Systemic Hypertension and Survival in Pulmonary Hypertension

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AI Tool Use Disclosure

During the preparation of this work, the authors used ChatGPT for the purpose of improving language, grammar, and readability.

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Key points:

Question:

How are systemic arterial pressure and heart rate associated with survival in PH?

Findings:

In this international cohort study including 12,771 incident PH patients, systemic blood pressure and heart rate were independently associated with survival. Higher systemic pressure correlated positively with cardiac index and tricuspid annular plane systolic excursion. Furthermore, systolic pressure and heart rate trajectories were associated with mortality. Results were externally validated in an independent UK cohort

Meaning:

In PH, higher systemic blood pressure is associated with improved survival, while high heart rate and declining systolic pressure trajectories are significant predictors of mortality.

96/100 Words

Abstract

Importance:

Pulmonary hypertension (PH), a progressive and life-threatening condition with rising prevalence among older adults, frequently coexists with systemic hypertension, the prognostic impact of which is poorly understood.

Objective:

To evaluate the association between systemic hypertension and survival in PH patients.

Design:

This multicenter study analyzed data from the PVRI GoDeep meta-registry, integrating global retrospective and prospective PH cohorts. Survival was assessed using multivariable Cox proportional hazards models, adjusted for key confounders, with sensitivity analyses to validate robustness. Independent, external validation was performed in a separate UK cohort

Setting:

Multicenter study involving PH referral centers across diverse geographic regions and healthcare systems worldwide with independent external validation.

Participants:

12,771 incident PH patients (median age 65 years, both sexes) diagnosed via right heart catheterization and comprehensive clinical data, encompassing all PH groups and age categories.

Exposures:

Center-reported diagnosis of systemic hypertension, baseline systolic systemic arterial pressure (sSAP) and heart rate as well as longitudinal sSAP and heart rate trajectories.

Main Outcomes and Measures:

All-cause mortality, adjusted for confounding variables including age, PH group, antihypertensive and PH-specific medications, and cardiac index

Results:

Higher baseline sSAP and pre-existing systemic hypertension were independently associated with improved survival. Hypertensive patients exhibited a 30% reduced mortality hazard (HR 0.74; 95% CI 0.68–0.79) compared to normotensive counterparts. Survival benefits correlated positively with increasing sSAP (80–180 mmHg), remained consistent across PH groups and age groups, and were particularly independent of antihypertensive and PH-specific medications. Elevated heart rate predicted higher mortality. sSAP increments correlated with improved cardiac index and tricuspid annular plane systolic excursion. Decreased sSAP and higher heart rate during follow-up correlated with higher mortality. External validation in a separate UK cohort confirmed these findings.

Conclusion and Relevance:

In this global PH cohort, higher systemic arterial pressure was associated with enhanced survival, while a higher baseline heart rate and declining systemic blood pressure during follow-up are significant predictors of increased mortality risk.

Introduction

Pulmonary hypertension (PH) is a chronic and life-threatening condition characterized by pulmonary vascular remodeling, which leads to increased right ventricular (RV) afterload and ultimately death due to right heart failure[1-3]. Traditionally, pulmonary arterial hypertension (PAH; Group 1 PH) was considered a disease primarily affecting young female patients[1,4]. However, recent studies have revealed a significant shift towards an older P(A)H patient population[1,4]. Epidemiological data indicate that over 10% of the Western population aged above 65 years suffers from PH, which is associated with increased mortality[5].

Aging of the PH population correlates with a higher prevalence of comorbidities with Chronic obstructive pulmonary disease (COPD), metabolic syndrome, and renal insufficiency being associated with increased mortality among PH patients[6-8]. However, limited evidence exists regarding the impact of systemic arterial hypertension on PH survival outcomes. To explore this relationship further, we utilized the international PVRI GoDeep meta-registry with external validation in the UK & ASPIRE P(A)H population[9].

