Association of pulmonary hypertension-targeted therapy and survival in precapillary pulmonary hypertension with mean pulmonary arterial pressure between 21 and 24 mmHg

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Shareable abstract (@ERSpublications)
PH was redefined to include patients with mPAP of 21–24 mmHg but randomised studies in these "mild PH" patients are missing. In the GoDeep meta-registry, PH-targeted therapy is associated with improved survival in PAH and CTEPH patients of this category. https://bit.ly/4gxz2eC

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Abstract

Introduction The definition of pulmonary hypertension (PH) was recently changed and led to a new subset of PH patients with mildly impaired pulmonary haemodynamics, characterised by a mean pulmonary artery pressure (mPAP) of 21–24 mmHg and with a pulmonary vascular resistance (PVR) >2 WU. We evaluated the association of PH-targeted therapy and outcome in mild precapillary PH using the PVRI GoDeep meta-registry.

Methods All patients with mild precapillary PH (mPAP 21–24 mmHg, pulmonary arterial wedge pressure ⩽15 mmHg and PVR >2 WU) diagnosed with pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) were enrolled. Patients were considered as "treated" if PH-targeted therapy was initiated within 6 months of diagnostic right heart catheterisation. Various statistical models, including in-depth sensitivity analyses, were used to examine the association between PH-targeted therapy and transplant-free survival.

Results 132 patients with group 1 or group 4 mild PH were identified, of whom 34 patients received PH-targeted therapy. There were no differences in baseline haemodynamics between untreated and treated groups, whereas treated patients suffered more frequently from renal comorbidities and required long-term oxygen treatment more often. Most prescribed were phosphodiesterase-5-inhibitors. PH-targeted therapy was associated with significantly higher survival rates. Cox-regression analyses revealed significantly reduced hazard ratios among treated patients adjusted for various confounders. Subgroup analyses in PAH (n=78) similarly indicated higher survival rates and reduced hazard ratios in treated patients.

Conclusion PH-targeted therapy may be associated with improved survival in PAH and CTEPH patients with mild PH. To mitigate potential bias of the results due to the retrospective study design, randomised controlled trials are warranted.

Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) represent chronic pulmonary vascular diseases (PVDs) characterised by progressive remodelling of the pulmonary arteries, resulting in a substantial increase of right ventricular (RV) afterload [1]. Large-scale, multicentric studies indicated normal pulmonary arterial (PA) pressure in healthy subjects of 14±3 mmHg [2]. Accordingly, PA pressure above 20 mmHg and pulmonary vascular resistance (PVR) above 2 WU were associated with impaired exercise capacity and survival highlighting the clinical relevance of mild PH [3–6]. Moreover, mild alterations in pulmonary haemodynamics exert a substantial impact on RV function, particularly influencing contraction patterns and (dys)synchrony, both recognised as important prognostic factors [7, 8].

Furthermore, small-scale prospective studies have suggested that without intervention, up to 60% of patients with mild PH may progress to mean pulmonary artery pressure (mPAP) ⩾25 mmHg during follow-up [9]. Combined with the significant delay of PH diagnosis, which itself is associated with an increased risk of PVD progression and mortality, the classical definition of PH was refined [10–13]: The previously established threshold of mPAP ⩾25 mmHg was redefined to mPAP >20 mmHg and the PVR threshold was revised from >3 WU to >2 WU [10]. This paradigm shift has brought to light a previously unrecognised subgroup of precapillary PH patients whose mPAP falls within the range of 21–24 mmHg, coupled with increased PVR and normal pulmonary arterial wedge pressure (PAWP) ⩽15 mmHg [10].

In the classical era, these patients were categorised as “PH exclusion” and therefore not included in clinical trials investigating the efficacy of PH-targeted medications [10, 14–19]. Thus, *post hoc* analyses of randomised controlled trials (RCTs) specifically for these patients are not feasible. However, due to the hitherto mentioned impaired survival of patients with mild PH the guidelines recommend treatment of this new subset of PH patients [10].

Considering this ambiguity, an important and largely unaddressed question arises: is there evidence for the benefit of PH-targeted therapy in patients with mild PH?

Methods

The Pulmonary Vascular Research Institute GoDeep meta-registry

Pulmonary Vascular Research Institute (PVRI)-GoDeep is a meta-registry that integrates PH registries from PH expert centres around the world with both retrospective and prospective data, as described previously [20, 21]. The hallmark inclusion criterion for enrolment in PVRI GoDeep is PH defined by elevated pulmonary artery pressure as diagnosed by right heart catheterisation, according to the definition of the PH World Symposium guideline at the time of diagnosis [22, 23]. Patient-related data from each local registry, once attached to the meta-registry, undergo a process of anonymisation, transformation, confirmation, validation, mapping and finally integration into the meta-registry, with automatic regular updates [20].

As of March 2024, 22 centres have entered a total of 31 581 patients into the meta-registry. Out of these, the PH centres in Giessen (80 patients), Graz (24), Sheffield (10), Baltimore (8), Cambridge (5) and London (5) had collected data of PAH and CTEPH patients which were enrolled in this study. The University of Giessen/University Hospital Ethics Committee and the responsible local ethic committees have approved the PVRI GoDeep central data repository, listed under ClinicalTrials.gov (NCT05329714).

Patient and data selection

The PVRI GoDeep meta-registry enrolled patients were screened for inclusion with group 1 or group 4 PH, mPAP between 21 and 24 mmHg, PVR >2 WU and PAWP ⩽15 mmHg [20]. Figure 1 shows the patient selection flowchart. The time of initial diagnosis and thus the starting point for all survival analyses was defined as the time of the first diagnostic right heart catheterisation at the time of inclusion in the registry. The time span for baseline data was set from −1 to 6 months around the date of initial diagnosis. If multiple data points were available for the same variable, the data point closest to the initial diagnosis was selected. Survival was documented on the basis of the patients’ follow-up examinations at the various PH centres. Transplant-free survival time was calculated as the duration in months between the date of diagnosis and the last documented follow-up visit at each centre, after which patients were censored for survival analyses.

