

# Comprehensive Exercise Capacity and Quality of Life Assessments Predict Mortality in Patients with Pulmonary Arterial Hypertension

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**Background:** The 6-minute walk test (6MWT) and cardiopulmonary exercise test (CPET) are exercise tests associated with physical function, quality of life and hemodynamic data in patients with pulmonary arterial hypertension (PAH). This study was conducted to assess correlations between exercise capacity, quality of life and disease functional classification, and to analyze the value of comprehensive assessments in predicting mortality in patients with PAH.

**Methods:** Fifty-four patients with PAH were enrolled. Comprehensive assessments including exercise capacity evaluated using the 6MWT and CPET, and health-related quality of life evaluated using the Short Form 36 (SF-36) questionnaire were performed in all participants. The patients were followed for 2 years with the end point of mortality.

**Results:** The survivors had a longer 6-minute walking distance, higher peak oxygen uptake and higher physical component score of the SF-36 than the non-survivors. In addition, exercise capacity combined with SF-36 predicted 2-year mortality in the patients with PAH. The patients with lower peak oxygen uptake (peak  $\text{VO}_2 < 11.03$  mL/kg/min) and lower physical component score (score  $< 44.54$ ) had a higher mortality rate than those with a higher peak  $\text{VO}_2$  and higher physical component score (adjusted hazard ratio = 19.95,  $p = 0.011$ ).

**Conclusions:** Comprehensive assessments of exercise capacity and quality of life can be used to predict 2-year mortality in patients with PAH.

**Key Words:** Comprehensive assessment • Exercise capacity • Pulmonary arterial hypertension • Quality of life

## INTRODUCTION

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Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure  $\geq 25$  mmHg, pulmonary artery wedge pressure  $\leq 15$  mmHg, and pulmonary vascular resistance  $> 3$  WU.<sup>1-3</sup> The etiologies of PAH are classified as idiopathic or non-idiopathic, with idiopathic PAH being rare, and non-idiopathic PAH being related to connective tissue diseases, congenital heart diseases, drugs, infectious diseases and other factors.<sup>4</sup> Several noninvasive parameters have been found to be prognostic predictors, including World Health Organization functional class (WHO FC), echocardiographic findings and physical functional evaluations.<sup>4-8</sup>

Exercise capacity is a useful tool to determine disease severity, and it has also been associated with the quality of life and hemodynamic measures.<sup>2-4</sup> The 6-minute walk test (6MWT) and cardiopulmonary exercise testing (CPET) are commonly used tools to objectively define exercise capacity. In patients with PAH, many studies have investigated correlations between exercise capacity and disease-related parameters including hemodynamic measures and health-related quality of life (HRQoL).<sup>6,9-11</sup> Previous studies have compared the characteristics and correlation of these two tests.<sup>7,12</sup> Currently, the 6MWT is more commonly used in the clinical evaluation and follow-up of the therapeutic effect for PAH patients due to its simplicity, negligible cost and high applicability to activities of daily living.<sup>13</sup> Compared to the 6MWT, CPET is thought to be more stressful for patients with a poor clinical condition.<sup>14</sup> However, there is still a lack of clear evidence comparing these two exercise tests in predicting major clinical outcomes.

The purposes of this study were to compare the performance in exercise capacity and quality of life between PAH survivors and non-survivors, to study correlations between hemodynamics, exercise capacity, and quality of life, and to analyze the value of comprehensive assessments in predicting mortality among patients with PAH.

## METHODS

### Participants

Patients with PAH referred from the out-patient clinic of the Department of Cardiology for CPET between January 2010 and December 2013 were enrolled consecutively, and followed for 2 years after exercise testing or until they died, which was identified from medical records and confirmed by cardiologists. The participants who died were defined as having an event, and those who survived were defined as being censored. The criterion of PAH for enrollment was a systolic pulmonary arterial pressure (SPAP) > 46 mmHg by echocardiography, confirmed by right heart catheterization in 56%.<sup>15</sup> Patients with pulmonary hypertension related to left-sided heart diseases were excluded. All patients with PAH received sequential therapy. All of the PAH patients were followed up every month. If their condition worsened,

add-on PAH-specific drugs were prescribed. The study was approved by the Institutional Review Board of our medical center [IRB number: 15-CT7-05 (150423-1)]. All participants were given thorough explanations of the study procedure, and written informed consent was obtained before enrollment.

