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INCREMENTAL VALUE OF CARDIOPULMONARY EXERCISE TESTING IN INTERMEDIATE-RISK PULMONARY ARTERIAL HYPERTENSION

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ABSTRACT

Background. Risk assessment in pulmonary arterial hypertension (PAH) is essential for prognostication. However, the majority of patients end-up in an intermediate risk status, offering insufficient guidance in clinical practice. The added value of cardiopulmonary exercise testing (CPET) in this setting remains undefined.

Methods. Two independent cohorts with idiopathic PAH at intermediate risk were used to develop (n=124) and externally validate (n=143) the prognostic model. Cross-validation on the overall population was used to strengthen the results of the analysis. Risk assessment was based on the simplified version of the ESC/ERS guidelines score. Discrimination and calibration were assessed.

Results. A risk score was constructed based on the beta-coefficient of the cross-validated model, including the stroke volume index (SVI) and the peak oxygen uptake (VO_2 peak). Patients were grouped based on cutoff values of the risk score allowing the highest discrimination in the overall cohort. Group 1, score ≤ 2 (101 patients) with VO_2 peak ≥ 14 ml/kg/min and SVI > 30 ml/m^2; Group 2, score between 2 and 5 (112 patients) with VO_2 peak between 9 and 14 ml/kg/min, and SVI between 20 and 50 ml/m^2; Group 3, score > 5 (46 patients) with VO_2 peak < 10 ml/kg/min and SVI < 30 ml/m^2.

The event-free survival rates at 1, 2 and 3 years, were 96%, 83% and 79% for Group 1, respectively; 82%, 67% and 52% for Group 2; 69%, 50% and 41% for Group 3.

Conclusions. Combinations of VO_2 peak and SVI may provide important information to further stratify intermediate-risk prevalent patients with idiopathic PAH.

Keywords: pulmonary arterial hypertension; oxygen uptake; cardiopulmonary exercise test; clinical worsening; validation.

Abbreviations List:

6MWD: 6-min walk distance

BNP: brain natriuretic peptide
CPET: cardiopulmonary exercise testing
CI: cardiac index
CW: clinical worsening
DLCO: diffusing capacity for carbon monoxide
ERA: Endothelin receptor antagonists
ERS/ESC: European Respiratory and Cardiology Societes
HR: heart rate
IPAH: idiopathic pulmonary arterial hypertension
mPAP: mean pulmonary artery pressure
PAH: pulmonary arterial hypertension
PAWP: pulmonary artery wedge pressure
PDE5: Phosphodiesterase type 5 inhibitors
$P_{ET}CO_2$: end-tidal carbon dioxide partial pressure
PVR: pulmonary vascular resistance
RAP: right atrial pressure
REVEAL: United States Registry to Evaluate Early and Long-Term PAH Disease Management registry
RV: right ventricular
SVI: stroke volume index
V_E: minute ventilation
VCP: ventilatory compensation point
VCO_2: carbon dioxide output
VO_2 peak: peak oxygen uptake
WHO: world health organisation

INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive and life-threatening disease with several therapeutic options (1). Risk assessment is essential for clinical decisions. The European Cardiology and Respiratory societies (ESC, ERS) score and the United States Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) score have emerged as the primary risk assessment tools to guide management (2,3). However, clinical decisions are increasingly characterised by significant uncertainty, especially in the follow-up period, when approximately 60% of patients are at intermediate risk (4,5,6,7,8). Such situations call for dynamic risk assessment with expert consensus recommending repeated measures during follow-up (2,9,10,11). Indeed, a patient's risk for adverse events is affected by the overall evolution of disease pathophysiology over time. In this setting, it is now clear that right ventricular (RV) function is a major determinant of survival (12,13,14) and RV contractile reserve or indeed response to exercise, assessed by cardiopulmonary exercise testing (CPET), may represent important tools to predict long-term outcome

(15,16,17,18,19). We therefore investigated the prognostic relevance of CPET added to clinical and hemodynamic variables in the reassessment of IPAH patients at intermediate risk after institution of targeted therapies.

METHODS

Derivation cohort

The derivation cohort consisted of 124 consecutive prevalent IPAH evaluated at the Sapienza University of Rome, Italy, between January 2008 and December 2013, and considered at intermediate risk, according to the simplified version of the ERS/ESC guidelines score (20).

Initial diagnosis relied on a right heart catheterization showing precapillary PH (mean pulmonary artery pressure, mPAP ≥ 25 mmHg, wedged PAP, PAWP ≤ 15 mmHg, pulmonary vascular resistance, PVR > 3 WU) and the use of an algorithm incorporating respiratory function tests, perfusion lung scan, computer tomography scan, echocardiography, and laboratory tests to exclude secondary causes, in agreement with updated guidelines (10,11). Baseline assessment at the time of enrollment included WHO class evaluation, invasive hemodynamic measurements, a 6-minutes walk-distance (6MWD) and a CPET (figure 1).

Validation cohort

A validation cohort of 143 consecutive IPAH patients was recruited at 3 referal centers with high volume of clinical practice, the University of Arizona of Tucson, Arizona, U.S.A, Hammersmith Hospital – Imperial College Healthcare NHS Trust, London, U.K., and the Sapienza University of Rome, Italy, between January 2014 and December 2019 with prospective follow-up. The baseline assessment at the time of enrollment included WHO class evaluation, invasive hemodynamics, 6MWD and CPET.

Patients were elegible if their clinical condition was considered intermediate risk, according to the simplified version of the ERS/ESC guidelines score, allowing for a strong external validation, as "temporal" and "geographic" validation (21). Both incident patients (from Hammersmith Hospital) and prevalent patients (from the University of Arizona and the Sapienza University of Rome) were included in the validation

cohort.

Risk assessment

Risk assessment was based on a simplified version of the ERS/ESC guidelines score, according to cut-off values reported for WHO functional class, 6MWD, right atrial pressure (RAP) and cardiac index (CI). The average method was considered, as recently reported (4,6,20), with each variable graded from 1 to 3, where 1= "low risk", 2 = "intermediate risk", and 3 = "high risk". The mean grade was rounded to the nearest integer, which was used to define the patient's risk group.

The REVEAL score 2.0 was also applied, with incorporation of etiology, age, sex, WHO functional class, systolic blood pressure, heart rate, right atrial pressure, PVR, 6MWD, lung diffusing capacity for carbon monoxide (DLCO), brain natriuretic peptide (BNP) levels, renal function, echocardiography of pericardial effusion, and previous hospitalization (minimum 7 variables considered) (3,7,8,20).

Outcomes and clinical worsening definitions

The same outcome measures were defined in both cohorts including all-cause mortality and clinical worsening (CW) events as defined as a reduction from baseline in the 6MWD by 15% plus worsening of WHO functional class, or nonelective hospitalization for PAH (i.e. need for i.v. diuretic or inotropic drugs, need for new PAH therapies, lung transplantation, or septostomy), or all-cause mortality. CW was assessed in each center by a multidisciplinary team, as recommended for patients follow-up (10,11).

