Exercise Tolerance In Patients With Idiopathic Pulmonary Artery Hypertension: Insight Into Risk Thresholds And Prediction Capacity For 5-Year Mortality

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Abstract

Background: Exercise tolerance is pivotal for risk-stratification in patients with idiopathic pulmonary artery hypertension (IPAH), yet optimal risk predictors and risk thresholds remain uncertain. This study aimed to investigate risk estimates of cardiopulmonary exercise testing (CPET) associated with 5-year mortality in patients with IPAH and explore their risk thresholds and prediction capacity.

Methods: Consecutive patients with IPAH who underwent right heart catheterization and CPET were retrospectively enrolled and followed up for five years. Multivariable Cox proportional hazards models were used to determine independent prognostic factors for mortality. The risk trend and threshold for mortality were exhibited using restricted cubic splines. Survival rates were estimated by Kaplan-Meier analysis stratified by various CPET parameters.

Results: Among 210 patients with IPAH (75.7% female), 37 (17.6%) died during a 34-month median follow-up. Three CPET variables were independently predictive of mortality in multivariable Cox regression analysis (all $P<0.05$), including oxygen uptake efficiency slope (OUES), peak oxygen pulse (VO_2/HR), and peak oxygen consumption (VO_2), in descending order of prediction power (χ^2 = 37.39 > 35.96 > 35.57). The levels of OUES at 0.91, peak VO_2/HR at 5.3 ml·min^{-1}·beat^{-1}, and peak VO_2 at 12.2 ml·kg^{-1}·min^{-1} were respectively identified as risk thresholds for mortality. Patients below these thresholds had significantly higher mortality risk (adjusted hazard ratio of OUES: 3.34; peak VO_2/HR: 3.76; and peak VO_2: 1.56) and lower survival rates (log-rank test, all $P<0.01$). The joint model (area under the curve [AUC] 0.838) of these CPET variables (AUC 0.724) and estimates in contemporary risk assessment tools (AUC 0.809) provided more excellent prediction capacity for 5-year mortality.

Conclusions: Suboptimal exercise tolerance indicated by OUES, peak VO_2/HR, and peak VO_2 under certain thresholds posed a higher mortality risk in patients with IPAH, and their joint combination further improved the prediction capacity.

Introduction

Idiopathic pulmonary artery hypertension (IPAH) is a rare but devastating disease characterized by progressive remodeling of the small pulmonary arteries, leading to increased pulmonary vascular resistance, right heart failure (HF), and even death [1]. Despite advances in modern therapeutics for pulmonary artery hypertension (PAH), such as various combinations of drugs and modes of administration, the long-term prognosis remains unsatisfactory [2]. Exploring prognostic indicators of adverse outcomes is thereby warranted to facilitate a more accurate and urgent risk stratification.

Cardiopulmonary exercise testing (CPET) permits the evaluation of exercise intolerance [3]. It has become a valuable tool that has the potential of non-invasively estimating disease severity, therapeutic response, and prognosis in patients with pulmonary hypertension (PH) [4-10]. Parameters that have been shown to embody these capabilities included peak oxygen consumption (VO_2), ventilation/carbon dioxide

output slope (VE/VCO_2 slope), end-tidal partial pressure of carbon dioxide at anaerobic threshold ($PETCO_2$@AT), and oxygen uptake efficiency slope (OUES). In recent years, there has been emerging data on the superiorities of OUES in predicting outcomes in patients with HF [11, 12] and PAH [7, 8] over other ventilatory efficiency parameters such as VE/VCO_2 slope. However, findings into CPET variables predictive of poor outcomes have been inconsistent and contradictory [4-10]. Notably, most of these variables and cut-off values were based on expert opinion or receiver operator characteristic curves (ROC). The dynamic risk range and thresholds for these CPET metrics associated with adverse outcomes, and the additional role in PAH risk-stratification according to current guidelines, were less explored.

Therefore, the purpose of this study was (1) to determine and compare the prognostic significance of risk parameters of CPET for predicting 5-year mortality, and (2) to explore their risk thresholds and whether they can further improve the prediction capacity compared to contemporary assessment tools for patients with IPAH.

Methods

Participants

Consecutive patients admitted to Fuwai Hospital from January 2015 to January 2020 with a newly diagnosed IPAH were retrospectively enrolled in this cohort. The diagnosis of IPAH was confirmed through right heart catheterization (RHC) according to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines. Baseline clinical data including demographics, World Health Organization functional class (WHO-FC), 6-minute walk distance (6MWD), and key laboratory tests were collected upon admission. The study was approved by the Fuwai Hospital Ethics Committee (No. 2018-1100). Written informed consent was obtained from all enrolled participants.

Cardiopulmonary Exercise Testing

All recruited patients underwent CPET using the COSMED Quark CPET system before receiving specific therapy. The test was conducted by an experienced medical staff blinded to patients' medical records, and the equipment was calibrated before the individual test. Oxygen therapy was ceased for at least 30 minutes before performing CPET. After a 3-minute resting and a subsequent 3-minute warm-up of unloaded pedaling, patients started to exercise on a cycle ergometer with electromagnetic brake at a progressively incremental work rate of 5-30 W/min according to the estimated exercise tolerance until reaching volitional exhaustion or symptoms limitation. Gas exchange parameters were measured by a metabolic cart on a breath-by-breath basis and averaged over 10-second intervals. Peak VO_2 was defined as the highest obtained average oxygen consumption measured over 30 seconds in the last minute of exercise. Peak VO_2/heart rate (HR) was calculated as peak VO_2 divided by peak heart rate. The ventilatory AT was detected by combining the V-slope method and ventilatory equivalents [13]. The VE/VCO_2 slope was identified as the slope of the linear regression relationship between minute ventilation (VE) and carbon dioxide production from resting to the peak exercise. The OUES represented the slope of the

regression line between VO_2 (*y* axis, $L \cdot min^{-1}$) and the logarithmically transformed VE (*x* axis, $L \cdot min^{-1}$) across the entire exercise course. Heart rate was measured every 1 minute. Heart rate reserve was calculated as the difference between peak and resting heart rate. Blood pressure was recorded at 3-minute intervals and when the patients expressed peak exercise.

