Performance of risk stratification scores and role of comorbidities in older vs younger patients with pulmonary arterial hypertension

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Abbreviations: PAH, pulmonary arterial hypertension; ESC, European Society of Cardiology; ERS, European Respiratory Society; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management 2.0; WHO, World Health Organization; CTD, connective tissue diseases; RHC, right heart catheterization; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; FPHN, French Pulmonary Hypertension Network; COMPERA 2.0, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0; sHTN, systemic hypertension; IHD, ischemic heart disease; AF, atrial fibrillation; DM, diabetes mellitus; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; BNP, brain natriuretic peptide; NT-proBNP, n-terminal pro BNP; 6MWD, 6-minute walking test; CI, cardiac index; DLCO, diffusing lung capacity for carbon monoxide

KEYWORDS:
pulmonary arterial hypertension;
comorbidities;
risk stratification scores;
young;
old

BACKGROUND: Risk scores are important tools for the prognostic stratification of pulmonary arterial hypertension (PAH). Their performance and the additional impact of comorbidities across age groups is unknown.
METHODS: Patients with PAH enrolled from 2001 to 2021 were divided in ≥65 years old vs <65 years old patients. Study outcome was 5-year all-cause mortality. French Pulmonary Hypertension Network (FPHN), FPHN noninvasive, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) and Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL 2.0) risk scores were calculated and patients categorized at low, intermediate and high risk. Number of comorbidities was calculated.
RESULTS: Among 383 patients, 152 (40%) were ≥65 years old. They had more comorbidities (number of comorbidities 2, IQR 1-3, vs 1, IQR 0-2 in <65 years patients). Five-year survival was 63% in ≥65 vs 90% in <65 years. Risk scores correctly discriminated the different classes of risk in the overall cohort and in the older and younger groups. REVEAL 2.0 showed the best accuracy in the total cohort (C-index 0.74, standard error-SE- 0.03) and older (C-index 0.69, SE 0.03) patients, whereas COMPERA 2.0 performed better in younger patients (C-index 0.75, SE 0.08). Number of comorbidities was associated with higher 5-year mortality, and consistently increased the accuracy of risk scores, in younger but not in older patients.
CONCLUSIONS: Risk scores have similar accuracy in the prognostic stratification of older vs younger PAH patients. REVEAL 2.0 had the best performance in older patients and COMPERA 2.0 had it in younger patients. Comorbidities increased the accuracy of risk scores only in younger patients.
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Pulmonary arterial hypertension (PAH) has been historically diagnosed in young adults and predominantly women, but over the last 3 decades, the average age at diagnosis has progressively increased.[1,2] Factors contributing to the growing incidence of PAH in older adults include the increased awareness of the disease, a more accurate diagnostic work-up, the overall ageing of the population and improved prognosis.[3-5]

Goal-directed treatments are based on a multidimensional risk stratification process that follows current European Society of Cardiology/European Respiratory Society guidelines recommendations.[6] Several registry-based studies proposed risk scores simplifying the European Society of Cardiology/European Respiratory Society tool that are regularly used in clinical practice.[1,7,8] Similarly, in the United States the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk calculator and its updated versions are regular part of the prognostication of patients.[9,10]

However, validated risk scores have been derived from relatively young PAH populations and, importantly, their performance in older patients remains unexplored and the potential additional influence of the more common cardiovascular and noncardiovascular comorbidities on risk stratification in older vs younger patients is unknown.

In this multicenter, retrospective, real-world registry study we sought to compare the accuracy of the main risk scores for prognostic stratification of PAH in older (i.e., ≥65 years) vs younger (i.e., <65 years) patients and to assess whether the coexistence of multiple comorbidities might have an impact on the prognosis in these 2 groups.

Methods

Study design

We retrospectively analyzed the data of patients ≥18 years old diagnosed with World Health Organization group 1 PAH from April 4, 2001 to November 11, 2021 at 7 tertiary care centers for the diagnosis and management of PAH (Trieste University Hospital, Trieste, Italy; Hammersmith Hospital, London, United Kingdom; IRCCS Ospedale Policlinico San Martino, Genova, Italy; University Hospital Spedali Civili of Brescia, Brescia, Italy; Fondazione G. Monasterio, Pisa, Italy; Niguarda Hospital, Milan, Italy; Udine University Hospital, Udine, Italy). Group 1 PAH was diagnosed according to 2015 European guidelines and included idiopathic, heritable, and drug-induced PAH, or PAH associated with connective tissue diseases (CTD), congenital heart diseases, HIV, or portal hypertension.[11] All patients underwent right heart catheterization at baseline to confirm pre-capillary pulmonary hypertension (PH) that was defined as mean pulmonary arterial pressure ≥25 mm Hg, pulmonary artery wedge pressure <15 mm Hg, and pulmonary vascular resistance (PVR) >3 Wood units. Complete diagnostic work-up was performed and patients with PH group 2 to 5 were excluded. Specific therapies included phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostacyclin analogs according to the recommendations existing at the time of patient evaluation. Data were completely anonymized. The institutional ethics board approved the study, and informed consent was obtained under the institutional review board policies of hospital administration. The study complies with the ISHLT Ethics statement. The study end-point was 5-year all-cause mortality. Follow-up was closed on 22nd February 2022. Patients were divided according to age in older (≥65 years old) and younger (<65 years old).

