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ORIGINAL ARTICLE
Heart failure

Long-term outcome of patients with combined post- and pre-capillary pulmonary hypertension

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Aims

Pulmonary hypertension (PH) is a complex clinical condition, and left heart disease is the leading cause. Little is known about the epidemiology and prognosis of combined post- and pre-capillary PH (CpcPH).

Methods and results

This retrospective analysis of the Swiss PH Registry included incident patients with CpcPH registered from January 2001 to June 2019 at 13 Swiss hospitals. Patient baseline characteristics [age, sex, mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP), pulmonary vascular resistance (PVR), and risk factors, including World Health Organization (WHO)-functional class (FC), 6 min walk distance (6MWD), and N-terminal pro-brain natriuretic peptide (NT-proBNP), treatment, days of follow-up, and events (death or loss to follow-up) at last visit] were analysed by Kaplan–Meier and Cox regression analyses. Two hundred and thirty-one patients (59.3% women, age 65 ± 12 years, mPAP 48 ± 11 mmHg, PAWP 21 ± 5 mmHg, PVR 7.2 ± 4.8 WU) were included. Survival analyses showed a significantly longer survival for women [hazard ratio (HR) 0.58 (0.38–0.89); $P = 0.01$] and a higher mortality risk for mPAP > 46 mmHg [HR 1.58 (1.03–2.43); $P = 0.04$] but no association with age or PVR. Patients stratified to high risk according to four-strata risk assessment had an increased mortality risk compared with patients stratified to low-intermediate risk [HR 2.44 (1.23–4.84); $P = 0.01$]. A total of 46.8% of CpcPH patients received PH-targeted pharmacotherapy; however, PH-targeted medication was not associated with longer survival.

Conclusion

Among patients with CpcPH, women and patients with an mPAP ≤46 mmHg survived longer. Furthermore, risk stratification by using non-invasively assessed risk factors, such as WHO-FC, 6MWD, and NT-proBNP, as proposed for pulmonary arterial hypertension, stratified survival in CpcPH, and might be helpful in the management of these patients.

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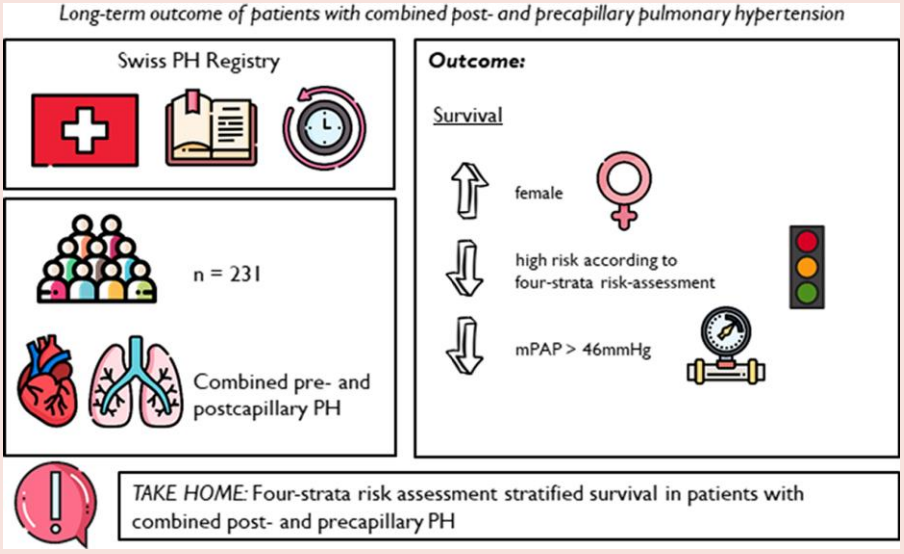
Graphical Abstract



Keywords Pulmonary hypertension • Combined post- and pre-capillary pulmonary hypertension • Left heart disease • Survival • CpcPH • PH-LHD

Introduction

Pulmonary hypertension (PH) is a haemodynamic condition that affects ~1% of the global population. It may be associated with a variety of cardiovascular and respiratory diseases. Left heart disease (LHD) is the leading cause of PH, and the global burden has doubled from 1990 to 2013.[1,2]

