Prognostic role of haemodynamics at follow-up in patients with pulmonary arterial hypertension: a challenge to current European Society of Cardiology/European Respiratory Society risk tools

Fabio Dardi, Daniele Guarino, Alberto Ballerini, Riccardo Bertozzi, Federico Donato, Francesco Cennerazzo, Monica Salvi, Elena Nardi, Ilenia Magnani, Alessandra Manes, Nazzareno Galiè and Massimiliano Palazzini

RHC risk tool

? RHC prognostic parameters

794 treatment-naive PAH patients
1 PAH centre

Systematic RHC:
Baseline → first follow-up

	Low risk	Intermediate–low	Intermediate–high	High risk
RV preload RAP mmHg	<8	8–9	10–14	>14
RV afterload E_a mmHg·mL^{-1} PVR WU PAC mL·mmHg^{-1}	<1.1 <6 >1.5	1.1–1.4 6–9 >1.1–1.5	>1.4–1.8 >9–14 0.7–1.1	>1.8 >14 <0.7
RV pump function CI L·min^{-1}·m^{-2} SVI mL·m^{-2} CE mL·mmHg^{-1} S_{vO_2} %	>2.5 >38 >1.5 >65	>2.3–2.5 >35–38 >1.1–1.5 >63–65	2.0–2.3 31–35 0.8–1.1 60–63	<2.0 <31 <0.8 <60
Three-strata RHC risk tool points assigned risk definition	1 Score <1.5	2 Score 1.5–2.49		3 Score ≥2.5
Four-strata RHC risk tool points assigned risk definition	1 Score <1.5	2 Score 1.5–2.49	3 Score 2.5–3.49	4 Score ≥3.5

C-index at first follow-up All-cause death				C-index at first follow-up All-cause death, hospitalisation and need of treatment escalation			
RHC risk tool three-strata	COMPERA 1.0	FPHR	Bologna	RHC risk tool three-strata	COMPERA 1.0	FPHR	Bologna
0.619	0.684	0.692	0.675	0.651	0.636	0.641	0.637
RHC risk tool four-strata		COMPERA 2.0		RHC risk tool four-strata		COMPERA 2.0	
0.629		0.726		0.669		0.655	

Graphical abstract Prognostic role, at follow-up, of a risk tool including only haemodynamic parameters in patients with pulmonary arterial hypertension in comparison to current validated European Society of Cardiology/European Respiratory Society risk tools. PAH: pulmonary arterial hypertension; RHC: right heart catheterization; RV: right ventricle; RAP: right atrial pressure; E_a: pulmonary artery elastance; PVR: pulmonary vascular resistance; WU: Wood unit; PAC: pulmonary arterial compliance; CI: cardiac index; SVI: stroke volume index; CE: cardiac efficiency; S_{vO_2}: mixed venous oxygen saturation; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry.

Prognostic role of haemodynamics at follow-up in patients with pulmonary arterial hypertension: a challenge to current European Society of Cardiology/European Respiratory Society risk tools

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Shareable abstract (@ERSpublications)
RAP and E_a are independent predictors of death at follow-up; haemodynamics' discriminative ability for clinical worsening is comparable to current ESC/ERS risk tools and is of added value to non-invasive parameters in patients with PAH https://bit.ly/3W4yoNV

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Abstract

Background Haemodynamic variables like right atrial pressure (RAP), cardiac index (CI), stroke volume index (SVI) and mixed venous oxygen saturation (S_{vO_2}) predict survival in patients with pulmonary arterial hypertension (PAH). However, there is the need to identify further prognostic haemodynamic parameters as well as to redefine their role in PAH risk stratification compared to current risk tools and non-invasive parameters.

Methods This cohort study includes treatment-naïve patients assessed at baseline and after first-line PAH therapy with clinical, functional, exercise, laboratory and haemodynamic evaluations. Using a stepwise multivariate Cox regression analysis, independent prognostic haemodynamic parameters were identified and stratified according to cut-offs already defined in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk table or defined based on the highest Chi-squared of the log-rank test. Their discriminatory power was tested for all-cause death and a combined end-point of death, hospitalisation and need of treatment escalation.

Results 794 patients with PAH were enrolled. At first follow-up, RAP and pulmonary artery elastance were independently associated with death. Because of high correlations between haemodynamic parameters, different multivariable analyses were done identifying six other variables (pulmonary arterial compliance, cardiac efficiency, pulmonary vascular resistance, S_{vO_2}, CI and SVI). Haemodynamic parameters were of no added prognostic value compared to ESC/ERS risk tools for the all-cause death end-point but they showed additional value to non-invasive parameters for the combined end-point and, when taken alone, had a discriminatory capacity comparable to ESC/ERS risk tools.

Conclusion Haemodynamics' discriminative ability for clinical worsening is comparable to current ESC/ERS risk tools and is of added value to non-invasive parameters.

Introduction

Pulmonary arterial hypertension (PAH) is characterised by pulmonary vascular remodelling leading to increased right ventricular (RV) afterload ultimately ending in RV failure and death. Current approved targeted PAH therapies, *e.g.* endothelin receptor antagonists, phosphodiesterase type-5 inhibitors/soluble

guanylate cyclase stimulators and prostaglandins/prostacyclin receptor agonists, are able to improve the outcome of patients with PAH [1–4], and their haemodynamic effect is mainly related to a reduction of pulmonary vascular resistance (PVR) and an increase of cardiac index (CI) with only minimal effect on mean pulmonary arterial pressure (mPAP) when used as monotherapies or sequential combination therapies [5]. When these drugs are used in upfront combination, they lead to a much more marked reduction in PVR with an increase in CI associated also with a significant reduction in mPAP [6–9]. European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines have identified right atrial pressure (RAP), CI, stroke volume index (SVI) and mixed venous oxygen saturation (S_{vO_2}) as the most consistently prognostic haemodynamic parameters [10, 11]. However, recently, sotatercept has been shown to improve the short-term outcome of patients with PAH but without a significant increase in CI/SVI as the haemodynamic effect seems to be mainly related to a significant improvement in PVR and mPAP together with other haemodynamic parameters with a less well-defined prognostic role in PAH [12, 13]. These haemodynamic effects are, moreover, associated with beneficial right heart echocardiographic reverse remodelling [12]. Owing to the widening of the therapeutic spectrum of patients with PAH and to the evidence of effective combination therapies associated with marked haemodynamic improvements [6, 7], it is important to identify new haemodynamic prognostic factors that can be further investigated as possible treatment goals. Furthermore, the role of haemodynamics in risk stratification should be compared to the one of current ESC/ERS risk tools as well as to the one of non-invasive parameters as the latter, despite being of undoubted relevance in predicting outcome, can be influenced to a greater extent by factors unrelated to the severity of PAH, making them potentially less suitable as treatment goals in some patients.

The aim of this work was to investigate the prognostic role of a wide set of haemodynamic parameters together with clinical, exercise and laboratory parameters assessed both at baseline and at first follow-up after first-line PAH-targeted treatment.

