A Retrospective Study on the Efficacy of PAH-targeted Therapy in Patients with Severe Pulmonary Hypertension in Chronic Lung Disease

li jieying

Guangzhou Medical College First Affiliated Hospital

sun zhang

Guangzhou Medical College First Affiliated Hospital

haiming Chen

Guangzhou Medical College First Affiliated Hospital

wenliang Guo

Guangzhou Medical College First Affiliated Hospital

chunli Liu

Guangzhou Medical College First Affiliated Hospital

Cheng Hong (✉ gyfyyhc@126.com)

The First Affiliated Hospital of Guangzhou Medical University, Guangzhou

Research article

Keywords: Severe pulmonary hypertension, Chronic lung disease, 2 PAH targeted drug, Survival rate, Prognosis

Posted Date: October 6th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-80027/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Using PAH-targeted therapy in severe pulmonary hypertension (PH) patients with chronic lung disease (CLD) is controversial as the pulmonary vasodilation could worsen hypoxemia.

Objective To investigate the efficacy of patients with severe PH-CLD to PAH targeted therapy.

Methods We retrospectively enrolled patients with severe PH-CLD in our study. Each patient underwent laboratory indicators and transthoracic echocardiography at baseline and after the therapy, and survival after therapy were also evaluated.

Results After PAH targeted therapy, NT - proBNP significantly decreased (1043.10(236.75-2697.50) pg/ml vs 287.10(21.00-555.90) pg/ml, $p=0.035$), whereas PaO₂ and the oxygenation index in blood gas analysis significantly increased (59.18± 30.12 mmHg vs 74.35(61.63-163.95)mmHg, $p=0.010$ and 177.21± 84.38 mmHg vs 286.22± 165.13 mmHg, $p=0.035$, respectively). But the difference at 1-,3- years survival rates between the two groups was not statistically significant (82.82% and 66.26% vs 75.87% and 20.23%, respectively, $p=0.094$). Multivariate regression analysis identified baseline mean right atrial pressure values and cardiac index as significant predictors of survival of patients with severe PH-CLD.

Conclusions PAH targeted therapy may have benefit in patients with severe PH-CLD and didn't worsen their hypoxemia. Right ventricular function might have an important impact on the survival of patients.

Introduction

Pulmonary hypertension (PH), defined as an elevated mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest on right heart catheterization^[1], is a frequent complication of chronic lung disease (CLD). According to the World Health Organization, the diagnosis of PH encompasses five distinct disease groups based on their pathological and hemodynamic characteristics^[1-2]. PH associated with respiratory system disorders and/or hypoxemia from pulmonary vascular diseases belongs to the group 3, including obstructive lung diseases and restrictive lung diseases. The actual prevalence of PH in CLD has been variable reported because of the differences in definition for PH over the years as well as of differences in the characteristics of the populations studied, and their incidence ranges from as low as 30% to as high as 85%^[3-10]. Furthermore, severe PH in chronic lung disease (PH-CLD), defined as mPAP > 35 mmHg or mPAP ≥ 25 mmHg and decreased cardiac output, is associated with greater mortality and worse clinical course^[4,9,11]. It has been shown that pulmonary arterial hypertension (PAH)-specific therapy can improve symptoms, exercise capacity and survival in patients with PAH^[12-14]. Very few studies have shown that PAH- specific therapy may be benefit in patients with severe PH in chronic lung disease^[10,15]. But using PAH-specific therapy in severe PH patients with lung disease is controversial as there is theoretical concern that the pulmonary vasodilation could worsen hypoxemia due to decreased ventilation perfusion (V/Q) matching^[16-17]. In order to gain better insight into the utility of PAH-specific therapy in severe PH-

CLD, we aimed to investigate the efficacy and prognostic risk factors of patients with severe PH-CLD to PAH targeted drug therapy.

Methods

The local ethics review committee approved the present study (IRB:201716012). We retrospectively reviewed consecutive patients were aged between 18 and 80 years and with a diagnosis of severe PH-CLD between January 2016 and December 2019 at the first affiliated hospital of Guangzhou medical university. Severe PH was defined as $mPAP > 35$ mmHg or $mPAP \geq 25$ mmHg with cardiac index < 2.0 L/(min.m²) at rest on right heart catheterization (RHC). The diagnostic criteria for chronic lung disease are based on pulmonary function test(PFT) and computed tomography(CT) results:(1) chronic obstructive pulmonary disease(COPD), considered in any patient with dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease and ; a post-bronchodilator FEV1/FVC confirms the presence of persistent airflow limitation and identifies the presence of COPD in patients with appropriate symptoms and predisposing risks^[18]; (2) restrictive: diagnosed according to the American Thoracic Society and European Respiratory Society guidelines, total lung capacity (TLC) $< 60\%$ predicted or TLC $< 80\%$ predicted and more than mild fibrosis on chest CT^[19];(3) bronchiectasis diagnosed by clinical work up and confirmed by high resolution computed tomography (HRCT)^[20]; We excluded the patients with lung cancer, asthma, tuberculosis and other allergic diseases or connective tissue diseases. Moreover, we did not include the patients who did not follow the therapy.

Patients were divided into two groups: PAH targeted therapy group and non-PAH targeted therapy group. All patients with general information, laboratory examination, lung function, echocardiography, right heart catheter hemodynamics and other indicators at the time of diagnosis and the last follow-up visit to the hospital were captured and reviewed, and the survival of the patients until February 2020 was recorded. Changes in the above indicators before and after treatment were compared and the risk prognostic risk factors of patients without lung transplantation were collected. The decision about initiation or escalation of targeted therapy was left to the physician. The date of RHC was defined as the date of PH diagnosis, and all baseline data were obtained within 2 weeks of the RHC.

