Long-term outcomes and prognostic predictors of patients with Takayasu's arteritis along with pulmonary artery involvement

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Abstract

Objective

This study aimed to investigate the clinical characteristics, results, and prognostic predictors of patients with Takayasu's arteritis (TAK) along with pulmonary artery involvement (PAI).

Methods

A total of 806 patients with TAK admitted to the Fuwai Hospital were screened. Clinical symptoms, imaging features, and prognosis were analysed, and patients were categorised into those with and those without pulmonary hypertension (PH). Additionally, risk factors associated with cardiac death and repeated hospitalisation were explored.

Results

Among 806 patients with TAK, 142 patients with PAI were included, 90.8% (n=129) of whom had PH diagnosed by right heart catheterisation and 9.2% (n=13) of whom did not. The median follow-up time was 54 (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 the 6-min walk distance (6MWD) and PH-targeted therapy were independent prognostic predictors of cardiac death and hospital readmissions.

Conclusion

This study found that that a significant proportion of patients with TAK along with PAI had PH. Patients with PH had worse prognosis than those without. Further 6MWD and PH-targeted therapy were independent prognostic predictors of cardiac death or repeated hospitalization. In the future, multi-centre clinical studies are needed to further prospectively clarify this issue.

Key words

Takayasu's arteritis, pulmonary artery involvement, pulmonary hypertension, predictors, prognosis

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Introduction

Takayasu's arteritis (TAK) is a rare large vasculitis that predominantly affects the aorta and its main branches, including the pulmonary and coronary arteries (1). The exact aetiology of this disease remains unknown. The most common demographic of affected individuals are women of childbearing age between 20 and 40 years of age (2). Clinical presentation greatly varies depending on the affected arteries and severity and duration of the disease. Due to the absence of specific symptoms and signs, early diagnosis of TAK is still very challenging for clinicians (3). It is not uncommon for patients with TAK to have pulmonary arterial involvement (PAI), although it is often overlooked during clinical assessment. The prevalence of PAI in patients with TAK has been reported to range from 13.3%–61.7% in different populations (4-6). PAI may lead to pulmonary hypertension (PH), which can result in catastrophic consequences (7).

Most previous studies on patients with TAK along 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 patients with TAK along with PAI, focusing on the differences between patients with and without PH. Furthermore, the prognostic factors for improving long-term outcomes were explored.

Materials and methods

Design and setting

This retrospective study was conducted by reviewing the electronic medical records of patients diagnosed with TAK who were admitted to the Fuwai Hospital, Bejing, China. The study protocol was approved by the institutional review board of the Fuwai Hospital (approval number: 2020-1399), which waived the requirement for informed consent due to the retrospective nature of this study and the removal of all personal identifiers. Data were not numbered in a way that was associated with personal identity. All collected data were password protected, and only research personnel were given access to them.

Study population

Patients with TAK who were admitted to the Fuwai Hospital between January 2008 and December 2019 were identified from electronic medical records. A total of 806 patients with TAK were hospitalised during the study period. Patients with PAI diagnosed with computer tomography angiography (CTA) were eligible for inclusion. The modified Ishikawa criteria, created by Sharma *et al*. for diagnosing TAK, were used because pulmonary artery lesions were included as a diagnostic criterion (8). Although the 1990 American College of Rheumatology (ACR) diagnostic criteria for TAK are commonly used in clinical practice, they emphasise aortic involvement more than the involvement of other arteries, limiting its clinical applicability in our study. PAI was determined by computed tomography pulmonary angiography (CTPA). Previous study showed that the vascular lesions caused by TAK included pulmonary artery stenosis, pulmonary artery occlusion, vascular wall thickening, and aneurysms (9, 10).

Pulmonary arterial systolic pressure (PASP) was based on the simplified Bernoulli equation, using peak tricuspid regurgitation velocity (TRV) and considering right atrial pressure. Right ventricular systolic pressure (RVSP) equals PASP if pulmonary stenosis or right ventricular outflow obstruction do not apply. The RVSP was calculated using the modified Bernoulli equation ($RVSP=4 \times v^2+RAP$), where v is the maximum velocity of the tricuspid valve regurgitation jet measured using continuous wave Doppler and RAP is the right atrial pressure measured via the central venous line (11, 12). The lack of PH was defined as an estimated PASP of <35 mmHg and a peak TRV of <2.8 m/s. If PASP and TRV values were above limit, right heart catheterization (RHC) was performed to confirm PH diagnosis as per the European Society of Cardiology Guidelines (13). PH related to patients with TAK along with PAI was defined as a mean pulmonary

arterial pressure of ≥25 mmHg, pulmonary artery wedge pressure of ≤15 mmHg, and pulmonary vascular resistance of >3 Wood Units at rest, as assessed by RHC (14,15). Only patients with PAI who completed RHC were included in the PH group. Patients with PH associated with left-sided heart failure or interstitial lung disease were excluded (Fig. 1).