Hemodynamic Studies

Hemodynamic assessment with RHC was performed at resting to facilitate the diagnosis of IPAH. Parameters composed of mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), mixed venous oxygen saturation, and cardiac output. Diagnostic criteria of IPAH include an mPAP $\geq$ 25 mmHg, and PVR > 3 Wood units at rest in the presence of a normal PCWP $\leq$ 15 mmHg when none of the definite PH etiologies (e.g., connective tissue disease, congenital heart defect, heritable, drugs or toxins-induced, severe lung or left-sided heart diseases, et al.) were found.

Follow-up and Outcome Measures

The primary clinical outcome was the rate of 5-year all-cause mortality. Follow-up information was obtained by telephone calls or routine clinical visits to monitor outcomes every three months during the first year and every six months after that. Patient deaths were confirmed by medical records or death certificates review. Overall survival time of patients was measured from the date of CPET until five years or to the date of patient death, whichever occurred first.

Statistical Analysis

Continuous and categorical variables were presented as the mean ± standard deviations and counts (proportions), respectively. Comparisons between the survivors and non-survivors were made by two-tailed independent samples *t*-tests for normally distributed variables and nonparametric Mann-Whitney *U* test for not normally distributed variables, while *chi*-square test was used for categorical variables. Cox proportional hazards regression analysis was performed to evaluate the prognostic value of different parameters. Variables included in multivariable models were based on their clinical relevance and statistical significance in the univariable analysis. To identify the risk thresholds and trends, the continuous association of individual CPET estimates with mortality was modeled using restrictive cubic splines models with four knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles adjusting for gender (female), WHO-FC, PVR, and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). The Kaplan-Meier survival curves were employed to depict the differences in the 5-year survival rate between patients with values above or below the risk thresholds estimated from cubic splines models. Curves were compared using the log-rank test. ROC analysis was used to evaluate the additional role of CPET parameters in risk prediction compared to European guidelines and identify the optimal prediction models. Correlations between CPET variables and pulmonary hemodynamics were also explored using the *Pearson* correlation coefficient. A two-sided $P<0.05$ was considered statistically significant. Statistical analyses were

performed using *R* statistical version 3.6.3 (*R* Project for Statistical Computing) within RStudio statistical software version 1.1.453.

Results

Baseline Characteristics

Of 211 consecutive patients with IPAH who underwent CPET, one was lost to follow-up due to lung transplantation, and the remaining 210 patients (51 men and 159 women, aged 31.9±10.0 years) were included in the final analysis. The majority presented with WHO-FC II and III, consisting of 105 and 91 individuals. The mean levels of NT-proBNP were 1302.2 pg/ml, with 6MWD 388.0±93.3 meters and the cardiac index 2.8±0.9 ml/min/m^2. A total of 180 (85.7%) patients received specific targeted therapy. Patients not receiving targeted therapy were mainly due to financial burden, intolerability, and cautions about adverse effects. During a median 34-month follow-up, 37 patients died in the entire cohort, accounting for a 17.6 % mortality rate.

Comparisons between Survivors and Non-Survivors

Demographics did not differ between survivors and non-survivors, whereas non-survivors had significantly worse WHO-FC (III/IV, 64.9% vs. 42.8%, *P*=0.007), and decreased 6MWD (352.5±110.4 vs. 396.3±87.4, *P*=0.042, **Table 1)**. Non-survivors also had higher mPAP, PVR, RAP, and lower cardiac index (all *P*<0.05). No group differences were observed in CPET-derived parameters for peak work rate, peak respiratory exchange rate, and peak heart rate. Distinctively, non-survivors had lower levels of heart rate reserve, peak VO_2, peak VO_2/HR, AT, peak systolic blood pressure (SBP), peak diastolic blood pressure, and had poorer ventilation efficiency (e.g., higher VE/VCO_2 Slope and lower $PETCO_2$@AT).

Predictors of 5-Year Mortality

In the univariable Cox regression analysis, WHO-FC, NT-proBNP, hemodynamic parameters, peak work rate, HRR, peak VO_2, peak VO_2/HR, peak SBP, AT, PETCO2@AT, VE/VCO_2 slope, and OUES were associated with an increased risk of 5-year mortality (all *P*<0.05, **Table 2**). To reduce collinearity between CPET parameters, separate multivariable Cox regression models were developed to assess their independent prognostic significance for mortality risk. As there were not enough primary outcomes, thereby avoiding overfitting for mortality, we only put gender (female), WHO-FC, PVR, and NT-proBNP into the multivariable analysis considering their clinical significance and chi-square values and *P* values in the univariable analysis. Each line in **Table 3** represents a separate model adjusting for gender (female), WHO-FC, PVR, and NT-proBNP. Among these CPET variables, OUES, peak VO_2/HR, and peak VO_2 remained independently associated with mortality, in descending order of prediction power (x^2 = 37.39 > 35.96 > 35.57). The lower these variables were, the higher the mortality risk (OUES: hazard ratio [HR] (95% confidence interval [CI]) 0.998 (0.996-0.999), *P*=0.005; peak VO_2/HR: 0.717 (95% CI 0.534-0.964), *P*=0.027; and peak VO_2: 0.868 (95% CI 0.758-0.995), *P*=0.042). The distribution of their levels in different

WHO-FC groups is demonstrated in **Fig. 1**. As cardiac function worsened, exercise capacity indicated by these parameters gradually declined (*P*-value for trend <0.05).

Risk Thresholds Exploration

As shown in **Fig. 2**, optimal exercise tolerance reflected by higher OUES, peak VO_2/HR, and peak VO_2 were beneficial in reducing mortality risk, yet associations of these metrics with mortality appeared to differ at low to moderate levels. For peak VO_2, there was a positive linear association, with the lowest mortality risk seen in those with peak VO_2 reaching approximately 20 ml·kg^{-1}·min^{-1}. The adjusted HR of 5-year mortality appeared to continuously escalate as peak VO_2 decreased below levels of 12.2 ml·kg^{-1}·min^{-1}. In contrast, the relationship between OUES and mortality was curvilinear, with maximal mortality between 0.5 and 0.91 among which the risk reaches the peak at 0.72, and with declining mortality risk above 0.91. Peak VO_2/HR between 1 and 5.3 ml·min^{-1}·beat^{-1} is associated with the highest excess mortality, whereas peak VO_2/HR ≥5.3 ml·min^{-1}·beat^{-1} corresponds to the threshold above which mortality risk starts to decrease and reach a steady-state above the estimated level of 6 ml·min^{-1}·beat^{-1} (*P*=0.828 for non-linearity for OUES; *P*=0.0324 for non-linearity for peak VO_2/HR).

