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The impact of cardiovascular comorbidities associated with risk for left heart disease on idiopathic pulmonary arterial hypertension: Data from the Hellenic Pulmonary Hypertension Registry (HOPE)

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Abstract

Whereas younger female patients were diagnosed with idiopathic pulmonary arterial hypertension (IPAH) in 1980s, it is now frequently encountered in elderly patients with cardiovascular comorbidities (CVCs) associated with increased risk for left heart disease. We present data until November 2019 regarding specific features and clinical outcomes of IPAH population from the Hellenic Pulmonary Hypertension Registry (HOPE). Patients were divided

into two groups based on the presence of ≥ or <3 CVCs, arterial hypertension, diabetes mellitus, obesity, presence of coronary artery disease, or atrial fibrillation. Overall, 77 patients with IPAH (55.1 [interquartile range, IQR: 24.1] years, 62.8% women) have been recorded. Fifteen patients (19.2%) had ≥3 CVCs, while 25 (32%) were over 65 years old. Patients with ≥3 CVCs were older, presented an almost equal female to male ratio, walked less in 6-min walk test, and had lower mean arterial pulmonary pressure and pulmonary vascular resistance at baseline than patients with less CVCs. Fewer patients with ≥3 CVCs received PAH-specific treatment compared to patients with less comorbidities ($n = 11$ [73.3%] versus $n = 58$ [95.5%], $p = 0.02$). During a median follow-up period of 3.8 (IQR: 2.7) years, 18 patients died (all-cause mortality 24.3%). Male sex and older age were independent predictors of mortality and/or lung transplantation, while CVCs did not have a significant impact on clinical outcomes. In this nationwide, register-based study, the epidemiology of IPAH involves older patients with CVCs, who seem to have less hemodynamic compromise, but worse functional impairment and are treated less aggressively with PAH pharmacotherapy.

KEYWORDS
cardiovascular comorbidities, elderly, idiopathic pulmonary arterial hypertension, survival, targeted therapy

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare heterogeneous disease of the pulmonary vasculature, defined by an increased mean pulmonary artery pressure (mPAP) >20 mmHg, a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and elevated pulmonary vascular resistance.[1] PAH may be associated with a wide spectrum of diseases, such as connective tissue disease, congenital heart disease, liver disease, HIV infection, or schistosomiasis.[2] It could also be induced by drugs and toxins, or be familial. When no other etiology is identified, it is characterized as idiopathic (IPAH), representing the most common subtype of PAH.[3]

Over the past decades, considerable changes have been observed in the IPAH phenotype. While the mean age of patients with IPAH in the first US National Institutes of Health registry was 36 years,[4] IPAH is now more frequently diagnosed in patients of advanced age, resulting in mean age at diagnosis between 50 and 65 years in current registries.[3,5] Furthermore, the formerly known female predominance may not be now present in the elderly patients.[6] Consequently, IPAH diagnosis in an aging population has led to an increasing prevalence of cardiovascular or other comorbidities that may affect the current therapeutic approach and clinical outcomes.[3]

The COMPERA registry revealed that patients with IPAH with cardiovascular comorbidities (CVCs) ("atypical IPAH") share features of both typical IPAH and PH associated with heart failure and preserved ejection fraction (HFpEF), suggesting that there may be a continuum between these conditions.[7]

Prompted by the increasing number of IPAH patients with an "atypical" phenotype in Greece, we aimed to determine particular differences in baseline clinical and hemodynamic parameters and trends in medical management among patients with IPAH with and without CVCs associated with increased risk for left heart disease (i.e., left ventricular diastolic dysfunction). In addition, we aimed to identify if CVCs among other risk factors predict outcome in patients with IPAH.

METHODS

Study design, patient population, and clinical variables

The Hellenic Pulmonary Hypertension Registry (HOPE) is an investigator-initiated, ongoing, national registry, launched in January 2015 which continues to enroll patients with all forms of pulmonary hypertension (PH).[5]

The Hope Registry has been approved by the Institutional Review Board of each 1 of the 10 participating PH expert centers in Greece, according to the Declaration of Helsinki. All patients provided written informed consent for their inclusion in the HOPE Registry. Documentation is web-based (PAH tool by Inovultus Lda, Portugal) and has been previously described.[5] The project is endorsed by the Hellenic Society for the Study of Pulmonary Hypertension.

The cut-off date for the baseline data analysis of the present study was November 30, 2019. A review of the database was conducted on December 31, 2020, when new deaths or lung-transplantation events up to this date were added. Inclusion criteria for this study were a diagnosis of IPAH according to the definitions of the 2015 guidelines,[2] age ≥18 years, and availability of data from right heart catheterization (RHC) at diagnosis showing an mPAP ≥25 mmHg, a PCWP ≤ 15 mmHg, and PVR ≥ 3WU.[2] Other causes of PH were excluded by echocardiography, pulmonary function testing, chest computed tomography scans, ventilation-perfusion scan, laboratory investigations of blood and serum and liver ultrasound using a standard diagnostic algorithm.[2] Patients with drug-related or heritable PAH were also excluded.

The present analysis contains both newly diagnosed (incident) and "prevalent" patients, that is, patients who were diagnosed with IPAH > 3 months before enrollment in the registry. Baseline data, that is, data at the time of first visit of patients at the PH center were collected. Patients with a full assessment at their first visit in PH expert centers before 2015 were prospectively enrolled in the registry as prevalent patients, using data collected after 2015. Patients who died before 2015 were not enrolled in the registry.