Statistical analyses

Data were analysed with R version 4.3.3 [24] using the package survival version 3.58 [25]. Tables were produced with the help of the package flextable version 0.9.5 [26]. Multiple imputations were conducted by multivariate imputation by chained equations using the package mice version 3.16.0 [27]. A sensitivity

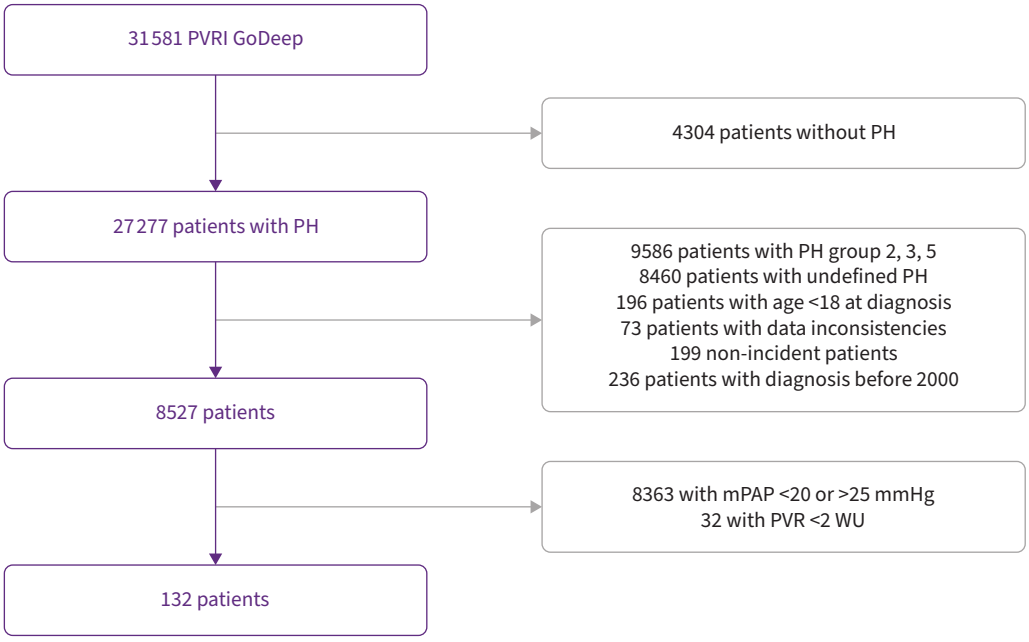

FIGURE 1 Patient selection in PVRI GoDeep. PVRI: Pulmonary Vascular Research Institute; PH: pulmonary hypertension; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance.

analysis of the treatment effect to unmeasured confounders was conducted using the survSensitivity function from the survSens package, version 1.1.0 [28]. Adjusted Kaplan–Meier curves were produced with the package adjustedCurves [29].

Data were extracted from the database on 22 March 2024. In this dataset, missing values were calculated from other available data whenever possible. A patient was considered to be treated with a medication if at least one report stated that the respective medication was prescribed to the patient within the first 6 months after diagnosis, to mitigate immortal time bias [30]. If there was no report the prescription of a specific drug or only after 6 months after diagnosis, the patient was considered to be untreated with the respective medication. Analyses were conducted on an intention-to-treat-like basis, without consideration of treatment discontinuation. All numeric parameters are presented as median (Q1, Q3), with comparisons conducted using t-test and Mann–Whitney U-test. Data from laboratory variables were log transformed before testing. Categorical parameters were analysed using chi-squared tests. Kaplan–Meier estimators were adjusted for patient's age as a natural spline with 2 degrees of freedom, as well as sex as strata and centre as a cluster [29]. Imputation was performed using PH centre (0% missing), diagnosis decade (0% missing), sex (0% missing), age at diagnosis (0% missing), mPAP (0% missing), PAWP (0% missing), PVR (0% missing), cardiac index (0% missing), World Health Organization (WHO) functional class (FC) (17% missing), creatinine (19% missing), B-type natriuretic peptide (BNP) (31% missing) and 6-min walk distance (6MWD) (39% missing). The accuracy of the imputation process is depicted in figure 2. In all Cox-regression analyses, in addition to treatment, PH centre, decade of diagnosis and sex were included as strata, as well as patient's age as a natural spline with 2 degrees of freedom and centre as a cluster. Further analyses with additional adjustment for WHO FC, 6MWD, PVR, PAWP, cardiac index, BNP, creatinine, PH group, renal comorbidities, oxygen treatment, cardiovascular disease and metabolic syndrome were performed. A propensity score-matching procedure with a 2:1 ratio was implemented, wherein all variables included in imputation were used post-imputation. Subgroup analyses were performed for patients included in propensity score matching, for PH group 1 patients, patients with cardiovascular disease (including atrial fibrillation, coronary artery disease and valvular heart disease among others) and for landmark analysis. Risk scores were calculated as previously described [10, 21, 31–33].

Results

Baseline characteristics

In March 2024, a total of 31 581 patients were enrolled in the PVRI GoDeep meta-registry, of whom 132 patients with incident group 1 or group 4 PH, mPAP between 21–24 mmHg, PVR >2 WU and PAWP

