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EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original Research Article

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Please cite this article as: Baccelli A, Rinaldo RF, Haji G, *et al*. Prognostic value of cardiopulmonary exercise testing in pulmonary arterial hypertension. *Eur Respir J* 2025; in press (https://doi.org/10.1183/13993003.02026-2024).

Prognostic value of cardiopulmonary exercise testing in pulmonary arterial hypertension

Andrea Baccelli[1], Rocco F. Rinaldo[2], Gulammehdi Haji[3], Rachel J. Davies[3], Francesco Lo Giudice[3], Wendy Gin-Sing[3], Beatrice Vigo[4], Stefano Centanni[5], J. Simon R. Gibbs[6], Luke S. Howard[3,6]

[1] Department of Respiratory Medicine, Royal Brompton Hospital, Guy's and St Thomas' NHS Foundation Trust, London, UK; [2] Respiratory Diseases Unit, AOU Città della Salute e della Scienza di Torino, Molinette Hospital, Department of Medical Sciences, University of Turin, Turin, Italy; [3] National Pulmonary Hypertension Service, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [4] Respiratory Unit, Azienda Ospedaliera Universitaria San Luigi Gonzaga, Orbassano, Italy; [5] Respiratory Unit, ASST Santi Paolo e Carlo, Department of Health Sciences, Università degli Studi di Milano, Milan, Italy; [6] National Heart & Lung Institute, Imperial College London, London, UK.

Correspondence to: Prof Luke S. Howard, National Pulmonary Hypertension Service, Hammersmith Hospital, Imperial College Healthcare Trust, 72 Du Cane Road, London W12 0HS, United Kingdom. Email: l.howard@imperial.ac.uk

Take home message: Cardiopulmonary exercise testing reflects underlying changes in haemodynamics and right ventricular function in PAH. A four-strata risk stratification model based on WHO-FC, BNP, and CPET score accurately predicts survival.

Keywords: pulmonary arterial hypertension, cardiopulmonary exercise testing, risk stratification, prognosis

ABSTRACT

Background. Current guidelines recommend a four-strata model based on World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD), and serum levels of brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) for risk stratification in patients with pulmonary arterial hypertension (PAH) during follow-up. We explored the relevance of using cardiopulmonary exercise testing (CPET) as the exercise parameter in place of 6MWD at first reassessment after treatment initiation in PAH.

Methods. Incident treatment-naïve patients with idiopathic, heritable, drug/toxins-induced, and connective tissue disease-associated PAH between 2010 and 2022 were analysed. Correlations between CPET and haemodynamic and right ventricular (RV) function parameters were explored and those which were significant were carried forward to assess association with survival. Independent predictors were used to derive a four-strata CPET score.

Results. 262 patients were included. CPET parameters showed better correlations with haemodynamics and RV function than 6MWD. The CPET score included peak oxygen uptake (peak VO_2), the slope relating ventilation to carbon dioxide production (VE/VCO_2 slope), and peak oxygen pulse. The four-strata model based on WHO-FC, BNP, and CPET score predicted survival at the time of the first re-evaluation, with better accuracy than the model including 6MWD (c-index 0.81 vs 0.71). The CPET score on its own also performed well (c-index 0.82) with a greater spread between categories. Treatment-associated changes in peak VO_2 and oxygen pulse predicted survival, while changes in 6MWD did not.

Conclusions. A simplified four-strata CPET score either alone or included with BNP and WHO-FC accurately predicts survival at follow-up in PAH.

INTRODUCTION

The importance of periodic risk assessment in patients with pulmonary arterial hypertension (PAH) has been highlighted by the latest European Respiratory Society/European Society of Cardiology (ERS/ESC) Guidelines on the diagnosis and management of pulmonary hypertension, with the addition of a four-strata risk score at follow-up to guide treatment decisions on a more granular level.[1]

Over time, multiple invasive and non-invasive prognostic parameters have been tested and incorporated into risk assessment tools.[2–10] The simplified four-strata prognostic model (low, intermediate-low, intermediate-high, high risk) based on WHO functional class (WHO-FC), serum levels of (NT-pro) brain natriuretic peptide (BNP) and six-minute walk distance (6MWD) introduced by the guidelines predicts survival in patients with PAH with observed 1-year mortality rates of 0–3%, 2–7%, 9–19%, and >20%, respectively.[5]

Cardiopulmonary exercise testing (CPET) represents the gold standard method for the assessment of exercise capacity. It is a non-invasive metabolic test that integrates ventilatory and cardiovascular parameters, providing a comprehensive analysis of exercise limitation. As such, CPET is able to shed light on the pathophysiological mechanisms underlying response to therapy in PAH, unlike the simpler and more widely used 6MWT.[11–13]

In recent years, a limited, yet growing, body of evidence has highlighted the prognostic relevance of multiple candidate CPET parameters.[14–21] However, the added value of CPET on top of the other commonly used clinical variables used for prognostication in PAH remains unexplored.

The main objective of the present study was to determine the additional prognostic value of cardiopulmonary exercise testing variables at first follow-up in PAH and validate the current ESC/ERS cut-offs. Because of the importance of haemodynamics in risk assessment, we sought to:

- understand the relationships between key CPET variables and prognostic invasive hemodynamic and non-invasive right ventricular function parameters
- explore the changes in CPET variables after start of therapy and relationship with mortality
- create a CPET score based on independent CPET predictors of mortality which would provide a single number integrating independent CPET variables
- compare a four-strata model incorporating this CPET score as the exercise variable to the currently recommended risk stratification model that includes 6MWD.

METHODS

Study design

Consecutive incident patients from our service were included prospectively into the TRIPHIC database which was approved under the research ethics committee number 17/LO/0563. Demographic, clinical, biochemical, hemodynamic, radiological, and functional data were collected and anonymized prior to analysis. The dataset as of 1st January 2023 was analysed.

Patients

Patients were selected based on the following inclusion criteria: 1) Treatment-naïve patients aged ⩾18 years diagnosed with idiopathic, heritable, drug/toxins-induced, HIV-associated, and connective tissue disease-associated PAH between January 2010 and January 2022 based on contemporaneous hemodynamic criteria and the European classification; 2) first reassessment after treatment initiation within a year from diagnosis, with 6MWT and CPET being performed on separate, consecutive days All other forms of PH were excluded. Further exclusion criteria were death before first reassessment and lack of CPET, BNP or 6MWD at follow-up.

Right heart catheterization

All patients underwent a baseline diagnostic right heart catheterization. Haemodynamic measurements included right atrial pressure (RAP), systolic, diastolic, and mean pulmonary arterial pressure (mPAP), and pulmonary arterial wedge pressure (PAWP). Cardiac output (CO) was measured by thermodilution or by the direct Fick method. Cardiac index was calculated as the CO divided by body surface area. Pulmonary vascular resistance was calculated as mPAP-PAWP divided by CO. Pulmonary artery blood samples were collected to measure mixed venous oxygen saturation (SvO_2). Haemodynamic data of the study population are presented in **Table 1**.

Cardiopulmonary exercise testing

A symptom-limited, incremental maximal CPET using a standard metabolic cart (CPX, Vyaire Medical, Basingstoke, UK) in the upright position was performed on an electromagnetically braked cycle-ergometer (Ergoline GmbH, Bitz, Germany) according to the American Thoracic Society guidelines and latest recommendations.[22,23] O_2 pulse at peak was computed from the formula oxygen consumption/heart rate. Ventilatory efficiency was determined by the ventilation/carbon dioxide production (VE/VCO_2) slope excluding resting measures up to the point of the respiratory compensation point.

Risk stratification

In line with the most recent recommendations, a four-strata approach was adopted. Cut-off levels for WHO-FC, BNP and 6MWD were taken from the 2022 European pulmonary hypertension guidelines.[1] A score of 1 was assigned for each parameter in low risk, 2 for intermediate-low risk, 3 for intermediate-high risk, and 4 for high-risk values, then an average was calculated for each patient, rounded to the nearest integer (**table**

S1). When deriving a CPET score, a similar approach was taken with cut-offs for already-established markers being used (VO_2 and VE/VCO_2 slope) as well as any new independent markers being adopted. To split the intermediate category to develop a four-strata CPET score, we followed the methodology from Kylhammar and colleagues[7] to create an intermediate-low CPET score (1.5-1.99) and intermediate-high CPET score (2-2.49).

Statistics

Normality was assessed through the Kolmogorov-Smirnov's test. Quantitative data are described with means and standard deviations (SD) or median and interquartile ranges (IQR) according to their distribution, and qualitative data with absolute frequencies and percentages. Missing data were not imputed. Patients who underwent lung transplantation were censored on the date of transplantation. Survival time was calculated from the date of diagnostic right heart catheterization (RHC) until death. Transplantation-free survival was analysed with Kaplan-Meier analysis and log-rank test. Survival time was calculated from the date of diagnostic RHC until death or last recorded clinical contact. Cox proportional hazards regression was used to assess the association between individual exercise parameters/risk category and survival, expressed as hazard ratios with 95% confidence intervals. A theory-driven model selection of co-variates was adopted, with candidate variables chosen because of their known prognostic relevance and pathophysiological correlations to strong hemodynamic risk factors. The multivariable model was then performed without a stepwise selection of the co-variates. For those parameters which have previously been proposed as predictors with published cut-offs, we used these. For new parameters, (e.g. peak oxygen pulse), time dependent receiver-operating characteristics (ROC) analysis was used to determine the area under the curve (AUC), and optimal thresholds were determined by the value maximizing the sum of sensitivity and specificity (Youden index).