Long-Term Survival Analysis

Kaplan-Meier curves for survival stratified by OUES, peak VO_2/HR, and peak VO_2 are shown in **Fig. 3**. When these parameters were expressed dichotomously based on the risk threshold derived from restrictive cubic splines, OUES, peak VO_2/HR, and peak VO_2 all predicted mortality well. Patients with OUES <0.91 (N=104) had a worse 5-year survival rate than those with OUES ≥ 0.91 (N=106) (72.1% vs. 92.5%, *P*=0.007). The unadjusted and adjusted HR of mortality was 4.84 (95% CI 2.20-10.65) and 3.34 (95% CI 1.38-8.05), respectively. Patients with peak VO_2/HR <5.3 (N=106) had a worse 5-year survival rate than those with peak VO_2/HR ≥5.3 ml·kg^{-1}·min^{-1} (N=104) (73.6% vs. 91.3%, *P*=0.002). The unadjusted HR of mortality was 3.42 (95% CI 1.61-7.24), and after adjustment for gender, WHO-FC, PVR, and NT-proBNP, the HR was 3.76 (95% CI 1.61-8.82). Similarly, patients with peak VO_2 ≤12.2 ml·kg^{-1}·min^{-1} exhibited a significantly lower survival rate than those with peak VO_2 >12.2 ml·kg^{-1}·min^{-1} (76.0% vs. 88.7%, *P*=0.0045); and the adjusted HR for mortality was 1.56 (95% CI 1.32-5.44).

Prediction Capacity for Mortality

ROC curves are plotted to determine the overall accuracy for mortality risk prediction (**Fig. 4**). The combination of OUES, peak VO_2/HR, and peak VO_2 (Model 4: area under the ROC curve [AUC]=0.724, 95% CI 0.648-0.801) outperformed the models with their components (Model 1: OUES, AUC=0.714; Model 2: peak VO_2/HR, AUC=0.652; and Model 3: peak VO_2: AUC=0.676). Model 5 included simplified risk estimates i.e., WHO-FC, 6MWD, NT-proBNP and cardiac index according to European PH guidelines, and it showed moderate accuracy for risk prediction (AUC=0.809, 95% CI 0.697-0.922). The joint combination (Model 6) of CPET parameters and the risk estimates in the simplified version of ESC/ERS PH guidelines

was preferable to the remaining models given its largest AUC and most excellent accuracy for mortality risk prediction (Model 6: AUC=0.838, 95% CI 0.736-0.941; Specificity 89.9%; Sensitivity 72.7%).

Correlations between CPET and Pulmonary Hemodynamics

As the heat map showed (**Fig. 5**), blue represents positive correlation, whereas red represents negative correlation. The darker the color, the stronger is the correlation. The OUES was negatively correlated with PVR (r=−0.49, P<0.001), sPAP (r=−0.43, P<0.001) and mPAP (r=−0.39, P<0.001), while negatively correlated with cardiac index (r=0.42, P<0.001). The peak VO_2/HR was negatively associated with PVR (r=−0.46, P<0.001), sPAP (r=−0.41, P<0.001), mPAP (r=−0.38, P<0.001), while negatively correlated with cardiac index (r=0.30, P<0.001). With respect to peak VO_2, positive correlations with PVR (r=−0.38, P<0.001), sPAP (r=−0.35, P<0.001), mPAP (r=−0.32, P<0.001), while negative correlations with cardiac index (r=0.47, P<0.001) were observed. It seemed that PVR, cardiac index, and mPAP were potential indicators that mediate cardiopulmonary function in conferring mortality risk.

Discussion

In this long-term follow-up study of 210 patients with IPAH, the OUES, peak VO_2/HR, and peak VO_2 were found to be independent markers for 5-year mortality. Notably, we offered a fresh perspective on the risk thresholds and prognostic impact of varying intensities of exercise capacity on mortality. The joint combination of these parameters can further improve the risk prediction capacity compared to contemporary assessment tools for patients with IPAH.

Identifying patients at higher mortality risk of IPAH remains an area of intense investigation and is of utmost importance to guide their therapeutic strategies. A growing body of evidence has shown the prognostic value of exercise tolerance in predicting survival in patients with PAH. For example, peak VO_2, $PETCO_2$@AT, VE/VCO_2 slope, oxygen pulse, and peak SBP during CPET were correlated with survival in patients with PAH [14]. Nonetheless, only peak VO_2 (≤10.4 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$) and peak SBP (≤120 mmHg) were independent predictors of mortality in the previous studies [6, 14]. These findings were in part in agreement with the results of our study conducted in patients with IPAH. Remarkably, we further enhanced the understanding of the risk threshold (12 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$) for capturing the dynamic trend in mortality risk. Consistently, exercise capacity is considered a vital component of the REVEAL 2.0 [15] and ESC/ERS risk stratification tools [16], and current guidelines recommend assessing exercise tolerance for decision-making [1, 17]. Accumulating evidence suggests that exercise training confers a protective effect on exercise capacity as indicated by improvement of peak VO_2 [18-20], possibly due to the increased capillary density of skeletal muscle [19] and optimized oxidative enzyme function in the peripheral muscles [21]. However, peak VO_2 was not proved as an independent predictor in some other PAH cohort studies [6, 22], probably ascribed to a lack of patient motivation and premature termination of exercise by the examiner. Overall, these discrepant findings could be attributed to the differences in sample size,

associated conditions, or comorbidities. In this matter, our findings may be better applicable to IPAH with fewer comorbidities.