Pulmonary hypertension is now defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg assessed by right heart catheterization (RHC). It is classified according to the World Health Organization (WHO) into five clinical groups: pulmonary arterial hypertension (PAH, Group 1), PH associated with LHD (Group 2), PH associated with lung disease and/or hypoxia (Group 3), PH associated with pulmonary artery obstructions [including chronic thromboembolic PH (CTEPH), Group 4], and PH with unclear and/or multifactorial mechanism (Group 5).[3]

Pulmonary hypertension is a chronic progressive disease. Patient-oriented care is essential for PH management, and current guidelines recommend the assessment of disease severity and prognosis at the time of diagnosis.[3] Past studies made efforts to identify the determinants of prognosis. Risk assessment plays a key role in the evaluation of prognosis. Therefore, assessment tools for risk stratification were implemented for patients with PAH.[3]

The Swiss PH Registry is a collaboration between 13 Swiss hospitals, which has been established in 1998. After inclusion of prevalent PH cases, patients newly diagnosed with PH were included from 2000 onwards. Originally, it focused on PAH/CTEPH, but entering patient data from all five diagnostic groups was allowed. The registry with its long-term follow-up data provided the opportunity to compare incident PH patients by assessing patients' characteristics and outcome.

This study focuses on patients with combined post- and pre-capillary (CpcPH-LHD), a subgroup of PH associated with LHD (PH-LHD), which is defined as a post-capillary condition with a pulmonary arterial wedge pressure (PAWP) >15 mmHg and a pulmonary vascular resistance (PVR) >2 WU.[3]

The aim of this study was to assess the baseline characteristics and the survival of a cohort of incident patients diagnosed with CpcPH. We looked for the potential association between baseline variables and overall mortality. Finally, we hypothesized that risk assessment stratification, as defined and validated for PAH, could also be applied to patients with CpcPH.

Methods

The design of the Swiss PH Registry has been described previously.[4–6] All participants gave written informed consent to have their data registered and used for research. The clarification of responsibility conducted by the Cantonal Ethics Review Board concluded that no further ethical approval is needed (BASEC-No. Req-2019-00662).

The present analysis focused on incident patients with CpcPH. Therefore, patients not fulfilling the updated criteria of post-capillary PH (mPAP >20 mmHg, PAWP >15 mmHg) and patients with isolated post-capillary PH (PVR <2 WU) were excluded.[3] Furthermore, patients were excluded if mandatory variables for diagnosis and classification such as mPAP, PAWP, or PVR were missing. If the baseline entry was before the year 2001, or in case of no documented follow-up visit, patients were also excluded from analysis.

Patient characteristics (age, gender, body mass index) and pulmonary haemodynamics (mPAP, PAWP, PVR, cardiac index) assessed by diagnostic RHC were retrieved at the time of diagnosis (baseline). Each patient was classified by the treating PH specialist at each centre to one of the five PH groups. The follow-up schedule varied depending on centres and individual patient factors, with at least yearly follow-ups. Events in the registry were defined as death, transplantation, or pulmonary endarterectomy. For this analysis, death was applied as an endpoint, and other events were excluded from our analysis.

The variables, which we further analysed, included baseline data such as age, gender, mPAP, and PVR. We used at least one of the three determinants of prognosis [WHO functional class (WHO-FC), 6 min walk distance (6MWD), and brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP, hereafter summarized as BNP)], acquired within 100 days of baseline RHC, for an initial four-strata risk assessment according to

the latest guidelines for PAH.[3] Furthermore, PAH-targeted drug therapies during the last visit were summarized as prostanoids (oral, subcutaneous, or intravenous), endothelin receptor antagonists, phosphodiesterase-5-inhibitors, soluble guanylate cyclase stimulators, and prostacyclin receptor agonists.

Baseline characteristics are summarized as mean ± standard deviation (SD). Survival analysis was performed using Kaplan–Meier survival function and graphically displayed by Kaplan–Meier survival curves. Outcome comparison between different groups was done based on the log-rank test and additionally with patients stratified by the median of mPAP, median PVR, and median age.

We additionally performed an univariate and multivariate Cox regression analysis (outcome: time to death) adjusting for potential confounding by age, sex, haemodynamic parameters (mPAP and PVR), risk at baseline according to the four-strata risk-assessment tool, and PH-specific therapy (no medication, monotherapy, combination therapy). Hazard ratios (HRs) were built to assess relative death risk. We tested the proportional hazard assumption for each covariate and calculated graphs of the scaled Schoenfeld residuals against the transformed time.

The analysis was done using R (Version 4.2.1, RStudio Version 1.2.1578).

