CHEST

Official publication of the American College of Chest Physicians

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Chest; Prepublished online February 17, 2011;
DOI 10.1378/chest.10-2327

Word counts
Abstract: 250 words
Body of text: 3283 words

Original Research

Survival of Chinese Patients with Pulmonary Arterial Hypertension in the Modern Management Era

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Financial Support

This study was sponsored by the Shanghai Pujiang Program (08PJ1408600), and the Shanghai Science and Technology Division of non-Governmental International Cooperation Projects (08410701600).

- **How does this advance the field?**

This study is the first to report survival of PAH in the modern management era in developing countries. Despite the high cost of treatment and financial constraints, survival of patients with PAH has improved in China. Survival of patients with CTDPAH is inferior to that of IPAH patients, and poorer survival is observed in male CTDPAH patients.

- **What are clinical implications?**

In the modern management era, PAH outcomes have improved markedly in China, as compared with previous years when no PAH targeted therapies were available. However, these results are far from ideal and improving PAH survival remains a challenge, emphasizing the need for further progresses in the field. As observed in other registries, CTDPAH survival is poorer than that of IPAH, at least in part because of other systemic complications of the disease.

ABSTRACT

Background: **In a previous study of Chinese patients with idiopathic pulmonary arterial hypertension (IPAH) in the non-targeted therapy era, we reported 1- and 3-year survival estimates of only 68% and 39%, respectively. However, it is not yet known whether the survival of patients with PAH is improved in the modern management era.**

Methods: **A retrospective cohort study was undertaken in 276 consecutive newly diagnosed "incident" patients with IPAH and connective tissue disease-associated pulmonary arterial hypertension (CTDPAH) referred between 2007 and 2009. Baseline characteristics and survival in two groups were compared.**

Results: **1- and 3-year survival estimates were 92.1% and 75.1%, respectively, in patients with IPAH, and 85.4% and 53.6%, respectively, in patients with CTDPAH. Patients with CTDPAH had a significantly lower mean pulmonary artery pressure, more pericardial effusion, and more severe impairment of the diffusion capacity of the lung for carbon monoxide (DL_{CO}) than patients with IPAH. A diagnosis of CTDPAH, WHO functional class III or IV, DL_{CO} < 80% of predicted, and the presence of pericardial effusion were independent predictors of mortality. The 1- and 3-year survivals of male patients were 93.5% and 77.5%, respectively, in those with IPAH, and 71.1% and 47.4%, respectively, in those with CTDPAH.**

Conclusions: **The survival of patients with PAH has been improved in China in the modern management era, despite the high costs of treatment and financial constraints. However, the survival of patients with CTDPAH is inferior to that of patients with IPAH. Our study**

also indicates poorer survival in male CTDPAH patients.

Abbreviations: BNP = brain natriuretic peptide; CI = cardiac index; CTDPAH = connective tissue disease-related pulmonary arterial hypertension; DL_{CO} = single-breath diffusion capacity of the lung for carbon monoxide; ERA = endothelin receptor antagonist; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HIV = human immunodeficiency virus; IPAH = idiopathic pulmonary arterial hypertension; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary arterial pressure; 6MWT = 6-minute walk test; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right heart catheterization; RV = right ventricular; R_{tot} = total airway resistance; SvO_2 = mixed venous oxygen saturation; SSc-PAH = systemic sclerosis-related pulmonary arterial hypertension; TLC = total lung capacity; TV = tricuspid valve; UA = uric acid; WHO = World Health Organization

Key words: idiopathic pulmonary arterial hypertension; connective tissue disease-related pulmonary arterial hypertension; targeted therapy; survival; clinical outcome

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating disease in which remodeling of the small pulmonary arteries leads to a progressive increase in pulmonary vascular resistance and right heart failure.[1,2] Over the past decade, the new treatments for PAH, e.g. prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 (PDE-5) inhibitors, have brought about dramatic improvements in clinical outcomes, and it is clear that newer PAH-specific drugs can significantly alter the natural history of the disease.[3-7] In the modern management era, 1-year survival among incident and prevalent cases of idiopathic, familial and anorexigen-associated PAH enrolled in a French registry was 83%.[6] With the advent of modern management in US, the 1-year estimate of survival was 88%, in patients with systemic sclerosis-related pulmonary arterial hypertension (SSc-PAH), and 95% in those with idiopathic pulmonary arterial hypertension (IPAH).[8]

We have previously reported a registry and survival study of Chinese patients with IPAH (N = 72) in 2007.[9] In this cohort study, survival estimates at 1 and 3 years were only 68% and 39%, respectively, which were similar to those recorded by the US National Institutes of Health (NIH) registry in the 1980s. Lack of effective treatment was the main cause of poor survival in this study. With the introduction of right heart catheterization (RHC) and a targeted treatment approach, the survival and the quality-of-life of patients with PAH have been improved gradually in China. After 2006, several types of targeted drugs for PAH became available in China, including bosentan, epoprostenol and PDE-5 inhibitors. Unfortunately, only a few patients can afford these drugs because of the high cost of treatment. The cost of bosentan, for example, was

more than €10, 000 per year,[10] and the cost of PDE-5 inhibitors was about €1,500 to €2,000 per year in China. Therefore, patients treated for PAH in developing countries may carry a heavy economic burden due to inadequate health insurance.