Statistical analysis was performed using GraphPad Prism (version 8.00; GraphPad Software, La Jolla, CA, USA) and SPSS 16(SPSS Inc. Chicago, IL, USA). Continuous variables are expressed as mean value $\pm$ standard deviation. For non-normal distribution, values are expressed as median (IQR: inter-quartile range). According to the distribution of variables, it was decided to use student t test or Mann-Whitney U test to compare the baseline conditions of the two groups of patients. Paired t test or Wilcoxon rank sum test were used to compare the baseline and follow-up data of the two groups of patients. Survival curves were constructed with the use of the Kaplan–Meier method with a statistical comparison that was based on the log-rank test statistic. Patients who were lost to follow-up were censored at the time of last contact, and the survival period starts from the day the right heart catheter is diagnosed. The end of the study is the date of death and the deadline for follow-up. Survival predictors were determined using Cox

proportional hazards regression analysis. Variables with $p \leq 0.20$ were considered for multivariate analysis. A p value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

Baseline characteristic in 49 severe PH patients associated with chronic lung disease, with a mean age of 55.87 ± 9.21 years and a mean BMI of 20.43 ± 3.87 kg/m², are shown in Table 1. There were 27 males (55.10%) and 15 patients had a history of smoking. The mean time between first respiratory symptom and PH was 154.83 ± 147.51 months. The proportion of patients with NYHA class III in PAH targeted treatment group was significantly higher than that in non-PAH targeted treatment group (80% vs 45.83%, $p = 0.013$). There were no significant differences in the number of patients receiving oxygen therapy, the number of smokers, the underlying lung diseases and the course of disease between the two groups.

Table 1
patient's demographic and clinical characteristics

Parameter	All patients	PAH targeted therapy group	Non-PAH targeted therapy group	<i>p</i> value
N	49	25	24	
Male, n(%)	27(55.10)	18(72.00)	9(37.5)	0.022#
Age years	55.87±9.21	54.63±9.37	57.11±9.05	0.327
BMI[kg/m ²]	20.43±3.87	20.69±3.63	20.20±4.13	0.656
Smoking, n(%)	15(30.61)	9(36.00)	6(25.00)	0.538
LTOT usage, n(%) (3l/min)	46(93.88)	23(92.00)	23(95.83)	0.833
Duration[months]	154.83±147.51	172.30±137.27	136.69±158.07	0.385
NYHA function class, n(%)				
I/II	10 (20.41)	3 (12.00)	7 (29.17)	0.090#
III	31 (63.27)	20 (80.00)	11 (45.83)	0.013#
IV	8 (16.33)	2 (8.00)	6 (25.00)	0.138#
Chronic lung disease, n(%)				
COPD	13 (26.53)	6 (21.43)	7 (28.00)	0.754#
ILD	11 (22.45)	5 (17.86)	6 (24.00)	0.742#
Bronchiectasis	18 (36.73)	10 (35.71)	8 (32.00)	0.769#
COPD&Bronchiectasis	7 (14.29)	4 (25.00)	3 (16.00)	1.000#
Arterial blood gas analysis				
PaO ₂ (mmHg)	71.23±34.43	54.08±22.27	85.85±38.26	0.009*
PaCO ₂ (mmHg)	53.04±15.49	56.26±17.01	56.72±17.95	0.845
AB(mmHg)	4.00±5.41	3.68±6.54	4.31±4.10	0.692
SPO ₂ (%)	92.80±7.21	91.87±7.96	93.77±6.36	0.341
Oxygenation index (mmHg)	236.51±129.70	183.75±86.82	279.76±152.00	0.025
Renal function				
Cr(umol/l)	75.62±28.3	83.79±35.04	68.13±18.09	0.060

BUN(mmol/l)	5.34±3.77	6.17±4.86	4.58±2.27	0.156
NT-proBNP(pg/ml)	1177.50 (201.15-2652.20)	2385.80±3861.6	1521.50±1731.30	0.297
Pulmonary function		N=15	N=26	
FEV1 %pre	52.91±27.20	47.44±19.36	58.38±32.90	0.221
FVC %pre	64.58±26.68	59.72±23.29	68.40±29.36	0.319
FEV1/FVC %	79.90±23.26	77.84±22.08	81.67±24.60	0.605
DLC0% pre	36.98±24.98	26.77±20.05 (n=10)	48.32±26.01 (n=12)	0.289
Echocardiography(mm)		N=20	N=31	
LA	26.00(22.00-30.05)	26.00(25.00-32.00)	28.12±6.69	0.960*
RV	26.00(22.00-30.50)	29.87±6.42	24.88±6.87	0.012
LVDd	38.84±6.76	36.43±6.75	40.96±6.14	0.018
LVDs	23.79±3.70	23.00(21.00-24.00)	24.55±3.86	0.101*
EF(%)	68.71±12.12	69.65±10.68	67.18±25.83	0.616
PASP(mmHg)	68.52±23.67	74.50(59.00-90.00)	65.18±25.83	0.255*
Pericardial effusion, n(%)	9(18.37)	4(16.00)	5(20.83)	0.725#
RHC(mmHg)				
mRAP	5.79±6.79	3.93±6.23	6.84±5.32	0.077
mRVP	28.00±9.63	29.37±9.68	26.58±9.55	0.295
mPAP	44.33±9.63	44.63±9.46	44.04±9.97	0.824
CO(L/min)	4.80±1.82	4.52±1.26	5.07±2.24	0.273
CI(L/min/m2)	2.91(2.47-3.75)	2.94±0.74	3.00(2.38-4.21)	0.539*
PVR(wood)	7.70±3.72	8.60±3.47	6.73±3.81	0.069
SvO2(%)	65.05±10.91	61.00(56.00-69.00)	67.89±11.13	0.072*
Risk stratification				
High-risk, n(%)	18 (36.73)	9 (36.00)	9 (37.50)	0.913#