### Exercise capacity determination

All participants were evaluated for exercise capacity using the 6MWT and CPET. The 6MWT was performed on a level surface with a self-determined speed according to a standardized protocol, and the total distance walked within 6 minutes was recorded.<sup>16</sup> The participants underwent CPET using an upright bicycle ergometer to evaluate the oxygen uptake at anaerobic threshold (ATVO<sub>2</sub>) and at peak exercise (peak VO<sub>2</sub>). CPET was evaluated by open circuit spirometry (Metamax 3B, Cortex Biophysik Co., Germany). Exercise testing began with an intensity of 0 W workload for a 1-minute warm-up, followed by incremental loading using a ramp protocol (10 W/min). Blood pressure was measured every two minutes, and 12-lead electrocardiography was monitored continuously during exercise testing. The end-point of CPET was determined according to the criteria of the American College of Sports Medicine. A physician and a physical therapist conducted the exercise testing according to the established guidelines. All patients completed the CPET smoothly.

### Health-related quality of life

HRQoL was determined using the Chinese version of the Short Form 36 questionnaire (SF-36), which comprised of a physical component score (PCS) and mental component (MCS) score.<sup>17</sup> The questionnaire was administered orally to all of the patients by the same therapist. The SF-36 was used to measure the following eight domains: physical functioning (PF), role limitations due to physical problems (RP), body pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The PCS was composed of PF, RP, BP and GH scores, while the MCS was composed of VT, SF, RE and MH scores.

### Hemodynamic measures

Hemodynamic measures of right heart catheterization including SPAP, mean pulmonary artery pressure,

pulmonary capillary wedge pressure, mean right atrial pressure, cardiac output and pulmonary vascular resistance were recorded. Standard echocardiography was performed using an ultrasound system (Sonos 7500; Philips Medical Systems, Andover, MA, USA) with an S3 phased-array transducer. Echocardiographic studies were performed following the recommendations of the American Society of Echocardiography, and estimated SPAP was calculated based on the simplified Bernoulli equation with peak tricuspid regurgitation velocity, while right atrial pressure was estimated according to the size and collapsibility of the inferior vena cava.<sup>18,19</sup>

### Statistical analysis

The Student's *t*-test was used to compare differences in continuous variables between the PAH survivors and non-survivors, and Fisher's exact test was used to compare between-group differences in categorical variables. Pearson's correlation was used to compare differences between continuous variables. Receiver operating characteristic (ROC) curves were plotted, and the optimal threshold values for exercise capacity measures and scores of the SF-36 questionnaire to predict mortality were determined by selecting the point at which the maximum summed value of sensitivity and specificity was achieved. Kaplan-Meier survival analysis and the log-rank test were used to analyze differences in mortality between groups. Univariate and multivariate Cox regression analyses were used to estimate the hazard ratio (HR) of potential prognostic factors. Multivariate Cox regression analysis was performed with adjustments for age, gender, WHO FC, and treatment type in different models. All statistical analyses were performed using SPSS version 19. A two-tailed *p* value of less than 0.05 was considered to be statistically significant. For multiple testing-adjusted corrections, the threshold *p*-values were computed using the step-down Bonferroni method to determine statistical significance.

## RESULTS

A total of 54 patients were included, with 3 males and 51 females. All of the patients were classified as having Group 1 PAH according to the WHO classification of pulmonary hypertension. Twenty-five patients were

classified as WHO FC II, 24 as WHO FC III, and 5 as WHO FC IV. The demographic and clinical data, hemodynamic measures and exercise capacity parameters are shown in Table 1. The hemodynamic measures of right heart catheterization were collected from 30 patients.

The demographic and clinical data, hemodynamic measures and exercise capacity parameters between the PAH survivors and non-survivors are also listed in Table 1. The PAH survivors had a lower WHO FC ( $p < 0.001$ ), lower SPAP ( $p = 0.001$ ), longer 6MWT distance ( $p = 0.042$ ), higher peak  $VO_2$  ( $p < 0.001$ ), higher  $ATVO_2$  ( $p = 0.001$ ) and higher PCS ( $p = 0.038$ ) than the PAH non-survivors. Further comparisons of the eight domains of the SF-36 revealed significantly higher scores of the physical functioning domain in the PAH survivors (Figure 1).