Data collection

The medical records and imaging findings of patients were collected, including patient age, sex, medical history, current medications, symptoms, physical signs, laboratory tests, echocardiogram, and CTPA results. Coronary artery disease associated with TAK 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 status of the patients. All patient data used in this study were mutually checked by two researchers to guarantee their accuracy and comprehensiveness.

Treatment and follow-up

The treatment plan was decided by the attending physicians. Clinical symptoms coupled with the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as radiological imaging (CT angiography, magnetic resonance angiography, and 18F-fluorodeoxyglucose positron emission tomography), were used to assess disease activity (16, 17). 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 repeated (>1) heart failure hospitalisations (*i.e.* major cardiovascular adverse events (MACEs)).

Statistical analyses

Continuous variables with normal distribution are reported as means ± standard deviations, and continuous variables without normal distribution are presented as medians (interquartile ranges). Categorical variables are presented as absolute numbers and percentages. Continuous variables were tested using the independent t-test or Mann–Whitney U-test. Categorical variables were analysed using the Fisher exact test. Survival curves were analysed 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 analyse the independent risk factors related to MACEs. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v. 21 (SPSS, Chicago, IL, USA).

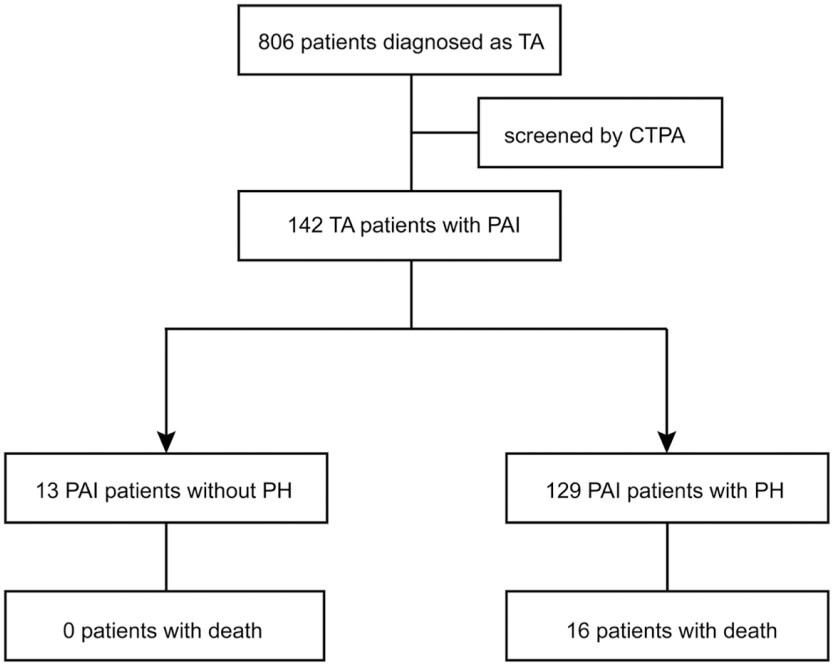

Fig. 1. Flow diagram of the study.
TAK: Takayasu's arteritis; CTPA: computed tomographic pulmonary angiography; PAI: pulmonary artery involvement; PH: pulmonary hypertension.

Results

Patient demographics

A total of 142 (17.6%) patients with TAK along with PAI were included in this study, comprising 110 women and 32 men, with a female:male ratio of 3.4:1. The mean age of patients was 40.3±13.0 years at hospital admission. PH was diagnosed by RHC in 90.8% (n=129) of patients. According to the suggestion at the time of discharge, 140 patients were regularly followed-up in the hospital. The median disease duration was 48 (range, 18–120) months before initial evaluation.

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 those without. Patients without PH had higher CRP levels and ESR, implying that they had higher disease activity than patients with PH (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 (p<0.05) results. There were no significant differences in age, sex, renal function, and comorbidities between groups (Table I).

Clinical manifestations

When admitted to our hospital, the most common symptom of patients with TAK along with PAI was exertional dyspnoea (81.0%, n=115), followed by chest tightness (71.1%, n=101), haemoptysis (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. It is worthy to note that the

proportion of dyspnoea and chest tightness in patients with PAI along with PH was significantly higher than that in patients with PAI without PH (Table I).