OUES, a useful submaximal exercise index of aerobic fitness, represents the absolute rate of increase in oxygen consumption per 10-fold increase in ventilation. A higher OUES represents more oxygen being delivered in the body, while a lower OUES represents an enormous amount of ventilation required for given oxygen uptake. Three main factors can influence the values of OUES, including arterial carbon dioxide setpoint, carbon dioxide production, and death space ventilation [23, 24]. An earlier investigation showed that the arterial carbon dioxide setpoint did not vary between normal individuals and HF during exercise [25]. As such, both systemic perfusion (related to carbon dioxide production) and pulmonary perfusion (related to dead space ventilation) are related to the magnitude of OUES. Previous literature has shown that OUES was strongly correlated with peak VO_2 and provided better predictive power over peak VO_2 in patients with left-sided HF [11, 26] and PAH [10]. These observations were consistent with our findings regarding the superiority of OUES over peak VO_2 in predicting adverse outcomes.

Peak VO_2/HR reflects the amount of oxygen consumed per heartbeat (i.e., the product of stroke volume and arteriovenous oxygen difference during exercise). It indirectly indicates the maximal myocardial oxygen supply and cardiac function reserve under stress. The correlation analysis supports that peak VO_2/HR is associated with decreased cardiac index and a higher mortality risk beyond the risk threshold. In comparison, a recent study explored the role of peak VO_2/HR in patients with chronic obstructive pulmonary disease and concluded that it might be an indicative parameter of lung hyperinflation, PH, and HF comorbidity [27]. Apart from this, we further supported the role of peak VO_2/HR in estimating long-term mortality risk in patients with IPAH. It emphasizes maintaining an appropriate cardiovascular function by individualized exercise training and aggressive specific drug treatments.

Meanwhile, interestingly, we found that VE/VCO_2 slope did not predict the poor outcome, in contrast to the previous literature [9, 12, 14, 28], but consistent with others [6, 8, 10, 11]. For example, Davies et al. [11] concluded that OUES rather than peak VO_2 and VE/VCO_2 slope was the most powerful predictor in patients with left-sided HF. Similar findings were also observed in patients with PAH [8, 10]. We proved that OUES provided better prognostic information than that provided by VE/VCO_2, and more meaningfully, shed light on their risk thresholds. This may be linked to the fact that OUES reflects not only the status of pulmonary perfusion but systemic perfusion. Nonetheless, opposite results showing that VE/VCO_2 plays a predominant role in predicting outcomes were observed in a study by Arena et al. [12]. Speculatively, underlying clues explaining these discrepancies include the β-blockers use, the study period, and the population inhomogeneity. Moreover, the 6MWD in our study did not associate with the outcome, which may be attributable to the selection of stable patients with relatively high values where peak VO_2, peak VO_2/HR, and OUES become more sensitive to functional exercise capacity.

The OUES seemed to be a vital predictive factor superior to the other CPET-derived parameters. There were curvilinear relationships between OUES and peak VO_2/HR and mortality risk. The joint combination of independent indicators – OUES, peak VO_2/HR, and peak VO_2 had a better prognostic prediction value than the simplified risk estimates in 5-year mortality. Close monitoring of these CPET variables may aid in better risk stratification and individualized therapy for patients with IPAH. The OUES and peak VO2/HR seem likely to further increase mortality risk at some low measurement levels. However, However, future studies are needed to explore the underlying exacerbating mechanisms and elaborate whether cardiopulmonary rehabilitation could serve as a critical strategy to alleviate exercise intolerance, ameliorate disease progression, and improve outcomes in patients with IPAH.

This long-term follow-up study characterized the continuous relationship between exercise tolerance and mortality risk. Greater statistical power using adjusted restrictive cubic splines models enhanced detection of the different associations seen with CPET risk thresholds and mortality, which have been rarely undertaken before. Several limitations also warrant discussion. First, our study only included patients with IPAH with a lower percentage of WHO-FC IV. The findings thereby may not be generalized to other PAH and those with poorer cardiac function. Second, although the data were prospectively collected, our analysis was retrospective in nature. Despite the multivariate adjustment, we cannot exclude the possibility of residual confounding and reverse causality. Finally, limited information was available on the PAH-specific treatments on the changes of the CPET variables. Future multi-center and large-scale studies are required to validate our findings and explore the potential aggressive therapeutic effects on exercise tolerance and disease outcomes.

Conclusions

Suboptimal exercise tolerance reflected by OUES, peak VO_2/HR, and peak VO_2 under certain thresholds provides excellent prognostic information for 5-year mortality in patients with IPAH. The joint combination of these parameters and simplified risk estimates can improve the risk prediction capacity compared to contemporary assessment tools for patients with IPAH.

List Of Abbreviations

AT, anaerobic threshold

CPET, cardiopulmonary exercise testing

IPAH, idiopathic pulmonary artery hypertension

mPAP, mean pulmonary artery pressure

6MWD, 6-minute walk distance

NT-proBNP, N-terminal prohormone of brain natriuretic peptide

OUES, oxygen uptake efficiency slope

PAH, pulmonary artery hypertension

PCWP, pulmonary capillary wedge pressure

$PETCO_2$@AT, end-tidal partial pressure of carbon dioxide at anaerobic threshold

PVR, pulmonary vascular resistance

RAP, right atrial pressure

RHC, right heart catheterization

VE, minute ventilation

VE/VCO_2 slope, ventilation/carbon dioxide

VO_2, oxygen consumption

WHO-FC, World Health Organization functional class

Declarations

Ethical approval and consent to participate

Ethical approval for this study was obtained from the Institution Review Board of the Fuwai Hospital Ethics Committee (No. 2018-1100).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZH and LY contributed to the study design, data analysis, manuscript drafting and revision. ZZ, QZ acquired data, critically reviewed, and revised the manuscript. YT, QJ, YZ, XL, AD, MH performed literature search. QL and ZL provided professional advice on data interpretation, critically reviewed, and revised the manuscript. All authors contributed substantially to the work and approved the final manuscript.

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Tables

Table 1 Baseline Characteristics of Study Population.

