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Original Article

Clinical characteristics and survival analysis of class I pulmonary arterial hypertension

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Abstract: Purpose: To analyze the clinical data and prognosis of patients with World Health Organization (WHO) functional class I pulmonary arterial hypertension (PAH). Methods: This research retrospectively analyzed the clinical data (baseline, laboratory as well as echocardiography and right heart catheterization data) of 63 class I PAH patients diagnosed and treated in the Department of Cardiology, First Affiliated Hospital of Zhengzhou University, between January 2021 and June 2022. The mean follow-up time was 10.7±6.5 months. The treatment and prognosis of the patients were analyzed. Results: Among the class I PAH patients, the average age at diagnosis was 39.7±12.7 years, with females accounting for 92.1%; 44.4% of patients were at grade III or IV; 55.6% were at medium-high risk. In the subgroup analysis, there were more cases with grade III/IV cardiac function (P=0.03) and high risk in idiopathic PAH (IPAH) group than those in congenital heart disease-associated (CHD-PAH) and connective tissue disease-associated PAH (CTD-PAH) groups (P=0.04). CHD-PAH patients tended to present with higher pulmonary systolic blood pressure, mean pulmonary artery pressure and pulmonary vascular resistance than CTD-PAH patients (P<0.01), while IPAH patients had worse right ventricular end-systolic and end-diastolic volumes (P<0.05). The three subgroups showed no obvious differences in echocardiographic indexes (right atrial size, right ventricular size and pulmonary artery systolic pressure) and related laboratory indexes (blood routines and hepatorenal function). In terms of the targeted drug therapy for PAH, the proportion of dual-drug combination therapy was the highest (48.1%), followed by monotherapy (35%) and triple combination therapy (15.9%). Nearly half (48.7%) of CTD-PAH cases were first diagnosed in the Rheumatology and Immunology Department, and all of them were given targeted drug therapy for PAH. After a mean follow-up of 10.7±6.5 months, a total of 8 endpoint events occurred, including 3 deaths due to CTD-PAH complicated with serious complications of other organs. The 1-year survival rate for all the included PAH patients was 95.2%. Conclusions: In the era of targeted therapy, class I PAH patients in China have a high early survival rate, a high proportion of combined therapy and strong multidisciplinary attention.

Keywords: Pulmonary arterial hypertension, targeted therapy, hemodynamics

Introduction

Pulmonary hypertension (PH) refers to changes in pulmonary vascular structure or function due to various inducements that result in increased pulmonary vascular resistance (PVR), right heart failure or even death, so it seriously threatens patients' physical and mental health [1]. Pulmonary arterial hypertension (PAH) is a rare disease that occurs in 15-50 people per million in the United States and Europe [2, 3]. PAH can be idiopathic, heritable, induced by drugs or toxins, or a result of conditions such as connective tissue disease, congenital heart disease and PH [4]. PH has a predilection for women aged 30 to 60 years, but it can also occur in men, often associated with poor clinical outcomes [5]. Thorough medical history, physical examination and comprehensive examination are necessary to determine whether a patient really has PAH. Initial symptoms include exertional dyspnea, fatigue and weakness [6, 7]. As the disease progresses, dyspnea may occur at rest, along with other clinical presentations such as chest pain, presyncope, syncope, lower limb edema, jugular vein expansion and abdominal distension [8].

Despite a low incidence of PAH, the long-term survival rate of patients with World Health

Organization (WHO)-functional classification class I/II PAH is significantly higher than that of patients with class III/IV PAH [9]. However, the WHO class I PAH also progresses rapidly, with poor prognosis and high mortality, leading to a survival no more than 3 years in most untreated patients [10]. Timely diagnosis of PAH is challenging for a number of reasons. As the disease develops, there are non-specific symptoms such as dyspnea or fatigue. Asthma, chronic heart failure, or even lack of health or depression are usually considered before PH is diagnosed [11].