Time-dependent ROC analyses of the prognostic models were performed and compared using the DeLong test. The Harrell's c-statistic was used to compare accuracy and discrimination of the two risk stratification methods. To further strengthen our findings, Akaike information criteria (AIC) was used to ensure that improved discrimination was not achieved at the cost of excessive model complexity. Lastly, the time-point considered for the AUC analysis was 5 years. Correlation coefficients between exercise parameters and other variables were determined by Spearman's rank correlation analysis. A p-value <0.05 was considered statistically significant. Statistical tests were performed using the Statistical Package for Social Sciences (version 28.0; SPSS, Chicago IL, USA), and STATA (version 18; StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristic and survival

Two hundred and sixty-two patients were included in the final analysis (**Figure 1**). Baseline characteristics are shown in **table 1 and supplementary table S2**. Patients included in the analysis did not significantly differ from the overall population (n=438), as shown in the **supplementary table S3**. One hundred fifty-three (58%) patients were receiving monotherapy at the time of the first reassessment, while 42% of patients were on combination therapy, including 14 on parenteral prostacyclin analogues (**supplementary table S4**). The median (IQR) follow-up time was 5.1 (3.6–8.1) years, with 13 years being the longest duration. During follow-up, 120 patients died and 2 underwent lung transplantation. For the study population, the Kaplan–Meier estimated survival rates 1, 3 and 5 years after diagnosis were 96%, 83% and 65%, respectively. For the overall population, the Kaplan–Meier estimated survival rates 1, 3 and 5 years after diagnosis were 92%, 78% and 61%, respectively.

CPET variables show stronger correlations with resting haemodynamics and RV function

Overall, CPET showed more and stronger correlations with invasive haemodynamics and RV function on CMR. Peak VO_2 (mL/min/Kg) significantly correlated with prognostically relevant hemodynamic parameters, such as mean right atrial pressure (mRAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2), as shown in **figure 2 and supplementary table S5**. The VE/VCO_2 slope displayed significant correlations with CI, SvO_2 and PVR. Peak O_2 pulse was the CPET variable with the highest number of significant correlations, the strongest ones being with PVR and CI. The 6MWD had significant correlations with mRAP, CI, PVR, and SvO_2 – the strongest one being with SvO_2 (rs 0.447; p<0.001), as shown in **supplementary table S5**. All examined CPET variables exhibited a significant correlation with the right ventricular ejection fraction (RVEF), as assessed by CMR, with the strongest relation involving peak O_2 pulse (rs 0.562; p<0.001), as illustrated in **supplementary figure S1 and table S6**. The 6MWD did not display a significant correlation with RVEF (p=0.14). Based on these data, we considered absolute VO_2, VE/VCO_2 slope and % predicted O_2 pulse to be the strongest correlates from CPET with recognised predictors of survival but continued to present data for % predicted VO_2 and absolute O_2 pulse for completeness.

Survival is associated with changes in CPET after treatment and not 6MWD or BNP

Baseline and follow-up clinical characteristics of patients stratified according to survival status at the end of the observation period are reported in **table 2**, as well as changes in CPET variables in the subset of patients with available exercise testing at both time points (n=198). Patients alive at the end of follow-up displayed a significantly higher 6MWD and lower BNP both at baseline and at the first re-evaluation, but with comparable mean changes after start of therapy. Survivors were characterized by a significant greater improvement in peak oxygen uptake, ventilatory efficiency, and %predicted peak oxygen pulse than non-survivors.

Exploring the prognostic value of treatment-associated changes in exercise parameters, only changes in peak oxygen uptake (mL/min/Kg) were associated with survival at multivariate Cox regression analysis, as shown in **supplementary table S7**.

CPET alone at follow-up predicts survival

Among the CPET variables considered for prognostication in PAH by the guidelines (peak VO_2 both as % predicted and weight-adjusted absolute value, and VE/VCO_2 slope) plus oxygen pulse as the additional parameter hereby investigated, only peak VO_2 (mL/min/Kg), peak O_2 pulse (%predicted) and the VE/VCO_2 slope emerged as independent predictors of survival at multivariate Cox regression analysis (**table 3**). Based on cut-offs derived from the study population (40% and 65%), % predicted peak O_2 pulse was able to significantly stratify survival in this population, as shown in **supplementary figure S2**. Using values from the ERS/ESC guidelines for peak VO_2 and VE/VCO_2 slope, we included % predicted Peak O_2 pulse and were thus able to derive a new standalone CPET score (**Table 4**).

Using the 4-strata CPET score (1-1.49, 1.5-1.99, 2-2.49, 2.5-3) in isolation, there was an even spread between categories with 72 patients in the low-risk, 88 in the intermediate-low risk, 44 in the intermediate-high risk, and 53 in the high-risk groups. Survival rates are shown in **figure 3A** (log-rank test $p<0.001$ for all group comparisons; c-index 0.82).

CPET score performs better in place of 6MWD in ESC/ERS four-strata risk model

A four-strata risk stratification model based on WHO-FC, BNP, and the CPET score (ESC/ERS^{CPET}) was applied to the study population, based on the cut-offs illustrated in **supplementary table S1**, obtaining a clear and statistically significant separation of mortality risk between each stratum. The Kaplan–Meier estimated transplant-free survival rates 3 and 5 years after diagnosis for the low risk at first follow-up group were 100% and 100%, respectively; for the intermediate-low risk group were 93% and 84%, respectively; for the intermediate-high risk group 62% and 43%, respectively; and for the high risk group 20% and 0%, respectively (log-rank test, $p<0.0001$ for all group comparisons; **figure 3B**). Although the patient numbers become smaller, we show excellent discrimination out to 10 years and 100% survival in the ESC/ERS^{CPET} low risk group, representing a truly very low-risk group with excellent prognosis, of which 10 (29%) were treated exclusively with calcium channel blockers (CCB) (**supplementary figures S5 and S6**).

To show our cohort and dataset align with published literature, we also produced the recommended four-strata model based on WHO-FC, BNP, and 6MWD (ESC/ERS^{6MWT}). The Kaplan–Meier estimated transplant-free survival rates 3 and 5 years after diagnosis for the low-risk at first follow-up group were 100% and 91%, respectively; for the intermediate-low risk group were 86% and 74%, respectively; for the intermediate-high

risk group 68% and 55%, respectively; and for the high risk group 22% and 0%, respectively (log-rank test, p<0.0001 for all group comparisons; **figure 3B**).

Applying the "French system" of counting the number of low-risk criteria, both models including either CPET score or 6MWD were significantly associated with survival at univariate and multivariate Cox regression analysis (**supplementary tables S8 and S9**) and the Kaplan-Meier transplant-free survival curves according to the number of low-risk criteria achieved at first follow-up are shown in **supplementary figures S3 and S4** (log-rank test p<0.0001 for all group comparisons).

Discrepancy in the risk category distribution between the ESC/ERS^{6MWT} and ESC/ERS^{CPET} strata risk models was observed in 68 patients (26%; κ 0.61; 95%CI: 0.58-0.65), as shown in **supplementary table S10**. In discordant cases, a significantly lower survival probability was found when the CPET score grade was higher than the 6MWD score, (p<0.001).

Time-dependent receiver operating characteristics (ROC) analysis and differences in concordance statistic were used to compare stratification strategies at 5 years**.** The ESC/ERS^{CPET} Cox model had a significantly higher c-index than the ESC/ERS^{6MWT} : 0.81 (95%CI: 0.75-0.87) vs 0.71 (95%CI: 0.64-0.78) respectively, p<0.001. The ESC/ERS^{CPET} Cox model had a higher AUC than the ESC/ERS^{6MWT}: 0.82 (95%CI: 0.78-0.86) vs 0.73 (95%CI: 0.69-0.77) respectively, p<0.001. ROC curves are shown in **figure 4**. The AIC values were 712 for ESC/ERS^{CPET} and 698 for ESC/ERS^{6MWT}.

Comparison of both scores in patients with and without cardiopulmonary comorbidities

The predictive performance of ESC/ERS^{CPET} and ESC/ERS^{6MWT} was also tested in the subgroups of patients with and without cardiopulmonary comorbidities. These were defined by the presence of at least 3 risk factors among BMI ≥30, systemic hypertension, diabetes mellitus, coronary artery disease, smoking history and TLCO <45% predicted[1]. In patients without cardiopulmonary comorbidities, the area under the ROC curve and c-index for the ESC/ERS^{CPET} were 0.79 (95%CI: 0.7-0.85) and 0.81 (95%CI: 0.74-0.83) respectively; for the ESC/ERS^{6MWT} they were 0.73 (95%CI: 0.69-0.8) and 0.72 (95%CI: 0.65-0.84). In patients with cardiopulmonary comorbidities, the area under the ROC curve and c-index for the ESC/ERS^{CPET} were 0.74 (95%CI: 0.67-0.81) and 0.72 (95%CI: 0.63-0.83) respectively; for the ESC/ERS^{6MWT} they were 0.70 (95%CI: 0.69-0.84) and 0.70 (95%CI: 0.61-0.79).

DISCUSSION

Risk stratification at baseline uses multiple parameters, including haemodynamics and imaging, as well as exercise capacity to guide a relatively straightforward binary decision between dual oral or triple therapy with intravenous prostacyclin.[1,24] There is inhomogeneity in response to treatment, however, thus risk stratification at first follow-up is critical for determining the best long-term treatment strategy.[3,5–7,25–28] Using the largest cohort to date of patients undergoing CPET following treatment, we tested and verified the hypothesis that a composite CPET score, on its own as well as in addition to WHO-FC and BNP, predicts survival in incident PAH patients evaluated within 12 months from treatment initiation.