Table 2 shows the correlations between exercise capacity, hemodynamics and SF-36 scores. The multiple testing-adjusted corrected *p*-values were calculated using the step-down Bonferroni method to set a threshold of  $p < 0.0007$  ( $0.05/67$ ) as statistically significant. The 6MWT was significantly positively correlated with peak  $VO_2$  and  $ATVO_2$  ( $r = 0.64$ ,  $p < 0.0001$ ;  $r = 0.54$ ,  $p < 0.0001$ ). Oxygen uptake was also significantly positively correlated with PCS ( $r = 0.60$ ,  $p < 0.0001$  for peak  $VO_2$ ;  $r = 0.58$ ,  $p < 0.0001$  for  $ATVO_2$ ), but not MCS or SF-36 total scores. There was no significant correlation between hemodynamics and exercise capacity.

For predicting two-year mortality, the ROC curves of 6MWT, peak  $VO_2$  and SF-36 PCS, MCS, total scores were analyzed. The area under the curve (AUC) values for peak  $VO_2$  and 6MWT were 0.857 and 0.672, respectively; the AUC values for SF-36 PCS, MCS and total score were 0.666, 0.462 and 0.576, respectively. The ROC curves of those with an AUC  $> 0.6$ , including peak  $VO_2$ , 6MWT and PCS, are shown in Figure 2. The optimal cut-off points for 6MWT, peak  $VO_2$ , and PCS in predicting 2-year mortality were determined by ROC curve analysis. The cut-off points were 331 m for the 6MWT (sensitivity = 0.732, specificity = 0.615), 11.03 mL/kg/min for peak  $VO_2$  (sensitivity = 0.683, specificity = 0.923), and 44.54 for PCS (sensitivity = 0.732, specificity = 0.692). The combined C-statistic for 6MWT, peak  $VO_2$  and PCS was 0.861 [95% confidence interval (CI) 0.752 to 0.971], which was higher than the individual C-statistic for 6MWT (0.672, 95% CI 0.494 to 0.849), peak  $VO_2$  (0.857, 95% CI 0.743 to 0.972) and PCS (0.666, 95% CI 0.508 to 0.824); however, the

**Table 1.** Demographics, baseline characteristics and exercise capacity in survivors and non-survivors of pulmonary hypertension

	All participants (N = 54)		Survivors (N = 41)		Non-survivors (N = 13)		p-value <sup>†</sup>
	N (%)	Mean ± SD	N (%)	Mean ± SD	N (%)	Mean ± SD	
Age (year)		43.09 ± 15.86		43.80 ± 16.19		40.85 ± 15.18	0.563
Height (cm)		155.53 ± 8.04		155.14 ± 8.41		156.74 ± 6.93	0.538
Weight (kg)		52.73 ± 14.43		52.36 ± 9.92		53.89 ± 24.27	0.743
BMI (kg/m <sup>2</sup> )		22.03 ± 4.74		22.18 ± 3.54		21.54 ± 7.55	0.674
Body fat (%)		28.11 ± 6.87		28.70 ± 6.52		26.24 ± 7.89	0.284
Gender							1.000
Male	3 (5.6)		2 (4.9)		1 (7.7)		
Female	51 (94.4)		39 (95.1)		12 (92.3)		
WHO FC							< 0.001
II	25 (46.3)		21 (51.2)		4 (30.8)		
III	24 (44.4)		20 (48.8)		4 (30.8)		
IV	5 (9.3)		0 (0)		5 (38.4)		
WHO Classification of PAH							
Group 1							
Idiopathic PAH	12 (22.2)		10 (24.4)		2 (15.4)		0.644
PAH associated with CTD	32 (59.3)		24 (58.5)		8 (61.5)		
PAH associated with CHD	10 (18.5)		7 (17.1)		3 (23.1)		
PAH-specific drug							
None	35 (64.8)		26 (63.4)		9 (69.2)		0.910
Endothelin receptor antagonist	15 (27.8)		12 (29.3)		3 (23.1)		
PDE5 inhibitor	4 (7.4)		3 (7.3)		1 (7.7)		
Echocardiographic parameters							
SPAP <sup>#</sup> (mmHg)		73.72 ± 36.08		60.13 ± 27.96		93.08 ± 26.41	0.001
LVEF (%)		64.11 ± 11.16		64.43 ± 11.04		63.70 ± 12.66	0.867
Cardiac catheterization parameters*							
CO (L/min)		3.42 ± 1.71		3.53 ± 2.01		2.87 ± 0.95	0.384
mPAP (mmHg)		50.75 ± 20.24		48.05 ± 18.08		59.80 ± 23.76	0.137
mRAP (mmHg)		7.96 ± 5.00		7.74 ± 4.68		8.56 ± 5.61	0.688
PCWP (mmHg)		12.93 ± 8.06		11.44 ± 4.57		15.80 ± 11.91	0.291
PVR (dyne/sec/cm <sup>2</sup> )		1145.41 ± 721.09		1135.92 ± 827.84		1471.97 ± 821.46	0.352
RVEF (%)		32.63 ± 11.01		33.07 ± 11.04		30.90 ± 11.62	0.648
Exercise capacity							
6MWT (m)		346.04 ± 90.16		360.04 ± 78.91		301.89 ± 111.20	0.042
ATVO <sub>2</sub> (mL/min/kg)		8.99 ± 2.78		9.70 ± 2.64		6.76 ± 1.93	0.001
HR <sub>AT</sub> (beats/min)		106.76 ± 14.71		106.00 ± 14.02		109.15 ± 17.09	0.506
Peak VO <sub>2</sub> (mL/min/kg)		12.06 ± 3.95		13.16 ± 3.64		8.56 ± 2.71	< 0.001
Peak heart rate (beats/min)		126.70 ± 20.72		127.46 ± 20.59		124.31 ± 21.79	0.637
Peak VE (L/min)		28.33 ± 11.31		29.14 ± 11.83		25.75 ± 9.45	0.350
HRQoL							
SF-36		53.38 ± 18.48		54.69 ± 17.43		49.27 ± 21.74	0.363
PCS		50.53 ± 9.23		51.99 ± 9.64		45.93 ± 6.01	0.038
MCS		49.94 ± 10.03		49.59 ± 9.65		51.03 ± 11.48	0.656