PAH-therapy drug		
PDE-5	13	13
Prostaglandin analogs	13	13
Abbreviations: * stands for rank sum test; # stands for chi-square test (Fisher's exact probability test), and the rest are independent sample T tests. N: number of cases; NYHA heart function classification: New York Heart Association class; PAH: pulmonary arterial hypertension; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PaO ₂ : artery Blood oxygen partial pressure; PaCO ₂ : arterial partial pressure of carbon dioxide; AB: actual alkali excess; SPO ₂ : arterial oxygen saturation; Cr: creatinine; BUN: urea nitrogen; NT-proBNP: N-terminal pro-brain natriuretic peptide; FEV1% : Forced expiratory volume in the first second as a percentage of the predicted value; FVC%: Forced vital capacity in percentage; FEV1/FVC: Forced expiratory volume in the first second/forced vital capacity; DLCO% pre: Carbon monoxide diffusion as a percentage of predicted value; LA: Left atrium diameter; RV: right ventricular diameter; LVDD: left ventricular end diastolic diameter; LVDs: left ventricular end systolic diameter; EF: ejection fraction; PASP: pulmonary artery systolic pressure; mRAP: mean right atrial pressure; mRVP: mean right ventricular Pressure; mPAP: mean pulmonary artery pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SvO ₂ : mixed venous oxygen saturation; PDE-5: type 5 phosphodiesterase inhibitor.		

PaO₂ and oxygenation index in the PAH targeted therapy group were lower than those in the non-PAH targeted therapy group ($p=0.009$, $p=0.025$). The right ventricular diameter (RV) of PAH targeted therapy group was larger than that of non PAH targeted therapy group ($29.87 \pm 6.42\text{mm}$ vs $24.88 \pm 6.87\text{mm}$, $p=0.012$), but the left ventricular end diastolic diameter (LVDD) was smaller ($36.43 \pm 6.75\text{mm}$ vs $40.96 \pm 6.14\text{mm}$, $p=0.018$). There was no significant difference in NT-proBNP, echocardiography, renal function, pulmonary function, hemodynamic index of right cardiac catheter, and the proportion of high-risk patients between the two groups.

Effects of PAH therapy

36 patients have complete data before and after follow-up. 19 patients in PAH targeted therapy group were followed up for a median of 6.00 (2.00-11.00) months, and 17 patients in non-PAH targeted therapy group were 3.00 (1.00-12.00) months. After treatment, NT-proBNP, PaO₂ and oxygenation index in the PAH targeted therapy group were significantly improved, but they did not improve in the non-PAH targeted therapy group. Baseline and follow-up variables for each group are shown in table 2. Figure 1 shows the change in NYHA functional class with treatment for each cohort.

Table 2

Comparison of parameters before and after therapy between the PAH targeted therapy group and the non-PAH targeted therapy group

	N	baseline	Follow-up	<i>p</i> value
PAH targeted therapy group	25			
NYHA function class, I+II/III/IV	22	3/17/2	5/13/4	0.427#
Blood gas analysis				
PaO ₂ (mmHg)	18	59.18±30.12	74.30(60.95-125.60)	0.010**
PaCO ₂ (mmHg)	18	57.46±15.93	56.18±17.01	0.746
SPO ₂ (%)	18	93.32±5.34	94.30(89.04-96.42)	0.728
Oxygenation index (mmHg)	18	177.21±84.38	286.22±165.13	0.011**
NT-proBNP(pg/ml)	18	1043.10(236.75-2697.50)	287.10(21.00-555.90)	0.035*
Echocardiography(mm)				
LA	17	27.29±4.52	26.63±5.88	0.812*
RV	19	29.56±6.83	27.81±9.08	0.436
LVDd	19	37.19±5.83	39.25±7.83	0.341
LVDs	19	23.00(21.43-24.70)	22.94±3.99	0.909
EF(%)	15	71.00(68.00-75.46)	72.80±10.61	0.760
PASP(mmHg)	12	73.67±14.51	69.42±37.08	0.681
non-PAH targeted therapy group	16			
NYHA function class I+II/III/IV	20	6/9/5	6/6/8	0.524#
Blood gas analysis				
PaO ₂ (mmHg)	16	87.48±38.57	87.23±22.63	0.950
PaCO ₂ (mmHg)	16	54.08±14.64	54.06±14.33	0.994
SPO ₂ (%)	16	93.71±4.31	94.35±3.07	0.438*
Oxygenation index (mmHg)	16	284.24±144.86	268.13±105.82	0.730*
NT-proBNP(pg/ml)	16	1039.60(178.52-1840.80)	541.80(90.81-2955.20)	0.605*
Echocardiography(mm)				

LA	14	27.50±3.25	26.07±3.99	0.169
RV	14	26.64±6.88	23.50(21.34-34.51)	0.593
LVDd	14	39.93±6.49	38.36±6.89	0.255
LVDs	14	25.46±3.97	23.46±4.93	0.110
EF(%)	14	69.00±8.60	71.42±5.92	0.649*
PASP(mmHg)		71.56±1.97	55.89±31.63	0.207*
Abbreviations: * stands for rank sum test, others are paired T test, #chi-square test, ** paired rank sum test. NYHA heart function classification: New York Heart Association class; PaO ₂ : arterial partial pressure of oxygen; PaCO ₂ : arterial partial pressure of carbon dioxide; AB: actual alkali surplus; SPO ₂ : arterial blood oxygen saturation; NT-proBNP: N-terminal brain natriuretic peptide Precursor; LA: left atrial diameter; RV: right ventricular diameter; LVDd: left ventricular end diastolic diameter; LVDs: left ventricular end systolic diameter; EF: ejection fraction; PASP: pulmonary artery systolic pressure.				

