


Figure 2

The Kaplan-Meier survival analysis (combined endpoint events) indicated that PAI patients with PH had a worse prognosis compared with PAI patients without PH( $P=0.027$ ).

## Supplementary Files

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