Rooting our approach in the pathophysiology of the disease, we first demonstrated that absolute VO_2 per kg and VE/VCO_2 slope correlate with haemodynamic and magnetic resonance measures of pulmonary hypertension severity, thus confirming the utility of the 2015/22 guideline recommendations for the use of CPET in risk stratification. This also supports the proposed removal of percent predicted peak VO_2 in the 7th World Symposium of Pulmonary Hypertension expert consensus.[28] Second, we showed that the oxygen pulse (a CPET surrogate of stroke volume) had the most correlations with other known predictors of survival.

Next, we showed that changes in these three CPET variables from baseline to first follow-up predict survival in a univariate model, unlike changes in 6MWD and BNP, and then that changes in peak VO_2 and O_2 pulse (% predicted) are independent predictors at multivariate analysis.

Following the 2015 European Guidelines, it was recognised that many patients fell in to a large intermediate risk group, and further refinement was proposed in the 2022 guidelines, by dividing the intermediate group in two.[1,29] Based on our findings, we developed a CPET score and have shown that using this instead of 6MWD provides better discrimination when used in the European four-strata score. Remarkably, we show that using CPET on its own without WHO-FC and BNP provides even better discrimination.

The recent 7th World Symposium highlighted the benefit of using haemodyamics to discriminate intermediate-low and intermediate-high further in to 4 risk categories.[28,30] CPET is likely to reflect pulmonary hypertension severity more than 6MWD given its closer relationship with peak cardiac output.[11,31–33] Cardiac output is the major determinant of peak exercise capacity, assessed by absolute VO_2, whereas maximum cardiac output may not be achieved in many patients undertaking 6MWT, in particular younger patients.[12,22,31] In PH, the major determinant of cardiac output is the stroke volume, which is known to be an independent predictor of survival.[11,25,26,31,34] Oxygen pulse is a surrogate of stroke volume as it relates to the amount of oxygen consumed with each heartbeat.[22] In PH, the oxygen pulse is typically at a plateau in the last few minutes of an incremental exercise test, thus reducing error in measurement and taking out any effort-related component.[35] Relatedly, Badagliacca and colleagues demonstrated that right ventricular fractional area change and oxygen pulse predicted clinical worsening at the time of diagnosis in a group of 130 idiopathic PAH patients.[20] Here we show that oxygen pulse at follow-up, as well as its change over time represent strong independent predictors of survival. Importantly however, oxygen pulse does not simply

reflect stroke volume, as it represents the product of stroke volume and arterial-venous difference in the content of oxygen at any given point. In the context of new drugs that potentially increase oxygen content and extraction, without significant increase in the resting cardiac output (e.g. Sotatercept)[36], the assessment of oxygen pulse in conjunction with haemoglobin may provide additional insights into treatment responses.

Similarly, the VE/VCO_2 slope is effort-independent, since it excludes resting and peak data points.[22] Physiologically and mathematically, it relates to the arterial CO_2 set point which reduces in accordance with heart failure severity and the physiological dead-space ventilation which reflects pulmonary vascular disease.[13,37–39] It is thus a reliably-observable composite measure of the severity of cardiopulmonary impairment. Lastly, CPET variables correlated well with measures of RV function on MRI, unlike 6MWD, so it is not surprising that it performs well in predicting outcomes.

What is particularly thought-provoking and impressive is that the standalone CPET score performs better on its own than with the inclusion of WHO-FC and BNP. It results in much larger numbers of patients falling into the low and high-risk groups, giving clearer guidance on when to stick with current therapy or escalate to more aggressive intravenous therapy. It may be that functional class and BNP, particularly the former, dilutes the predictive capacity of CPET.

The main rationale for the 4-strata risk score in the European Guidelines was to divide up the large amorphous group of intermediate risk patients, by subdividing the cut-offs of the previously used parameters, and this has certainly improved risk stratification. Nonetheless, using this approach, we observe that, as well as still having only a small number of low and high-risk patients, CPET in place of 6MWD provides better separation between the intermediate-low and intermediate-high groups (**figure 3B**). The value of CPET has been confirmed also by Badagliacca et al., who showed that stroke volume index (SVI) and peak VO_2 can provide important information to further stratify IPAH patients who are at intermediate-risk after institution of targeted therapies.[19] More recently, peak VO_2 in place of 6MWD resulted in a better discrimination of intermediate-high risk patients in a prevalent PAH cohort from the Spanish registry.[40] We therefore speculate, based on our observations in consecutive patients at first follow-up, that the closer correlation of CPET than 6MWD with haemodynamics and RV function may account for the greater separation of the two categories. This is supported by the recent observation of the added benefit of including stroke volume index and SvO_2 over the standard ESC/ERS^{6MWT}.[30] This requires invasive testing. Gaining good separation of intermediate-low and -high is clearly important as the therapeutic decisions are radically different in terms of complexity and it may help guide treatment decisions, which now include sotatercept.[24]

There are of course potential limitations in this study which opens up the opportunity for further work. This is a single centre database study, based on consecutively recruited patients. Two of the three measures in the CPET score and their cut-offs were pre-defined and taken from existing guidelines, then validated in our cohort, but the oxygen pulse cut-offs were derived from our cohort and this requires further external

validation. There were also some missing data, but we showed how the overall and study population did not significantly differ, thus reducing the risk of selection bias in this study..

CONCLUSION

We have demonstrated the utility of CPET by being the first study to validate the ESC/ERS 2015/22 guideline prognostic cut-offs and its benefit over 6MWD in terms of physiological correlation with haemodynamics and RV function. It performs better in predicting long-term survival when measured at first follow-up, both in absolute terms and change from baseline and, in addition to WHO-FC and BNP, provides value in separating intermediate-low from intermediate-high groups, which is a major treatment decision point with significant consequences for patients in terms of burden of therapy.

SUPPORT STATEMENT

A. Baccelli is recipient of a “Società Italiana di Pneumologia/Italian Respiratory Society (SIP/IRS)” research fellowship.

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TABLES

Table 1. Baseline demographic, clinical and functional characteristics of the study group.

	N=262
Age at diagnosis, years	54 (16)
Female, n (%)	162 (62%)
BMI, kg/m^2 #	27 (23-31)
PAH aetiology, n (%) Idiopathic CTD-associated Heritable Drug/Toxins-associated HIV-associated	 167 (64%) 67 (26%) 13 (5%) 9 (3%) 6 (2%)
WHO-FC, I/II/III/IV, n (%)	1/ 25 (10%)/ 193 (74%)/ 43 (16%)
BNP, ng/L #	234 (73-515)
6MWD, m	269 (142)
Acute vasodilator responders, n (%)	17 (6%)
Comorbidities, n (%)	
Smoking status, active/ex-/never smoker	42 (16%)/ 81 (31%)/ 139 (53%)
Smoking history, pack-year	22 (18)
Coronary arteries disease	34 (13%)
Systemic hypertension	96 (37%)
Diabetes Mellitus	50 (19%)
Atrial fibrillation	18 (7%)
Obesity	81 (31%)
Asthma	22 (8%)
COPD	26 (10%)
ILD	19 (7%)
Chronic Kidney Disease	21 (8%)
Thyroid disease	35 (13%)

Haemodynamics	
Mean systemic BP at the time of RHC, mmHg	95 (16)
Hb at the time of RHC, g/dL	14.6 (2.1)
Mean RAP, mmHg	9 (5)
Mean PAP, mmHg	49 (13)
Mean PAWP, mmHg	10 (4)
Cardiac index, L/min/m^2	2.2 (0.7)
PVR, WU$^{\#}$	10.2 (6.5-14.7)
SvO_2, %	65 (9)

All quantitative data: mean (standard deviation), unless otherwise specified. $^{\#}$median (interquartile range). BMI indicates body mass index; WHO-FC, World Health Organization functional class; BNP, Brain natriuretic peptide; 6MWD, 6-minute walking distance; BP, blood pressure; RHC, right heart catheterization; Hb, haemoglobin; CPET, Cardiopulmonary exercise testing; RAP, right atrial pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation.

Table 2. Baseline and follow-up demographic, clinical and functional characteristics of the study population stratified by survival.

	SURVIVORS (N=142)	NON-SURVIVORS (N=120)	p-value
Age at diagnosis, years	47 (15)	62 (14)	<0.001
Female, n (%)	97 (68%)	65 (55%)	0.028
PAH aetiology, n (%)			
Idiopathic	98 (59%)	69 (41%)	0.002
CTD-associated	25 (37%)	42 (63%)	
Heritable	11 (86%)	2 (14%)	
Drug/Toxins-associated	5 (56%)	4 (44%)	
HIV-associated	3 (50%)	3 (50%)	
Comorbidities			
Coronary arteries disease	11	23	0.005
Systemic hypertension	38	58	<0.001
Diabetes Mellitus	18	32	0.003
Atrial fibrillation	8	10	0.359
Obesity	44	37	0.919
Chronic kidney disease	3	18	<0.001
WHO-FC baseline, I/II/III/IV	1/20/98/23	0/5/95/20	0.042
WHO-FC reassessment, I/II/III/IV	13/63/65/1	1/17/98/4	<0.001
BNP baseline, ng/L [#]	198 (48-381)	287 (96-742)	<0.001
BNP reassessment, ng/L [#]	51 (23-90)	156 (71-370)	<0.001
6MWD baseline, m	322 (134)	206 (125)	<0.001
6MWD reassessment, m	379 (128)	263 (131)	<0.001
***Cardiopulmonary exercise testing* (baseline data availability: survivors n=108; non-survivors n=90)**			
Peak VO_2 baseline, mL/min/Kg	13.2 (4)	10.3 (3.3)	<0.001
Peak VO_2 reassessment, mL/min/Kg	15.5 (4.6)	11.1 (3.8)	<0.001
Peak VO_2 baseline, %pred	52 (14)	47 (13)	0.008
Peak VO_2 reassessment, %pred	62 (16)	51 (15)	<0.001
VE/VCO_2 slope baseline	48.9 (16.9)	57.6 (18.5)	0.001
VE/VCO_2 slope reassessment	41.2 (9.8)	53.5 (17.2)	<0.001
Peak O_2 pulse baseline, mL/beat	8.7 (3.4)	7.9 (2.8)	0.007
Peak O_2 pulse reassessment, mL/beat	9.9 (4.2)	9.6 (4.3)	0.531
Peak O_2 pulse baseline, %predicted	64 (16)	63 (21)	0.852
Peak O_2 pulse reassessment, %predicted	72 (18)	63 (21)	<0.001
Changes after treatment initiation			
Δ 6MWD, m	67 (103)	53 (87)	0.322
Δ BNP, ng/L	-201 (283)	-204 (506)	0.949
Δ PeakVO_2, mL/min/Kg	2.7 (3.2) *n=108*	0.6 (2.4) *n=90*	<0.001
Δ PeakVO_2, %pred	12 (12) *n=108*	2 (11) *n=90*	<0.001
Δ VE/VCO_2 slope	-8.3 (12.8) *n=108*	-2.9 (14.2) *n=90*	0.008
Δ Peak O_2 pulse, mL/beat	2.1 (3.2)	1.7 (3.5)	0.062