Variables	Survivors (n=173)	Non-Survivors (n=37)	All (n=210)	*P*-value
Age, years	31.9±10.0	33.4±13.5	32.2±10.7	0.538
Female, n (%)	135(78.0)	24(64.9)	159(75.7)	0.09
BMI, kg/m^2	22.6±3.5	22.1±3.2	22.5±3.5	0.369
WHO-FC, I/II/III/IV, n	7/92/71/3	0/13/20/4	7/105/91/7	0.007
6MWD, m	396.3±87.4	352.5±110.4	388.0±93.3	0.042
NT-proBNP, pg/mL	1145.2±803.0	2036.2±1254.1	1302.2±957.8	<0.001
Targeted Therapy†, n (%)	147(85.0)	33(89.2)	180(85.7)	0.506
Hemodynamics				
RAP, mmHg	4.9±4.1	7.7±4.9	5.4±4.4	<0.001
sPAP, mmHg	88.5±24.2	98.2±21.1	90.2±23.9	0.026
mPAP, mmHg	56.8±16.0	65.7±15.6	58.4±16.3	0.002
PVR, Wood Units	12.0±5.8	15.5±7.7	12.6±6.3	0.002
PCWP, mmHg	7.2±3.4	9.6±2.8	7.6±3.4	<0.001
CO, ml/min	4.7±1.6	4.0±1.1	4.6±1.5	0.018
CI, $ml/min/m^2$	2.9±0.9	2.4±0.6	2.8±0.9	0.010
SvO_2, %	69.7±7.7	68.2±7.4	69.5±7.6	0.285
CPET				
Peak WR, W	72.9±24.9	64.4±25.3	71.4±25.2	0.062
Peak RER	1.1±0.1	1.2±0.3	1.1±0.2	0.404
Peak HR, min^{-1}	143.2±19.3	137.9±24.8	142.3±20.4	0.225
HRR, min^{-1}	21.9±9.9	17.2±10.3	21.1±10.1	0.009
Peak VO_2, $ml{\cdot}kg^{-1}{\cdot}min^{-1}$	13.2±3.6	11.1±2.3	12.8±3.5	<0.001
Peak VO_2/HR, $ml{\cdot}min^{-1}{\cdot}beat^{-1}$	5.6±1.7	4.9±1.5	5.5±1.6	0.023
Peak SBP, mmHg	131.4±35.0	111.5±19.1	127.9±33.6	<0.001
Peak DBP, mmHg	86.3±22.1	78.7±13.0	84.9±21.0	0.007
AT, $ml{\cdot}kg^{-1}{\cdot}min^{-1}$	10.0±2.5	9.0±2.4	9.8±2.5	0.033

$PETCO_2$@AT, mmHg	29.4±5.4	26.1±5.0	28.8±5.5	<0.001
VE/VCO_2 Slope	46.4±16.8	57.8±18.5	48.4±17.6	<0.001
OUES	0.97±0.32	0.76±0.83	0.94±0.31	<0.001

Data are expressed as mean ± SD or number (percentage). AT, anaerobic threshold; BMI, body mass index; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; HRR, heart rate reserve; mPAP, mean pulmonary artery pressure; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OUES, oxygen uptake efficiency slope; PCWP, pulmonary capillary wedge pressure; $PETCO_2$@AT, end-tidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SvO_2, venous oxygen saturation; VCO_2, carbon dioxide output; VE, minute ventilation; VO_2, oxygen consumption; WHO-FC, World Health Organization Functional Class; WR, work rate.

Table 2 Univariate Cox Regression Analysis of Risk Factors Associated with Mortality.

Variables	Hazard Ratio	95% CI	χ^2	*P*-value
Age	1.009	0.980-1.039	0.372	0.546
Female	0.548	0.279-1.077	3.136	0.092
BMI	0.945	0.859-1.041	1.313	0.253
WHO-FC (III/IV vs I/II)	2.188	1.112-4.308	5.399	0.023
NT-proBNP	1.001	1.000-1.001	29.707	<0.001
6MWD	0.997	0.993-1.002	1.601	0.206
sPAP	1.016	1.003-1.029	6.121	0.014
mPAP	1.025	1.007-1.043	7.937	0.005
PCWP	1.151	1.049-1.262	9.15	0.003
PVR	1.065	1.024-1.108	10.032	0.004
RAP	1.107	1.037-1.183	9.524	0.002
CO	0.707	0.534-0.936	5.692	0.015
CI	0.563	0.356-0.890	5.988	0.014
SvO_2	0.990	0.953-1.028	0.287	0.592
Peak WR	0.984	0.970-0.998	4.837	0.021
Peak RER	1.840	0.697-4.862	1.609	0.219
Peak HR	0.988	0.973-1.002	2.884	0.988
HRR	0.001	0.915-0.978	10.812	0.001
Peak VO_2	0.808	0.722-0.905	13.54	<0.001
Peak VO_2/HR	0.717	0.557-0.923	6.578	0.010
Peak SBP	0.981	0.968-0.995	7.031	0.004
Peak DBP	0.986	0.965-1.007	1.651	0.197
AT	0.857	0.755-0.973	5.717	0.017
$PETCO_2$@AT	0.915	0.866-0.968	9.631	0.002
VE/VCO_2 Slope	1.021	1.009-1.034	11.735	0.001
OUES	0.997	0.996-0.999	15.737	<0.001

AT, anaerobic threshold; BMI, body mass index; CI, cardiac index; CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; HRR, heart rate reserve; mPAP, mean pulmonary artery pressure; 6MWD, 6-minute walk distance; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OUES, oxygen uptake efficiency slope; PCWP, pulmonary capillary wedge pressure; $PETCO_2$@AT, end-tidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RER, respiratory exchange ratio; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure; SvO_2, venous oxygen saturation; VCO_2, carbon dioxide output; VE, minute ventilation; VO_2, oxygen consumption; WHO-FC, World Health Organization; Functional Class; WR, work rate.

Table 3 Multivariable Cox Regression Analysis of CPET Variables Associated with Mortality.

Variables	Hazard Ratio	95% CI	χ^2	C-index	*P*-value
VE/VCO_2 Slope†	1.009	0.992-1.025	33.65	0.740	0.298
Peak SBP†	0.985	0.971-1.000	34.84	0.765	0.056
HRR†	0.978	0.942-1.016	33.83	0.742	0.252
AT†	0.963	0.835-1.111	33.30	0.737	0.605
$PETCO_2$@AT†	0.958	0.898-1.022	33.61	0.741	0.195
Peak WR†	0.988	0.970-1.006	34.21	0.744	0.180
Peak VO_2†	0.868	0.758-0.995	35.57	0.751	0.042
Peak VO_2/HR†	0.717	0.534-0.964	35.96	0.755	0.027
OUES†	0.998	0.996-0.999	37.39	0.771	0.005

†Each line in table represents a separate Cox regression model adjusting for Gender (female), WHO-FC, PVR, and NT-proBNP. AT, anaerobic threshold; CI, confidence interval; HR, heart rate; HRR, heart rate reserve; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OUES, oxygen uptake efficiency slope; $PETCO_2$@AT, end-tidal partial pressure of carbon dioxide at anaerobic threshold; PVR, pulmonary vascular resistance; SBP, systolic blood pressure; VCO_2, carbon dioxide output; VE, minute ventilation; VO_2, oxygen consumption; WHO-FC, World Health Organization Functional Class; WR, work rate.

