

Exercise feature and predictor of prognosis in patients with pulmonary artery stenosis-associated pulmonary hypertension

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Abstract

Aims The prognosis is poor for patients with pulmonary artery stenosis-associated pulmonary hypertension (PAS-PH). Identifying predictors of prognosis in PAS-PH is crucial to preventing premature death, which has rarely been investigated. We aimed to explore the cardiopulmonary exercise testing (CPET) parameters to predict the prognosis of these patients.

Methods We prospectively included all patients with PAS-PH who underwent CPET between September 2014 and June 2021 in Fuwai Hospital (ClinicalTrials.gov ID: NCT02061787). The primary outcome was clinical worsening, including death, rehospitalization for heart failure, or deterioration of PH.

Results Seventy-two patients were included in this study. A median of 2-year follow-up revealed that 18 (25%) patients experienced clinical worsening. The 1-year, 3-year, and 5-year event-free survival rates were 92.5%, 81.7%, and 62.7%, respectively. Patients with clinical worsening demonstrated significantly worse baseline haemodynamics and poorer exercise capacity than their counterparts. Multivariable Cox regression identified that peak O₂ pulse could independently predict clinical worsening [hazard ratio: 0.344, 95% confidence interval (CI) 0.188–0.631, $P < 0.001$], outperforming other parameters. Peak O₂ pulse correlated with PH severity. Incorporating peak O₂ pulse into the simplified 2015 European Society of Cardiology/European Respiratory Society risk stratification improved the accuracy for predicting clinical worsening (pre vs. post area under the curve: 0.727 vs. 0.846, $P < 0.001$; net reclassification index: 0.852, 95% CI 0.372–1.332, $P < 0.001$; integrated discrimination index 0.133, 95% CI 0.031–0.235, $P = 0.011$).

Conclusions The prognosis is poor for PAS-PH, and exercise intolerance and ventilation inefficiency are commonly observed. Peak O₂ pulse independently predicted the prognosis of these patients. A low peak O₂ pulse identified patients at high risk of clinical deterioration and served for risk stratification of PAS-PH.

Keywords Takayasu arteritis; Pulmonary hypertension; Pulmonary artery stenosis; Cardiopulmonary exercise testing; Peak O₂ pulse

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Introduction

Pulmonary artery stenosis (PAS) is a congenital or acquired malformation that may involve the main, branched, lobar, segmental, or distal levels of the pulmonary arterial tree.¹ Being a heterogeneous condition, PAS could manifest from either intrinsic lesions or extrinsic compression attributable

to a series of diseases, including Takayasu arteritis, fibrosing mediastinitis, and congenital heart diseases.^{2–5} Although the aetiology of PAS varies, similarities have been observed in its pathophysiology and clinical manifestations. Blood flow obstruction in PAS can directly elevate pulmonary artery pressure when lumen size stenosis is haemodynamically significant, and the redistribution of flow to non-obstructed

arteries may result in endothelial dysfunction and vascular remodelling,⁶ which further increases pulmonary vascular resistance (PVR) and causes pulmonary hypertension (PH).³ Notably, patients with PAS who advance to PH have a poor prognosis,⁷ with a mortality rate as high as 33.3%,^{8,9} and PAS predominantly affects young females, with an average age of 45 at death.⁸ Therefore, to prevent premature death, it is crucial to identify predictors of prognosis, which is whereas rarely investigated.

Cardiopulmonary exercise testing (CPET) is a non-invasive tool used to comprehensively evaluate the exercise capacity and functional status of patients with PH,¹⁰ and it is recommended by the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) PH guidelines for risk stratification in pulmonary arterial hypertension (PAH).¹¹ Moreover, CPET can predict the prognosis of patients with PH.^{12,13} Previous studies have predominantly evaluated the predictive value of CPET in idiopathic PAH^{13,14} and chronic thromboembolic PH¹²; however, the predictive value of CPET in patients with PAS-PH remains unclear.

Therefore, this study aimed to explore the non-invasive CPET parameters to predict the prognosis of patients with PAS-PH. Moreover, we evaluated the applicability of the 2015 ESC risk stratification for these patients and attempted to refine the risk assessment tool.

Methods

Study population

We prospectively enrolled all the patients diagnosed with PAS and PH at Fuwai Hospital in Beijing, China, between September 2014 and June 2021. The inclusion criteria were as follows: (1) patients diagnosed with PAS attributable to Takayasu arteritis, fibrosing mediastinitis, or congenital pulmonary artery stenosis, and diagnosis of Takayasu arteritis was in accordance with the American College of Rheumatology in 1990¹⁵ and/or the modified Ishikawa criteria¹⁶; (2) patients diagnosed with PH based on right heart catheterization (RHC) according to guidelines¹¹; and (3) patients who underwent CPET. Additionally, the following information was gathered: demographic data, physical examination, 6-min walking distance (6MWD), World Health Organization functional class (WHO-FC), plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), parameters derived from transthoracic echocardiography, RHC, and CPET. The study conformed to the principles outlined in the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Fuwai Hospital and registered on ClinicalTrials.gov (Identifier: NCT02061787) and written informed consent was obtained from all the participants.