	n=108	*n=90*	
Δ Peak O_2 pulse, %predicted	9.2 (14.9) *n=108*	-0.4 (12.7) *n=90*	<0.001

All quantitative data: mean (standard deviation), unless otherwise specified. #median (interquartile range). WHO-FC indicates World Health Organization functional class; BNP, Brain natriuretic peptide; 6MWD, 6-minute walking distance; VO_2, oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio.

Table 3. Univariate and multivariate Cox regression analysis of CPET parameters assessed at the first re-evaluation.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Peak VO_2 (mL/min/Kg)	0.75 (0.70-0.81)	**<0.001**	0.78 (0.75-0.89)	**<0.001**
Peak VO_2 (%predicted)	0.94 (0.93-0.96)	**<0.001**		
VE/VCO_2 slope	1.05 (1.04-1.06)	**<0.001**	1.03 (1.02-1.06)	**<0.001**
Peak O_2 pulse (mL/beat)	0.99 (0.93-1.04)	0.605		
Peak O_2 pulse (%predicted)	0.97 (0.96-0.98)	**<0.001**	0.96 (0.94-0.98)	**<0.001**

VO_2 indicates oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio.

Table 4. Cardiopulmonary exercise testing variables and cut-off values used for standalone CPET score.

	Low risk	Intermediate risk	High risk
Points assigned	1	2	3
Peak VO_2 (mL/min/Kg)	>15	11-15	<11
VE/VCO_2 slope	<36	36-44	>44
Peak O_2 pulse (%predicted)	>65	40-65	<40

	Low risk	Intermediate-low risk	Intermediate-high risk	High risk
CPET Score	1-1.49	1.5-1.99	2-2.49	2.5-3

Peak VO_2 indicates peak oxygen uptake; VE/VCO_2 slope, the slope relating minute ventilation to carbon dioxide production; O_2 pulse, oxygen pulse.

FIGURE CAPTIONS

Figure 1. Study population flowchart. Flow diagram showing the study population and excluded patients. PAH indicates Pulmonary Arterial Hypertension; CPET, Cardiopulmonary exercise testing; BNP, Brain natriuretic peptide; 6MWD, 6-minute walking distance; WHO-FC, World Health Organization functional class

Figure 2. Relations between cardiopulmonary exercise testing parameters and haemodynamic variables. Upper row: left panel shows correlation between peak VO_2 and CI, middle panel shows correlation between peak VO_2 and SvO_2, right panel shows correlation between the VE/VCO_2 slope and CI. Lower row: left panel shows correlation between the VE/VCO_2 slope and SvO_2, the middle panel shows correlation between O_2 pulse and CI, right panel shows correlation between O_2 pulse and SvO_2. VO_2 indicates oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio.

Figure 3. Kaplan-Meir survival curves at first follow-up. Panel A shows transplant-free survival according to the four-strata CPET score risk groups at follow-up. Panel B shows transplant-free survival according to the four-strata ESC/ERS^{6MWT} (dotted line) and ESC/ERS^{CPET} (solid line) risk categories at follow-up.

Figure 4. Receiver operating characteristics (ROC) curves and areas under the curve (AUC) of the CPET score, ESC/ERS^{6MWT} and ESC/ERS^{CPET} risk stratification models. The AUC (95%CI) for the CPET score was 0.82 (0.77-0.86), for the ESC/ERS^{CPET} was 0.82 (0.78-0.86), for the ESC/ERS^{6MWT} was 0.73 (0.69-0.77).