Results

Epidemiology of baseline characteristics

The patient flow is shown in *Figure 1*. One thousand one hundred and sixty-nine of 1427 patients in the Swiss PH Registry were excluded due to not fulfilling haemodynamic criteria of CpcPH. Twenty-seven patients were excluded due to missing follow-up visit. In summary, 231 patients with CpcPH were included in our analysis.

Baseline characteristics are shown in *Table 1*. Of the 231 patients with haemodynamic CpcPH, 137 (59.3%) were females. The mean time of follow-up was 1361 days (3.7 years), the range varied from 20 to 5586 days (up to 15.3 years). Overall, 86 of 231 (37%) patients died within the follow-up. Our cohort presented with a mean mPAP of 47.7 mmHg (±11.2) and median of 46 mmHg (40–56) and mean PVR of 7.2 WU (±4.8) and median of 5.8 WU (4.2–9.2). Only 41 patients (17.8%) were initially diagnosed with PH associated with LHD (Group 2). The remaining were classified within the other PH groups, as shown in *Table 1*. A total of 46.8% of patients received PH-targeted pharmacotherapy at the time of the last visit.

Table 2 summarizes the baseline characteristics of patients with and without treatment. Patients receiving pharmacotherapy were slightly younger, had higher PVR, and were mostly classified within another WHO Group (mostly PAH and CTEPH) and not as Group 2 PH.

Kaplan–Meier analysis of survival

Kaplan–Meier curves stratified by gender and the medians of age (≤68 vs. >68 years), mPAP (≤46 vs. >46 mmHg), and PVR (≤5.8 vs. >5.8 WU) are shown in *Figure 2A–D*. *Figure 2E and F* illustrates the Kaplan–Meier curves by the four-strata risk class and PH-targeted pharmacotherapy given during follow-up as no medication, mono- and combination therapy.

The analysis indicated a significantly longer survival for females compared with males ($P = 0.011$), mPAP ≤46 mmHg compared with >46 mmHg ($P = 0.035$), and patients categorized as 'low risk' compared with 'high risk' according to four-strata risk assessment ($P = 0.015$). Referring to age and PVR the analysis did not show a significant difference in survival time. Focusing on the established medication at the time of our last visit, we could not reveal a significant difference in the survival time of patients receiving medication compared with patients without PH-specific pharmacotherapy.

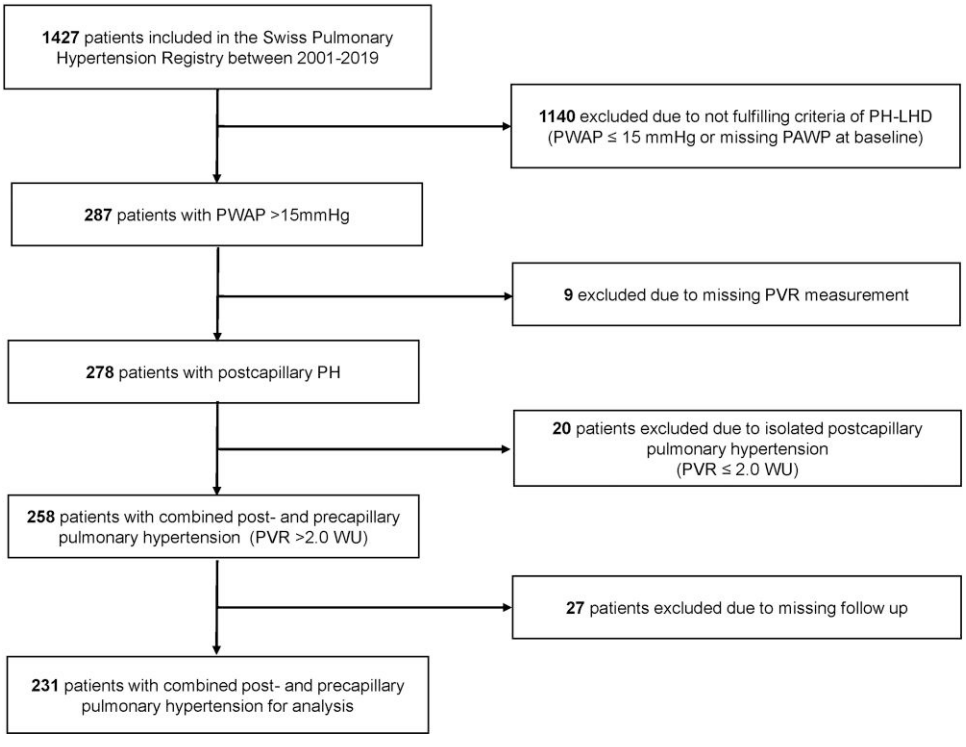


Figure 1 Enrolment of the study cohort. mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