The first episode of CW was taken into consideration for the analysis.

The study was conducted in accordance with the amended Declaration of Helsinki, and within the context of regular care. All patients provided written informed consent for data being used for research purposes. Approval for the use of this data was obtained by the local Ethical Committee (Rome: protocol n. 423/2020; London: DB Triphic/17/LO/0565; Tucson: IRB #1100000621).

Right heart catheterization

Hemodynamic evaluation was made using standard techniques, as recommended by guidelines and previously described (10,11,22).

Cardiopulmonary exercise test

All centers have a high volume of clinical practice for PAH and CPET. Each center analysed their own data sharing a common approach for data analysis.

All patients performed a symptom-limited incremental cycle ergometer CPET with 10-15 Watt/min workload increments. All patients were able to complete a maximal test and no patient was on supplemental O_2. Oxygen uptake (VO_2), carbon dioxide output (VCO_2), minute ventilation (V_E) and end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$) were measured breath-by-breath (Quark CPET, Rome, Italy; Carefusion, for University of Arizona; Master Screen CPX; Jaeger; Hoechberg, Germany for Hammersmith) and averaged every 5 s for subsequent analysis. Heart rate (HR) was monitored via 12 leads ECG. The O_2 pulse was calculated as the VO_2/HR ratio at peak exercise. The anaerobic threshold was detected by the V-slope method. Peak work rate (WR), peak VO_2 and peak V_E were defined, respectively, as the highest level of exercise and the highest VO_2 and V_E that could be sustained for at least 15 s during the last stage of incremental exercise. The slope of V_E over VCO_2 ($\Delta V_E/\Delta VCO_2$) during incremental test was measured from unloaded pedalling to the ventilatory compensation point (VCP) and, for patients who did not reach the VCP it was measured from unloaded pedalling to peak exercise. The dead space volume of the facemask was subtracted from the total V_E before calculating individual V_E/VCO_2 slopes and ratios.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median (interquartile range [IQR] 25%-75%) for non-normally distributed variables. Normality was assessed using the Kolmogorov-Smirnov test. Categorical data are expressed as counts and proportions. Missing data were handled by multiple imputation with chained equations. Two-group comparisons were done with unpaired, two-tailed t tests for means if the data were normally distributed or with Wilcoxon's rank-sum tests if the data were not. Chi square or Fisher's exact tests were used to analyze the categorical data. Regression analysis was

performed to assess the relationship between variables. Cox proportional hazards regression methods were used to identify risk factors for clinical worsening. The proportional-hazards assumption was tested using log-minus-log plots for categorical variables and the Schoenfeld residuals plots for continuous variables.

Because of the large number of variables that were being assessed compared to the relative low number of events occurred, a strict univariate p-value criterion ($p < 0.05$) was used to identify which variables to include in the multivariable model. Collinearity was assessed by using bivariate linear regression between continuous variables or Spearman's rank correlation for categorical variables.

An overall analysis on all data (derivation and validation cohorts combined) using 5-fold cross-validation was performed for the final model. The risk score was constructed based on the coefficients obtained from the least absolute shrinkage and selection operator (LASSO) regression Cox analysis. Subsequently, a linear combination method was adopted. The score was then normalized with 10 being the highest scoring and 0 being the lowest scorning model as follows:

(Score-MinScore)/(MaxScore-MinScore)*10

where MaxScore is the maximum and Min Score is the minimum possible value that could be obtained.

The patients were grouped based on cutoff values allowing the most significant (log-rank test) split in the Kaplan-Meier curves of the overall cohort.

Discrimination by the c-index and calibration plot have been assessed and calculated at different time-points (12, 24 and 36 months follow-up) using cross-validation method. The Harrel's C index has also been calculated as an overall measure not depending on time.

All statistical analysis was performed using SPSS software (version 25.0, IBM) and open source package for R.

RESULTS

Derivation cohort and prognostic modeling

Physiologic, clinical, hemodynamic and CPET data of the patients of the derivation cohort are summarized in Table 1 (Table 2 reports rates of missing values for each variable). Age and sex distributions were typical. Most of the patients had WHO functional class III with impaired exercise capacity. All 124 patients were intermediate risk based on ESC/ERS criteria. According to the REVEAL 2.0 score, 74 (59.7%) patients were intermediate risk, while 35 (28.2%) were low risk and 15 (12.1%) high risk.

Median time from diagnosis to enrollment was 237 days (IQR 110-1324). The majority of the patients were treated with oral (67 patients, 54.0%; ERA or PDE5i) monotherapy, fitting with contemporary guidelines, that were less insistent on combination therapies at that time. Eleven patients (8.9%) were on double oral combination therapy (ERA andr PDE5i) and 25 (20.2%) on parenteral prostanoid plus oral drug.

During a median follow-up of 34 months (IQR 19-53), 74 patients experienced CW (51.2%) (19 [15.3%] deaths; 17 [13.7%] hospitalizations for right heart failure; 38 [30.6%] worsening in WHO class and 6MWD). The event-free survival rates were 87%, 68% and 57% at 1, 2 and 3 years, respectively.

Six-MWD, mPAP, CI, SVI, PVR, VO_2 peak (ml/min/kg) and O_2 pulse predicted CW by univariate analysis (Table 3). In multivariate analysis, variables were selected from the least absolute shrinkage and selection operator (LASSO) regression Cox analysis. The absolute VO_2 peak (ml/min/kg) and SVI emerged as independent predictors of clinical worsening (Table 4).

Validation cohort

The 143 idiopathic PAH patients in the validation cohort were similar to those of the derivation cohort with respect to physiological, clinical and hemodynamic measures, but with more impaired exercise capacity (Table 1 and 2). All the patients were ESC/ERS intermediate risk. According to the REVEAL 2.0 score, 75 (52.4%) patients were intermediate risk, while 46 (32.2%) were low risk and 22 (15.4%) high risk.

For the 101 prevalent patients, treatments started at diagnosis and ongoing at the time of enrollment were ERAs in 20 (19.8%), PDE5is in 21 (20.8%), parenteral treprostinil in 21 (20.8%), double oral combination in 12 (11.9%), parenteral prostanoid plus oral in 27 (26.7%). Median time from diagnosis to enrollment was 184 days (IQR 121-898) from diagnosis. In this cohort sequential combination therapy was started at the time of enrollment in 78 (78.8%) patients. Thus, 10 (9.9%) patients remained on oral monotherapy (ERA or PDE5i), 40 (39.6%) patients were on double oral combination (ERA+PDE5i), 34 (33.7%) patients were on

parenteral prostanoid plus oral, 2 (2.0%) patients in triple oral combination, and 16 (15.8%) patients in triple combination including parenteral prostanoid.