Currently, the treatment for PH includes supportive therapies, such as diuretics, supervised rehabilitation, birth control advice and oxygen supplementation if necessary [12]. For PAH, current pharmacological treatments target three pathways of endothelial factors that regulate vasoconstriction/vasodilation and proliferation/mitosis [6]. Patients at low or moderate risk should be treated orally with endothelin receptor antagonists and phosphodiesterase-5 inhibitors or soluble guanylate cyclase stimulators, respectively. For high-risk patients, triple therapy should be considered, including subcutaneous or intravenous administration of prostacyclin analogues. For those with PAH and severe cardiopulmonary complications, initial single drug treatment is recommended [13]. With the introduction of multiple targeted drugs and the deepening understanding of PAH in major clinical centers, the survival of PAH patients has significantly improved [14]. In this study, the clinical data and follow-up results of PAH patients admitted to our hospital after the diagnosis and treatment of pulmonary vascular diseases were summarized, their clinical characteristics and treatment status were clarified, and the prognosis was analyzed, so as to provide a reference basis for the development and changes of PAH in recent years.

Participants and methods

Research participants

A retrospective analysis was performed on 103 patients diagnosed with pulmonary arterial hypertension and underwent right heart catheterization (RHC) in the Department of Cardiology, the First Affiliated Hospital of Zhengzhou University, from January 2021 to June 2022. Inclusion criteria: (1) Patients who met the PAH diagnosis proposed by the *Chinese Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension 2018* [1], that is, mean pulmonary artery pressure (mPAP) at rest ≥25 mmHg (measured by the RHC), pulmonary arterial wedge pressure (PAWP) ≤15 mm Hg, and PVR >3 Wood U; (2) Patients who received targeted drug therapies; (3) Patients with complete clinical data. Exclusion criteria: (1) Patients with normal hemodynamics but class II, III, IV or V PH; (2) Patients with other cardiovascular malformations or diseases (especially anomalous pulmonary vein connection and coronary artery disease); (3) Patients with incomplete clinical data. After screening according to the inclusion and exclusion criteria, a total of 63 PAH patients were finally enrolled. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

Research design

General information, biochemical test results, echocardiography data, RHC hemodynamic data, targeted therapy regimens, follow-up results and survival data of 63 patients with PAH were collected and analyzed. General data mainly covered sex, age at initial diagnosis, body surface area (BSA) and cardiac function classification. Biochemical tests examined patients' hepatorenal function, blood routine, arterial blood gas analysis, N-terminal pro-B type natriuretic peptide (NT-proBNP) and blood lipids. Echocardiography primarily recorded the right ventricular anteroposterior diameter, right atrium left-right diameter, inner diameter of pulmonary artery and tricuspid regurgitation velocity. The hemodynamic data of RHC included aortic systolic pressure (sBP), systolic pulmonary artery pressure (sPAP), mPAP, right atrial mean pressure, PAWP, PVR, cardiac index, arterial oxygen saturation (SaO_2), mixed venous oxygen saturation (SvO_2), right ventricular end-diastolic volume (RVEDV), right ventricular end-systolic volume (RVESV) and right ventricular ejection fraction (RVEF).

The targeted therapy regimen was determined by the attending physicians, taking factors such as the patient's condition and family economic status into consideration. This study did not