Table 1 Baseline characteristics of patients

Demographics	
Number of patients	231
Female	137 (59.3%)
Age, years	65 ± 12
Body mass index, kg/m^2	28.8 ± 7.2
Haemodynamic characteristics	
Mean pulmonary artery pressure, mmHg	48 ± 11
Cardiac index, L/min/m^2	2.5 ± 0.8
Cardiac output, L/min	4.7 ± 1.5
Pulmonary artery wedge pressure, mmHg	21 ± 5
Pulmonary vascular resistance, WU	7.2 ± 4.8
Diagnostic group as listed in the Swiss PH registry	
Pulmonary arterial hypertension (Group 1)	103
PH associated with left heart disease (Group 2)	41
PH associated with lung disease (Group 3)	32
Chronic thromboembolic PH (Group 4)	47
Unclear and/or multifactorial (Group 5)	8
Follow-up	
Days	1361 ± 1170
Years	3.7 ± 3.2
PH-specific medication established at last visit	108 (46.8%)
Monotherapy	53
Dual therapy	43
Triple therapy	12
Pulmonary endarterectomy performed	5
Risk stratification at baseline (four-strata risk)[a]	
Low risk	5
Intermediate: low risk	52
Intermediate: high risk	135
High risk	31
Not classified	8
Concomitant cardiovascular disease	
Arterial hypertension	57 ($n = 105$[b])
Diabetes mellitus	26 ($n = 101$[b])
Coronary artery disease	32 ($n = 102$[b])
Obesity (body mass index ≥30 kg/m^2)	90 ($n = 225$[b])

Data are given as mean ± SD or numbers (%).
PH, pulmonary hypertension.
[a]Determinants of prognosis: WHO FC, 6 MWD, BNP, or NT-proBNP.
[b]*n* shows the number of subjects with available information.

Cox regression

The univariate Cox regression analysis is illustrated in *Figure 3* and revealed that male sex, higher mPAP, and being classified as high risk within up to 100 days of diagnosis were associated with significantly increased relative death risk. Females had 42% reduced mortality risk within the time of follow-up compared with males [HR = 0.58, 95% confidence interval (CI) 0.38–0.89; $P = 0.012$]. Mean pulmonary artery pressure >46 mmHg increased the relative death risk by 58% compared with mPAP ≤46 mmHg [HR = 1.58 (95% CI 1.03–2.43); $P = 0.04$] and high-risk patients had a 144% higher probability of death compared with intermediate low risk [HR = 2.44 (95% CI 1.23–4.84); $P = 0.01$]. Of interest, age at time of diagnosis, a higher PVR or pharmacotherapy revealed no association with the outcome.

Multivariate Cox regression analysis reinforced the results from univariate analysis, showing that male sex and high risk near diagnosis are associated with increased death risk (*Figure 4*).

Discussion

The Swiss PH Registry provides comprehensive long-term data on the epidemiology of various PH groups in Switzerland. The present study focused on a group of patients who are frequently seen in PH centres, but on whom long-term data are scarce, namely patients with CpcPH. In the present analysis, we could demonstrate that male sex and a very high mPAP at diagnosis are associated with a higher probability of death, whereas age, PVR, and PH-targeted therapy are not. Of interest, we could show that the four-strata risk-assessment tool for PAH using the widely available parameters WHO-FC, 6MWD, and BNP was also able to stratify risk in patients with CpcPH.

Pulmonary hypertension associated with LHD is the most frequent group of PH and due to the lack of specific pharmacotherapy management is mainly based on general measures for PH and treatment of LHD. In our registry, 231 of 251 patients (92%) with post-capillary PH were categorized as CpcPH. This high proportion does not reflect the estimated prevalence of CpcPH within PH-LHD according to previous studies, which is ~20–30%.[3,7–9] This discrepancy may be due to the design of the Swiss PH Registry, which was originally created for the follow-up of patients with pre-capillary pulmonary vascular disease, who would qualify for PAH-targeted drug therapy. This is also reflected by the fact that in the present cohort of CpcPH, despite the increased PAWP, the majority of patients were clinically classified by the treating PH specialist as having PAH, CTEPH, or PH associated with lung disease. It may well be that a significant proportion of the CpcPH patients, who per definition had an increased PVR of >2 WU, were classified as PAH in order to facilitate a trial of PAH-targeted pharmacotherapy.