Risk assessment

For this specific study the following risk scores were estimated at baseline (see Supplementary Appendix for complete description):

French Pulmonary Hypertension Network (FPHN) and FPHN non invasive,[1] Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA 2.0)[8] and REVEAL 2.0.[10]

Comorbidities

The following comorbidities were collected: systemic hypertension, ischemic heart disease , atrial fibrillation, diabetes mellitus (DM), obesity (i.e., BMI $\geq$ 30 kg/m^2), chronic kidney disease (CKD), and mild-moderate chronic obstructive pulmonary disease (COPD). Patients with COPD were only included in the registry if COPD was not judged to be the underlying etiology of the PH. Finally, the total number of coexisting comorbidities was calculated.

Statistical analysis

Descriptive statistics were expressed as mean $\pm$ standard deviation or median and interquartile range, as appropriate, for continuous variables and counts and percentage for categorical variables. Cross-sectional comparisons between groups were made by the ANOVA test on continuous variables or the nonparametric Mann−Whitney U test when necessary. The chi-square or Fisher exact tests were calculated for discrete variables. Kaplan-Meier curves for 5-year survival were estimated and compared across risk categories for each risk score using the log-rank test, both in the overall population and, separately, in the younger and older patients' groups. First year and average annual mortality rates were derived. Univariable Cox regression models were performed to evaluate the association between each risk score and the primary outcome and multivariable Cox regression models were performed to assess the association between the total number of comorbidities and the primary outcome adjusted by each of the considered risk scores. The same models were then assessed separately in the younger and older patient's groups. An interaction term between age group and number of comorbidities was tested to assess the potential influence of age group in the association with the outcome. Harrell's C indexes were derived in the overall cohort and in the $\geq$65 years old and <65 years old groups as a measure of the accuracy of the risk scores and of the number of comorbidities in outcome prediction. The REVEAL 2.0 score was used as a continuous variable in Cox regression and to derive Harrel's C indexes, whereas was grouped into 3 strata of risk (low = 0-6 points, intermediate = 7-8 points, high=$\geq$9 points) for survival tables and Kaplan Meier curves. A p value <0.05 was considered as statistically significant. Stata version 17 (Stata Corp., College Station, TX) was used for statistical analysis and GraphPad Prism version 9 (GraphPad Software, La Jolla, CA) for illustrations.

Results

Among the 383 patients included, 86% were incident cases. The main characteristics of the overall population are shown in Table 1. Median age was 60 years (IQR 47-73, see Figure S1 for age distribution), 67% of patients were females. The more frequent etiology was idiopathic PAH (37%), followed by CTD-associated PAH (32%). Regarding comorbidities, 41% had systemic hypertension, 13% ischemic heart disease, 7% atrial fibrillation, 25% obesity, 17% DM, 20% CKD, and 21% COPD (mean forced expiratory volume -FEV1- 1.9 $\pm$ 0.5; predicted FEV1 78 $\pm$ 20%; FEV1/forced vital capacity-FVC- 0.7 $\pm$ 0.1). The median number of comorbidities/patient was 1 (IQR 0-2).

Main characteristics in older vs younger patients

Patients $\geq$65 years old were 152 (40% of the overall study cohort, median age 75 years IQR 70-78, 73% were females). Compared to patients <65 years old (n = 231, median age 49 years IQR 39-57), they more likely had CTD-associated PAH and a higher burden of comorbidities, with the exception of obesity and DM (number of comorbidities 2, IQR 1-3, vs 1, IQR 0-2 in <65 years old patients).

Older patients showed similar symptomatic status at presentation, but higher Brain Natriuretic Peptide (BNP)/N-terminal BNP (NT-proBNP) concentrations and lower 6-minute walking test (6MWD) compared to younger patients. Echocardiographic metrics were overall similar, but $\geq$65 years patients had larger left atrial area (21 $\pm$ 7 cm^2 vs 18 $\pm$ 6 cm^2). Invasive right heart catheterization data showed higher pulmonary pressures and PVR in younger vs older, whereas pulmonary artery wedge pressure and cardiac index (CI) were not significantly different (Table 1).

Oral and parenteral treatment, and rates of single, dual, and triple therapy were not different among the 2 age groups.

Risk score distribution and association between risk scores and all-cause mortality risk in older vs younger patients

As shown in Figure 1, risk distribution in younger vs older patients was significantly different for each of the assessed score.

At 5-year follow-up, 78 patients died (20% of the total population). Survival at 5 years was 63% in $\geq$65 years old group vs 90% in patients aged <65 years.

The Kaplan-Meier survival curves estimates according to the risk category in the total cohort and across age groups for each of the assessed risk scores are shown in Figure S2 and in Figure 2, respectively.