Table 1. Comparison between PAH and other types of pulmonary hypertension

Variables	Pulmonary arterial hypertension (n=63)	Other types of pulmonary hypertension (n=16)	P
Sex, n (%)			<0.01
Male	5 (7.9)	11 (68.8)	
Female	58 (92.1)	5 (31.2)	
Age (years)	38.8±12.0	53.1±16.7	<0.01
Heart rate (beats/min)	84.8±12.7	81.6±16.6	0.41
Hemoglobin (g/L)	129.8±23.6	139.0±36.5	0.22
Leukocyte count ($\times 10^9$/L)	5.6±2.3	7.3±1.8	<0.01
Platelet count ($\times 10^9$/L)	165.0 (132.5, 219.0)	210.0 (172.2, 296.0)	0.03
Uric acid (umol/L)	335.6±119.4	433.9±182.2	<0.01
Urea (mmol/L)	5.6±2.1	7.9±4.9	<0.01
eGFR	108.7±19.1	80.0±31.1	<0.01
Total bilirubin (umol/L)	10.5 (7.0, 16.3)	17.3 (11.9, 27.6)	<0.01
Direct bilirubin (umol/L)	4.3 (3.0, 6.8)	7.9 (5.1, 11.0)	<0.01
Indirect bilirubin (umol/L)	5.5 (3.7, 8.3)	9.4 (6.5, 15.9)	<0.01

Note: PAH, Pulmonary Arterial Hypertension; eGFR, Estimated Glomerular Filtration Rate.

interfere with treatment regimens. Currently, there are four major types of PAH targeted therapeutic drugs commonly used in clinical practice, (1) Phosphodiesterase type 5 inhibitors (PDE5i): Tadalafil and Sildenafil; (2) Endothelin receptor antagonists (ERA): Bosentas, Ambrisentan and Opsutan; (3) Guanylate cyclase (sGC) stimulator: Adempas (Riociguat); (4) IP receptor agonist: Selexipag; (5) Prostacyclin vasodilator: Remodulin. Patients were treated with either a single drug or a combination of two or three drugs.

Patients were followed up once every 3 to 6 months by telephone, outpatient or inpatient visits to record their treatment and survival status. The follow-up endpoints were defined as all-cause death, readmission due to disease deterioration and adjusted medication for disease deterioration. The follow-up endpoints and survival rate were analyzed.

Statistical methods

This study employed SPSS 21.0 statistical software for data analyses. Measurement data were described as mean ± standard deviation if they were normally distributed or as interquartile range otherwise. Count data were represented by number of cases (percentages). For measurement data with normal distribution and skewed distribution, the independent sample t test and the Mann-Whitney U test were used for comparisons, respectively, while the inter-group comparisons of the count data were made by the crosstab chi-square test (χ^2). Patient survival was analyzed using the Kaplan-Meier survival curve. P<0.05 was used to indicate the presence of statistical significance.

Results

General information of patients

Of the 103 patients, 22 had normal hemodynamics, 16 had other types of PH, and 63 had PAH. The mean age of PAH patients at their first visit in the cardiology department was 39.7±12.7 years, which was significantly younger compared with patients with other types of PH (*P*<0.01). The disease showed a predilection for women, with a significant sex difference (92.1% vs. 31.2%, *P*<0.01) (**Table 1**). Compared with other types of PH, PAH patients had lower platelet (*P*<0.05) and leukocyte counts (*P*<0.01), reduced uric acid and urea and bilirubin levels (*P*<0.01), and higher eGFR (*P*<0.01).

Comparison of data among patients with different types of PAH

The subjects were further classified into three categories: Idiopathic PAH (IPAH), congenital heart disease-associated PAH (CHD-PAH) and connective tissue disease-associated PAH (CTD-PAH), with their main differences lying in

