Influence of age in the assessment of therapeutic response in patients with pulmonary arterial hypertension

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Influence of age in the assessment of therapeutic response in patients with PAH

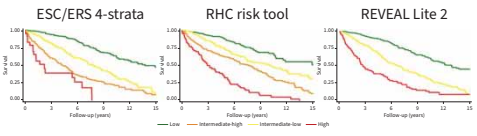
Single-centre cohort study
794 treatment-naive patients with PAH at baseline and 706 patients at first follow-up

To characterise the clinical, functional and haemodynamic profiles, as well as treatment response, across different age groups

	At baseline		Improvement
	≤65 years	>65 years	
WHO-FC	Lower	Higher	Greater improvement in ≤65 years
6MWD	Higher	Lower	
BNP/ NT-proBNP	Lower	Higher	
RV-pre-load	Equal	Equal	Similar improvement
RV afterload	Higher	Lower	
RV pump function	Better	Worse	

To evaluate whether a low-risk haemodynamic profile can be a valid treatment goal in patients aged >65 years not attaining low-risk noninvasive criteria

Age-adjusted survival at first follow-up



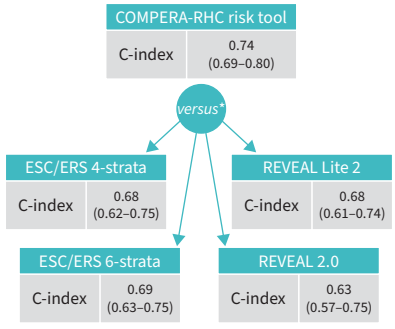
C-index at first follow-up in patients aged >65 years

ESC/ERS 4-strata	RHC risk tool	REVEAL Lite 2
0.65 (0.61–0.70)	0.66 (0.61–0.71)	0.66 (0.62–0.71)

Cox regression of noninvasive risk tools in patients aged >65 years reaching a low RHC risk stratum

	HR (95% CI)	p-value
ESC/ERS 4-strata	1.53 (0.99–2.36)	0.056
REVEAL Lite 2	1.30 (0.84–2.01)	0.240

To assess the additional prognostic value of haemodynamics in complementing noninvasive risk assessment in patients aged <44 years



Haemodynamic evaluation of treatment response appears to be less dependent on age. In patients aged <44 years, integrating haemodynamic parameters into noninvasive risk assessment may enhance prognostic stratification. Additionally, achieving a low-risk haemodynamic profile could be considered a valid treatment goal for patients aged >65 years who fail to reach a low-risk status on noninvasive assessments

Graphical abstract PAH: pulmonary arterial hypertension; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RV: right ventricle; ESC: European Society of Cardiology; ERS: European Respiratory Society; RHC: right heart catheterisation; REVEAL: Registry to Evaluate Early and Long-term PAH Disease Management; HR: hazard ratio; COMPERA: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension. *: p<0.05 for comparisons between all risk tools *versus* the COMPERA-RHC risk tool.

Influence of age in the assessment of therapeutic response in patients with pulmonary arterial hypertension

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Shareable abstract (@ERSpublications)
Compared to noninvasive risk stratification, haemodynamics is less age-dependent, has added prognostic value in patients aged <44 years and can be a valid treatment goal in patients with PAH aged >65 years not reaching a low-risk noninvasive assessment https://bit.ly/42Y1OAn

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Abstract

Background In patients with pulmonary arterial hypertension (PAH), current European guidelines recommend achieving a low-risk profile, primarily based on World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD) and natriuretic peptides. However, these noninvasive parameters are influenced by age. We investigated the impact of age on treatment response and evaluated the prognostic role of haemodynamic-based risk assessments.

Methods Treatment-naïve PAH patients from a single-centre registry were included, stratified by age. Clinical and functional measures and haemodynamics were assessed at baseline and after initial PAH-targeted therapy. Prognostic discrimination was performed using noninvasive (European Society of Cardiology/European Respiratory Society 4-strata, REVEAL Lite 2) and haemodynamic-based risk models (including a purely haemodynamic – RHC – risk tool) with Cox regression and C-statistics.

Results 794 PAH patients were enrolled. Elderly individuals exhibited worse WHO-FC, higher levels of natriuretic peptides and shorter 6MWD, despite lower right ventricular (RV) afterload, likely due to comorbidities and worse RV function. Improvement of WHO-FC, levels of natriuretic peptides and 6MWD is lower in the elderly, despite comparable haemodynamic changes across the age groups. In older patients, noninvasive risk tools overestimated RHC risk tool severity and demonstrated a reduced prognostic accuracy. In patients aged >65 years reaching a low-risk haemodynamic profile, noninvasive risk tools were of no added prognostic value. Conversely, haemodynamics provided independent prognostic information in younger patients.

Conclusions Haemodynamics is less influenced by age than noninvasive risk assessment and is of added prognostic value to noninvasive assessment in younger patients. Achieving a low-risk haemodynamic profile can be a valid therapeutic target when noninvasive criteria are not met in patients aged >65 years.

Introduction

Pulmonary arterial hypertension (PAH) is characterised by pulmonary vascular remodelling leading to increased right ventricular (RV) afterload, ultimately resulting in RV failure and death. In all contemporary registries, elderly patients exhibit a higher risk of all-cause mortality [1–5]; however, whether this is attributable to comorbidities, distinct disease phenotypes, variations in treatment patterns or a reduced response to PAH-targeted therapies remains unclear. This issue is particularly relevant as current registries indicate an increasing age at PAH diagnosis [1, 2, 5, 6].