Methods

Study Population

All patients from the Pulmonary Vascular Research Institute (PVRI) GoDeep meta-registry who had right heart catheter (RHC)-confirmed PH, diagnosed by a PH expert center according to international guidelines were included (eFigure 1)[1,10]. Systolic and diastolic systemic arterial pressure as well as heart rate were recorded at rest during the initial RHC. To ensure data robustness, measurements were also collected during a −3 to +12 months period around the initial diagnosis, and the median values from this period were used for the analyses. All other variables were taken from the initial RHC, using the value closest to diagnosis when multiple data points were available. Follow up variables for heart rate and systolic arterial pressure were taken between 12 and 36 months after diagnosis. As of September 2025, 34 centers had entered 39,260 patients into GoDeep, out of which 12,771 qualified for the analysis (eFigure 1), originating from the PH centers in Giessen, Sheffield, Nashville, Baltimore, London, Minneapolis, Zurich, Hamburg, Cambridge, Okayama, Thessaloniki, Stanford, Perth, Beijing, Athens, Johannesburg, Cincinnati, Gold Coast, Pavia, Sunshine Coast, Pittsburgh. The PVRI GoDeep registry was approved by the University of Giessen Ethics Committee and the relevant local ethics committees (NCT05329714).

External Validation

An independent external validation cohort was defined using two UK-based registries: the National Cohort Study of Idiopathic and Heritable PAH (NCT01907295, East of England Ethics Committee: 13/EE/0203) and the Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre (ASPIRE) registry (Ethics Committee: 16/YH/0352 & 22/EE/0011). Systemic hypertension was defined as sSAP >140 mmHg and/or dSAP >90 mmHg. Detailed registry descriptions and ethical approvals are provided in the eMethods.

Statistical Analysis

Data were analyzed with R version 4.5.2. A complete-case analysis was conducted, including only participants with no missing data. Continuous variables were summarized as means and standard deviations (SDs) for normally distributed data and medians [Q1, Q3] for data that are not normally distributed. For survival analyses, patients were censored at the date of the last follow-up visit. We employed Cox proportional hazards models to evaluate the association between systemic hypertension (as diagnosed by the respective referral center) and survival, adjusting for sex, center, diagnosis decade, BMI, mPAP and PVR. In analyses restricted to patients with PAH, treatment with PAH-specific drugs was additionally included as a covariate. Age was modeled using a natural spline with two degrees of freedom. To account for potential confounding, adjusted Kaplan-Meier curves were estimated using inverse probability of treatment weighting (IPTW). Non-linear associations were examined using restricted cubic splines for continuous variables. Interaction analyses were performed where data were indicated. Sensitivity analyses, including E-values to assess the impact of unmeasured confounders and the Heller Explained Relative Risk method were conducted to ensure robustness. A detailed description of the statistical methods is available in the eMethods.

Results

Baseline Characteristics

The median age of the GoDeep study population was 65 [53, 73] years, with 5,399 (42%) being male and 3,595 (28%) diagnosed with group 1 PH (Table 1). Pulmonary hemodynamics were severely impaired, as indicated in Table 1. The median sSAP was 130 [120, 150] mmHg and the median heart rate 77 [67, 87] bpm. PAH patients were younger, predominantly female, and exhibited more severe pulmonary hemodynamic impairment compared to the overall PH population (Table 1). PAH patients more frequently received PH-targeting therapies. Median follow-up time was 2.4 [0.5, 5.5] years.

Out of 12,771 PH patients, 6,870 originated from centers in which comorbidity reporting included the presence or absence of systemic hypertension (eFigure 1). Within this cohort, systemic hypertension was reported as a comorbidity in 2,946 (43%) patients. In the PAH group, systemic hypertension was reported in 783 (36%) patients. The prevalence of systemic hypertension increased with the decade of diagnosis, reaching up to 48% among PH patients diagnosed after 2010 (33% before 2010 vs 48% after 2010, χ^2 $p<0.001$). Baseline characteristics stratified by diagnosed systemic hypertension are detailed in eTable 1.

In 160 patients (1.3%) lung or heart transplantation was performed and was considered as an event in the transplant-free survival analyses. The overall 1-, 3-, and 5-year survival rates for PAH patients were 88%, 70%, and 56%, respectively, while the 1-, 3-, and 5-year survival of the overall PH population was 86%, 68%, and 55%.

Association of Center-Reported Systemic Hypertension and Outcome

Baseline characteristics of the patients originating from centers reporting systemic hypertension as a comorbidity largely corresponded to those of the overall cohort (Table 1 and eTable 1). Surprisingly, patients with center-reported systemic hypertension had significantly higher survival rates than those without systemic hypertension in adjusted Kaplan-Meier analysis (Figure 1Aa).