For the 42 incident patients who were treatment naïve at enrollment 8 (19.0%) were placed on ERAs, 19 (45.2%) PDE5, 12 (28.6%) double oral combination (ERA+PDE5i), and 3 (7.1%) parenteral prostanoid plus oral therapy.

Over 27 median months (IQR 13-46), 49 patients experienced a CW (34.3%) (17 [11.9%] deaths; 11 [7.7%] hospitalizations for right heart failure; 21 [14.7%] worsening in WHO class and 6MWD). The event-free survival rates were 85%, 74% and 65% at 1, 2 and 3 years, respectively. The survival rates were 93%, 89% and 85% at 1, 2 and 3 years, respectively.

Among the validation cohort, 41 patients (28.7%) had favorable long-term outcomes with more than 3 years event-free survival. Nine patients (6.3%) died and 21 (14.7%) had clinical worsening in the first 12 months of follow-up.

Discrimination for time to event models reflects the ability to distinguish higher-risk from lower-risk individuals. The c-statistic is the probability that from a random pair of patients the one who suffered a CW event first has a higher predicted probability of CW. The c-statistic was 0.80 (C.I. 0.69-0.90) in the derivation cohort and 0.74 (C.I. 0.64-0.86) in the validation cohort. As the c-statistic value did not decrease substantially in the independent validation data set (unchanged range of discriminatory ability, between 0.70 and 0.80)(23), the model can be considered as having reasonable discrimination.

Risk score model and cross validation

To increase the straight of the results an overall analysis on all data (derivation and validation cohorts combined, 259 patients) has been performed using 5-fold cross-validation. The absolute VO_2 peak (ml/min/kg) and SVI remained independently associated with adverse outcome after cross-validation, with HRs values very close to the model developed from the initial derivation cohort (Table 4).

In this analysis a risk score was constructed based on the variables selected from the least absolute shrinkage and selection operator (LASSO) regression Cox analysis, as previously mentioned. Subsequently, a linear combination method was adopted using the beta-coefficient. The score was then normalized with 10 being the highest scoring and 0 being the lowest scoring model. The patients were grouped based on cutoff values

allowing the most significant (log-rank test) split in the Kaplan Meier curves of the overall cohort.

Group 1 with score ≤ 2, including 101 patients; Group 2 with score between 2 and 5, including 112 patients; Group 3 with score > 5, including 46 patients. In Group 1 we observed a VO_2 peak ≥ 14 (maximum observed 23) ml/kg/min associated with SVI > 30 (maximum observed 60) ml/m^2; in Group 2 we observed a VO_2 peak between 9 and 14 ml/kg/min, and SVI between 20 and 50 ml/m^2; in Group 3 we observed VO_2 peak < 10 (minimum observed 5) ml/kg/min associated with SVI < 30 (minimum observed 10) ml/m^2 (Figure 2).

Figure 3 shows the Kaplan-Meier event-free survival curves of the three groups. The event-free survival rates at 1, 2 and 3 years, were 96%, 83% and 79% for Group 1, respectively; 82%, 67% and 52% for Group 2; and 69%, 50% and 41% for Group 3 (Group 1 vs 2, p<0.001; Group 1 vs 3, p<0.001; Group 2 vs 3, p<0.001).

The survival rates at 1, 2 and 3 years were 99%, 96% and 92% for Group 1; 95%, 87% and 81% for Group 2; 82%, and 75% and 68% for Group 3, respectively (Group 1 vs 2, p=0.04; Group 1 vs 3, p<0.001; Group 2 vs 3, p<0.008)(figure 4).

Accordingly to the REVEAL 2.0 score, of the 81 patients at low risk, 56 (69.1%) were in Group 1 and 25 (30.8%) in Group 2. Of the 137 patients at intermediate risk, 42 (30.6%) were in Group 1, 71 (51.8%) in Group 2, and 24 (17.5%) in Group 3. Of the 33 patients at high risk, 15 (45.4%) were in Group 2 and 18 (54.5%) in Group 3.

Discrimination and calibration of the cross-validated prognostic model

The c-statistic was used for discrimination measurements at different time-points. At 12 months the c-statistic was 0.74 (C.I. 0.67-0.82), while at 24 and 36 months it was, respectively, 0.76 (C.I. 0.68-0.83) and 0.75 (C.I. 0.65-0.84). The Harrel's C index, as an overall time-independent measure, was 0.75 (C.I. 0.65-0.83).

As the c-statistic values were between 0.70 and 0.80, the model can be considered as having reasonable discrimination.

Calibration describes how accurately the estimates or predictions of event-free survival from a model reflect the event-free survival in the observed data. A calibration plot for the cross-validated model at different time-points is shown in figure 5. It plots the Kaplan-Meier estimates at 12, 24 and 36 months against the

predicted probabilities at the same time points. This provides evidence that the model overestimates the CW rate for high risk patients at 12 months, as the predictions are larger than the actual observed rates of the event, while results more balanced at 24 and 36 months.

DISCUSSION

The results show that SVI and VO_2 peak may provide important information to further stratify IPAH patients who are at intermediate-risk after institution of targeted therapies. Our study confirms intermediate-risk patients follow various clinical trajectories: 28.7% (41) have favorable long-term outcomes with more than 3 years event-free survival, while 14.7% (21) have clinical worsening within 12 months. This observation reinforces the ESC/ERS guidelines to follow IPAH patients closely with periodic risk reassessment.

As discussed, multiple registries have demonstrated that most intermediate-risk patients remain intermediate risk after initial treatment (4,5,6,7,8,24,25), considered an unsatisfactory clinical response (10,11,26). Our findings confirm that this group of patients still have a high mortality rate of 6.3% at 1-year follow-up and that there is a need to stratify this group further to decide on treatment intensity.

Recent data from the French registry, gathered through serial hemodynamic measures and analysis showed the beneficial effects of the SVI to further risk stratify PAH patients after initial treatment (27). Our study confirms that SVI is an independent prognostic variable in intermediate risk patients, allowing high discrimination in combination with VO_2 peak. Indeed, the SVI cut-point of > 46 ml/m^2 identified in the French cohort was only present in 9.0% (13) of the intermediate risk patients in our cohort, marking them as low risk (0% mortality). A cut-point of 38 ml/m^2 (13) increased the proportion to 30.0% (43) but was unsatisfactory due to a higher CW rate to 30% (13). Both cut-point values in isolation provided insufficient discriminatory power for the majority of the intermediate risk patients. In our study the risk score built from the combination of the SVI and the VO_2 peak was able to reassign 39.9% of patients (Group-1) as having low-risk (1% and 4% 1-year mortality and CW rate, respectively), characterized by SVI > 30 ml/m^2 associated with VO_2 peak ≥ 14 ml/m^2. On the other hand 17.8% of patients (Group-3), characterized by SVI < 30 ml/m^2 associated with very low VO_2 peak (<10 ml/m^2), were identified as high risk (Group-3, 18% and 31% 1-year mortality and CW rate, respectively). These numbers are in accordance to the high-risk mortality range reported in current guidelines (10,11) and the SVI values associated with Group-3 are very close to the

lower quartile (< 31ml/m^2) of SVI distribution associated with very poor prognosis in the French registry (27). Moreover, a significant proportion of patients fell into an unsatisfactory clinical response group still requiring alternative add-on treatments ranging from double oral (if the patients had been on oral monotherapy) to switching to a soluble guanylate cyclase stimulator, triple oral combination, or triple combination therapy with parenteral prostanoids. Parenteral prostanoids might therefore be considered a more appropriate alternative for those patients resulting at higher risk (Group-3).