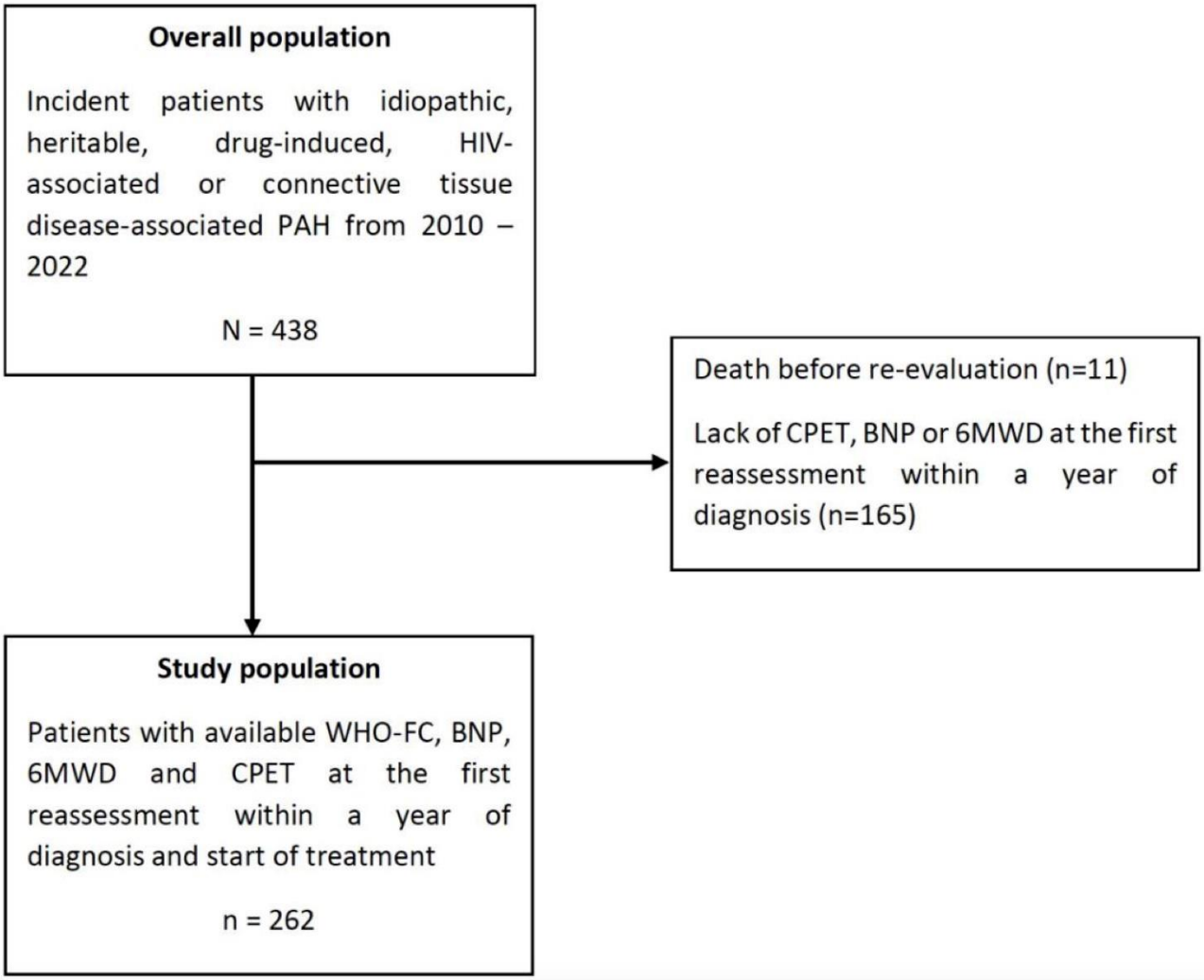


Figure 1

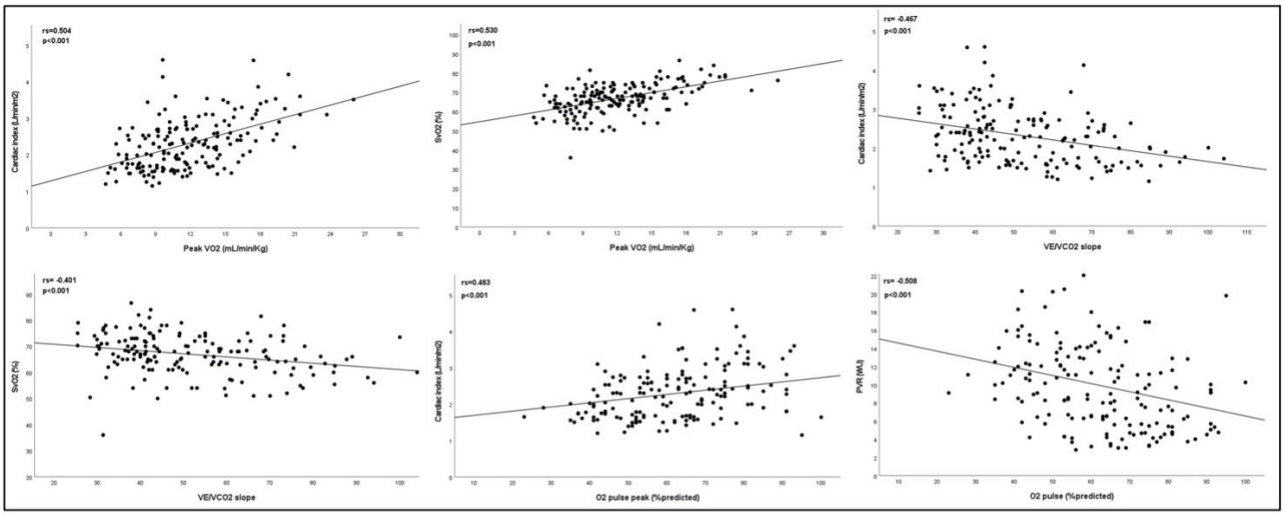


Figure 2

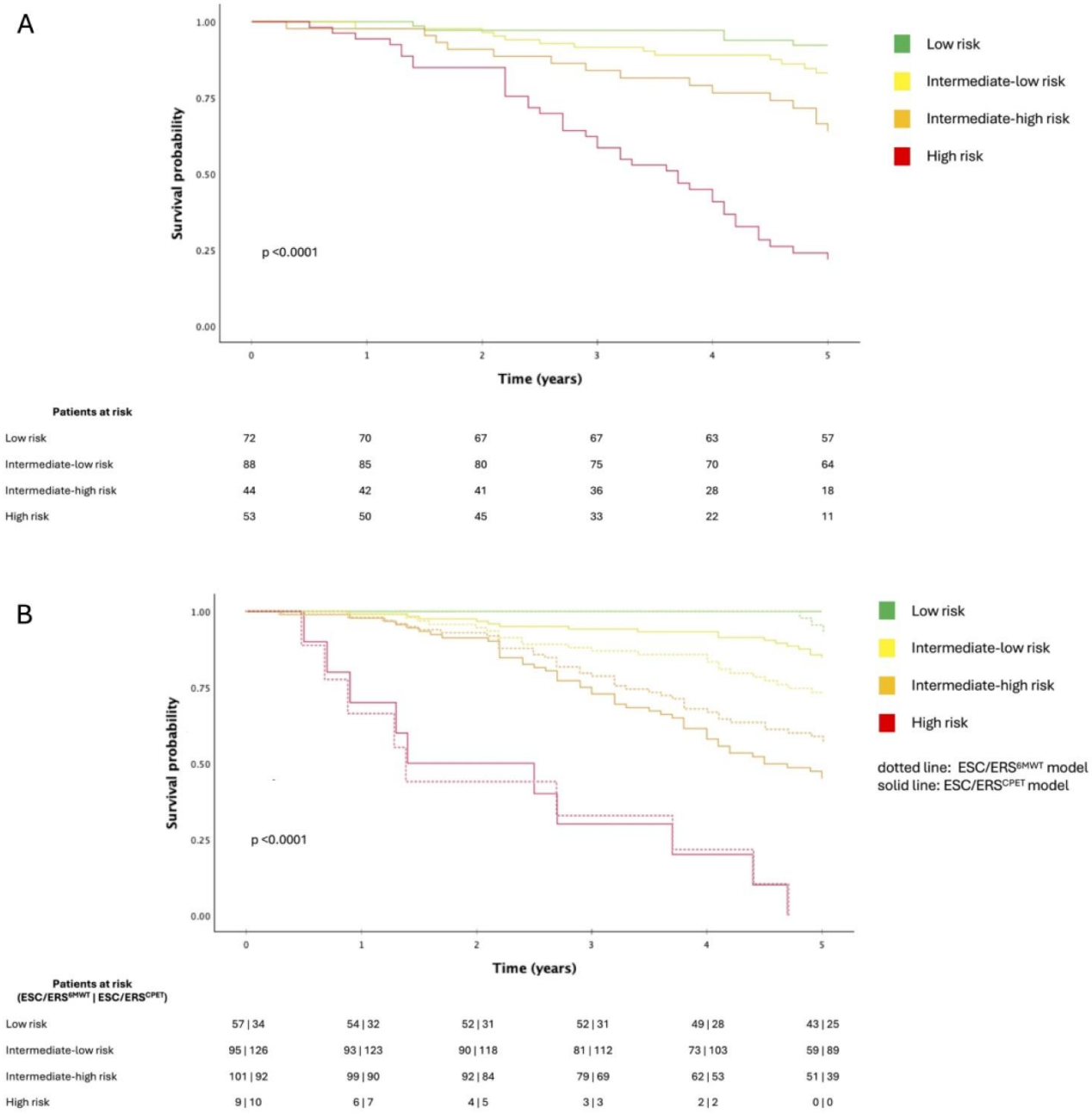


Figure 3

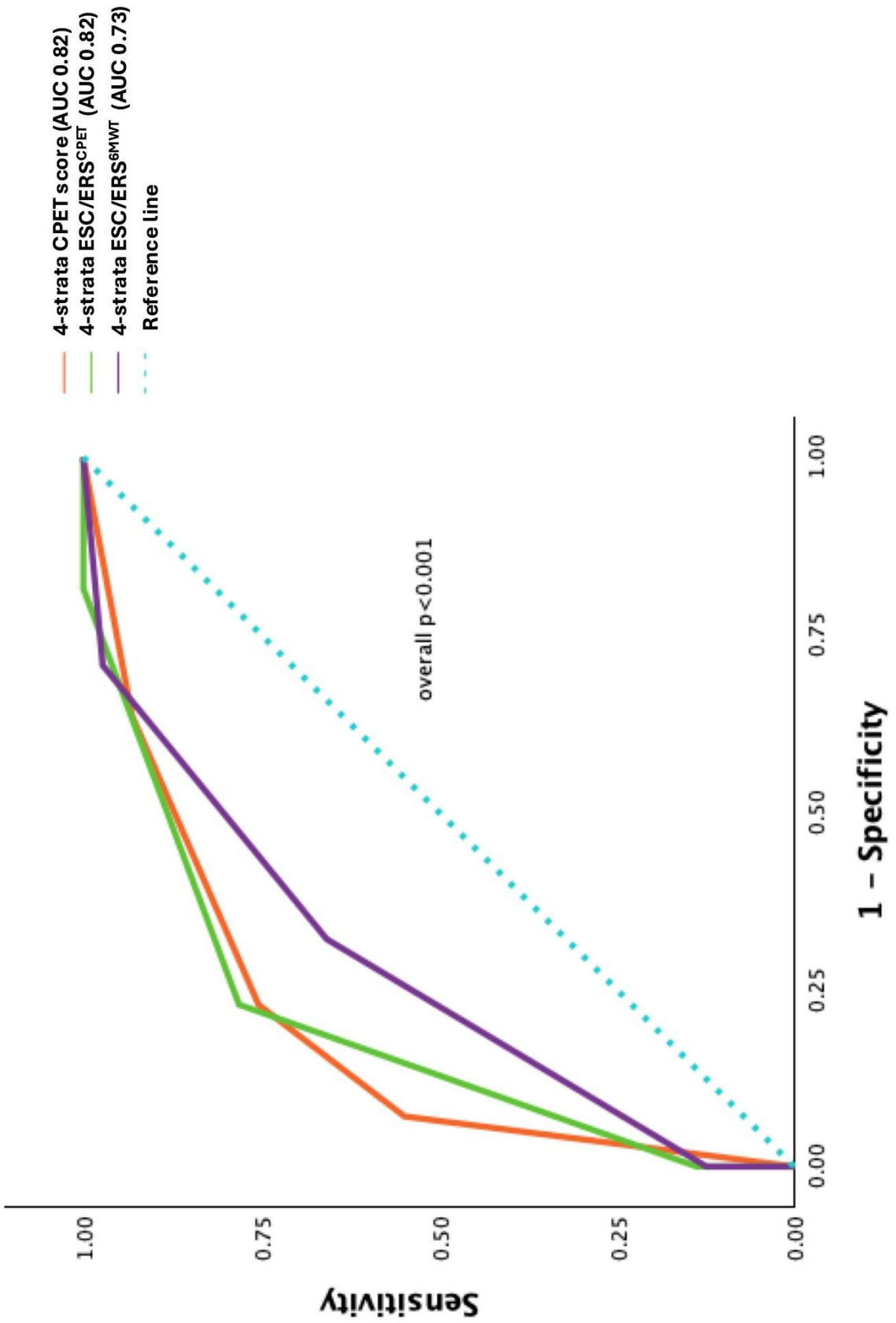
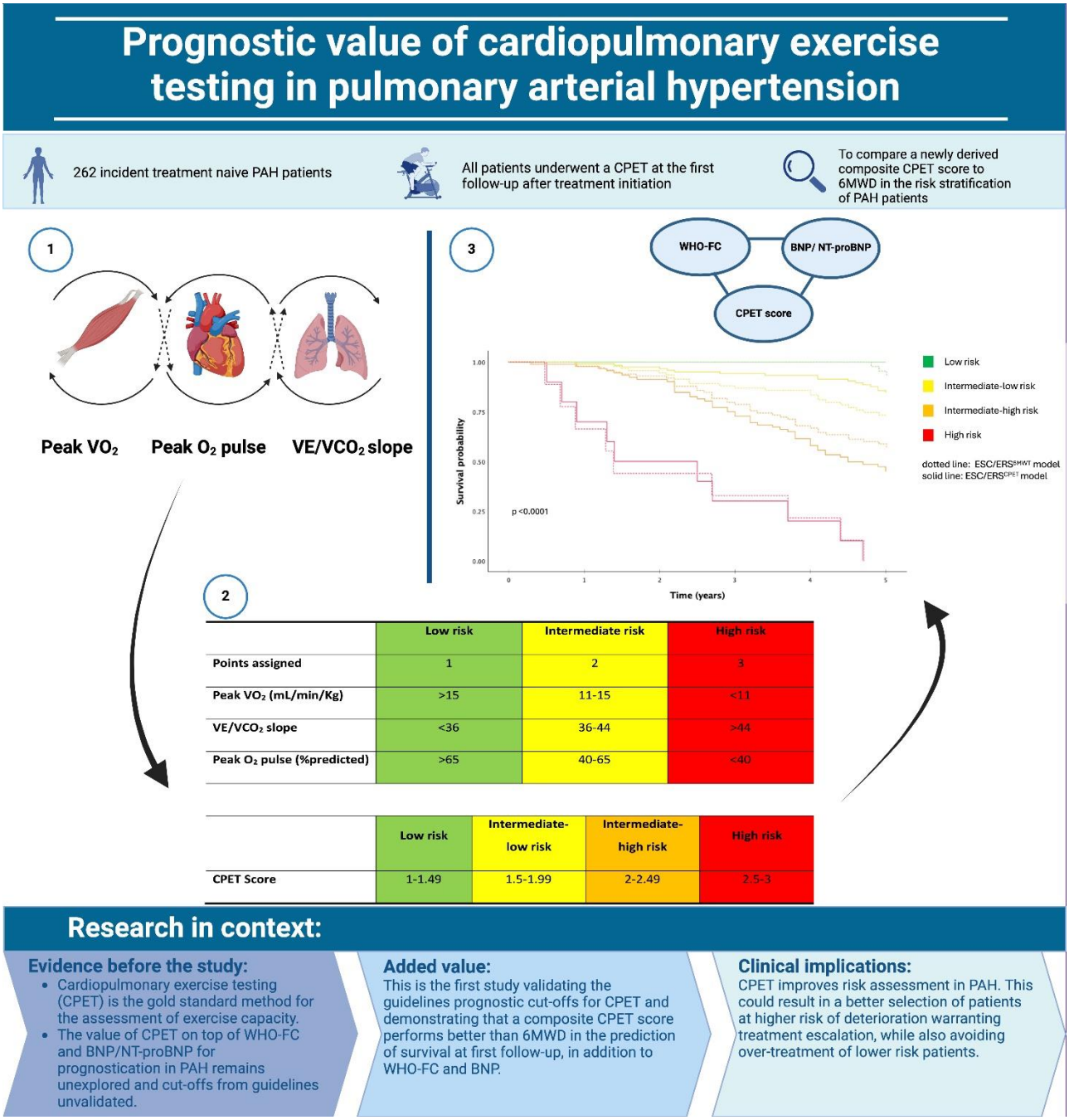