Published data estimate that >80% of patients with post-capillary PH are >65 years old.[7] Our cohort revealed a mean age of 65.4 years and a median age of 68 years at baseline and with an age range of 21–90 years. Our data show no significant association between age at the time of diagnosis (younger vs. older than median) and mortality risk.

Similarly to patients with PAH, females with CpcPH had a significantly longer survival compared with males according to Kaplan–Meier analysis ($P = 0.011$), which is also emphasized by a lower HR in the univariate Cox regression analysis [HR 0.58 (95% CI 0.38–0.89)]. This finding is consistent with not only long-term follow-up data from patients with PH due to valvular heart disease, but also registry data from patients with PAH, including the Swiss PH Registry.[4,10] Furthermore, a female predominance in patients with PH due to heart failure with preserved ejection fraction has been previously reported.[11] The impact of specific aetiologies of chronic LHD leading to CpcPH should be further investigated.

Currently, risk stratification for PAH patients at baseline is recommended with a comprehensive three-strata model, and the four-strata risk-assessment tool is recommended at first follow-up at 3 months for risk stratification.[3] Data from the COMPERA analysis in 2021 have proved that four-strata risk assessment is more sensitive to prognostically relevant changes in risk than the three-strata model also when used at the time of diagnosis.[12] That is why we chose to use the clinically

Table 2 Baseline characteristics of patients adjusted for pulmonary hypertension–specific pharmacotherapy

	All patients	No therapy	Monotherapy	Combined therapy
n	231	123 (53.3%)	53 (22.9%)	55 (23.8%)
Age, years	65.4 ± 12.4	67.5 ± 11.7	64.6 ± 10.8	61.7 ± 14.5
Female	137 (59.3%)	70 (56.9%)	30 (56.6%)	37 (67.3%)
Diagnostic group as listed in the Swiss PH registry				
Pulmonary arterial hypertension (Group 1)	103	38	30	35
PH associated with left heart disease (Group 2)	41	35	2	4
PH associated with lung disease (Group 3)	32	21	8	3
CTEPH (Group 4)	47	27	9	11
Unclear and/or multifactorial (Group 5)	8	2	4	2
Haemodynamic parameters				
mPAP, mmHg	48 ± 11	46.0 ± 10.6	49.5 ± 10.9	49.9 ± 12.4
PVR, WU	7.2 ± 4.8	6.1 ± 3.6	8.1 ± 5.8	8.8 ± 5.6
PAWP, mmHg	20.9 ± 5.4	21.1 ± 5.4	20.2 ± 4.6	21.0 ± 6.1
Cardiac output, L/min	4.70 ± 1.51	4.9 ± 1.5	4.8 ± 1.6	4.2 ± 1.4
Cardiac index, L/min/m^2	2.5 ± 0.81	2.6 ± 0.8	2.5 ± 0.7	2.3 ± 0.8

Data are given as mean ± SD or numbers (%).
CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.

more feasible four-strata risk-assessment tool with simple measures (WHO-FC, 6MWD, and BNP) obtained up to 100 days from baseline in our CpcPH cohort. Our data indicated that the four-strata risk-assessment tool for PAH had prognostic value also in patients with CpcPH estimated at time of diagnosis up to 100 days. In particular, patients classified as high risk had a significantly shorter survival, as shown in Kaplan–Meier analysis ($P = 0.015$) and a higher mortality risk [HR 2.44 (95% CI 1.23–4.84); $P = 0.01$]. However, our raw registry data were partly incomplete, so we based the risk stratification on at least one of the three determinants of prognosis. Taking into account that the four-strata risk-assessment tool is validated for at least two variables, we point this out as a limitation of our study, but potentially also as advantage, as even with a limited number of variables, the proposed risk strata were able to stratify patients with CpcPH according to their survival.