Cardiopulmonary exercise testing

A symptom-limited CPET was performed on a cycle ergometer using a COSMED Quark CPET system. The work rate increased gradually after a 3-min rest and warm-up using a ramp protocol until the maximum exercise limit was attained. During CPET using breath-by-breath gas analysis, the following were measured: minute ventilation (VE), oxygen uptake (VO₂), and carbon dioxide output (VCO₂). Heart rate was assessed continuously, and blood pressure was recorded every 3 min.

Peak VO₂, obtained by averaging the highest 30-s value of VO₂ during the final minute of exercise, was reported as the absolute value and percentage of the prediction. A combination of the V-slope method and ventilatory equivalents was used to identify the anaerobic threshold. The VE/VCO₂ slope was derived from linear regression of the relationship between VE and VCO₂ during the entire exercise period. Additionally, the oxygen pulse at peak exercise (peak O₂ pulse) was calculated by dividing peak VO₂ by peak heart rate; the oxygen uptake efficiency slope (OUES) was determined using the following equation: VO₂ = OUES × log₁₀VE + b.¹⁴ Finally, peak circulatory power was calculated using the product of peak VO₂ and peak systolic blood pressure.¹³

Echocardiography and RHC

Standard transthoracic echocardiography and RHC were conducted by experienced cardiologists in all patients, as previously described.¹⁷ The left ventricular diameter at end-diastole (LVEDD) and right ventricle diameter at end-diastole (RVEDD) were measured in the left ventricular long-axis view and apical four-chamber view, respectively. The ejection fraction (EF) was determined using the Simpson biplane method, and the systolic pulmonary artery pressure (PASP) was calculated using the modified Bernoulli equation.¹⁸

Furthermore, experienced cardiologists performed RHC via the internal jugular or femoral veins. Key pressure values, which included right atrial pressure, systolic pulmonary artery pressure (sPAP), diastolic PAP (dPAP), mean PAP (mPAP), and pulmonary arterial wedge pressure (PAWP), were continuously recorded. Mixed venous oxygen saturation (S_vO₂) was also recorded. Moreover, cardiac output was assessed using the indirect Fick's method, and the cardiac index and PVR were calculated using standard formulas.¹⁹ Pulmonary arterial compliance (PAC) was calculated as follows: PAC = stroke volume (SV)/pulmonary arterial pulse pressure = (cardiac output/heart rate)/(sPAP – dPAP).

Risk stratification

An abbreviated version of the 2015 ESC/ERS PH risk stratification²⁰ was used to categorize patients with PAS-PH

into low-risk, intermediate-risk, or high-risk groups. The following variables were collected for risk stratification: WHO-FC, 6MWD, NT-proBNP level, right atrial pressure, cardiac index, and S_vO_2 level, and each variable was graded according to the cut-off values proposed in the guidelines.¹¹ Next, the sum of all grades was divided by the number of available variables and rounded to the nearest integer. Finally, the risk group was determined using the aforementioned integers.²⁰

Outcome and follow-up

Clinical worsening was defined as a composite of (i) death, (ii) rehospitalization for heart failure, or (iii) deterioration of PH ($\geq 15\%$ reduction in 6MWD, worsening WHO-FC, or initiation of parenteral prostacyclin therapy). Participants were followed up using in-hospital or outpatient medical charts and by phone calls until outcome events or the end of the study (8 December 2021). Additionally, the clinical worsening-free survival time was calculated from baseline to the occurrence of the outcome or censored date (8 December 2021), and the endpoint events were adjudicated by two senior clinicians. All disagreements were resolved through discussions with supervisors (ZHZ and ZHL).

Statistical analysis

Continuous and categorical data were expressed as mean (\pm standard deviation) or median (interquartile range) based on the distribution and as frequencies (percentages), respectively. Baseline characteristics were compared using independent sample *t*-tests or Wilcoxon rank sum tests (continuous variables) and Pearson chi-square tests or Fisher exact tests (categorical variables).

The prognostic parameters for clinical worsening were investigated using Cox regression analysis. Specifically, univariable Cox regression analyses were performed, and the Wald chi-square test statistic was calculated. Receiver operating characteristic (ROC) curves and area under the curve (AUC) were used to compare the ability of the CPET parameters to predict clinical worsening. Considering the collinearity among CPET parameters, various multivariable Cox proportional hazards models were developed based on the four CPET parameters with the best discriminative capacity, adjusted for demographics at first, and then other potential confounders ($P < 0.05$, univariable Cox regression). Notably, the variable with lower Wald statistic was omitted when collinearity existed between two variables (correlation coefficient > 0.60).

After the independent CPET predictors were identified, their correlations with echocardiographic and haemodynamic parameters were evaluated using Spearman correlation analysis and visualized using a heatmap. One-way analysis of var-

iance (ANOVA) and Bonferroni tests were used to compare CPET parameters in the different risk groups. Cox analyses were performed to evaluate the additive prognostic value of the CPET predictors in the abbreviated version of the 2015 ESC/ERS PH risk stratification. ROC curves were created, and the DeLong test was used to compare AUC. The net reclassification index and integrated discrimination index were used to compare the different models' clinical usefulness and net benefit.