Of note, the risk score based on the beta coefficient of the SVI and the VO_2 peak of the cross-validated model remained useful when the REVEAL 2.0 score was applied to the overall population, allowing further stratification into clinically meaningful groups with different outcomes those patients at intermediate-risk, as well as those at low-risk. On the other hand, patients with REVEAL 2.0 high-risk were already identified at higher risk.

The additional prognostic utility of SVI and VO_2 peak is potentially related to how the variables represent aspects of RV adaptation. Indeed, functional reserve of the RV is the main determinant of exercise increase in CI and thus it follows that there is prognostic relevance to the cardiovascular and pulmonary systems ability to respond to exercise in order to meet metabolic demands (28-32). In fact, variables related to RV functional reserve have been implicated in the pathophysiology of PAH (12-13). In this setting VO_2 peak has been strongly associated with exercise CI, which resulted the only independent predictor of VO_2 peak (29).

Wensel R. et al. investigated the importance of RV functional reserve in idiopathic or familial PAH, showing the incremental prognostic value of VO_2 peak in combination with PVR (33). Indeed, as it is now better known that most of symptomatology and outcome in PAH is determined by RV structure and function adaptation to afterload (12,13), integrating CPET in the risk assessment would be expected to be a useful addition to risk discrimination (33-36).

We have previously shown in low-risk prevalent IPAH patients the benefit of CPET in clinical and hemodynamic assessment (37). The combination of VO_2 peak ≥15.7 ml/kg/min (≥60% p.v.) and Δ CI ≥0.40 l/min/m^2 or the VO_2 peak ≥18.7ml/kg/min (≥70% p.v.) *per se* confirmed clinical improvement and stability after institution of targeted therapies with excellent Se (100%) and NPV (100%). Thus, it is no surprise that there may be additive value of VO_2 peak together with SVI at rest to reassess a more advanced group of IPAH patients compared with the low-risk cohort.

The V_E/VCO_2 did not independently predict outcome in contrast to some previous studies (38,39,40) but in agreement with others (33). These discrepancies may be explained by differences in size and characteristics of source population. Therefore, the present results may be applicable only to intermediate-risk IPAH, as included in the present study.

In addition, current guidelines recommend the practice of repeated right heart catheterization for risk assessment in the follow-up of patients with PAH (10,11). If the only measured variable of prognostic relevance is SVI, as suggested by the present results, there may be an option for non-invasive alternatives. For example, inert gas rebreathing may be as accurate as thermodilution when compared to gold standard Fick method in patients with an oxygen saturation ≥ 90%, even though a lesser degree of precision may require a larger number of repetitions of the measurements (41,42). Moreover, magnetic resonance imaging-derived SVI and RV end-diastolic volume at follow-up have been shown to be of prognostic relevance in IPAH (43). Thus, whether repeated RHC can be replaced by noninvasive assessment of SVI when combined with CPET would be worth testing in future studies.

Finally, the added value of VO_2 peak and SVI measurements to the 4-strata model (44) based on refined cut-off levels for WHO functional class, 6MWD and BNP/NT-proBNP needs to be further investigated.

Limitations

First, the validation cohort considered in the present study is relatively small. However, an overall analysis on all the patients by cross-validation confirmed the signal that CPET provides added-value in risk assessment in intermediate risk PAH. Second, the results are limited to IPAH with intermediate-risk disease. Third, 8 patients in the derivation cohort with exercise-induced opening of a foramen ovale were excluded from the analysis to preserve the relevance of ventilatory measurements. Fourth, different independent predictors of outcome may emerge in larger scale studies or from longitudinal risk assessment at different time-point. Future multi-center collaborations are needed. Fifth, there was a different case mix between the two validation cohorts, as an incident cohort had fewer patients in the lowest risk strata and more patients in the highest risk strata compared with the prevalent cohort. Furthermore, more patients were receiving combination therapy in the validation cohort. Mitigating this is the fact that we only considered patients in the same intermediate risk strata. It should also be noted that a restrictive inclusion criteria limiting the mixed population to the intermediate risk would not address the immortal time bias associated with patients

not surviving to diagnosis. However, Benza RL. et al. (45) showed that the REVEAL risk calculator, developed in a predominantly prevalent cohort, is nonetheless effective at predicting risk in newly-diagnosed patients. Thus, it is recognized that while immortal time bias may be an intractable problem when prevalent patients are used to estimate an aggregate curve, and a delayed entry model (46) may account for as in the present study, it may not be an important issue in risk assessment (47).

CONCLUSIONS

In recent years we have seen ESC/ERS guidelines address the principles on how to appropriately assess risk among PAH patients to guide escalation of therapy. Unfortunately, current risk assessment tools can sometimes be unhelpful as the majority of patients sit in an intermediate risk category after initial treatment. The present study shows that in the intermediate risk IPAH population, the addition of VO_2 peak to SVI, more closely reflecting RV pathophysiology, may provide important information to patient's management and potentially adding decision support for different sequential treatment approaches to IPAH patients.

TAKE HOME MESSAGE

The combinations of VO_2 peak and SVI may provide important information to further stratify intermediate-risk prevalent patients with idiopathic PAH.

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Conflict of interest disclosure. R Badagliacca has received fees as speaker and scientific consultant for GSK, UT, Dompè, Bayer, Ferrer, MSD, Janssen, AOPOrphan Pharmaceuticals. CD Vizza has received fees as speaker and scientific consultant for GSK, UT, Dompè, Bayer, MSD. F Rischard has received research grants from Actelion, Bayer, UT, Phase Bio, Acceleron and NHLBI of the NIH. The other authors: nothing to declare.

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FIGURE LEGENDS

Figure 1. Patients distribution algorithm for the derivation cohort.