Several recent meta-analyses have focused on finding a predictor of outcome in PH-LHD. Some haemodynamic measures, either alone or combined, have been described to be associated with outcome in PH-LHD: PVR, PAP, pulmonary arterial compliance, transpulmonary pressure gradient, and diastolic pressure gradient.[3,8,9,11] The most consistent data are available for PVR. Multiple studies have shown that increases in PAP and PVR are associated with worse outcome.[3,9,10,13,14] In our cohort, we found a significantly shorter survival and higher mortality risk in patients with mPAP >46 mmHg [$P = 0.035$; HR 1.58 (95% CI 1.03–2.43)]. In contrast, our data did not show a significant difference regarding PVR, which may be explained by the fact that we only included patients with an elevated PVR >2 WU defining CpcPH. The median PVR with 5.8 WU was relatively high in our cohort, which may explain that even patients below the threshold already had an elevated mortality risk and sensitivity analysis of alternative PVR cut offs could not detect significant results for lower or higher cut offs. In 2020, a large retrospective cohort study of patients undergoing RHC in the Veterans Affairs healthcare system from 2008 to 2016 showed that a PVR ≥2.2 WU was associated with adverse outcomes also among patients with post-capillary PH (mPAP ≥19 mmHg, PAWP >15 mmHg).[14] Our cohort has a mean PVR of 7.2 WU, indicating a severe pre-capillary component. Taking this into account, the increase in PVR >5.8 vs. ≤5.8 WU was not associated with an impact on the outcome.

Finally, we looked at the established therapy at the time of the last visit. The current ESC/ERS guidelines state 'limited and conflicting evidence for the use of drugs approved for PAH in patients with group 2 PH'.[3] Surprisingly, 46.8% of patients had a PH-targeted medication established at time of last visit. This may be attributed to the fact that in our registry, despite the clearly elevated PAWP, only 41 patients (17.8%) were categorized as PH-LHD Group 2. We assume that the majority of patients were assigned to other groups than Group 2 according to a physician's decision most likely based on clinical data and the elevated PVR. The present analysis did not reflect this because it looked at the prognosis in patients haemodynamically defined CpcPH irrespective of concomitant clinical features and irrespective of the predominant clinical group, as there were no pre-specified clinical criteria. Furthermore, we assume a relevant selection bias because the registry originally intended to include patients with pulmonary vascular disease suffering from pre-capillary PH, and thus, our data are not representative of the entire collective of patients undergoing RHC in cardiology clinics including patients with isolated post-capillary PH. In the present analysis, we included patients according to current guidelines with an mPAP >20 mmHg; however, most of the patients received their diagnosis of PH before 2022 and thus, the vast majority of patients had an mPAP well above 25 mmHg and thus our results may not apply to patients with an mPAP between 20 and 25 mmHg. Looking at the subgroups adjusted for PH-targeted pharmacotherapy in detail, we observed that patients receiving PH-targeted therapy showed a lower mean age and higher mean PVR. The severe pre-capillary component in a large proportion of our cohort may have influenced clinicians' decision-making. Currently, available PH-targeted drugs are pulmonary vasodilators