Figure 4



Graphical abstract

Prognostic value of follow-up cardiopulmonary exercise testing in pulmonary arterial hypertension

SUPPLEMENTARY MATERIAL

TABLES

Table S1. Variables and cut-off values used for risk stratification.

Simplified ESC/ERS four-strata risk assessment tool				
	Low risk	**Intermediate-low risk**	**Intermediate-high risk**	**High risk**
Points assigned	1	2	3	4
WHO-FC	I or II	-	III	IV
BNP (ng/L)	<50	50-199	200-800	>800
6MWD (m)	>440	320-440	165-319	<165
Proposed four-strata risk assessment tool incorporating the CPET score				
	Low risk	**Intermediate-low risk**	**Intermediate-high risk**	**High risk**
Points assigned	1	2	3	4
WHO-FC	I or II	-	III	IV
BNP (ng/L)	<50	50-199	200-800	>800
CPET score	1-1.49	1.5-1.99	2-2.49	2.5-3

WHO-FC indicates World Health Organization functional class; BNP, Brain natriuretic peptide; 6MWD, 6-minute walking distance; CPET, Cardiopulmonary exercise testing.

Table S2. Baseline echocardiographic, cardiopulmonary exercise testing and pulmonary function test characteristics of the study group.

	N=262
Echocardiography (N=262)	
TAPSE/SPAP, mm/mmHg	0.225 (0.120)
RA area, cm^2	24.1 (7.3)
Pericardial effusion, n (%)	35 (14%)
Cardiopulmonary exercise testing (N= 198)	
Peak VO_2, mL/min/Kg	11.8 (3.9)
Peak VO_2, %pred	50 (14)
AT, %VO_2max (n=112)	38 (10)
Peak work, Watts	61 (32)
Peak Work, %predicted	52 (24)
VE/VCO_2 slope	52.9 (18.2)
VO_2/W slope	7 (3)
Peak O_2 pulse, mL/beat	7.8 (3.2)
Peak O_2 pulse, %predicted	64 (19)
Breathing reserve, %	34 (18)
Heart rate reserve, %	20 (16)
RER	1.07 (0.11)
PetCO_2, KPa	2.9 (0.8)
Peak PaCO_2, kPa (n=128)	4.03 (0.87)
Dead Space, % (n=125)	41 (11)
A-a gradient, kPa (n=122)	7.46 (2.66)
Peak Lactate, mmol/L (n=128)	4.8 (2.1)
Peak systolic BP, mmHg	117 (23)
Peak, diastolic BP, mmHg	78 (14)
Pulmonary Function Tests (N=262)	
FEV_1, %predicted	84 (18)
FVC, %predicted	91 (20)

TLCO, %predicted	53 (20)
KCO, %predicted	65 (22)

All quantitative data: mean (standard deviation), unless otherwise specified. TAPSE indicates tricuspid annular plane systolic excursion; SPAP, systolic pulmonary artery pressure; RA right atrial; VO_2, oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio; VO_2/W slope, slope relating oxygen consumption to workload ratio; RER, respiratory exchange ratio; $PetCO_2$, end-tidal partial pressure of carbon dioxide; $PaCO_2$, arterial partial pressure of carbon dioxide; A-a gradient, alveolar to arterial gradient for oxygen; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; TLCO, transfer factor of the lung for carbon monoxide; KCO, transfer coefficient of the lung for carbon monoxide.

Table S3. Demographics and baseline characteristics of overall and study populations.

	Overall population (N=438)	Study population (N=262)
Age, years	56 (17)	54 (16)
Female, n (%)	267 (61%)	162 (62%)
BMI, kg/m^2 #	28 (24-31)	27 (23-31)
PAH aetiology, n (%)		
Idiopathic	276 (63%)	167 (64%)
CTD-associated	118 (27%)	67 (26%)
Heritable	18 (4%)	13 (5%)
Drug/Toxins-associated	13 (3%)	9 (3%)
HIV-associated	13 (3%)	6 (2%)
WHO-FC, I/II/III/IV, n (%)	2/ 44 (10%)/ 310 (71%)/ 82 (19%)	1/ 25 (10%)/ 193 (74%)/ 43 (16%)
BNP, ng/L #	269 (75-619)	234 (73-515)
6MWD, m	252 (144)	269 (142)
Mean RAP, mmHg	9 (5)	9 (5)
Mean PAP, mmHg	50 (13)	49 (13)
Mean PAWP, mmHg	10 (4)	10 (4)
Cardiac index, L/min/m^2	2.3 (0.7)	2.2 (0.7)
PVR, WU#	10.4 (6.5-15.1)	10.2 (6.5-14.7)

All quantitative data: mean (standard deviation), unless otherwise specified. #median (interquartile range). BMI indicates body mass index; CTD, connective tissue disease; WHO-FC, World Health Organization functional class; BNP, Brain natriuretic peptide; 6MWD, 6-minute walking distance; RAP, right atrial pressure; PA, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

Table S4. PAH medications used at the time of the first follow-up visit.

	Study population (N=262)
Monotherapy	153
Combination therapy	109
Combination therapy inc. IV/SC PCA	14
CCB	17
PDE5i	211
ERA	129
PCA	14

CCB indicates calcium channel blocker; ERA, endothelin receptor antagonists; PDE5i, phosphodiesterase-5 inhibitors; sGCs, stimulator of soluble guanylate cyclase; IV, intravenous; SC, subcutaneous; PCA, prostacyclin analogues.

Table S5. Relations between exercise variables and hemodynamic variables.

		Peak VO_2 ml/min/Kg	Peak VO_2 %predicted	VE/VCO_2 slope	Peak O_2 pulse %predicted	6MWD
Mean RAP	Rs	**-.254****	**-.174***	0.106	**-.170***	**-.310****
	p-value	0.001	0.022	0.171	0.026	<0.001
Mean PAP	Rs	-0.078	**-.256****	0.091	**-.317****	0.043
	p-value	0.302	0.001	0.233	<0.001	0.537
Cardiac Index	Rs	**.504****	**.380****	**-.467****	**.483****	**.369****
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001
PVR	Rs	**-.340****	**-.398****	**.326****	**-.508****	**-.171***
	p-value	<0.001	<0.001	<0.001	<0.001	0.015
SvO_2	Rs	**.530****	**.398****	**-.401****	**.261****	**.447****
	p-value	<0.001	<0.001	<0.001	0.001	<0.001

RAP indicates right atrial pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation; VO_2, oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio; 6MWD, 6-minute walk distance; rs, r squared. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table S6. Relation between exercise variables and RVEF as assessed by cardiac magnetic resonance.