Risk scores correctly discriminated 3 different classes of risk in the overall study population and in the older and younger groups (p values<0.05). Table 2 summarizes for each risk score the mortality rates at first year and the average annual mortality in the first 5 years according to risk category and age group. For both first-year mortality and average annual mortality, all the scores were proven to overestimate mortality for the <65 years old group, whereas mortality rates for the $\geq$65 years old were consistent with

Table 1 Characteristics of the Total Study Population and Divided According to Age Group

Demographics	Total *N* = 383	Age<65 *N* = 231 (60%)	Age≥ 65 *N* = 152 (40%)	*p* value
Age (years)	60 (47-73)	49 (40-57)	75 (70-78)	<0.001
Sex male. (%)	125 (33)	84(36)	41(27)	0.055
Incident PAH (%)	326 (86%)	189 (82%)	137 (91%)	0.012
PAH Group (%)				<0.001
1.1- Idiopatic	143 (37%)	83 (36%)	60 (39%)	
1.2- Heritable	16(4)	14(6)	2(1)	
1.3- Drugs and toxin induced	8 (2%)	8 (3%)	0 (0%)	
1.4- PAH associated with	2 (1%)	2 (1%)	0 (0%)	
1.4.1- Connective tissue disease	122 (32%)	47 (20%)	75 (49%)	
1.4.2-HIV	14 (4%)	12 (5%)	2 (1%)	
1.4.3- Portal hypertension	48 (13%)	41 (18%)	7 (5%)	
1.4.4-Congenital heart disease	29 (8%)	23 (10%)	6 (4%)	
1.4.5- Schistosomiasis	1 (<1%)	1 (<1%)	0 (0%)	
Comorbidities				
sHTN (%)	157 (41%)	66 (29%)	91 (60%)	<0.001
IHD (%)	49 (13%)	18 (8%)	31 (20%)	<0.001
AF (%)	26 (7%)	8 (3%)	18 (12%)	0.001
Obesity (BMI ≥ 30 kg/m^2) (%)	94 (25%)	65 (30%)	29 (19%)	0.029
DM (%)	64 (17%)	34 (15%)	30 (20%)	0.200
CKD (%)	77 (20%)	26 (11%)	51 (34%)	<0.001
COPD (%)	80 (21%)	39 (17%)	41 (27%)	0.017
Total number comorbidities	1 (0-2)	1 (0-2)	2 (1-3)	<0.001
Clinical variables				
WHO class (%)				0.50
I	23 (6%)	16 (7%)	7 (5%)	
II	130 (35%)	83 (36%)	47 (32%)	
III	181 (48%)	104 (45%)	77 (53%)	
IV	40 (11%)	26 (11%)	14 (10%)	
Systolic blood pressure	123 ± 18	121 ± 17	126 ± 19	0.012
Heart rate	80 ± 15	82 ± 16	78 ± 14	0.029
6 MWT (meters)	301 ± 141	337 ± 144	249 ± 119	<0.001
NT-proBNP (pg/ml)	790 (255, 2228)	484 (168, 1583)	1290 (281, 2700)	0.010
BNP (pg/ml)	245 (88, 597)	198 (77, 484)	328 (154, 762)	0.012
eGFR CKD-EPI	76 ± 27	87 ± 25	58 ± 21	<0.001
Hb (g/dl)	14 ± 2	14 ± 2	14 ± 2	0.36
BRMP2+ (%)	12(3)	11(5)	1(1)	0.024
DLCO predicted (%)	49 ± 20	54 ± 21	42 ± 16	<0.001
Echocardiography				
TAPSE (%)	1.7 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	0.25
RA area (cm^2)	24 (7)	24 (7)	25 (7)	0.069
RV dysfunction (%)	231 (65%)	144 (67%)	87 (62%)	0.32
LA area (cm^2)	19 (7)	18 (6)	21 (7)	<0.001
RVSP (mmHg)	75 (23)	77 (25)	73 (21)	0.15
Pericardial effusion (%)	94 (27%)	58 (28%)	36 (26%)	0.72
TR moderate-severe (%)	177 (49%)	67 (46%)	78 (54%)	0.109
Right heart catheterization				
mRA (mmHg)	8 (4)	8 (5)	8 (4)	0.15
sPAP (mmHg)	75 (20)	78 (21)	70 (18)	<0.001
dPAP (mmHg)	30 (11)	32 (11)	28 (10)	<0.001
mPAP (mmHg)	46 ± 13	48 ± 13	42 ± 11	<0.001
PAWP (mmHg)	10 (4)	10 (5)	9 (4)	0.27
PVR (WU)	10 (6)	10 (6)	9 (5)	0.041
CI (l/min/m^2)	2.4 (0.8)	2.4 (0.8)	2.3 (0.8)	0.16

(*continued on next page*)

Table 1 (*Continued*)

Demographics	Total *N* = 383	Age<65 *N* = 231 (60%)	Age≥ 65 *N* = 152 (40%)	*p* value
Prognostic scores				
FPHN	1 (0, 2)	1 (0, 2)	1 (0, 2)	0.24
FPHN noninasive	0 (0, 1)	1 (0, 1)	0 (0, 1)	0.029
COMPERA 2.0	2 (1, 2)	1 (1, 2)	2 (1, 2)	0.026
REVEAL 2.0	9 (7, 12)	8 (6, 11)	10 (8, 12)	<0.001
Treatment				
PDE5-i/sGS-s (%)	147 (64)	154 (67)	93 (61)	0.302
ERA (%)	233 (61)	140 (61)	93 (62)	0.888
Prostanoids (%)	14 (4)	9 (4)	5 (3)	0.501
Monotherapy (%)	190 (50)	121 (53)	69 (46)	0.45
Dual combination therapy (%)	139 (36)	78 (34)	61 (40)	0.47
Triple combination therapy (%)	7 (2)	4 (2)	3 (2)	0.9