As indicated in eFigure 2, after IPTW adjustment covariates were balanced better. In Cox-regression analysis with adjustment for potential confounders, systemic hypertension was associated with significantly reduced hazard ratios for the overall PH group (HR: 0.74 [0.68, 0.79]) as well as for PAH, idiopathic PAH (IPAH, group 1.1), and PH groups 2–4, respectively (Figure 1Ab). Sensitivity analyses further confirmed a robust association between systemic hypertension and improved survival of PH patients (Figure 1Ac and 1Ad).

As an alternative approach, systemic hypertension was defined using hemodynamic measurements at study entry (sSAP >140 mmHg and/or dSAP >90 mmHg) within the GoDeep cohort, excluding the UK subgroup (GoDeep-UK PH) to avoid any overlap of individual patients. According to this definition, 4,575 (36%) patients were classified as hypertensive. Patients with hemodynamics-based systemic hypertension again demonstrated significantly better survival than those without systemic hypertension (Figure 1B).

External validation was conducted by combining the National Cohort Study of Idiopathic and Heritable PAH with the ASPIRE cohort (UK&ASPIRE cohort). Baseline characteristics of this cohort largely corresponded to those of the GoDeep(-UK) cohort (eTable 2 and 3). Median follow-up time in the validation cohort was 4.5 [2.0, 5.6] years. Corresponding to the GoDeep-UK cohort, patients with hemodynamics-based systemic hypertension in the UK&ASPIRE cohort demonstrated significantly better survival than those without systemic hypertension (Figure 1B).

Association of Systemic Blood Pressure and Heart Rate with Outcome

Next, we analyzed the association between sSAP and survival in PAH patients (n=3,595) and the overall PH cohort (n=12,771), irrespective of the presence or absence of systemic hypertension as dichotomous variable.

As shown in Figure 2, an inverse association was observed between sSAP and hazard ratio both for the PAH and the overall PH population: higher sSAP was associated with a lower hazard ratio, regardless of PH severity (defined by PVR ≤5 WU and >5 WU). Consistent findings were noted in the IPAH subgroup (eFigure 3), and when analyzing diastolic systemic arterial pressure

(eFigure 4). Of note, hypertensive patients (sSAP >140 mmHg) had significantly reduced hazard ratios compared to normotensive patients (sSAP 110 – 140 mmHg), whereas hypotensive patients (sSAP <110 mmHg) had significantly increased hazard ratios (Figure 3).

We next stratified patients into quartiles of sSAP to further analyze its impact on mPAP-dependent mortality. Baseline characteristics of patients within these quartiles are presented in eTable 4 and eTable 5. Figure 2A focusing on PAH patients shows that mortality is strongly dependent on mPAP up to about 45 mmHg and then flattens up. This association between mPAP and hazard ratio was “dose-dependently” modified by the sSAP quartiles, with higher systemic blood pressure associated with lower mortality (Figure 2A). The parallel displacement of spline plots across sSAP quartiles suggests that systemic blood pressure significantly modulates the mortality risk associated with mPAP. Correspondingly, the link between increasing PVR levels and augmented mortality in PAH patients was also modulated by the sSAP quartiles, again showing a parallel displacement of spline plots across these quartiles (eFigure 5). Moreover, sSAP showed a weak but significant correlation with the tricuspid annular plane systolic excursion (TAPSE, spearman rho=0.139, $p<0.001$).

An inverse pattern was observed for heart rate, where higher values were consistently associated with increased hazard ratios across the entire heart rate spectrum, both in the entire PAH study population and in the more moderate (PVR ≤5 WU) and severe (PVR >5 WU) PAH subgroups (Figure 2 and 3). When stratifying into heart rate quartiles, both the association of mPAP with mortality and PVR with mortality were “dose-dependently” shifted to higher hazard ratios with increasing heart rates (eFigure 6; baseline characteristics in eTable 6 and eTable 7).

Similar associations between sSAP, dSAP, heart rate, and the sSAP- and heart rate-dependent modulation of mPAP- and PVR-related hazard ratios were observed across the overall PH population (Figure 2B, 3B, and eFigure 4B, 5B, and 6B).