Methods

Population

The study was conducted according to the guidelines of the Declaration of Helsinki [14] and was conducted within the context of regular care. Data from all consecutive ⩾18 years old, treatment-naïve patients with idiopathic/heritable/drug-induced (I/H/D)-PAH, connective tissue disease (CTD)-associated-PAH and congenital heart disease-associated (CHD)-PAH who were referred to the Pulmonary Vascular Disease Centre of Bologna University Hospital were included in a prospective electronic registry (ARCA) approved by the Ethics Committee of the St. Orsola-Malpighi Hospital (109/2016/U/Oss). Patient data were pseudonymised and the patients, or their legally authorized representative, provided written informed consent for their use. PAH was diagnosed considering a cut-off ⩾25 mmHg for mPAP and >3 Wood units (WU) for PVR. The observation period was from 2003 to December 2022. Patients were treated according to ESC/ERS PH guidelines valid at the time the patients were followed [15–19], and targeted PAH sequential combination therapy was indicated according to a goal-oriented treatment strategy if treatment goals were not met. Despite different treatment recommendations in the different study periods, sequential combination therapy was prescribed in a relatively homogeneous way over the whole study period, according to the treatment goals applied in our centre (as already previously described by Dardi *et al.* [20]).

Assessment

Non-invasive and invasive parameters were systematically collected at baseline and 3–6 months after starting first-line targeted PAH treatment (first follow-up). The non-invasive parameters collected were: age, gender, PAH aetiology, World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD), creatinine and estimated glomerular filtration rate (eGFR) using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [21], haemoglobin level, brain natriuretic peptide (BNP) or N-terminal pro-hormone BNP (NT-proBNP), body mass index (BMI), and comorbidities such as dysthyroidism, systemic hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation and obesity (defined as a BMI ⩾30 $kg \cdot m^{-2}$). BNP/NT-proBNP values were categorised into four groups according to the cut-offs proposed by Hoeper *et al.* [22]. The parameters collected during right heart catheterization (RHC), performed in clinically stable conditions after fluid balance optimisation, were heart rate (HR), RAP, systolic/diastolic/mean pulmonary arterial pressure (s/d/mPAP), systolic systemic blood pressure (SBP), pulmonary arterial wedge pressure (PAWP), cardiac output (CO) and S_{vO_2}. Calculated derived parameters were PVR (calculated as (mPAP − PAWP)/CO), CI (calculated as CO/body surface area (BSA)), stroke volume (SV) (calculated as CO/HR), SVI (calculated as CI/HR), pulmonary artery (PA) elastance (E_a) (calculated as sPAP/SV), PA compliance (PAC) (calculated as SV/(sPAP − dPAP)), cardiac efficiency (CE) (calculated as SV/mPAP), RV power (calculated as mPAP × CI), RV stroke work

index (RVSWI) (calculated as SVI ×(mPAP – RAP)×0.0136) and resistance-compliance (RC) product (calculated as PVR×PAC). Risk stratification was assessed according to current ESC/ERS PH guidelines risk table derived tools: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) three-strata (1.0) [23] and four-strata (2.0) [22, 24] risk tools, French Pulmonary Hypertension Registry (FPHR) invasive risk assessment strategy [25] and the multiparametric simplified model proposed in our centre [26]. The FPHR methodology defines only the low-risk group anyway, as suggested in previous works, we considered the presence of three or four low-risk variables to be low risk, the presence of one or two low-risk variables to be intermediate risk, and no low-risk variables to be high risk [27].

Statistics

Baseline variables are presented as n (%) for categorical data, and medians (interquartile range) for the continuous data. Patient characteristics have been compared using Pearson's Chi-squared test or Fisher's exact test for categorical variables (applying Bonferroni correction for multiple pairwise comparisons). Comparisons between baseline characteristics were analysed using the Dunn test with Bonferroni correction. The paired Wilcoxon signed-rank test and McNemar test were used to compare changes from baseline to follow-up. We considered p-values <0.05 to be statistically significant.

Cox univariate analysis was performed for all variables to assess their relation to survival and all parameters with a p-value <0.1 were included in the multivariate Cox proportional risk model using the stepwise selection method. Variables with a p-value <0.05 were considered to be independently related to prognosis. All-cause death was considered as primary outcome, survival was displayed using Kaplan–Meier plots and the difference between subgroups tested for significance using the log-rank test. Patients lost to follow-up or undergoing lung transplantation were censored as alive at the time of last contact/lung transplantation.

For the baseline survival analysis, the date of baseline RHC was used as the starting point to determine length of survival. Proportional hazards assumptions were tested on the basis of Schoenfeld residuals. Variables not fitting proportional hazards assumption were considered as time varying covariates in the final model.

We defined two cut-offs for each haemodynamic variable identified as independently prognostic on the multivariate Cox regression analyses. For variables with already defined cut-offs [10, 11], the same values were considered. For variables without already defined cut-offs in the current ESC/ERS PH guidelines risk table, the value with highest chi2 of the log-rank test corresponding to a 1-year all-cause mortality <5% was chosen (0.1 mmHg·m^{-1} steps were used for E_a, 0.1 mL·mmHg^{-1} steps were used for PAC and CE; 1 WU steps were used for PVR); the second cut-off was chosen considering the highest χ^2 of the log-rank test corresponding to a 1-year all-cause mortality >5%. For a further subdivision into four strata, the intermediate range of values for each parameter was further subdivided according to the median value of the intermediate strata.

As targeted PAH therapy is able to modify most haemodynamic parameters, potentially interfering with their prognostic role when evaluating the value before treatment escalation, and considering that clinical worsening due to PAH progression usually translates into the need of non-elective hospitalisation or targeted PAH treatment escalation (the latter, in turn, being able to reduce the risk of hospitalisations [1, 2]), an exploratory analysis considering a combined end-point of clinical worsening including all-cause death and/or non-elective all-cause (and PAH-related as a secondary analysis) hospitalisation and/or need of PAH-targeted treatment escalation was performed to test the additive predictive value of haemodynamic parameters to current ESC/ERS risk tools at first follow-up. Hospitalisations were independently reviewed by two investigators (F. Dardi and D. Guarino) and categorised as PAH related or not based on information available in medical records.

Eventually, we defined a haemodynamic risk tool (RHC risk tool) considering all the haemodynamic variables significant at multivariate Cox regression analyses and grouping them in three criteria: RV preload (including RAP), RV afterload (including E_a, PVR and PAC) and RV pump function (including CI, SVI, CE and S_{vO_2}). Applying the cut-off values proposed in current ESC/ERS PH guidelines, or identified with the methodology described above, variables were graded 1–3 (1: low risk, 2: intermediate risk and 3: high risk) or 1–4 (1: low risk, 2: intermediate–low risk, 3: intermediate–high risk, and 4: high risk) for the three- and four-strata risk scores calculation, respectively. For each haemodynamic criterion we chose the parameter with the worst prognostic value to avoid potential risk underestimation. For each patient, the sum of all grades was divided by the number of available variables and rounded to the nearest

integer to define the risk group [22, 28]. To evaluate the added value of haemodynamic parameters to non-invasive parameters (*i.e.* WHO-FC, 6MWD and BNP/NT-proBNP) the COMPERA-RHC four-strata risk tool was developed considering both the three haemodynamic criteria and the three non-invasive parameters. The c-statistic was used to compare the discrimination capacity of the RHC risk tool *versus* current ESC/ERS risk tools. Akaike's information criterion and Bayesian information criterion were also provided.

Statistical analyses were performed using STATA/SE V.15.1 (StataCorp).