6MWT, 6-minute walking test; AF, atrial fibrillation; BNP, brain natriuretic peptide; BRMP2+, mutation of bone morphogenetic protein receptor type 2; CI, cardiac index; CKD, chronic kidney disease; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; COPD, chronic obstructive pulmonary disease; DLCO, diffusing lung capacity for carbon monoxide; DM, diabetes mellitus; dPAP, diastolic PAP; eGFR CKD-EPI, estimated glomerular filtration rate with chronic kidney disease epidemiology collaboration calculator; ERA, endothelin receptor antagonist; FPHN, French Pulmonary Hypertension Network; Hb, haemoglobin; IHD, ischemic heart disease; LA, left atrium; RVSP, right ventricle systolic pressure; mPAP, mean PAP; NT-proBNP, n terminal BNP; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PDE5-i, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; RA, right atrium; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management 2.0; RV, right ventricle; sGS-s, soluble guanylate cyclase stimulators; sHTN, systemic hypertension; sPAP, systolic PAP; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

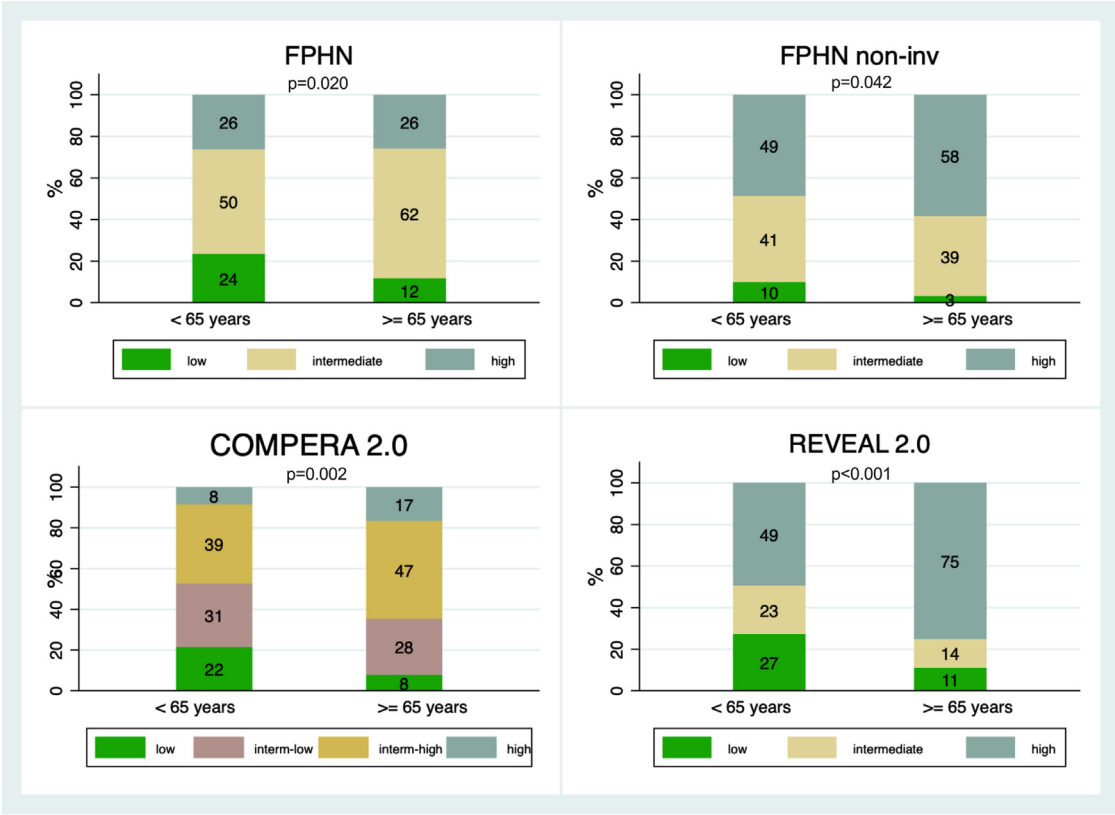

Figure 1 Distribution of risk scores categories in <65 years old vs ≥65 years old patients. Chi-square *test was used for comparison.* COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN, French Pulmonary Hypertension Network; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management.