Additionally, a restricted cubic spline with three knots was performed to identify the dose-response relationship and test linearity between the predictors and clinical worsening. The Kaplan-Meier method was used to generate the survival curve, and the log-rank test was performed. Statistical significance was set at $P < 0.05$. All statistical tests were performed using the statistical package for the social science (SPSS) software (version 22.0; IBM SPSS Statistics, IBM Corp., Armonk, NY, USA) and R (version 4.0.5, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and follow-up outcomes

Overall, 87 consecutive patients with PAS were diagnosed with PH by RHC between September 2014 and June 2021. All patients with PH were evaluated for the safety and feasibility of undergoing CPET, and 15 of them refused the procedure because of clinical instability or other personal reasons (*Table S1*). Ultimately, 72 patients were included in this study.

Table 1 shows the characteristics of all included patients. The patients' mean age and 6MWD were 49 ± 14 years and 386 ± 96 m, respectively. Of all the patients, 54 (75%) were female, and 51.4% were in advanced functional classes (III or IV). PAS was attributed to Takayasu arteritis in most patients (68.1%), fibrosing mediastinitis in 22.2%, and congenital pulmonary artery stenosis in 9.7%. At baseline, 8.3%, 52.8%, and 20.8% of patients underwent percutaneous transluminal pulmonary angioplasty alone, PAH-targeted therapy alone, and percutaneous transluminal pulmonary angioplasty in addition to PAH-targeted therapy, respectively. During a median follow-up of 1.8 (0.6–2.8) years, 18 (25%) patients experienced clinical worsening, including four deaths and 14 rehospitalizations for heart failure or deterioration of PH.

At baseline, despite the similar demographics, patients who experienced clinical worsening had significantly more advanced PH and poorer haemodynamics compared with patients without clinical worsening, which were reflected by larger right ventricle and significantly higher mPAP (42.1 ± 13.7 mmHg vs. 53.0 ± 14.8 mmHg, $P = 0.006$) and PVR (6.9 ± 4.3 Wood units vs. 13.6 ± 6.5 Wood units,

Table 1 Demographic, clinical, echocardiographic, and haemodynamic characteristics of study population

Variables	Total (n = 72)	No event (n = 54)	Event (n = 18)	P value
Age, years	49 ± 14	50 ± 14	46 ± 15	0.315
Female, n (%)	54 (75.0)	38 (70.4)	16 (88.9)	0.209
BMI, kg·m ⁻²	22.6 ± 3.5	22.7 ± 3.0	22.3 ± 4.7	0.697
WHO-FC				0.134
I/II, n (%)	35 (48.6)	29 (53.7)	6 (33.3)	
III/IV, n (%)	37 (51.4)	25 (46.3)	12 (66.7)	
6MWD, m	386 ± 96	398 ± 95	351 ± 91	0.105
Hypertension, n (%)	24 (33.3)	21 (38.9)	3 (16.7)	0.149
Diabetes mellitus, n (%)	12 (16.7)	7 (13.0)	5 (27.8)	0.144
Dyslipidaemia, n (%)	18 (25.0)	16 (29.6)	2 (11.1)	0.209
<i>Echocardiographic parameters</i>				
LA, mm	32.2 ± 5.7	32.6 ± 5.4	31.2 ± 6.7	0.376
LVEDD, mm	40.8 ± 6.3	42.1 ± 4.5	36.2 ± 8.6	<0.001
RVEDD, mm	29.9 ± 7.6	29.0 ± 6.8	33.4 ± 9.4	0.023
RVEDD/LVEDD	0.76 ± 0.27	0.69 ± 0.20	0.98 ± 0.36	<0.001
LVEF, %	65.1 ± 5.2	65.2 ± 4.3	63.5 ± 6.9	0.144
PASP, mmHg	76.2 ± 27.1	74.8 ± 28.2	80.9 ± 22.8	0.403
TAPSE, mm	17.4 ± 2.9	17.7 ± 2.8	16.1 ± 2.6	0.036
Pericardial effusion, n (%)	4 (5.6)	3 (5.6)	1 (5.6)	1.000
<i>Haemodynamic parameters</i>				
S _v O ₂ , %	70.6 ± 7.3	72.5 ± 5.9	65.0 ± 8.4	<0.001
RAP, mmHg	6.2 ± 5.2	6.0 ± 5.3	6.9 ± 4.8	0.525
mPAP, mmHg	44.9 ± 14.7	42.1 ± 13.7	53.0 ± 14.8	0.006
PAWP, mmHg	9.0 ± 3.6	9.4 ± 3.1	7.8 ± 4.7	0.141
CI, L·min ⁻¹ ·m ⁻²	3.1 ± 0.9	3.3 ± 0.9	2.6 ± 0.6	0.001
SV, mL	61.4 ± 23.1	67.7 ± 22.5	42.9 ± 12.4	<0.001
PVR, Wood units	8.6 ± 5.7	6.9 ± 4.3	13.6 ± 6.5	<0.001
TPR, Wood units	11.4 ± 5.8	9.8 ± 4.5	16.1 ± 6.8	0.001
PAC, mL·mmHg ⁻¹	1.25 ± 1.13	1.42 ± 1.22	0.75 ± 0.57	0.029
<i>Laboratory tests</i>				
NT-proBNP, pg·mL ⁻¹	515 (116, 1557)	265 (103, 828)	1883 (923, 3,115)	0.001
Hs-CRP, mg·L ⁻¹	2.3 (1.0, 4.3)	2.3 (0.9, 4.6)	2.4 (1.2, 5.1)	0.771
ESR, mm/h	7 (3, 16)	7 (3, 18)	7 (2, 16)	0.112
<i>Cardiopulmonary exercise testing parameters</i>				
RER	1.03 ± 0.10	1.03 ± 0.11	1.04 ± 0.09	0.915
Peak WR, watts	66.2 ± 24.4	70.6 ± 24.8	52.7 ± 18.1	0.008
AT VO ₂ , mL·min ⁻¹ ·kg ⁻¹	10.6 ± 2.8	11.1 ± 2.7	9.3 ± 2.6	0.016
Peak VO ₂ , mL·min ⁻¹ ·kg ⁻¹	13.1 ± 3.4	13.7 ± 3.3	11.2 ± 3.1	0.009
Peak VO ₂ (% pred.)	48.4 ± 15.9	51.3 ± 16.5	39.8 ± 10.4	0.007
VE/VCO ₂ slope	42.8 ± 9.2	42.1 ± 9.4	44.6 ± 8.7	0.330
Peak P _{ET} CO ₂ , mmHg	27.9 ± 5.5	26.6 ± 6.8	24.2 ± 3.7	0.071
Peak O ₂ pulse, mL·beat ⁻¹	6.1 ± 1.9	6.6 ± 1.9	4.7 ± 1.1	<0.001
OUES	1068.3 ± 396.1	1148.1 ± 408.2	851.0 ± 265.0	0.001
Peak CircP, mmHg·mL·kg ⁻¹ ·min ⁻¹	1892.5 ± 691.1	2055.33 ± 673.9	1442.3 ± 530.8	0.001
<i>Aetiology</i>				
Takayasu arteritis, n (%)	49 (68.1)	34 (63.0)	15 (83.3)	0.275
Congenital PA stenosis, n (%)	7 (9.7)	6 (11.1)	1 (5.6)	
Fibrosing mediastinitis, n (%)	16 (22.2)	14 (25.9)	2 (11.1)	
<i>Treatment at baseline</i>				
PTPA ^a alone, n (%)	6 (8.3)	5 (9.3)	1 (5.6)	0.622
PAH-specific therapy ^b alone, n (%)	38 (52.8)	26 (48.1)	12 (66.7)	0.173
Transcatheter interventions + PAH-specific therapy, n (%)	15 (20.8)	11 (20.4)	4 (22.2)	0.867
Corticosteroids/immunosuppressants, n (%)	37 (51.4)	25 (46.3)	12 (66.7)	0.134