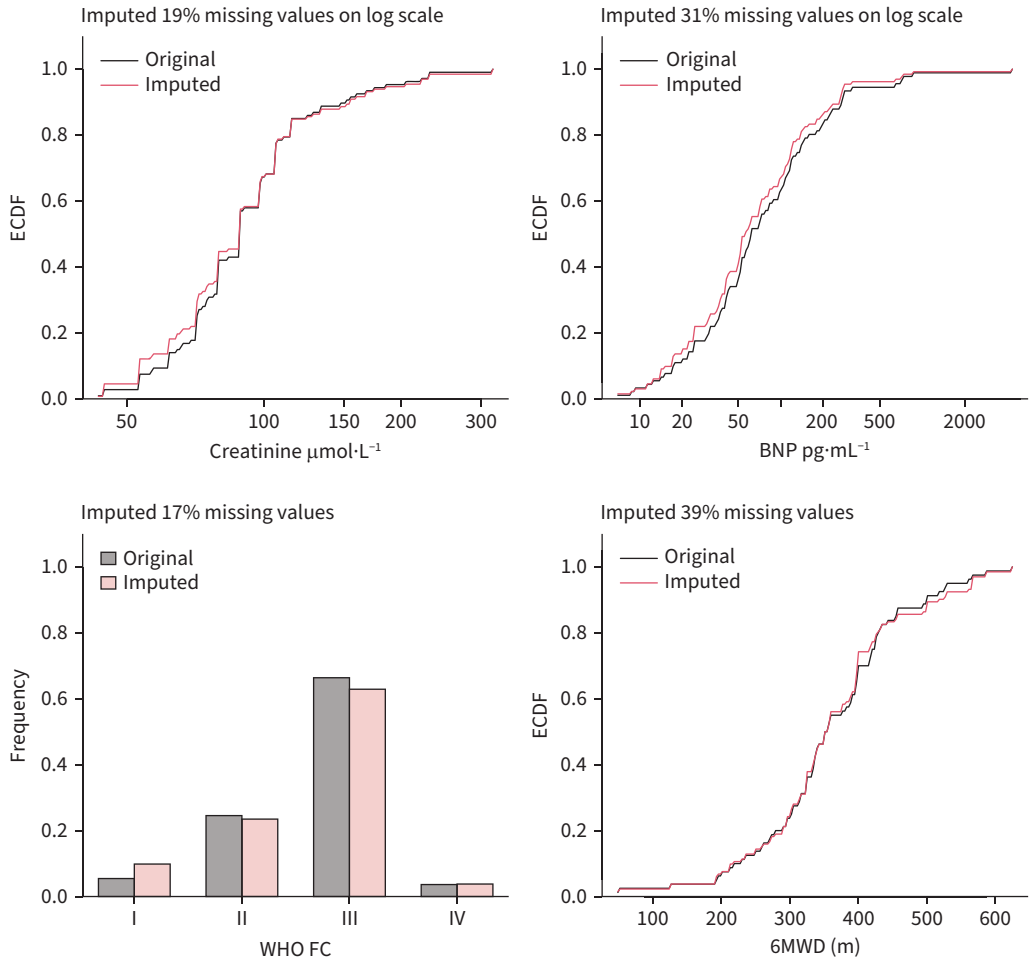

FIGURE 2 Sanity check of the imputation. The diagrams show the empirical cumulative distributions of the variables for which values were imputed. The black line shows the distribution of the original data, the red lines show the distributions of the variables, including the imputed values. WHO FC: World Health Organization functional class; BNP: B-type natriuretic peptide; 6MWD: 6-min walk distance; ECDF: empirical cumulative distribution function.

⩽15 mmHg were identified. 47% of the patients were diagnosed between 2000 and 2010, 39% between 2010 and 2020 and 14% from 2020 to the present. The flow chart showing patient selection is shown in figure 1.

The median age of the study population was 69 (60, 75) years and 44 (34%) were male. As shown in table 1, pulmonary haemodynamics showed a mildly impaired median mPAP of 23 (22, 24) mmHg, with a significant elevation of PVR (3.2 (2.7, 3.9) WU). Relevant impairment of cardiac index and PVR was observed in 57% and 61% of the included patients (defined as cardiac index <2.5 $L \cdot min^{-1} \cdot m^{-2}$ and PVR >3 WU). Only six patients (5%) had a PAWP between 13 and 15 mmHg. Most patients were at WHO FC III and comorbidities were frequent (table 2). Pulmonary function tests showed no major abnormalities in forced expiratory volume in 1 s (FEV_1) (80.00% (69.58%, 95.98%)) or FVC (86.47% (75.90%, 100.31%)), indicating the absence of relevant pulmonary comorbidities. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) was consistently reduced (56.70% (44.88%, 65.93%)), which may be due to the reduction of lung vascular surface area. Further baseline characteristics are depicted in table 1. Comorbidities reported by the respective PH expert centres are listed in table 2. Median follow-up time was 28 (9, 65) months. 1-, 3- and 5-year transplant-free survival rates of the overall study population was 91%, 75% and 59%, respectively.

Prevalence and characteristics of PH-targeted treated in mild PH

34 patients (26%) of the included patients received PH-targeted therapy within 6 months after diagnosis. Baseline characteristics stratified by treatment are shown in tables 1–3. Of note, there were no differences in age, sex, WHO FC, 6MWD, BNP or pulmonary haemodynamics between untreated and treated groups

TABLE 1 Patients' characteristics at baseline stratified by pulmonary hypertension treatment

Treatment	Treated (n=34)	Untreated (n=98)	Overall (n=132)	p-value	p-value (U-test)
Age at diagnosis, years					
Median (Q1, Q3)	69 (56, 76)	69 (61, 75)	69 (60, 75)	0.435	0.619
Missing	0 (0)	0 (0)	0 (0)		
Sex					
Male	11 (32)	33 (34)	44 (33)	>0.999	
Missing	0 (0)	0 (0)	0 (0)		
BMI, kg·cm^2					
Median (Q1, Q3)	26 (23, 29)	26 (23, 29)	26 (23, 29)	0.681	0.757
Missing	0 (0)	1 (1)	1 (0.76)		
WHO FC					
I	0 (0)	6 (7.6)	6 (5.5)	0.080	
II	7 (23)	20 (25)	27 (25)		
III	21 (68)	52 (66)	73 (66)		
IV	3 (9.7)	1 (1.3)	4 (3.6)		
Missing	3 (8.8)	19 (19)	22 (17)		
mPAP, mmHg					
Median (Q1, Q3)	22 (22, 24)	23 (21, 24)	23 (22, 24)	0.791	0.781
Missing	0 (0)	0 (0)	0 (0)		
PAWP, mmHg					
Median (Q1, Q3)	8 (6.2, 9.8)	8 (5.2, 10)	8 (5.8, 10)	0.620	0.824
Missing	0 (0)	0 (0)	0 (0)		
PVR, WU					
Median (Q1, Q3)	3.3 (2.5, 4)	3.2 (2.8, 3.9)	3.2 (2.7, 3.9)	0.545	0.942
Missing	0 (0)	0 (0)	0 (0)		
CI, L·min^{-1}·m^{-2}					
Median (Q1, Q3)	2.4 (2, 3)	2.4 (2.2, 2.9)	2.4 (2.1, 2.9)	0.770	0.894
Missing	0 (0)	0 (0)	0 (0)		
6MWD, m					
Median (Q1, Q3)	350 (260, 420)	350 (320, 420)	350 (300, 420)	0.466	0.531
Missing	8 (24)	44 (45)	52 (39)		
BNP, pg·mL^{-1}					
Median (Q1, Q3)	78 (50, 120)	59 (33, 140)	61 (36, 130)	0.384	0.430
Missing	11 (32)	30 (31)	41 (31)		
Creatinine, µmol·L^{-1}					
Median (Q1, Q3)	88 (80, 110)	88 (71, 110)	88 (71, 110)	0.185	0.152
Missing	5 (15)	20 (20)	25 (19)		
Metabolic syndrome					
True	12 (35)	30 (31)	42 (32)	0.771	
Missing	0 (0)	0 (0)	0 (0)		
Cardiovascular disease					
True	24 (71)	66 (67)	90 (68)	0.892	
Missing	0 (0)	0 (0)	0 (0)		
Renal comorbidities					
True	10 (29)	10 (10)	20 (15)	0.016	
Missing	0 (0)	0 (0)	0 (0)		
Cancer					
True	5 (15)	11 (11)	16 (12)	0.817	
Missing	0 (0)	0 (0)	0 (0)		
Sleep apnoea syndrome					
True	2 (5.9)	9 (9.2)	11 (8.3)	0.810	
Missing	0 (0)	0 (0)	0 (0)		
Oxygen treatment					
True	17 (50)	13 (13)	30 (23)	<0.001	
Missing	0 (0)	0 (0)	0 (0)		