Results

The analysis cohort included 794 PAH targeted treatment-naïve patients at baseline and 706 patients who had a follow-up RHC. Baseline characteristics are shown in table 1. Among the baseline cohort (n=794), a primary outcome occurred in 426 patients (54%) over a median follow-up duration of 5.8 years (2.4–11 years); 19 patients (2.4%) were lost to follow-up. Overall survival at 1, 3, 5 and 10 years from baseline evaluation was 91% (89–93%), 78% (75–81%), 68% (65–72%) and 47% (43–51%), respectively. Survival according to the different PAH aetiologies is shown in supplementary table S1 and supplementary figure S1.

The most frequent initial treatment strategy after baseline RHC was monotherapy in 646 patients (81%), followed by initial combination therapy in 148 patients (19%). 71 (17%) of I/H/D-PAH patients were responder to acute vasoreactivity test and were treated with calcium channel blockers (CCBs) and, among them, 53 (12%) were long-term responder to CCBs.

After a median of 5 (4–9) months, 706 patients underwent a complete re-evaluation including RHC. 88 patients were not re-evaluated because of: death (58, 66%), loss to follow-up (17, 19%), lung transplantation (1, 1%), or frailty or decline of RHC (12, 14%).

Changes from baseline to first follow-up of modifiable variables are reported in table 2.

Predictors of all-cause death at the time of baseline RHC are shown in table 3. Independent baseline predictors of death at the multivariate Cox regression analyses were age, male gender, CTD-PAH aetiology, eGFR, 6MWD and RAP. Because of 301 missing baseline values for BNP/NT-proBNP, this variable was included only in a separate multivariate analysis showing its independent prognostic value displacing eGFR and RAP (supplementary table S2).

Predictors of all-cause death at the time of first follow-up are shown in table 4. Because of 550 missing baseline values for BNP/NT-proBNP, this variable was not included in further multivariate analysis. RAP and E_a are the haemodynamic variables identified as independent predictors of all-cause death at multivariate analysis.

Owing to significant correlations between haemodynamic variables (supplementary table S3), we compared Cox regression models by adding sequentially only haemodynamic variables at first follow-up with correlation coefficients <0.6 (absolute value) and gaining a significant improvement in log likelihood (table 5). In these models, RAP, E_a, PAC, CE, PVR, S_{vO_2}, CI and SVI at follow-up RHC were associated with the risk of death when adjusted for age, gender, PAH aetiology, 6MWD and WHO-FC. We conducted a sensitivity analysis excluding patients with uncorrected CHD or responder to CCBs treatment obtaining comparable results (supplementary table S4).

The optimal cut points for E_a, PAC, CE and PVR, identified from the log-rank test highest Chi-squared analyses, are shown in supplementary figure S2.

We tested the added value of these eight haemodynamic parameters (RAP, E_a, PAC, CE, PVR, S_{vO_2}, CI and SVI) to current ESC/ERS risk tools in predicting all-cause mortality at first follow-up (supplementary table S5), and we found that only RAP was consistently of additive prognostic value for all risk tools. The respective risk tools were highly statistically significant in all bivariate analyses ($p<0.001$).

Considering a combined end-point including all-cause death, non-elective all-cause hospitalisation and need of treatment escalation we observed that after first-line treatment, 291 patients (41%) needed treatment escalation and 142 (20%) underwent a non-elective hospitalisation (58% PAH-related, 42% not PAH-related) as first event. These events were more frequent in patients treated with initial monotherapy than in patients treated with initial combination therapy (66% *versus* 43%, $p<0.001$). When we tested the

TABLE 1 Baseline characteristics

	All	I/H/D-PAH	CTD-PAH	CHD-PAH	p-value
Patients, n	794	425	222	147	
Age years	55 (39–69)	55 (39–68)[#¶]	66 (55–74)[#+]	41 (32–54)[¶+]	<0.001
Male gender	234 (29)	159 (37)[#]	25 (11)[#+]	50 (34)[+]	<0.001
Aetiology		Idiopathic: 347 (82) Heritable: 67 (16) Drug-induced: 11 (2)	SSc: 169 (76) Undiff/mixed: 24 (11) SLE: 15 (7) RA: 8 (3) Sjogren: 6 (3)	Eisenmenger: 79 (54) R-L shunt: 28 (19) Small defects: 8 (5) Corrected: 32 (22)	
WHO-FC		[#¶]	[#+]	[¶+]	<0.001
I	26 (3)	10 (2)	6 (3)	10 (7)	
II	214 (27)	115 (27)	38 (17)	61 (41)	
III	527 (66)	291 (69)	161 (72)	75 (51)	
IV	27 (4)	9 (2)	17 (8)	1 (1)	
6MWD m (n=)	387 (295–468) (n=750)	402 (310–497)[#] (n=410)	332 (241–419)[#+] (n=198)	421 (338–478)[+] (n=142)	<0.001
BNP/NT-proBNP ng·L^{-1}	n=493	n=271	n=141	n=81	0.078
<50/<300	114 (23)	67 (25)	21 (15)	26 (32)	
50–200/300–650	116 (24)	64 (24)	35 (25)	17 (21)	
200–800/650–1100	101 (20)	58 (21)	28 (20)	15 (19)	
>800/>1100	162 (33)	82 (30)	57 (40)	23 (28)	
eGFR mL/min/1.73m^2 (n=)	73 (55–89) (n=768)	73 (57–88)[#¶] (n=409)	61 (44–79)[#+] (n=217)	85 (72–99)[¶+] (n=142)	<0.001
Haemoglobin g·dL^{-1}	14.2 (12.8–15.9)	14.6 (13.3–16)[#¶]	12.9 (11.6–14.2)[#+]	15.3 (13.6–17.2)[¶+]	<0.001
Dysthyroidism	158 (20)	74 (17)[#]	62 (28)[#+]	22 (15)[+]	0.002
BMI kg·m^{-2}	24 (21–28)	25 (22–28)[¶]	24 (22–28)[+]	22 (19–25)[¶+]	<0.001
Obesity	130 (16)	78 (18)[¶]	38 (17)[+]	14 (10)[¶+]	0.042
Systemic hypertension	320 (40)	173 (41)[¶]	104 (47)[+]	43 (29)[¶+]	0.003
Diabetes mellitus	94 (11)	68 (16)[#¶]	15 (7)[#]	11 (7)[¶]	<0.001
Coronary artery disease	84 (11)	54 (13)[¶]	24 (11)	6 (4)[¶]	0.014
Atrial fibrillation	85 (11)	37 (9)[¶]	21 (9)[+]	27 (18)[¶+]	0.004
HR bpm	80 (71–90)	80 (71–90)	82 (71–93)	80 (72–90)	0.170
RAP mmHg	6 (4–10)	7 (4–10)	6 (4–11)	6 (4–9)	0.495
mPAP mmHg	51 (41–62)	51 (42–61)[#¶]	44 (36–55)[#+]	68 (48–83)[¶+]	<0.001
sPAP mmHg	84 (67–100)	84 (69–98)[#¶]	73 (59–89)[#+]	105 (80–125)[¶+]	<0.001
E_a mmHg·mL^{-1}	1.65 (1.13–2.43)	1.59 (1.16–2.31)[¶]	1.54 (0.98–2.20)[+]	2.08 (1.32–3.00)[¶+]	<0.001
PAWP mmHg	8 (6–10)	8 (6–10)[¶]	8 (6–10)[+]	9 (7–11)[¶+]	<0.001
SBP mmHg	120 (108–137)	120 (108–136)[#]	126 (112–140)[#+]	118 (106–133)[+]	0.003
CI L·min^{-1}·m^{-2}	2.3 (1.9–2.8)	2.2 (1.9–2.7)	2.3 (1.9–2.9)	2.4 (2.0–2.9)	0.069
SVI mL·m^{-2}	29 (23–36)	29 (23–35)	30 (24–36)	29 (23–39)	0.542
CE mL·mmHg^{-1}	0.99 (0.67–1.47)	1.01 (0.70–1.43)[¶]	1.09 (0.74–1.67)[+]	0.74 (0.51–1.19)[¶+]	<0.001
RV power mmHg*L·min^{-1}	114 (91–147)	112 (94–141)[#¶]	103 (78–130)[#+]	150 (110–210)[¶+]	<0.001
RVSWI mL*mmHg	16.4 (12.8–21.8)	16.3 (13.2–21.3)[#¶]	14.5 (11.2–18.1)[#+]	23.2 (16.3–32.1)[¶+]	<0.001
RC product min	10 417 (8947–12 453)	10 545 (9259–12 172)[#]	9676 (8289–11 175)[#+]	11 806 (8028–16 274)[+]	<0.001
PVR WU	10.7 (7.1–15.3)	10.8 (7.6–15)[#¶]	9.2 (6.2–13.2)[#+]	14.0 (7.5–21.7)[¶+]	<0.001
PAC mL·mmHg^{-1}	0.98 (0.69–1.46)	0.99 (0.72–1.41)[¶]	1.01 (0.74–1.64)[+]	0.91 (0.58–1.34)[¶+]	0.012
S_{vO_2} %	65.0 (57.4–71.1)	63.5 (56.9–69.8)[¶]	64.2 (55.8–70)[+]	71.8 (65.4–76.6)[¶+]	<0.001
PAH initial treatment		[#]	[#+]	[+]	<0.001
Mono	646 (81)	352 (83)	161 (73)	133 (90)	
Combo	148 (19)	73 (17)	61 (27)	14 (10)	
PAH end follow-up treatment					0.321
Mono	331 (42)	187 (44)	89 (40)	55 (37)	
Combo	463 (58)	238 (56)	133 (60)	92 (63)	
Bologna baseline risk		[¶]	[+]	[¶+]	<0.001
Low	143 (18)	66 (16)	33 (15)	44 (30)	
Intermediate	473 (60)	259 (61)	121 (54)	93 (63)	
High	178 (22)	100 (23)	68 (31)	10 (7)	
COMPERA 1.0 baseline risk		[¶]	[+]	[¶+]	<0.001
Low	235 (30)	118 (28)	51 (23)	66 (45)	
Intermediate	472 (59)	262 (62)	135 (61)	75 (51)	
High	87 (11)	45 (10)	36 (16)	6 (4)	