Table 2. Comparison of hemodynamic data among PAH subgroups

Variables	IPAH (n=15)	CHD-PAH (n=9)	CTD-PAH (n=39)	*P*
Age (years)	39.7±12.7	31.0±12.4	40.3±11.2	0.11
Gender, n (%)				1
Male	1 (6.7)	1 (11.1)	3 (7.7)	
Female	14 (93.3)	8 (88.9)	36 (92.3)	
BSA (m^2)	1.6±0.1	1.5±0.2	1.6±0.1	0.20
Heart rate (beats/min)	85.1±14.3	82.2±15.8	85.2±11.5	0.81
sBP (mmHg)	117.4±17.1	114.2±11.4	121.5±16.6	0.42
Right atrial pressure (mmHg)	5.7±3.1	4.3±2.8	3.9±2.8	0.13
sPAP (mmHg)	89.0±33.6	101.9±14.2	67.4±20.1	<0.01
mPAP (mmHg)	54.2±24.3	64.6±11.4	40.2±10.8	<0.01
PAWP (mmHg)	7.6±3.0	6.2±2.4	6.3±3.2	0.37
Cardiac output ($L{\cdot}min^{-1}$)	5.0±1.9	4.4±1.8	5.3±2.4	0.54
Cardiac index ($L{\cdot}min^{-1}{\cdot}m^{-2}$)	3.1±1.3	2.9±1.1	3.3±1.3	0.57
PVR (Wood U)	12.2±10.5	15.5±7.1	7.5±4.2	<0.01
SvO_2 (%)	66.3±9.6	68.4±5.4	68.6±8.0	0.64
SaO_2 (%)	94.4±3.1	90.8±4.3	93.7±4.1	0.11
RVEDV (ml)	357.0 (261.5, 419.5)	--	242.5 (214.8, 305.5)	0.02
RVESV (ml)	284.5 (195.5, 367.5)	--	176.0 (143.0, 220.8)	0.03
RVEF (%)	16.5 (13.2, 31.0)	--	27.0 (18.0, 31.0)	0.28

Note: PAH, Pulmonary Arterial Hypertension; BSA, Body Surface Area; sBP, Aortic Systolic Pressure; sPAP, Systolic Pulmonary Artery Pressure; mPAP, Mean Pulmonary Artery Pressure; PAWP, Pulmonary Arterial Wedge Pressure; PVR, Pulmonary Vascular Resistance; SvO_2, Mixed Venous Oxygen Saturation; SaO_2, Arterial Oxygen Saturation; RVEDV, Right Ventricular End-Diastolic Volume; RVESV, Right Ventricular End-Systolic Volume; RVEF, Right Ventricular Ejection Fraction.

hemodynamic indexes. Among them, CHD-PAH was associated with higher sPAP, mPAP and PVR levels at diagnosis, while CTD-PAH was associated with relatively low levels (P<0.01). Similarly, IPAH was significantly worse than CTD-PAH in measures of right cardiac function, such as RVESV and RVESV (P<0.05) (**Table 2**).

In terms of echocardiographic measures, there were no significant differences among the three subgroups in right atrial size, right ventricular size or sPAP. Similarly, related laboratory indicators, such as blood routine and hepatorenal function, were not significantly different among the subgroups (**Table 3**).

Targeted therapies for different PAH subclasses

Almost half of CTD-PAH patients had a history of seeking medical advice and taking targeted drugs (48.7%), and the unit that treated these patients and gave the targeted therapy was the Rheumatology and Immunology Department. In contrast, IPAH and CHD-PAH were mainly diagnosed for the first time (P<0.01) (**Figure 1A**). Of them, the number of patients with grade III/IV cardiac function in the IPAH group was significantly higher than that in the CHD-PAH and CTD-PAH groups (P=0.03). After risk stratification, it can be seen that there were more high-risk patients in the IPAH group than those in the other two groups (P=0.04) (**Table 4**).

Among the targeted drug treatments in each subgroup, the two-drug combination accounted for the highest proportion (48.1%), followed by monotherapy (35%) and triple combination therapy (15.9%). Monotherapy accounted for the highest proportion in CTD-PAH patients (38.5%), while triple combination therapy accounted for the highest proportion in IPAH patients (40%) (**Figure 1B**).