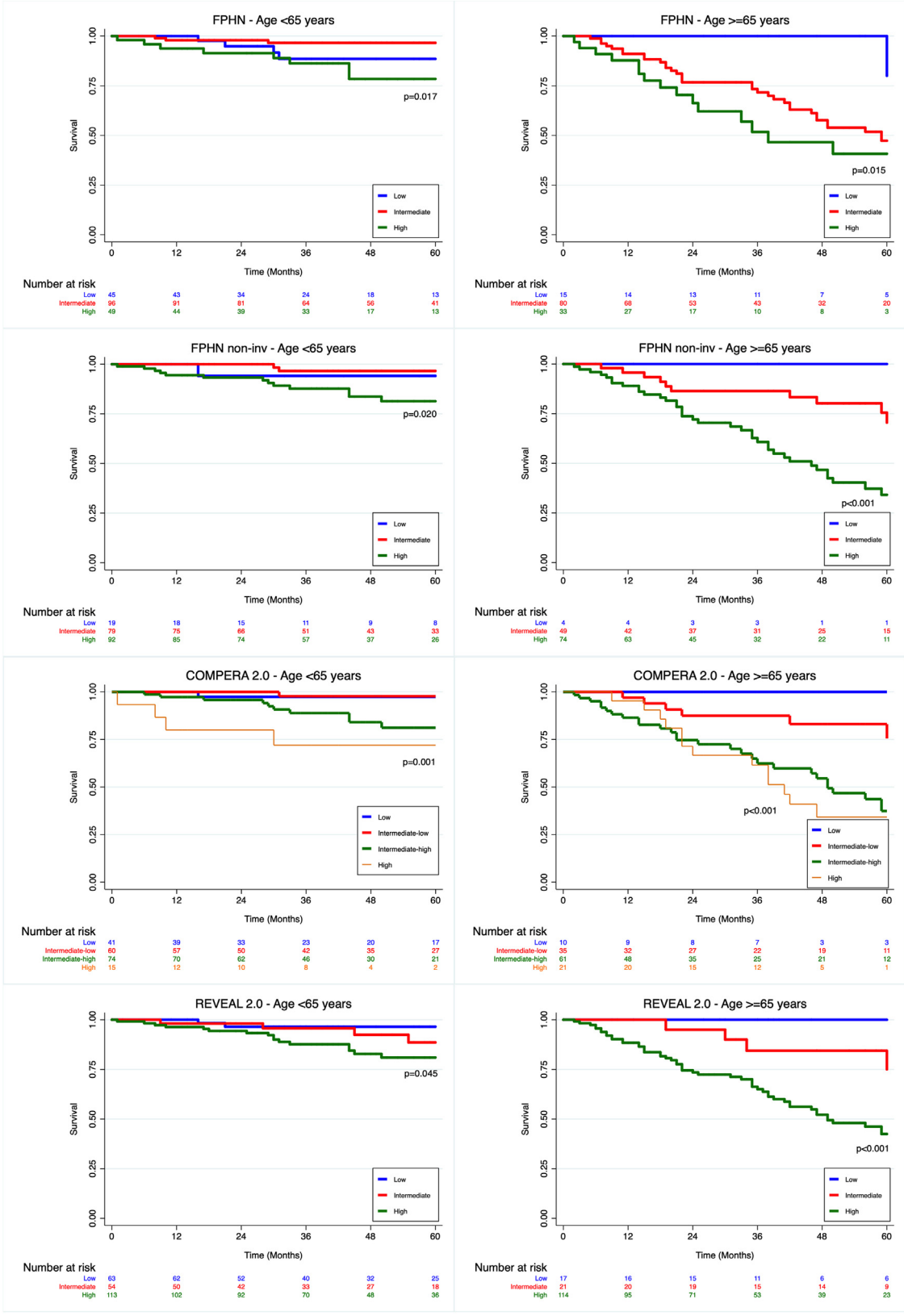

Figure 2 Kaplan-Meier survival curves according to the risk category in 65 years old vs ≥65 years old patients for each of the assessed risk scores. COMPERA 2.0, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0; FPHN, French Pulmonary Hypertension Network; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management

Table 2 First Year Mortality and Average Annual Mortality in the Total Population and in <65 Years Old vs ≥65 Years Old Patients Across Different Risk Scores Categories

	FPHN			FPHN non-inv			COMPERA 2.0			REVEAL 2.0		
	Total	<65 years	≥65 years	Total	<65 years	≥ 65 years	Total	<65 years	≥ 65 years	Total	<65 years	≥ 65 years
First-year mortality												
Low Risk	0	0	0	0	0	0	0	0	0	0	1	0
Intermediate-Low risk[a]	4	2	8	1	0	4	1	0	2	1	2	0
Intermediate-High risk	-	-	-	-	-	-	7	2	12	-	-	-
High Risk	8	5	11	7	5	10	10	18	4	7	3	10
Average annual mortality												
Low Risk	2	2	2	1	1	0	0	1	0	1	0	0
Intermediate-Low risk[a]	5	1	11	2	1	5	2	0	4	2	2	4
Intermediate-High risk	-	-	-	-	-	-	8	3	14	-	-	-
High Risk	8	4	16	8	4	15	14	8	17	8	3	13

COMPERA 2.0, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0; FPHN, French Pulmonary Hypertension Network; REVEAL 2.0, Registry to Evaluate Early and Long-term 2.0.

Note that rates are calculated per 100 person-years.

[a]=for FPHN, FPHN non-inv and REVEAL 2.0 scores refers to intermediate class of risk.

the estimated annual mortality by guidelines (i.e., low risk <5%, intermediate risk 5%-20%, high risk >20%), although with <20% rates for the high risk category.[6].