Figures

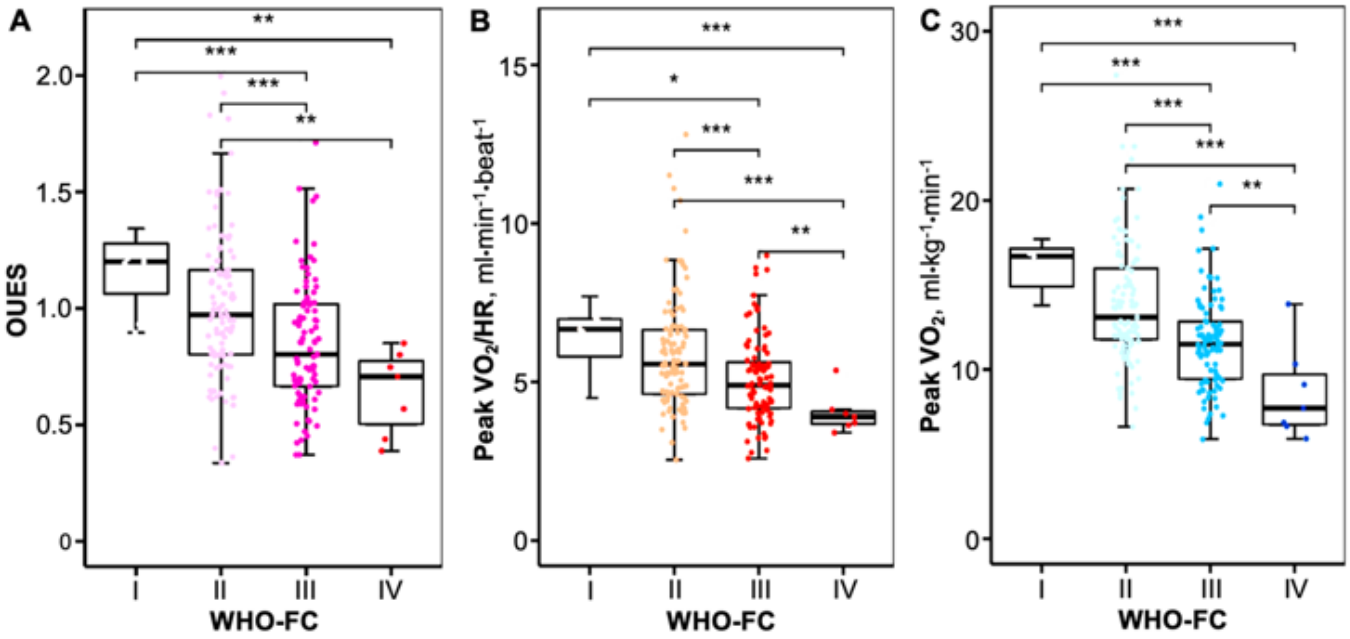

Figure 1

Boxplots of OUES **(A)**, peak VO_2/HR **(B)**, and peak VO_2 **(C)** in WHO-FC groups. OUES, oxygen uptake efficiency slope; VO_2, oxygen consumption; HR, heart rate; WHO-FC, World Health Organization Functional Class. Between-group differences: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

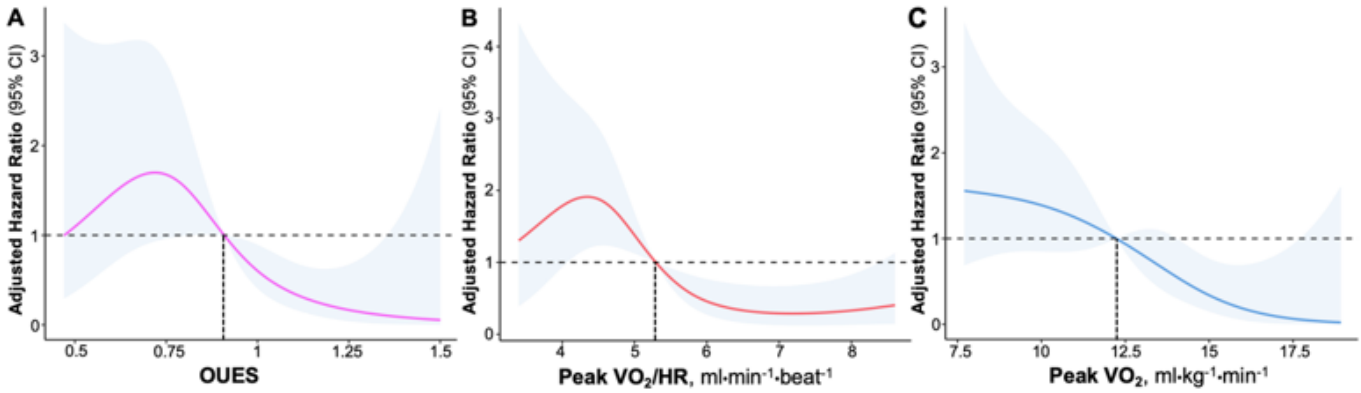

Figure 2

Restrictive cubic splines of associations between 5-year mortality risk and OUES **(A)**, Peak VO_2/HR **(B)**, and Peak VO_2 **(C)**. The restrictive cubic splines models were adjusted for gender, WHO-FC, PVR, and NT-proBNP, with knots at the 5^{th}, 35^{th}, 65^{th}, and 95^{th} percentiles. The horizontal dash line indicates a null hazard ratio equal to 1. The solid line denotes the estimated hazard ratio. The shaded area represents the 95% confidence limits. The hazard ratio is per each absolute increase of 1 unit of individual CPET

parameter level. HR, heart rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OUES, oxygen uptake efficiency slope; PVR, pulmonary vascular resistance; VO_2, oxygen consumption; WHO-FC, World Health Organization Functional Class.