The following CVCs associated with left heart disease were recorded: arterial hypertension, diabetes mellitus (any type), obesity (body mass index [BMI]: ≥30 kg/m^2), and presence of evidence of significant coronary artery disease (CAD) (history of myocardial infarction, history of percutaneous coronary intervention, angiographic evidence of CAD [>50% stenosis in ≥1 vessel], previous coronary artery bypass grafting, or stable angina) according to the modified AMBITION criteria,[8] as well as the presence of atrial fibrillation, a well-known marker of left heart disease. Smoking habits have been also analyzed.

In terms of baseline clinical variables, World Health Organization Functional Class (WHO FC), six-minute walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP), hemodynamic parameters, echocardiographic markers of left heart disease, lung function test parameters including diffuse lung capacity for carbon monoxide were analyzed. Data regarding supportive treatment and PAH targeted pharmacotherapy at baseline were also recorded. Only 50% of patients had a complete follow-up with functional and hemodynamic parameters. Therefore, our primary outcome was a composite endpoint of death and/or lung transplantation. We also searched for predictors of the composite endpoint that were collected at the baseline visit.

Risk stratification

An abbreviated version of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification strategy was used to estimate 1-year mortality risk. As proposed by Hoeper et al.,[9] we analyzed WHO FC, 6MWD, NT-proBNP, right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SvO2) at baseline if available. The cut-off values proposed in the European guidelines[2] were graded 1–3 (1: low risk, 2: intermediate risk, and 3: high risk). For each patient, the sum of all grades was divided by the number of available variables and rounded to the next integer to define the risk group.[9,10]

Statistical methods

Patients were divided into two groups based on the presence of < versus ≥3 CVCs for left heart disease (i.e., left ventricular diastolic dysfunction). Data were presented as mean ± standard deviation (SD) for continuous variables with normal distribution, and as median and interquartile range (IQR) for non-normally distributed variables. Categorical variables were presented as frequencies and percentages (%). Continuous variables were compared using the t-test for independent samples or the Mann–Whitney U test, while the χ^2 test or the Fisher exact test was used to assess categorical variables. Kaplan Meier analysis was conducted to estimate free-transplantation survival. Log-rank test was used to identify a statistical difference in survival between various groups.

Univariate Cox regression analysis was used to identify predictors of mortality and/or lung transplantation in the total IPAH cohort. Variables without missing values with a $p < 0.2$ in univariate Cox regression analysis, as well as variables with clinical significance, were combined together to build multivariable prediction models. Given the small sample size and the number of events we could not use more than four variables in a model. We present as the main model, the one that entails variables of utmost clinical significance for our

population. Akaike information criterion (AIC) was used to test for the best model fit. Results are presented as hazard ratio (HR) and 95% confidence Intervals (CI). A p-value < 0.05 was considered statistically significant in this study. Data were analyzed using the SPSS version 26.0 and R 4.1.0 software.

RESULTS

Baseline characteristics

Till November 24, 2019, a total of 528 patients with PH from 10 PH centers from all over Greece had been enrolled into the HOPE registry. Initially, 85 patients had been registered at the IPAH cohort. After exclusion of patients not fulfilling the inclusion criteria for the present analysis (i.e., two patients without an available RHC and six patients not fulfilling the hemodynamic criteria for a diagnosis of precapillary PH), 77 patients with IPAH were eligible for the present study (Figure 1). Baseline demographic and clinical characteristics of the overall IPAH population and among IPAH patients with ≥ or <3 CVCs associated with increased risk for left heart disease are presented in Table 1.

Of patients with IPAH (median age 55.1; IQR: 23.2 years) almost two-thirds (62.8%) were women, 32.5% were elderly (>65 years old), and half of them (50.6%) were severely symptomatic (NYHA III/IV). Less than half of patients ($n = 37$, 48.1%) were newly diagnosed. Arterial hypertension and obesity were the most frequently encountered CVCs in more than one-third of the overall IPAH cohort, followed by diabetes mellitus affecting one-fifth of patients. More than one-third of

patients were current or ex-smokers. About one-fifth of the IPAH population ($n = 15$, 19.5%) had at least three comorbidities, while the rest of them had two or less cardiovascular comorbidities. Patients with ≥3 CVCs were older, mainly elderly, had a higher BMI and more severe symptoms (73.3% NYHA III/IV) compared to patients with less CVCs (Table 1). No difference was detected in sex distribution between the two groups; however, the female to male ratio in the group with more CVCs morbidities was 1.1/1, while in the group with less comorbidities was 1.8/1.

In terms of functional capacity, IPAH patients with more CVCs achieved a shorter 6-MWD than patients with less CVCs. RHC revealed a significantly lower mPAP and PVR in patients with CVCs compared to patients with less CVCs (Table 1). Vasoreactivity test was recorded in 35 patients with IPAH (45.4%) and was positive in 7 patients (20%), of which only 1 had three cardiovascular comorbidities. In terms of echocardiographic parameters, the median left ventricular ejection fraction was 60%, with no significant difference in the left atrial area between patients with more or less three CVCs. Lung function tests were performed in 46 patients (59.7%) and revealed no difference in diffusion lung capacity (DLCO) or forced expiratory volume and Tiffennau index between the two groups (Table 1).