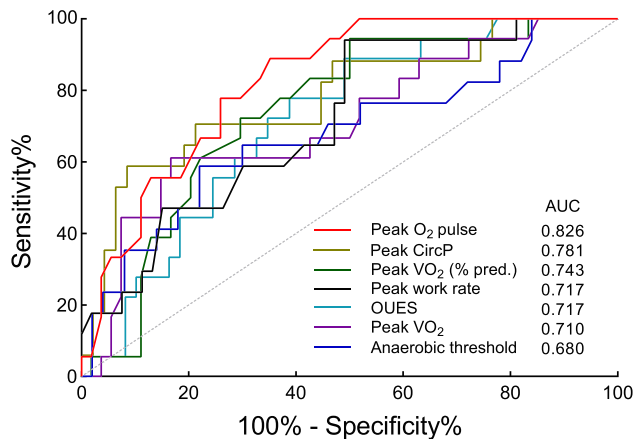
6MWD, 6-min walking distance; AT, anaerobic threshold; BMI, body mass index; CI, cardiac index; CircP, circulatory power; CPET, cardio-pulmonary exercise testing; ESR, erythrocyte sedimentation rate; Hs-CRP, high-sensitive C reactive protein; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; OUES, oxygen uptake efficiency slope; PA, pulmonary artery; PAC, pulmonary arterial compliance; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; P_{ET}CO₂, partial pressure of end-tidal carbon dioxide; PTPA, percutaneous transluminal pulmonary angioplasty; PVR, pulmonary vascular resistance; RAP, right atrium pressure; RER, respiratory exchange rate; RVEDD, right ventricular end-diastolic diameter; SV, stroke volume; S_vO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance; VCO₂, carbon dioxide output; VE, minute ventilation; VO₂, oxygen uptake; WHO-FC, World Health Organization functional class; WR, work rate.

^aPercutaneous transluminal pulmonary angioplasty included pulmonary artery balloon angioplasty and stenting.

^bPAH-specific therapy included endothelin receptor antagonists, nitric oxide-cGMP enhancers, and prostacyclin analogues or receptor agonists.

$P < 0.001$). Notably, patients with clinical worsening also experienced significantly worse exercise capacity, including lower peak VO_2 , peak VO_2 pulse, peak circulatory power, and OUES ($P < 0.05$), than those without clinical worsening.

Figure 1 Receiver operator characteristic curve of CPET parameters in predicting clinical worsening in PAS-PH. AUC, area under the curve; CircP, circulatory power; CPET, cardiopulmonary exercise testing; OUES, oxygen uptake efficiency slope; PAS-PH, pulmonary arterial stenosis-associated pulmonary hypertension; VO_2 , oxygen uptake.



