Validity of 2015 ESC Risk Assessment in Idiopathic Pulmonary Arterial Hypertension in China

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Validity of 2015 ESC risk assessment in idiopathic pulmonary arterial hypertension in China

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ABSTRACT (230)

Background: The 2015 European pulmonary hypertension guidelines recommend a risk stratification strategy for pulmonary arterial hypertension (PAH). We aimed to investigate the validation and potential prognostic information in our patients.

Methods: The risk assessment variables proposed by the PH guidelines was performed, using World Health Organization function class, 6-min walking distance, brain natriuretic peptide or its N-terminal fragment, right arterial pressure, cardiac index, mixed venous saturation, right atrium area, pericardial effusion, peak oxygen consumption and ventilatory equivalents for carbon dioxide. An abbreviated version also was applied.

Results: The 392 patients were enrolled between 2009 and 2018. After a median interval of 13 months, re-evaluation assessments were available for 386 subjects. The PH guidelines risk tool may effectively discriminate three risk group and mortality ($p< 0.001$) both at baseline and re-evaluation. Meanwhile, its simplified risk version was valid for baseline and accurately predicted the risk of death in all risk group ($p< 0.001$). At the time of re-evaluation, the percentage of low risk group has an increase, but a greater proportion achieved high risk group and a lesser proportion maintained in intermediate risk group.

Conclusions: The 2015 European PH guidelines and its simplified version risk stratification assessment present effective discrimination of different risk groups and accurate mortality estimates in patients with IPAH. Changes of risk proportion at re-evaluation implicated that natural treatment decisions may not be consistently with goal-oriented treatment strategy.

Keywords: pulmonary arterial hypertension, idiopathic pulmonary arterial hypertension, risk assessment, guideline, prognosis

Abbreviations

BMI = body mass index; BNP = brain natriuretic peptide; CCB = calcium channel blocker; CI = cardiac index; 95% CI = 95% confidence interval; CO = cardiac output; CPET = cardiopulmonary exercise testing; ESC/ERS = European Society of Cardiology/European Respiratory Society; IPAH = idiopathic pulmonary arterial hypertension; 6MWD = 6-minute walk distance; NT-proBNP = N-terminal fragmental of pro-brain natriuretic peptide; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PE = pericardial effusion; PVR = pulmonary vascular resistance; RA = right atrium; RAP = mean right atrial pressure; SvO_2 = mixed venous oxygen saturation; VE/VCO_2 = ventilatory equivalents for carbon dioxide; VO_2 = oxygen consumption; WHO FC = World Health Organization functional class;

Background

The assessment of the prognosis of patients has been considered as an important section in patients with pulmonary arterial hypertension (PAH), different baseline and follow-up variables have been utilized individually or combined to predict outcome. Up to date, the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines proceedings summarized risk stratification strategy advances [1], each focusing on different countries or registries, including REVEAL studies [2,3], Swedish PAH Registry [4], COMPERA [5], and French PH Network [6], *et al*. The updated analysis of risk stratification recommended a flexible and comprehensive approach, using the clinical features, right ventricular function, heamodynamic parameters, biomarkers and exercise. Based on the cut-off values gathered from 2015 ESC/ERS guidelines, three risk categories were defined as a low-, intermediate-or high- risk group [1].

The accuracy of this risk assessment strategy has been validated by the COMPERA Registry, mortality rate was significantly different between the three risk strata for baseline as well as follow-up [5]. However, COPERA study used an abbreviated version risk analysis, including six variables, World Health Organization (WHO) function class (FC), 6-min walking distance (6MWD), brain natriuretic peptide (BNP) or N-terminal fragment of proBNP (NT-proBNP), right arterial pressure (RAP), cardiac index (CI) and mixed venous oxygen saturation (S_VO_2), not capturing disease progression, syncope, echocardiography and cardiopulmonary exercise testing (CPET) data. These findings confirm and extend previous study by Kylhammar *et al.* [4], who used the same subset of

parameters (plus right atrial area and the presence/absence of pericardial effusion). Although simplified variables could discriminate the risk groups, the most reliable dataset from echocardiography and CPET needed to determine. Similarly, the risk assessment of French PH Network proposed by European PH guidelines in patients with idiopathic PAH (IPAH) was available to work at baseline and follow-up [6]. In fact, the risk stratification tool itself has a level of evidence C, also, the cut-off points derived from several studies [1]. Accordingly, it is necessary to validate the efficiency of this instrument in a real-world cohort in specific treatment era.

The principle aims of the current study was to apply the risk assessment from the 2015 ESC/ERS guidelines to a newly diagnosis cohort of patients with IPAH in China. We attempted to test the discrimination of the risk instrument presented in guidelines and to explore the potential prognostic changes at follow-up.

Methods

Study patients

All newly diagnosed patients with IPAH (>=18 years of age at diagnosis) were retrospectively reviewed in Shanghai Pulmonary Hospital between January, 2009 and September, 2018. IPAH at baseline was set by right heart catheterization (RHC) according to standard criteria: a mean pulmonary artery pressure (mPAP)≥ 25 mmHg and pulmonary vascular resistance (PVR) >3 Woods units at rest in the presence of a normal pulmonary artery wedge pressure (PAWP ≤15 mmHg) [1]. Patients were excluded if they have definite causes for PAH, such as

connective tissue disease and congenital heart disease, those with portopulmonary hypertension, chronic pulmonary thromboembolism, pulmonary hypertension due to left heart diseases and lung diseases and/or hypoxaemia. Major endpoint was defined as all-cause mortality and no patients received lung or heart-lung transplantation. The study was conducted according to the principles of the Declaration of Helsinki, and was approved by the Shanghai Pulmonary Hospital Ethics Committee (K19-054). Written informed consent was obtained from all participants.