Risk stratification

According to the applied risk score all patients had available more than four out of six variables required for its calculation, with the majority of them ($n = 60$, 78%) having at least five variables available.
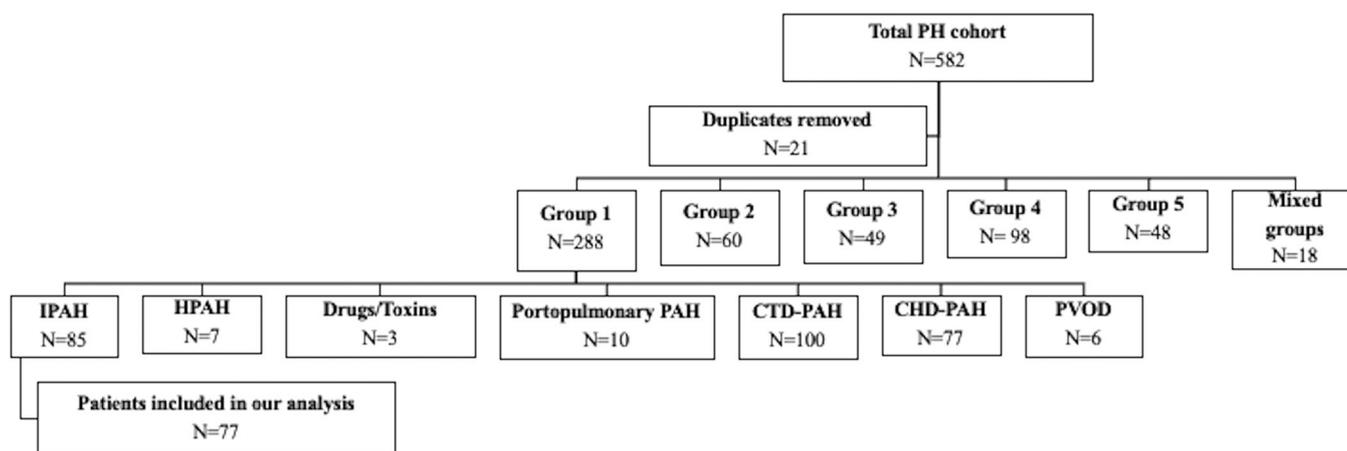
FIGURE 1 Flow chart of the study participants. CHD-PAH, pulmonary arterial hypertension related with congenital heart disease; CTD-PAH, pulmonary arterial hypertension related with connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; PVOD, pulmonary vascular obstructive disease.

TABLE 1 Baseline characteristics in IPAH with ≥3 and <3 cardiovascular comorbidities for left heart disease in Greece.

	IPAH	≥3 CVCs	<3 CVCs	p value*
Subjects, n (%)	**77**	15 (19.5)	62 (80.5)	
Female, n (%)	48 (62.3)	8 (53.3)	40 (64.5)	0.423
Age, years (IQR)	55.1 (24.1)	69.8 (17.8)	52.1 (23.3)	**0.001**
Elderly (>65 years old), n (%)	25 (32.5)	10 (66.7)	15 (24.1)	**0.002**
BMI, (kg/m^2) (IQR)	27.9 (6.7)	30.9 (4.1)	27.1 (5.8)	**<0.001**
Comorbidities, n (%)				
Arterial hypertension	30 (38.9)	13 (86.6)	17 (27.4)	**<0.001**
Diabetes	18 (23.4)	13 (86.6)	4 (6.4)	**<0.001**
Atrial fibrillation	9 (11.7)	5 (33.3)	4 (6.4)	**0.004**
Coronary artery disease	9 (11.7)	6 (40)	3 (4.8)	**<0.001**
Obesity (BMI > 30 kg/m^2)	26 (33.8)	12 (80)	14 (22.6)	**<0.001**
Smoker, n (%)	28 (36.4)	6 (40)	22 (35.4)	0.712
Functional parameters and biomarkers				
NYHA, n (%)				**0.049**
I/II	38 (48.4)	4 (26.6)	34 (54.8)	
III/IV	39 (50.6)	11 (73.3)	28 (45.2)	
6-MWD, M (IQR), (n = 55)	420 (148.5)	322 (197.8)	431 (128.3)	**0.003**
NT-proBNP, pg/ml (IQR) (n = 55)	503 (1125.6)	556 (969)	481.5 (1269.9)	0.862
SatO$_2$, % (IQR)	93 (8)	88 (14)	94 (8.0)	0.157
Echocardiography				
LVEF (%) (IQR)	60 (5)	60 (5)	60 (5)	0.808
LA diameter (cm) (IQR)	3.7 (0.5)	3.8 (0.4)	3.1 (0)	0.209
Hemodynamics				
RAPm, mmHg (IQR)	9 (6)	10 (10)	8 (6)	0.146
mPAP, mmHg (IQR)	48 (17)	39 (19)	49 (16)	**0.011**
PAWP, mmHg (IQR)	11 (6)	11 (4)	10 (6)	0.259
PVR, WU (IQR)	8.8 (6.1)	6.4 (4.2)	9.8 (5.2)	**0.008**
CO, L/min	4.2 (2)	4.7 (2.2)	4 (1.6)	0.766
CI, L/min/m^2 (IQR)	2.3 (0.9)	2.4 (0.8)	2.3 (0.9)	0.968
SVO$_2$, % (IQR) (n = 63)	66.5 (9.2)	65 (7.2)	68 (8.2)	0.094
Risk stratification, n (%)				0.435
Low risk	28 (55.8)	5 (33.3)	23 (37.1)	
Intermediate risk	40 (42.9)	7 (46.6)	33 (53.2)	
High risk	9 (1.3)	3 (20.0)	6 (9.6)	
Spirometry (n = 57)				
FEV1 % (IQR)	83 (25.7)	82.8 (18.1)	83 (32.3)	0.775
FEV1/FVC % (IQR)	79 (16.7)	80 (17.5)	79 (13.6)	1
TLC % (IQR)	77.1 (15.1)	77 (7.9)	77.2 (15.0)	0.665
DLCO/SB % (IQR)	58 (41)	51.5 (27.4)	59.7 (39.2)	0.395

(Continues)

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T A B L E 1 (Continued)