ATVO<sub>2</sub>, oxygen uptake at anaerobic threshold; BMI, body mass index; CHD, congenital heart diseases; CO, cardiac output; CTD, connective tissue diseases; HRQoL, health-related quality of life; HR<sub>AT</sub>, heart rate at anaerobic threshold; LVEF, left ventricular ejection fraction; MCS, mental component score; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PCS, physical component score; PCWP, pulmonary capillary wedge pressure; PDE5 inhibitor, phosphodiesterase type 5 inhibitor; peak VO<sub>2</sub>, oxygen uptake at peak exercise; PVR, pulmonary vascular resistance; RVEF, right ventricular ejection fraction; SD, standard deviation; SF-36, short form-36; SPAP, estimate systolic pulmonary arterial pressure; VE, minute ventilation; WHO FC, world health organization functional classification; 6MWT, six-minute walk test.

\* Cardiac catheterization parameters were obtained from a subgroup of patients who received right heart catheterization (N = 30).

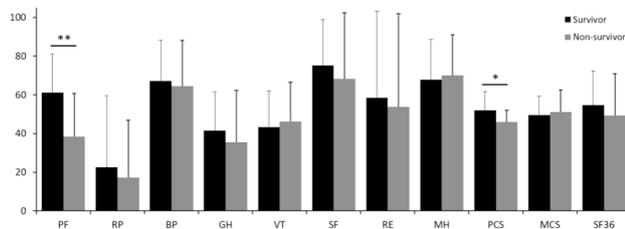
<sup>#</sup> SPAP was obtained by echocardiography with calculation from simplified Bernoulli equation. <sup>†</sup> p-value compared between PAH survivors and non-survivors, using student's *t* test.

difference was not statistically significant for the existence of overlapping CIs.

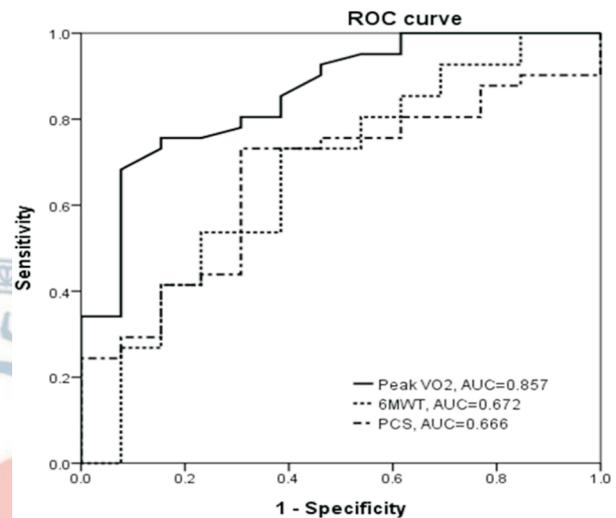
The 2-year mortality rate of our study group was 24.1%. Kaplan-Meier analysis and the log-rank test for 2-year mortality based on peak VO<sub>2</sub>, 6MWT, and PCS of SF-36 according to the above cut-off points are illustrated in Figure 3. The log-rank test revealed a statistically significant difference between the survival rates of the PAH patients with high and low peak VO<sub>2</sub> (p < 0.001). The mean survival time was 712 days for those with a high peak VO<sub>2</sub>, and 485 days for those with a low peak VO<sub>2</sub>. Similarly, the patients with a longer distance on the 6MWT had a significantly higher rate of survival compared to those with a short distance on the 6MWT (mean

survival times of 656 days and 519 days, respectively, p = 0.022). The patients with a higher PCS also had a significantly higher rate of survival compared to those with a lower PCS (p = 0.005).