Follow-up data of different PAH subclasses

After a mean follow-up of 10.7±6.5 months, a total of 8 endpoint events occurred, including 3 deaths due to CTD-PAH with serious complications of other organs. The 1-year survival rate of all PAH patients was 95.2%, with no significant

Table 3. Comparison of echocardiographic and laboratory indicators among PAH subgroups

Variables	IPAH (n=15)	CHD-PAH (n=9)	CTD-PAH (n=39)	*P*
Echocardiographic indexes				
Right ventricle anteroposterior diameter (mm)	20.8±6.6	22.0±6.6	19.7±5.7	0.57
Right atrium left-right diameter (mm)	40.3±11.1	41.6±10.8	38.4±9.8	0.65
Right atrium superior-inferior diameter (mm)	47.2±8.2	51.9±12.1	48.2±10.2	0.53
Tricuspid regurgitation velocity (m/s)	3.6±1.0	4.1±1.0	3.8±0.9	0.46
sPAP (mmHg)	57.0 (37.0, 89.0)	99.0 (77.0, 103.0)	70.0 (45.0, 94.5)	0.41
Laboratory indexes				
Hemoglobin (g/L)	131.4±27.9	136.0±26.8	127.7±21.4	0.61
ProBNP (pg/ml)	846.2 (113.8, 2052.0)	202.7 (102.0, 1940.0)	798.7 (65.3, 2484.0)	0.97
Uric acid (umol/L)	364.0 (300.0, 379.5)	336.0 (272.0, 396.0)	318.5 (235.8, 371.0)	0.46
Urea (mmol/L)	6.2 (4.8, 7.9)	5.6 (3.9, 5.7)	4.7 (3.6, 6.5)	0.12
eGFR	112.1 (92.4, 119.8)	121.9 (105.2, 127.6)	108.0 (96.4, 117.9)	0.20
ALT	22.0 (20.0, 28.0)	19.0 (17.8, 22.5)	23.0 (18.8, 32.2)	0.47
AST	21.0 (14.0, 35.5)	16.0 (13.5, 22.0)	19.0 (14.5, 25.0)	0.54
Total bilirubin (umol/L)	10.7 (5.3, 20.7)	12.3 (8.5, 14.5)	10.0 (7.0, 13.7)	0.64
Direct bilirubin (umol/L)	4.9 (2.6, 8.6)	5.1 (4.1, 6.3)	4.3 (3.0, 5.9)	0.57
Indirect bilirubin (umol/L)	5.8 (2.3, 9.4)	6.6 (5.0, 9.1)	5.2 (3.9, 7.9)	0.76

Note: PAH, Pulmonary Arterial Hypertension; sPAP, Systolic Pulmonary Artery Pressure; NT-proBNP, N-terminal pro-B type Natriuretic Peptide; ALT, Alanine Transaminase; AST, Aspartate Transaminase; eGFR, Estimated Glomerular Filtration Rate; IPAH, Idiopathic Pulmonary Arterial Hypertension; CHD-PAH, Congenital Heart Disease-associated Pulmonary Arterial Hypertension; CTD-PAH, Connective Tissue Disease-associated Pulmonary Arterial Hypertension.