Moreover, the current European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension guidelines advocate for achieving a low-risk profile as a treatment goal. However,

attaining a low-risk profile based on ESC/ERS risk assessment tools is inherently age-dependent [7]. This dependency may lead to overtreatment of elderly patients, especially when using noninvasive risk stratification tools, since their core parameters (*i.e.* World Health Organization functional class (WHO-FC), 6-min walk distance (6MWD) and brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP) levels) [8–10] can be significantly influenced by age and comorbidities, independent of PAH severity [7, 11–14]. Conversely, for younger, otherwise healthy patients, low WHO-FC, BNP/NT-proBNP levels, and preserved 6MWD may lead to an underestimation of PAH severity, potentially resulting in undertreatment.

The aims of this work were to 1) characterise the clinical, functional and haemodynamic profiles of PAH patients and their response to targeted treatment across different age groups; and 2) assess the prognostic significance of haemodynamic parameters in various age groups and evaluate whether a low-risk haemodynamic profile can be considered a valid treatment goal.

Methods

Population

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki [15] and within the context of routine clinical care. Data were collected from all consecutive treatment-naïve patients, aged ⩾18 years, diagnosed with idiopathic (I), heritable (H) or drug-induced (D)-PAH, connective tissue disease-associated (CTD)-PAH, or congenital heart disease associated (CHD)-PAH. Patients were referred to the pulmonary vascular disease centre at Bologna University (Bologna, Italy) from 2003 to December 2022 and were included in a prospective electronic registry (ARCA) approved by the ethics committee of the St. Orsola-Malpighi Hospital (Bologna) (109/2016/U/Oss). Patient data were pseudonymised, and all patients, or their legally authorised representative, provided written informed consent for data usage. PAH was diagnosed based on mean pulmonary artery pressure (mPAP) ⩾25 mmHg and pulmonary vascular resistance (PVR) >3 Wood Units. Patients were treated according to ESC/ERS pulmonary hypertension guidelines in effect at the time of their follow-up [16–20]. If treatment goals were not achieved, PAH-targeted sequential combination therapy was initiated according to a goal-oriented treatment strategy. Despite variations in treatment recommendations over different study periods, the prescription of sequential combination therapy remained relatively consistent throughout, aligning with the treatment goals established at our centre, as described previously [21, 22].

For analysis, patients were stratified into two groups: younger patients (aged ⩽65 years) and older patients (aged >65 years), based on the prognostic [1] and clinical [6] relevance of this age cut-off, as applied in previous studies [6, 7, 11]. An additional analysis was conducted by dividing the population based on the age tertiles identified at first follow-up (<44 years, 44–63 years and >63 years).

Assessment

Noninvasive and invasive parameters were systematically collected at baseline and 3–6 months after initiation of first-line PAH targeted treatment (first follow-up). The noninvasive parameters included age, gender, PAH aetiology, WHO-FC, 6MWD, creatinine and estimated glomerular filtration rate (eGFR) calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [23], haemoglobin level, BNP or NT-proBNP, body mass index (BMI), diffusing capacity of the lungs for carbon monoxide (D_{LCO}), dysthyroidism and cardiovascular comorbidities such as systemic hypertension, diabetes mellitus, coronary artery disease, atrial fibrillation and obesity (defined as BMI ⩾30 kg·m^{-2}). Pulmonary comorbidity was defined as the coexistence of D_{LCO} <45% and evidence of mild parenchymal lung disease on high-resolution computed tomography (HRCT); if D_{LCO} was missing, HRCT findings alone were considered. BNP/NT-proBNP values were categorised into four groups based on the cut-offs proposed by Hoeper *et al*. [9].

Right heart catheterisation (RHC) was performed in clinically stable conditions after fluid balance optimisation. The recorded parameters included heart rate (HR), right atrial pressure (RAP), systolic/diastolic/mean pulmonary artery pressure (s/d/mPAP), systolic systemic blood pressure, pulmonary arterial wedge pressure (PAWP), cardiac output and mixed venous oxygen saturation (S_{vO_2}). The following derived haemodynamic variables were calculated: PVR ((mPAP−PAWP)/cardiac output), cardiac index (cardiac output/body surface area), stroke volume (cardiac output/HR), stroke volume index (SVI) (cardiac index/HR), pulmonary artery elastance (E_a) (sPAP/stroke volume), pulmonary artery compliance (PAC) (stroke volume/(sPAP−dPAP)), cardiac efficiency (stroke volume/mPAP), RV power (mPAP×cardiac index), RV stroke work index (RVSWI) (SVI×(mPAP–RAP)×0.0136) and the resistance–compliance product (PVR×PAC).

Risk stratification was performed using validated noninvasive risk tools, *i.e.* the ESC/ERS pulmonary hypertension guidelines-recommended four-stratum noninvasive risk tool (ESC/ERS 4-strata) [9, 10]

(supplementary figure S1A) and the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) Lite 2 [8] (supplementary figure S1B). Additionally, a recently proposed RHC-based risk tool was applied, incorporating parameters reflecting RV pre-load (RAP), RV afterload (E_a, PVR and PAC) and RV pump function (cardiac index, SVI, cardiac efficiency and S_{vO_2}), as previously described (RHC risk tool) [24] (supplementary figure S1C). Baseline risk stratification also included assessment using three-stratum risk tools, *i.e.* Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) 1.0 [25], Bologna simplified risk table [22] and REVEAL 2.0 [26].

At first follow-up, the performance of the RHC risk tool, as well as a combined approach integrating the three components of the RHC risk tool (RV pre-load, RV afterload and RV pump function) with the three main noninvasive prognostic parameters (WHO-FC, 6MWD, BNP/NT-proBNP), *i.e.* COMPERA-RHC, already previously described [24], was compared to validated risk models recommended at follow-up [27], including the recently proposed refined six-stratum ESC/ERS risk score (ESC/ERS 6-strata) [28].