Continued

TABLE 1 Continued

	All	I/H/D-PAH	CTD-PAH	CHD-PAH	p-value
FPHR baseline risk		¶	+	¶+	0.002
Low	198 (25)	100 (24)	47 (21)	51 (35)	
Intermediate	414 (52)	226 (53)	111 (50)	77 (52)	
High	182 (23)	99 (23)	64 (29)	19 (13)	

Data are presented as n (%) or median (IQR). I/H/D: idiopathic/heritable/drug-induced; PAH: pulmonary arterial hypertension; CTD: connective tissue disease; CHD: congenital heart disease; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; R-L: right to left; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-hormone BNP; eGFR: estimated glomerular filtration rate; BMI: body mass index; HR: heart rate; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; sPAP: systolic pulmonary artery pressure; E_a: pulmonary artery elastance; PAWP: pulmonary artery wedge pressure; SBP: systolic blood pressure; CI: cardiac index; SVI: stroke volume index; CE: cardiac efficiency; RV: right ventricle; RVSWI: RV stroke work index; RC: resistance-compliance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; S_{vO_2}: mixed venous oxygen saturation; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry. #¶+: p<0.05 between respective pairs.

additive predictive value of haemodynamic parameters for the combined end-point (supplementary table S6), all parameters emerge as predictive independently from the ESC/ERS risk tool considered (each of which was highly statistically significant in all bivariate analyses; p<0.001).

We defined the RHC risk tool considering only the eight haemodynamic parameters identified at multivariate Cox regression analyses with the above defined cut-offs (figure 1). Its discriminatory ability was comparable to ESC/ERS risk tools only when considering the combined end-point of all-cause death+all-cause non-elective hospitalisation+need of treatment escalation, while for all-cause death, despite being well calibrated for 1-year mortality, its discriminatory ability was inferior (tables 6 and 7). We repeated the analysis including only patients with available BNP/NT-proBNP at first follow-up (supplementary table S7) and also considering a combined end-point of all-cause death+PAH-related non-elective hospitalisation (73% heart failure, 14.5% supraventricular arrhythmias, 6% angina due to left main coronary artery compression, 4.5% haemoptysis, 2% cerebrovascular accidents)+need of treatment escalation (supplementary table S8) obtaining comparable results. Combining the three haemodynamic criteria to non-invasive parameters (*i.e.* WHO-FC, 6MWD and BNP/NT-proBNP), the derived COMPERA-RHC four-strata risk tool showed the added discriminatory value of haemodynamics to the three non-invasive parameters for the combined end-point (supplementary table S9).

Discussion

In the present study, we evaluated the prognostic role of haemodynamic parameters together with clinical, functional, exercise and laboratory variables at baseline and at first follow-up after first-line initial treatment in patients with I/H/D-PAH, CTD PAH and CHD-PAH. The main findings were: 1) cardiovascular comorbidities do not have an additive prognostic role when corrected for age, gender and PAH aetiology, which are the most prognostically relevant non-modifiable parameters; 2) haemodynamic parameters reflecting both RV afterload and RV function are of prognostic relevance at first follow-up after starting first-line targeted PAH treatment but not at baseline; and 3) in comparison with current ESC/ERS risk tools, haemodynamic parameters are of no added value in predicting all-cause death, but the predictive value of haemodynamics alone is comparable to current ESC/ERS risk tools and of added value to non-invasive parameters (*i.e.* WHO-FC, 6MWD and BNP/NT-proBNP) for a combined end-point of all-cause death, non-elective hospitalisation and need of PAH treatment escalation.

Contemporary PH registries describe a significant increase in the age of patients with PAH over the last four decades associated with a significant increase of comorbidity burden [29–32]. Beyond representing a challenge for a correct diagnostic characterisation, the presence of comorbidities can have a significant impact on prognosis. Cardiovascular comorbidities such as coronary artery disease [29, 33] and diabetes mellitus [33, 34] have been shown to be associated with survival but, when adjusted for age, the impact of cardiovascular comorbidities seems to be less relevant [30, 33]. Our data corroborate that, as in most contemporary registries, age is independently associated with prognosis [35–37], and it seems to have a higher impact than cardiovascular comorbidities on survival. We confirmed also the independent negative prognostic impact of male gender [35, 37, 38] and CTD-PAH aetiology [35].