Risk stratification

Risk assessment was performed according to the 2015 ESC/ERS PH guideline, and patients were categorized as 'Low risk', 'Intermediate risk' or 'High risk' (Table 1) [5]. An abbreviated version of this guideline risk stratification strategy used WHO FC, 6MWD, BNP, NT-proBNP, RAP, CI and S_VO_2. The cut-off values proposed in the guidelines were graded 1, 2 and 3 (1= low risk, 2= intermediate risk and 3= high risk). When the baseline 6-MWD did not detect, it was considered as a grade of 3 [4]. For each patient, the sum of all grades was divided by the number of available variables. The mean grade was rounded to the next integer to define the risk group. For the follow-up risk stratification, we chose the visit that included follow-up hemodynamics after the baseline risk assessment at least 3 months. If no hemodynamic follow-up was available, we selected the follow-up visit that contained most of the data, such as echocardiography or CPET. Variables listed in the guidelines that are not captured both at baseline and follow-up are disease progression and syncope.

Statistical analysis

Continuous variables are expressed as mean ± SD or medians with corresponding 25th and 75th percentiles [interquartile range (IQR)]. Categorical variables are expressed as numbers and percentages. When data were not normally distributed, a nonparametric test was used. Changes between baseline and re-evaluation were assessed using Chi-squared test where appropriate. Survival analyses were performed using the Kaplan-Meier method, truncated at 5 years, and were compared using the log-rank test. Survival time was calculated from the date of diagnostic RHC to the date of finial follow-up, and re-evaluation to finial follow-up. Survival was compared for patients who was remained in the low, intermediate or high risk group, improved to the low or intermediate risk group, or worsened to the intermediate or high risk group. Univariable and multivariable Cox proportional hazard regression was performed to assess the risk of death, using the respective low risk group as reference. Patients were censored at termination 31 December 2018. A p-value less than 0.05 was considered statistically significant. All analyses were performed using the SPSS 14.0 statistical software package (Statistical Package for Social Science, Chicago, IL, USA).

Results

Study patients

The baseline data reviewed total newly 392 patients with IPAH who fulfilled the criteria, including eleven variables of interest for this study (Table 1). Out of the 10 variables at baseline, at least four variables were available in all 392 patients, at least ten in 59 (15%) patients, and at least eight in 177 (45%) patients. All

patients underwent the RHC examination. The characteristics of these patients in baseline was shown in Table 2. At the time of diagnosis, most patients (67%) were women and mean age was 40 years old. The 260 (67%) patients were in WHO FC III or IV, whereas 34% were in FC I-II. All cause death survival in the overall study patients (n=392) in shown in Supplementary Figure S1. For the initial treatment, 258 (66%) patients received in monotherapy, 101 (26%) in combination therapy, and 33 (8%) in no specific/CCB therapy. At baseline, 186 (48%) patients used PDE5-i treatment in monotherapy group, and 68 (17%) patients used PDE5-I plus ERA (Supplementary Table S1).

Risk assessment at baseline and mortality

At the time of diagnosis, 96 (25%) of patients were in the Low risk, 267 (68%) in the Intermediate risk, and 29 (7%) in the High risk group, respectively (Table 2). After the diagnosis of IPAH within 5 years, 141 (36%) patients had died, 19 (20%) in the Low risk group, 104 (39%) in the Intermediate risk group, and 18 (62%) in the High risk group. In the Low risk group, the survival rate at 1-, 2-, 3-, 4-, and 5-year was 99%, 98%, 91%, 88% and 83%, respectively. The corresponding survival was 88%, 75%, 67%, 57% and 52% in the Intermediate risk group, respectively and 69%, 62%, 51%, 40% and 33% in the High risk group, respectively ($p< 0.001$ for all group comparisons;) The predictive values of each variable at baseline is shown in Figure 1a.

Similarly, using simplified version, all six variables were available in 322 patients, 76 (24%) of patients were in the Low risk, 207 (64%) in the Intermediate risk, and 39 (12%) in the High risk group, respectively (Supplementary Table S2). Accordingly, the survival differences in the three risk

categories were still statistical significance (p< 0.001 for all group comparisons; Figure 1b) The predictive values of each variable in those patients at baseline is shown in Figure 2.

Risk assessment at re-evaluation and mortality

At the end of follow-up, among the 106 patients with missing re-evaluation information, 82 (21%) patients were below two variables, and 24 lost to follow-up for specified reasons (Supplementary Figure S2). For re-evaluation assessment, out of the 10 variables, at least two variables were available in 286 patients, at least eight in 11 (4%) patients, and at least four in 210 (73%) patients, respectively. Median interval between diagnosis and re-evaluation was 13 [5, 33] months. At the time of re-evaluation, 85 (30%) of patients were in the Low risk, 159 (56%) in the Intermediate risk, and 42 (15%) in the High risk group, respectively. There were a greater proportion of patients attaining High risk group and a lesser proportion of patients with Intermediate risk group, although the percentage of Low risk group has an increase (p< 0.001, Figure 3). Only 46 (16%) of these re-evaluation patients were available for hemodynamic data, however, 186 (65%) for right area, 253 (88%) for pericardial effusion, and 88 (31) for CPET.

The characteristics of these patients in re-evaluation was shown in Table 3. At re-evaluation, 147 (51%) patients received in monotherapy, 126 (44%) in combination therapy, and 13 (4%) in no specific/CCB therapy. Within combination therapy group, 102 (36%) patients used PDE5-I plus. Compared with those variables at baseline, there was significant improvement 6MWD, CI, PVR, SvO_2 and proportion of combination therapy (Supplementary Table S3).

After re-evaluation of these patients within 5 years, 36 (13%) patients had died, 4 (8%) in the Low risk group, 16 (10%) in the Intermediate risk group, 7 (17%) in the High risk group, and 9 (3%) in censor. In the Low risk group, the survival rate at 1-, 2-, 3-, 4-, and 5-year was 94%, 91%, 89%, 82% and 76%, respectively. The corresponding survival was 75%, 66%, 54%, 46% and 38% in the Intermediate risk group, respectively and 53%, 28%, 25%, 21% and 18% in the High risk group, respectively ($p< 0.001$ for all group comparisons; Figure 4) The predictive values of each variable from multivariable Cox analysis at re-evaluation are shown in Supplementary Figure S3. WHO FC, 6MWD, NT-proBNP/BNP and SVO_2 were independent predictors. From baseline to re-evaluation, the changes in the risk assessment were associated with a shift in the mortality risk ($p< 0.001$ for all group comparisons; Figure 5)

Discussion

There was much evidence to support that the multiparametric approach stratified the PAH patients in different risk groups for mortality. According to the risk status, different strategies can be utilized to guide therapeutic decisions [7]. However, the validation of these comprehensive risk assessments for Chinese IPAH patients is indefinite. The main findings of this study can be demonstrated as follows, (1) the 2015 European PH guideline risk stratification effectively discriminated a Low, Intermediate and High risk at baseline and re-evaluation assessments; (2) and accurately predicted the risk of death in patients with IPAH; (3) its simplified version risk strategy was valid for baseline; (4) the percentage of Low risk group has an increase at re-evaluation, but a greater proportion of patients achieved High risk group and a lesser proportion maintained in

Intermediate risk group. Despite of the methodical risk assessments are applicable for Chinese patients with IPAH, actual treatment seems not consistent with this goal-oriented treatment strategy.