Statistics

Baseline and first follow-up variables are presented as n (%) for categorical data and as median (interquartile range (IQR)) for the continuous data. Improvement in WHO-FC, BNP/NT-proBNP and risk class was defined as either an improvement of at least one category or persistence in the most prognostically favourable category.

Patient characteristics were compared using Pearson's Chi-squared test or Fisher's exact test for categorical variables, with Bonferroni correction applied for multiple pairwise comparisons. Continuous variables were compared using the Mann–Whitney test or the Dunn test with Bonferroni correction for multiple pairwise comparisons. The paired Wilcoxon signed-rank test was used to compare changes from baseline to follow-up. A p-value <0.05 was considered statistically significant.

Cox analysis was performed to evaluate the prognostic value of selected variables, considering parameters with a p-value <0.05 as significantly associated with prognosis. Variables that did not meet the proportional-hazards assumption on the basis of Schoenfeld residuals were treated as time-varying covariates. All-cause death was considered as outcome. Causes of death were independently reviewed by two investigators (F. Dardi and D. Guarino) based on available medical records. Patients lost to follow-up or those who underwent lung transplantation were censored as alive at the time of last contact or lung transplantation.

Survival was analysed using Kaplan–Meier curves, and the differences between subgroups were assessed with the log-rank test. For survival analysis, the date of first follow-up RHC was used as the starting point to determine length of survival. The C-statistic was calculated to estimate the discriminatory ability of the risk tools. Calibration was evaluated by the D'Agostino and Nam modification of the Hosmer–Lemeshow Chi-squared approach for survival data. Internal validation of RHC and COMPERA-RHC risk scores was performed using the bootstrap method. Following Steyerberg *et al.*'s [29] recommendations, we applied a standard bootstrap procedure (1000 iterations) and estimated the optimism of each bootstrap sample.

Finally, we developed a simplified COMPERA-RHC risk assessment tool by integrating noninvasive variables with three key haemodynamic parameters. The model with the highest C-index was selected. If multiple models had comparable C-index values, the one with the lowest Akaike Information Criterion (AIC) was chosen.

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

Results

Characteristics of the patient cohort at baseline

The analysis cohort included 794 treatment-naïve PAH patients. The characteristics of the study population have been described in detail previously [24]. Briefly, among the baseline cohort (n=794), a primary outcome occurred in 426 (54%) patients over a median (IQR) follow-up period of 5.8 (2.4–11) years; 19 (2.4%) patients were lost to follow-up.

After a median (IQR) 5 (4–9) months, 706 patients underwent a complete re-evaluation including RHC. 88 patients were not re-evaluated with RHC due to the following reasons: death (n=58, 66%), loss to follow-up (n=17, 19%), lung transplantation (n=1, 1%) and frailty/decline of RHC (n=12, 14%).

Baseline characteristics stratified by age at diagnosis are presented in table 1 and in supplementary tables S1–S4.

TABLE 1 Baseline characteristics according to the age at diagnosis

	All	⩽65 years	>65 years	p-value
Patients	794	534	260	
Age years	55 (39–69)	45 (34–56)	72 (69–76)	
Male	234 (29)	148 (28)	86 (33)	0.120
PAH aetiology				<0.001
I/H/D	425 (53)	299 (56)	126 (48)	
CTD	222 (28)	99 (19)	123 (47)	
CHD	147 (19)	136 (25)	11 (4)	
WHO-FC				<0.001
I	26 (3)	22 (4)	4 (2)	
II	214 (27)	178 (33)	36 (14)	
III	527 (66)	316 (59)	211 (81)	
IV	27 (4)	18 (4)	9 (3)	
6MWD m	387 (295–468) n=750	424 (334–500) n=522	312 (248–388) n=228	<0.001
BNP/NT-proBNP	n=493	n=305	n=188	<0.001
<50/<300 ng·L^{-1}	114 (23)	95 (31)	19 (10)	
50–200/300–650 ng·L^{-1}	116 (24)	69 (23)	47 (25)	
200–800/650–1100 ng·L^{-1}	101 (20)	57 (19)	44 (23)	
>800/>1100 ng·L^{-1}	162 (33)	84 (27)	78 (42)	
Heart rate beats·min^{-1}	80 (71–90)	81 (73–90)	78 (70–86)	0.001
RAP mmHg	6 (4–10)	7 (4–10)	6 (4–10)	0.610
mPAP mmHg	51 (41–62)	56 (44–67)	44 (38–53)	<0.001
sPAP mmHg	84 (67–100)	89 (71–106)	75 (62–88)	<0.001
E_a mmHg·mL^{-1}	1.65 (1.13–2.43)	1.78 (1.13–2.58)	1.47 (1.11–2.02)	<0.001
PAWP mmHg	8 (6–10)	8 (6–10)	8 (7–10)	0.026
SBP mmHg	120 (108–137)	117 (106–132)	129 (115–145)	0.003
Cardiac index L·min^{-1}·m^{-2}	2.3 (1.9–2.8)	2.4 (1.9–3.0)	2.2 (1.9–2.7)	0.016
SVI mL·m^{-2}	29 (23–36)	29 (23–38)	30 (24–35)	0.299
Cardiac efficiency mL·mmHg^{-1}	0.99 (0.67–1.47)	0.90 (0.61–1.44)	1.14 (0.82–1.52)	<0.001
RV power mmHg·L^{-1}·min^{-1}	114 (91–147)	123 (101–159)	101 (78–120)	<0.001
RVSWI mL·mmHg^{-1}	16.4 (12.8–21.8)	18.5 (13.8–23.8)	14.9 (11.7–17.7)	<0.001
RC product min	10 417 (8947–12 453)	11 038 (9328–13 056)	9687 (8396–10 862)	<0.001
PVR WU	10.7 (7.1–15.3)	11.6 (7.5–17.2)	9.1 (6.8–12.5)	<0.001
PAC mL·mmHg^{-1}	0.98 (0.69–1.46)	0.95 (0.66–1.48)	1.08 (0.79–1.45)	0.015
Systemic arterial saturation %	95 (92–97)	95 (92–98)	95 (92–97)	0.589
S_{vO_2} %	65.0 (57.4–71.1)	67.0 (58.5–73.3)	62.3 (55.7–68.6)	<0.001
COMPERA 1.0 baseline risk				<0.001
Low	235 (30)	202 (38)	33 (13)	
Intermediate	472 (59)	284 (53)	188 (72)	
High	87 (11)	48 (9)	39 (15)	
REVEAL 2.0 baseline risk				<0.001
Low	307 (39)	266 (50)	41 (16)	
Intermediate	211 (26)	152 (28)	59 (23)	
High	276 (35)	116 (22)	160 (61)	
Bologna baseline risk				<0.001
Low	143 (18)	128 (24)	15 (6)	
Intermediate	473 (60)	321 (60)	152 (58)	
High	178 (22)	85 (16)	93 (36)	
RHC risk tool baseline risk				0.364
Low	114 (14)	79 (15)	35 (14)	
Intermediate	473 (60)	309 (58)	164 (63)	
High	207 (26)	146 (27)	61 (23)	