In the modern therapy era, the survival of the patients with PAH has been significantly improved in western countries. However, the impact of newer specific treatments on the survival of patients with PAH in developing countries remains unclear. The aim of the present study was to investigate the survival of patients with PAH and compare the clinical characteristics of patients with IPAH and connective tissue disease-associated pulmonary arterial hypertension (CTDPAH) in China, a large developing country with an increasing usage of novel targeted therapies.

MATERIALS AND METHODS

Study Patients

We performed a retrospective cohort study of consecutive patients with IPAH and CTDPAH who were diagnosed between 2007 and 2009 at 5 national referral pulmonary vascular centers in China located in the northern, north-eastern, central, southern and eastern regions, according to a standardized diagnostic and management approach for PAH. Details of all newly diagnosed "incident" cases were recorded in a database at the time of diagnosis before any targeted treatments for PAH were started. The follow-up period for analysis of survival data ended in May, 2010. The primary endpoints were death or data censoring.

The study was conducted in accordance with the provisions of the Declaration of Helsinki

reviewed and was approved by Ethics Committees at each study center. Written informed consent was obtained from all patients when they were recruited to the study.

Inclusion and Exclusion Criteria

PAH was diagnosed via the following hemodynamic criteria: mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest or ≥ 30 mm Hg with exercise, pulmonary capillary wedge pressure (PCWP) ≤ 15mm Hg, and pulmonary vascular resistance (PVR) > 3 Wood units.[11] Patients were excluded if they had evidence of pulmonary venous hypertension (PCWP >15 mm Hg), significant chronic obstructive pulmonary disease [a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) < 70% and FEV_1 < 60% of predicted] or interstitial lung disease, portal hypertension, chronic thromboembolic disease, or obstructive sleep apnea.[12] Interstitial lung disease was defined on the basis of a combination of pulmonary function tests and chest x-rays, and high-resolution computed tomography of the chest, if needed. The diagnosis of portal hypertension was excluded based on clinical findings and Doppler echography of the liver. A diagnosis of portal hypertension was based on hemodynamic measurement of a hepatic venous pressure gradient of more than 5 mm Hg, or the presence of esophageal varices on endoscopy.[13] Patients with chronic thromboembolic disease were excluded based on the results of ventilation and perfusion scanning, contrast-enhanced computed tomography, and, if necessary, pulmonary angiography. The obstructive sleep apnea was based on prior polysomnographic evaluation with an apnea index (AI) of >5 apneas/hour.[14] Patients were also excluded if they tested positive for antibodies to human immunodeficiency virus (HIV),

had a history of anorexigen use, or had any other disease known to be associated with pulmonary hypertension.

Algorithms for deciding the therapeutic approach for PAH were similar in the two etiologic groups. ERAs (bosentan) or PDE-5 inhibitors (sildenafil or vardenafil) were mainly used in those who had a negative response to acute pulmonary vasodilator testing.[15] Combination therapies were initiated when patients could not be improved by monotherapy. Other treatments that patients had been receiving were continued during the study, including diuretics, warfarin and digoxin.

Statistical Analysis

Continuous variables were compared using Student's *t*-test. Categorical variables were compared using the chi-square statistic. Survival analysis was performed using the Kaplan-Meier method to investigate the time from diagnosis of IPAH or CTDPAH to death. A multivariable Cox proportional hazards model was also performed to determine the variables associated with an increased risk of death. A 2-tailed *P* value less than .05 was used to indicate statistically significant differences. All computations were performed using the SPSS 13.0 statistical software package (SPSS Inc. Chicago, IL, USA).

RESULTS

Demographic Characteristics

A total of 276 patients were diagnosed and treated, including 173 patients with IPAH and 103

patients with CTDPAH. In patients with CTDPAH, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, mixed connected tissue disease, and arthritis accounted for 38%, 22%, 11%, 10% and 4% of the population, respectively. The baseline demographic and clinical characteristics of the two etiologic groups are shown in Table 1. Most patients in both groups were female. At the time of diagnosis, patients in the CTDPAH group were significantly older than those in the IPAH group (mean age difference, 8.12 years). However, no differences were found between the groups with regard to WHO functional class. The mean duration from the onset of symptoms to diagnosis, 6MWT distances, biochemical markers, and other clinical characteristics were similar in the two groups of patients.

The median duration of follow-up was 2.75 years. No patients underwent lung transplantation during the study period.

Pulmonary Function and Echocardiography Findings

Patients with CTDPAH had lower percentages of predicted values for FVC and TLC than patients with IPAH (Table 2), although the differences were not statistically significant. The FEV_1 value was mildly decreased in patients with CTDPAH compared with patients with IPAH, but the diffusing capacity of the lung for carbon monoxide (DL_{CO}) was significantly reduced in patients with CTDPAH compared with those with IPAH ($P = .007$). In both groups, total airway resistance (R_{tot}) was close to predicted values.

At diagnosis, echocardiography findings were available for 262 of the 276 patients (95%). As shown in Table 3, the two etiologic groups had similar left and right heart sizes but a

significantly higher proportion of patients in the CTDPAH group had a pericardial effusion compared with the IPAH group (P = .03).

Hemodynamic Findings

Baseline RHC revealed severe PAH in both groups of patients (Table 4). Patients with IPAH had significantly higher mPAP and pulmonary vascular resistance (PVR) values than patients with CTDPAH. However, there were no significant differences in right atrial pressure (RAP), cardiac index (CI), mixed venous oxygen saturation (SvO_2), and the acute response to vasodilators between the two groups of patients.