	IPAH	≥3 CVCs	<3 CVCs	*p* value*
Medication, *n* (%)				
Oxygen	24 (31.2)	7 (46.7)	17 (27.4)	0.149
Diuretics	44 (57.1)	10 (66.7)	34 (54.8)	0.406
Anticoagulants	29 (37.6)	7 (46.7)	22 (35.5)	0.423
CCB	9 (11.7)	1 (6.7)	6 (9.7)	0.366
PAH treatment, *n* (%)	**69 (89.6)**	**11 (73.3)**	**58 (93.5)**	**0.042**
Monotherapy	45 (65.2)	9 (81.8)	36 (62.1)	0.734
Combination	24 (34.8)	2 (18.2)	22 (37.9)	
Double combination	23 (29.9)	2 (18.2)	21 (33.8)	1.00
Triple combination	1 (1.3)	0 (0)	1 (1.7)	
PDE5 inhibitors	44 (63.8)	9 (81.8)	35 (60.3)	0.803
Riociguat	2 (2.9)	0 (0)	2 (3.4)	1.00
ERA	43 (62.3)	5 (45.5)	38 (65.5)	**0.05**
Prostanoids	6 (8.7)	0 (0)	6 (10.3)	0.591

Note: Continuous variables are presented as median value with interquartile range (IQR). Categorical variables are presented as absolute count and percentage (%).

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blockers; CI, Cardiac Index; DLCO, diffusing capacity for carbon monoxide; ERA, endothelin receptor antagonists; FC, functional class; FEV1, forced expiratory volume during the first second of expiration; FVC, forced vital capacity; IPAH, idiopathic pulmonary arterial hypertension; LA, left atrium; LVEF, ejection fraction of left ventricle; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; 6-MWD, six-minute-minute walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAWP, pulmonary artery wedge pressure; PDE5, phosphodiesterase type 5 inhibitors; PVR, pulmonary vascular resistance; SatO2, arterial oxygen saturation on air at rest; SvO2, oxygen saturation in pulmonary artery; TLC, total lung capacity.

*Statistical significance is defined as *p* value < 0.05.

Eventually, more than half of patients with IPAH (55.8%) were stratified as low-risk at baseline, only 1.3% were considered high risk, while the rest of them were classified as intermediate risk (Table 1). In general, no significant difference was detected in terms of risk stratification between patients with ≥3 or <3 CVCs for left heart disease (Table 1).

Medical therapy

As far as supportive therapy is concerned, about one-third of patients with IPAH received oxygen therapy at baseline, more than half of them were on diuretics, while almost 4 out of 10 received an oral anticoagulant. No difference was noted between groups. All patients with a positive vasoreactivity test received a calcium channel blocker.

Almost 9 out of 10 patients with IPAH received a targeted PAH medical therapy at baseline. In the total cohort, the majority of patients received monotherapy (64.3%), while more than one-third of them were on combination therapy. Phosphodiesterase type 5 (PDE5) inhibitors and endothelin receptor agonists (ERAs) have been equally administered among IPAH patients. Prostanoid use was limited in 8.7% of patients with IPAH at baseline.

Fewer patients with ≥3 CVCs received a targeted PAH therapy compared to patients with less cardiovascular comorbidities (73.3% vs. 95.5%, *p* = 0.02) (Table 1). The majority of patients with ≥3 CVCs received monotherapy, while only two patients were on combination therapy (18.2%). PDE5 inhibitors were administered in 72.7% of patients with ≥3 CVCs followed by ERAs, which were used in less than half of patients. A preference for ERAs has been noted among IPAH patients with less CVCs compared to those with more (65.5% vs 45.5%, *p* = 0.049; (Table 1).

Survival

The survival status of almost all patients could be ascertained with the exception of 3 (3.8%) patients

(one from the group with more CVCs and two from the IPAH group with less than three CVCs) who were lost to follow-up. These patients were excluded from survival analysis. Of the whole cohort ($n = 74$), all-cause mortality was 24.3% over a median follow-up period of 3.8 (IQR: 2.7) years (73.7 deaths in 1000 patient-years). There were 18 deaths; 6 in the IPAH group with ≥3 CVCs (mortality rate, 42.8%) and 12 in the IPAH group with <3 CVCs (mortality rate, 19.6%). The cause of death is presented in Table 2. Two patients, a 42-year-old man and a 35-year-old woman with IPAH without cardiovascular comorbidities, underwent lung transplantation at the University Hospital of Vienna, Austria. Overall, the 1-, 3-, and 5-year free transplantation survival rates were 90.4%, 79.7%, and 67.0%, respectively. Males, elderly, NYHA III/IV, and patients with an increased risk score for 1-year mortality had significantly reduced survival at 1-, 3-, and 5 years compared to females, younger patients (≤ 65 years old), non- or mildly symptomatic patients (NYHA I/II), and patients at low risk (Table 3 and Figure 2). No significant difference in survival was detected in patients with IPAH and ≥3 CVCs compared to those with less CVCs (Table 3).

Predictors of death/or transplantation

In univariable analysis (Table 4), mortality and/or transplantation in patients with IPAH was predicted by male sex (HR: 3.64, 95% CI: 1.45–9.13, $p = 0.006$), age (HR: 1.04, 95% CI: 1.01–1.07, $p = 0.02$) and particularly advanced age (HR: 4.60, 95% CI: 1.82, 11.59, $p = 0.001$), smoking (HR: 3.12, 95% CI: 1.21–7.07, $p = 0.018$), advanced NYHA class (HR: 4.04, 95% CI: 1.46–11.19, $p = 0.007$), worse risk status for 1-year mortality (HR: 2.31, 95% CI: 1.18–4.54, $p = 0.015$) and DLCO/SB% (HR: 0.93, 95% CI: 0.88–0.98, $p = 0.007$). Cardiovascular comorbidity burden for left heart disease was not a predictor of long-term mortality or transplantation.

