

The impact of pulmonary arterial hypertension-targeted therapy on survival in Chinese patients with idiopathic pulmonary arterial hypertension

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ABSTRACT

The survival rates of Chinese patients with idiopathic pulmonary arterial hypertension (IPAH) and familial pulmonary arterial hypertension (PAH) on conventional therapy at 1 and 3 years were 68.0% and 38.9%, respectively. Our aim was to update recent knowledge on the demographics, clinical course, hemodynamic features, disease management, and survival of adult patients with IPAH. This retrospective and observational study was conducted at the largest tertiary referral center in China. Ninety patients with IPAH who underwent initial evaluation at Fu Wai Hospital from January 2006 through November 2009 were retrospectively enrolled. The primary outcome was death. Statistical analyses used included independent sample *t* test, nonparametric test, Kaplan-Meier method, and Cox proportional hazards analysis. Of the 90 patients enrolled, the median age was 32 years with female predominance. The median interval from onset of symptoms to diagnosis was 14 months. Patients exhibited severe exercise limitation and hemodynamic abnormalities at diagnosis. Only 10.6% had a positive vasoreactivity test, while calcium channel blockers were given to 22.2% of patients. Fifty-nine patients (65.6%) received PAH-targeted therapies during follow-up. Our survival rates of 84.1%, 73.7%, and 70.6% at 1-, 2-, and 3-years compared favorably with predicted survival based on the National Institutes of Health equation which showed 1-, 2-, and 3-years survival rates of 67.7%, 55.9%, and 47%, respectively. For the patients receiving conventional therapy solely, the 1- and 3-years survival rates were 67.0% and 49.3%, respectively. Younger age, lower body mass index, presence of pericardial effusion, and absence of PAH-targeted therapy were independently associated with mortality. We concluded that patients with IPAH were still diagnosed too late, and while survival rates have improved in the modern treatment era, there is still room for improvement.

Key Words: hemodynamics, pulmonary hypertension, risk factors, survival, targeted therapy

Idiopathic pulmonary arterial hypertension (IPAH) is a rare disease with poor outcome.^[1] A registry study of Chinese patients with IPAH and familial pulmonary arterial hypertension (PAH) was conducted at our center between January 1999 and October 2004.^[2] In that cohort study, survival estimates at 1, 2, 3, and 5 years were 68.0%, 56.9%, 38.9%, and 20.8%, respectively.^[2]

Three classes of pulmonary vasodilators (defined as PAH-targeted therapy) have been approved for treatment

of PAH in recent years, including prostanoids, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. Several observational studies have demonstrated that current PAH-specific therapies improve long-term survival in patients with IPAH.^[3-8] In the French registry study, estimate survival at 1, 2, and 3 years was 85.7%, 69.6%, and 54.9%, respectively, in the modern treatment era.^[9] In the Pulmonary Hypertension Connection registry

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study, 1-, 3-, and 5-year survival estimates were 92%, 75%, and 66%, respectively.^[10] PAH-targeted therapies have been introduced in China since 2006. Our studies have shown that short-term therapy of sildenafil is safe and effective for Chinese patients with PAH;^[11,12] therefore, the prognosis of Chinese patients with IPAH has also, most likely, been improved.

However, data regarding the clinical characteristic and survival of adult patients with IPAH in China in the modern treatment era remain limited. Therefore, in the present study, we update recent knowledge on the demographics, clinical course, hemodynamic features, disease management, and outcomes of adult Chinese patients with IPAH.

MATERIALS AND METHODS

Study population

All 90 adult patients who received a diagnosis of IPAH at Fu Wai Hospital from January 2006 through November 2009 were retrospectively enrolled. All the patients were incident cases. The PAH diagnosis was confirmed using right heart catheterization with a mean pulmonary artery pressure above 25 mmHg, a pulmonary capillary wedge pressure below 15 mmHg, and pulmonary vascular resistance above 240 dyn·s·cm⁻⁵.^[1] IPAH was defined as PAH unexplained by any secondary cause.^[1] This work was approved by the Institutional Review Boards of Fu Wai Hospital.