A comprehensive assessment is used since no single variable provides sufficient diagnostic and prognostic information. As we known, 2015 ESC/ERS guidelines recommended 13 variables and REVEAL risk score consisted of 19 variables [1,2]. The number of variables seems possible to discriminate risk groups accurately, but not all variables may be done in PH centers. Except for the symptom's progression and syncope, the variables we selected in present study included all RHC parameters, BNP or NT-proBNP, and 6WMD at baseline. Meanwhile, RA area were available in 235 (60%) patients, pericardial effusion in 357 (91%) patients, and CPET in 100 (26%) patients (Table 2 and Table 3). It was significantly discrimination of different risk group, i.e. 25% patients were in the Low risk, 68% in the Intermediate risk, and 7% in the High risk group, respectively. If we used same simplified version of risk criteria, the proportion of high risk group was 12% (Supplementary Table 2). Our results were closed to previous findings by the Swedish PH registry, which the proportion of low-, intermediate- and high-risk patients respectively was 23%, 67% and 10% (530 patients with PAH, 49% IPAH patients) [4]. However, in COMPERA IPAH subgroup study, the proportion of high risk group increased to 19% [5]. The reasons for these differences are partly attributed to different variables used for risk assessment, or severity of different parameters. For example, 6MWD was 299±123m in COMPEAR IPAH subgroup, but 369±107m in our study. Our previous study has been reported 6MWT values in Chinese patients with IPAH were significantly higher than those recorded in foreign registries [3,8-10].

Hence, it is necessary to discuss the feasibility of statistical risk calculation method. Given that echocardiography and CPET were not available for all studies, most reliable indicators needed to further determine.

Regardless of whether regular follow-up, the three risk groups had significantly different long-term survival at baseline as well as in re-evaluation. It suggested that 13 variables of 2015 ESC/ERS guidelines were relatively stable to discriminate risk stratification. However, we still found that an increased proportion of High risk group and a lesser proportion of patients with Intermediate risk group, although the percentage of Low risk group has an increase (Figure 3). The changes in risk category reflected that patients in Low risk group may be benefit from initial treatment on the one hand, but those in Intermediate- and High-risk groups seem not be sufficient. In our study, primary combinations of PAH targeted drugs were observed in 26% of all patients and in 28% of High risk patients, which implicated that combination treatment goal was not achieved in majority of our patients. Ample evidence was proposed to use of initial monotherapy or combination therapies in patients with naïve PAH [11-16]. And initial combination therapy could improve exercise capacity and prognosis compared with initial monotherapy [12,14]. It is intelligible the treatment goals are not always realistic and physicians may modify the therapeutic strategies with advanced disease or severe co-morbidities. Certainly, the improved survival rates may be attributable to success of specific treatment, the increasing economic burden for patients can't be ignored [8,12]. Even at the time of re-evaluation, over 50% patients are still in monotherapy or no specific therapies condition after all.

Of note, the parameters of echocardiography and CPET were used for risk

stratification in our study, including RA area, pericardial effusion, Peak VO_2 and VE/VCO_2 slope proposed by 2015 PH guidelines. Presence of pericardial effusion is common and thought to be an important indicator for right heart failure in patients with PAH [18,19]. Fendtad *et al*. has reported even modest degrees of pericardial fluid are associated with a significant increase in mortality in patients with PAH [20]. In current study, we also found the degree of severe pericardial effusion in High risk group was a higher estimate as well as increased risk of death (Table 3 and Figure 3). A preserved RA function is crucial to maintain sufficient right heart function, partly since the change of RA size alters the motion of the tricuspid annulus [21]. Accordingly, impaired right ventricle systolic function and RA dilation (RA area> $18cm^2$) were associated with worse long-term survival in patients with IPAH [22,23]. Grapsa *et al*. has reported that clinical deterioration was better associated with RA rather than RV remodeling in patients with PAH [24]. Despite there was no difference of RA area between baseline and re-evaluation, both of them were still in moderate degree of increases (median was $22cm^2$ at baseline and $23cm^2$ in re-evaluation). Our data suggested that the parameters of pericardial effusion and RA area were useful information for the risk stratification strategy.

CPET may provide suggestive information in patients with PAH both circulation impairment and ventilatory inefficiency [25]. Lower peak VO_2 and higher VE/VCO_2 slope were consider to establish the severity of exercise capacities or to assess outcomes [26-29]. Wensel *et al.*, has reported that average peak VO_2 and VE/VCO_2 slope during exercise was 11.2±0.5 mL/min/kg and 54±2 (2002) [27], and 13±5 mL/min/kg and 54±18 (2013) [28], respectively, also patients with peak $VO_2 \leq$ 10.4 mL/min/kg had poor survival. Our data showed

that peak VO_2 was 14±4 mL/min/kg and VE/VCO_2 slope was 54±2 at baseline. Reference to the criteria of 2015 ESC PH guidelines, the value of above two parameters were in Intermediate risk group. However, the two variables of CPET were all removed from Cox multivariable model equation (at last step). This does not mean that CPET *per se* are not relevant, but that exercise function might be not superior to resting hemodynamics or echocardiography in our study. Although CPET is not widely utilized in patients with PAH, an increasing recognition of potential values should be emphasized [30]. The 26% (100/392) patients of our study have CPET values, but, further studies need still more valuable information to evaluate comprehensive score system for risk.