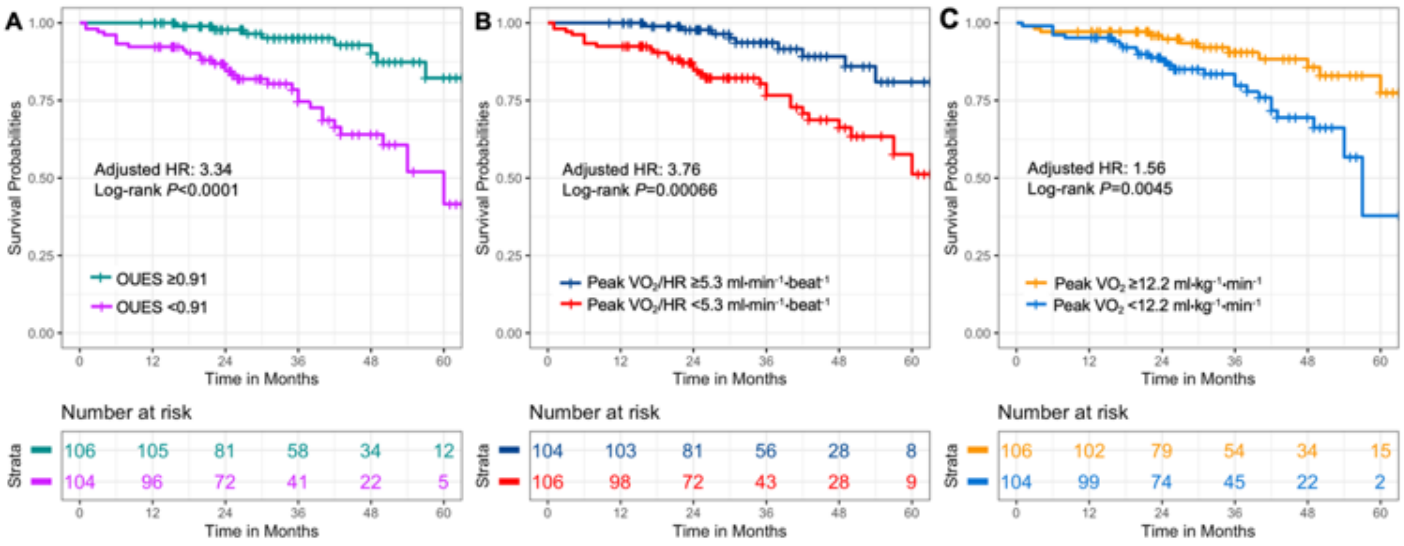

Figure 3

Kaplan-Meier curves for survival stratified by OUES **(A)**, Peak VO_2/HR **(B),** Peak VO_2 **(C)**. Adjusted HR indicates hazard ratio adjusted for gender, WHO-FC, PVR, and NT-proBNP. HR, heart rate; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OUES, oxygen uptake efficiency slope; PVR, pulmonary vascular resistance; VO_2, oxygen consumption; WHO-FC, World Health Organization Functional Class.