Baseline and follow-up variables

The following data were collected through review of patient records while the patients remained stable: age at diagnosis; gender; date of symptom onset; date of diagnosis; height; weight; systemic blood pressure; heart rate; World Health Organization (WHO) functional class; 6-Minute Walk Distance (6MWD) with concurrent Borg dyspnea scale; echocardiographic parameters; hemodynamics assessed by right heart catheterization; and medication. Hemodynamic parameters included mean right atrial pressure, mean pulmonary artery pressure, cardiac output, cardiac index, pulmonary vascular resistance, and mixed venous oxygen saturation. Standard two-dimensional echocardiographic evaluation and pulmonary vasoreactivity testing were performed as previously described.^[13] An acute response to acute vasodilator testing was defined as a decrease in mean pulmonary arterial pressure by at least 10 mmHg to an absolute level of less than 40 mmHg without a reduction in cardiac output.^[1]

As there were no protocol-mandated treatments, supportive therapy such as anticoagulation, digitalis, and diuretics were prescribed as necessary. PAH-targeted therapies were initiated as considered appropriate according to

availability. The only licensed treatments for PAH in China were iloprost and bosentan, and most of the patients could not afford these drugs due to inadequate health insurance. Additionally, as sildenafil is only prescribed for PAH as off label in China, some patients refused that therapy. All patients selected treatment on a voluntary basis after exploring all therapy available to them. These are the main reasons why some patients do not receive PAH-specific therapy in the modern treatment era.^[14]

Follow-up data were obtained by telephone interviews with patients, their families, or physicians, in addition to review of patient records. The primary endpoint was death. The date and cause of death were verified by medical records or death certificates. Survival was estimated from the date of diagnosis through 31 May 2010 (the last date of contact), or to death. During follow-up, four patients missed their appointments and survival was determined as the last date of contact. Predicted survival was calculated for each patient based on the National Institutes of Health (NIH) equation.^[15]

Statistics

Continuous variables were presented as mean ± standard deviation or median (Q1, Q3). Categorical variables were presented as frequencies and percentages. Differences between two groups were assessed by independent sample *t* test or nonparametric test (Mann-Whitney test). Survival analysis was performed using the Kaplan-Meier method. Univariable Cox proportional hazards analysis was used to examine the relationships between survival and demographic, clinical, WHO functional class, 6MWD, and hemodynamic variables measured at diagnosis. All variables with a *P* < 0.05 were then tested in a stepwise-forward multivariable Cox proportional hazards analysis (6MWD were not tested due to the limited number available). Data are expressed as hazard's ratio (HR) with 95% confidence interval (CI). The two-sided significance level was set at 0.05. Statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, Ill.).

RESULTS

Patient characteristics

Baseline characteristics of all 90 patients are listed in Table 1. The median age was 32 and females predominated at 63.3%. The female-to-male ratio was 1.7:1. The mean body mass index was 22.1±3.3 kg/m². Exercise capacity, as assessed by 6MWD, was impaired in subjects (354±81 m, *n* = 46). Patients in WHO functional Classes II and III accounted for 91%. The median duration from the onset of symptoms to diagnosis was 14 months.

Thirty-one patients (34.4%) received conventional therapy solely. Seventy-two patients (80%) were treated with

digoxin, and 80 patients (88.9%) with diuretics at baseline. Seventy-one (78.9%) received warfarin. Of the 85 patients who underwent acute vasodilator testing, 10.6% had a positive vasoreactivity test. Calcium channel blockers were given to 22.2% of patients.

Fifty-nine patients (65.6%) received PAH-targeted therapies. Forty-eight patients were treated with sildenafil, one patient with vardenafil, and four with inhaled iloprost. Of the three patients who received transition therapy, one transitioned from sildenafil to iloprost, one from bosentan to vardenafil, and another from iloprost to bosentan. Of

the three patients who received combination therapy, two combined iloprost with sildenafil, and one combined bosentan with vardenafil.

Hemodynamics

As shown in Table 2, the patients had severe pulmonary hypertension with an increase in mean pulmonary artery pressure (62 ± 19 mmHg), markedly high pulmonary vascular resistance, and reduced cardiac index.