Predictive accuracy of risk scores in older vs younger patients

The 4 risk scores were all associated with the risk of 5-year mortality (Table S1). In the total study cohort the highest accuracy in outcome prediction was observed for the REVEAL 2.0 score (C index 0.74, standard error [SE] 0.03), followed by the COMPERA 2.0 score (C index 0.73, SE 0.03) (Figure 3 and Table S1). When the predictive accuracy was tested separately according to the age group, risk scores demonstrated a similar accuracy in ≥65 years old vs <65 years old patients, with COMPERA 2.0 showing numerically higher, but not statistically significant different, accuracy in <65 years old vs ≥65 years old patients (p = 0.22). REVEAL 2.0 score had the highest accuracy in the older group (C index 0.69, SE 0.03) and COMPERA 2.0 score in the younger group (C index 0.75, SE 0.08) as well as in the older group (C index 0.69; Figure 3 and Table S1).

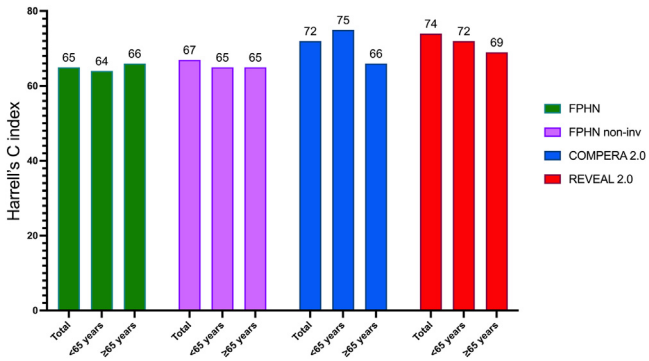

Figure 3 Accuracy of risk scores in the 5-years mortality outcome prediction in the overall study cohort and according to age group. *Standard errors are reported in Table S1.* COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN, French Pulmonary Hypertension Network; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management.

Prognostic implications of comorbidities

In the overall study population, the total number of comorbidities was independently associated with an increased risk of mortality after adjustment for each risk score with the exception of REVEAL 2.0 score (Figure 4 and Table S2). Noteworthy, when assessed separately according to age group, the association between the total number of comorbidities and the risk of death was statistically significant in patients <65 years after adjustment for each risk score, whereas there was not significant association with mortality risk in ≥ 65 years old patients, with a significant interaction between age group and total number of comorbidities after adjustment for all the risk scores (Figure 4 and Table S2). Consistently, the addition of the total number of comorbidities to each risk score determined an increased accuracy in patients <65 years old but not in patients ≥65 years (Figure 5). Among single comorbidities, obesity and CKD increased the most the accuracy of risk scores in younger patients (Table S3).

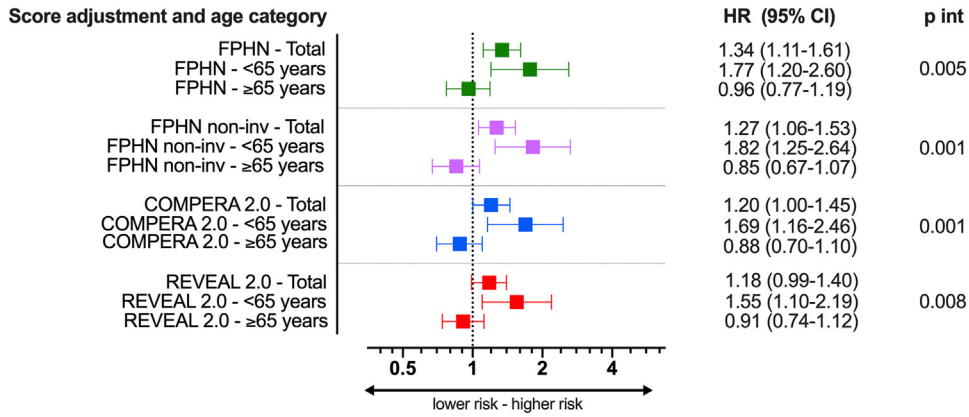

Figure 4 Risk scores adjusted association between total number of comorbidities and the 5-years mortality risk in the overall study cohort and in 65 years old vs ≥65 years old patients. *Note: HRs are reported for every additional comorbidity (minimum 0 to maximum 7). Interaction is tested between age group and total number of comorbidities.* CI, confidence interval**;** COMPERA 2.0, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension 2.0; FPHN, French Pulmonary Hypertension Network; HR, hazard ratio; p int, p for interaction; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management.

Discussion

In this study we demonstrated a good predictive accuracy of the more largely adopted risk scores both in older (≥65 years old) vs younger (<65 years old) PAH patients, supporting their use in clinical practice for the survival prediction regardless of age. However, we observed some age-related differences in their performance which might suggest an age-oriented selection of the preferential risk stratification tool. All risk scores correctly estimated the mortality risk in the older group, but had a general tendency to overestimate it in younger patients.

Despite the higher comorbidity burden in older patients, we found a different prognostic influence of comorbidities in younger vs older patients and the addition of the total number of coexisting comorbidities to the risk scores incremented their accuracy only in the younger group. This could promote the research of alternative prognostic parameters according to patients' age.