Regarding renal dysfunction, it has been described as an independent predictor of prognosis in PAH [29, 35, 39, 40]. Our data corroborate its independent prognostic role at baseline (only after BNP/NT-proBNP

TABLE 2 Clinical, laboratory and haemodynamic variables at baseline and at first follow-up

Variable	Baseline	First follow-up	p-value
WHO-FC			<0.001
I	25 (3)	105 (15)	
II	199 (28)	349 (49)	
III	464 (66)	249 (35)	
IV	18 (3)	3 (1)	
6MWD m (n=)	403 (314–482) (n=649)	440 (350–535) (n=649)	<0.001
BNP/NT-proBNP ng·L^{-1}	n=151	n=151	<0.001
<50/<300	35 (23)	45 (30)	
50–200/300–650	35 (23)	52 (34)	
200–800/650–1100	51 (34)	30 (20)	
>800/>1100	30 (20)	24 (16)	
eGFR mL/min/1.73m^2 (n=)	75 (57–91) (n=586)	75 (59–93) (n=586)	0.065
Haemoglobin g·dL^{-1}	14.2 (12.9–15.9)	13.9 (12.7–15.4)	<0.001
BMI kg·m^{-2}	24.2 (21.5–27.9)	23.9 (21.3–27.4)	0.013
HR bpm	80 (71–90)	80 (70–90)	0.713
RAP mmHg	6 (4–10)	7 (4–9)	0.176
mPAP mmHg	51 (41–63)	44 (35–57)	<0.001
sPAP mmHg	85 (66–100)	73 (56–94)	<0.001
E_a mmHg·mL^{-1}	1.64 (1.12–2.39)	1.10 (0.75–1.75)	<0.001
PAWP mmHg	8 (6–10)	9 (7–10)	<0.001
SBP mmHg	121 (110–137)	114 (104–129)	<0.001
CI L·min^{-1}·m^{-2}	2.3 (2.0–2.8)	2.8 (2.3–3.5)	<0.001
SVI mL·m^{-2}	30 (24–37)	37 (29–44)	<0.001
CE mL·mmHg^{-1}	0.99 (0.67–1.49)	1.46 (0.91–2.10)	<0.001
RV power mmHg*L·min^{-1}	115 (94–147)	125 (97–160)	<0.001
RVSWI mL*mmHg	16.7 (13.1–22.3)	18.0 (13.9–23.7)	<0.001
RC product min	10 417 (8986–12 473)	9755 (8282–11 515)	<0.001
PVR WU	10.6 (7.0–15.3)	6.9 (4.3–11.1)	<0.001
PAC mL·mmHg^{-1}	0.99 (0.70–1.47)	1.43 (0.94–2.06)	<0.001
S_{vO_2} %	65.9 (58.3–71.6)	68.8 (62–74.6)	<0.001
Bologna risk			<0.001
Low	138 (20)	309 (44)	
Intermediate	426 (60)	355 (50)	
High	142 (20)	42 (6)	
COMPERA 1.0 risk			<0.001
Low	223 (32)	406 (57)	
Intermediate	418 (59)	275 (39)	
High	65 (9)	25 (4)	
FPHR risk			<0.001
Low	192 (27)	366 (52)	
Intermediate	367 (52)	264 (37)	
High	147 (21)	76 (11)	

Data are presented as n (%) or median (IQR). WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-hormone BNP; eGFR: estimated glomerular filtration rate; BMI: body mass index; HR: heart rate; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; sPAP: systolic pulmonary artery pressure; E_a: pulmonary artery elastance; PAWP: pulmonary artery wedge pressure; SBP: systolic blood pressure; CI: cardiac index; SVI: stroke volume index; CE: cardiac efficiency; RV: right ventricle; RVSWI: RV stroke work index; RC: resistance-compliance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; S_{vO_2}: mixed venous oxygen saturation; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry.

exclusion), but not at first follow-up. Moreover, we documented no significant improvement of renal function from baseline to first follow-up assessment, as already documented in other registries [41], despite a significant improvement of most haemodynamic parameters, but RAP. An interaction between RAP and renal function in prognostic stratification has previously been described; however, this interaction seems relevant only for high RAP values [39], while in our cohort median RAP at baseline was within the normal range. These data may suggest that renal function, despite being influenced by haemodynamic

TABLE 3 Univariable and multivariable Cox proportional hazards regression at baseline

		Univariate		Multivariate[#]	
	n	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	794	1.05 (1.04–1.05)	<0.001	1.03 (1.02–1.04)	<0.001
Male gender	794	1.28 (1.04–1.57)	0.018	2.27 (1.79–2.87)	<0.001
Aetiology	794				
CTD *versus* I/H/D		2.51 (2.02–3.12)	<0.001	1.67 (1.30–2.14)	<0.001
CHD *versus* I/H/D		0.79 (0.60–1.04)	0.088		
WHO-FC *versus* I	794				
II		2.95 (1.20–7.26)	0.019		
III		6.92 (2.85–16.80)	<0.001		
IV		31.33 (11.86–82.77)	<0.001		
6MWD m	750	0.995 (0.994–0.995)	<0.001	0.996 (0.995–0.997)	<0.001
BNP/NT-proBNP ng·L^{-1} *versus* <50/<300 ng·L^{-1}	493				
50–200/300–650		1.83 (1.16–2.89)	0.009		
200–800/650–1100		2.50 (1.57–4.00)	<0.001		
>800/>1100		3.90 (2.63–5.78)	<0.001		
eGFR mL/min/1.73 m^2	768	0.97 (0.97–0.98)	<0.001	0.993 (0.987–0.998)	0.014
Haemoglobin g·dL^{-1}	794	0.91 (0.87–0.95)	<0.001		
Dysthyroidism	794	1.20 (0.95–1.52)	0.118		
BMI kg·m^{-2}	794	1.02 (1.00–1.04)	0.039		
Obesity	794	1.20 (0.94–1.55)	0.146		
Systemic hypertension	794	1.33 (1.09–1.61)	0.004		
Diabetes mellitus	794	1.67 (1.26–2.22)	<0.001		
Coronary artery disease	794	1.83 (1.39–2.42)	<0.001		
Atrial fibrillation	794	1.67 (1.28–2.19)	<0.001		
Heart rate bpm	794	1.01 (1.00–1.01)	0.038		
RAP mmHg	794	1.09 (1.07–1.11)	<0.001	1.04 (1.01–1.06)	0.002
mPAP mmHg	794	0.99 (0.99–1.00)	0.004		
sPAP mmHg	794	1.00 (0.99–1.00)	0.153		
E_a mmHg·mL^{-1}	794	1.13 (1.05–1.21)	0.001		
PAWP mmHg	794	1.04 (1.00–1.07)	0.035		
SBP mmHg	794	1.00 (0.99–1.01)	0.622		
CI L·min^{-1}·m^{-2}	794	0.69 (0.60–0.80)	<0.001		
SVI mL·m^{-2}	794	0.97 (0.96–0.98)	<0.001		
CE mL·mmHg^{-1}	794	0.84 (0.72–0.99)	0.038		
RV power mmHg*L·min^{-1}	794	0.99 (0.99–1.00)	<0.001		
RVSWI mL*mmHg	794	0.95 (0.94–0.97)	<0.001		
RC product min	794	0.99 (0.99–1.00)	0.008		
PVR WU	794	1.01 (0.99–1.02)	0.277		
PAC mL·mmHg^{-1}	794	0.79 (0.67–0.93)	0.005		
S_{vO_2} %	794	0.95 (0.94–0.96)	<0.001		

HR: hazard ratio; CTD: connective tissue disease; I/H/D: idiopathic/heritable/drug-induced; CHD: congenital heart disease; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-hormone BNP; eGFR: estimated glomerular filtration rate; BMI: body mass index; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; sPAP: systolic pulmonary artery pressure; E_a: pulmonary artery elastance; PAWP: pulmonary artery wedge pressure; SBP: systolic blood pressure; CI: cardiac index; SVI: stroke volume index; CE: cardiac efficiency; RV: right ventricle; RVSWI: RV stroke work index; RC: resistance-compliance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; S_{vO_2}: mixed venous oxygen saturation. [#]: excluding BNP/NT-proBNP.

status [42], should be considered more likely as a patient-related comorbid condition than as a marker of PAH targeted treatment response (although a possible interaction with other non-modifiable parameters was not analysed).