Treatments

Patients who started treatment with calcium channel blockers (CCBs) accounted for 1.9% of the CTDPAH and 3.5% of IPAH population. At baseline, there were no differences between the etiologic groups in the treatment of choice for PAH (Table 1). Most patients were treated with a PDE-5 inhibitor (sildenafil or vardenafil) because of their financial constraints and inadequate health insurance. At the last follow-up, patients with CTDPAH were more likely to be receiving immunosuppressant therapy, including prednisolone, hydroxychloroquine and cyclophosphamide. As shown in Table 1, 60 patients with CTDPAH who were treated with prednisolone accounted for 58.3% of this group, and 9 patients who were treated with hydroxychloroquine accounted for 8.7%. 10 patients were treated with cyclophosphamide monthly.

Survival Analysis

During the study, there were 47 deaths (25 with IPAH and 22 with CTDPAH) and 7 patients (5 with IPAH and 2 CTDPAH) were lost to follow-up. Cardiovascular deaths (heart failure or sudden death) accounted for 90% of the deaths in the IPAH group and 80% in the CTDPAH group. Despite the similarities in hemodynamic parameters and targeted treatments in the two etiologic groups, there were significant survival differences between the groups (Fig 1). The 1-, 2- and 3-year survival of patients with IPAH was estimated to be 92.1%, 80.1% and 75.1%, respectively, and the mean survival time was (31.3 ± 0.85) months. In comparison, patients with CTDPAH had a significantly shorter survival time than patients with IPAH (log-rank test, *P* = .04). Their 1-, 2- and 3-year survival was estimated to be 85.4%, 75.6% and 53.6%, respectively, and their mean survival time was (28.5 ± 1.39) months.

Multiple variable analysis showed that a diagnosis of CTDPAH, WHO functional class III and IV, DL_{CO} < 80% of predicted, and the presence of pericardial effusion were significant independent predictors of death (Table 5). However, age, gender, mPAP, and 6MWT were not independent risk factors for mortality.

We also explored the influence of the baseline WHO functional classification (classes I and II *vs* classes III and IV) on survival in the entire cohort. Patients in WHO classes III and IV at the time of diagnosis had significantly worse survival than patients in WHO classes I and II (Fig 2). The 1- and 3-year survival was estimated to be 99.1% and 91.1%, respectively, in patients in WHO classes I and II, and 82.7% and 52.7%, respectively, in patients in WHO classes III and IV.

Among patients in WHO classes III and IV at baseline, there was also a significant difference

in survival between patients with IPAH and those with CTDPAH (Fig 3). In patients with IPAH, the 1-, 2- and 3-year survival was estimated to be 87.6%, 69.7% and 63.9%, respectively, as compared with 76.0%, 59.4% and 33.9%, respectively, in those with CTDPAH. Thus, patients with CTDPAH in WHO classes III and IV at baseline have a poorer prognosis than patients with IPAH in WHO classes III and IV, and the WHO functional classification is associated with mortality in the modern management era.

Influence of Pericardial Effusion

The influence of pericardial effusion on survival was investigated in the entire cohort. Patients with pericardial effusion had a significantly shorter survival than patients without pericardial effusion (Fig 4). In those without pericardial effusion, 1- and 3-year survival was estimated to be 92.5% and 73.9%, respectively, as compared with 85.4% and 67.9%, respectively, for patients with pericardial effusion.

Influence of Gender

Although gender was not an independent risk factor in mortality in our study, there was a significant difference between the two etiologic groups in the survival of male patients (Fig 5). In male patients with IPAH, the 1- and 3-year survival was estimated to be 93.5% and 77.5%, respectively, as compared with 71.1% and 47.4% respectively, in male patients with CTDPAH. However, there was no significant difference between the two etiologic groups in the survival of female patients, and in the entire cohort, there was no significant survival difference between

male and female patients. This finding suggests that the significant difference in survival between the two etiologic groups (see above) may be attributable, at least in part, to the poorer survival of male patients.

DISCUSSION

The present study is one of the largest cohort studies from China concerning the clinical characteristics and survival of patients with PAH in the modern management era. Several clinical trials in Chinese patients with PAH have demonstrated the benefit of newer targeted therapies.[16, 17] Therefore, it is important to examine the outcome of targeted treatment with these agents for various PAH subtypes in China.

In an earlier study, Schachna et al.[18] identified increasing age as a risk factor for PAH associated with scleroderma. However, while patients with CTDPAH have an older age at disease onset than patients with IPAH, older age was not found to be an independent risk factor for mortality in our study. We found that like systemic vascular resistance, pulmonary vascular resistance increases with age, probably due to reduced compliance of the pulmonary vascular bed. With increasing age, the advance of PAH may be promoted via several important pathogenic pathways.

We found that 6WMD values in Chinese patients were significantly higher than those recorded in France (310 to 333 m).[19] The major reason is that Chinese patients have a relatively younger age; most elderly patients were not diagnosed in China because of the inadequate healthcare system and poor economic conditions. The mean age of diagnosis in China is similar

to that recorded by the NIH registry in the 1980s (mean age, 36 years).[20]

Baseline hemodynamic data in our study indicated that patients with IPAH had significantly higher mPAP and PVR values than patients with CTDPAH, but there were no significant differences in RAP, cardiac index, and mixed venous oxygen saturation. With the development of PAH, mPAP may decrease as a function of a decrease in cardiac output, and patients with CTDPAH may have a decreased ability to adapt to the higher PVR. Campo et al. suggest that specific components of right ventricular (RV) dysfunction contribute to increased mortality in SSc-PAH.[21] In addition, the pathophysiology of PAH and the RV response in SSc may differ from that of other forms of PAH.[21, 22] The absence of a difference in WHO functional class in the two groups indicates that there was no significant difference in disease severity at the time of diagnosis. Possibly, patients with CTDPAH may have more advanced RV dysfunction.