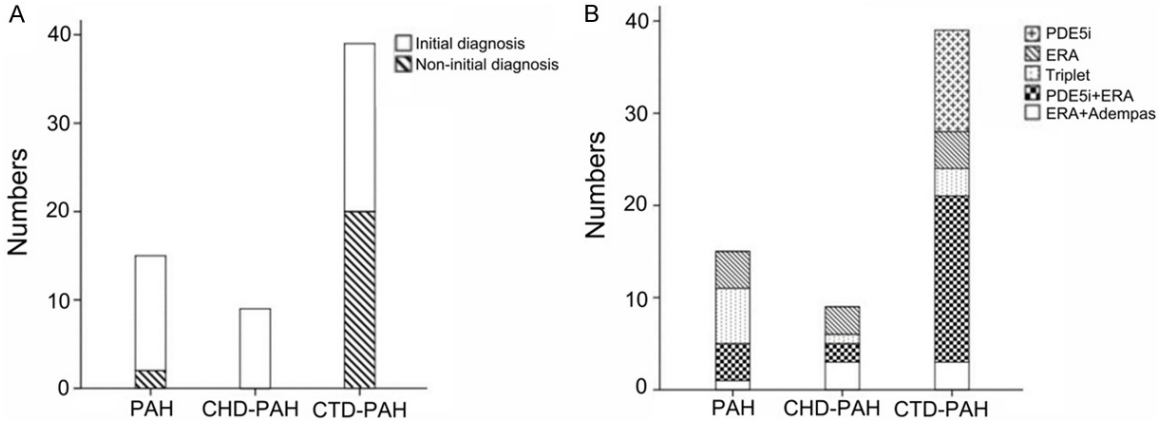

Figure 1. Initial diagnosis and targeted drug therapies in three pulmonary arterial hypertension subgroups. A: Diagnosis of the three subgroups; B: Distribution of targeted drug therapy regimens in the three subgroups.

difference in the overall end-point event rate among PAH subgroups (*P*=0.13) (**Figure 2**).

Discussion

For PH, there is still a lack of epidemiological data in the general population in China, and the etiological distribution of the class I PAH causes is also significantly different from that of Western countries. CHD-PAH is the most common type in China, followed by IPAH and CTD-PAH [15], which are different from IPAH, hereditary PAH or drug-related PAH that make up the majority of cases in Western countries [16]. Among the subjects in this study, there was an obvious population selection bias due to sample size and geographical reason, including only three categories of PAH (IPAH, CHD-PAH and CTD-PAH). The etiological classification of PAH is not discussed in this paper. However, almost half of CTD-PAH patients started targeted drug therapy when they visited the Rheumatology and Immunology Department, an indirect reflection of the increasing

Table 4. Different types of medication and survival outcomes among PAH patients

Variables	Total (n=63)	IPAH (n=15)	CHD-PAH (n=9)	CTD-PAH (n=39)	p
Cardiac function classification					0.03
I/II	35 (55.6)	4 (26.7)	6 (66.7)	25 (64.1)	
III/IV	28 (44.4)	11 (73.3)	3 (33.3)	14 (35.9)	
Risk stratification					0.04
Low risk	28 (44.4)	3 (20)	4 (44.4)	21 (53.8)	
Medium risk	25 (39.7)	6 (40)	4 (44.4)	15 (38.5)	
High risk	10 (15.9)	6 (40)	1 (11.1)	3 (7.7)	

Note: PAH, Pulmonary Arterial Hypertension; IPAH, Idiopathic Pulmonary Arterial Hypertension; CHD-PAH, Congenital Heart Disease-associated Pulmonary Arterial Hypertension; CTD-PAH, Connective Tissue Disease-associated Pulmonary Arterial Hypertension.

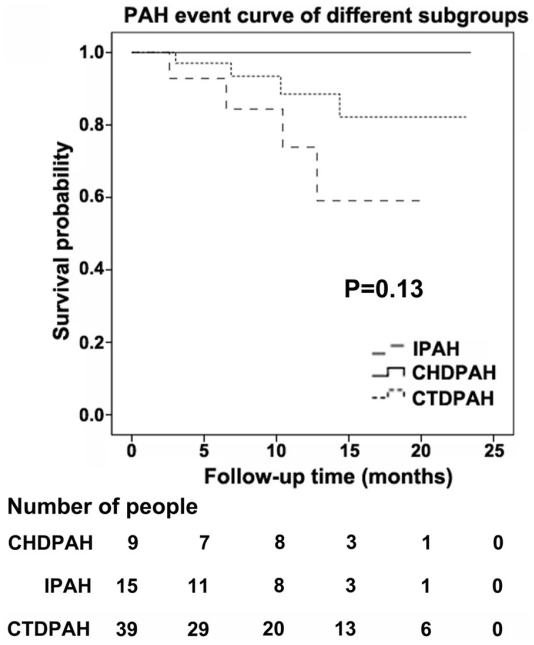

Figure 2. Survival function of pulmonary arterial hypertension subgroups.

importance this department attaches to CTD-PAH. With the updating of guidelines and growing consensus on CTD-PAH to guide the diagnosis and treatment of the disease [17], it is believed that early diagnosis and intervention can improve the prognosis of such patients in China.