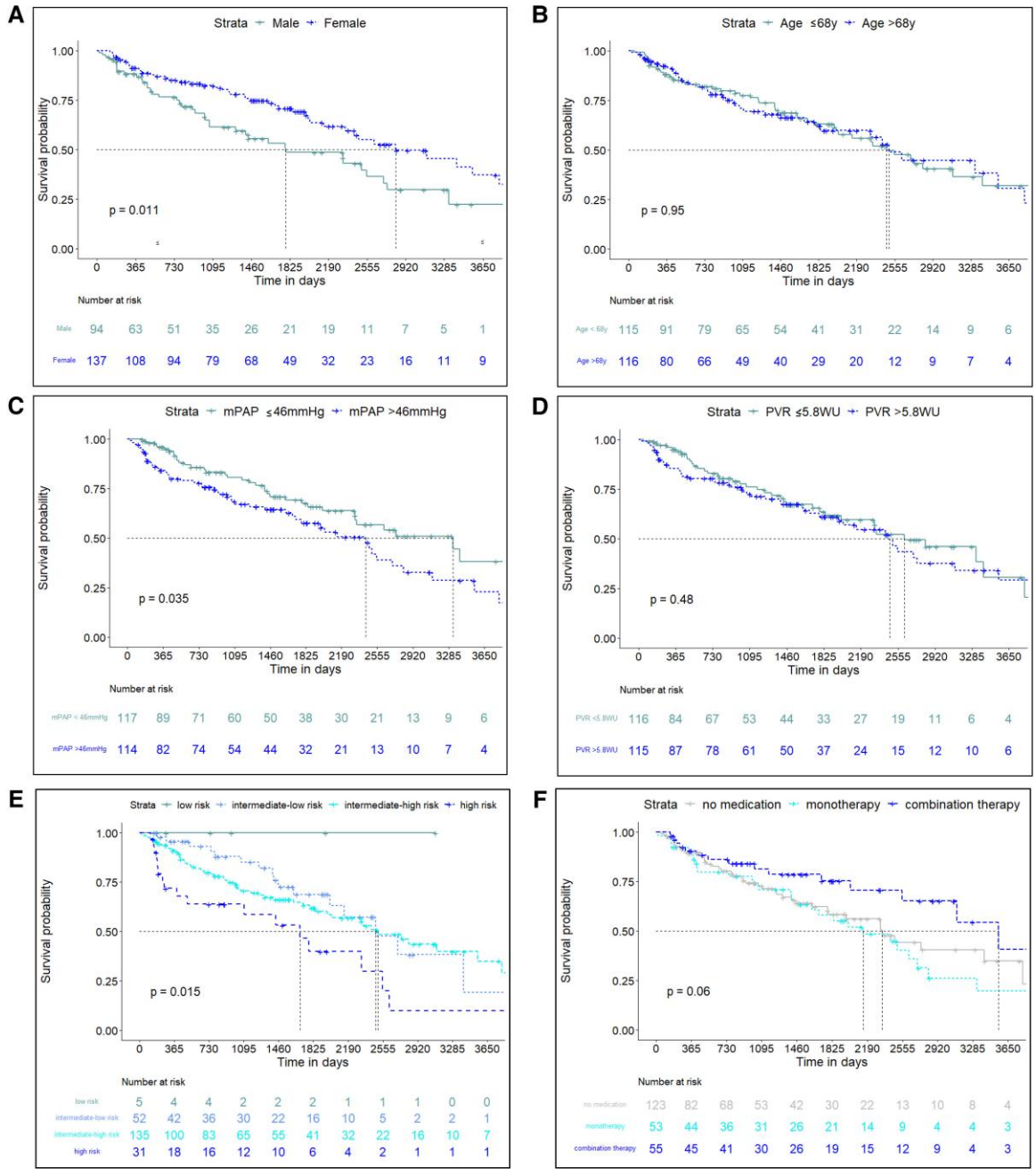


Figure 2 Kaplan–Meier survival curves and number at risk for all patients stratified by (*A*) gender, (*B*) age (cohort split at median age of 68 years), (*C*) mean pulmonary artery pressure (cohort split at median of 46 mmHg), (*D*) pulmonary vascular resistance (cohort split at median of 5.8 WU). The dashed lines indicate 50% survival and the corresponding *P*-value refers to the comparison of median survival by the log-rank test. The number at risk is presented in a table below the survival curves. The timeline is presented in days. (*E* and *F*) Kaplan–Meier survival curves and number at risk for all patients stratified by (*E*) risk at baseline and (*F*) pulmonary hypertension–targeted pharmacotherapy. The dashed lines indicate 50% survival and the corresponding *P*-value refers to the comparison of median survival by the log-rank test. The number at risk is presented in a table below the survival curves. The timeline is presented in days.

primarily acting on PVR. Therefore, elevated PVR has been discussed as a potential criterion for the indication of pharmacotherapy in past studies and might have had an impact on treatment decisions of our cohort as well.[15] Kaplan–Meier and Cox regression analyses did not show a significant difference between CpcPH patients receiving monotherapy, combination therapy, and patients without medication. However, as this is a retrospective analysis in a heterogeneous group, drawing conclusion about the effect of vasodilator therapies in subgroups is hazardous. It remains unclear if treatment might have possibly prevented worse survival rates in those patients under targeted