Several predictors without missing values have been combined in quadruplets to find the best model that could better predict clinical outcomes (Supporting Information: Table 1). We present as the main model to predict the composite endpoint of mortality and/or transplantation, the one that included sex, age, risk stratification status, and CVCs, since it entails variables of major clinical significance. According to this model only male sex and advanced age independently predicted mortality and/or transplantation (Figure 3).

DISCUSSION

In this real-life nationwide cohort, almost one to five patients (19.5%) with IPAH have equal or more than three CVCs associated with increased risk for left heart disease, which is in accordance with European cohorts.[11] Compared to IPAH patients with fewer CVCs, patients with ≥3 CVCs have a different phenotype in terms of sex distribution and age and different clinical and

TABLE 2 Cause of death.

	Total IPAH cohort	≥3 CVCs for LHD	<3 CVCs for LHD
Death	18	6	12
Sudden cardiac death	1	1	0
Left heart failure	2	2	0
Right heart failure	5	1	5
Sepsis	2	0	3
Respiratory failure	2	1	1
Unknown	5	1	2
Lung transplantation	2	0	2

Abbreviations: CVCs, cardiovascular comorbidities; IPAH, idiopathic pulmonary hypertension; LHD: left heart disease

TABLE 3 Free-transplantation survival in IPAH cohort.

Variables	Sex		Age		NYHA		CVCs for LHD		Risk stratification score		
	Male	Fe-male	>65 years	≤65 years	I/II	III/IV	≥3	<3	Low	Intermediate	High
1-year survival, %	81.5	95.7	76.0	95.9	97.3	83.5	92.9	89.9	96.3	89.3	77.8
3-year survival, %	57.2	93.5	56.3	91.3	88.4	70.9	76.2	80.5	92.4	76.6	50.0
5-year survival, %	48.4	77.9	32.8	88.4	84.9	48.8	50.0	78.0	61.6	54.4	50.0
p value*	<0.001		<0.001		0.012		0.26		0.04		

Abbreviations: CVCs, cardiovascular comorbidities; LHD, left heart disease; NYHA, New York Heart Association.

*Statistical significance is defined as p value <0.05.
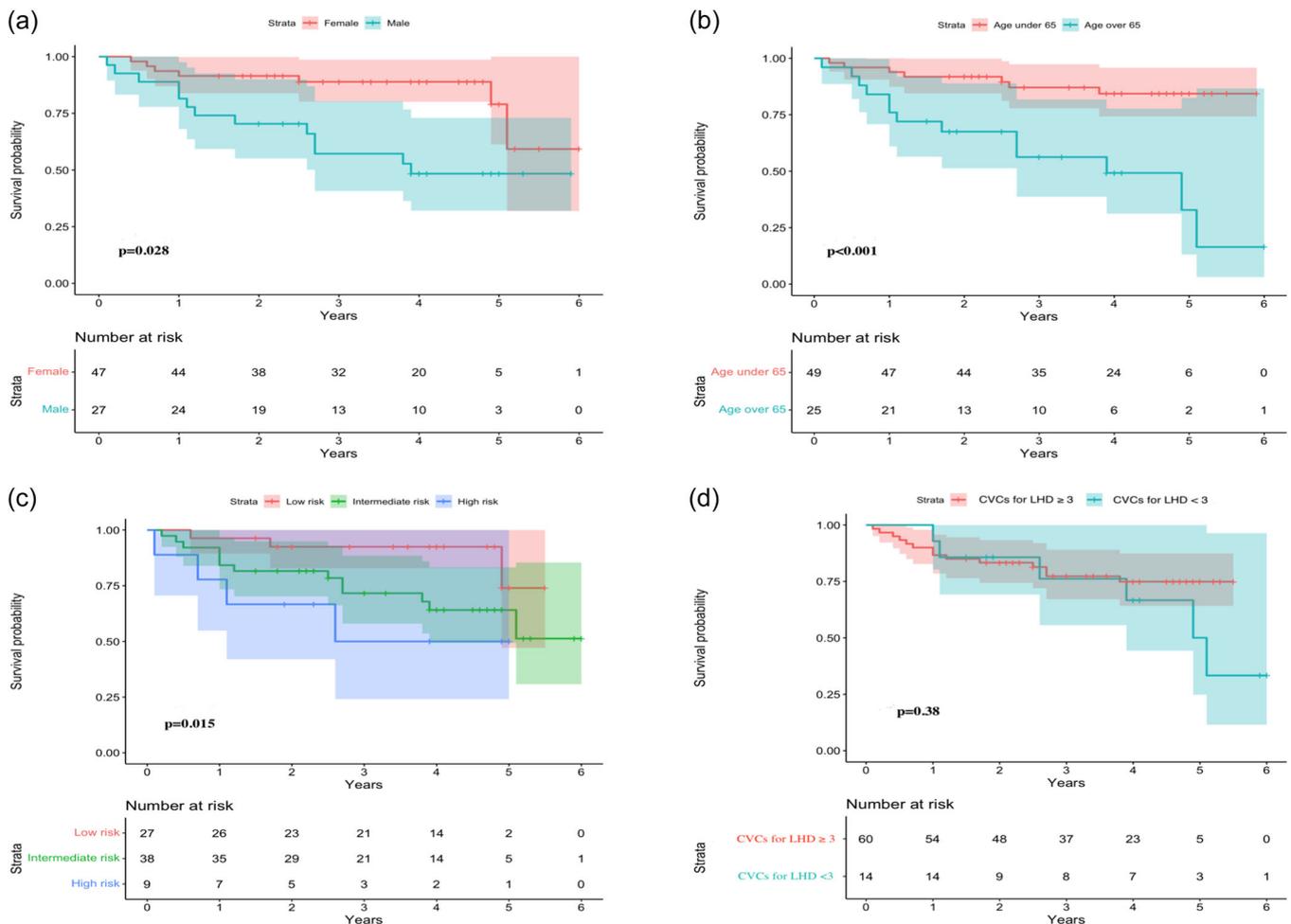
FIGURE 2 Survival in patients with idiopathic pulmonary arterial hypertension (IPAH) according to: (a) sex (male and female), (b) age (>65 years old and ≤65 years old), (c) risk score (low-, intermediate-, high-risk for 1-year mortality), and (d) the presence of cardiovascular comorbidities (CVCs) for left heart disease (LHD) (≥3 and <3). $p < 0.05$ indicates statistical significance between the groups.

hemodynamic characteristics (worse functional status, lower mPAP, and PVR).