Distribution of misdiagnoses

The median time from the onset of initial symptoms to definitive diagnosis was 15.5 months (range, 2–247 months). The most common misdiagnoses of patients with TAK along 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) (Supplementary Table S1).

Imaging findings

Eleven patients (7.7%) had a PASP <35 mmHg and TRV <2.8 m/s as diagnosed by echocardiogram. Two patients with a PASP ≥35 mmHg underwent RHC but did not fulfil the criteria for PH diagnosis. Seventy-three (51.4%) patients only had PAI 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 than in those with 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 groups. The characteristics of pulmonary artery lesions in patients with TAK along with PAI are summarised in Table II.

Treatment and prognosis

Most patients (67.6%, n=96) received prednisone treatment with suggested initial dosages of 0.5–1 mg/kg/day. The maintenance dose is 5mg and 10mg. 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 PH-targeted therapy, including sildenafil,

Table I. Anthropometric and clinical characteristics of PAI patients diagnosed as TAK with and without PH.

Variables	PAI without PH (n=13)	PAI with PH (n=129)	*p*
Clinical characteristics			
Age, years	38.3 ± 14.5	40.5 ± 13.0	0.564
Disease duration, months	24 (11, 48)	48 (24, 120)	0.031
Female, n (%)	10 (76.9%)	100 (77.5%)	0.961
BMI (kg/m2)	22.9 ± 3.1	22.3 ± 3.5	0.542
WHO FC I-II	10 (76.9%)	45 (34.9%)	0.003
WHO FC III-IV	3 (23.1%)	84 (65.1%)	0.003
Comorbidities, n (%)			
Hypertension	5 (38.5%)	23 (17.8%)	0.075
Dyslipidaemia	3 (23.1%)	11 (9.2%)	0.121
Diabetes mellitus	1 (7.7%)	0 (0.0%)	0.092
CAD	1 (7.7%)	1 (0.8%)	0.175
PAD	8 (61.5%)	47 (36.4%)	0.077
Smoking	1 (7.7%)	2 (1.6%)	0.252
Symptoms, n (%)			
Chest tightness	4 (30.8%)	97 (75.2%)	0.001
Chest pain	2 (15.4%)	7 (5.4%)	0.160
Dyspnoea	5 (38.5%)	110 (85.3%)	<0.001
Cough	1 (7.7%)	13 (10.1%)	1.000
Haemoptysis	1 (7.7%)	21 (16.3%)	0.415
Fever	0 (0.0%)	1 (8.0%)	1.000
Fatigue	2 (15.4%)	12 (9.3%)	0.483
Blood test			
CRP, mg/l	15.9 ± 15.5	8.0 ± 10.4	0.014
ESR, mm/h	22.9 ± 21.1	11.1 ± 14.8	0.009
TBIL, mmol/L	11.7 ± 6.9	21.2 ± 14.0	0.017
NTpro-BNP, pg/mL	365.6 (63.3, 612.5)	710.0 (237.8, 2027.0)	0.017
eGFR (ml/min/1.73m^2)	92.8 ± 19.1	91.1 ± 21.2	0.78
ECHO			
RVD, mm	21 ± 3	30 ± 8	<0.001
LVD, mm	47 ± 4	40 ± 7	<0.001
LVEF, %	64 ± 4	65 ± 7	0.871
TAPSE, mm	19 ± 2	17 ± 4	0.134
PASP, mmHg	NA	80 ± 24	<0.001
Disease activity, n (%)	7 (53.8%)	19 (14.7%)	0.001
6MWD, m	538.7 ± 35.6	425.5 ± 77.0	<0.001
Medications, n (%)			
Prednisone	11 (84.6%)	85 (65.9%)	0.169
Immunosuppressants	2 (15.4%)	8 (6.2%)	0.217
PH-targeted agents	0 (0.0%)	107(82.9%)	<0.001

Data are presented as the means ± SD, median or as numbers and percentages.
PAI: pulmonary artery involvement; TAK: Takayasu's arteritis; PH: pulmonary hypertension; BMI: body mass index; CAD: coronary artery disease; PAD: peripheral arterial disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TBIL: total bilirubin; eGFR: estimated glomerular filtration rate; RVD: right ventricular diameter; LVD: left ventricular diameter; LVEF, left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; PASP: pulmonary arterial systolic pressure; NA: not applicable; 6MWD: 6-minute walk distance.

Table II. The characteristics of pulmonary artery lesions of TAK patients with PAI.