The major strengths of our study were the availability of complete data for invasive hemodynamics and noninvasive echocardiography and CPET variables at diagnosis in patients with IPAH. There are several limitations in present study. First, this is a retrospectively study in a single center and the sample size was not large enough to provide sufficient patients numbers in three risk stratification. Second, the follow-up assessments were not standardized and the proportion of RHC testing was lower at re-evaluation. However, we selected the follow-up visit that contained most of the data, such as echocardiography or CPET. So, 88% patients at re-evaluation assessments had values of pericardia effusion, 65% of right atrium area, and approximately 30% of CPET. Additionally, despite of median interval between diagnosis and re-evaluation was 13 months, ~15% of that was over 24 months, which may be biased towards the time-effect test. Finally, this study does not include prognostic variable, such as age, sex, comorbidities, disease progression and syncope, and the individual risk is further modified by these factors. Further studies should organize more prospective

studies or explore exiting registries in China.

Conclusions

In conclusion, the present data show that 2015 ESC/ERS PH guidelines and its simplified version risk stratification strategy may effectively discriminate different risk groups at baseline and re-evaluation. Meanwhile, our study validated an accurate prediction of mortality. Noninvasive echocardiography assessment might help identify predictive usefulness of risk categorization strategies. The parameters of CPET seems to be less sensitive to the risk level designation, but need to be clarified in future and prospective studies. Changes of risk proportion at re-evaluation implicated that natural treatment decisions may not behave consistently with goal-oriented treatment strategy, but, our patients with IPAH may benefit from initial therapy.

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Author Contributions

R.Z. and L.W. contributed to the study design, study conduct, supervision, scientific overview, data analysis, editing of the manuscript, and were also directly involved in the patients' recruitment and care. S.G.G and C.L. contributed to patient enrolment, data analysis, scientific interpretation, drafting, and editing the original manuscript. Q.H.Z., R.J., W.H.W., C.J.L. and H.L.Q. contributed to recruitment of participants, data collection, curation, and formal analysis. All authors have reviewed the manuscript, approved the final version for submission, participated in the design of the study, patient enrolment, and meet criteria for authorship.

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Availability of data and materials

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

Ethics approval and consent to participate

The protocol was approved by the independent ethics committee at Shanghai Pulmonary Hospital Ethics Committee (Protocol reference number: K19-054) and all patients provided written informed consent before participation.

Consent for publication

Not applicable.

Conflict of interests

None of authors has any conflict of interest to declare regarding the content of this paper.

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Table 1. Variables and cut-off values from the risk assessment from ESC/ERS 2015 guidelines*

	Low risk	Intermediate risk	High risk
WHO FC	I, II	III	IV
6MWD, meter	> 440	165-440	< 165
BNP, ng/L	< 50	50-300	> 300
NT-proBNP, ng/L	< 300	300-1400	> 1400
Haemodynamics			
RAP, mmHg	< 8	8-14	> 14
CI, L/min/m^2	≥ 2.5	2.0-2.4	≤ 2.0
SvO_2, %	> 65	60-65	< 60
Imaging (echocardiography)			
RA area, cm^2	< 18	18-26	> 26
Pericardial effusion	No	No or minimal	Yes
Cardio-pulmonary exercise testing			
Peak VO_2, mL/min/kg	> 15 (> 65% pred.)	11-15 (35-65% pred.)	< 11 (< 35% pred.)
VE/VCO_2 slope	< 36	36-44.9	≥ 45

*Simplified version included WHO FC, 6MWD, NT-proBNP, BNP, RAP, CI and SvO %.
BNP: brain natriuretic peptide; CI: cardiac index; ESC: European Society of Cardiology; ERS: European Respiratory Society; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal fragmental of pro-brain natriuretic peptide; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO FC: World Health Organization functional class;

Table 2. Characteristics of IPAH patients in baseline risk stratification

	N	Low risk	Intermediate risk	High risk	All
Subjects, n (%)		96 (25)	267 (68)	29 (7%)	392
Age, years		35±14	42±16	39±16	40±16
Female, n (%)		70 (73)	180 (67)	14 (48)	264 (67)
BMI, kg/m^2		23±6	22±4	23±3	23±4
WHO FC, n (%)					
Class I-II		69 (72)	63 (24)	0 (0)	132 (34)
Class III		27 (28)	188 (70)	19 (66)	234 (60)
Class IV		0 (0)	16 (6)	10 (35)	26 (7)
6MWD, meters	392	436±97	364±100	280±95	379±107
BNP, ng/L	164	46 (24, 94)	262 (149, 438)	661 (306, 880)	211 (65, 426)
NT-proBNP, ng/L	250	162 (40, 267)	1096 (542, 1892)	2428 (1949, 3771)	748 (255, 1679)
Hemodynamics					
RAP, mmHg	389	4 (2, 7)	6 (4, 10)	15 (12, 17)	6 (3, 10)
mPAP, mmHg	392	53 (45, 63)	58 (50, 69)	63 (56, 80)	58 (48, 68)
PAWP, mmHg	392	7 (6, 10)	8 (5, 10)	10 (7, 11)	8 (5, 10)
CI, L/min/m^2	388	3.2 (2.8, 3.7)	2.2 (1.9, 2.7)	1.6 (1.5, 1.8)	2.4 (1.9, 3.0)
PVR, Wood units	392	9 (7, 12)	15 (11, 18)	20 (16, 26)	14 (9, 18)
S_VO_2, %	388	72 (68, 76)	60 (56, 65)	46 (42, 52)	62 (56, 69)
Echocardiographic variables					
RA area, cm^2	235	16 (13, 20)	23 (18, 33)	38 (29, 47)	22 (16, 30)
No PE, n (%)		90 (94)	163 (61)	7 (24)	260 (66)
Minimal PE, n (%)		1 (1)	73 (27)	15 (52)	89 (25)
PE, n (%)		0 (0)	5 (2)	3 (10)	8 (2)
Cardiopulmonary exercise testing					
Peak VO_2, mL/min/kg	100	18±4	12±3	9±2	14±4
VE/VCO_2 slope	100	36±7	62±36	79±22	56±33
Initial therapies (within 3 months after diagnosis), n (%)					
No specific/CCB therapy		13 (14)	20 (8)	0 (0)	33 (8)
Monotherapy		68 (71)	169 (63)	21 (72)	258 (66)
Combination therapy		15 (16)	78 (29)	8 (28)	101 (26)