Predictors of clinical worsening in patients with PAS-PH

In the total cohort, the 1-year, 3-year, and 5-year event-free survival rates were 92.5%, 81.7%, and 62.7%, respectively. Univariable Cox regression identified that parameters derived from echocardiography, RHC, and CPET were associated with clinical worsening, including LVEDD, RVEDD, mPAP, cardiac index, S_vO_2 , PAC, work rate, anaerobic threshold, peak VO_2 , OUES, peak circulatory power, peak O_2 pulse, and NT-proBNP (all $P < 0.05$) (Table S2). The ability of the CPET parameters to predict clinical worsening was compared using ROC (Figure 1). Additionally, peak O_2 pulse outperformed all other CPET parameters in predicting prognosis, with the highest AUC [AUC 0.826; 95% confidence interval (CI):0.729–0.923; $P < 0.001$], followed by peak circulatory power (AUC 0.781; 95% CI:0.645–0.917) and peak VO_2 (% pred.) (AUC 0.743; 95% CI: 0.620–0.866). Table 2 shows the optimal cut-offs for other CPET parameters to predict adverse events. Furthermore, multivariable Cox analysis was employed to identify the independent predictors of clinical worsening (Table 3). Peak VO_2 (% pred.), peak O_2 pulse, OUES, and peak circulatory power were inversely associated with the risk of clinical worsening after adjusting for several demographic characteristics, including age, sex, and body mass index (Model 1). However, only peak O_2 pulse remained independently associated with clinical worsening [hazard ratio (HR) 0.344, 95% CI 0.188–0.631, $P < 0.001$] after adjusting for total pulmonary

Table 2 ROC curve analysis for CPET variables in predicting clinical worsening

Variable	Cut-off value	Clinical worsening		
		Sensitivity%/specificity%	AUC (95% CI)	P value
Peak O ₂ pulse	5.85	88.9/64.8	0.826 (0.729–0.923)	<0.001
Peak CircP	1351.42	58.8/91.5	0.781 (0.645–0.917)	<0.001
Peak VO ₂ (% pred.)	51.50	94.4/50.0	0.743 (0.620–0.866)	0.002
OUES	1127.00	88.9/51.0	0.717 (0.589–0.846)	0.007
Peak WR	71.00	94.1/50.9	0.717 (0.583–0.851)	0.007
Peak VO ₂	11.37	61.1/83.3	0.710 (0.566–0.854)	0.008
AT	9.22	58.8/78.0	0.680 (0.521–0.839)	0.028

AT, anaerobic threshold; CircP, circulatory power; CPET, cardiopulmonary exercise testing; OUES, oxygen uptake efficiency slope; ROC, receiver operating characteristic; VO_2 , oxygen uptake; WR, work rate.

Table 3 Unadjusted and adjusted hazard ratios for CPET parameters

Variables	Univariate analysis		Adjusted Model 1 ^a		Adjusted Model 2 ^b	
	Crude HR (95%CI)	P value	Adjusted HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Peak VO ₂ (% pred.)	0.955 (0.923–0.989)	0.009	0.911 (0.863–0.963)	<0.001	0.961 (0.912–1.004)	0.075
Peak O ₂ pulse	0.403 (0.258–0.631)	<0.001	0.375 (0.228–0.616)	<0.001	0.344 (0.188–0.631)	<0.001
OUES	0.998 (0.996–0.999)	0.008	0.998 (0.996–0.999)	0.011	0.999 (0.997–1.000)	0.139
Peak CircP	0.998 (0.997–1.000)	0.007	0.999 (0.997–1.000)	0.011	0.999 (0.998–1.000)	0.113

BMI, body mass index; CI, confidence interval; CircP, circulatory power; CPET, cardiopulmonary exercise testing; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; NT-proBNP, N-terminal pro-brain natriuretic peptide; OUES, the oxygen uptake efficiency slope; TPR, total pulmonary resistance; VO_2 , oxygen uptake.

^aAdjusted for age, sex, and BMI.

^bAdjusted for TPR, LVEDD, and NT-proBNP.

resistance, LVEDD, and NT-proBNP (**Model 2**). Moreover, a restricted cubic spline confirmed that the O₂ pulse was linearly associated with clinical worsening (non-linear $P = 0.734$) (*Figure 2*). ROC curve analysis revealed that the optimal cut-off value of O₂ pulse for clinical worsening prediction was 5.85 mL·beat⁻¹ (sensitivity 88.9%, specificity 64.8%). Patients were stratified into peak O₂ pulse >5.85 mL·beat⁻¹ and peak O₂ pulse ≤5.85 mL·beat⁻¹ accordingly. Kaplan–Meier event-free survival curves confirmed that PAS patients

with a peak O₂ pulse >5.85 mL·beat⁻¹ had a significantly better prognosis than those with a peak O₂ pulse of ≤5.85 mL·beat⁻¹ (log-rank $P < 0.001$) (*Figure 3*).

Peak O₂ pulse associated with severity of PH in patients with PAS-PH

Table 4 shows that the peak O₂ pulse was positively associated with LVEDD ($r = 0.683, P < 0.001$) and inversely related to RVEDD ($r = -0.206, P = 0.085$). Similarly, significant correlations were observed between the peak O₂ pulse and haemodynamic parameters, including mPAP ($r = -0.309, P = 0.008$), PVR ($r = -0.486, P < 0.001$), cardiac index

Figure 2 Association between the peak O₂ pulse and clinical worsening of PAS-PH patients. CI, confidence interval; HR, hazard ratio; PAS-PH, pulmonary arterial stenosis associated pulmonary hypertension.