PAH is shown to be significantly related to estrogen [18, 19], which may explain the relatively high proportion of female patients with PAH. In this study, 92.1% of the patients were female, which is consistent with previous findings. In addition, the average age at diagnosis of IPAH (39±12 years) in this study was older than that reported previously [14, 20, 21], which supports the increasing trend of the overall age at diagnosis of the disease [22].

Compared with other major PH types, PAH patients have stable hepatorenal function ($P<0.01$), which may be associated with fewer complications. Echocardiography, as an important means in the screening and evaluation of PH, has good sensitivity and accuracy in diagnosing PH, but this approach may lead to large errors in estimating pulmonary artery pressure in some patients. The guideline points out that peak tricuspid regurgitation velocity ≥3.4 m/s, regardless of other signs of PH, indicates a high probability of PH, and further examination, including RHC, is recommended [1]. In this study, the tricuspid regurgitation velocity and the sPAP differed insignificantly among the three PAH subgroups, but statistical significance was presented in sPAP in RHC, which further validates that echocardiography should be used as a diagnostic standard for PH instead of replacing RHC to be a diagnostic criterion.

In 2006, targeted drugs for PAH entered the Chinese market, significantly improving the survival rate of PAH patients in China. In 2011, a Chinese study showed that the 1- and 3-year survival rates of IPAH patients were 92.1% and 75.1%, respectively [10], which were significantly improved compared with that in 2007 when there was no targeted drug [14]. With the declining price of PAH targeted drugs over the past decade, especially the marketing of Chinese targeted drugs in the past 5 years and the attention and coverage of national medical insurance, the use of PAH targeted drugs has made further progress. Adempas (Riociguat) is currently the only target drug with dual indications for PAH and CTEPH. The PATENT-1 study

showed that Adempas can significantly improve hemodynamic parameters and cardiac function in PAH patients, and delay clinical deterioration [23]. Moreover, Adempas demonstrated favorable efficacy and safety for the treatment of CTD-PAH and after surgical correction of CHD-PAH, contributing to a 2-year survival rate as high as 93% [24]. Sequential triple combination therapy of Adempas with Selexipag can reduce the risk of deterioration/death of PAH patients by 37% [25]. Several randomized controlled trials published in recent years have shown that both sequential combination therapy and initial combination therapy can significantly reduce the occurrence of clinical exacerbations in PAH patients [26-28].

With the clinical use of these targeted drugs, a number of studies have shown a further improvement in the survival of PAH patients compared to that a decade ago [29, 30], which is closely related to the standardization and improvement of medication regimens for patients. Different from the previous data on PAH targeted therapy in China, where monotherapy accounted for the majority of treatment [10, 14, 31], a growing number of combined medication regimens have emerged in recent years [29-31]. Among them, there is not only the classical PDEi5+ERA scheme, but also the combined application of ERA + Adempas. In our study, more than half (54%) of PAH patients received initial combination therapy, with a one-year survival rate of 90.9%, which is consistent with the higher survival rate reported in recent years.

Conclusion

In conclusion, with the increasing attention on PAH, the updating of guidelines in various related fields, the expansion of medical insurance coverage and the reduction of drug costs, the application of targeted drugs has become increasingly standardized and popular, which improves the survival rate of patients with class I PAH. The increased interest in this field is particularly evident in the Rheumatology and Immunology Department. However, there are limitations in the results due to sample size and sample bias in this study. Also, we only analyzed treatment regimens and outcomes in class I PAH patients, but not differences in efficacy among patients with different treatments. Therefore, it is necessary for this center, as well as more centers and multiple disciplines to carry out larger samples and more in-depth prospective studies to provide a basis for the prevention and treatment of class I PAH.

Disclosure of conflict of interest

None.

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