Association of Systemic Blood Pressure, Heart Rate, and Outcome in Patients with Group 2-4 PH

We additionally evaluated whether the associations observed in the PAH group and the overall PH cohort were consistent across the different PH groups. Baseline characteristics stratified by PH group are detailed in eTable 8. As shown in eFigure 7, the hitherto described associations were consistently replicated across all PH groups. Interaction analysis showed virtually superimposable spline curves for the association of sSAP and survival regardless of PH group (eFigure 8Aiv). Interaction analysis for heart rate, however, revealed meaningful differences (eFigure 8). While heart rate was associated with survival in PH Group 1 and 3, it was not prognostic in PH Group 2 and 4 (eFigure 8Biv)).

Independence of sSAP-Survival Relationship from Systemic Antihypertensive and PAH Therapy and Age

We investigated whether antihypertensive medication might underlie the observed relationship between sSAP, heart rate and survival of PH patients. We included only patients from centers with reporting of antihypertensive drug usage and focused on those patients not receiving angiotensin-converting enzyme inhibitors (ACEi), angiotensin-receptor blocker (ARB), β-blockers or calcium channel blockers (n=545). Baseline characteristics of these patients are presented in eTable 9 and eTable 10. The association between increasing sSAP and decreasing mortality of the PH patients and the PAH patients was fully reproduced in the absence of anti-hypertensive drugs (Figure 4 and eFigure 9). Similarly, when pooling all overall PH and PAH patients never receiving any PAH-specific medication, the association between systemic blood pressure and survival was again reproduced (Figure 4 and eFigure 9). Notably, a positive correlation between sSAP and cardiac index was noted (Figure 4D). Inversely, BNP negatively correlated with sSAP (Figure 4D). Similar results were obtained for heart rate (eFigure 9).

Sensitivity Analyses

We performed sensitivity analyses to analyze the robustness of the hitherto described associations between sSAP and survival. Compared with the reference group (sSAP 110–140 mmHg), the E-values for sSAP <110 mmHg were 1.96, 2.10, and 1.94 for the overall PH cohort,

PAH subgroup, and IPAH subgroup, respectively; for sSAP >140 mmHg, the corresponding E-values were 1.81, 2.01, and 1.90. These values indicate the minimum strength of association that an unmeasured confounder would need to have with both the respective sSAP category and mortality, beyond the measured covariates, to fully explain away the observed association. To eliminate potential variables as confounders, sensitivity analyses further confirmed that the association between sSAP and survival remained robust after adjusting for several potential confounders, such as cardiac index, pulmonary arterial pulse pressure, systemic pulse pressure, and the established ESC/ERS risk score (eFigure 10). Similar results were observed across all ages, WHO functional classes and cardiac index categories (eFigures 8 and 11). A decrease in hazard ratio with increasing sSAP was particularly evident in patients classified as WHO FC III and IV, whereby the hazard ratio initially decreases but then plateaus at around 110 mmHg. Furthermore, interaction analyses showed nearly identical spline curves for the sSAP–survival association, regardless of age or cardiac index categories. To account for potential geographic variations, interaction analyses were performed comparing the USA and Europe. The association between sSAP, heart rate, and survival was consistent across both geographic regions (eFigure 8).

Prognostic Relevance of sSAP and Heart Rate Changes during Follow-Up

Follow-up data, including pulmonary hemodynamics and sSAP, were available for 1241 patients (9.7%) and for heart rate for 1229 patients (9.6%). Within a median interval of 19 [15, 25] months between the diagnostic and first follow-up RHC, the median changes in sSAP and heart rate were -6 [-20, 6.5] mmHg and -2 [-11, 7] bpm, respectively. Patients receiving PH-specific therapy showed no significant differences in sSAP changes during follow-up compared to those without PH-specific therapy during follow-up (p=0.26). As shown in eFigure 12, a decline in sSAP during follow-up, though available only for a limited number of patients, was associated with increased mortality, whereas an increase tended to correlate with improved survival. Whereas there was no

association between any degree of decreasing heart rate and mortality, an increasing heart rate was associated with higher mortality, particularly in patients with ≤5 WU (eFigure 12).