Univariate Cox regression analysis for 6MWT, peak VO<sub>2</sub> and PCS showed a statistically significant increase in the HR of 2-year mortality (for 6MWT < 331 m vs. 6MWT ≥ 331 m, HR = 3.40, p = 0.032; for peak VO<sub>2</sub> < 11.03



**Figure 1.** Scores of the eight domains of Short-Form 36 between PAH survivors and non-survivors. BP, bodily pain; GH, general health; MCS, mental component score; MH, and mental health; PCS, physical component score; PF, physical functioning; RE, role limitations due to emotional problems; RP, role limitations due to physical problems; SF, social functioning; SF36, total score; VT, vitality.

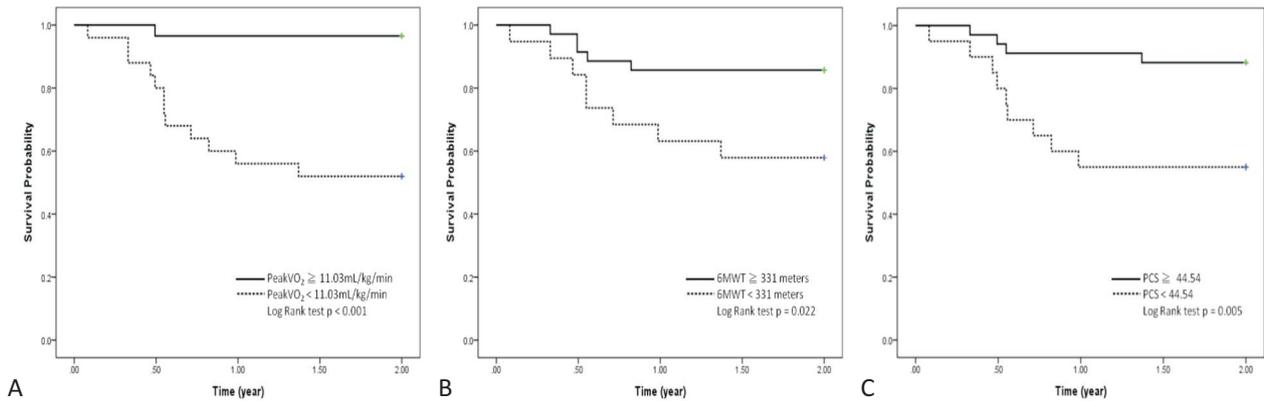


**Figure 2.** Receiver operating characteristic curves and corresponding values of area under curve of peak oxygen uptake, 6-minute walk test and physical component score of short-form 36 for discriminating PAH patients with or without mortality.

**Table 2.** Correlation between exercise capacity, hemodynamics and SF-36

	6MWT	Peak VO <sub>2</sub>	ATVO <sub>2</sub>	PCS	MCS	SF36	CO <sup>#</sup>	mPAP <sup>#</sup>	PVR <sup>#</sup>	mRAP <sup>#</sup>	RVSP <sup>#</sup>	PCWP <sup>#</sup>
6MWT	1	0.64*	0.54*	0.34	0.06	0.26	0.33	-0.13	-0.19	-0.28	-0.04	-0.09
Peak VO <sub>2</sub>		1	0.92*	0.60*	0.03	0.37	0.60	-0.20	-0.28	-0.30	-0.19	-0.21
ATVO <sub>2</sub>			1	0.58*	0.03	0.36	0.59	-0.16	-0.28	-0.29	-0.20	-0.28
PCS				1	-0.05	0.62*	0.24	0.01	0.15	-0.20	-0.02	-0.05
MCS					1	0.70*	-0.04	-0.02	0.13	-0.02	0.08	0.22
SF36						1	0.05	-0.05	0.23	-0.17	-0.003	0.11
CO							1	-0.37	-0.67*	-0.12	-0.49	0.25
mPAP								1	0.80*	0.05	0.92*	-0.220
PVR									1	0.26	0.83*	-0.30
mRAP										1	0.07	0.18
RVSP											1	-0.23
PCWP												1