As compared with patients in functional Classes I and II, patients in functional Classes III and IV had significantly higher pulmonary vascular resistance, lower cardiac output, and mixed venous oxygen saturation.

Echocardiography

The results of echocardiography were listed in Table 3. The mean systolic PAP was 89 ± 25 mmHg, and the mean left ventricular end-diastolic diameter (LVEDD) was 35 ± 7 mm. The mean left ventricular ejection fraction was $65 \pm 8\%$. Pericardial effusion was presented in 24.4% of patients. The median of right ventricular end-diastolic diameter (RVEDD) was much smaller in the group of patients in functional Classes I and II than in the group in functional Classes III and IV (30 vs. 34 mm, respectively; $P = 0.003$). The pulmonary artery systolic pressure was higher in the Class III and IV group than in the Class I and II group (Table 3).

Survival

During a median follow-up period of 16 months, 22 patients died; of those patients, one died suddenly, one of cardiogenic shock, and the remaining of right-sided heart failure. For the entire cohort, the observed survival at 1, 2, and 3 years was 84.1%, 73.7%, and 70.6%, respectively. In contrast, the predicted survival at 1 year was 67.7%, at 2 years 55.9%, and at 3 years 47.0% (Fig. 1).

For the patients who received conventional therapy only, the Kaplan-Meier survival curves demonstrated that the 1-, 2-, and 3-year survival rates were 67.0%, 57.5%, and 49.3%, respectively. Similarly, the 1-, 2-, and 3-year predicted survival rates were 67.0%, 55.0%, and 46.0%, respectively.

Baseline predictors of survival

Univariable Cox proportional hazards regression analysis showed that younger age, lower body mass index, lower

Table 1: Baseline characteristics of all patients

Variables	Value
Age (years)	32 (25, 41)
Female, <i>n</i> (%)	57 (63.3)
Body mass index (kg/m ²)	22.1 ± 3.3
Heart rate (beats/min)	79 ± 14
Systolic blood pressure (mmHg)	110 (100, 120)
Diastolic blood pressure (mmHg)	71 (70, 85)
History of syncope, <i>n</i> (%)	20 (22.2)
6MWD ^a (m)	354 ± 81
WHO functional class	3 (2, 3)
I	3 (3.3)
II	36 (40)
III	46 (51.1)
IV	5 (5.6)
Time from symptom onset to diagnosis ^a (months)	14 (8, 48)
NT-proBNP ^a (fmol/mL)	989 (550, 1850)
Uric acid (μmol/L)	379 ± 112
Total bilirubin (μmol/L)	21 (15, 32)
High density lipoprotein (mmol/L)	1.1 ± 0.3
Responders to acute pulmonary vasodilator testing ^a , <i>n</i> (%)	9 (10.6)
Conventional therapy only	31 (34.4)
Digoxin, <i>n</i> (%)	72 (80.0)
Diuretics, <i>n</i> (%)	80 (88.9)
Warfarin, <i>n</i> (%)	71 (78.9)
Calcium channel blockers, <i>n</i> (%)	20 (22.2)
PAH-targeted therapy, <i>n</i> (%)	59 (65.6)
Sildenafil, <i>n</i> (%)	48 (81.4)
Vardenafil, <i>n</i> (%)	1 (1.7)
Iloprost, <i>n</i> (%)	4 (6.8)
Transitions therapy, <i>n</i> (%)	3 (5.1)
Combination therapy, <i>n</i> (%)	3 (5.1)
Patients who died, <i>n</i> (%)	22 (24.4)

Values are mean ± SD, median (Q1, Q3) or *n* (%) when appropriate. **6MWD**: 6-Minute Walk Distance; **mPAP**: mean pulmonary arterial pressure; **NT-proBNP**: N-terminal pro-brain natriuretic peptide; **PVR**: pulmonary vascular resistance; **WHO**: World Health Organization. ^a6MWD, *n* = 46, time from symptom onset to diagnosis, *n* = 88, NT-proBNP *n* = 81, acute pulmonary vasodilator testing *n* = 85

Table 2: Variables of hemodynamics measured by right heart catheterization in different WHO functional classes