Discussion

This international study analyzed over 12,000 PH patients to explore systemic blood pressure, heart rate, and survival relationships. Key results include: i) P(A)H patients with diagnosed systemic hypertension exhibited better survival rates compared to those without; ii) sSAP measured at PH diagnosis correlated with RV function and was a strong positive predictor of survival, which was independently validated in a separate UK cohort; iii) Higher sSAP "dose-dependently" reduced mortality risk based on mPAP and PVR; iv) Heart rate was inversely associated with survival; v) sSAP correlated with cardiac index, BNP, and TAPSE; vi) These trends persisted across all PH groups and were unaffected by age, systemic and pulmonary arterial stiffness, cardiac index, WHO functional class, P(A)H risk scores, systemic antihypertensive medications or PAH-medications; vii) Longitudinal sSAP and heart rate trajectories were associated with survival.

Demographic shifts worldwide influence the prevalence and characteristics of numerous diseases, including a notable increase in the age of PH patients[11]. Registry studies have documented a rise in several comorbidities including systemic hypertension across different PH populations[12,13]. In the current study, 43% of the enrolled patients were diagnosed with systemic hypertension, with its prevalence increasing in more recent decades of diagnosis. Strikingly, these patients demonstrated significantly higher survival rates compared to those without systemic hypertension[14,15]. We observed a robust positive association between SAP values measured around the time point of PH diagnosis and survival across a broad blood pressure range. Similarly, increased dSAP was associated with improved survival, both in the PAH and the overall PH cohorts. External validation was performed in an independent UK cohort. In contrast, hypotensive patients showed significantly increased hazard ratios compared with normotensive patients.

Similar to patients with left heart disease, severe right heart failure, combined with the inability to generate sufficient RV stroke volume to maintain adequate left heart filling, may lead to a drop in

systemic blood pressure and an autoregulatory increase in heart rate (baroreflex)[14,16-19]. Along this line, we indeed observed a strong correlation between sSAP and cardiac index. Thus, the severity of the underlying PH disease and the sequelae of right heart failure and low cardiac output may well contribute to the markedly increased mortality noted in the PH patients at the lower end of systemic blood pressure and the higher end of heart rate.

However, the detrimental effects of low systolic and diastolic systemic blood pressure values and elevated heart rate were also observed in patients with only moderate PH and after adjusting for the ESC/ERS 2022 risk stratification tool. Furthermore, we did not observe a U-shaped relationship between systemic blood pressure values and mortality. Such a pattern would typically be expected if low cardiac output states were harmful at the lower end of the blood pressure spectrum and if the known adverse effects of systemic hypertension became apparent at the higher end. Thus, additional underlying mechanisms are to be considered.

β-blockers and agents targeting the renin-angiotensin-aldosterone system were the most widely used anti-hypertensive drugs. These agents have also been considered as candidates for beneficially influencing lung vascular and/or RV remodeling in PH, however, with up to now controversial results[20-23]. It could nevertheless be hypothesized that the observed association between higher sSAP values and reduced mortality might be partially attributable to a pharmacological effect of these drugs. When analyzing only patients who had never received these medications, the association between increasing systemic blood pressure and decreasing hazard ratios was consistently reproduced. This finding makes a causative role of systemic antihypertensive drugs in the association of systemic hypertension with survival of PH very unlikely. While higher sSAP might reflect improved hemodynamic tolerance and adherence to blood pressure-lowering PAH therapies, it is important to consider the potential for reverse causality or confounding. It is possible that more advanced PH patients receive more intensive PAH-specific therapies, which would lower their sSAP during follow-up and potentially lead to a reverse causality pattern. This could explain why the association appears to be slightly attenuated

in patients not receiving such treatments. Nevertheless, the correlation persists even in patients never treated with PAH-specific medications, suggesting additional physiological associations.

The relationship between systemic hemodynamics and RV perfusion is complex. In PH, RV perfusion may be compromised by increased myocardial oxygen demand, absolute or relative capillary rarefaction, a reduced gradient between coronary arterial pressure and RV intracavitary pressure, and a reduced diastolic perfusion period at higher heart rates[24-2627,28]. Although the exact mechanism remains to be fully elucidated, our findings showed that higher sSAP correlated with improved cardiac index, BNP, and RV contractility. Moreover, longitudinal sSAP and heart rate changes predicted mortality.