Median time to follow-up of all 49 patients in severe PH-CLD was 9 (2.0-28) months. There were 5 deaths during the follow-up period in the targeted therapy group and the median survival time was 10 (4.5-34.5) months, compared with 8 deaths in those with no targeted therapy whose median survival time was 13 (1.0-31.0) months. Estimated survival rates at 1 and 3 years in patients on targeted therapy compared to no targeted therapy were 82.82% versus 75.87% and 66.26% versus 20.23%, respectively, but there was no significant difference in survival observed those with targeted therapy and no targeted therapy($p=0.094$). Their Kaplan-Meier survival curves are shown in Figure 2.

Prognostic risk factors

According to the Nice classification system of PH^[1], the cut-off values of NT-proBNP, NYHA cardiac function classification, cardiac index (CI), and mixed venous oxygen saturation(SvO₂) are 1400pg/ml, 2.5L/min/m² and 65%, respectively. Right atrial pressure(RAP) and right ventricular pressure(RVP) determine the cut-off value by the area under the ROC curve (RAP 9.5mmHg, the area under the ROC curve is 0.610, 95%CI 0.404-0.815; RVP 27.5mmHg, the area under the ROC curve is 0.648, 95%CI 0.458-0.835).On univariate Cox regression analysis, only NT-proBNP (2.247 95%CI 0.687-7.356; $p=0.040$) and CI(HR=1.426 95%CI 0.897-2.267; $p=0.034$) were predictors of survival, while NYHA functional class, , hemodynamics, Pulmonary function tests(PFT) parameters and the use of targeted therapy were not. Table 3 shows that mean RAP (HR=16.127 95%CI 1.651-157.508 $p=0.017$) and CI(HR=1.426 95%CI 0.897-2.267; $p=0.034$)can independently predict the mortality of patients with severe pulmonary hypertension associated with lung disease on multivariate analysis.

Table 3

Univariate and multivariate COX proportional hazards analysis of various variables in predicting survival of patients with severe pulmonary hypertension in chronic lung disease.

	Univariate		multivariate	
	HR(95%CI)	<i>p</i>	HR(95%CI)	<i>p</i>
Gender	1.434(0.465-4.422)	0.531		
Age years	1.014(0.955-1.077)	0.653		
BMI(kg/m ²)	1.003(0.850-1.182)	0.976		
Chronic lung disease	0.751(0.417-1.351)	0.339	0.283(0.027-2.960)	0.292
Smoking	1.269(0.378-4.259)	0.700		
NYHA function class	2.182(0.720-6.609)	0.168	0.506(0.065-3.925)	0.514
Laboratory examination				
NT-proBNP(pg/ml)	2.247(0.687-7.356)	0.040	1.456(0.348-6.092)	0.607
Cr(umol/l)	1.004(0.985-1.024)	0.655		
BUN(mmol/l)	1.004(0.881-1.145)	0.948		
Arterial blood gas analysis (mmHg)				
PaO ₂	1.836(0.400-8.426)	0.435		
PaCO ₂	1.019(0.985-1.055)	0.279		
SPO ₂ (%)	1.902(0.599-6.041)	0.275		
PAH-targeted therapy	2.466(0.810-7.502)	0.094	0.070(0.004-1.195)	0.066
Echocardiography(mm)				
LA	1.037(0.933-1.154)	0.497		
RV	0.983(0.899-1.075)	0.706		

LVDD	1.038(0.946-1.138)	0.430		
LVDS	1.008(0.880-1.154)	0.909		
EF(%)	0.976(0.906-1.052)	0.531		
PASP(mmHg)	0.998(0.968-1.028)	0.884		
Pericardial effusion	1.683(0.507-5.590)	0.395		
Pulmonary function				
FEV1/FVC%	1.646(0.334-8.122)	0.541		
FEV1%	0.999(0.975-1.023)	0.935		
FVC%	2.014(0.405-10.031)	0.393		
DLCO%	0.983(0.878-1.100)	0.764		
Hemodynamics (mmHg)				
RAP	2.363(0.758-7.360)	0.138(9.5)	16.127(1.651-157.508)	0.017
RVP	4.547(0.958-21.579)	0.057(27.5)	1.230(0.118-12.768)	0.863
mPAP	1.011(0.954-1.071)	0.721		
CO(L/min)	0.862(0.235-3.163)	0.822(0.4)		
CI(L/min/m ²)	1.426(0.897-2.267)	0.034(0.2.5)	0.154(0.024-0.994)	0.049
PVR(wood)	0.982(0.830-1.161)	0.830		
S _v O ₂ (%)	0.957(0.910-1.006)	0.087	0.047(0.002-1.257)	0.068
Abbreviations: HR=heart rate; NYHA heart function classification: New York Heart Association class; BMI: body mass index; PaO ₂ : artery Blood oxygen partial pressure; PaCO ₂ : arterial partial pressure of carbon dioxide; AB: actual alkali excess; SPO ₂ : arterial oxygen saturation; Cr: creatinine; BUN: urea nitrogen; NT-proBNP: N-terminal pro-brain natriuretic peptide; FEV1% : Forced expiratory volume in the first second as a percentage of the predicted value; FVC%: Forced vital capacity in percentage; FEV1/FVC: Forced expiratory volume in the first second/forced vital capacity; DLCO% pre:				

Carbon monoxide diffusion as a percentage of predicted value; LA: Left atrium diameter; RV: right ventricular diameter; LVDd: left ventricular end diastolic diameter; LVDs: left ventricular end systolic diameter; EF: ejection fraction; PASP: pulmonary artery systolic pressure; mRAP: mean right atrial pressure; mRVP: mean right ventricular Pressure; mPAP: mean pulmonary artery pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SvO₂: mixed venous oxygen saturation;