		Peak VO_2 ml/min/Kg	Peak VO_2 %predicted	VE/VCO_2 slope	Peak O_2 pulse %predicted	6MWD
RVEF (CMR)	Rs	**.453****	**.348****	**-.320****	**.562****	0.242
	p-value	<0.001	0.001	0.003	<0.001	0.14

RVEF indicates right ventricular ejection fraction; VO_2, oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio; 6MWD, 6-minute walk distance; rs, r squared. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table S7. Univariate and multivariate Cox regression analysis of treatment-associated changes in exercise variables at first re-evaluation.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
Δ Peak VO_2, ml/min/Kg	0.83 (0.75-0.92)	**<0.001**	0.98 (0.96-0.99)	**0.024**
Δ Peak VO_2, %predicted	0.96 (0.94-0.98)	**<0.001**		
Δ VE/VCO_2 slope	1.03 (1.01-1.05)	**0.043**		
Δ Peak O_2 pulse %predicted	0.97 (0.96-0.98)	**<0.001**		
Δ 6MWD, m	1 (1-1.01)	0.787		

VO_2, oxygen consumption; VE/VCO_2 slope, slope relating minute ventilation to carbon dioxide production ratio; 6MWD, 6-minute walk distance.

Table S8. Univariate and multivariate Cox regression analysis of low-risk criteria assessed at first re-evaluation.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
WHO-FC I or II	0.30 (0.16-0.56)	**<0.001**	0.38 (0.22-0.65)	**<0.001**
BNP <50 ng/L	0.26 (0.14-0.48)	**<0.001**	0.40 (0.23-0.70)	**0.001**
CPET score <1.5	0.16 (0.06-0.38)	**<0.001**	0.39 (0.21-0.73)	**0.003**

WHO-FC indicates World Health Organization functional class; BNP, Brain natriuretic peptide; CPET, Cardiopulmonary exercise testing.

Table S9. Univariate and multivariate Cox regression analysis of low-risk criteria assessed at first re-evaluation.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	**p-value**	**Hazard ratio (95% CI)**	**p-value**
WHO-FC I or II	0.30 (0.16-0.56)	**<0.001**	0.47 (0.27-0.81)	**0.006**
BNP <50 ng/L	0.26 (0.14-0.48)	**<0.001**	0.34 (0.20-0.60)	**<0.001**
6MWD >440 m	0.23 (0.09-0.57)	**<0.001**	0.29 (0.14-0.60)	**<0.001**

WHO-FC indicates World Health Organization functional class; BNP, Brain natriuretic peptide; 6MWD, 6-minute walk distance.

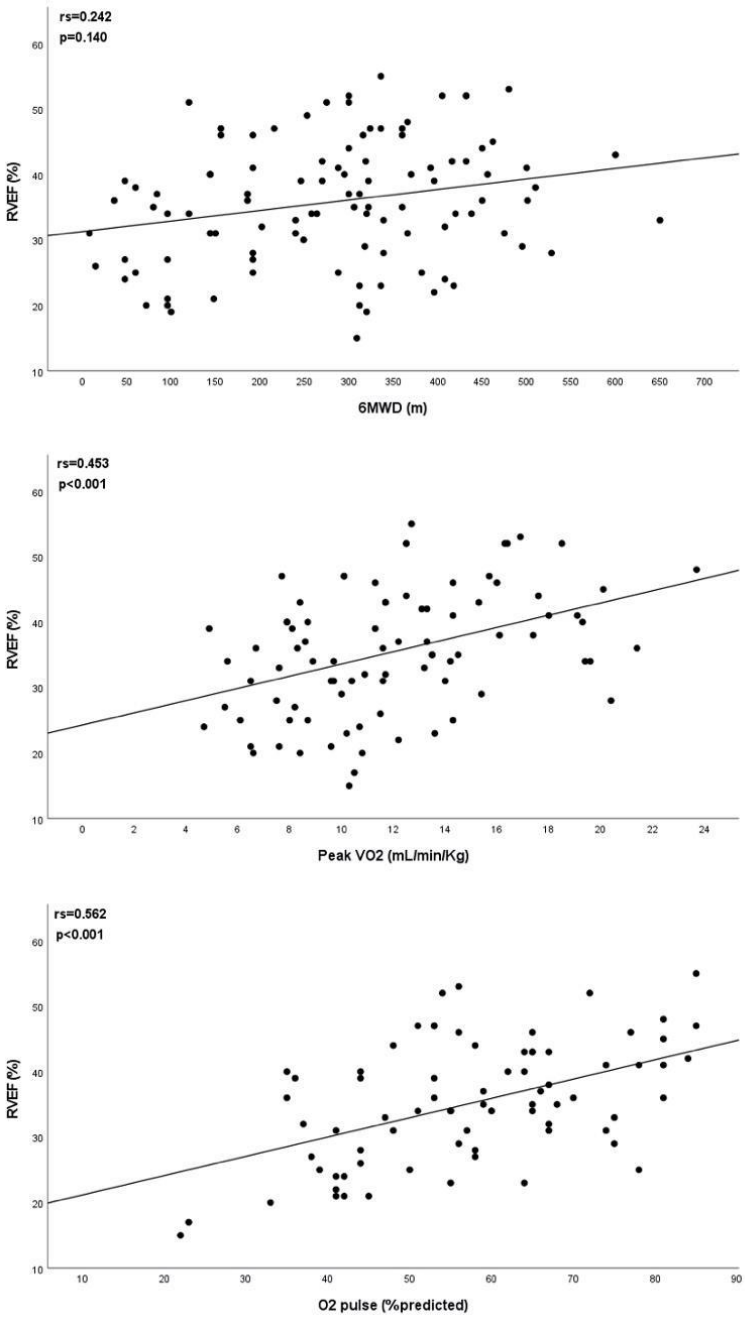
Table S10. Risk category distribution between the ESC/ERS four-strata risk stratification model and the newly proposed prognostic tool with the CPET score.

		ESC/ERS^{6MWT}			
		Low	Intermediate-low	Intermediate-high	High
ESC/ERS^{CPET}	Low	**32**	2	-	-
	Intermediate-low	25	**77**	24	-
	Intermediate-high	-	16	**76**	-
	High	-	-	1	**9**

Darker shading indicates CPET score classifies as higher risk than standard model.
Medium shading indicates no change in risk category.
Lighter shading indicates CPET score classifies as lower risk than standard model.

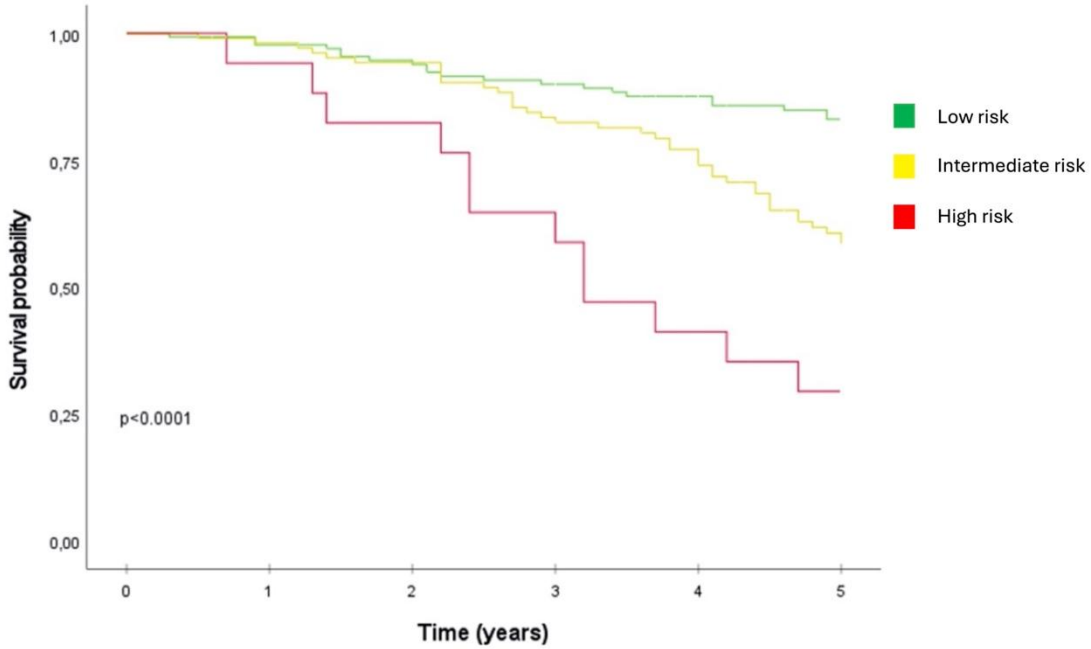
FIGURES

Figure S1. Relation between exercise parameters and right ventricular ejection fraction (RVEF), assessed by cardiac magnetic resonance.