Recently, a cluster analysis of 841 IPAH patients from the COMPERA registry[12] has demonstrated three different IPAH phenotypes; the "typical" IPAH phenotype including young predominantly female patients, without cardiovascular comorbidities, non-smokers, with a preserved DLCO ≥ 45%; the "HFpEF like" phenotype describing women of older age with frequent comorbidities, no smoking history, and DLCO mostly ≥45%; and the cardiopulmonary phenotype consisting of mostly elderly men with a history of smoking, abundant cardiovascular risk factors, and a low DLCO. In accordance with our results, patients with the "HFpEF like" phenotype and the cardio-pulmonary phenotype presented worse functional status and better hemodynamics compared to patients with "typical" IPAH.[12] Patients from these two clusters were predominantly on monotherapy, while the

majority of patients with "typical" IPAH received a combination therapy. In our cohort, less patients with ≥3 CVCs associated with a risk for left heart disease received PAH therapy at baseline compared to those with less CVCs. Only 18.2% of patients with ≥3 CVCs received a combination therapy at baseline, which is in line with a former analysis of the COMPERA registry on patients with typical and "atypical" PAH.[7] However, no difference was noted between the two groups with regard to the total number of administered PAH drugs, in contrast to the COMPERA registry in which less patients with "atypical" IPAH received a combination therapy compared to those with a "typical" IPAH.[7] Recently, a secondary analysis from the GRIPHON trial on patients with a significant number of CVCs for left heart disease showed that selexipag as "add on" therapy reduced the risk of a morbidity/mortality event compared to placebo irrespective of a patient's comorbidity status.[13]

TABLE 4 Predictors of composite endpoint of death and/or lung transplantation.

Variables	Univariable analysis		
	HR	95% CI	p value*
Male sex	3.64	1.45, 9.13	**0.005**
Age, years	1.04	1.01, 1.07	**0.02**
Elderly (>65 years old)	4.60	1.82, 11.59	**<0.001**
BMI, kg/m²	0.94	0.87,1.03	0.19
Smoking	3.12	1.21, 7.07	**0.018**
Risk factors for LVDD (≥3)	1.53	0.58, 4.08	0.38
NYHA (III/IV)	4.04	1.46, 11.19	**0.007**
Risk score (for every added point)	2.31	1.18, 4.54	**0.015**
6MWD, m	0.997	0.992, 1.002	0.22
NT-proBNP, ng/L	1.00	1.00, 1.00	0.084
mRAP, mmHg	1.05	0.95, 1.16	0.27
mPAP, mmHg	0.98	0.95, 1.02	0.56
PAWP, mmHg	0.99	0.87, 1.13	0.89
PVR, WU	0.98	0.88, 1.08	0.64
CO, L/min	0.95	0.70, 1.29	0.77
CI, L/min/m²	0.86	0.44, 1.68	0.66
SVO2%	0.95	0.91, 1.00	0.05
FEV1%	0.98	0.94, 1.02	0.29
FEV1/FVC%	1.01	0.97, 1.06	0.51
TLC%	0.99	0.96, 1.03	0.699
DLCO/SB%	0.93	0.88, 0.98	**0.007**
PAH therapy (Yes/No)	1.31	0.29, 5.73	0.72
PAH therapy (For every added drug)	1.30	0.62, 2.73	0.48

Abbreviations: BMI, body mass index; CI, Cardiac Index; CI, confidence intervals; DLCO/SB, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume during the first second of expiration; FVC, forced vital capacity; HR, hazard ratio; 6-MWD: six-minute walk distance; mRAP, mean right atrial pressure; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; SvO2, oxygen saturation in pulmonary artery; TLC, total lung capacity.

*Statistical significance is defined as p value <0.05.

A worse survival was noted in patients with the cardiopulmonary phenotype compared to the other two clusters in the COMPERA cohort.[12] Our study, did not demonstrate a difference in survival between patients with more and less CVCs, but this may be attributed to the small number of participants and the fact that we distinguished patients only according to their cardiovascular phenotype irrespective of their pulmonary phenotype. To distinguish patients in two groups, we used the presence of <3 versus ≥3 CVCs associated with left heart disease as done in the AMBITION study[14] (plus atrial fibrillation). As stated in a previous analysis of the COMPERA registry, the use of the AMBITION criteria did not manage to distinguish patients into distinct disease phenotypes, as no difference in survival had been detected between the "atypical" and the "typical" IPAH,[7] implying that additional parameters, such as age, sex, and DLCO% may be needed to build a certain patient phenotype (as demonstrated in a cluster analysis).[12] This hypothesis was confirmed as these factors seem to predict mortality and/or transplantation. In specific, male sex, advanced age, worse functional status, a modified ESC risk stratification status, smoking history, and reduced DLCO predicted survival.