\* The multiple testing-adjusted corrections p-values were computed by stepdown Bonferroni to set a threshold of p < 0.0007 as statistically significant. <sup>#</sup> Hemodynamic data was from a subgroup of patients who received right heart catheterization (N = 30). ATVO<sub>2</sub>, oxygen uptake at anaerobic threshold; CO, cardiac output; MCS, mental component score; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PCS, physical component score; PCWP, pulmonary capillary wedge pressure; peak VO<sub>2</sub>, oxygen uptake at peak exercise; PVR, pulmonary vascular resistance; RVSP, right ventricular systolic pressure; SF-36, short form-36; 6MWT, six-minute walk test.



**Figure 3.** Kaplan-Meier overall survival by peak oxygen uptake (A), 6-minute walk test (B), and physical component score (C).

mL/kg/min vs. peak  $VO_2 \geq 11.03$  mL/kg/min, HR = 17.75,  $p = 0.006$ ; for PCS < 44.54 vs. PCS  $\geq 44.54$ , HR = 4.65,  $p = 0.011$ ). After adjusting for age, gender, WHO FC and treatment type, further multivariate Cox regression analysis including 6MWT, peak  $VO_2$  and PCS were analyzed in different models, as shown in Table 3. The adjusted HR (AHR) of 6MWT < 331 m decreased to 2.84 ( $p = 0.077$ ) after adjusting for baseline characteristics, while the HR of peak  $VO_2 < 11.03$  mL/kg/min remained significantly higher after adjusting for 6MWT in addition to baseline characteristics (AHR = 16.14,  $p = 0.026$ ). However, the HR decreased to 10.96 after additional adjustment for PCS ( $p = 0.064$ ). For PCS < 44.54, the HR decreased after adjusting for 6MWT and peak  $VO_2$  in addition to base-

line characteristics (AHR = 1.98,  $p = 0.293$ ). For the above prognostic predictors, combined parameters were significantly better in predicting 2-year mortality in the patients with PAH, particularly a combination of peak  $VO_2$  and PCS (Table 4).

### DISCUSSION

This study demonstrated that exercise capacity and the physical component of the SF-36 differed between the PAH survivors and non-survivors. Furthermore, comprehensive assessments with exercise capacity and quality of life were better predictors of 2-year mortality in

**Table 3.** Significant predictors for two-year mortality in patients with PAH

Variables	No. of patients	Death No. (%)	Crude HR (95% CI)	Model 1	Model 2	Model 3
				Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
<b>6MWT (m)</b>						
$\geq 331$	35	5 (13.9)	1.00	1.00	1.00	1.00
< 331	19	8 (42.1)	3.40 (1.11-10.39)*	2.84 (0.89-9.01)	1.34 (0.40-4.55)	1.43 (0.41-5.05)
<b>Peak <math>VO_2</math> (mL/min/kg)</b>						
$\geq 11.03$	29	1 (3.3)	1.00	1.00	1.00	1.00
< 11.03	25	12 (48.0)	17.75 (2.30-136.82)#	19.74 (1.90-204.95)*	16.14 (1.39-186.91)*	10.96 (0.87-138.29)
<b>PCS</b>						
$\geq 44.54$	34	4 (11.4)	1.00	1.00		1.00
< 44.54	20	9 (45.0)	4.65 (1.43-15.14)*	3.66 (1.00-13.46)		1.98 (0.55-7.10)

Multivariate Cox regression analysis was performed for 6MWT, peak  $VO_2$ , and PCS.

Model 1: adjusted for age, gender, WHO FC, and treatment type in each variable. Model 2: adjusted for 6MWT and peak  $VO_2$  in addition to Model 1. Model 3: adjusted for PCS in addition to Model 2.

\*  $p < 0.05$ ; #  $p < 0.01$ .

CI, confidence interval; HR, hazard ratio; PCS, physical component score; peak  $VO_2$ , oxygen uptake at peak exercise; 6MWT, six-minute walk test.