Variables	PAI without PH (n=13)	PAI with PH (n=129)	*p*
Vascular walls thickening, n (%)	4 (30.8%)	13 (10.1%)	0.081
Stenosis, n (%)	11 (84.6%)	114 (88.4%)	1.000
Occlusion, n (%)	12 (92.3%)	105 (81.4%)	0.547
Aneurysm, n (%)	1 (7.7%)	51 (39.5%)	0.049
Situ thrombosis, n (%)	1 (7.7%)	5 (3.9%)	1.000

Data are presented as numbers and percentages.
TAK: Takayasu's arteritis; PAI: pulmonary artery involvement; PH: pulmonary hypertension.

Table III. MACE between PAI patients diagnosed as TAK with and without PH.

Variables	PAI without PH (n=13)	PAI with PH (n=129)	*p*
Follow-up time, (month)	78 (29, 99)	54 (30, 80)	0.410
Repeated hospitalisation, n (%)	1 (7.7%)	31 (24.0%)	0.319
Cardiac death, n (%)	0 (0.0%)	16 (12.4%)	0.375

Data are presented as the median or as numbers and percentages.
MACE: major adverse cardiac event; PAI: pulmonary arterial involvement; TAK: Takayasu's arteritis; PH: pulmonary hypertension.

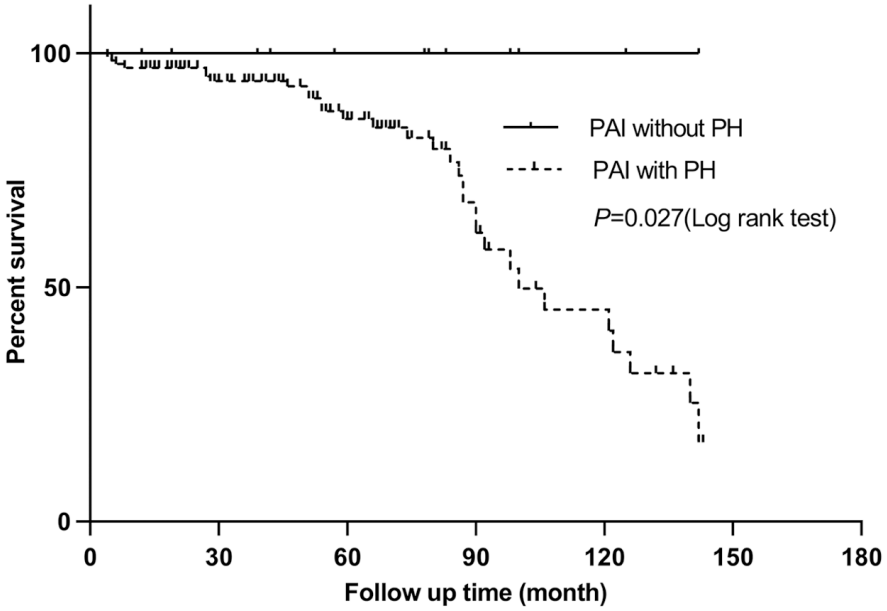

Fig. 2. The comparison of survival analysis in pulmonary artery involvement caused by Takayasu's arteritis patients with or without pulmonary hypertension.

Table IV. Risks related with MACE in TAK patients with PAI.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.024 (0.995-1.054)	0.099		
WHO functional class	1.900 (1.028-3.512)	0.041		
6MWD	0.993 (0.990-0.997)	<0.001	0.994 (0.990-0.998)	0.002
NTpro-BNP	1.000 (1.000-1.000)	0.052		
TBIL	1.030 (1.008-1.052)	0.006		
TAPSE	0.894 (0.800-0.999)	0.048		
Ratio of RV/LV	4.669 (2.004-10.880)	<0.001		
Disease activity	1.828 (0.636-5.251)	0.263		
PH-targeted treatment	0.246 (0.100-0.607)	0.002	0.228 (0.109-0.763)	0.012

TAK: Takayasu's arteritis; PAI: pulmonary artery involvement; WHO: world health organization; 6 MWD: 6-min walk distance; RV: right ventricle; LV: left ventricle; TBIL: total bilirubin; TAPSE: tricuspid annular plane systolic excursion; PH: pulmonary hypertension.

tadalafil, ambrisentan, bosentan, and treprostinil. The follow-up time was not significantly different between both groups. In the PAI with PH group, 16 patients died from right heart failure caused by PH associated with TAK PAI, whereas no patient died in the PAI without PH group. There were no significant differences in single endpoint events between groups (Table III).

The Kaplan-Meier survival analysis (combined endpoint events) indicated that patients with PAI and PH had worse prognosis compared with patients with PAI 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, right ventricle/left ventricle ratio, and PH-targeted treatment were related to composite endpoint events. The multivariate Cox proportional regression hazard model showed that 6MWD and PH-targeted therapy were independent predictors of cardiac death or repeated hospitalisations (Table IV).