Risk status at baseline predicted mortality in our study; however, it was not an independent predictor in multivariable analysis. An explanation could be the small sample size and the lack of a significant number of high-risk patients in our cohort. As stated in a previous study, this could be related to an earlier diagnosis due to an easier patient access to cardiovascular, especially echocardiographic, screening in Greece.[5] An observational study by Xanthouli et al.[11] in 90 patients with a "typical" PAH phenotype and 52 patients with PAH and cardiac or pulmonary comorbidities concluded that risk stratification based on ESC/ERS-guidelines could only be confirmed in patients without comorbidities, but not in patients with PAH and comorbidities, suggesting that in patients with IPAH, comorbidities confound the overall clinical profile; therefore, conventional risk models may not adequately capture differences in prognosis. As a consequence, an adapted clinical score may be necessary to be applied in PAH patients with CVCs.

Elderly with IPAH had more CVCs and worse survival than younger patients with IPAH. Moreover, older age was a strong independent predictor of mortality in the overall IPAH cohort. Data from the COMPERA Registry revealed that the female/male ratio in 378 newly diagnosed elderly patients (>65 years old) was almost even (1.2/1), while elderly patients presented worse functional status, better hemodynamics, received less frequently a combination therapy, and presented worse survival than younger patients.[6] Similarly, a Japanese Registry on elderly patients with IPAH or hereditary PAH (HPAH) revealed that elderly patients with IPAH/HPAH showed poorer exercise capacity and impaired gas exchange, but better pulmonary hemodynamics than younger patients.[15] However, no difference in survival was detected.

Hazard ratio
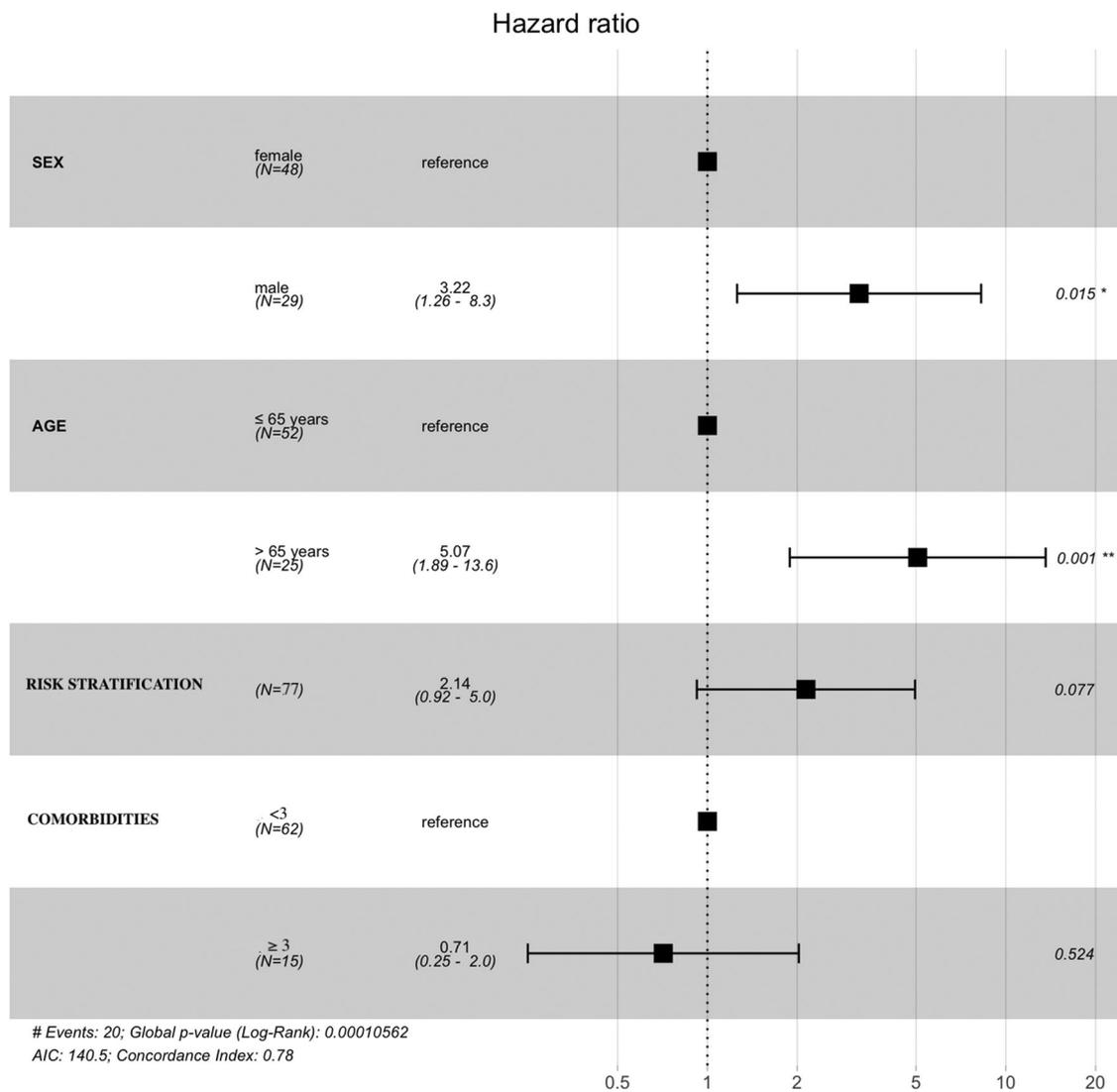
FIGURE 3 Multivariable cox regression analysis predicting mortality and/or transplantation. *$p < 0.05$, AIC, Akaike information criterion; CI, confidence intervals; Comorbidities, cardiovascular comorbidities associated with left heart disease; HR, hazard ratio; risk stratification, an abbreviated version of the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk stratification strategy.