Data are presented as n (%) unless otherwise specified. PH: pulmonary hypertension; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CI: cardiac index, BMI: body mass index; WHO FC: World Health Organization functional class; WU: Wood units; 6MWD: 6-min walk distance; BNP: B-type natriuretic peptide; ESC: European Society of Cardiology; ERS: European Respiratory Society; Int.: intermediate. p-values are for the comparison of the stratified treatment groups; differences between groups of continuous variables were tested using ANOVA, differences between groups of categorical variables were tested using chi-squared tests. Additionally, a Mann–Whitney U-test was performed (p-value U-test).

TABLE 2 Comorbidities and risk scores stratified by pulmonary hypertension treatment

Treatment	Treated (n=34)	Untreated (n=98)	Overall (n=132)	p-value
Cardiovascular disease				
True	24 (71)	66 (67)	90 (68)	0.892
Arterial hypertension				
True	17 (50)	47 (48)	64 (48)	0.995
Coronary artery disease				
True	2 (5.9)	5 (5.1)	7 (5.3)	>0.999
Valvular heart disease				
True	2 (5.9)	5 (5.1)	7 (5.3)	>0.999
Arrhythmia				
True	8 (24)	21 (21)	29 (22)	0.988
Metabolic syndrome				
True	12 (35)	30 (31)	42 (32)	0.771
Obesity				
True	8 (24)	22 (22)	30 (23)	>0.999
Diabetes mellitus				
True	2 (5.9)	5 (5.1)	7 (5.3)	>0.999
Hyperlipidaemia				
True	2 (5.9)	5 (5.1)	7 (5.3)	>0.999
ESC/ERS 4-strata				
Low	4 (12)	13 (13)	17 (13)	0.097
Int.–low	19 (56)	70 (71)	89 (67)	
Int.–high	11 (32)	15 (15)	26 (20)	
high	0 (0)	0 (0)	0 (0)	
ESC/ERS 2022				
Low	4 (12)	16 (16)	20 (15)	0.718
Int.	30 (88)	82 (84)	112 (85)	
High	0 (0)	0 (0)	0 (0)	

Data are presented as n (%). PH: pulmonary hypertension; ESC: European Society of Cardiology; ERS: European Respiratory Society.

at baseline (p>0.05, respectively). Most prescribed were phosphodiesterase-5 inhibitors (85%), followed by endothelin-receptor antagonists (26%) and prostanoids (12%, including inhalative, subcutaneous or intravenous prostacyclin analoga as well as oral prostacyclin receptor agonists). 12% of the patients received upfront combination therapy; treatment was not escalated in any of them during follow-up. Treated patients had a higher prevalence of renal comorbidities (29% *versus* 10%, p=0.016) and oxygen treatment (50% *versus* 13%, p<0.001) at baseline. Cardiovascular comorbidities were frequent in both treated and untreated patients (71% *versus* 67%, p=0.89). In 18 (22%) of the untreated patients, PH-targeted therapy was started later than 6 months after diagnosis.

Among treated patients, 12%, 88% and 0% were categorised as low, intermediate and high risk, respectively, compared with 16%, 84% and 0% of untreated patients using the European Society of Cardiology (ESC)/European Respiratory Society (ERS) 3-strata risk score at baseline (table 2). When using the ESC/ERS 4-strata risk score, 12%, 56%, 32% and 0% were categorised as low, intermediate–low, intermediate–high and high risk at baseline. For untreated patients, the corresponding percentages were 13%, 71%, 15% and 0% (table 2).

Association of PH-targeted therapy with transplant-free survival

During the median follow-up time of 28 (9, 65) months, 46 (35%) patients died. The cause of death was reported for 30 of these patients, with 80% attributed to cardiopulmonary events, 13% to cancer and 7% to other reasons. PH-targeted therapy was associated with a significant improvement of 1-, 3- and 5-year transplant-free survival rates (97%, 86% and 78%), compared with patients without treatment as indicated in figure 3a (88%, 70% and 50%; p<0.01). Cox-regression analysis revealed significantly reduced hazard ratios (HRs) among treated patients (HR 0.21, 95% confidence interval (CI) 0.20–0.22; p<0.001, figure 4a). To enhance statistical robustness, we performed multivariable Cox-regression analyses with adjustment for various confounders, including BNP, renal function, WHO FC and pulmonary haemodynamics, as indicated in figure 4a. Of note, in all tested models PH-targeted treatment was associated with significantly reduced HR. Follow-up data for assessing the ESC/ERS 4-strata risk score

were available for 64 patients. As shown in figure 5, treated patients more frequently showed a tendency towards improvement in their follow-up risk score compared with untreated patients with mild PH. Among the treated patients, 88% either remained in the same risk score group or showed improvement, compared with 69% of the untreated patients.

Sensitivity and subgroup analyses

Additionally, we performed propensity score matching to harmonise control and treatment groups; again, PH-targeted therapy was associated with significantly improved HR (figure 3b). Similar results were obtained in subgroup of patients with cardiovascular comorbidities (figure 4b). Sensitivity analyses indicated that none of the risk factors significantly altered the HR of PDE5i when separately adding or excluding as a covariable from the Cox-regression model (figure 4a). Furthermore, subgroup and sensitivity analyses in patients with a complete dataset (without need for imputation) and with landmark analysis revealed that PH-targeted therapy was again associated with improved HR (figure 4b).