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. PAH: pulmonary arterial hypertension; I/H/D: idiopathic/heritable/drug-induced; CTD: connective tissue disease; 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-BNP; 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; SVI: stroke volume index; RV: right ventricle; RVSWI: RV stroke work index; RC: resistance–compliance; PVR: pulmonary vascular resistance; WU: Wood Units; PAC: pulmonary arterial compliance; S_{vO_2}: mixed venous oxygen saturation; COMPERA: Comparative: Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; REVEAL: Registry to Evaluate Early and Long-term PAH Disease Management; RHC: right heart catheterisation.

Characteristics of the patient cohort at follow-up

Clinical, laboratory and haemodynamic variables, noninvasive and RHC risk tools at baseline and at first follow-up, along with their absolute changes (Δ) stratified by age at diagnosis, are presented in table 2 and supplementary tables S5–S8.

A stacked columns chart of risk assessment at baseline and at first follow-up for different risk tools, according to age, is shown in supplementary figure S2.

Due to the number of missing BNP/NT-proBNP values, we conducted sensitivity analyses including only patients with available BNP/NT-proBNP values and excluding patients with two or more missing variables at the first follow-up (n=34, 4.8%) (supplementary tables S6 and S8), yielding comparable results. The comparisons of Δ between patients aged ⩽65 *versus* >65 years were consistent when considering both absolute and percentage changes (table 2 and supplementary tables S5 and S8). Similarly, consistent results were observed regardless of the initial treatment strategy (supplementary table S7).

Survival according to noninvasive risk tools (*i.e.* ESC/ERS 4-strata and REVEAL Lite 2) and the RHC risk tool at first follow-up is presented in supplementary figures S3 and S4 (Kaplan–Meier curves are also provided adjusted for age). Despite the overlap of patients classified as low risk by both the noninvasive and RHC risk tools, the identified low-risk groups demonstrated comparable age-adjusted survival.

Risk categorisation according to RHC risk tool versus noninvasive risk tools

Risk class categorisation was discordant between ESC/ERS 4-strata and RHC risk tool in 418 (59%) patients at first follow-up, and in 345 (49%) patients between REVEAL Lite 2 and the RHC risk tool (supplementary tables S9A and S10A). A similar percentage of discordance was observed when considering only patients with available BNP/NT-proBNP values (supplementary tables S9B and S10B). In both cases, risk reclassification was influenced by age. In particular, when including only patients with available BNP/NT-proBNP values, older age played a role in the reclassification into a lower risk class by the RHC risk tool (supplementary tables S9C and S10C).

The characteristics of patients achieving a low-risk profile according to ESC/ERS 4-strata, REVEAL Lite 2, and RHC risk tools are presented in supplementary tables S11 and S12. Notably, patients identified as low risk by the noninvasive risk tools exhibited a haemodynamic profile with most prognostic factors in the low-risk range.

Added value of haemodynamics to noninvasive risk tools

The added value of the haemodynamic variables included in the RHC risk tool over noninvasive risk tools at the first follow-up is presented in supplementary tables S13 and S14. A significant interaction with age was observed in the prognostic relevance of haemodynamic parameters. Specifically, haemodynamics provided additional prognostic information in younger patients (particularly in the first tertile of age). Similar findings were obtained when restricting the analysis to patients classified as low-risk according to noninvasive risk tools at the first follow-up (supplementary tables S15 and S16).

Discrimination accuracy of the different risk tools at first follow-up

The discrimination accuracy of the RHC and COMPERA-RHC risk scores in the overall population at first follow-up, as measured by the C-index, was 0.629 (95% CI 0.599–0.658) and 0.688 (95% CI 0.660–0.716), respectively. The modified Hosmer–Lemeshow test yielded p-values of 0.08 and 0.57, respectively. The scores were internally validated using the bootstrap method. The mean optimism (0.012 and 0.011, respectively) was subtracted from the apparent performance measure to estimate the internally validated performance, resulting in a C-index of 0.617 and 0.677, with a calibration slope of 1.01 for both scores.