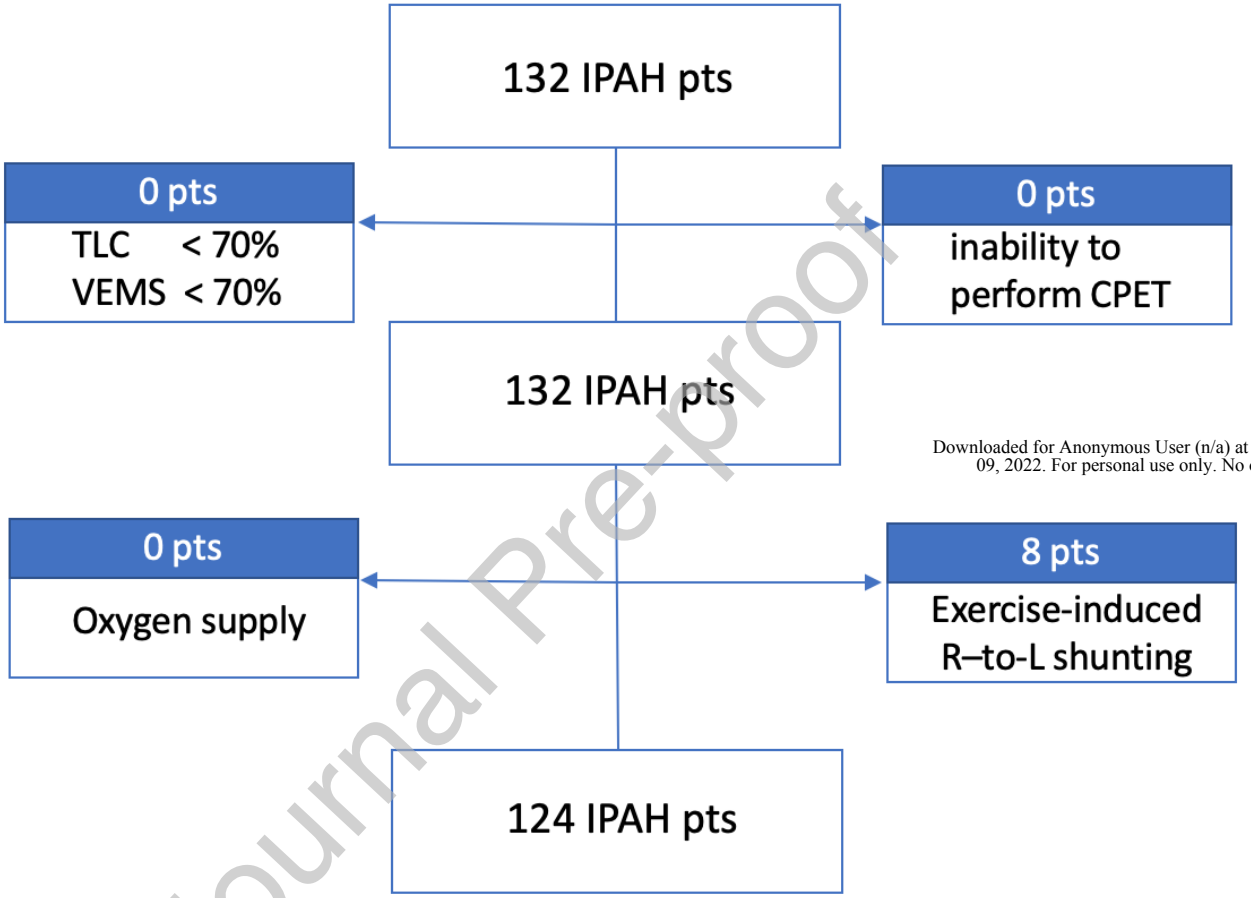


Figure 2. Related values of peak VO_2 and SVI corresponding to the cutoff values of the prognostic score (between 0 and 10).

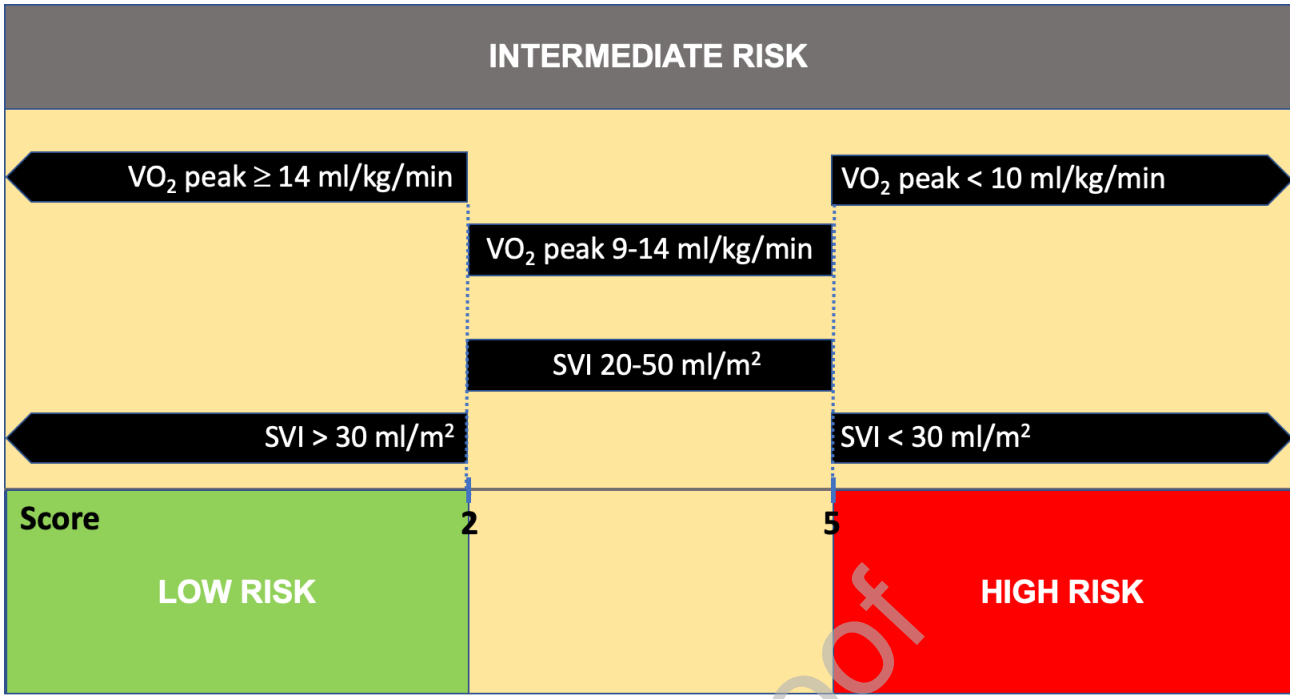
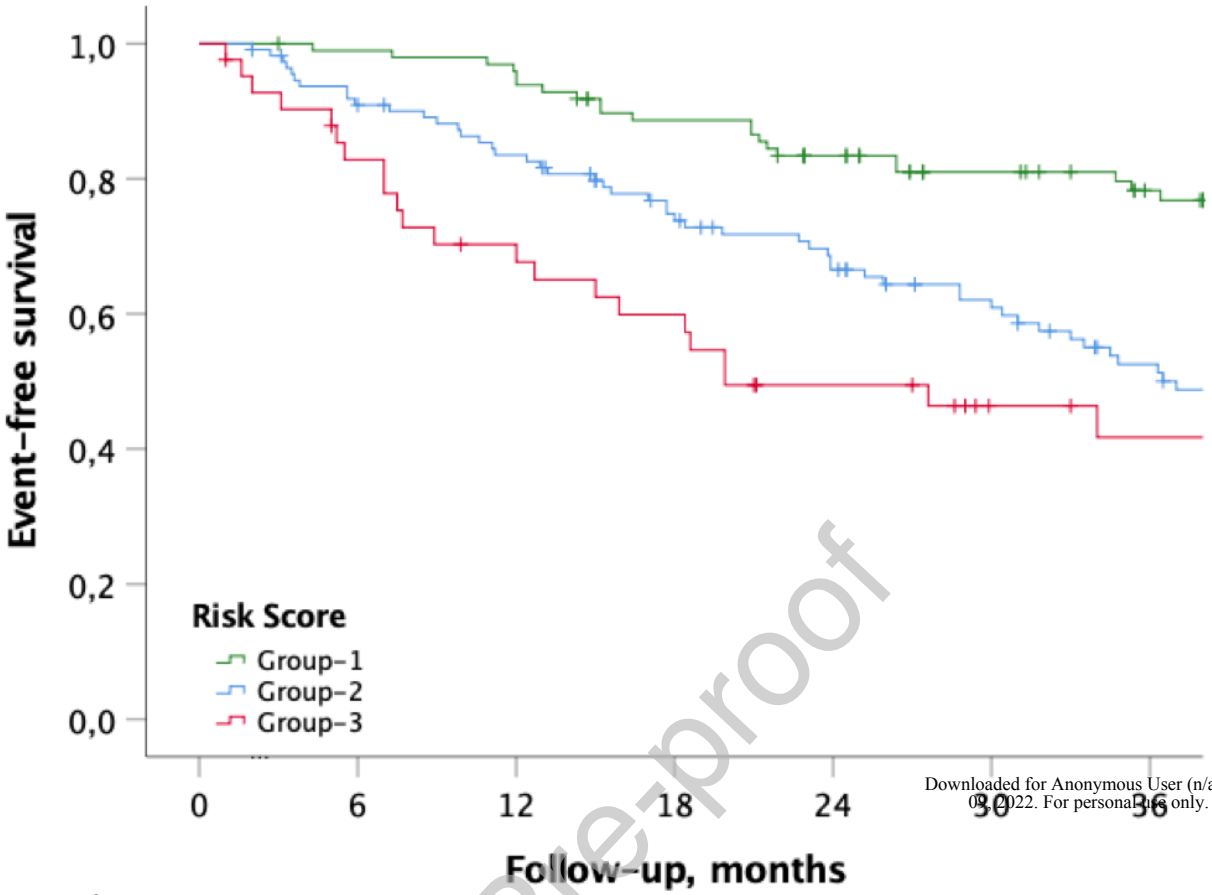