It is of interest that left atrial diameter and LVEDD (left ventricular end-diastolic diameter) tended to be higher in the CTDPAH group, indicating potential subtle diastolic dysfunction in our study. Indeed, some CTD will affect the heart with possible subsequent cardiac diastolic dysfunction.[21] Hinderliter et al.[23] reported that the presence of a pericardial effusion in patients with PAH is thought to be due to increased RAP. In our study, baseline echocardiography revealed that a significantly higher proportion of patients with CTDPAH had a small or large pericardial effusion, and those with pericardial effusion showed a significantly shorter survival time than patients without pericardial effusion. However, there was no significant difference in RAP between the two etiologic groups. The presence of pericardial effusion was an important risk factor influencing survival. This finding may be a reflection of systemic inflammatory

disease or left heart disease.[24]

Currently, there is a lack of data on the survival of patients with PAH in China. After 2006, we established a small number of pulmonary hypertension referral centers in each region of the country and standardized the diagnosis and treatment of PAH. Almost all patients can undergo RHC and acute pulmonary vasodilator testing to facilitate drug selection. We observed better survival with newer targeted therapies than with traditional therapies. The 1-year and 3-year survival of IPAH patients was 92.1% and 75.1%, respectively, which was significantly higher than that recorded in the registry study of Chinese patients with IPAH prior to 2006.[9]

For patients with CTDPAH, the 1- and 3-year survival was 85.4% and 53.6%, which was higher than that reported in pre-2006 studies, such as 1- and 3-year survivals of 78% and 47%, respectively, in patients with SSc-PAH reported in all incident cases of CTDPAH by the UK National registry.[25] While the improved survival may be attributed to advances in targeted treatment approaches, there are important differences between patients with PAH treated in China and those treated in western countries. The main reason for the differences lies in the economic burden for patients with severe PAH in whom targeted drug therapy is not always possible. For many Chinese families, 40% of the annual cost of drug therapy for PAH accounts for 100% of their total income (data not shown). Despite these difficulties, our study population was treated with PAH-targeted therapies in similar proportions to non-Chinese populations. For instance, the recent French registry study showed that 76.8% of PAH patients received PAH-targeted therapies, a similar proportion to that in our study population.

In the present study, WHO functional class III or IV was an independent predictor of mortality,

although patients with IPAH and CTDPAH had a similar WHO functional status at baseline. D'Alonzo et al.[20] reported that the median survival of untreated patients with IPAH in WHO functional classes III and IV was 2.5 years. Since there is often a long period from the onset of symptoms to the diagnosis of PAH, early recognition of this predictive factor is important.

Interestingly, we found that there was a different survival in male patients with PAH. The 1-year survival was estimated to be 77.5% in male patients with IPAH, and 47.4% in male patients with CTDPAH (P = .01). However, the survival of female patients between the etiologic groups or between male and female patients in the entire cohort was not significantly different, and gender was not an independent risk factor for mortality. This suggests that the survival difference may be attributed to poorer survival of male patients. Until now, male sex has not been definitively associated with survival in patients with SSc-PAH, including those aged > 50 years. Both IPAH and CTDPAH are more common in females, but little is known about how gender influences disease development.[26] We speculated that that estrogen metabolites and estrogen exposure may play an important role. Estrogen may be protective as it induces insulin-like growth factor, which has been associated with improved myocardial contractility.[27] Males with PAH also have a lower right ventricular ejection fraction than females, and physiological increases in circulating estrogen levels may attenuate pulmonary arterial vasoconstriction.[27, 28]

This was an observational study with a cohort limited to a 3-year diagnosis period. As it was a retrospective cohort study, the possibility of selection bias could not be avoided. In addition, predictors of survival were limited to baseline demographic and hemodynamic variables because all patients did not have follow-up hemodynamic studies at the same time intervals. Although we

used a standardized diagnostic and therapy approach for patients with PAH, according to current guidelines and the availability of specific drugs, there were a number of patients with PAH who could not use these drugs because of the high costs of treatment and financial constraints. Consequently, these patients had to choose a relatively inexpensive medicine or give up on treatment.

As in western countries, the survival of patients with PAH was improved in China, despite the inadequate healthcare system and treatment constraints. However, the survival of patients with CTDPAH is inferior to that of patients with IPAH. Patients with CTDPAH had a lower mPAP and more severe impairment of DL_{CO}, but had similar WHO functional status and similar hemodynamic parameters. Independent risk factors for death were a diagnosis of CTDPAH, WHO functional class III or IV, $DL_{CO} < 80\%$ of predicted, and the presence of pericardial effusion. Our study also indicates poorer survival in male CTDPAH patients. As a long period of time between the onset of symptoms and diagnosis of PAH may lead to severe disease that can be more difficult to manage, the lack of an early diagnosis may be predictive of a poor prognosis.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contribution of all investigators who participated in this study. We also thank the patients who participated in the study.

Author contributions: Prof Jing (China) and Prof Humbert (France) contributed to conception, designing the study, acquisition of data, reading and critical revision of the manuscript, and approving the final manuscript; Dr Zhang and Dr Dai contributed to recruiting the patients,

drafting the submitted article, interpreting the data, performing statistics analysis of data and approving the final manuscript. Prof Xie, Prof Yu, Prof Wu, Prof Pan, Dr Yuan, Dr Jiang, and Dr He contributed to enrolling the subjects, data acquisition and approving the final manuscript.