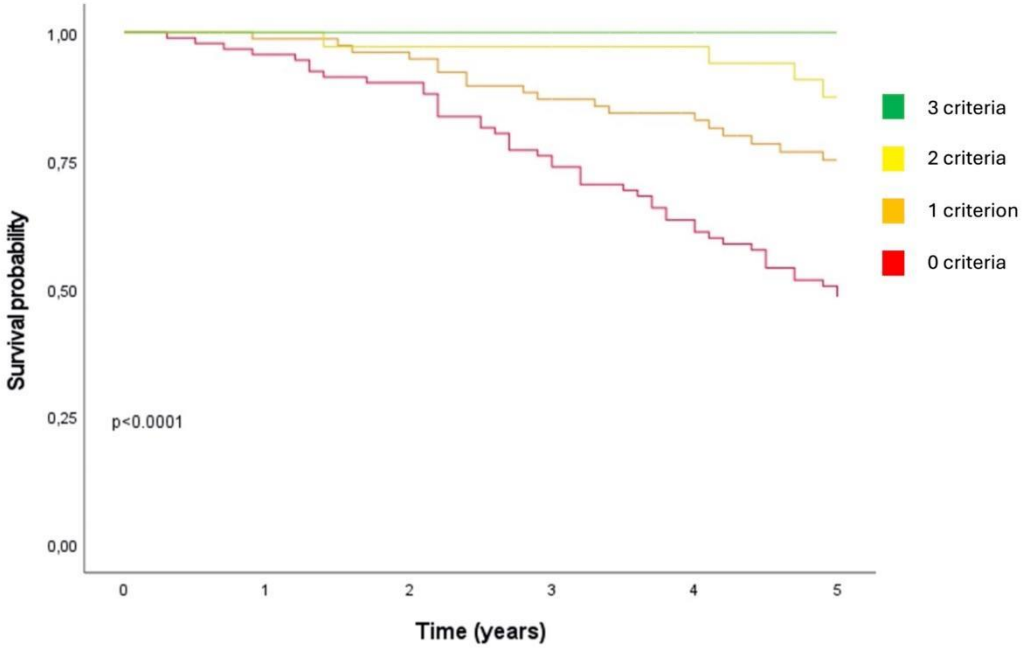
RVEF indicates right ventricular ejection fraction; 6MWD, 6-minute walk distance; VO_2, oxygen consumption.

Figure S2. Transplant-free survival according to the three-strata peak O_2 pulse (%predicted) scores assessed at the first re-evaluation.



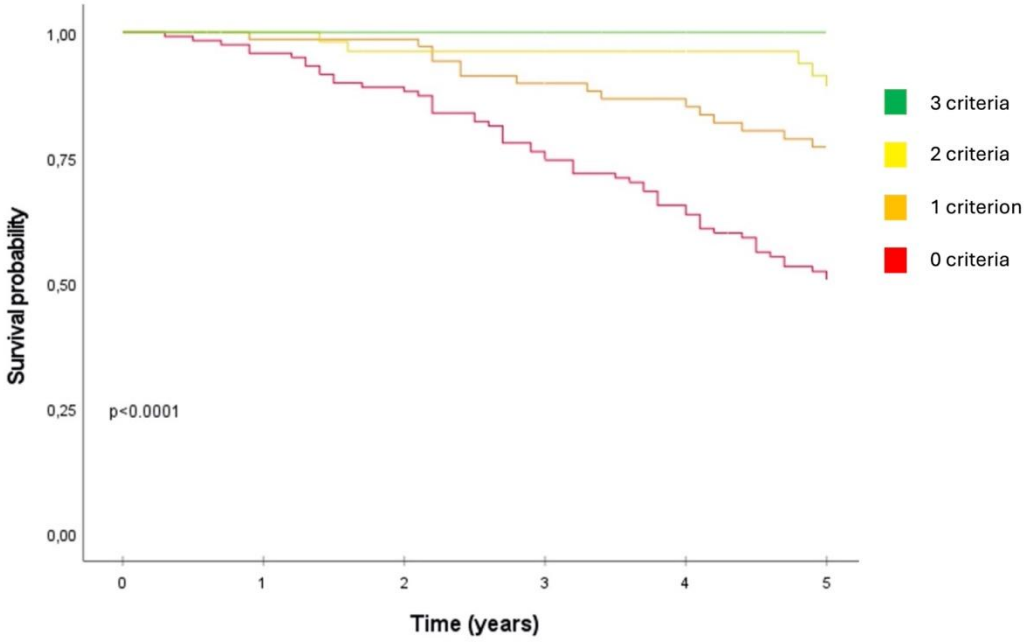
Patients at risk						
Low risk	136	129	122	115	104	92
Intermediate risk	104	102	97	85	72	53
High risk	17	16	14	11	7	5

Figure S3. Transplant-free survival according to the number of low-risk criteria (BNP <50 ng/L, WHO FC I-II and a CPET score <1.5).



Patients at risk						
0 criteria	92	88	82	69	54	43
1 criterion	78	77	74	66	60	47
2 criteria	38	36	34	33	30	26
3 criteria	36	34	33	33	30	27

Figure S4. Transplant-free survival according to the number of low-risk criteria (BNP <50 ng/L, WHO FC I-II and a 6MWD >440 m).



Patients at risk						
0 criteria	119	114	104	89	71	54
1 criterion	70	69	69	61	55	48
2 criteria	56	52	48	48	45	38
3 criteria	17	17	17	17	15	13

Figure S5. Long-term transplant-free survival according to the four-strata ESC/ERS^{6MWT} and ESC/ERS^{CPET} risk categories at follow-up.

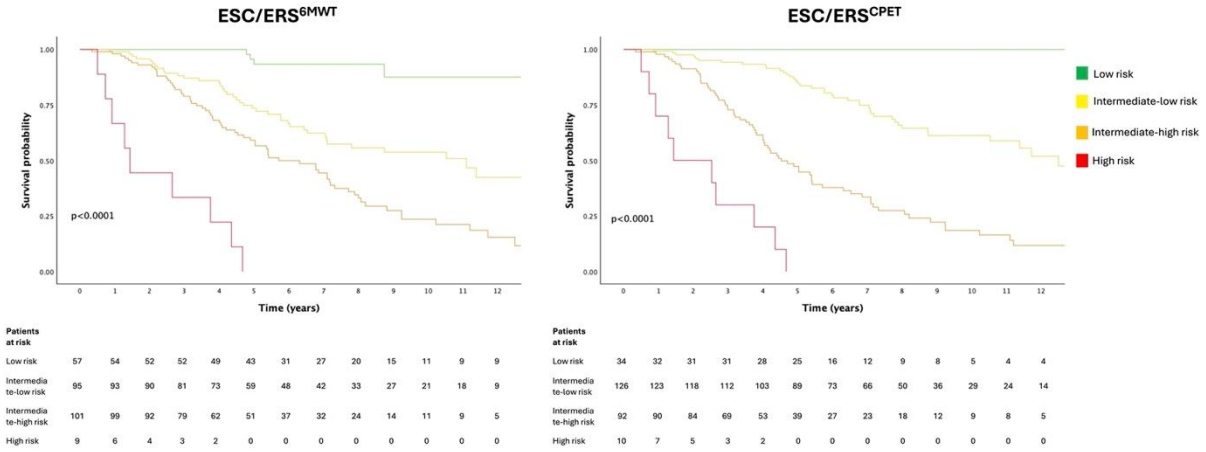
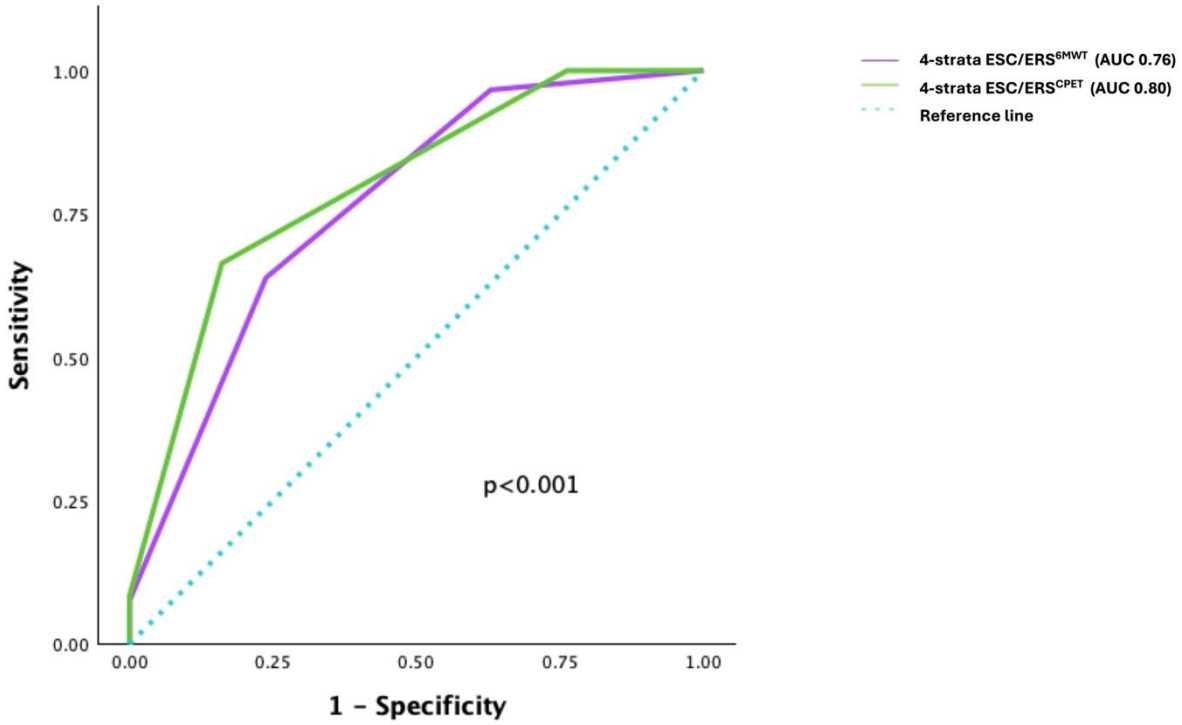


Figure S6. Receiver operating characteristics (ROC) curves and areas under the curve (AUC) of the ESC/ERS^{6MWT} and ESC/ERS^{CPET} models for long-term survival.



Supplementary figure S7. Transplant-free survival according to the four-strata ESC/ERS^{6MWT} and ESC/ERS^{CPET} risk categories at follow-up in patients with and without cardiopulmonary comorbidities.