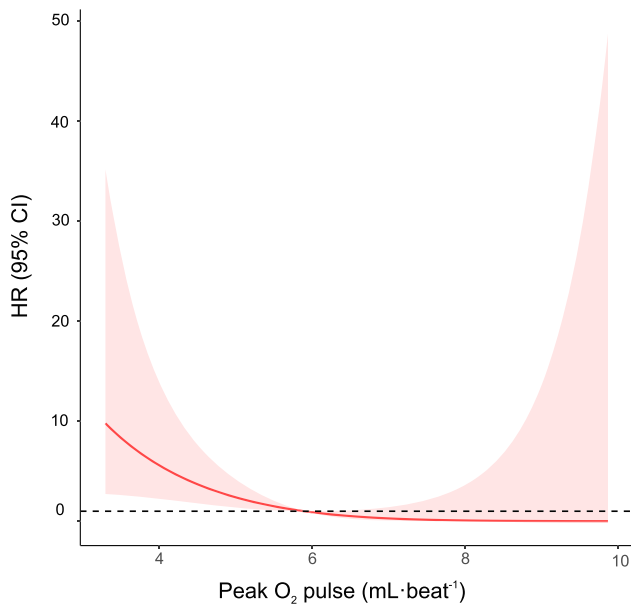
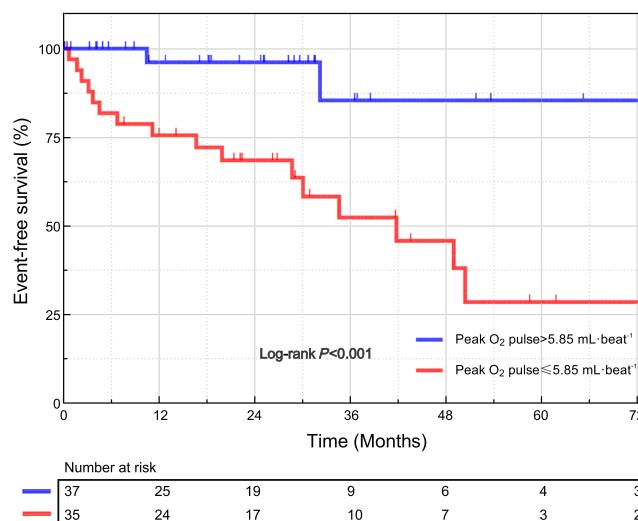


Table 4 Associations between peak O₂ pulse and clinical parameters

Variables	r	P value
LVEDD	0.683	<0.001
RVEDD	-0.206	0.085
RVEDD/LVEDD	-0.440	<0.001
PASP	-0.330	0.005
TAPSE	0.376	0.002
mPAP	-0.309	0.008
SV	0.557	<0.001
CI	0.341	0.004
S _v O ₂	0.446	<0.001
PVR	-0.486	<0.001
TPR	-0.474	<0.001
PAC	0.519	<0.001

CI, cardiac index; LVEDD, left ventricular end-diastolic diameter; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial compliance; PASP, pulmonary arterial systolic pressure; PVR, pulmonary vascular resistance; RVEDD, right ventricular end-diastolic diameter; SV, stroke volume; S_vO₂, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; TPR, total pulmonary resistance.

Figure 3 Kaplan–Meier event-free survival curves based on the optimal cut-off of the peak O₂ pulse.



($r = 0.341$, $P = 0.004$), SV ($r = 0.557$, $P < 0.001$), and S_vO_2 ($r = 0.446$, $P < 0.001$). *Figure S1* shows the correlations between the major CPET parameters and pulmonary haemodynamics.

Risk assessment and refinement of risk stratification

According to the abbreviated version of the 2015 ESC/ERS PH risk stratification, 34 (47%) patients were categorized as low risk, 36 (50%) as intermediate risk, and 2 (3%) as high risk. Additionally, the 2015 ESC/ERS PH risk stratification was identified as a significant predictor of clinical worsening (HR 3.698, 95% CI 1.724–7.932, $P < 0.001$) with a concordance index of 0.735, which was further improved by integrating peak O_2 pulse into the risk assessment (*Table S3*).

Furthermore, a comparison of the ROC curves for predicting clinical worsening between the 2015 ESC/ERS PH risk stratification and the combined model was performed, and a significant improvement in accuracy was observed when including peak O_2 pulse in the risk stratification (AUC 0.727 vs. 0.846, $P < 0.001$) (*Figure 4*). Compared with the 2015 ESC/ERS PH risk stratification, the combined model had significantly improved discriminatory power (net reclassification index 0.852, 95% CI 0.372–1.332, $P < 0.001$; integrated discrimination index 0.133, 95% CI 0.031–0.235, $P = 0.011$).

Sensitivity analysis

We further compared the baseline characteristics of the included ($n = 72$) and excluded ($n = 15$) participants, precluding

the potential bias introduced by the exclusion of patients (*Table S1*). The demographics, echocardiographic parameters, and haemodynamics were comparable between the included and excluded patients. Therefore, the exclusion did not cause bias in this study's conclusion.