Disclosure statement: M. H. has relationships with drug companies including Actelion, BayerSchering, GSK, Lilly, Novartis, Pfizer and United Therapeutics, in addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. Z-C. J. has relationships with drug companies including Actelion, BayerSchering, Pfizer and United Therapeutics, in addition to being investigator in trials involving these companies, relationships include consultancy service and membership of scientific advisory boards. No other authors has any conflict of interest to declare regarding the content of this paper.

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Figure Legends

FIGURE 1. Survival rate of patients with PAH in the modern management era. 1-, 2- and 3-year survival was estimated to be 92.1%, 80.1% and 75.1%, respectively, in patients with IPAH, and 85.4%, 75.6% and 53.6%, respectively, in patients with CTDPAH.

FIGURE 2. Survival rate of patients with WHO functional classes I and II versus those with classes III and IV. 1- and 3-year survival was estimated to be 99.1% and 91.1%, respectively, in patients in WHO functional classes I and II, and 82.7% and 52.7%, respectively, in patients in WHO functional classes III and IV.

FIGURE 3. Survival estimates for patients in WHO functional classes III and IV with IPAH and CTDPAH. Survival estimates in patients with CTDPAH indicate higher mortality than in those with IPAH. 1-, 2- and 3-year survival was estimated to be 87.6%, 69.7% and 63.9%, respectively, in patients with IPAH, and 76.0%, 59.4% and 33.9%, respectively, in patients with CTDPAH.

FIGURE 4. Survival rate of patients with presence of pericardial effusion. 1- and 3-year survival for patients without pericardial effusion was estimated to be 92.5% and 73.9%, respectively, and 85.4% and 67.9%, respectively, for patients with pericardial effusion.

FIGURE 5. Survival rates of male patients with PAH. 1- and 3-year survival was estimated to be

93.5% and 77.5%, respectively, in male patients with IPAH, and 71.1% and 47.4% respectively, in male patients with CTDPAH. For female patients, there was no significant difference in survival between the two etiologic groups.

TABLES

Table 1—*Patient Demographics and Functional Assessment Findings* [*]

Variable	IPAH (N = 173)	CTDPAH (N = 103)	*P* Value[a]
Age (years)	33.4 ± 15.3	41.5 ± 13.8	.01
Female (n, %)	121 (69.9)	88 (85.4)	.04
Height (cm)	159.0 ± 14.7	159.9 ± 10.7	.58
Weight (kg)	56.0 ± 16.1	55.5 ± 12.1	.80
Body surface area (m^2)	1.5 ± 0.3	1.6 ± 0.2	.83
WHO functional classification (n, %):			.22
Classes I and II	83 (48.0)	45 (44.7)	
Classes III and IV	90 (52.0)	58 (56.3)	
Time from onset of symptoms to diagnosis (years)	3.4 ± 4.3	2.9 ± 3.3	.39
6MWT (meters)	394.0 ± 114.2	383.8 ± 106.7	.51
Serum BNP concentration (fmol/L)	1025.0 ± 859.0	1171.4 ± 928.4	.45
Serum UA concentration (μmol/L)	386.6 ± 120.9	361.5 ± 143.9	.13
Targeted therapy (n, %):			.55
Bosentan	30 (17.3)	17 (16.5)	
Iloprost	3 (0.2)	1 (0.1)	
Sildenafil	54 (31.2)	27 (26.2)	
Vardenafil	52 (30.0)	32 (31.1)	
Immunosuppressants (n, %):			
Prednisolone	-	60 (58.3)	
Hydroxychloroquine	-	9 (8.7)	
Cyclophosphamide	-	10 (9.7)	

[*]Values are expressed as means ± SD or n (%).

[a]*P* values were determined by Student's *t*-test.

BNP = brain natriuretic peptide; CTDPAH = connective tissue disease-related pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; 6MWT = 6-minute walk test; UA = uric acid.

Table 2—*Baseline Pulmonary Function Findings* [*]

Variable (% predicted)	IPAH (N = 173)	CTDPAH (N = 103)	*P* Value
FVC	86.0 ± 15.5	81.9 ± 17.8	.079
FEV_1	80.2 ± 15.8	75.8 ± 17.2	.064
TLC	95.5 ± 16.9	89.6 ± 17.2	.063
DL_{CO}	75.3 ± 16.2	72.7 ± 15.1	.007
R_{tot}	121.6 ± 40.5	133.7 ± 44.6	.088

[*]Values are expressed as means ± SD of the percentage of measured to predicted values (% predicted). FEV_1= forced expiratory volume in 1 second; FVC = forced vital capacity; DL_{CO} = single-breath diffusion capacity of the lung for carbon monoxide; R_{tot} = total airway resistance; TLC = total lung capacity.

Table 3—*Baseline Echocardiographic Findings* [*]

Variable	IPAH (N = 173)	CTDPAH (N = 103)	*P* Value
Left atrial diameter (mm)	30.9 ± 6.8	32.6 ± 5.7	.07
LVEF (%)	64.3 ± 9.9	64.1 ± 8.2	.85
LVEDD (mm)	36.3 ± 6.8	38.0 ± 6.6	.06
Right atrial diameter (mm)	65.7 ± 13.3	63.6 ± 10.2	.13
Right ventricular diameter (mm)	32.2 ± 9.3	30.7 ± 10.5	.28
TV regurgitant velocity (m/s)	4.5 ± 0.9	4.3 ± 0.7	.35
Tricuspid systolic pressure (mm Hg)	83.7 ± 30.8	78.3 ± 20.9	.27
Pulmonary artery systolic pressure (mm Hg)	94.6 ± 26.9	87.4 ± 25.3	.06
Pericardial effusion (n, %)	23 (13.3%)	22 (21.4%)	.03

[*]Values are expressed as means ± SD or n (%).

LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; RAP = right atrial pressure; TV = tricuspid valve.

Table 4—*Baseline Right Heart Catheterization Findings* [*]

Variable	IPAH (N = 173)	CTDPAH (N = 103)	*P* Value
mPAP (mm Hg)	63.1 ± 18.0	51.9 ± 15.6	.001
PCWP (mm Hg)	12.9 ± 4.7	12.4 ± 3.8	.25
RAP (mm Hg)	12.3 ± 6.4	11.9± 5.2	.59
CI (L/min/m^2)	2.5 ± 0.9	2.6 ± 0.9	.50
PVR (Wood units)	17.1 ± 9.9	12.9 ± 7.7	.001
SvO_2 (%)	62.4 ± 10.7	61.5 ± 11.1	.55
Acute vasoreactivity (n, %)	6 (3.5%)	2 (1.9%)	.07

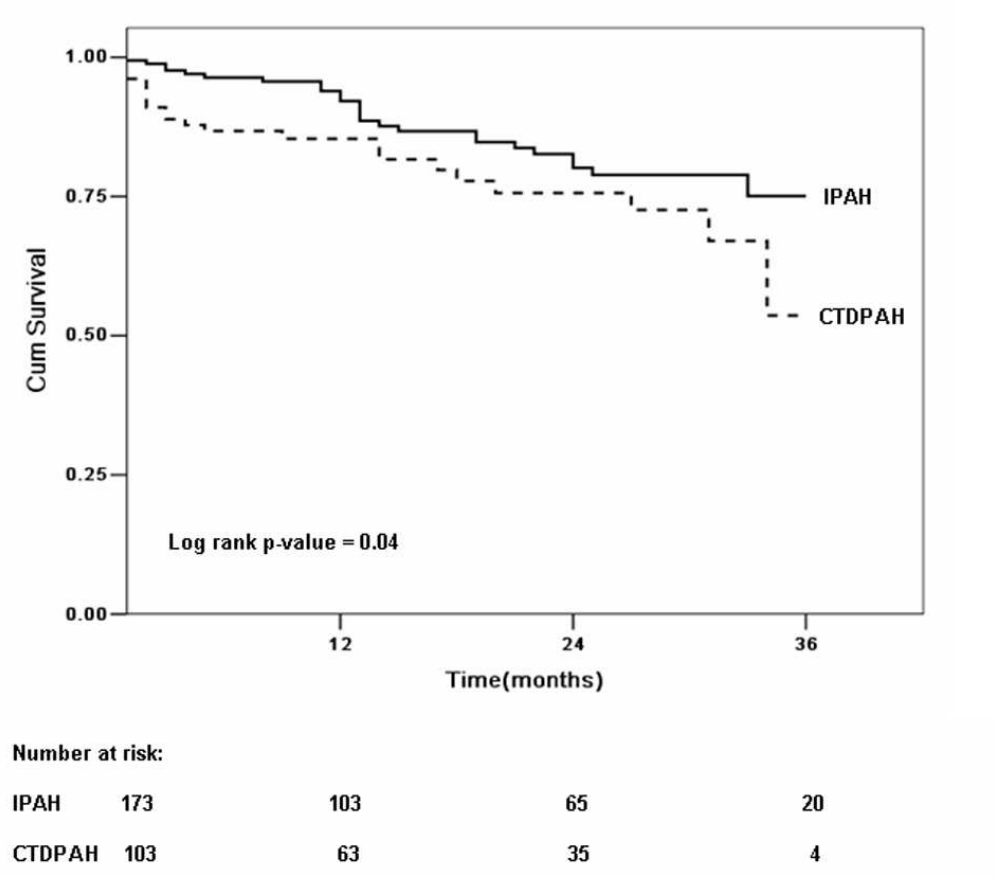
[*]Values are expressed as means ± SD or n (%).

CI = cardiac index; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SvO_2 = mixed venous oxygen saturation .

Table 5—*Multivariate Cox Proportional Hazards Model Estimates of Risk Factors for Mortality in the Entire Cohort*

Variable	Hazard Ratio	95% Confidence Interval	*P* Value
CTDPAH	2.33	0.95-2.78	.043
Age (per 10 years)	1.00	0.97-1.10	.67
Female sex	0.78	0.40-1.51	.37
WHO functional class III or IV	4.41	2.78-7.01	.001
RAP (per 1 mm Hg)	1.08	1.03-1.14	.08
mPAP (per 10 mm Hg)	1.02	0.99-1.03	.06
CI (per 1 L/min/m^2)	0.32	0.18-0.56	.13
FEV_1 (per 10% predicted)	0.97	0.95-0.99	.06
TLC (per 10% predicted)	0.98	0.95-1.02	.23
DL_{CO} (per 10% predicted)	0.92	0.86-1.00	.03
6MWT (per 100 meters)	0.99	0.99-1.00	.06
Pericardial effusion present	2.15	1.07-4.33	.032

Abbreviations as in Tables 1 to 4.