Values are expressed as mean±SD, medians (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; BNP: brain natriuretic peptide; CCB: calcium channel blocker; CI: cardiac index; mPAP: mean pulmonary arterial

pressure; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal fragmental of pro-brain natriuretic peptide; PAWP: pulmonary artery wedge pressure; PE: pericardial effusion; PVR: pulmonary vascular resistance; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO FC: World Health Organization functional class;

Table 3. Characteristics of IPAH patients in re-evaluation risk stratification

	N	Low risk	Intermediate risk	High risk	All
Subjects, n (%)		85 (30)	159 (56)	42 (15)	286
WHO FC, n (%)					
Class I-II		48 (56)	28 (18)	0 (0)	76 (27)
Class III		8 (9)	94 (59)	20 (48)	122 (43)
Class IV		0 (0)	6 (4)	19 (45)	25 (9)
6MWD, meters	135	472±69	370±106	204±154	396±120
BNP, ng/L	43	25 (13, 42)	297 (150, 453)	726 (385, 874)	184 (64, 453)
NT-proBNP, ng/L	224	74 (40, 142)	1160 (541, 2403)	1691 (1444, 2844)	806 (146, 2326)
Hemodynamics					
RAP, mmHg	46	5 (3, 7)	10 (6, 12)	12 (5, 14)	6 (4, 11)
mPAP, mmHg	46	43 (34, 52)	64 (57, 70)	78 (68, 84)	57 (40, 65)
PAWP, mmHg	46	9 (7, 11)	10 (6, 11)	10 (8, 14)	10 (7, 11)
CI, L/min/m^2	46	3.5 (3.2, 4.6)	2.3 (1.9, 2.6)	1.9 (1.6, 2.0)	2.6 (2.2, 3.4)
PVR, Wood units	46	5 (4, 8)	15 (12, 20)	21 (17, 22)	10 (5, 15)
S_VO_2, %	46	74 (71, 78)	60 (52, 63)	50 (41, 58)	65 (58, 74)
Echocardiographic variables					
RA area, cm^2	186	15 (12, 18)	22 (18, 29)	45 (37, 52)	23 (17, 34)
No PE, n (%)		74 (87)	91 (57)	19 (45)	170 (67)
Minimal PE, n (%)		2 (2)	45 (28)	12 (29)	73 (29)
PE, n (%)		0 (0)	3 (2)	7 (17)	10 (4)
Cardiopulmonary exercise testing					
Peak VO_2, mL/min/kg	88	17±3	12±3	9±1	13±4
VE/VCO_2 slope	88	35±5	56±25	81±48	52±28
Therapies (within 3 months after re-evaluation), n (%)					
No specific/CCB therapy		5 (6)	7 (4)	1 (2)	13 (4)
Monotherapy		54 (64)	77 (48)	16 (38)	147 (51)
Combination therapy		26 (31)	75 (47)	25 (60)	126 (44)

Values are expressed as mean±SD, medians (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; BNP: brain natriuretic peptide; CCB: calcium channel blocker; CI: cardiac index; mPAP: mean pulmonary arterial pressure; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal fragmental of pro-brain natriuretic peptide; PAWP: pulmonary artery wedge pressure; PE:

pericardial effusion; PVR: pulmonary vascular resistance; RA: right atrium; RAP: right atrial pressure; SvO_2: mixed venous oxygen saturation; VE/VCO_2: ventilatory equivalents for carbon dioxide; VO_2: oxygen consumption; WHO FC: World Health Organization functional class;

Figure Legends

Figure 1. The survival estimates in patients with idiopathic pulmonary arterial hypertension at baseline according to (a) the 2015 ESC/ERS risk stratification strategy; (b) a simplified version.

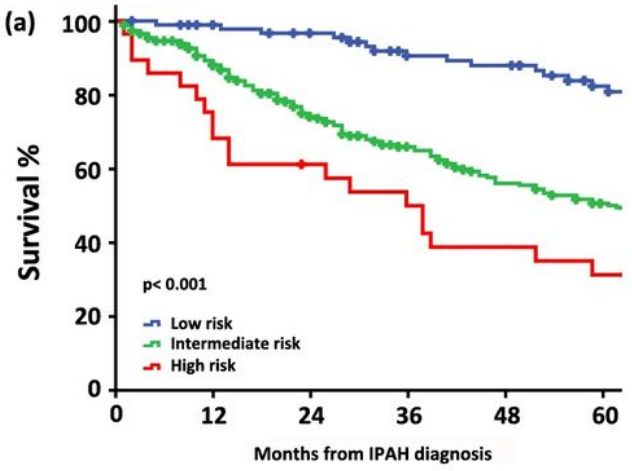
Figure 2. Forest plot based on the prognostic values of 6-min walking distance (6MWD), World Health Organization (WHO) function class (FC), brain natriuretic peptide (BNP) or N-terminal fragment of proBNP (NT-proBNP), right arterial pressure (RAP), cardiac index (CI) and mixed venous oxygen saturation (S_VO_2), right atrium (RA) area and pericardial effusion (PE) in the Intermediate risk (IR) and High risk (HR) groups. Values for the variables were obtained from baseline. The reference value is from the respective Low risk group.

Figure 3. Change in three risk groups in patients with idiopathic pulmonary arterial hypertension from baseline to re-evaluation.