	Total	WHO functional Class I/II	WHO functional Class III/IV	<i>P</i> value
Mixed venous oxygen saturation ^a (%)	65 ± 8	69 ± 7	63 ± 8	< 0.001
Mean right atrial pressure ^a (mmHg)	8 (4, 12)	7 (4, 12)	8 (5, 13)	0.196
mPAP (mmHg)	62 ± 19	58 ± 15	65 ± 21	0.075
Cardiac index (L/min/m ²)	2.0 (1.7, 2.4)	2.3 (1.7, 2.9)	1.9 (1.7, 2.2)	0.007
PVR (dyn·s·cm ⁻⁵)	1320 (926, 1774)	1060 (802, 1660)	1460 (1151, 1913)	0.007

Values are mean ± SD or median (Q1, Q3) when appropriate. **mPAP**: mean pulmonary arterial pressure; **PVR**: pulmonary vascular resistance. ^aMixed venous oxygen saturation, I/II *n* = 38, III/IV *n* = 51; mean right atrial pressure, I/II *n* = 37, III/IV *n* = 49

6MWD, higher NT-proBNP, lower mixed venous oxygen saturation, lower cardiac out, presence of pericardial effusion, higher mean right atrial pressure, greater pulmonary vascular resistance, and absence of PAH-targeted therapy were significantly and negatively associated with survival (Table 4). Multivariable Cox proportional hazards regression analysis revealed that younger age, lower body mass index, presence of pericardial effusion, and absence of PAH-targeted therapy were independently associated with an increased risk of death (Table 5).

DISCUSSION

This is one of the largest studies of outcomes in Chinese adult patients with IPAH in the modern treatment era. We observed that outcome in Chinese patients with IPAH has improved as compared with either historical data or predicted survival based on NIH equation. Younger age,

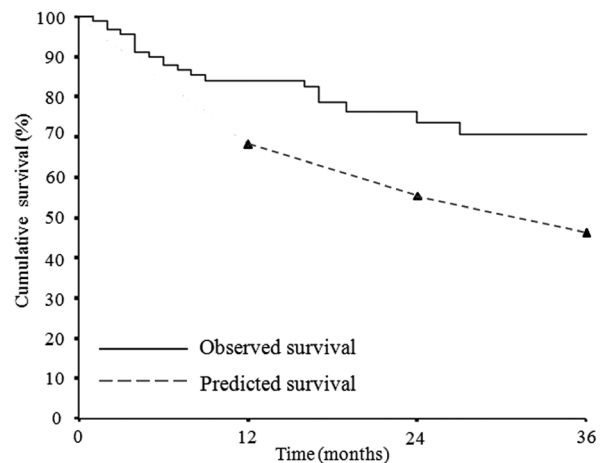


Figure 1: For the entire cohort, the observed survival at 1, 2, and 3 years was 84.1%, 73.7%, and 70.6%, respectively. The observed survival rates for patients with IPAH were about 20% higher than the predicted survival based on the National Institutes of Health equation.

Table 3: Echocardiographic variables in different WHO functional classes

	Total	WHO functional Class I/II	WHO functional Class III/IV	P value
Left atrial diameter ^a (mm)	29±5	29±4	29±5	0.688
LVEDD ^a (mm)	35±7	37±7	34±7	0.060
LVEF ^a (%)	65±8	65.6±7.0	64.1±9.0	0.402
RVEDD ^a (mm)	32 (28, 39)	30 (26, 38)	34 (31, 40)	0.003
Pulmonary artery systolic pressure ^a (mmHg)	89±25	80±26	94±22	0.014
Pericardial effusion, n (%)	22 (24.4)	6 (15.4)	16 (31.4)	0.08

Values are mean ± SD or median (Q1, Q3) when appropriate. **LVEDD:** left ventricular end-diastolic diameter; **LVEF:** left ventricle ejection fraction; **RVEDD:** right ventricular end-diastolic diameter. ^aLeft atrial diameter, I/II n = 37, III/IV n = 50; LVEDD, I/II n = 37, III/IV n = 50; LVEF, I/II n = 37, III/IV n = 50; RVEDD, I/II n = 37, III/IV n = 49; Pulmonary artery systolic pressure, I/II n = 28, III/IV n = 45