Among modifiable parameters we confirmed the independent prognostic relevance of WHO-FC, 6MWD and, despite not being tested at first follow-up due to missingness, BNP/NT-proBNP [25, 35]. At baseline no haemodynamic variable was of independent prognostic relevance except RAP (but only when BNP/NT-proBNP was excluded). The poor prognostic predictability of haemodynamic parameters at baseline evaluation, before targeted PAH therapy, has already been described in other cohorts [37, 43, 44]. This can

TABLE 4 Univariable and multivariable Cox proportional hazards regression at first follow-up

	Univariate			Multivariate[#]	
	n	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	706	1.04 (1.03–1.05)	<0.001	1.03 (1.02–1.04)	<0.001
Male gender	706	1.28 (1.02–1.60)	0.034	1.94 (1.48–2.53)	<0.001
Aetiology					
CTD *versus* I/H/D		2.63 (2.07–3.35)	<0.001	1.92 (1.44–2.55)	<0.001
CHD *versus* I/H/D		1.32 (0.99–1.77)	0.060	1.11 (0.79–1.54)	0.554
WHO-FC *versus* I	706				
II		3.54 (2.26–5.55)	<0.001	1.90 (1.16–3.12)	0.011
III		8.18 (5.23–12.78)	<0.001	2.51 (1.45–4.37)	0.002
IV		17.19 (5.12–57.67)	<0.001	6.02 (1.67–21.75)	0.006
6MWD 10 m	649	0.94 (0.93–0.95)	<0.001	0.9997 (0.9996–0.9999)[¶]	0.002
BNP/NT-proBNP ng·L^{-1} *versus* <50/<300 ng·L^{-1}	156				
50–200/300–650		4.97 (1.16–21.33)	0.031		
200–800/650–1100		7.77 (1.81–33.32)	0.006		
>800/>1100		33.74 (7.72–147.51)	<0.001		
eGFR mL/min/1.73 m^2	586	0.97 (0.97–0.98)	<0.001		
Haemoglobin g·dL^{-1}	684	0.97 (0.93–1.01)	0.173		
Dysthyroidism	706	1.22 (0.95–1.56)	0.127		
BMI kg·m^{-2}	706	1.00 (0.98–1.02)	0.924		
Obesity	706	1.04 (0.77–1.40)	0.797		
Systemic hypertension	706	1.34 (1.08–1.65)	0.007		
Diabetes mellitus	706	1.77 (1.32–2.38)	<0.001		
Coronary artery disease	706	1.69 (1.25–2.28)	0.001		
Atrial fibrillation	706	1.93 (1.44–2.59)	<0.001		
Heart rate bpm	706	1.00 (1.00–1.01)	0.382		
RAP mmHg	706	1.12 (1.10–1.15)	<0.001	1.09 (1.06–1.12)	<0.001
mPAP mmHg	706	1.00 (1.00–1.01)	0.217		
sPAP mmHg	706	1.00 (1.00–1.01)	0.017		
E_a mmHg·mL^{-1}	706	1.20 (1.13–1.27)	<0.001	1.16 (1.07–1.27)	0.001
PAWP mmHg	706	1.04 (1.00–1.08)	0.032		
SBP mmHg	706	1.00 (0.99–1.01)	0.790		
CI L·min^{-1}·m^{-2}	706	0.62 (0.54–0.71)	<0.001		
SVI mL·m^{-2}	706	0.96 (0.95–0.97)	<0.001		
CE mL·mmHg^{-1}	706	0.71 (0.62–0.82)	<0.001		
RV power mmHg*L·min^{-1}	706	0.99 (0.99–1.00)	<0.001		
RVSWI mL*mmHg	706	0.96 (0.95–0.97)	<0.001		
RC product min	706	1.00 (1.00–1.00)	0.012		
PVR WU	706	1.02 (1.01–1.04)	<0.001		
PAC mL·mmHg^{-1}	706	0.68 (0.60–0.78)	<0.001		
S_{vO_2} %	706	0.95 (0.94–0.96)	<0.001		
		Log likelihood		−1696.98	
		AIC		3407.96	
		BIC		3439.28	

HR: hazard ratio; CTD: connective tissue disease; I/H/D: idiopathic/heritable/drug-induced; CHD: congenital heart disease; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-hormone BNP; eGFR: estimated glomerular filtration rate; BMI: body mass index; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; sPAP: systolic pulmonary artery pressure; E_a: pulmonary artery elastance; PAWP: pulmonary artery wedge pressure; SBP: systolic blood pressure; CI: cardiac index; SVI: stroke volume index; CE: cardiac efficiency; RV: right ventricle; RVSWI: RV stroke work index; RC: resistance-compliance; PVR: pulmonary vascular resistance; PAC: pulmonary arterial compliance; S_{vO_2}: mixed venous oxygen saturation; AIC: Akaike's information criterion; BIC: Bayesian information criterion. [#]: excluding BNP/NT-proBNP; [¶]: time varying covariate.

be at least in part explained by the more tight correlation of haemodynamic parameters to PAH therapeutic response than other non-invasive parameters (*i.e.* WHO-FC, 6MWD and BNP/NT-proBNP) that, despite being sensitive to treatment, are more influenced by non-PAH-related factors and, thus, may better reflect patients' overall prognosis beyond the PAH-related reduced life expectancy (*i.e.* a patient with a persistently low 6MWD due to poor physical performance despite a satisfactory improvement of

TABLE 5 Comparison of multivariable Cox regression models for haemodynamic variables at first follow-up

	First follow-up Model 1		First follow-up Model 2		First follow-up Model 3	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age years	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Male gender	1.95 (1.50–2.54)	<0.001	1.92 (1.48–2.50)	<0.001	1.93 (1.48–2.51)	<0.001
CTD aetiology	1.87 (1.42–2.47)	<0.001	1.90 (1.44–2.51)	<0.001	1.91 (1.44–2.52)	<0.001
6MWD, 10 m[#]	0.9997 (0.9995–0.9999)	0.001	0.9997 (0.9995–0.9999)	0.001	0.9997 (0.9996–0.9999)	0.001
WHO-FC	1.42 (1.14–1.78)	0.002	1.42 (1.14–1.78)	0.002	1.48 (1.19–1.85)	0.001
RAP mmHg	1.09 (1.06–1.12)	<0.001	1.08 (1.06–1.11)	<0.001	1.09 (1.06–1.12)	<0.001
PAC mL·mmHg^{-1}	0.77 (0.66–0.91)	0.002				
CE mL·mmHg^{-1}			0.76 (0.64–0.91)	0.003		
PVR WU					1.02 (1.01–1.03)	0.001
Log likelihood	−1696.59		−1698.24		−1698.40	
AIC	3407.18		3410.47		3410.80	
BIC	3438.48		3441.80		3442.12	