Discussion

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

Pulmonary vascular damage caused by TAK has not received sufficient attention under clinical settings. For example, the ACR diagnostic criteria for TAK does not include pulmonary artery lesions (18). The prevalence of PAI among patients with TAK is still unclear, with varying percentages (13.3%–61.7%) across different studies depending on disease duration, diagnostic criteria, and study populations (4-6, 19). During our study period, among the 806 patients with TAK, 17.6% were diagnosed with PAI by CTPA. Diagnosis of PH should be emphasised among patients with TAK and PAI. Previous studies have indicated that PH is associated with poor prognosis. Toledano *et al*. reported a mortality rate of 20.5% in patients with PAI and 33.3% among patients with PH (20). Yang *et al*. reported that 58.8% of patients with TAK along with PAI had PH as assessed by echocardiography (9). 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 (13). In contrast, PH was prevalent in 90.8% of patients in our study and was diagnosed

by RHC, which is considered the gold standard for diagnosis. It is important to note that nine patients had an estimated PASP of <50 mmHg but showed signs of PH on RHC, suggesting that echocardiography lent a misdiagnosis rate of 7% (9/129). Another reason for this difference could be related to disease duration, which was longer in this study than in other studies (10, 13).

PAI in patients with TAK is often lately diagnosed or misdiagnosed because of nonspecific respiratory manifestations and a lack of symptoms of systemic vessel involvement (16). The main clinical manifestations in our study were dyspnoea, chest tightness, haemoptysis, cough, fatigue, and chest pain, which were related to disease duration, severity, and the study population. Patients with TAK along 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 3–72 months in these patients (21-23). In our study, the median time from the onset of initial symptoms to definitive diagnosis was 15.5 (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, indicating 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 TAK. However, the risk factors affecting the prognosis of these patients remain unclear. A univariate regression analysis illustrated that World Health Organization functional class, 6MWD, TBIL, tricuspid annular plane systolic excursion, right ventricle/left ventricle ratio, and PH-targeted treatment were related to composite endpoint events. After adjusting for confounders, 6MWD and PH-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 patients with TAK along with PAI and PH, PH-targeted therapy is necessary to improve prognosis. Yang *et al*. found that the risk of death or readmission significantly increased if PASP was ≥100 mmHg in patients with TAK along with PAI (9). However, our results did not support this finding. This could be due to a PASP value that is lower than baseline values in patients with severe right heart failure, significantly decreasing cardiac output at the end stage. Interestingly, their study demonstrated that patients with an ESR ≥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 than those without. The reason for this phenomenon is unclear. This could be related to the decline of the body's inflammatory response in patients with TAK along with PAI and PH at the end stage.

A previous study found that both initial 6MWD values and any subsequent changes are predictive of morbidity and mortality in patients with PH, highlighting the use of 6MWD in clinical management and trials (24-26). Our results suggest that baseline 6MWD significantly worsens prognosis, with lower values indicating a higher risk of death or readmission. Investigations focusing on the efficiency of targeted treatment of PH associated with TAK 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 decreases in brain natriuretic peptide levels and improvements in 6MWD results were observed throughout an 8-year follow-up (27). Wang *et al*. found that PH-targeted therapy was useful in a small sample of patients with TAK along with PAI and PH (28). 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*. (29), we did not find a relationship between PAI and disease activity. This is in accordance with a report from China (30). The discrepancy between these results could be due to differences in TAK disease stage because of the gradual onset of the disease. One good news from Erbasan *et al*. (31) is that biological agents, such as infliximab and/or tocilizumab, that are used in the treatment of TAK are capable of remedying certain vascular lesions and may provide additional benefits to patients with TAK who do not sufficiently respond to conventional synthetic disease-modifying antirheumatic drug treatment.

This study has some limitations. This study was retrospective and conducted in a single centre. Two patients were lost to follow-up, which may have led to an underestimation of mortality. However, as a national research centre for TAK, our centre is a referral region, with patients coming from all over the country, including cities and rural and remote areas. Therefore, the patients with TAK along with PAI in this study are representative of patients in other areas. Moreover, a long-term follow-up was conducted for these patients.

Conclusions

This study found that a high proportion of patients with TAK along with PAI had PH. Patients with PH had a worse prognosis than those without. Moreover, 6MWD and PH-targeted therapy were found to be independently associated with cardiac death and repeated hospital admission risk. In the future, multicentre clinical studies are needed to prospectively further clarify this issue.

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