Survival rate of patients with PAH in the modern management era
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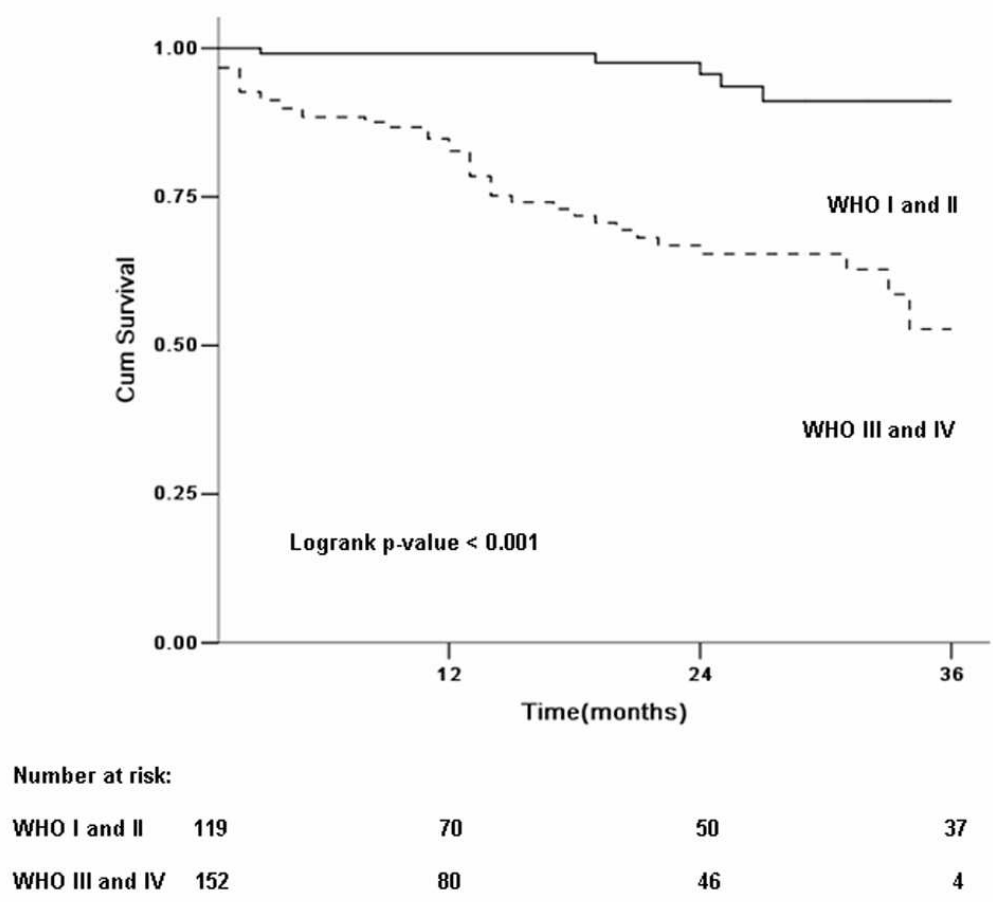

Survival rate of patients with WHO functional classes I and II versus those with classes III and IV
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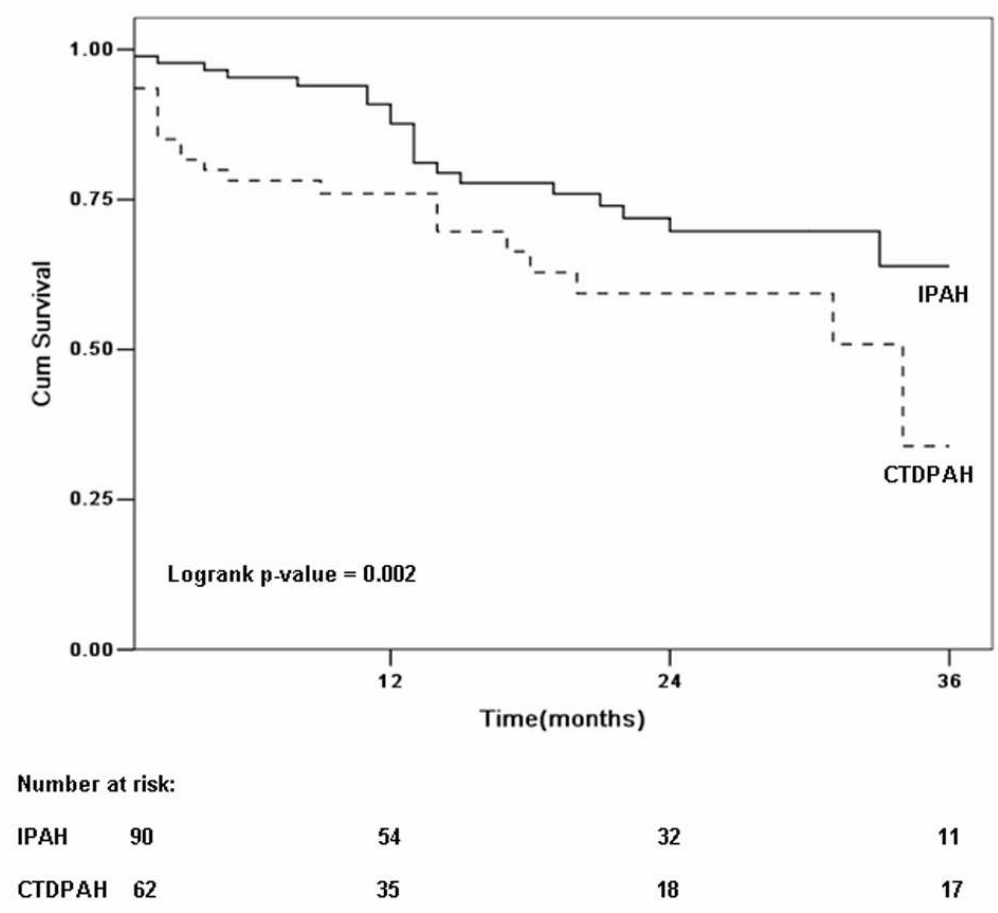