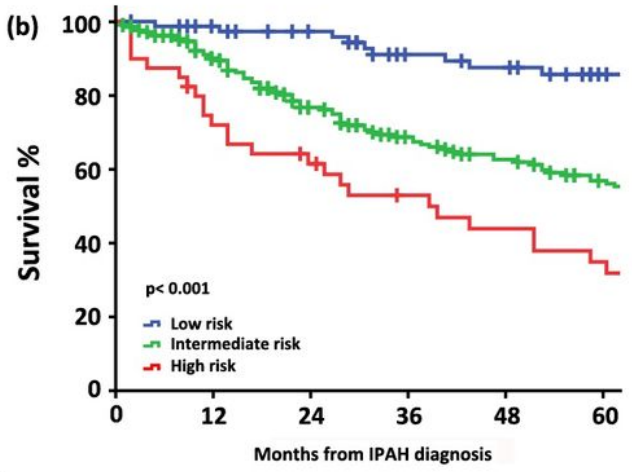
Figure 4. Survival estimates in patients with idiopathic pulmonary arterial hypertension at re-evaluation according to the 2015 ESC/ERS risk stratification strategy.

Figure 5. The survival estimates in patients with idiopathic pulmonary arterial hypertension according to the 2015 ESC/ERS risk category from baseline to re-evaluation. This figure was based on n= 286 patients.

Figures



Months after enrolment	Patients at risk, n			Survival, %		
	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
0	96	267	29	100	100	100
12	95	219	21	99	88	69
24	90	168	19	98	75	62
36	73	138	15	91	67	51
48	70	110	12	88	57	40
60	58	96	10	83	52	33



Months after enrolment	Patients at risk, n			Survival, %		
	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
0	76	207	39	100	100	100
12	75	170	28	99	90	72
24	70	130	23	97	76	61
36	56	104	19	91	68	52
48	49	88	15	87	62	43
60	46	74	12	85	56	34

Figure 1

The survival estimates in patients with idiopathic pulmonary arterial hypertension at baseline according to (a) the 2015 ESC/ERS risk stratification strategy; (b) a simplified version.

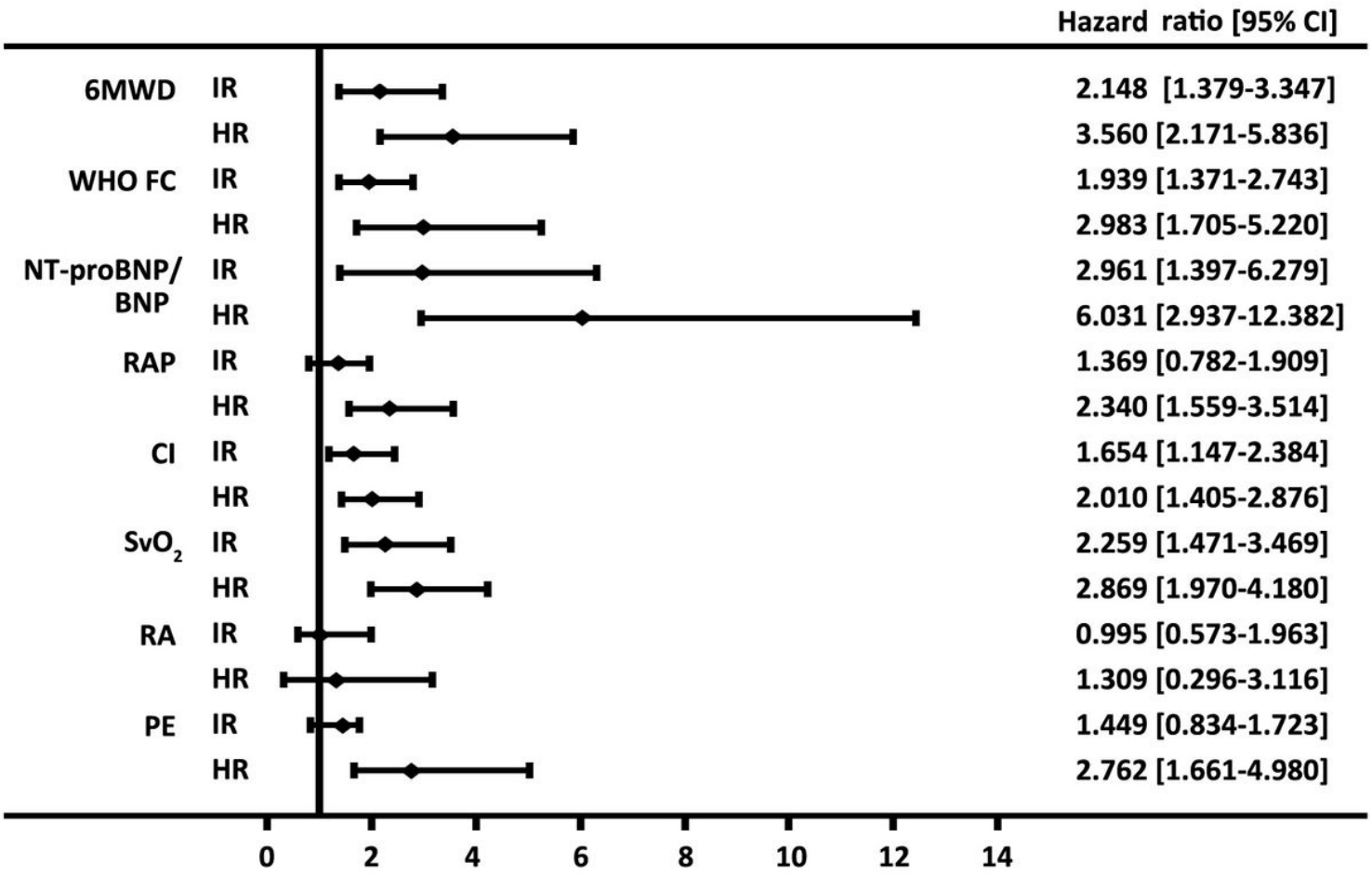


Figure 2

Forest plot based on the prognostic values of 6-min walking distance (6MWD), World Health Organization (WHO) function class (FC), brain natriuretic peptide (BNP) or N-terminal fragment of proBNP (NT-proBNP), right arterial pressure (RAP), cardiac index (CI) and mixed venous oxygen saturation (SVO2), right atrium (RA) area and pericardial effusion (PE) in the Intermediate risk (IR) and High risk (HR) groups. Values for the variables were obtained from baseline. The reference value is from the respective Low risk group.