	First follow-up Model 4		First follow-up Model 5		First follow-up Model 6	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age year	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Male gender	1.79 (1.38–2.33)	<0.001	1.77 (1.36–2.32)	<0.001	1.81 (1.39–2.36)	<0.001
CTD aetiology	1.80 (1.37–2.35)	<0.001	1.84 (1.40–2.42)	<0.001	1.79 (1.37–2.36)	<0.001
6MWD, 10 m[#]	0.9997 (0.9995–0.9999)	0.001	0.9997 (0.9995–0.9999)	0.001	0.9997 (0.9995–0.9999)	0.001
WHO-FC	1.44 (1.15–1.80)	0.001	1.48 (1.18–1.85)	0.001	1.46 (1.17–1.83)	0.001
RAP mmHg	1.09 (1.06–1.11)	<0.001	1.09 (1.06–1.12)	<0.001	1.09 (1.06–1.12)	<0.001
S_{vO_2} %	0.98 (0.97–0.99)	0.004				
CI L·min^{-1}·m^{-2}			0.84 (0.71–0.98)	0.024		
SVI mL·m^{-2}					0.99 (0.97–0.999)	0.036
Log likelihood	−1699.07		−1700.42		−1700.78	
AIC	3412.15		3414.83		3415.57	
BIC	3443.48		3446.16		3446.89	

HR: hazard ratio; CTD: connective tissue disease; 6MWD: 6-min walk distance; WHO-FC: World Health Organization functional class; RAP: right atrial pressure; PAC: pulmonary arterial compliance; CE: cardiac efficiency; PVR: pulmonary vascular resistance; AIC: Akaike's information criterion; BIC: Bayesian information criterion; S_{vO_2}: mixed venous oxygen saturation; CI: cardiac index; SVI: stroke volume index. [#]: time varying covariate.

haemodynamic profile after PAH therapy will still have a poor prognosis in relation to his poor physical status; this will be captured more precisely by the 6MWD rather than by the haemodynamic parameters, which improve independently from patient overall physical status).

At first follow-up, differently from baseline evaluation, haemodynamic parameters emerged as prognostic at multivariate analyses. In particular, the most important were RAP and E_a.

RAP is the most consistently prognostic haemodynamic parameter also in other PAH cohorts [35, 37, 44, 45], and we documented the added prognostic role of RAP, especially for high-risk values, to current ESC/ERS risk tools applied in our cohort. However, as BNP/NT-proBNP seems to have a better all-cause death prognostic predictability than RAP [25, 46], as demonstrated also at baseline evaluation, and considering the high number of missingness for BNP/NT-proBNP at first follow-up, we cannot exclude that these findings may be related only to BNP/NT-proBNP missing values.

E_a has already been described as prognostically relevant but only in patients with left-sided heart failure [47, 48]. To the best of our knowledge this is the first systematic work highlighting its prognostic role at follow-up in patients with PAH. From a pathophysiological point of view E_a is a measure of total RV load that has been most commonly approximated by the formula sPAP/SV [49]. This highlights the importance of RV afterload in PAH prognostic stratification beyond RV function. What is even more interesting is that also the two main components, steady and pulsatile, of RV afterload, which are respectively described by PVR and PAC [50], emerge as significant in separated multivariate models. In particular, the model including PAC was the best fitting one. PAC and PVR already emerge as prognostic in other cohorts [35, 37, 43, 44, 51, 52]

	Low risk	Intermediate–low	Intermediate–high	High risk
RV preload RAP mmHg	<8	8–9	10–14	>14
RV afterload E_a mmHg·mL^{-1} PVR WU PAC mL·mmHg^{-1}	<1.1 <6 >1.5	1.1–1.4 6–9 >1.1–1.5	>1.4–1.8 >9–14 0.7–1.1	>1.8 >14 <0.7
RV pump function CI L·min^{-1}·m^{-2} SVI mL·m^{-2} CE mL·mmHg^{-1} S_{vO_2} %	>2.5 >38 >1.5 >65	>2.3–2.5 >35–38 >1.1–1.5 >63–65	2.0–2.3 31–35 0.8–1.1 60–63	<2.0 <31 <0.8 <60
Three-strata RHC risk tool points assigned risk definition	1 Score <1.5	2 Score 1.5–2.49		3 Score ≥2.5
Four-strata RHC risk tool points assigned risk definition	1 Score <1.5	2 Score 1.5–2.49	3 Score 2.5–3.49	4 Score ≥3.5

FIGURE 1 RHC risk tool. RHC: right heart catheterisation; RV: right ventricle; RAP: right atrial pressure; E_a: pulmonary artery elastance; PVR: pulmonary vascular resistance; WU: Wood unit; PAC: pulmonary arterial compliance; CI: cardiac index; SVI: stroke volume index; CE: cardiac efficiency; S_{vO_2}: mixed venous oxygen saturation.

and similar best discriminating cut-offs were identified [37]. The cut-off of 6 WU of PVR is also very close to the cut-off of 5 WU identified in the REVEAL registry [27]. Haemodynamic parameters more related to RV pump function (*i.e.* CI, SVI, S_{vO_2}) already have a defined prognostic role in PAH [10, 11], which is confirmed in our work. In our analysis we also identified CE as an independent prognostic parameter.

When we tested the additive prognostic value to current ESC/ERS risk tools of the eight haemodynamic parameters identified at first follow-up multivariate analyses, they did not demonstrate an additive prognostic value for the all-cause death end-point (exceptions were RAP and, when tested together with COMPERA 2.0 risk tool, high-risk values of PAC, S_{vO_2}, CI and SVI but, as already stated, we cannot exclude that these findings may be related to BNP/NT-proBNP missingness). The limited relevance of haemodynamic parameters in predicting all-cause death in addition to non-invasive parameters (WHO-FC, 6MWD and BNP/NT-proBNP) has already been documented [22, 24, 25, 46, 53] and it was confirmed in our work also by the lower discriminatory power of the elaborated RHC risk tool compared to COMPERA 2.0 (table 7).

However, when we evaluated a combined end-point including all-cause death, non-elective hospitalisation and need of treatment escalation, all haemodynamic parameters, despite the limit of BNP/NT-proBNP missing values, were of additive prognostic value to the ESC/ERS risk tools. Moreover, the elaborated RHC risk tool had a higher discriminative ability for the combined end-point than for all-cause mortality, and the predictive power of the former, for the combined end-point, was at least comparable to that of the other risk tools. Furthermore, when haemodynamic parameters were added to COMPERA 2.0, they demonstrated an additive discriminative power, also when restricting the analysis to only patients with available BNP/NT-proBNP (supplementary table S9). On the other side, the c-index of the current ESC/ERS risk tools was worse for the combined end-point than for all-cause mortality (this behaviour is similar to that of the non-modifiable parameters that emerged from the multivariate analysis: age, gender and PAH aetiology; data not shown). This can be of relevance as in current registries the increasing age and the increasing prevalence of comorbidities may limit the value of all-cause death as the only end-point to investigate the predictors of PAH-related outcome. In fact, up to ∼50% of deaths in patients with comorbidities are not due to PAH in the COMPERA registry [33, 54], while to tailor PAH treatment, it is of utmost importance to define predictors of PAH-related outcome. Moreover, the need for PAH targeted treatment escalation and the hospitalisations are key components of the composite primary end-point of morbimortality driven PAH trials [1–3], proving to be sensitive to PAH treatments whose effect on mortality, instead, is still controversial.