Characteristics of older vs younger patients

Demographics of PAH has changed in the last decades. Particularly age at diagnosis has progressively increased in the major international registries and this also implied important changes in the current patients' characteristics.[1,7,9,12] In our multicenter cohort of PAH median age at diagnosis was 60 years, higher compared to the FPHN and REVEAL registry, but lower compared to the COMPERA registry,[1,7,9] and patients ≥65 years old were about 33% of the overall population. We defined older patients if

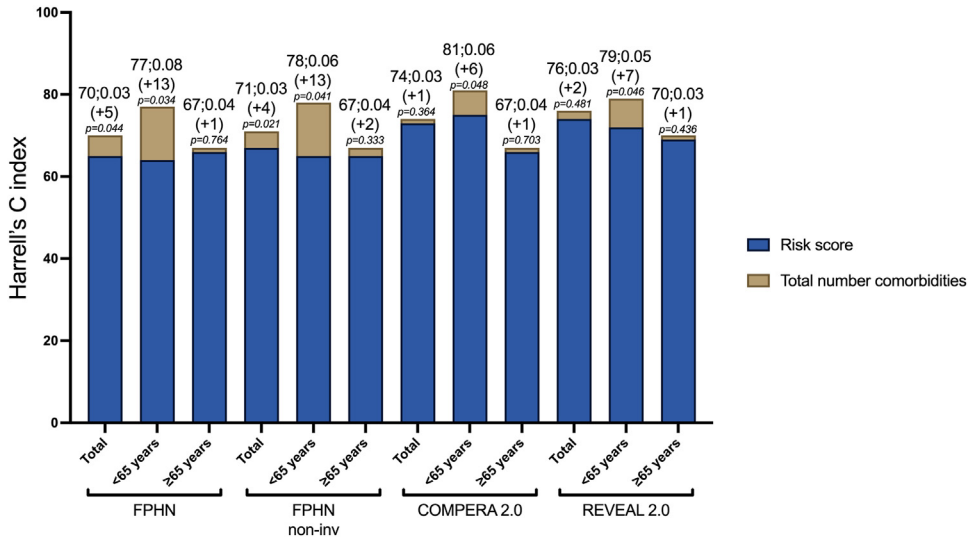

Figure 5 Incremental accuracy in the 5-years mortality outcome prediction provided by the addition of the total number of comorbidities to risk scores in the overall study cohort and according to age group. Absolute value and *standard errors are reported; in brackets the increase in C-statistics obtained with the addition of total number of comorbidities (significant p values < 0.05).* CI, confidence interval**;** COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN, French Pulmonary Hypertension Network; HR, hazard ratio; REVEAL 2.0, Registry to Evaluate Early and Long-term PAH Disease Management.

≥65 years old at baseline according to previous studies adopting the same cut-off.[2,13-15] Moreover, the age distribution in our cohort was skewed around the 65 years threshold as demonstrated by the wide difference in median age between younger (49 years) and older (75 years) group.

Age also influences the underlying characteristics of PAH patients and may influence the decisions on treatment. In trials populations, higher proportion of CTD-associated PAH, worse symptoms and more impaired functional status despite a less severe hemodynamics have been reported in older age subgroups.[14] This was confirmed by several observational and registry studies which also reported, as expected, a heavier comorbidity burden in older patients.[12,13,16] Consistently, in our study patients ≥65 years old had higher BNP/NT-proBNP and worse 6MWD despite lower mean pulmonary arterial press and PVR. Diffusing lung capacity for carbon monoxide was also lower as previously reported.[17,18] The prevalence of single comorbidities in our cohort was lower compared to the COMPERA cohort and more similar to the REVEAL and Swedish registries.[16,19,20] The higher number of concomitant comorbidities we have observed with increasing age was already reported in previous analyses from large registries.[16,19]

Age has been also associated with less aggressive treatment in PAH,[12,13,16] being this explained by different reasons including less responsiveness of pulmonary vasculature of older patients to pulmonary vasodilators, lower adherence to treatment, higher exposure to tolerability issues and adverse reactions.[2,21,22] Comorbidities are directly involved since they can affect tolerability/risk of adverse events, and politherapy may reduce adherence.[23] In our population, older and younger patients only apparently received similar therapy, since patients in the older group presented worse clinical status, higher risk and should have been theoretically treated more aggressively. The relatively low rate of combination therapy might be explained by the long period of inclusion, with patients enrolled earlier less likely being treated with upfront combination therapy, and by the predominance of incident cases, as previously found in studies on incident PAH.[11,16]