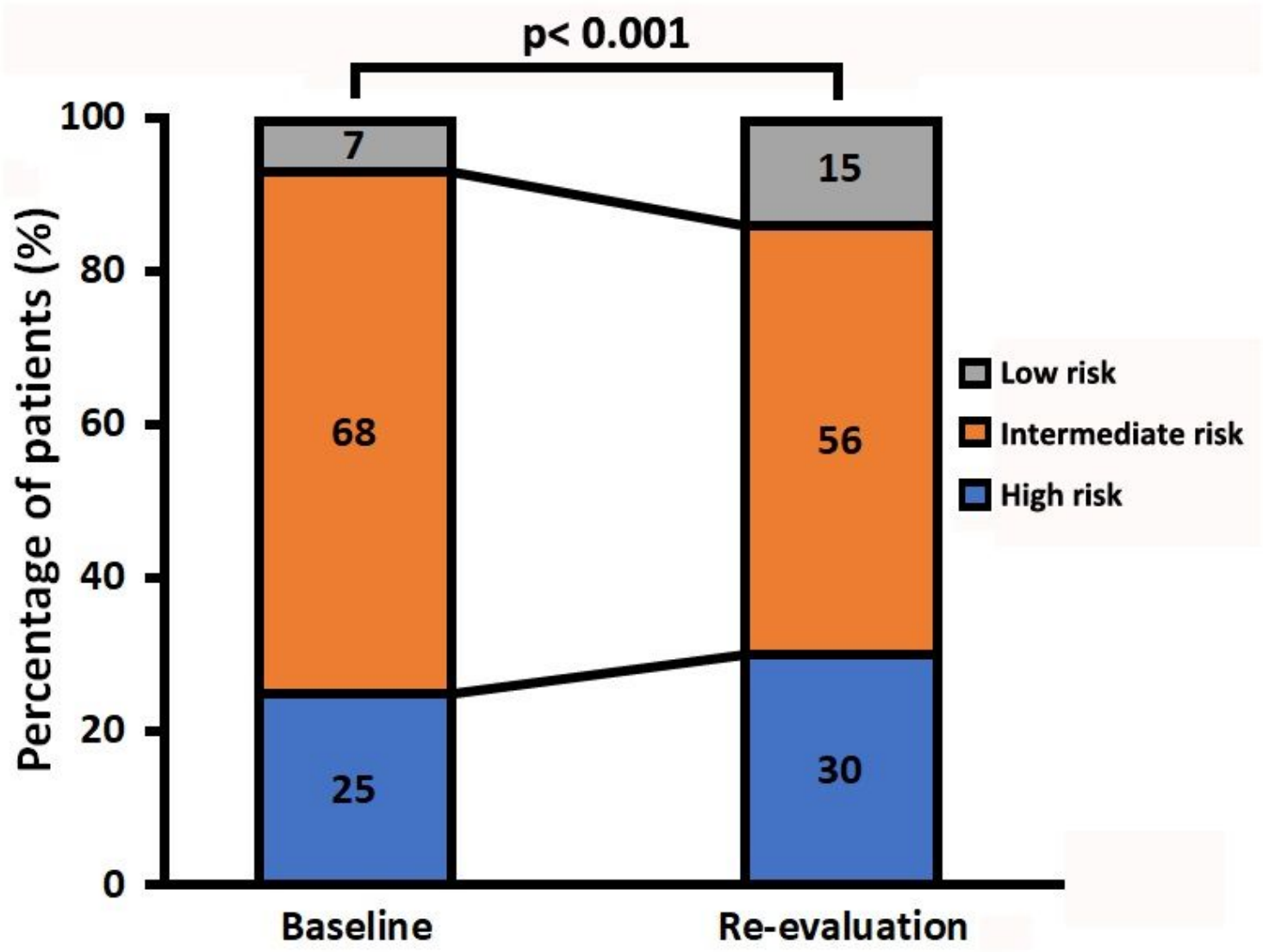
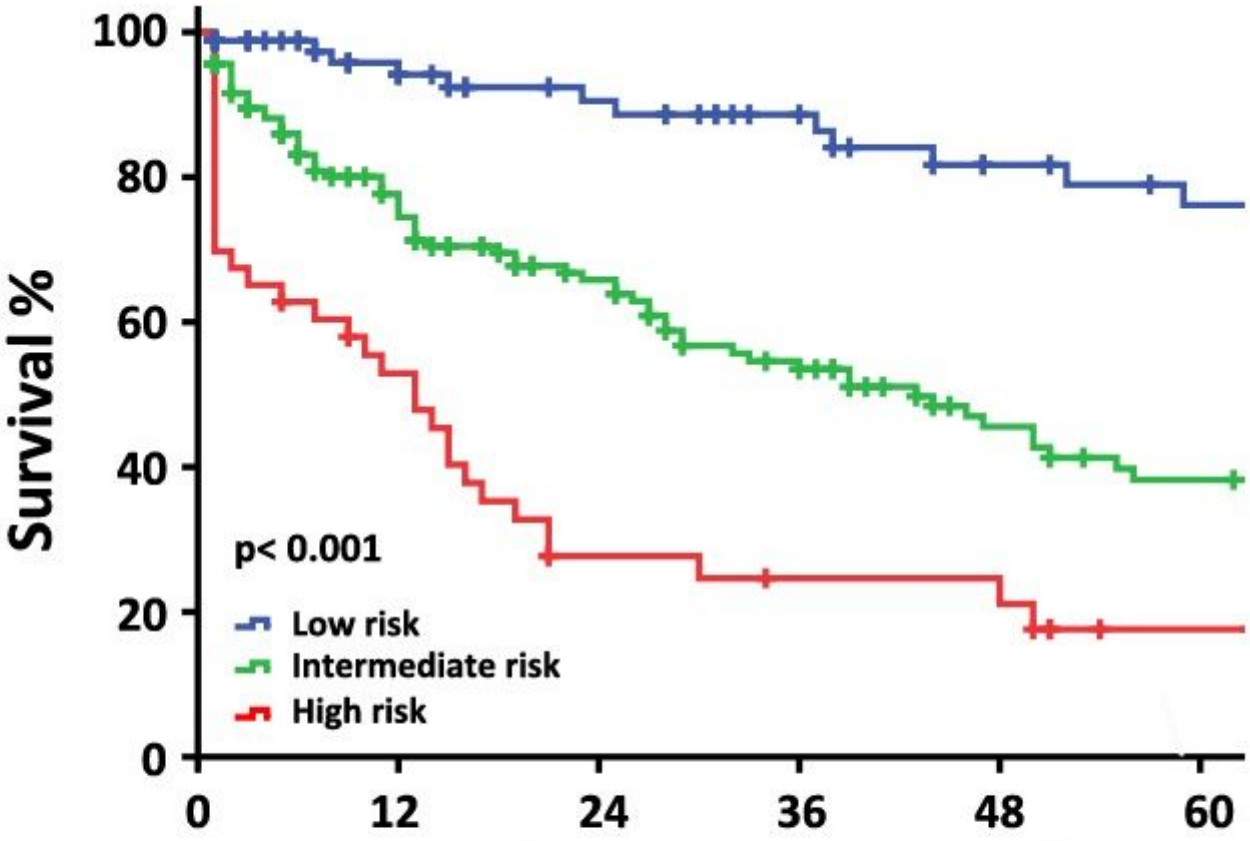