Association of PH-targeted therapy with transplant-free survival in patients with pulmonary arterial hypertension (group 1)

Group 1 PH patients (59% of the study population) showed a marked impairment of pulmonary haemodynamics: mPAP 23 (21, 24) mmHg, PVR 3.3 (2.7, 4) WU, PAWP 8 (6, 9) mmHg, cardiac index 2.4 (2, 3.1) $L \cdot min^{-1} \cdot m^{-2}$, as shown in tables 3 and 4. Of these, 27% received PH-targeted therapies, without significant baseline differences between treated and untreated patients (table 3). Subgroup analysis in patients with group 1 PH again showed significant association between PH-targeted treatment and improved HR (figure 4c). 1-, 3- and 5-year transplant-free survival rates of group 1 PH patients without PH-targeted therapy was 82%, 62% and 42%, whereas treated patients had meaningful higher transplant-free survival rates (95%, 77% and 71%, $p<0.01$; figure 3b). Once again, propensity score matching and landmark analysis revealed significantly improved HR in group 1 PH patients (figure 4d).

Discussion

This study investigates the association of PH-targeted therapy with transplant-free survival on a newly recognised group of precapillary PH patients (group 1 and 4) according to the updated ESC/ERS guidelines [10]. In patients with mild PH, characterised by mPAP between 21 and 24 mmHg, PVR >2 WU and PAWP ⩽15 mmHg, PH-targeted (mono)therapy demonstrated significant and robust associations with improved transplant-free survival rates in this meta-registry.

Recent comprehensive registry studies and meta-analyses have revealed that even mild impairment of pulmonary haemodynamics is linked to decreased survival rates [2, 10, 34–36]. Notably, even slight increases in RV afterload exert a substantial impact on RV function: mild PH can induce RV dyssynchrony, potentially indicative of early RV–PA uncoupling, a factor known to influence prognosis in PH [8, 37]. Furthermore, diagnostic delays in PH, often attributable to nonspecific symptoms in the initial stages, have been linked to poorer survival outcomes [11, 13, 38].

It is noteworthy that patients with mild PH are at risk for progressing to overt PH, with longitudinal studies suggesting that up to 60% of mild PH patients may develop mPAP ⩾25 mmHg during follow-up catheterisation [9]. Recognising the clinical significance of even mild alterations of pulmonary haemodynamics, recent guidelines have broadened the definition of PH by lowering the thresholds for mPAP and PVR that define precapillary PH [10, 14]. Yet, there is a lack of RCTs investigating the efficacy of PH-targeted drugs in this subgroup of patients with mild PH. The absence of evidence guiding the treatment of patients in the “grey-zone” of mild pulmonary haemodynamic impairment stems from their systematic exclusion in prior clinical trials [10, 15–19]. Thus, any *post hoc* analyses of these trials are impractical [15–19].

However, selected expert centres already initiated treatment for these patients based on individualised decisions after appropriate information. In patients with chronic thromboembolic pulmonary disease without PH (CTEPD), PH-targeting therapies are commonly employed. Small-scale studies exploring interventional (balloon pulmonary angioplasty) and surgical therapy in CTEPD patients have shown potential for improving morbidity and even mortality [39, 40]. Similarly, findings from the EDITA study indicate that early intervention in PH associated with systemic sclerosis may lead to improvements in cardiac index and concordantly PVR [41]. However, evidence regarding the impact of PH-targeted therapies on mortality in PAH patients remains scarce.

Utilising the unique data of the worldwide recruiting multicentre PVRI GoDeep meta-registry, we included 132 patients with mild precapillary PH and mPAP between 21–24 mmHg, including 34 patients who

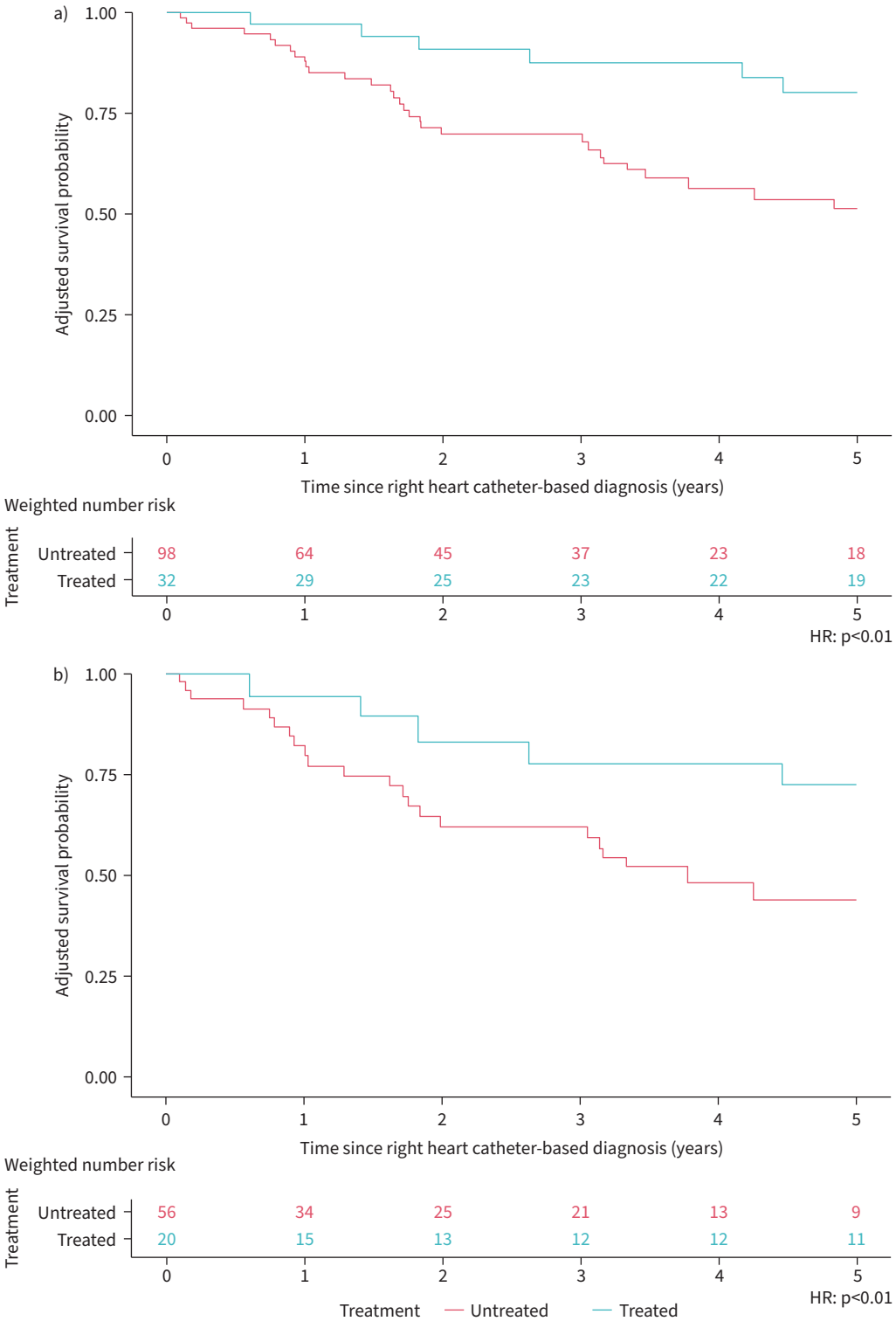

FIGURE 3 Adjusted Kaplan–Meier survival analysis comparing mild pulmonary hypertension (PH) patients receiving PH-targeted therapy *versus* untreated patients. Kaplan–Meier estimators were adjusted for patient's age as a natural spline with two degrees of freedom, as well as sex as strata and centre as cluster. a) Adjusted Kaplan–Meier for overall study group. b) Adjusted Kaplan–Meier for PH group 1. HR: hazard ratio.