**Table 4.** Combined significant predictors for two-year mortality

Variables	No. of Patients	Death No. (%)	Crude HR (95% CI)	p-value	Adjusted HR* (95% CI)	p-value
<b>Peak VO<sub>2</sub> (mL/min/kg) and 6MWT (m)</b>						
≥ 11.03 and ≥ 331	25	1 (4.0)	1.00		1.00	
≥ 11.03 and < 331	4	0 (0)	--		--	
< 11.03 and ≥ 331	10	4 (40.0)	12.19 (1.36-109.28)	0.025	12.90 (0.99-167.76)	0.051
< 11.03 and < 331	15	8 (53.3)	17.45 (2.18-139.81)	0.007	18.45 (1.79-190.63)	0.014
<b>Peak VO<sub>2</sub> (mL/min/kg) and PCS</b>						
≥ 11.03 and ≥ 44.54	24	1 (4.2)	1.00		1.00	
≥ 11.03 and < 44.54	5	0 (0)	--		--	
< 11.03 and ≥ 44.54	10	3 (30.0)	8.06 (0.84-77.50)	0.071	9.10 (0.74-112.56)	0.085
< 11.03 and < 44.54	15	9 (60.0)	20.32 (2.56-161.16)	0.004	19.95 (1.98-200.97)	0.011
<b>6MWT (m) and PCS</b>						
≥ 331 and ≥ 44.54	26	2 (7.7)	1.00		1.00	
≥ 331 and < 44.54	9	3 (33.3)	4.70 (0.79-28.18)	0.090	1.82 (0.19-17.27)	0.603
< 331 and ≥ 44.54	8	2 (25.0)	3.26 (0.46-23.12)	0.238	1.45 (0.14-15.00)	0.754
< 331 and < 44.54	11	6 (54.5)	9.61 (1.93-47.76)	0.006	7.84 (1.46-42.20)	0.017

\* Adjusted for age, gender, WHO functional classification and treatment types.

CI, confidence interval; HR, hazard ratio; PCS, physical component score; peak VO<sub>2</sub>, oxygen uptake at peak exercise; 6MWT, six-minute walk test.

the patients with pulmonary hypertension.

CPET and 6MWT are commonly used for measuring exercise capacity, and the 6MWT is more commonly used due to its convenience.<sup>13,20</sup> CPET and 6MWT are also correlated with HRQoL, WHO FC and hemodynamic parameters in PAH patients.<sup>6,21-23</sup> In a study by Zotter-Tufaro et al., a cut-off value of 330 m for the 6MWT was an independent predictor of hospitalization for heart failure and/or cardiac-related mortality in patients with PAH associated with heart failure and preserved ejection fraction.<sup>24</sup> We identified an optimal cut-off value of 331 m for the 6MWT in predicting the survival of PAH patients, which is similar to the aforementioned study. However, the 6MWT may not be a sufficient surrogate endpoint to assess treatment effect.<sup>25,26</sup> Various physiological measures obtained from CPET can potentially provide more information to differentiate the cause of dyspnea on exertion, mechanisms of exercise limitation, and to detect the degree of disease severity and changes in hemodynamics, which the 6MWT cannot.<sup>27,28</sup> Although Barst et al. demonstrated that the 6MWT was correlated to cardiac output and pulmonary vascular resistance, Miyamoto et al. and Guazzi et al. found that the 6MWT was weakly correlated to hemodynamic studies,<sup>5,13</sup> and there is limited supportive evidence for the use of the 6MWT as a prognostic marker.<sup>10,14,25</sup> Instead, utilization

of peak VO<sub>2</sub> in CPET to predict survival in PAH patients is more efficient. With good effort, peak VO<sub>2</sub> from CPET closely reflects an individual's maximal oxygen uptake, which is the gold standard measurement of aerobic capacity.<sup>10,29,30</sup> Several studies have also indicated that peak VO<sub>2</sub> is a good predictor of survival and time to clinical worsening in patients with PAH, with reported cut-off values of 10.4 mL/kg/min and 11.6 mL/kg/min in peak VO<sub>2</sub>.<sup>20,31,32</sup> We found a similar optimal cut-off value of 11.03 mL/kg/min for peak VO<sub>2</sub> in predicting the survival of PAH patients. A previous study also reported good estimation of cardiac output from oxygen uptake during progressive exercise.<sup>33</sup> However, in our study, both 6MWT and peak VO<sub>2</sub> did not show significant associations with hemodynamic parameters. In addition, we performed the CPET with a bicycle ergometer instead of a treadmill, and the upright sitting position could lower the physical stress of patients with poorer functional status. All patients finished the CPET without any complication, suggesting that CPET with a bicycle ergometer is safe for PAH patients with poor functional status.