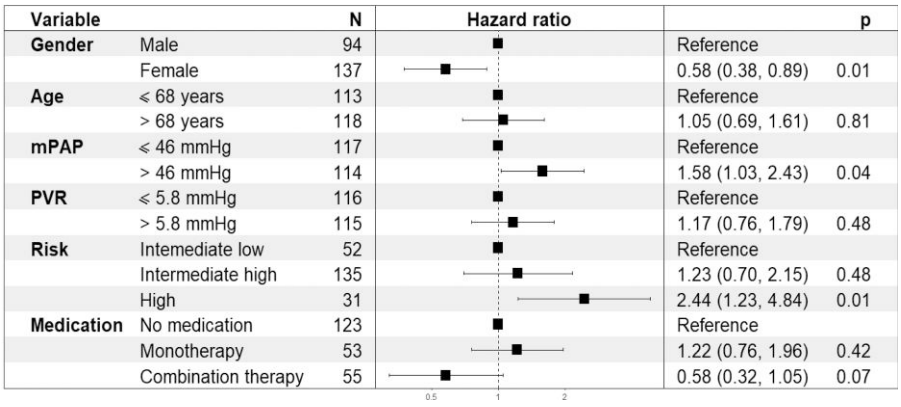


Figure 3 Univariate Cox regression analysis of survival.

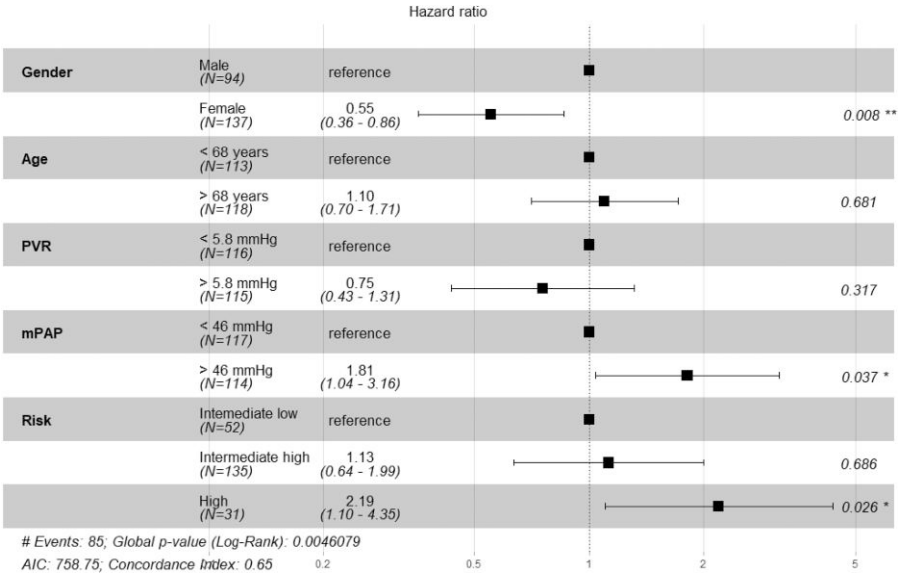


Figure 4 Multivariate Cox regression analysis of survival. The covariates used in the analysis are gender, age, pulmonary vascular resistance, mean pulmonary artery pressure, and risk according to the four-strata risk-assessment tool.

PH therapy and thus, the effect of vasodilator therapies as used in PAH should be investigated in properly designed randomized controlled trials in patients with CpcPH.

Conclusions

This long-term retrospective data analysis in patients with CpcPH shows that female sex and lower mPAP are associated with longer survival. In accordance with data for patients with PAH, the simple four-strata risk-assessment tool using WHO-FC, 6MWD, and BNP was also able to stratify survival in CpcPH patients, which may help physicians and patients in the management of this heterogeneous patient population.

Lead author biography

Anna Titz graduated from Heinrich Heine University Dusseldorf, Germany, with a degree in medicine in 2017. After specializing in internal medicine, she is currently working as a pulmonology resident at University Hospital Zurich, Switzerland. In addition, she takes part in clinical research focusing on patients with pulmonary hypertension and high-altitude medicine.

Data availability

Data can be made available upon request.

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Consent

All participants gave written informed consent to have their data registered and used for research.

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Conflict of interest: A.M.D. reports personal fees from Astra Zeneca, Gebro Pharma, GSK, and MSD and financial support to attend scientific meetings from Janssen and OrPha Swiss outside the submitted work. S.A.G. reports grants and personal fees from MSD, Gebro, and Orpha outside the submitted work. M.L. reports personal fees from Janssen, personal fees from MSD, and personal fees from OrphaSwiss outside the submitted work. S.U. receives research grants from the Swiss National Science Foundation, Zurich, and Swiss Lung League and EMDO foundation and grants, travel support and consultancy fees from Orpha Swiss, Janssen SA, MSD SA, and Novartis, all unrelated to the present work. All other authors report no conflicts of interest.

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