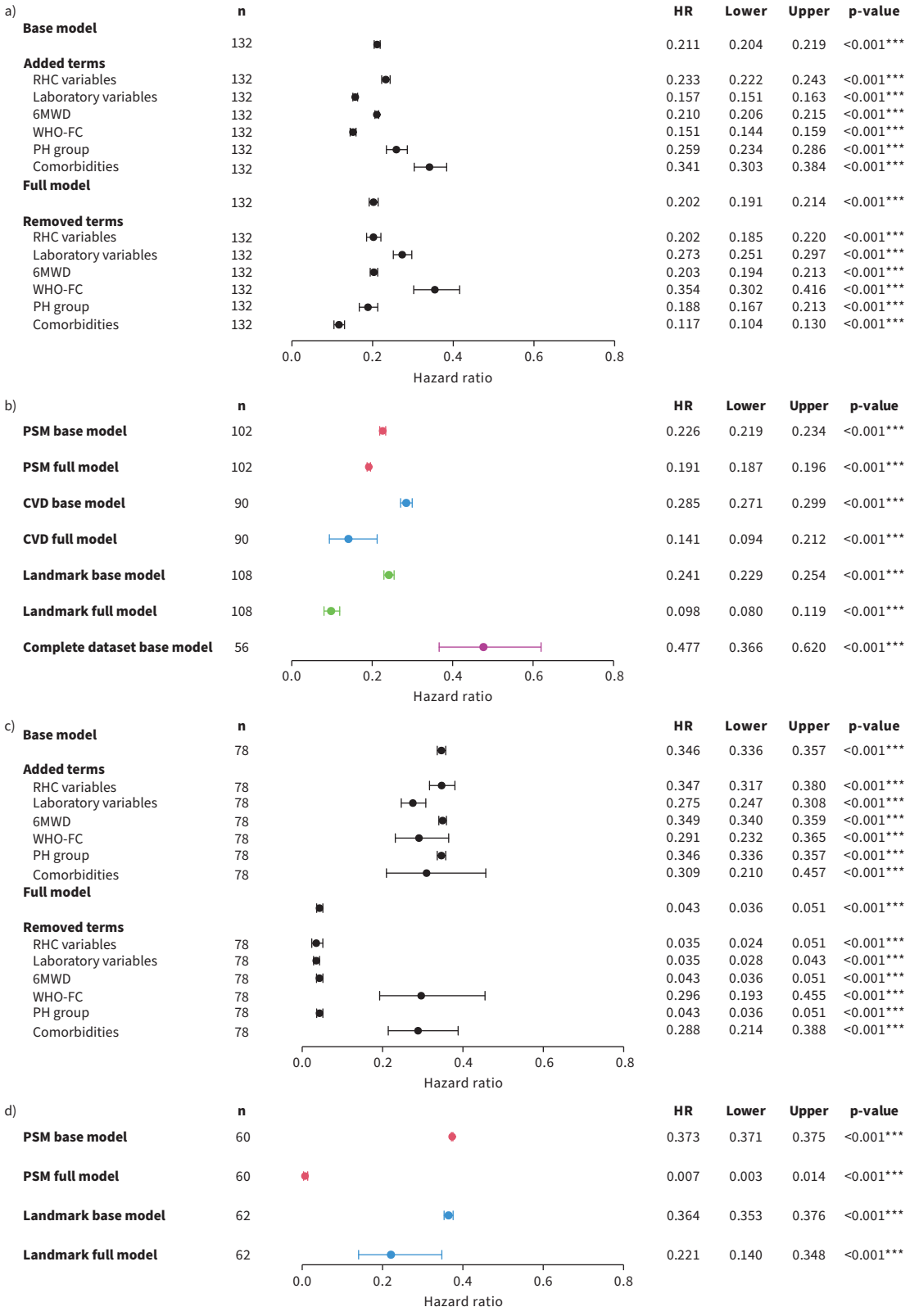

FIGURE 4 Cox-regression models exploring the association between pulmonary hypertension (PH)-targeted therapy and mortality risk. a) Base model: PH-targeted therapy adjusted for PH centre, diagnosis decade and sex as strata, along with patient's age as a natural spline with 2 degrees of freedom and centre as a cluster. Full model: base model with additional adjustment for World Health Organization (WHO) functional class (FC), 6-min walk distance (6MWD), pulmonary vascular resistance (PVR), pulmonary arterial wedge pressure (PAWP), cardiac index (CI), B-type natriuretic peptide, creatinine, PH group, renal comorbidities, oxygen treatment, cardiovascular disease (CVD) and metabolic syndrome. First estimates from

the base model are shown with the respective terms added and afterwards the estimates from the full model from which the respective terms were removed. b) Subgroup examinations are depicted. The estimates for the analysis for the base and the full model for patients included in the propensity score matching and patients with cardiovascular disease are then presented, as well as the base model for the complete dataset (without imputation) and landmark analysis. c) Base and full model for PH group 1 patients only. First estimates from the base model are shown with the respective terms added and afterwards the estimates from the full model from which the respective terms were removed. d) Subgroup examinations for patients included in the propensity score matching, as well as patients with landmark analysis are depicted. The diagrams show the estimates with 95% confidence intervals. The p-values are from Wald z-tests. BMI: body mass index; RHC: right heart catheterisation; HR: hazard ratio; lower, upper: lower and upper limits of the 95% confidence interval of the HR; PSM: propensity score matching.

received PH-targeted therapy within 6 months of right heart catheter-based diagnosis [21, 42]. Most of the patients received PH-targeted monotherapy with phosphodiesterase-5 inhibitors. The prevalence of cardiovascular comorbidities was high and there is lack of empirical data substantiating the benefit of combination therapy under these conditions [15].