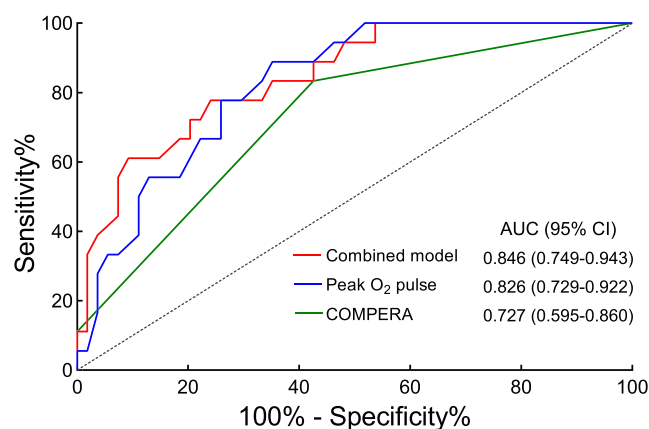
In this study, 39 patients did not reach respiratory exchange rate (RER) ≥ 1.05 . Hence, we further investigated the predictive ability among patients with RER ≥ 1.05 and < 1.05 , respectively. We observed that peak O_2 pulse was still a significant predictor of clinical worsening in patients with RER ≥ 1.05 (HR 0.508, 95% CI 0.261–0.990, $P = 0.047$) or patients with RER < 1.05 (HR 0.330, 95% CI 0.179–0.611, $P < 0.001$) (*Tables S4* and *S5*).

Discussion

To our knowledge, this is the first study to explore the non-invasive CPET predictors of prognosis in patients with PAS-PH. The prognosis is poor in patients with PAS-PH, and the 1-year, 3-year, and 5-year event-free survival rates were 92.5%, 81.7%, and 62.7%, respectively. We observed that peak O_2 pulse was a powerful and independent prognostic marker of clinical worsening in PAS-PH, outperforming the peak VO_2 and VE/ VCO_2 slope. The peak O_2 pulse was also significantly correlated with disease severity. The abbreviated version of the 2015 ESC risk stratification independently predicted the prognosis of patients with PH, and integrating peak O_2 pulse into risk stratification could considerably improve predictive ability.

The CPET is the gold standard for evaluating exercise capacity and can assess exercise performance comprehensively and objectively. On the contrary, 6MWD is subject to pa-

Figure 4 Receiver operator characteristic curve of the abbreviated version of the 2015 ESC/ERS PH risk stratification and the combined risk stratification strategy. AUC, area under the curve; CI, confidence interval. DeLong test pairwise comparison: Combined model vs. abbreviated version of the 2015 ESC/ERS PH risk stratification $P < 0.001$. Abbreviated version of the 2015 ESC/ERS PH risk stratification vs. peak O_2 pulse $P = 0.090$. Peak O_2 pulse vs. combined model $P = 0.424$.



tients' as well as doctors' motivation and could not provide information on ventilatory response to exercise.²¹ CPET is recommended for clinically evaluating PAH and chronic thromboembolic PH¹¹; however, limited data exist on the exercise characteristics and prognostic potential of CPET in PAS-PH. In this study, we observed that exercise intolerance and ventilation inefficiency were common in patients with PAS-PH, with a moderate-to-severe decrease in peak VO_2 according to Weber's class²² and a moderate-to-severe increase in the VE/VCO_2 slope according to ventilatory class, similar to PAH and CTEPH. PAH was attributable to pulmonary vascular remodelling, and CTEPH emanated from chronic thrombi obstruction and secondary microvasculopathy, whereas inflammatory destruction or congenital malformation characterized PAS-PH. In contrast to other types of PH, arterial stiffness and dilation adjacent to proximal stenosis were distinctive features of PAS-PH, particularly Takayasu arteritis.²³ Despite the varied aetiologies and pulmonary artery morphologies on imaging, similar pathophysiological alterations could be observed in different types of PH. Secondary to narrowed pulmonary artery lumen, pulmonary perfusion was impaired in PH, leading to compromised cardiac output and exaggerated ventilation-perfusion mismatch, which could be reflected by reduced peak VO_2 and elevated VE/CO_2 slope.^{24,25} Recently, peak VO_2 and VE/VCO_2 slope are the most commonly used CPET-derived indicators for diagnosis, prognosis, and therapeutic guidance. However, our results showed that peak O_2 pulse, an indicator that has received less attention, outperformed peak VO_2 and VE/VCO_2 slope in predicting the prognosis of patients with PAS-PH.

According to Fick's formula, the O_2 pulse is defined as VO_2 divided by heart rate, which can also be expressed as the product of SV and arterial-venous oxygen difference ($\Delta\text{C(a-v)}\text{O}_2$). Representing VO_2 ejected per cardiac contraction, O_2 pulse is considered a non-invasive estimation of SV, and Accalai *et al.*²⁶ recently demonstrated a strong linear relationship between O_2 pulse and measured SV at peak exercise in patients with heart failure. According to the reference standards recommended by the Fitness Registry and the Importance of Exercise National Database Registry, the mean peak O_2 pulse observed in this study was much lower than the normal value, reflecting an impaired ventricular SV,²⁷ and the possible mechanisms included right ventricular dysfunction and ventricular interdependence. In PAS, obstruction of blood flow causes elevated pulmonary artery pressure and right ventricular afterload, which may further lead to a drop in SV despite adaptive right ventricular hypertrophy and dilation. Moreover, through a negative ventricular interaction, the dilated right ventricle compresses the left ventricle, affecting the left ventricular preload and increasing the SV during exercise.²⁸ The pathophysiological changes described above could be validated by the significant correlations observed between O_2 pulse,

echo-derived, and haemodynamic parameters in our study. As expected, the peak O_2 pulse was positively correlated with LVEDD and RVEDD/LVEDD ratios, exhibiting strong and moderate relationships, respectively. Additionally, the gold standard of SV measured by RHC at rest and right ventricular afterload determinants (PVR and PAC) were significantly related to O_2 pulse. Therefore, the peak O_2 pulse is a reliable substitute for the invasive RHC, and its abnormal reduction elucidates the underlying mechanisms of exertional intolerance in PAS-PH.