Figure 3. Kaplan-Meier event-free survival curves of the three Groups of patients, based on the risk score created from the beta-coefficient of SVI and peak VO_2. Group 1: score ≤ 2; Group 2: score between 2 and 5; Group 3: score > 5 (Group 1 vs 2, p<0.001; Group 1 vs 3, p<0.001; Group 2 vs 3, p<0.001).

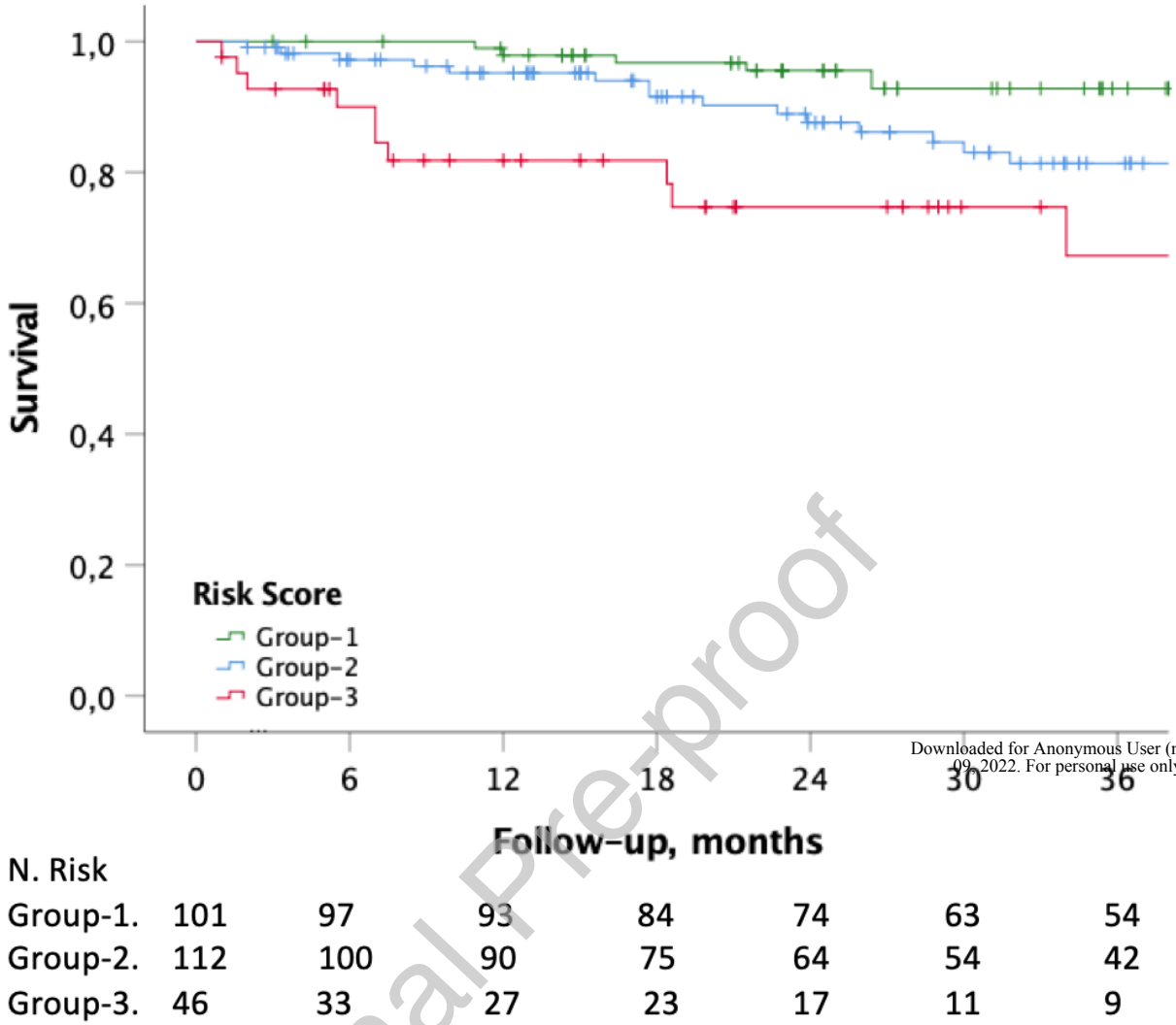
LEGEND - *SVI*: stroke volume index.