Finally, the practical implication of the results of this study is to provide clinicians with a further tool to discriminate the risk of clinical worsening, which performs at least as well as COMPERA 2.0, when

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TABLE 6 Risk discrimination characteristics of the proposed RHC risk tool three-strata *versus* COMPERA 1.0, FPHR and Bologna simplified risk table strategies for all-cause death and the combined end-point (all-cause death+all-cause non-elective hospitalisation+need of treatment escalation)

	All-cause death				All-cause death+all-cause non-elective hospitalisation +need of treatment escalation			
	RHC risk tool three-strata	COMPERA 1.0	FPHR	Bologna	RHC risk tool three-strata	COMPERA 1.0	FPHR	Bologna
C-statistic (95% CI)	0.619[#¶+] (0.589–0.648)	0.684[#] (0.659–0.708)	0.692[¶] (0.666–0.719)	0.675[+] (0.651–0.700)	0.651 (0.628–0.673)	0.636 (0.615–0.658)	0.641 (0.619–0.663)	0.637 (0.614–0.659)
AIC	4083.62	3982.70	3992.33	4005.33	6106.86	6114.77	6108.13	6114.87
BIC	4088.18	3987.26	3996.89	4009.89	6111.42	6119.33	6112.69	6119.43
1-year event-free survival % (95% CI)								
Low	96.9 (93.9–98.4)	98.5 (96.6–99.3)	98.3 (96.2–99.2)	99.0 (96.9–99.7)	88.5 (84.0–91.8)	84.2 (80.2–87.4)	84.7 (80.5–88.0)	86.2 (81.7–89.6)
Intermediate	93.6 (90.2–95.8)	85.4 (80.5–89.1)	91.9 (87.8–94.6)	88.4 (84.5–91.4)	66.2 (60.7–71.2)	55.6 (49.5–61.3)	63.1 (57.0–68.7)	61.9 (56.6–66.8)
High	79.1 (70.4–85.5)	72.0 (50.1–85.6)	66.4 (54.4–75.9)	78.1 (62.1–88.0)	44.4 (35.1–53.2)	28.0 (12.4–46.0)	33.3 (22.9–44.0)	37.1 (22.7–51.6)

RHC: right heart catheterisation; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry; AIC: Akaike's information criterion; BIC: Bayesian information criterion. [#¶+]: p<0.05 between respective pairs.

TABLE 7 Risk discrimination characteristics of the proposed RHC risk tool four-strata *versus* COMPERA 2.0 risk tool for all-cause death and the combined end-point (all-cause death+all-cause non-elective hospitalisation+need of treatment escalation)

	All-cause death		All-cause death+all-cause non-elective hospitalisation +need of treatment escalation	
	RHC risk tool four-strata	COMPERA 2.0	RHC risk tool four-strata	COMPERA 2.0
C-statistic (95% CI)	0.629[#] (0.599–0.658)	0.726[#] (0.701–0.750)	0.669 (0.645–0.692)	0.655 (0.632–0.678)
AIC	4073.59	3933.11	6080.40	6075.77
BIC	4078.15	3937.66	6084.96	6080.33
1-year event-free survival % (95% CI)				
Low	97.3 (94.0–98.8)	99.4 (97.4–99.8)	89.2 (84.3–92.6)	86.5 (82.2–89.8)
Intermediate–low	97.3 (93.8–98.9)	94.9 (90.1–97.4)	78.3 (71.8–83.5)	73.2 (65.6–79.3)
Intermediate–high	87.5 (82.0–91.3)	80.7 (74.4–85.6)	56.8 (49.6–63.3)	48.7 (41.5–55.5)
High	78.6 (67.5–86.3)	77.3 (53.7–89.9)	36.0 (25.3–46.8)	31.8 (14.2–51.1)

RHC: right heart catheterisation; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHR: French Pulmonary Hypertension Registry; AIC: Akaike's information criterion; BIC: Bayesian information criterion. [#]: p<0.05 for the comparison.

considered alone, and is of added value to COMPERA 2.0, when combined with the non-invasive parameters WHO-FC, 6MWD and BNP/NT-proBNP. This can be of value, for example, considering patients in whom a low-risk profile according to non-invasive criteria is not achievable due to non-PAH-related interfering factors or, on the other side, considering that reaching a low risk of death at 1 year according to current risk tools does not necessarily imply a low risk of clinical worsening [55], and a close follow-up may be relevant in patients at risk of future clinical deterioration in order not to delay further targeted PAH treatment uptitration.

The limitations of our work include the retrospective analyses of a prospective registry as in all other studies on this topic. We documented the lack of an independent prognostic role of cardiovascular comorbidities in a cohort that is younger compared to the ones in which such comorbidities have documented a predictive role [29, 33]. However, this aspect can strengthen our results as it has been documented that comorbidities seem to have a more relevant prognostic role in younger patients [56]. We have not included in our evaluation data from other investigations such as echocardiography, cardiac magnetic resonance and cardiopulmonary exercise test because they were not systematically assessed at both baseline and follow-up.

Finally, BNP/NT-proBNP values were available at first follow-up evaluation only in 22% of patients. Nevertheless, this may be a limitation only in the analyses including COMPERA 1.0 score (in which BNP/NT-proBNP was present in 70% of patients at follow-up in the validating study) [23] or COMPERA 2.0 (for which, however, the maintenance of its discriminative power when BNP/NT-proBNP is missing has been recently described) [57], and we performed sensitivity analyses including only patients with BNP/NT-proBNP values available at first follow-up (supplementary table S7 and S9) showing consistent results. Moreover, BNP/NT-proBNP values are influenced by numerous factors unrelated to PAH severity [58] and, therefore, despite its undoubted prognostic role in patients with PAH, its role in tailoring PAH treatment in patients with comorbidities influencing its blood value remains to be defined.

In conclusion, we identified eight haemodynamic parameters reflecting both RV afterload and RV function being prognostically relevant at first follow-up after starting first-line PAH targeted treatment, and we determined discriminatory cut-offs for the variables not yet defined in the current ESC/ERS PH guidelines risk table. Eventually, we documented that these haemodynamic parameters alone have a predictive value that is comparable to current ESC/ERS risk tools and are of added value to the non-invasive parameters WHO-FC, 6MWD and BNP/NT-proBNP for a combined end-point of all-cause death, non-elective hospitalisation and need of PAH treatment escalation.

Provenance: Submitted article, peer reviewed.

Data availability Data are available on reasonable request. All data relevant to the study are included in the article or its supplementary material. No data provided in the article can be traced to individuals that participated in the study. To allow independent interpretation of the clinical study results, all authors had access to anonymised data, to fulfil their roles under the International Committee of Medical Journal Editors criteria.

Ethics statement: Data from all consecutive patients with pulmonary hypertension who were referred to the Pulmonary Vascular Disease Centre of the Bologna University are included in a prospective electronic registry (ARChivio Elettronico Ipertensione Polmonare) approved by the Ethics Committee of the St Orsola-Malpighi Hospital (109/2016/U /U/Oss).

Conflict of interest: F. Dardi reports consulting fees from Janssen and Chiesi Farmaceutici, and lecture fees from Janssen, in the past 36 months. D. Guarino has nothing to disclose. A. Ballerini has nothing to disclose. R. Bertozzi has nothing to disclose. F. Donato has nothing to disclose. F. Cennerazzo has nothing to disclose. M. Salvi has nothing to disclose. E. Nardi has nothing to disclose. I. Magnani has nothing to disclose. A. Manes participated on the TASC advisory board for Janssen in the past 36 months. N. Galiè reports consulting and lecture fees from Janssen and Ferrer in the past 36 months. M. Palazzini reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events, and support for attending meetings and/or travel from Janssen, in the past 36 months.

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