The C-index of the RHC and COMPERA-RHC risk tools at first follow-up across different age groups, compared to other risk assessment tools (ESC/ERS 4-strata, REVEAL Lite 2, ESC/ERS 6-strata and REVEAL 2.0), is shown in figure 1a and b and in supplementary figures S5A and S5B.

In patients aged >65 years, the discriminatory performance of the RHC risk tool was comparable to that of the other risk assessment tools, except for REVEAL 2.0. However, after adjusting the RHC risk tool for gender and PAH aetiology, the discrepancy in discriminatory ability was no longer observed in this age group (C-index of the gender- and PAH aetiology-adjusted RHC risk tool 0.70 (95% CI 0.66–0.75) *versus* C-index of categorical REVEAL 2.0 0.70 (95% CI 0.66–0.74), p-value=0.806; and *versus* C-index of continuous REVEAL 2.0 0.73 (95% CI 0.68–0.77), p-value=0.315).

TABLE 2 Clinical, laboratory and haemodynamic variables at baseline and at first follow-up and their absolute changes (Δ) according to the age at diagnosis

	Baseline	First follow-up	p-value at baseline *versus* first follow-up	Δ	p-value Δ age ⩽65 *versus* >65 years
WHO-FC					<0.001
⩽65 years			<0.001	265 (54)	
I	21 (4)	96 (19)			
II	166 (34)	260 (53)			
III	290 (59)	132 (27)			
IV	13 (3)	2 (1)			
>65 years			<0.001	79 (37)	
I	4 (2)	9 (4)			
II	33 (15)	89 (41)			
III	174 (81)	117 (54)			
IV	5 (2)	1 (1)			
6MWD m					0.001*
⩽65 years (n=471)	434 (352–505)	485 (387–564)	<0.001	42 (3–88)	
>65 years (n=178)	332 (265–402)	360 (290–434)	<0.001	18 (−9–70)	
BNP/NT-proBNP					0.025
⩽65 years (n=78)			0.037	46 (59)	
<50/<300 ng·L^{-1}	25 (32)	35 (45)			
50–200/300–650 ng·L^{-1}	16 (20)	23 (29)			
200–800/650–1100 ng·L^{-1}	24 (31)	11 (14)			
800/>1100 ng·L^{-1}	13 (17)	9 (12)			
>65 years (n=78)			0.255	32 (41)	
<50/<300 ng·L^{-1}	11 (14)	11 (14)			
50–200/300–650 ng·L^{-1}	21 (27)	32 (41)			
200–800/650–1100 ng·L^{-1}	29 (37)	20 (26)			
>800/>1100 ng·L^{-1}	17 (22)	15 (19)			
ESC/ERS 4-strata					<0.001
⩽65 years			<0.001	362 (74)	
Low	120 (24)	281 (57)			
Intermediate-low	184 (38)	97 (20)			
Intermediate-high	169 (35)	101 (21)			
High	17 (3)	11 (2)			
>65 years			<0.001	125 (58)	
Low	14 (6)	44 (20)			
Intermediate-low	71 (33)	65 (30)			
Intermediate-high	114 (53)	96 (45)			
High	17 (8)	11 (5)			
REVEAL Lite 2					<0.001
⩽65 years			<0.001	345 (70)	
Low	211 (43)	291 (59)			
Intermediate	153 (31)	136 (28)			
High	126 (26)	63 (13)			
>65 years			<0.001	104 (48)	
Low	32 (15)	64 (30)			
Intermediate	63 (29)	73 (34)			
High	121 (56)	79 (36)			
RHC risk tool					0.004
⩽65 years			<0.001	292 (60)	
Low	62 (13)	159 (32)			
Intermediate-low	128 (26)	122 (25)			
Intermediate-high	201 (41)	151 (31)			
High	99 (20)	58 (12)			
>65 years			<0.001	153 (71)	
Low	28 (13)	69 (32)			
Intermediate-low	70 (32)	76 (35)			
Intermediate-high	83 (39)	54 (25)			
High	35 (16)	17 (8)			

Data are presented as n (%) or median (interquartile range), unless otherwise stated. WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; ESC: European Society of Cardiology; ERS: European Respiratory Society; REVEAL: Registry to Evaluate Early and Long-term PAH Disease Management; RHC: right heart catheterisation. *: p<0.05 also for % Δ comparisons.