Outcome of older vs younger patients and performance of risk scores

With increasing age, the overall survival of PAH proportionally decreases.[12,13,16,24] In the Swedish Registry, patients 18 to 45 years had about 1.5 and 2.5 highest transplant-free 5-year survival compared to 65 to 74 and ≥75 years patients.[16] Our results were consistent with the literature, with 1.5 to 2-fold higher mortality in ≥65 years old patients over the observation period. More limited response to pulmonary vasodilators, less aggressive treatment approach and the competing risk of dying for alternative causes are reasons for the age-related difference in outcome.[2] Since in older patients the clinical assessment has multiple challenges, validation of the current strategies for risk stratification in older categories is essential. As previously reported,[16] in our cohort ≥65 years old patients presented higher risk at baseline. Of note, the accuracy of risk scores in older vs younger subjects was not significantly different for 3 of the 4 tested risk stratification tools, and REVEAL 2.0 score demonstrated the highest accuracy in the ≥65 years subgroup. The inclusion in the equation of age, specific etiology (CTD-associated PAH), renal function and diffusing lung capacity for carbon monoxide may have contributed to the increased performance of the REVEAL 2.0 compared to other risk scores in the older category.[5,10,17,25] COMPERA 2.0 showed, higher nonstatistically significant accuracy in the <65 years vs ≥65 years old subgroup and its performance in the younger group was the highest among the assessed risk scores. The 3 variables-based categorization, with 6MWD potentially affected by the reduced mobility related to ageing and NT-proBNP/BNP influenced by age per se, likely explain the age-related difference in the performance of COMPERA 2.0. Our data, thus, support current guidelines' recommendations on risk stratification, which do not discriminate between younger and older patients,[6] but at the same time introduce the concept of a differential approach to risk stratification based on age which claims for further investigations in future larger studies. However, regardless the adopted risk score, in <65 years old patients survival curves demonstrated lower mortality estimates as compared to the predicted mortality according to the guidelines risk classification, whereas in ≥65 years old patients mortality estimates were consistent with the predicted mortality, despite the <20% mortality in the high risk category.[6] This might be explained by the better strategies of treatment which are probably more effective and more aggressively implemented in the younger classes.

The role of comorbidities

With increasing age, the overall number of comorbidities in PAH population has increased.[12,16,23] The comorbidities more frequently associated with PAH have been demonstrated to potentially exert a negative prognostic influence,[25-28] and can reduce adherence to treatment by promoting drug interaction and adverse effects.[23,29] The epidemiology of comorbidities differs between younger and older patients, whereas less is known about the different prognostic impact across age groups. According to former studies,[12,16,19] in our population comorbidities were more frequent in the older subgroup, with the exception of obesity and DM. Nevertheless, after adjustment for the stratification risk scores, the total number of coexisting comorbidities was significantly associated with higher mortality only in patients <65 years old with a significant interaction with age category, and it was able to increase the accuracy of the risk stratification scores in younger but not in older patients. To the best of our knowledge, this is the first demonstration of an age-related difference in the prognostic implications of comorbidities in the setting of PAH. A potential explanation is that the high prevalence of comorbidities in older patients might have diluted the impact on prognosis. Alternatively, other aspects such as the reduced effect of PAH-specific therapies in older groups could have a predominant impact

on the outcome. It has also to be noted that, after the addition of the number of comorbidities, REVEAL 2.0 score confirmed the highest accuracy in the overall population and in ≥65 years old patients, and COMPERA 2.0 score in <65 years old patients.

Limitations

As with all observational studies, our study suffers from the common bias due to its retrospective design. The study population was enrolled in selected tertiary care centers for PAH management, thus imposing a selection bias. Due to the long enrollment period, we cannot exclude changes in therapeutic strategies across the study period. Since the period of inclusion closed before the release of the last European guidelines for the management of PAH,[6] diagnostic criteria were based on the 2015 version of guidelines.[11] The relatively small sample size limited the strength of our findings, which need to be tested in larger cohorts. Risk scores were calculated at baseline, thus no information is available on their performance when re-calculated at follow-up. A simple sum of comorbidities instead of a validated comorbidity index, that is, Charlson index, was chosen as the Charlson index includes age and some variables which are specific etiologies of type 1 PAH (i.e., CTD, HIV, liver diseases). Alternative factors associated with worse outcome in older individuals, such as socio-economic conditions and frailty, were not available and should be investigated in future dedicated studies.

Conclusions

In this multicenter real-world registry, older patients (i.e., ≥ 65 years old) were about 33% of the overall PAH population and presented distinguishing characteristics and higher mortality compared to younger patients. Available risk scores showed similar accuracy in the prognostic stratification of older vs younger patients supporting their systematic implementation in clinical practice regardless of age. Among the assessed risk scores, REVEAL 2.0 was the more accurate in mortality risk prediction of older patients, whereas COMPERA 2.0 was the more accurate in younger patients. Finally, although the higher burden was observed in the older group, comorbidities were associated with higher mortality only in younger patients, increasing the accuracy of all the evaluated risk scores in this subgroup. Our findings can be considered an additional step towards the individualization of care in PAH patients.

Disclosure statement

D.S. has been an advisory board member for Merck, Novo Nordisk, Acceleron, Janssen, Novartis and has received speaker fees from Novartis, none related to the present study. P.A. has received speaker and/or advisor fees from Janssen and MSD generally related to the topic of PAH, and speaker and/or advisor fees from AstraZeneca, Novartis, Boehringer Ingelheim, Bayer, Vifor, and Daiichi-Sankyo outside the scopes of the present work. F.L.G. has received speaker and/or advisor fees from Janssen and MSD related to the topic of PAH but not to the scope of this paper.

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