Table 4: Predictors of mortality in IPAH using univariate Cox analyses

Variables	HR	95% CI	P value
Age (per 10 years increase)	0.54	0.32-0.90	0.019
Gender (female/male)	0.74	0.32-1.73	0.489
Body mass index (per 1SD increase)	0.55	0.35-0.87	0.010
Heart rates (per 10 beats/min increase)	1.15	0.86-1.54	0.354
Systolic blood pressure (per 20 mmHg increase)	0.66	0.38-1.15	0.142
Diastolic blood pressure (per 10 mmHg increase)	0.89	0.62-1.28	0.519
History of syncope	1.76	0.72-4.33	0.216
6MWD ^a (per 100 m increase)	0.50	0.25-0.995	0.048
WHO functional class (III/IV: I/II)	2.04	0.80-5.24	0.138
In NTproBNP ^a (fmol/mL, per 1SD increase)	1.60	1.01-2.55	0.045
Uric acid (per 100 μmol/L increase)	1.24	0.87-1.76	0.238
Total bilirubin (per 1 μmol/L increase)	0.97	0.93-1.01	0.145
High density lipoprotein (per 1 mmol/L increase)	0.35	0.07-1.69	0.192
Mixed venous oxygen saturation ^a (per 5% increase)	0.75	0.59-0.96	0.021
Left atrial diameter (per 1 mm increase)	0.93	0.84-1.01	0.097
LVEF ^a (per 5% increase)	0.89	0.73-1.08	0.238
Pericardial effusion (Y/N)	3.14	1.30-7.60	0.011
Mean right atrial pressure ^a (per 5 mmHg increase)	1.28	1.04-1.58	0.022
mPAP (per 20 mmHg increase)	1.28	0.89-1.84	0.179
Cardiac output (per 1 L/min increase)	0.57	0.34-0.95	0.031
Cardiac index (per 1 L/min/m ² increase)	0.45	0.20-1.02	0.057
PVR (per 100 dyn·s·cm ⁻¹⁵ increase)	1.06	1.01-1.12	0.033
Acute vasoreactivity ^a	0.52	0.07-3.95	0.530
Absence of PAH-targeted therapy	3.84	1.61-9.17	0.002

6MWD: 6-Minute Walk Distance; **CI:** confidence interval; **HR:** hazard ratio; **In:** natural logarithm; **LVEF:** left ventricle ejection fraction; **mPAP:** mean pulmonary arterial pressure; **NT-proBNP:** N-terminal pro-brain natriuretic peptide; **PVR:** pulmonary vascular resistance; **SD:** standard deviation; **WHO:** World Health Organization. ^aNT-proBNP, n = 81, 6MWD, n = 46, mixed venous oxygen saturation, n = 89, mean right atrial pressure, n = 86, LVEF, n = 87, acute pulmonary vasodilator testing, n = 85

Table 5: Independent predictors of mortality in IPAH using multivariate Cox analyses (n = 77)

Variables	HR	95% CI	P value
Age (per 10 years increase)	0.54	0.29-0.98	0.042
Body mass index (per 1 SD increase)	0.51	0.29-0.91	0.024
Pericardial effusion	5.31	1.88-15.05	0.002
Absence of PAH-targeted therapy	8.57	2.88-25.47	<0.001

CI: confidence interval; HR: hazard ratio; SD: standard deviation

lower body mass index, presence of pericardial effusion, and absence of PAH-targeted therapy were independently associated with prognosis in patients with IPAH.

The female-to-male ratio of Chinese adult patients with IPAH was similar to those previously reported. The NIH registry of primary pulmonary hypertension demonstrated a 1.7:1 female-to-male ratio.^[16] The French Registry reported a 1.9:1 ratio.^[17] Our study confirmed female predominance.