Our findings highlight that PH-targeted therapy was associated with improved survival rates in mild precapillary PH (with and without propensity score matching), in group 1 mild PH patients with and without cardiopulmonary or renal comorbidities, mild PH patients with long-term oxygen treatment, as well as in various Cox-regression models and sensitivity analyses, highlighting the statistical robustness of the presented results.

Most of the patients exhibited significant functional capacity impairment (WHO FC III). Accordingly, cardiac index and PVR were markedly compromised (defined as a cardiac index <2.5 $L \cdot min^{-1} \cdot m^{-2}$ and PVR >3 WU) in >50% of the patients, with only a minority demonstrating borderline PAWP (13–15 mmHg [10, 43]), which may indicate significant RV impairment in spite of the only “mild” PH. In line, most of the patients were classified as intermediate risk, using the ESC/ERS 3- and 4-strata risk models, which are well established estimators of risk in PAH and CTEPH [21, 33, 44, 45]. The high prevalence of comorbidities, particularly cardiovascular and renal ones, may nonetheless exert a notable influence

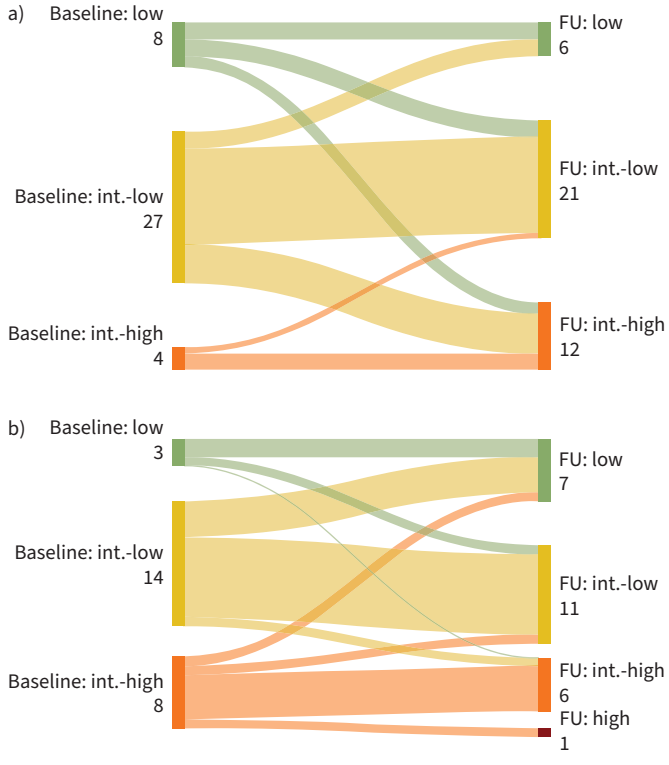

FIGURE 5 Change in European Society of Cardiology/European Respiratory Society 4-strata risk from baseline to follow-up (FU) within 6–60 months for (a) untreated and (b) treated patients. Int.: intermediate.

TABLE 3 Patients' characteristics at baseline stratified by treatment for pulmonary hypertension group 1 (PAH)

Treatment	Treated (n=21)	Untreated (n=57)	Overall (n=78)	p-value	p-value (U-test)
Age at diagnosis, years					
Median (Q1, Q3)	66 (57, 72)	68 (63, 75)	68 (61, 75)	0.359	0.305
Missing	0 (0)	0 (0)	0 (0)		
Sex					
male	5 (24)	17 (30)	22 (28)	0.810	
Missing	0 (0)	0 (0)	0 (0)		
BMI, kg·cm^{-2}					
Median (Q1, Q3)	25 (23, 27)	27 (22, 29)	26 (22, 29)	0.342	0.552
Missing	0 (0)	1 (1.8)	1 (1.3)		
WHO FC					
I	0 (0)	6 (14)	6 (9.8)	0.098	
II	5 (26)	11 (26)	16 (26)		
III	11 (58)	24 (57)	35 (57)		
IV	3 (16)	1 (2.4)	4 (6.6)		
Missing	2 (9.5)	15 (26)	17 (22)		
mPAP, mmHg					
Median (Q1, Q3)	22 (22, 24)	23 (21, 24)	23 (21, 24)	0.907	0.861
Missing	0 (0)	0 (0)	0 (0)		
PAWP, mmHg					
Median (Q1, Q3)	8 (7, 9)	8 (6, 9)	8 (6, 9)	0.474	0.674
Missing	0 (0)	0 (0)	0 (0)		
PVR, WU					
Median (Q1, Q3)	3.2 (2.5, 4.1)	3.3 (2.9, 3.9)	3.3 (2.7, 4)	0.638	0.787
Missing	0 (0)	0 (0)	0 (0)		
CI, L·min^{-1}·m^{-2}					
Median (Q1, Q3)	2.5 (2, 3.2)	2.4 (2.2, 3)	2.4 (2, 3.1)	0.498	0.636
Missing	0 (0)	0 (0)	0 (0)		
6MWD, m					
Median (Q1, Q3)	330 (260, 430)	330 (310, 390)	330 (290, 410)	0.929	0.922
Missing	3 (14)	32 (56)	35 (45)		
BNP, pg·mL^{-1}					
Median (Q1, Q3)	80 (48, 120)	94 (42, 190)	85 (42, 150)	0.992	0.526
Missing	5 (24)	23 (40)	28 (36)		
Creatinine, µmol·L^{-1}					
Median (Q1, Q3)	88 (82, 110)	89 (73, 110)	88 (74, 110)	0.706	0.814
Missing	3 (14)	17 (30)	20 (26)		
Metabolic syndrome					
True	7 (33)	14 (25)	21 (27)	0.626	
Missing	0 (0)	0 (0)	0 (0)		
Cardiovascular disease					
True	14 (67)	37 (65)	51 (65)	>0.999	
Missing	0 (0)	0 (0)	0 (0)		
Renal comorbidities					
True	4 (19)	7 (12)	11 (14)	0.693	
Missing	0 (0)	0 (0)	0 (0)		
Cancer					
True	2 (9.5)	5 (8.8)	7 (9)	>0.999	
Missing	0 (0)	0 (0)	0 (0)		
Sleep apnoea syndrome					
True	1 (4.8)	5 (8.8)	6 (7.7)	0.912	
Missing	0 (0)	0 (0)	0 (0)		
Oxygen treatment					
True	9 (43)	5 (8.8)	14 (18)	0.002	
Missing	0 (0)	0 (0)	0 (0)		
PAH subgroup					
PAH (not further specified) (1)	6 (29)	25 (44)	31 (40)	0.328	
IPAH (1.1)	4 (19)	9 (16)	13 (17)		
hPAH (1.2)	0 (0)	2 (3.5)	2 (2.6)		