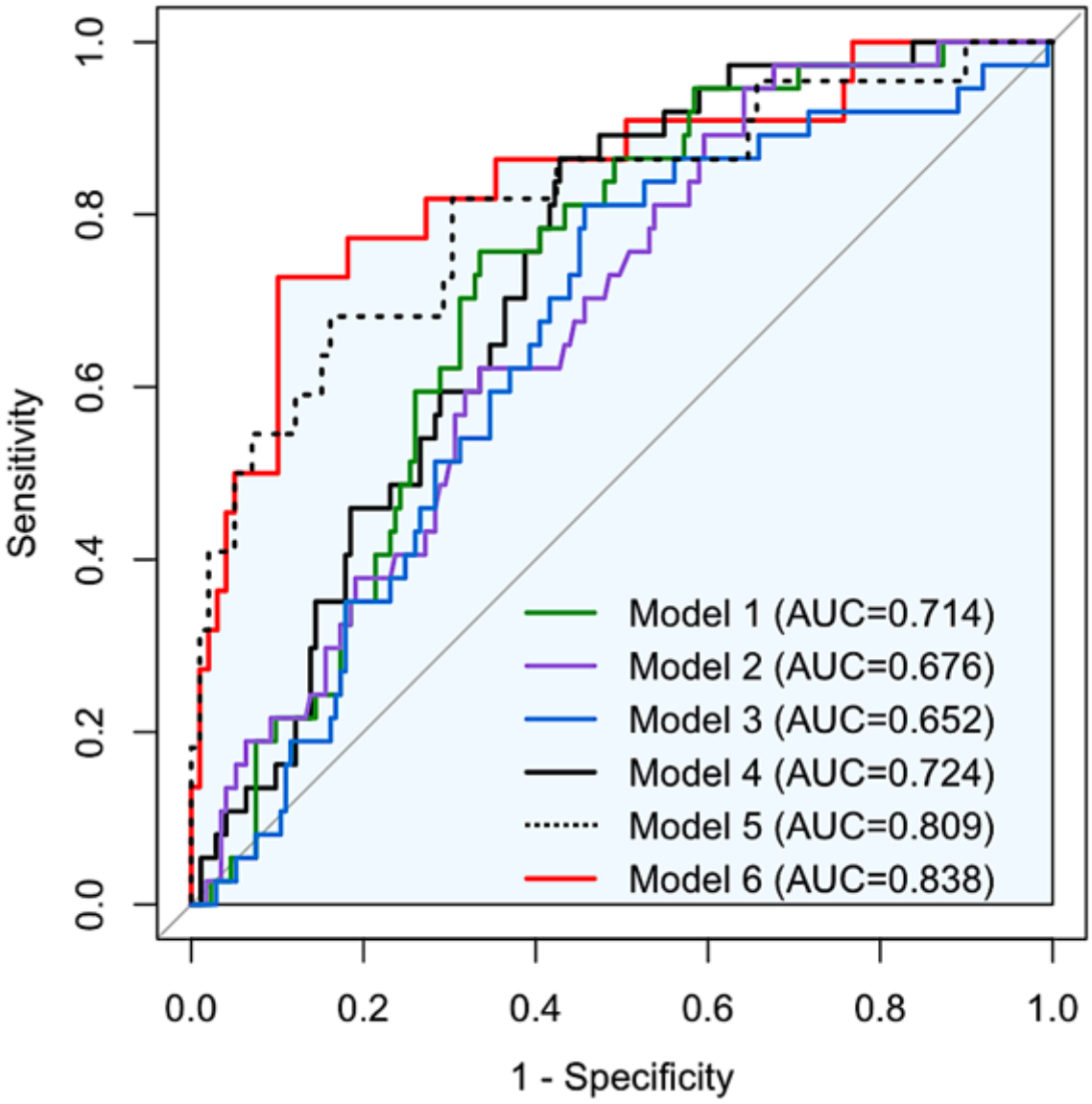

Figure 4

Risk prediction models for 5-year mortality in patients with IPAH. Each ROC curve represents one model. Parameters incorporated in each model are as follows. Model 1: OUES (AUC=0.714, 95% CI 0.635-0.793). Model 2: peak VO_2/HR (AUC=0.652, 95% CI 0.561-0.744). Model 3: peak VO_2 (AUC=0.676, 95% CI 0.591-0.762). Model 4: the combination of OUES, peak VO_2/HR and peak VO_2 (AUC=0.724, 95% CI 0.648-0.801). Model 5: risk estimates in the simplified version of the risk assessment strategy proposed by European PH guidelines, including WHO-FC, 6MWD, NT-proBNP, and Cardiac index (AUC=0.809, 95% CI 0.697-0.922). Model 6: parameters in model 5 and model 6 (AUC=0.838 95% CI 0.736-0.941; Specificity 89.9%; Sensitivity 72.7%). AUC, area under the receiver operating characteristic curve; CI, confidence interval; HR, heart rate; IPAH, idiopathic pulmonary artery hypertension; OUES, oxygen uptake efficiency slope; PH, pulmonary hypertension; ROC, receiver operator characteristic curve; VO_2, oxygen consumption; WHO-FC, World Health Organization Functional Class.

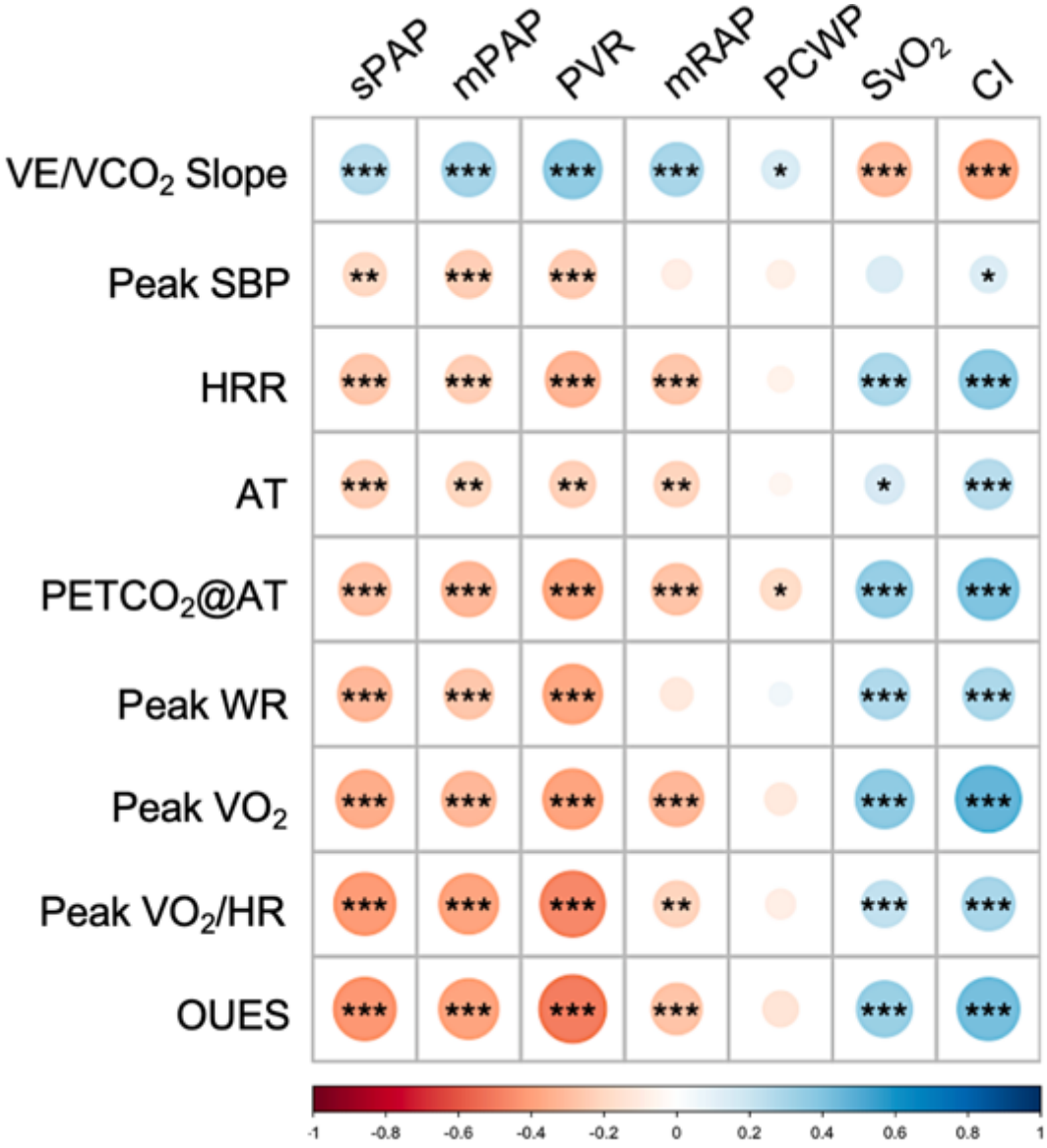

Figure 5

The heatmap of correlations between pulmonary hemodynamics and cardiopulmonary exercise testing parameters. Blue represents positive correlation, whereas red represents negative correlation. The darker the color, the stronger is the correlation. Asterisk reflects significant Pearson correlation coefficient: $^{*}P < 0.05$; $^{*}P < 0.05$; $^{*}P < 0.001$.