Early diagnosis of IPAH is still a challenge. The median duration from symptoms onset to diagnostic right heart catheterization was 14 months in the present study, which is similar to that from the REVEAL registry (13.6 months).^[18] The predominant WHO functional classes at diagnosis were Class III and Class IV, also close to what was recorded in the Chinese registry study (61%).^[2] Furthermore, the patients had severe exercise limitation, suggesting no improvement in patients' severity at diagnosis as compared with previous study.^[2] Last, the patients showed a similar severity of hemodynamic abnormalities as compared with that reported previously.^[2,18,19] Thus, continued efforts are required to improve early diagnosis.

The value of the NIH equation may be compromised by improved standards of care for PAH patients. However, we showed that the estimated survival in the 31 patients receiving conventional therapy was similar to the predicted survival based on the NIH equation. This finding validates the application of the NIH equation to predict survival in our population who did not receive targeted therapy.

The observed survival rates for all patients at 1, 2, and 3 years were higher than the predicted survival based on the NIH equation. The survival rates from the present study were also better than historical data from our center.^[2] Furthermore, the survival rate in our series was comparable with that reported recently, which showed that estimated 1- and 3-year survival rates were between 82.9-92.1% and between 54.9-75.1%, respectively.^[9,10,19,20] Our results demonstrated that the survival of patients with IPAH has improved in China as it has in western countries.

Considering the similar severity of exercise limitation, functional classes, and hemodynamic abnormalities at

diagnosis between the present study and the Chinese registry study conducted prior to 2006,^[2] lead-time bias due to earlier diagnosis and selected bias of less severely diseased patients were probably not the reasons for improved survival. Several observational studies have reported a survival benefit in PAH patients treated with PAH-targeted therapy when compared with either historical controls or predicted survival based on the NIH equation.^[3,4,7] The absence of PAH-targeted therapy was an independent predictor of mortality in the present study; thus, the improved survival may be partly attributed to the availability of PAH-targeted therapies. One reason for improved survival may have been the use of warfarin as it was associated with improved survival,^[21,22] and was used in 78.9% of patients in this study as compared with 50% in the Chinese registry study.^[2] A final reason for improved survival may be the less frequent use of calcium channel blockers as they may have a detrimental effect on the outcome of patients who are not vasoreactive.^[1] The use of calcium channel blockers decreased from 90.3% in the registry study^[2] to 22.2% in the present study.

Although survival in Chinese patients with IPAH has improved greatly, there is still room for improvement. The number of patients receiving PAH-targeted therapy was smaller than that of previous studies.^[9] Bosentan was one of the most widely used drugs for PAH in western countries,^[9,18] while it was rarely used in China due to economic burden. Previous studies demonstrated that between 10.3% and 12.6% of patients with IPAH had a positive vasoreactivity test.^[17,23] Similarly, we found that 10.6% of patients were acute vasodilator responders. However, calcium channel blockers were administered to 22.2% of patients, indicating that many patients who have a negative acute vasodilator response are still being treated with potentially harmful calcium channel blockers' therapy.

Shorter 6MWD and the presence of any degree of pericardial effusion have proven consistent predictors of mortality.^[9,24-27] We confirmed that shorter 6MWD and the presence of pericardial effusion were associated with poor prognosis. Previous studies have demonstrated that higher NT-proBNP, elevated mean right atrial pressure, reduced cardiac output, increased pulmonary vascular resistance, and reduced mixed venous oxygen saturation were important predictors of death.^[7,9,15,24,28] Similarly, we found that impaired right ventricular function predicted poor outcome. A somewhat unexpected finding was that younger age at diagnosis was a significant predictor of death and was thought to be similar to a study from India.^[29] However, compared with older patients (above median age), younger patients had more severe hemodynamic impairment (data not shown). Interestingly, we identified lower body mass index as a risk factor for mortality, independent of right atrial pressure. The association between low weight z-score

on presentation and mortality has also been described recently in pediatric patients with IPAH,^[30] though the reason remains unknown.

Of noted, there are several limitations of the present study. This was a retrospective, observational, single-center study. However, the present study was conducted at the largest tertiary referral center in China and would complement existing data. While most risk factors were included in the study, there were some other potential predictors that were not included in our database.

Patients with IPAH are still diagnosed too late. The survival of adult Chinese patients with IPAH has been improved in the modern treatment era. However, there is still room to improve.

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