Continued

TABLE 3 Continued

Treatment	Treated (n=21)	Untreated (n=57)	Overall (n=78)	p-value	p-value (U-test)
Drug- and toxin-induced PAH (1.3)	0 (0)	1 (1.8)	1 (1.3)		
Connective tissue disease (1.4.1)	10 (48)	16 (28)	26 (33)		
HIV infection (1.4.2)	0 (0)	1 (1.8)	1 (1.3)		
Portal hypertension (1.4.3)	1 (4.8)	0 (0)	1 (1.3)		
Congenital heart disease (1.4.4)	0 (0)	3 (5.3)	3 (3.8)		
Missing	0 (0)	0 (0)	0 (0)		

Data are presented as n (%) unless otherwise specified. PH: pulmonary hypertension; PAH: pulmonary artery hypertension; mPAP: mean pulmonary arterial pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure; CI: cardiac index, BMI: body mass index; WHO FC: World Health Organization functional class; WU: Wood units; 6MWD: 6-min walk distance; BNP:B-type natriuretic peptide; PAH: pulmonary artery hypertension; IPAH: idiopathic pulmonary hypertension; hPAH: hereditary pulmonary hypertension; HIV: human immunodeficiency virus; ESC: European Society of Cardiology; ERS: European Respiratory Society; Int.: intermediate. p-values are for the comparison of the stratified treatment groups; differences between groups of continuous variables were tested using ANOVA and Mann–Whitney U-test, differences between groups of categorical variables were tested using chi-squared tests.

alongside mild PH. However, subgroup analyses revealed that PH-targeted therapy remained associated with improved survival rates, irrespective of adjustments for various confounders or when restricted to group 1 PH. Even in the presence of comorbidities (which may affect WHO FC additionally to PH), PH-targeted therapy was associated with significantly reduced HRs.

One might hypothesise that initiating PH-targeted therapy early could have a meaningful impact on the "natural trajectory" of mild PH. One of the primary determinants of symptoms and survival is the RV [46]. Even mild, chronic elevation of RV afterload significantly affects its complex architecture and function [7]. Once RV failure develops, treatment necessitates high expertise, and in some cases, irreversible RV failure leads to early death among PH patients, underscoring the importance of early PH-targeted treatment. Our findings suggest that early treatment of even mild forms of precapillary PH in both group 1 and group 4 patients could significantly influence outcomes across all tested models, justifying the use of PH-targeted drugs in these patient populations.

However, this study is limited by its retrospective study design and therefore the findings should be considered exploratory. Additionally, a relatively small number of patients was included, making separate analysis for group 4 patients unfeasible. The decision to initiate PH-specific drugs was determined by the respective clinicians, thus potentially introducing a selection bias. However, comparison of the baseline characteristics of the treated *versus* the nontreated patients did not indicate any "advantage", but rather a "disadvantage" at baseline of the treatment group, and detailed statistical analyses, including propensity matching and sensitivity analyses support the robustness of the survival advantage of the treated patients in our GoDeep cohort. To mitigate potential biases, we took measures to limit a potential immortal time bias, further substantiated by using various regression models, propensity score matching, subgroup as well as in-depth sensitivity analyses, all underscoring the robustness of our results. Follow-up pulmonary haemodynamics are missing, thus the natural trajectory in the untreated group and haemodynamic changes in the treated group cannot be delineated. Another limitation is the lack of pulmonary haemodynamics during exertion (either exercise or volume challenge), which could offer insights into PVD and latent

TABLE 4 Risk scores by pulmonary hypertension treatment for pulmonary hypertension group 1

Treatment	Treated (n=21)	Untreated (n=57)	Overall (n=78)	p-value
COMPERA 4-strata				
Low	3 (14)	9 (16)	12 (15)	0.230
Int.–low	11 (52)	39 (68)	50 (64)	
Int.–high	7 (33)	9 (16)	16 (21)	
ESC/ERS 2022				
Int.	18 (86)	46 (81)	64 (82)	0.858

Data are presented as n (%). ESC: European Society of Cardiology; ERS: European Respiratory Society.

left-heart diseases. This is particularly relevant given the comparatively high age of our study population compared with typical idiopathic pulmonary hypertension, potentially reflecting a PAH cohort with cardiopulmonary comorbidities ("atypical" PAH). However, most included patients had a PAWP <13 mmHg, indicating minimal impact from left-heart diseases in this regard. Additionally, it should be noted that the absence of information regarding interventional or surgical treatment for mild CTEPH patients may influence the presented survival rates. However, subgroup analyses conducted solely in PAH (group 1 PH) patients, in whom such treatment options are not available, revealed similar results to those of the overall study population. The subgroup of mild CTEPH patients in our cohort was too small to run a separate statistical analysis for these patients, which should be performed upon future enlargement of this cohort. Moreover, only Riociguat but not PDE5i is approved for CTEPH patients. Most of the included patients were enrolled in Giessen, which may lead to a selection bias. Additionally, pulmonary function tests excluded major obstructive and restrictive ventilatory disorders. However, computed tomography data are not available in the PVRI GoDeep registry; thus, we cannot exclude moderate interstitial abnormalities, particularly in PAH associated with connective tissue disease. This may contribute to the notably impaired D_{LCO} of the study population and oxygen dependency. As a further limitation, cardiovascular death encompasses various causes, not limited to right heart failure, such as stroke and acute myocardial infarction. Last, we have no information about smoking status of the patients. Prospective studies to corroborate the efficacy of PH-targeted therapy in mild PH are needed.

In conclusion, patients with precapillary PH of group 1 and 4, and mPAP ranging from 21–24 mmHg, may benefit from PH-targeted treatment.

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This study is registered at www.clinicaltrials.gov with identifier number NCT05329714.

Ethics statement: The University of Giessen/University Hospital Ethics Committee and the responsible local ethic committees have approved the PVRI GoDeep central data repository.

Conflict of interest: A. Yogeswaran reports nonfinancial support from the University of Giessen during the conduct of the study, and personal fees from MSD outside the submitted work. P.M. Hassoun reports personal fees from Merck

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