Discussion

It has been shown a positive effect by using endothelin receptor antagonists, phosphodiesterase 5-inhibitors and prostacyclin analogs to prevent vascular proliferation, remodeling and dilating pulmonary arteries in PAH patients. The use of the above medications is referred to PAH targeted therapy. Current guidelines clearly recommend that PAH-targeted drugs should not be used in patients with mild pulmonary hypertension related to chronic lung diseases^[1]. This is because some studies have reported that PAH-targeted drugs may worsen gas exchange in chronic lung disease due to the inhibition of hypoxic vasoconstriction, which cause pulmonary blood flow from more seriously to less seriously affected lung segments^[21-24]. However, based on smaller case series, patients in severe PH-CLD might benefit from PAH-targeted therapy^[10,15]. Guidelines has recommended that patients with severe PH-CLD should be included in prospective clinical trials to investigating the effects of PAH-targeted therapy^[15]. Our study retrospectively analyzed the effects of PAH targeted drugs and survival in that subgroup patients to provided more effective information for guiding clinical practice. Our study shows that PAH-targeted therapy can improve the NT-proBNP, PaO₂ and oxygenation index of patients in severe PH-CLD, but it cannot improve the prognosis of the patients; cardiac index and right cardiac index is an independent risk factor predicting the prognosis of patients. Pulmonary hypertension is a common complication of CLD, especially in patients with advanced lung disease, which can reach 50%. The occurrence of pulmonary hypertension is often related to the decline of the patient's motor function and the deterioration of hypoxemia, which affects the survival rate of patients^[25-26]. On the basis of a similar degree of airflow limitation in patients with COPD, the 5-year survival rate of patients with mPAP>25mmHg decreased from 62.2% to 36.3% compared with those without elevated pulmonary artery pressure^[27], in patients with bronchiectasis, combined The blood oxygen saturation of PH patients decreased by 4-8%, and the 5-year survival rate decreased by 33.2%^[28]. Similarly, the risk of death in patients with IPF complicated by PH increased significantly. The results of the study showed that when sPAP ≤ 35 mmHg, 36-50 mmHg>50mmHg, the median survival time gradually decreased, respectively 4.8, 4.1 and 0.7 years^[29].

Changes in lung parenchymal structure caused by lung diseases can reduce pulmonary capillary bed and increase the pulmonary vascular resistance. It has been confirmed that most patients have an mPAP between 20 and 30mmHg caused by chronic lung disease^[30] and furthermore, the rate of PH progression in lung disease is normally slow. Weitzenblum *et al.*^[31] conducted a 5-year study on COPD patients, which mainly using right heart catheters to monitor the progress of pulmonary artery pressure, they found

that the average pulmonary artery pressure increased by about 0.5mmHg per year. However, a subset of patients develop severe PH that was defined as the mPAP was ≥ 35 mmHg and present with severe hypoxemia, hypercapnia, and very low CO diffusing capacity (DLCO), which progressive gas exchange abnormalities are disproportionate to ventilatory impairment. Therefore, it gave rise to the idea with “out of proportion” PH. The NICE Guidelines have suggested categorizing the disease as severe PH-CLD which hemodynamic thresholds is mPAP greater than 35 mm Hg or mPAP greater than or equal to 25 mm Hg combined with a low cardiac index (≤ 2.5 L/min/m²) [10].

Chaouat *et al.* [4] and Thabut *et al.* [5] summarized the clinical features of severe PH-CLD. All patients showed obvious exertional dyspnea, severe hypoxemia, hypocapnia and severely decreased DLCO. But patients in severe PH-CLD described by our study demonstrated grossly impaired DLCO, relatively mild airflow obstruction, hypoxemia and hypocapnia, despite similar haemodynamics. It may be because the patients in our study are not limited to restrictive lung diseases, but also include COPD, bronchiectasis and other diseases that can cause pulmonary ventilation dysfunction, and most of the patients have received oxygen therapy which can improve hypoxemia. In addition, these are only 30.61% smokers in our study. Animal experiments show that smoking can enhance the expression of pulmonary artery vascular growth factor in rats and up-regulate its downstream tyrosine kinase receptors, both can cause inflammatory vascular remodeling [32]. Changes in the pulmonary vascular bed and vascular remodeling are the main factors causing hypoxia on the basis of the same degree of airway obstruction and decreased diffusion function. Therefore, the patients in our study may differ from previous studies due to the lack of vascular changes caused by smoking.

PAH targeted therapy can improve NT-proBNP in patients with severe PH-CLD, but it can't improve NYHA function class and echocardiographic parameters. NT-proBNP is mainly secreted by the ventricles and is a powerful predictor of heart failure [33]. It is not only proved to be related to right ventricular function in patients with idiopathic pulmonary hypertension [34], but also an indicator of right heart dysfunction and can predict the survival in patients with severe PH-CLD [35]. There was no significant difference in age and renal function between the two groups in our study. NT-proBNP only reflects the patient's cardiac function status. Therefore, we hypothesized that PAH targeted therapy can improve the patient's right heart function, but due to the short follow-up time, the cardiac structural indicators measured by echocardiography in the early follow-up period will not change significantly. Moreover, emphysema and lung lesions reduce the quality of ultrasound imaging, thereby reducing the sensitivity and specificity of echocardiography [36], and it is difficult to find early changes in the heart structure. Rechecking the right heart catheterization every 3-6 months to early assess the patient's efficacy is of guiding significance for timely adjustment and formulation of individualized treatment plans.