Survival estimate for patients in WHO functional classes III and IV with IPAH and CTDPAH
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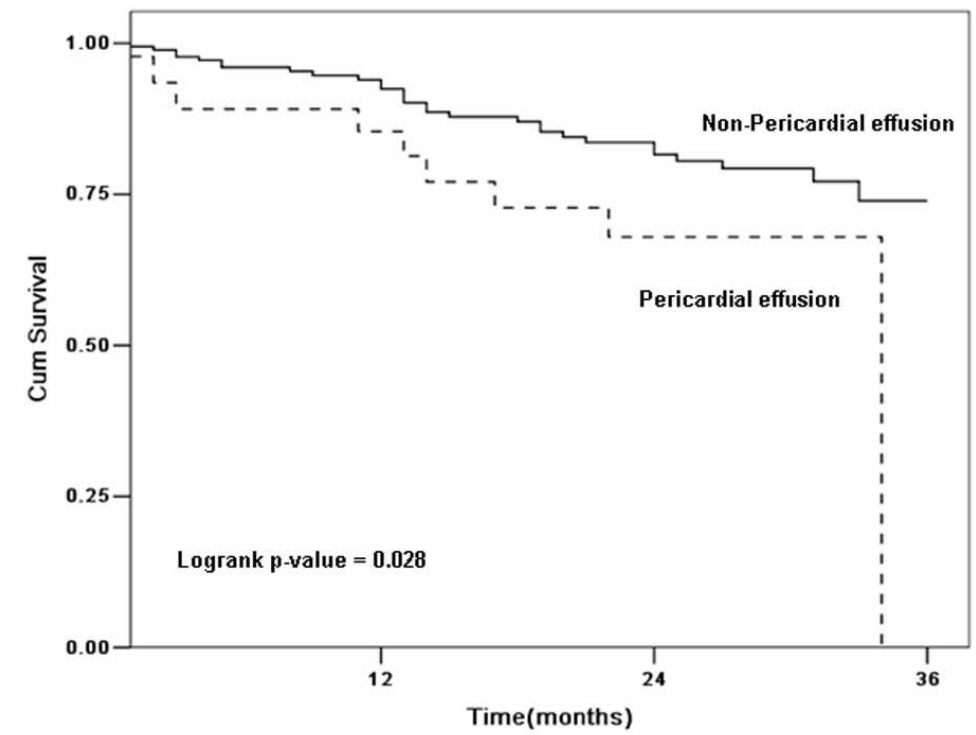
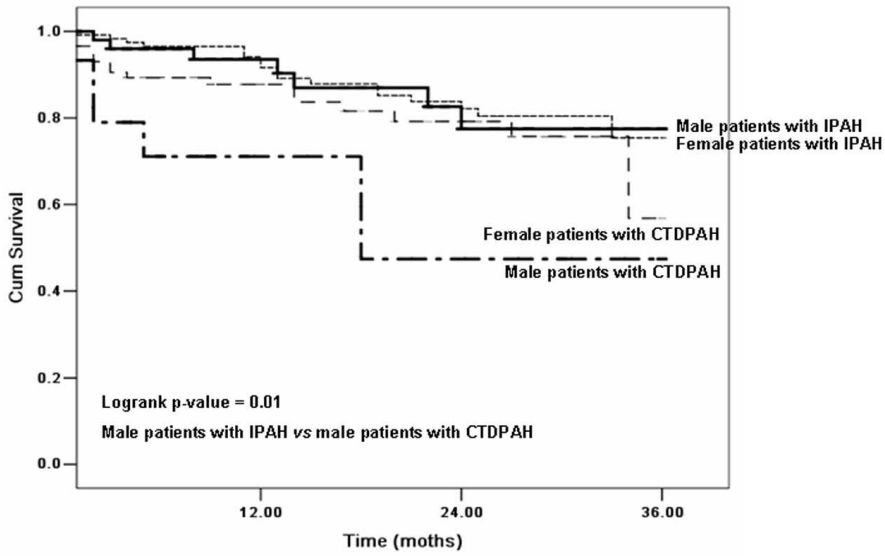


Number at risk:			
Non-Pericardial effusion			
183	123	81	23
Pericardial effusion			
45	23	14	14

Survival rate of patients with presence of pericardial effusion
80x80mm (300 x 300 DPI)



Number at risk:				
Male IPAH	52	38	15	15
Male CTDPAH	15	9	2	2
Female IPAH	121	74	50	15
Female CTDPAH	88	57	33	3

Survival rates of male patients with PAH. 1- and 3-year survival was estimated to be 93.5% and 77.5%, respectively, in male patients with IPAH, and 71.1% and 47.4% respectively, in male patients with CTDPAH. For female patients, there was no significant difference in survival between the two etiologic groups.
119x87mm (300 x 300 DPI)

Survival of Chinese Patients with Pulmonary Arterial Hypertension in the Modern Management Era

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Chest; Prepublished online February 17, 2011;
DOI 10.1378/chest.10-2327