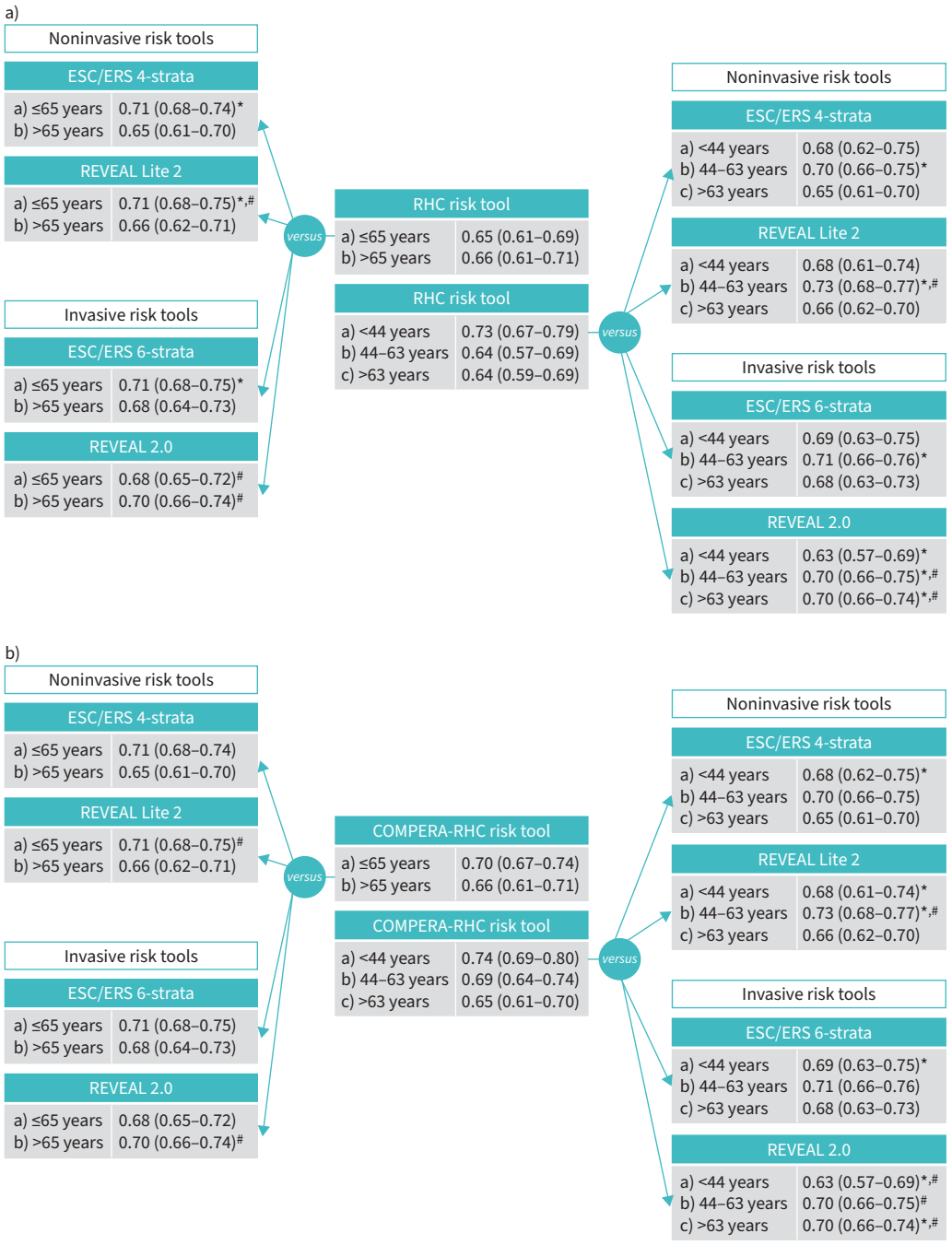

FIGURE 1 C-index of a) right heart catheterisation (RHC) and b) Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)-RHC risk tools compared to other risk tools. ESC: European Society of Cardiology; ERS: European Respiratory Society; REVEAL: Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management. *: p<0.05 *versus* RHC/COMPERA-RHC risk tool for the same age group. #: p<0.05 for the corresponding continuous REVEAL score *versus* RHC/COMPERA-RHC risk tool for the same age group.

The RHC and COMPERA-RHC risk tools demonstrated the highest discriminatory ability in the youngest tertile of patients. In this subgroup, the COMPERA-RHC risk tool outperformed all other risk assessment tools in terms of discriminatory performance (consistent results were documented excluding patients with CHD; data not shown).

Survival according to COMPERA-RHC risk tool at first follow-up is presented in supplementary figure S6.

TABLE 3 Prognostic role of noninvasive risk tools in patients achieving a low right heart catheterisation risk category

	Patients n	HR (95% CI)	p-value
ESC/ERS 4-strata			
⩽65 years	159	4.56 (2.83–7.35)	<0.001
>65 years	69	1.53 (0.99–2.36)	0.056[¶]
Only patients with BNP/NT-proBNP available			
⩽65 years	31	8.01 (1.82–35.36)	0.006[¶]
>65 years	28	1.53 (0.39–6.08)	0.543[¶]
Excluding patients with ⩾2 missing variables at first follow-up			
⩽65 years	156	4.31 (2.63–7.05)	<0.001
>65 years	66	1.70 (1.07–2.69)	0.024[¶]
REVEAL Lite 2[#]			
⩽65 years	159	5.14 (3.10–8.54)	<0.001
>65 years	69	1.30 (0.84–2.01)	0.240[¶]
Only patients with BNP/NT-proBNP available			
⩽65 years	31	5.54 (1.73–17.73)	0.004[¶]
>65 years	28	1.22 (0.46–3.27)	0.687[¶]
Excluding patients with ⩾2 missing variables among WHO-FC, 6MWD and BNP/NT-proBNP			
⩽65 years	156	5.06 (2.99–8.55)	<0.001
>65 years	66	1.36 (0.86–2.13)	0.190[¶]

HR: hazard ratio; ESC: European Society of Cardiology; ERS: European Respiratory Society; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; REVEAL: Registry to Evaluate Early and Long-term PAH Disease Management; WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance. [#]: comparable results were obtained also considering REVEAL Lite 2 as a continuous score. [¶]: p>0.05 when corrected for age.

Prognostic role of noninvasive risk tools in patients achieving a low RHC risk category at first follow-up

Among patients classified as low risk by the RHC risk tool, ESC/ERS 4-strata and REVEAL Lite 2 provided no additional prognostic value in those aged >65 years (table 3). Due to the number of missing BNP/NT-proBNP values, sensitivity analyses were conducted including only patients with BNP/NT-proBNP values available and excluding those with two or more missing variables at first follow-up. These analyses yielded consistent results (table 3).

A simplified COMPERA-RHC risk tool

We found that, after adjusting for unmodifiable independent prognostic factors identified in the RHC risk tool derivation study (age, gender and CTD-PAH aetiology [24]), the three key components of the risk tool (RV pre-load, RV afterload, RV pump function) retained independent prognostic significance (RV pre-load: HR 1.48, 95% CI 1.32–1.66, p<0.001; RV afterload: HR 1.19, 95% CI 1.04–1.36, p=0.012; RV pump function: HR 1.48, 95% CI 1.04–1.35, p=0.010).