Figure 3

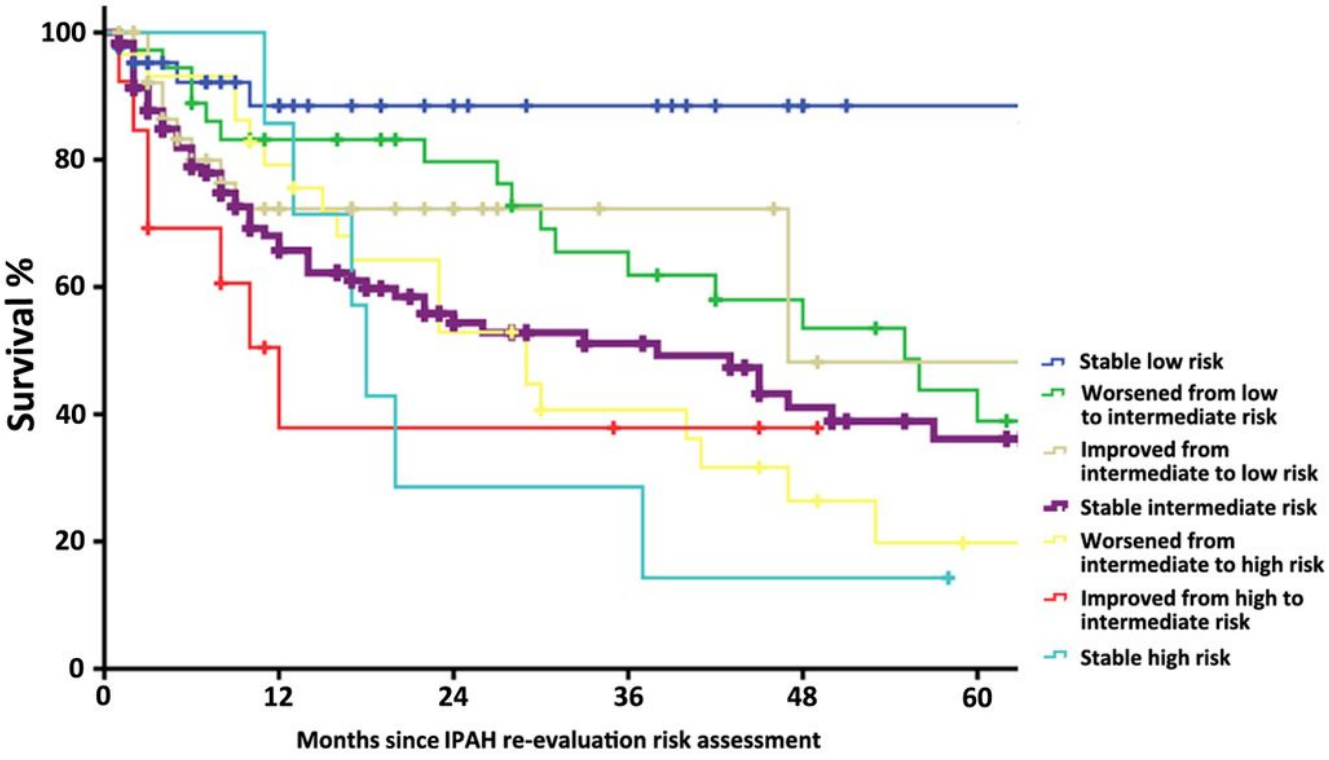
Change in three risk groups in patients with idiopathic pulmonary arterial hypertension from baseline to re-evaluation.



Patients at risk, n						
Low risk	85	59	49	48	38	28
Intermediate risk	159	94	69	50	33	26
High risk	42	22	12	9	7	6

Figure 4

Survival estimates in patients with idiopathic pulmonary arterial hypertension at re-evaluation according to the 2015 ESC/ERS risk stratification strategy.



	Patients at risk, n						
Months after enrolment	Stable low risk	Worsened from low to intermediate risk	Improved from intermediate to low risk	Stable intermediate risk	Worsened from intermediate to high risk	Improved from high to intermediate risk	Stable high risk
0	43	36	41	117	29	13	7
12	30	30	19	58	23	6	6
24	25	24	11	39	15	4	2
36	25	18	7	31	11	4	2
48	25	13	4	20	6	4	1
60	23	9	3	14	4	4	1

	Survival, %						
Months after enrolment	Stable low risk	Worsened from low to intermediate risk	Improved from intermediate to low risk	Stable intermediate risk	Worsened from intermediate to high risk	Improved from high to intermediate risk	Stable high risk
0	100	100	100	100	100	100	100
12	97	83	80	66	79	84	71
24	95	80	76	54	53	69	57
36	92	62	72	51	45	61	29
48	92	58	48	43	40	51	29
60	89	44	48	36	26	40	14

Figure 5

The survival estimates in patients with idiopathic pulmonary arterial hypertension according to the 2015 ESC/ERS risk category from baseline to re-evaluation. This figure was based on n= 286 patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BMCPulmMedSupplementalMaterial.pdf