Our research shows that PAH-targeted drugs can improve PaO₂ and oxygenation index in arterial blood gases in patients with severe PH-CLD. Different from previous reports that PAH-targeted drugs worsen their oxygenation or do not affect PaO₂ [15,37] may therefore account for the degree of pulmonary vascular remodeling, types of PAH targeted drugs and approach of administration. One of the main driving forces

behind the development of pulmonary hypertension in the context of underlying lung disease is pulmonary arterial vasoconstriction caused by hypoxia. Many studies have shown a close relationship between the degree of alveolar hypoxia and mPAP or pulmonary vascular resistance^[5,6]. But several studies have found that reversing hypoxemia with oxygen therapy does not completely reverse pulmonary hypertension in COPD patients^[38-39]. It is obvious that hypoxia may not be the only mechanism leads to the development of PH-CLD. Furthermore, pathologic studies in subjects with lung disease have identified remodeling of the pulmonary vessels and it will aggravated as the disease progresses^[40-41]. Hypoxemia in these patients may be due to a significant decrease in circulatory reserve function rather than impaired respiratory function^[42] so that PAH targeted therapy can improve patients' pulmonary vascular remodeling to improve hypoxemia. On the other hand, in our study, only 5-phosphodiesterase inhibitors and prostacyclin analogs were used in patients and both of them may selectively and preferentially expand the pulmonary blood vessels in the lighter lung area. It has been reported^[43] that phosphodiesterase 5 inhibitor and inhaled iloprost, treprostinil, or nitric oxide in advanced lung disease may improve patients' arterial oxygenation, DLCO, dyspnea and quality of life because of their mode of distribution. In contrast, other studies have found that endothelin receptor inhibitors can worsen the gas exchange process of patients with lung diseases by changing the sensitivity of the carotid body to hypoxia^[44].

Very few controlled trials have evaluated the impact of targeted therapy on survival. Lange *et al.*^[45] compared patients who received PAH therapy with a control cohort which received no PAH therapy and they found the survival was significantly better in patients who received PAH therapy, while we found PAH targeted therapy cannot improve the prognosis of patients with severe PH. This may be explained that their study included patients with mild-to-moderate PH in survival analysis and only severe PH patients in our study. Direct comparison with our cohort is therefore not possible. But undeniably, this difference may also be caused by the small sample size and short follow-up time of this study. Our study found although the patients who received PAH therapy have worse right heart function and oxygenation, and their condition is relatively more serious, the changes in NYHA functional class and their survival seem to be significantly better, which suggests that PAH-targeted drug therapy has a certain effect. However, we have not yet fully clarified the efficacy of PAH-targeted therapy in patients with severe PH-CLD, which may be reflected in the quality of life and symptoms. Further research is required to investigate the function of PAH-targeted drugs.

As in previous studies^[35], right atrial pressure and cardiac index turned out to be predictors of survival and both of them were derived from right heart catheterisation. This reaffirms existing recommendations to obtain invasive haemodynamic measurements at the time of diagnosis. Moreover, cardiac index and right atrial pressure are indicators of right ventricular dysfunction. Right ventricular dysfunction is common in patients with lung disease, and it is more obvious with pulmonary hypertension^[46]. In a cohort study of COPD patients, Freixa *et al.*^[46] reported that about 30% of patients with echocardiographic enlargement of the right ventricle, and evidence of chronic cor pulmonale was found in more than 40% of COPD patients^[47]. Right ventricular hypertrophy was observed in autopsy of 2/3 of

patients with chronic bronchitis^[48] and 1/3 of patients with emphysema^[44]. When mPAP>25mmHg indicates that at least 50% of the pulmonary vascular bed has been damaged, which has a significant impact on right ventricular function^[49]. Sato *et al.*^[50] used cardiac magnetic resonance to assess the structure and function of the right heart in patients with pulmonary hypertension, and they found that the occurrence of PH would lead to right ventricular hypertrophy, a decrease in reserve function, and a decrease in right ventricular ejection fraction. Decreased right ventricular function leads to decreased CI and increased right atrial pressure. It is failure of the RV that leads to increased morbidity and mortality in PH. Our study demonstrates that right atrial pressure and CI predicts survival on multivariate analysis. This may reflect that improving patient RV function will become one of the targets of future treatment in severe PH-CLD.

Insufficient

Our research has several limitations. First, most of the patients are seriously ill and suffered from cardiac insufficiency and decreased exercise capacity, so that they can't complete the 6-minute walking distance test, which results in the lack of this objective indicator for evaluating patients' activity endurance; Second, the number of cases is small, and no further subgroup analysis can be done to explore whether the effects of PAH targeted drugs on different lung diseases are consistent; Third, our study is a retrospective, single-center study, which may have caused selection bias. The specific role of PAH targeted therapy needs further study.

Conclusion

PAH targeted therapy may have benefit in patients with severe PH-CLD and did not worsen their hypoxemia. But it can't improve their prognosis. Right ventricular function might have an important impact on the survival of patients.

Abbreviations

NYHA heart function classification: New York Heart Association class; PAH: pulmonary arterial hypertension; BMI: body mass index; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PaO₂: artery Blood oxygen partial pressure; PaCO₂: arterial partial pressure of carbon dioxide; AB: actual alkali excess; SPO₂: arterial oxygen saturation; Cr: creatinine; BUN: urea nitrogen; NT-proBNP: N-terminal pro-brain natriuretic peptide; FEV1% : Forced expiratory volume in the first second as a percentage of the predicted value; FVC%: Forced vital capacity in percentage; FEV1/FVC: Forced expiratory volume in the first second/forced vital capacity; DLCO% pre: Carbon monoxide diffusion as a percentage of predicted value; LA: Left atrium diameter; RV: right ventricular diameter; LVDd: left ventricular end diastolic diameter; LVDs: left ventricular end systolic diameter; EF: ejection fraction; PASP: pulmonary artery systolic pressure; mRAP: mean right atrial pressure; mRVP: mean right ventricular

Pressure; mPAP: mean pulmonary artery pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SvO₂: mixed venous oxygen saturation; PDE-5: type 5 phosphodiesterase inhibitor.

Declarations

Availability of data and materials

Data analyzed in the current study are not publicly available. They may be made available from the corresponding authors upon reasonable request.

Acknowledgements

We thank all the researchers in our team and thank all patients and their families involved in the study.

Funding

No funding.