Based on these findings, we developed different simplified COMPERA-RHC risk models by integrating noninvasive parameters with only three haemodynamic variables, one for each risk tool component. The C-index and AIC values for these models are reported in supplementary table S17. Notably, combinations that included S_{vO_2} as the RV pump function parameter demonstrated the highest C-index and the lowest AIC. Given its strong prognostic value (confirmed in other registries [28]), S_{vO_2} was incorporated into the final simplified model.

For the RV afterload component, PAC provided the greatest discriminatory ability and the lowest AIC (simplified COMPERA-RHC risk tool) (figure 2). Substituting PAC with either E_a or PVR resulted in C-index values comparable to the original COMPERA-RHC risk tool in the overall population (p=0.122 and p=0.490, respectively) and across different age groups (supplementary figure S7). Survival curves based on the simplified COMPERA-RHC risk tools are presented in supplementary figure S8.

Discussion

In the present study, we evaluated the clinical, functional and haemodynamic profile, as well as the response to PAH-targeted treatment, stratified by age. Additionally, we assessed the prognostic significance

	Low risk	Intermediate-low	Intermediate-high	High risk
WHO-FC	I, II		III	IV
6MWD m	>440	320–440	165–319	<165
BNP ng·L^{-1} NT-proBNP ng·L^{-1}	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100
RAP mmHg	<8	8–9	10–14	>14
PAC# mL·mmHg^{-1}	>1.5	>1.1–1.5	0.7–1.1	<0.7
S_{vO_2} %	>65	>63–65	60–63	<60
Simplified COMPERA-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 2 Simplified Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)-right heart catheterisation (RHC) risk tool. WHO-FC: World Health Organization functional class; 6MWD: 6-min walk distance; BNP: brain natriuretic peptide; NT-proBNP: N-terminal pro-BNP; RAP: right atrial pressure; PAC: pulmonary arterial compliance; S_{vO_2}: mixed venous oxygen saturation. #: substituting PAC with pulmonary artery elastance or pulmonary vascular resistance resulted in a discriminative ability comparable to that of the original COMPERA-RHC risk tool (which includes eight haemodynamic variables).

of haemodynamics across different age groups and investigated whether a low-risk haemodynamic profile can represent a valid treatment goal in patients with I/H/D-PAH, CTD-PAH and CHD-PAH (graphical abstract). The main findings were as follows: 1) elderly patients with PAH had worse WHO-FC, higher BNP/NT-proBNP level and lower 6MWD despite a less severe RV afterload, probably due to a higher prevalence of comorbidities and a worse RV function; 2) the reduced improvement observed in noninvasive risk tools among elderly patients was not attributable to a different response in the RHC risk tool following first-line treatment; 3) in elderly patients, noninvasive risk tools tended to overestimate disease severity compared to the RHC risk tool and demonstrated reduced discriminatory power for all-cause mortality at the first follow-up, which was comparable to that of the RHC risk tool; 4) noninvasive risk tools provided no additional age-adjusted prognostic value in patients aged >65 years reaching a low-risk haemodynamic profile; and 5) the RHC risk tool exhibited the highest discriminatory power for all-cause mortality in younger patients (aged <44 years) and, in these patients, it added prognostic value to noninvasive risk assessments.

In our cohort, younger patients, despite having a more severe RV afterload at baseline, had a better WHO-FC, BNP/NT-proBNP level and 6MWD. This had already been described in other registries [5–7, 11] and randomised control trial cohorts [30]. In our study, this appeared to be related both to the impact of comorbidities and age on noninvasive risk stratification parameters and to worse RV function in the elderly.

WHO-FC, BNP/NT-proBNP and 6MWD are influenced by factors with different distributions and prevalence across age groups, such as eGFR, CTD-PAH aetiology, anaemia and cardiovascular comorbidities, including systemic hypertension, diabetes mellitus, coronary artery disease and atrial fibrillation [7, 11–14]. Therefore, a risk stratification approach based solely on noninvasive parameters seemed to penalise elderly patients when compared to a risk assessment based exclusively on haemodynamics. This was evident both in risk categorisation at baseline and in the reclassification of risk according to the RHC risk tool (supplementary tables S3, S9 and S10). This finding was also reflected in recent studies documenting an older age in high-risk patients according to the ESC/ERS 4-strata at baseline [9, 10] and, when assessed at follow-up, a haemodynamic severity in high-risk patients that was closer to the intermediate-risk rather than the high-risk range values of the ESC/ERS pulmonary hypertension guidelines risk table [28, 31, 32].

The worse RV function in the elderly was suggested, consistent with literature data [5–7, 11, 30], by lower indices of RV afterload (*i.e.* mPAP, PVR, PAC and E_a), associated with RAP and SVI values comparable to those of younger patients, implying RV uncoupling at lower afterload values in the elderly. Similarly, other parameters indicative of RV function, such as RVSWI, RV power and cardiac efficiency, were worse in elderly patients.

Regarding treatment response, our findings aligned with previous studies reporting that the improvement in WHO-FC [33], BNP/NT-proBNP [33, 34] and 6MWD [6, 30, 33], as well as the likelihood of risk stratification improvement or achievement of a low-risk profile according to noninvasive risk tools, was

lower in the elderly [7, 35], regardless of the first-line treatment strategy. However, our study provides new insights by highlighting that the reduced improvement in noninvasive risk tools was not correlated with a different improvement in the RHC risk tool.