N. Risk							
Group-1.	101	97	93	84	74	63	54
Group-2.	112	100	90	75	64	54	42
Group-3.	46	33	27	23	17	11	9

Figure 4. Kaplan-Meier survival curves of the three Groups of patients, based on the risk score created from the beta-coefficient of SVI and peak VO_2. Group 1: score ≤ 2; Group 2: score between 2 and 5; Group 3: score > 5 (Group 1 vs 2, p=0.04; Group 1 vs 3, p<0.001; Group 2 vs 3, p<0.008).

LEGEND - *SVI*: stroke volume index.



N. Risk							
Group-1.	101	97	93	84	74	63	54
Group-2.	112	100	90	75	64	54	42
Group-3.	46	33	27	23	17	11	9

Figure 5. Calibration curves of the cross-validated model obtained at different time-points: T= 12 months; T= 24 months; T= 36 months. For each percentile of predicted probabilities, the average predicted probability is plotted against the Kaplan-Meier estimate. Perfect calibration is represented by the dotted line through the origin with slope equal to 1.

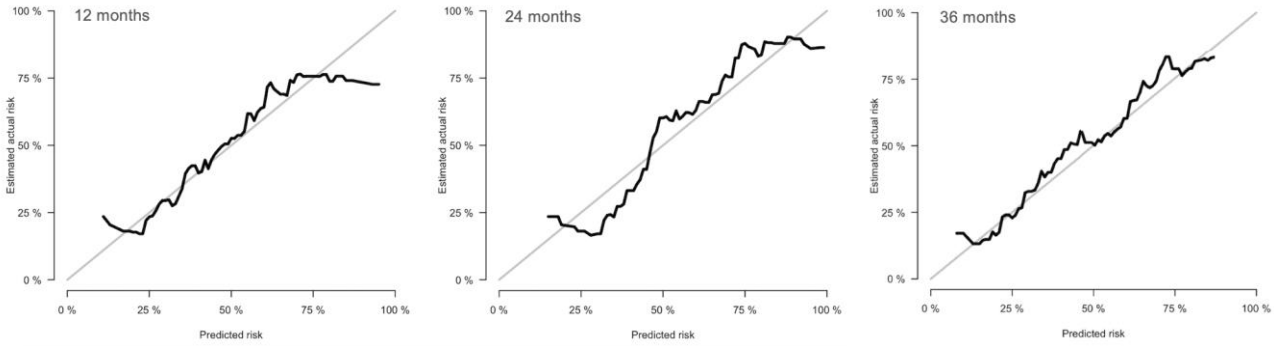


Table 1. Demographic, clinical, hemodynamic and exercise characteristics of the study population.

	Validation cohort	**Derivation cohort**	**p**
Baseline			
Idiopathic PAH, n (%)	143 (100)	124 (100)	
Age, years	56±14	57±10	ns
Weight, Kg	78±20	74±17	ns
Height, cm	165±10	163±8	ns
BSA, m^2	1.8±0.3	1.8±0.2	ns
Gender, M:F	50:93	49:75	ns
DLCO, %	53±19	57±14	ns
Comorbidities			< 0.001
Systemic hypertension, n (%)	28 (19.5)	11 (8.9)	
Diabetes, n (%)	24 (16.8)	6 (4.8)	
Coronary artery disease, n (%)	12 (8.4)	3 (2.4)	
Hypercholesterolemia, n (%)	30 (20.9)	16 (12.9)	
Thyroid disease, n (%)	20 (13.9)	8 (6.4)	
WHO, class	3.0±0.3	2.9±0.3	ns
WHO II, n (%)	11 (7.7)	11 (8.9)	
WHO III, n (%)	126 (88.1)	113 (91.1)	
WHO IV, n (%)	6 (4.2)	0 (0)	
6MWD, m	358 (276-430)	400 (350-430)	< 0.001
BNP, pg/ml	180 (70-334)291±331	232 (106-443)342±401	ns
Hemodynamics			
mPAP, mmHg	47.0±12.4	50.0±12.3	ns
RAP, mmHg	7.9±4.6	8.8±4.5	ns
CI, $l/min/m^2$	2.5±0.6	2.4±0.4	ns
SVI, ml/m^2	32.8±9.2	31.8±6.4	ns
PAWP, mmHg	8.5±3.4	9.2±3.4	ns
PVR, WU	9.3±4.8	10.1±4.8	ns
Cardiopulmonary exercise test			
HR peak, beats/min	119±20	124±17	ns
VO_2 peak, ml/Kg/min	10.8±3.8	13.7±3.2	< 0.01
VO_2 peak, % predicted	48±16	57±15	< 0.01
VO_2 pulse peak, ml/beat	6.9±2.2	7.5±1.8	0.03
V_E peak, l/min	38.1±21.1	46.1±15.6	0.01
V_E/VCO_2 slope	51.1±16.9	48.3±14.0	ns
Work peak, Watts	48±27	58±22	0.01
Risk Scores			
ESC/ERS, n (%)			ns
intermediate	143 (100)	124 (100)	
REVEAL 2.0, n (%)			ns
low	46 (32.2)	35 (28.2)	
intermediate	75 (52.4)	74 (59.7)	

high	22 (15.4)	15 (12.1)	
Number ESC/ERS low-risk criteria, n	0	0	ns
Therapy			
ERA, n (%)	12 (8.4)	35 (28.2)	< 0.01
PDE5i, n (%)	24 (16.8)	32 (25.8)	< 0.01
Epoprostenol, l i.v., n (%)	0 (0)	4 (3.2)	< 0.01
Treprostinil s.c., n (%)	0 (0)	17 (13.7)	< 0.01
Prostanoid + oral, n (%)	37 (25.8)	25 (20.2)	ns
ERA + PDE5i, n (%)	52 (36.4)	11 (8.9)	< 0.01
Triple oral, n (%)	2 (1.4)	0 (0)	< 0.01
Prostanoid + double oral, n (%)	16 (11.2)	0 (0)	< 0.01

BSA: body surface area*; DLCO:* diffusing capacity of the lung for carbon monoxide; *WHO*: World Health Organization; *6MWD*: non-encouraged 6-minute walk distance; *BNP*: brain natriuretic peptide; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *PAWP*: mean pulmonary artery wedge pressure; *PVR*: pulmonary vascular resistance; *HR peak*: peak heart rate; *VO_2 peak*: maximal oxygen uptake; *VO_2 pulse peak*: peak O_2 pulse defined as the ratio between VO_2 and HR; *V_E peak*: peak minute ventilation; *V_E/VCO_2 slope:* relationship between minute ventilation and carbon dioxide production; *ERA*: endothelin receptor antagonist; *PDE5i*: phosphodiesterase 5 inhibitor. *Prostanoid*: parenteral prostanoid (epoprostenol i.v., treprosti nil s.c.); *Triple oral*: ERA + PDE5i + selexipag.