Author Contributions

Jie-Ying Li, Sun Zhang and Wen-Liang Guo contributed to the conception and design of the work, to data analysis and interpretation, and to the drafting and substantial revision of the work. Jie-Ying Li, Sun Zhang and Jie-Long Lin have made contribution to acquisition of data. Chun-Li Liu and Cheng Hong revised the manuscript. All authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (approval number: IRB:201716012).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC / ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)[J]. *Eur Heart J*, 2016,37(1): 67-119. doi: 10.1093/eurheartj/ehv317. Epub 2015 Aug 29.
2. Pulmonary Vascular Disease Group of Cardiovascular Branch of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiovascular Disease. Chinese Guidelines for Diagnosis and Treatment of Pulmonary Hypertension 2018[J]. *Chinese Journal of Cardiovascular Disease*, 2018, 46(12):933- 964. doi: 10.3760/cma.j.issn.0253-3758.2018.12.006
3. Oswald-Mammosser M, Weitzenblum E, Quoix E, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy[J]. Importance of pulmonary artery pressure. *Chest* 1995; 107: 1193–1198. doi: 10.1378/chest.107.5.1193
4. Chaouat A, Bugnet AS, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease[J]. *Am J Respir Crit Care Med* 2005; 172: 189–194. doi 10.1378/chest.107.5.1193
5. Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation[J]. *Chest* 2005; 127: 1531–1536. doi: 10.1378/chest.127.5.1531.
6. Scharf SM, Iqbal M, Keller C, et al. Hemodynamic characterization of patients with severe emphysema[J]. *Am J Respir Crit Care Med* 2002; 166: 314–322. doi: 10.1164/rccm.2107027.
7. Mejía M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension[J]. *Chest* 2009; 136: 10–15. doi: 10.1378/chest.08-2306. Epub 2009 Feb 18.
8. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognized entity[J]. *Eur Respir J* 2005; 26: 586–593. doi: 10.1183/09031936.05.00021005.
9. Andersen KH, Iversen M, Kjaergaard J, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease[J]. *J Heart Lung Transplant*. 2012;31(4):373–80. doi: 10.1016/j.healun.2011.11.020. Epub 2012 Jan 9.
10. Seeger W, Adir Y, Barberà, Joan Albert, et al. Pulmonary Hypertension in Chronic Lung Diseases[J]. *Journal of the American College of Cardiology*, 2013, 62(25): D109-D116. doi: 10.1016/j.jacc.2013.10.036.
11. Rosenkranz Stephan, Lang Irene M, Blindt Rüdiger et al. Pulmonary hypertension associated with left heart disease: Updated Recommendations of the Cologne Consensus Conference 2018[J]. *Int. J. Cardiol.*, 2018, null: 53-62. doi: 10.1016/j.ijcard.2018.08.080.
12. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-

- blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117(23):3010-3019. doi: 10.1161/CIRCULATIONAHA.107.742510. Epub 2008 May 27.
13. Galie, N. Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 119, 2894–2903 (2009). doi: 10.1161/CIRCULATIONAHA.108.839274. Epub 2009 May 26.
 14. Sitbon, O. Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N. Engl. J. Med.* 373, 2522–2533 (2015). doi: 10.1056/NEJMoa1503184.
 15. Hoeper MM, Andreas S, Bastian A, et al. Pulmonary hypertension due to chronic lung disease: updated recommendations of the Cologne Consensus Conference 2011. *Int J Cardiol* 2011;154(Suppl):45–53. doi: 10.1016/S0167-5273(11)70492-2.
 16. Raghu G, Million-Rousseau R, Morganti A, et al. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *Eur Respir J.* 2013;42:1622–32. doi: 10.1183/09031936.00104612.
 17. Valerio G, Bracciale P, Grazia DA. Effect of bosentan upon pulmonary hypertension in chronic obstructive pulmonary disease. *Ther Adv Respir Dis.* 2009;3:15–21. doi: 10.1177/1753465808103499.
 18. Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet.* 2017;389(10082):1931-1940. doi:10.1016/S0140-6736(17)31222-9.
 19. Hariri LP, Smith ML, Mino-Kenudson M, et al. Pulmonary Pathology Society Perspective on the 2018 American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society Idiopathic Pulmonary Fibrosis Clinical Practice Guidelines. *Ann Am Thorac Soc.* 2020;17(5):550-554. doi: 10.1513/AnnalsATS.201910-801PS.
 20. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J.* 2017;50(3):1700629. Published 2017 Sep 9. doi: 10.1183/13993003.00629-2017.
 21. Kataoka M, Satoh T, Manabe T, et al. Oral sildenafil improves primary pulmonary hypertension refractory to epoprostenol [J]. *Circ. J.* 2005; 69: 461–5. doi: 10.1253/circj.69.461.
 22. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension[J]. *Ann. Intern. Med.* 2002; 136: 515–22. doi: 10.7326/0003-4819-136-7-200204020-00008.
 23. Hoeper MM, Faulenbach C, Golpon H, et al. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension[J]. *Eur. Respir. J.* 2004; 24: 1007–10. doi: 10.1183/09031936.04.00051104.
 24. Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study[J]. *Am. J. Respir. Crit. Care Med.* 2005; 171:1292–7. doi: 10.1164/rccm.200410-1411OC.
 25. Cuttica MJ, Kalhan R, Shlobin OA, et al (2010) Categorization and impact of pulmonary hypertension in patients with advanced COPD[J]. *Respir Med* 104(12):1877–1882. doi:

- 10.1016/j.rmed.2010.05.009.
26. Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis[J]. *Chest* 129(3):746–752. doi: 10.1378/chest.129.3.746.
 27. Barberà, Joan Albert, Blanco I. Management of Pulmonary Hypertension in Patients with Chronic Lung Disease[J]. *Current Hypertension Reports*, 2015, 17(8):62. doi: 10.1007/s11906-015-0574-9.
 28. Öcal S, Portakal O, Öcal A, et al. Factors associated with pulmonary hypertension and long-term survival in bronchiectasis subjects[J]. *Respiratory Medicine*, 2016, 119:109-114. doi: 10.1016/j.rmed.2016.08.027.
 29. Nadrous H F, Pellikka PA, Krow M, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis[J]. *Chest* 2005;128:2393-2399. doi: 10.1378/chest.128.4.2393.
 30. Hervé Mal. Prevalence and diagnosis of severe pulmonary hypertension in patients with chronic obstructive pulmonary disease[J]. *Current opinion in pulmonary medicine*, 2007, 13(2):114-119. doi: 10.1097/MCP.0b013e32801d217f.
 31. Weitzenblum E, Sautegeau A, Ehrhart M, et al. Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease[J]. *Am Rev Respir Dis* 1984; 130:993–998. doi: 10.1164/arrd.1984.130.6.993.
 32. Geiger R, Berger R M F, Hess J, et al. Enhanced expression of vascular endothelial growth factor in pulmonary plexogenic arteriopathy due to congenital heart disease[J]. *Journal of Pathology*, 2000, 191(2):202-207. doi: 10.1002/(SICI)1096-9896(200006)191:2<202::AID-PATH608>3.0.CO;2-D.
 33. Ponikowski P, Voors A A, Anker S D, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure[J]. *European Heart Journal*, 2016, 18(8):2129. doi: 10.1093/eurheartj/ehw128.
 34. Blyth KG, Groenning BA, Mark PB, et al. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension[J]. *Eur Respir J* 2007; 29: 737–744. doi: 10.1183/09031936.00095606.
 35. Brewis M J, Church A C, Johnson M K, et al. Severe pulmonary hypertension in lung disease: Phenotypes and response to treatment[J]. *European Respiratory Journal*, 2015, 46(5). doi: 10.1183/13993003.02307-2014.
 36. Brennan JM, Blair JE, Goonewardena S, et al. Reappraisal of the use of inferior vena cava for estimating right atrial pressure. *J. Am. Soc. Echocardiogr.* 2007; 20: 857–61. doi: 10.1016/j.echo.2007.01.005.
 37. Vitulo P, Stanziola A, Confalonieri M, et al. Sildenafil in severe pulmonary hypertension associated with chronic obstructive pulmonary disease: A randomized controlled multicenter clinical trial[J]. *J Heart Lung Transplant* 2016.2016.04.010. doi: 10.1016/j.healun.2016.04.010.
 38. Timms RM, Khaja FU, Williams GW. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease[J]. *Ann Intern Med* 1985; 102: 29–36. doi: 10.7326/0003-4819-102-1-29.

39. Ghofrani HA, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension[J]. *Ann. Intern. Med.* 2002; 136: 515–22. doi: 10.7326/0003-4819-136-7-200204020-00008.
40. Wright JL, Petty T, Thurlbeck WM (1992) Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial[J]. *Lung* 170(2):109–124. doi: 10.1007/BF00175982.
41. Magee F, Wright JL, Wiggs BR, et al. Pulmonary vascular structure and function in chronic obstructive pulmonary disease[J]. *Thorax* 43(3):183–189. doi: 10.1136/thx.43.3.183.
42. Santos S, Peinado VI, Ramirez J, et al. Characterization of pulmonary vascular remodelling in smokers and patients with mild COPD[J]. *Eur Respir J* 19(4):632–638. doi: 10.1183/09031936.02.00245902.
43. Scott, K W. A clinicopathological study of fatal chronic airways obstruction[J]. *Thorax*, 1976, 31(6):693-701. doi: 10.1136/thx.31.6.693.
44. Leopold, J. G, Gough, J. The Centrilobular Form of Hypertrophic Emphysema and its Relation to Chronic Bronchitis[J]. *Thorax*, 12(3):219-235. doi: 10.1136/thx.12.3.219.
45. Lange Tobias J, Baron Miriam, Seiler, Isabella, et al. Outcome of patients with severe PH due to lung disease with and without targeted therapy[J]. *Cardiovasc Ther*, 2014, 32: 202-8. doi: 10.1111/1755-5922.12084.
46. Freixa X, Portillo K, Pare C, et al. Echocardiographic abnormalities in patients with COPD at their first hospital admission[J]. *European Respiratory Journal*, 2013, 41(4):784-791. doi: 10.1183/09031936.00222511.
47. Wrobel JP, Thompson BR, Stuart-Andrews CR, et al. Intermittent positive pressure ventilation increases diastolic pulmonary arterial pressure in advanced COPD. *Heart Lung*. 2015;44(1):50-56. doi:10.1016/j.hrtlng.2014.10.006
48. Scott, K W. A clinicopathological study of fatal chronic airways obstruction[J]. *Thorax*, 1976, 31(6):693-701. doi: 10.1136/thx.31.6.693.
49. Hilde J M, Skjorten I, Grøtta O J, et al. Right ventricular dysfunction and remodeling in chronic obstructive pulmonary disease without pulmonary hypertension[J]. *J Am. Coll. Cardiol.*, 2013, 62: 1103-1111. doi: 10.1016/j.jacc.2013.04.091.
50. Sato T, Tsujino I, Oyama-Manabe N, et al. Right atrial volume and phasic function in pulmonary hypertension[J]. *International Journal of Cardiology*, 2013, 168(1):420-426. doi: 10.1016/j.ijcard.2012.09.133.

Figures

Figure 1

Changes of NYHA function class before and after follow-up in the two groups Note: steady: stable cardiac function; improved: improved cardiac function; deteriorated: deteriorated cardiac function

Figure 2

Survival curve of PAH targeted drug therapy group and non-PAH targeted drug therapy group (K-M method)