Exercise tests evaluate physical ability rather than mental status. Therefore, exercise capacity should correlate to a physical component more than to a mental component. Previous studies have suggested that the 6MWT is significantly correlated to HRQoL in PAH patients, par-

ticularly the PCS but not MCS.<sup>22,34-36</sup> In our study, we found a significant correlation between oxygen uptake and PCS of the SF-36, but not in the mental component of the SF-36. However, the 6MWT was not correlated to PCS, MCS or total SF-36 score.

The impact of PAH on HRQoL is at least as severe as chronic illnesses such as renal failure and chronic obstructive pulmonary disease, and therefore the disease burden of PAH on the quality of life of the patients and their caregivers has received increasing attention.<sup>37</sup> A systematic review of HRQoL in patients with PAH reported that the generic SF-36 was the most widely used instrument.<sup>38</sup> Observational studies have also revealed associations between hemodynamic measurements and HRQoL, and that the quality of life can be improved by reducing the symptoms of PAH.<sup>39,40</sup> Roman et al. reported that the SF-36 determined a worse prognosis in patients with PAH and chronic thromboembolic pulmonary hypertension in a Spanish cohort.<sup>41</sup> Fernandes et al. also reported that PCS was a prognostic marker in PAH patients, with a cut-off value of 32. The authors emphasized pre-determined PCS as a determinant of PAH treatment response.<sup>42</sup> In our study, the optimal cut-off points for the 6MWT, peak VO<sub>2</sub> and SF-36 scores in predicting 2-year mortality were determined by ROC curves. The AUC was higher in peak VO<sub>2</sub> than in 6MWT and PCS. These results suggest that exercise capacity is appropriate to predict 2-year mortality in patients with PAH. In addition, the physical component of HRQoL at a cut-off value of 44.54 predicted 2-year mortality (log-rank test  $p = 0.005$ ), but not total SF-36 score ( $p = 0.050$ ). In our study, further multivariate Cox regression analysis indicated the contribution of baseline characteristics to disease mortality. As for oxygen uptake, the HR of peak VO<sub>2</sub> < 11.03 mL/kg/min remained significantly higher in model 2 after adjusting for 6MWT. However, with additional adjustments for PCS, the HR decreased to a non-significant level, thus indicating the partial contribution of the patient's quality of life to disease mortality.

When evaluating a participant for health and disability status, a more comprehensive assessment should include not only the degree of organ damage, but also the function and disease impact, reflecting the concept of the International Classification of Functioning, Disability and Health.<sup>43</sup> Our study results aimed to provide a more comprehensive assessment of patients with PAH

through evaluating their exercise capacity and impact of disease on their quality of life. We further combined two prognostic predictors to test for any better prediction of 2-year mortality in the patients with PAH. The results suggested a better prognostic prediction with a combination of peak VO<sub>2</sub> and 6MWT (AHR = 18.45,  $p = 0.014$  for low peak VO<sub>2</sub> and short 6MWT), and peak VO<sub>2</sub> and PCS (AHR = 19.95,  $p = 0.011$  for low peak VO<sub>2</sub> and low PCS), indicating the important correlation between aerobic capacity and quality of life in predicting disease mortality. These results give additional clinical insights into the importance of multi-dimensional assessments for patients with PAH.

### Study limitations

There are several limitations to this study. Our study population included 54 patients with 94.4% being female. The study population was small, and the included population was different from the general PAH population, with a male to female ratio of approximately 1:2.<sup>44,45</sup> Furthermore, other underlying diseases which can contribute to disease-related mortality were not recorded. In addition, a low rate of PAH-specific drug prescriptions was observed in our study group, although the importance of early aggressive treatment has been raised.<sup>46</sup> We did not analyze the impact of PAH-specific drugs on the patients' outcomes in the current study, however the aim of this study was to compare the prognostic value of the 6MWT and peak oxygen uptake in PAH patients. During the study period, the sequential therapy strategy did not change in any of the PAH patients. In addition, not all patients in the study group had available data on hemodynamic parameters, which resulted in lower significance in some parameters. Therefore, we did not further analyze the impact of hemodynamic parameters on the patients' outcomes. In future studies with a larger study sample size, we will work to include these hemodynamic variables in multivariate analysis.

### CONCLUSIONS

In conclusion, exercise capacity and the physical component of the SF-36 differed among the PAH survivors and non-survivors. In addition, we suggest that comprehensive assessments with exercise capacity and qual-

ity of life can be used to predict 2-year mortality in patients with PAH.

## CONFLICT OF INTEREST

All of the authors declare no conflict of interest.

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