Variables are reported as mean ± standard deviation and median (interquartile range).

Table 2. Available values for each variable in the two cohorts of patients.

	Validation cohort	**Derivation cohort**
Baseline		
Idiopathic PAH, n (%)	143 (100)	124 (100)
Age, n (%)	143 (100)	124 (100)
Weight, n (%)	143 (100)	124 (100)
Height, n (%)	143 (100)	124 (100)
BSA, n (%)	143 (100)	124 (100)
Gender, n (%)	143 (100)	124 (100)
DLCO, n (%)	131 (91.6)	120 (96.7)
Comorbidities, n (%)	143 (100)	124 (100)
WHO, n (%)	143 (100)	124 (100)
6MWD, n (%)	128 (89.5)	119 (95.9)
BNP, n (%)	96 (67.2)	92 (74.2)
Hemodynamics		
mPAP, n (%)	143 (100)	124 (100)
RAP, n (%)	143 (100)	124 (100)
CI, n (%)	143 (100)	124 (100)
SVI, n (%)	143 (100)	124 (100)
PAWP, n (%)	143 (100)	124 (100)
PVR, n (%)	143 (100)	124 (100)
Cardiopulmonary exercise test		
HR peak, n (%)	143 (100)	124 (100)
VO_2 peak, n (%)	134 (93.7)	124 (100)
VO_2 pulse peak, n (%)	134 (93.7)	124 (100)
V_E peak, n (%)	134 (93.7)	124 (100)
V_E/VCO_2 n (%)	134 (93.7)	124 (100)
Work peak, n (%)	143 (100)	124 (100)
Risk Scores		
ESC/ERS, n (%)	143 (100)	124 (100)
REVEAL 2.0, n (%)	143 (100)	124 (100)
Number ESC/ERS low-risk criteria, n	143 (100)	124 (100)
Therapy, n (%)	143 (100)	124 (100)

BSA: body surface area*; DLCO:* diffusing capacity of the lung for carbon monoxide; *WHO*: World Health Organization; *6MWD*: non-encouraged 6-minute walk distance; *BNP*: brain natriuretic peptide; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *PAWP*: mean pulmonary artery wedge pressure; *PVR*: pulmonary vascular resistance; *HR peak*: peak heart rate; *VO_2 peak*: maximal oxygen uptake; *VO_2 pulse peak*: peak O_2 pulse defined as the ratio between VO_2 and HR; *V_E peak*: peak minute ventilation; *V_E/VCO_2 slope:* relationship between minute ventilation and carbon dioxide production; *ERA*: endothelin receptor antagonist; *PDE5i*: phosphodiesterase 5 inhibitor. *Prostanoid*: parenteral prostanoid (epoprostenol i.v., treprosti nil s.c.); *Triple oral*: ERA + PDE5i + selexipag.

Variables are reported as mean ± standard deviation and median (interquartile range).

Table 3. Univariate analysis for clinical worsening prediction.

	Unit	Wald	HR	CI (95%)	p
Baseline					
Age, years	1	0.6	1.0	0.98-1.03	ns
Sex, male	1	0.3	1.1	0-72-1.81	ns
WHO, class	1	0.01	1.0	0.48-2.26	ns
6MWD, m	1	16.3	0.99	0.98-0.99	0.0001
BNP, pg/ml	1	0.67	1.0	0.99-1.001	ns
Hemodynamics					
mPAP, mmHg	1	6.9	1.02	1.00-1.03	0.008
RAP, mmHg	1	0.8	1.02	0.97-1.07	ns
CI, l/min/m^2	1	8.1	0.46	0.27-0.78	0.004
SVI, ml/m^2	1	28.8	0.91	0.88-0.94	0.0001
PVR, WU	1	3.9	1.04	1.00-1.08	0.04
Cardiopulmonary exercise test					
HR peak, beats/min	1	0.03	1.00	0.98-1.01	ns
VO_2 peak, ml//Kg/min	1	21.8	0.83	0.77-0.90	0.0001
VO_2 peak, % pred	1	13.2	0.96	0.95-0.98	0.0001
VO_2 pulse peak, ml/beat	1	9.9	0.79	0.68-0.91	0.002
V_E peak, l/min	1	0.4	0.99	0.97-1.01	ns
V_E/VCO_2 slope	1	2.9	1.01	0.99-1.02	ns
Work peak, Watts	1	0.05	0.99	0.98-1.01	ns
Days from diagnosis	1	0.7	1.00	1.00-1.001	ns

WHO: World Health Organization; *6MWD*: non-encouraged 6-minute walk distance; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *SVI*: stroke volume index; *PVR*: pulmonary vascular resistance; *HR*: peak heart rate; *VO_2 peak*: maximal oxygen uptake (ml/kg/min; % predicted value); *VO_2 pulse peak*: peak O_2 pulse defined as the ratio between VO_2 and HR; *V_E peak*: peak minute ventilation; *V_E/VCO_2 slope:* relationship between minute ventilation and carbon dioxide production.

Table 4. Cox regression models for event-free survival prediction: Model-1 for the derivation cohort; Model-2 for the crossvalidation overall cohort.

	Unit	HR	(95% CI)	p
Model-1				
VO_2 peak, ml/kg/min	1	0.89	0.82-0.97	< 0.01
SVI, l/m^2	1	0.94	0.90-0.97	< 0.001
Model-2				
VO_2 peak, ml/kg/min	1	0.87	0.81-0.93	< 0.001
SVI, l/m^2	1	0.97	0.95-0.99	0.01

BSA: body surface area*; DLCO:* diffusing capacity of the lung for carbon monoxide; *WHO*: World Health Organization; *6MWD*: non-encouraged 6-minute walk distance; *BNP*: brain natriuretic peptide; *mPAP*: mean pulmonary arterial pressure; *RAP*: mean right atrial pressure; *CI*: cardiac index; *PAWP*: mean pulmonary artery wedge pressure; *PVR*: pulmonary vascular resistance; *HR peak*: peak heart rate; *VO_2 peak*: maximal oxygen uptake; *VO_2 pulse peak*: peak O_2 pulse defined as the ratio between VO_2 and HR; *V_E peak*: peak minute ventilation; *V_E/VCO_2 slope:* relationship between minute ventilation and carbon dioxide production; *ERA*: endothelin receptor antagonist; *PDE5i*: phosphodiesterase 5 inhibitor. *Prostanoid*: parenteral prostanoid (epoprostenol i.v., treprostinil s.c.); *Triple oral*: ERA + PDE5i + selexipag.

Variables are reported as mean ± standard deviation and median (interquartile range).