Moreover, the univariable Cox and ROC analyses indicated that peak O_2 pulse was strongly related to the outcomes, with the best predictive ability of clinical worsening. This association remained significant after adjusting for the established PH risk factors. Particularly, the additive prognostic value of the peak O_2 pulse to the previously established risk stratification strategy was observed, which further confirmed the superiority of the peak O_2 pulse as a prognostic marker, and this finding is consistent with those of previous studies. Badagliacca *et al.*²⁹ investigated the additive prognostic value of CPET in 102 patients with idiopathic PAH and observed that only peak O_2 pulse and right ventricular fractional area change emerged as independent predictors among a series of CPET and echocardiographic and haemodynamic parameters. Laukkanen *et al.*³⁰ also demonstrated a linear correlation between peak O_2 pulse and cardiovascular mortality beyond several conventional risk factors. Additionally, longitudinal changes in O_2 pulse during treatment have been suggested to predict survival in patients with PAH.³¹ However, conflicting data exist on whether peak O_2 pulse is a stronger predictor than peak VO_2 , and the prognostic value of CPET parameters may vary depending on the characteristics of the study population and outcomes of interest.^{30,32}

Other new CPET markers were also examined in our study, including OUES and peak circulatory power, as our primary aim was to explore the exercise profile of patients with PAS-PH fully. Notably, OUES is a submaximal exercise parameter of cardiorespiratory fitness, whereas peak circulatory power reflects cardiac pump function by combining cardiac output and blood pressure at peak exercise.^{13,33} Although their additive values on top of traditional clinical and haemodynamic indicators were not found in multivariable analysis, both of these parameters showed stronger prognostic value over peak VO_2 and required further exploration. Therefore, in addition to emphasizing the unique value of the peak O_2 pulse in PAS-PH, we recommend all potentially helpful metrics to be included in CPET reports, which will maximize the data collected through expired gas analysis and physiological monitoring. Overall, the CPET is an ideal tool for constructing a risk stratification framework that can guide clinical decision making and goal-oriented therapy.

Limitation

This study had a few limitations. First, one major drawback was that 16% of the patients were not included because of a lack of CPET data. However, we compared baseline characteristics between the included and excluded participants (Table S1) and observed that they were comparable in terms of demographic factors and disease severity. Therefore, the exclusion did not bias the current study. Second, this study had a relatively small sample size owing to the rarity of PAS-PH, representing a single-centre experience, which may have led to non-significant results regarding aetiology, therapeutic strategies, and several previously established CPET predictors. Therefore, the generalizability of our conclusions might be limited, and multicentre, large-scale studies are warranted to validate our findings. Third, 39 patients did not reach a $RER \geq 1.05$, indicating that the peak O_2 pulse observed in these patients might not truly reflect the maximal exercise capacity. However, we performed a sensitivity analysis in patients with $RER \geq 1.05$ and $RER < 1.05$, respectively, and peak O_2 pulse could predict clinical worsening, irrespective of $RER \geq 1.05$. Notably, a $RER < 1.05$ is commonly observed in patients with pulmonary hypertension.^{34–36} Consequently, failure to reach $RER \geq 1.05$ did not undermine the predictive value of the CPET parameters, and $RER < 1.05$ may be a clinical characteristic of some patients with PH rather than an indicator of failed maximum exercise.

Conclusions

The prognosis is poor for PAS-PH, and exercise intolerance and ventilation inefficiency are generally observed. In this study, peak O_2 pulse independently predicted the prognosis of patients with PAS-PH, and a low peak O_2 pulse identified patients at high risk of clinical deterioration and served for risk stratification of PAS-PH. Finally, CPET is a vital component of routine examinations and risk assessment for PAS-PH.

Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Correlations between CPET parameters and pulmonary hemodynamics.

Legends: CI, cardiac index; CircP, circulatory power; mPAP, mean pulmonary arterial pressure; OUES, oxygen uptake efficiency slope; PAC, pulmonary arterial compliance; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SV, stroke volume; S_vO_2 , mixed venous oxygen saturation; TPR, total pulmonary resistance; VCO_2 , carbon dioxide output; VE, minute ventilation; VO_2 , oxygen uptake.

* $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$.

Table S1. Baseline characteristics of included and excluded participants.

Table S2. Univariable Cox analysis for clinical worsening prediction.

Table S3. Prognostic value of abbreviated version of the 2015 ESC/ERS PH risk stratification combined with peak O_2 pulse.

Table S4. Univariable Cox analysis for clinical worsening prediction in patients with $RER < 1.05$.

Table S5. Univariable Cox analysis for clinical worsening prediction in patients with $RER \geq 1.05$.

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