This discrepancy resulted in an opposite trend between improvement of the noninvasive risk tools, characterised by a lower percentage of low-risk patients at the first follow-up in the elderly cohort, and the recently proposed RHC risk tool, which showed an equal distribution of low-risk patients at the first follow-up in both age cohorts.

Notably, renal function, a well-known factor influencing BNP/NT-proBNP levels [12], was significantly worse in elderly patients and showed a minimal improvement only in younger patients. This might have contributed to the attenuated BNP/NT-proBNP improvement observed in elderly patients.

In our cohort, we observed a reduced all-cause death discriminative power of noninvasive risk tools in patients aged >65 years, which was comparable to that of the RHC risk tool. This finding aligned with the reduced performance of noninvasive risk assessment in patients with comorbidities [33]. Considering risk tools that include haemodynamics (*i.e.* REVEAL 2.0 and ESC/ERS 6-strata), the RHC risk tool appeared to be inferior only to REVEAL 2.0 in elderly patients. However, after adjusting the RHC risk tool for the unmodifiable covariates, except age, included in REVEAL 2.0 (*i.e.* gender and PAH aetiology), the difference was no longer apparent.

Although patients classified as low risk by the noninvasive risk tools and RHC risk tool exhibited different haemodynamic profiles (better in low-risk patients according to the RHC risk tool) and different WHO-FC, BNP/NT-proBNP levels, and 6MWD (better in low-risk patients according to noninvasive risk tools), the two groups had the same age-adjusted survival (supplementary figures S3 and S4). Moreover, in patients aged >65 years who reached a low-risk profile according to the RHC risk tool, noninvasive risk tools provided no added prognostic value. This suggested that achieving a low risk haemodynamic profile, when the limitation to achieving a low noninvasive risk stratum was not due to haemodynamic impairment, could represent a valid treatment goal in these patients. This was also in line with the recent findings showing that patients classified as intermediate-low risk according to ESC/ERS 4-strata, but with "good haemodynamics", had the same 1-year prognosis as low-risk patients [28].

In the youngest patient cohort (aged <44 years), our analysis demonstrated that the RHC risk tool exhibited the highest discriminative power for all-cause mortality, at least comparable to other invasive and noninvasive risk stratification tools. Furthermore, haemodynamic parameters provided additional prognostic value to noninvasive risk tools within this age group, even among patients classified as low-risk according to noninvasive criteria.

However, due to the substantial number of missing BNP/NT-proBNP values, we were unable to conduct adequate sensitivity analyses to assess this hypothesis exclusively in patients with available BNP/NT-proBNP data. Consequently, we cannot draw definitive conclusions on the additive prognostic role of haemodynamic variables in young patients identified as low-risk according to the ESC/ERS 4-strata model, given recent findings indicating a lack of prognostic significance of haemodynamic parameters in an age-adjusted analysis of patients classified as low-risk by the ESC/ERS 4-strata model in a dataset without missing values [28].

Nonetheless, we performed a sensitivity analysis excluding patients with two or more missing variables among WHO-FC, 6MWD and BNP/NT-proBNP (a scenario in which the REVEAL Lite 2 model has been shown to maintain good discriminative capacity [8]) and obtained supportive results. Importantly, in our study, integrating haemodynamics *ab initio* into risk stratification, rather than using a two-step approach as recently proposed [28], alongside key noninvasive prognostic parameters (*i.e.* the COMPERA-RHC risk tool), appeared to provide the highest discriminative capacity in patients aged <44 years.

Notably, we found that a simplified COMPERA-RHC risk tool incorporating only three haemodynamic variables (figure 2) exhibited equivalent discriminative ability both in the overall cohort and across different age groups.

Finally, the noninvasive risk tools and RHC risk tool identified two low-risk populations with similar causes of death. Mortality due to heart failure was ~50%, underlining that PAH is a progressive disease. Haemodynamics did not seem able to identify patients free from long-term PAH worsening, and close

follow-up is necessary to detect the risk of clinical deterioration. The pathobiology of PAH, therefore, remains complex, and the degree of "progression" of the vascular proliferative disease requires more refined tools to be identified, predicted and prevented.

The limitations of our work include the retrospective analyses of a prospective registry, as in all other studies on this topic. Data come from a single-centre registry, and we did not include investigations such as echocardiography, cardiac magnetic resonance and cardiopulmonary exercise testing because they were not systematically assessed at both baseline and follow-up. Finally, BNP/NT-proBNP values were available at first follow-up evaluation in only 22% of patients. Nevertheless, it has been recently demonstrated that the ESC/ERS 4-strata risk model maintains some of its discriminative power when one of the three parameters is unavailable [36], while the REVEAL Lite 2 risk score maintains good discrimination when only one of the variables with higher prognostic value (*i.e.* WHO-FC, 6MWD and BNP/NT-proBNP) is missing [8]. We performed multiple sensitivity analyses, including only patients with BNP/NT-proBNP values available or excluding patients with two or more missing variables among WHO-FC, 6MWD and BNP/NT-proBNP at the first follow-up, showing consistent results.

In conclusion, risk stratification based on WHO-FC, 6MWD and BNP/NT-proBNP allows for a basic assessment, whose interpretation must consider all interfering factors not related to PAH haemodynamic severity. An accurate, comprehensive haemodynamic evaluation could identify the therapeutic response in a way less biased by these factors. This could be helpful in better tailoring treatment for patients aged >65 years who do not reach a low-risk noninvasive profile, as achieving of a low risk haemodynamic profile in these patients could be a valid treatment goal. In contrast, younger patients (aged <44 years) could obtain a more precise prognostic stratification by systematically adding haemodynamics to a noninvasive risk assessment.

Data availability: Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary material. No data included in the article can be traced back 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.

Provenance: Submitted article, peer reviewed.

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

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