A strength of our study over previous studies is that we included only patients classified in the IPAH group to achieve greater homogeneity at the expense of a more limited sample size.[11] In addition, we added atrial fibrillation as a fifth factor that is associated with left heart disease, similarly to Rosenkranz et al.[13] Due to the limited sample size, the multivariable model used up to four variables in the total cohort. Additionally, information regarding only the initial assessment at first visit is presented. Consequently, we cannot comment on possible changes in functional parameters, hemodynamics, risk status, and PAH treatment over time. Additionally, we admit that there are missing data on routine aspects of PAH evaluation. The phenotype of an elderly patient with significant comorbidities for left heart disease and

less severe hemodynamics may explain why attending physicians opted not to perform acute vasodilation testing in half of our patients with IPAH. Missing data in PFTs may be explained by the fact that some patients with less typical IPAH were referred by general cardiology or HFpEF clinics. Furthermore, lack of an association between CVCs and mortality is likely driven by a low power to detect an effect. Finally, this study included CVCs related mostly to HFpEF, and not risk factors for valvular heart disease, cardiomyopathies, or heart failure with (mildly) reduced ejection fraction.

In conclusion, patients with IPAH and a cardiovascular phenotype for left ventricular diastolic dysfunction do not present a female predominance, are older and more symptomatic, while they have better
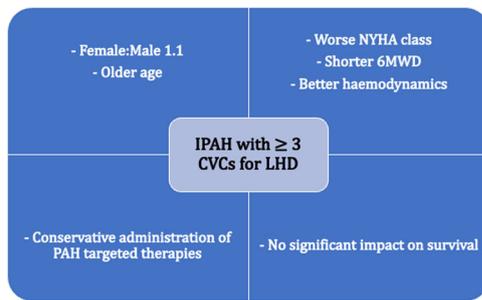
FIGURE 4 Special demographic, functional, hemodynamic, and treatment features of patients with idiopathic pulmonary arterial hypertension and ≥3 cardiovascular comorbidities (CVCs) associated with left heart disease (LHD) in the HOPE Registry. 6MWD, six-minute walking distance; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension.

hemodynamics and receive less aggressive targeted therapy for PAH (Figure 4). Male sex and advanced age independently predicted death and/or lung transplantation in the total IPAH population, while risk status and the presence of ≥3 CVCs were not independent predictors of the primary endpoint. IPAH with cardiovascular comorbidities is an emerging phenotype that differs significantly compared to "typical" IPAH in terms of demographics, functional status, hemodynamics, and treatment strategy and response. Further larger prospective cohort studies are warranted taking into consideration other risk factors as well, such as the pulmonary component, to identify differences in survival.

AUTHOR CONTRIBUTIONS

Alexandra Arvanitaki and Elena Vrana contributed equally to the acquisition, analysis, and interpretation of data and drafted and revised the article for important intellectual content. George Giannakoulas made a substantial contribution to the concept and design of this study and revised the article critically for important intellectual content. The rest of the authors contributed to the acquisition of patients' data and revised the article critically for important intellectual content.

CONFLICTS OF INTEREST

Alexandra Arvanitaki has been the recipient of the International Training and Research Fellowship EMAH Stiftung Karla Voellm, Krefeld, Germany. Anastasia Anthi reports receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas, Bayer, ELPEN, GSK, MSD, Lilly, and United Therapeutics. Eftychia Demerouti has been an advisory board member for Actelion Pharmaceuticals Hellas, MSD Hellas, and GlaxoSmithKline and an honorarium speaker for Actelion Pharmaceutical Hellas and MSD Hellas. Ioanna Mitrouska reports receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas, Bayer, ELPEN, MSD, and GSK. Katerina K. Naka reports lecture fees from Novartis, Medtronic, and Abbott, while she serves as an investigator in randomized clinical trials and/or registries sponsored by Novartis, Merck, Amgen, BMS, Boehringer Ingelheim, Pfizer, and Actelion Pharmaceutical Hellas, outside the submitted work. Stylianos E. Orfanos reports has been receiving research grants and/or honoraria and/or consultancy fees from Actelion Pharmaceutical Hellas, Bayer, ELPEN, Galenica-Ferrer, GSK, MSD, Pharmaserve Lilly, PharmaSwiss, Pfizer, and United Therapeutics. Georgia Pitsiou reports receiving honoraria and consultancy fees from Actelion Pharmaceutical Hellas, Bayer, ELPEN, MSD, and GSK. Ioannis Stanopoulos reports receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas. Iraklis Tsangaris reports has been receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas, Bayer, ELPEN, GSK, Pfizer, Lilly, and United Therapeutics. Athanasios Manginas reports consultation fees from Astra Zeneca, Bayer, ELPEN, Actelion Pharmaceuticals Hellas, and MSD. George Giannakoulas reports has been receiving honoraria and consultancy fees from Actelion Pharmaceuticals Hellas, Bayer, ELPEN, Galenica-Ferrer, GSK, Pfizer, Lilly, MSD, and United Therapeutics. The remaining authors declare no conflicts of interest. The remaining authors declare no conflicts of interest.

ETHICS STATEMENT

The HOPE Registry received ethical approval by the Institutional Review Board of every participating center (Institutional Review Board of AHEPA University Hospital, Thessaloniki, Institutional Review Board of Mediterraneo Hospital, Athens, Institutional Review Board of Attikon University General Hospital, Athens, Institutional Review Board of Onassis Cardiac Surgery Center, Athens, Institutional Review Board of Hippokration University General Hospital, Athens, Institutional Review Board of Heraklion University Hospital, Crete, Institutional Review Board of the University Hospital of Ioannina, Institutional Review Board of "G. Papanikolaou" Hospital, Thessaloniki, Institutional Review Board of the University Hospital of Alexandroupolis, Institutional Review Board of "Laiko" General Hospital) according to the Declaration of Helsinki, and all patients provided written informed consent for their inclusion in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.