RV function can additionally be influenced by systemic hemodynamics through ventricular interdependence[29,30]. Even when right coronary artery perfusion is held constant, RV function is dependent and positively influenced by LV developed pressure[31,32]. Septal bowing into the left ventricle, as occurring in severe PH, may negatively impact RV contraction time and function and is worsened by lower pressures within the left ventricular cavity[29]. Thus, increased LV afterload with hypertension may provide better matching of right-left ventricular contraction times and RV pressure generation under PH conditions.

Of course, well known detrimental effects of long-term elevated blood pressure levels will not be offset in PH, but given the high mortality of these patients due to right heart failure, advantageous effects of high blood pressure on RV performance might outweigh long-term disadvantageous effects of systemic hypertension observed in the general population[33].

Taken together, the associations between systemic hypertension, sSAP, heart rate, and survival observed in this large real-world analysis establish sSAP and heart rate as integrated physiologic markers of RV reserve. While it is biologically plausible that higher sSAP mediates improved RV function, as discussed above, our study design cannot distinguish whether sSAP acts as a true mediator or reflects higher cardiac output in PH. Prospective trials are therefore warranted to delineate the mechanisms underlying these associations in patients with PH.

Limitations

This study has limitations. First, a significant limitation is the incomplete assessment of RV function. While we included subgroup analyses using echocardiographic parameters, the lack of sophisticated RV function data, such as cardiac MRI or pressure-volume loop-based analysis of RV-PA coupling, limits the ability to definitively characterize the mechanistic interplay between systemic hemodynamics and RV function. Consequently, the observed associations, while statistically significant, should be interpreted with caution. Second, the combination of retrospective and prospective data collection introduces potential biases. Since the excess mortality associated with systemic hypertension typically accrues over decades of cumulative exposure, our observation period may not have fully captured the long-term impact of elevated systemic blood pressure. Another potential limitation of our findings is the possibility of a survival bias related to age-impact on systemic and pulmonary vascular stiffness. However, sensitivity analyses demonstrated consistency of our findings across all age groups and measures of systemic arterial and pulmonary arterial stiffness and pulse pressures. Moreover, we performed age-stratified analyses using age quartiles and evaluated potential effect modification by age. The association between sSAP and outcomes remained consistent across age strata, and no significant interaction between age and sSAP was observed. A further limitation is that our study does not provide evidence for clinical blood pressure management strategies as we were not able to evaluate the effects of antihypertensive intensification, dose, or duration. Consequently, our conclusions focus on the physiological role of sSAP in risk stratification rather than providing direct therapeutic recommendations. Moreover, parameters such as BNP as well as follow-up data were only available in a subset of patients for the analyses on longitudinal changes. Missing data, a common issue in real-world registries, may affect interpretation associated with potential selection bias. However, this analysis is based on a real-world data set, the largest PH patient cohort analyzed to date, and its core findings remained robust across all statistical approaches, including sensitivity analyses, adjustments for potential (unmeasured) confounders, and external validation.

Nevertheless, residual confounding and unmeasured factors such as frailty may have an impact on the observed association of sSAP and outcomes.

Conclusion

If validated in future studies, the association of systemic hypertension with survival observed in PH patients would consequently influence risk stratification, placing sSAP and heart rate as integrative markers of prognosis specifically for this patient population.

Figure Legends

Figure 1. Association Between Systemic Hypertension Reported as Co-morbidity and Mortality of PH Patients

A) Analyses for patients from centers with reporting of systemic hypertension. a) Adjusted Kaplan-Meier survival estimates with 95% confidence bands. PH patients with systemic hypertension compared to those without. b) Hazard ratios for patients with systemic hypertension compared to patients without systemic hypertension for the overall study group, PH groups 1-4 and IPAH (PH group 1.1). c) Sensitivity analysis analyzing the impact of adding or removing covariable terms to/from the Cox proportional hazards model from the full model the overall study group on the estimated hazard ratio for systemic hypertension. The diagram shows the estimates with 95% confidence intervals. The P-values are from Wald z-tests. The upper half shows the estimates from the full model from which the respective terms were removed, the lower half shows the estimates from the base model with the respective terms added. The last four lines in each half refer to the addition or removal of all terms to or from the model that refer to the indicated groups of variables. The hazard ratios estimated from the full model and the base model are given as reference. d) Variable importance assessed by Heller's explained relative risk scores for the full model for the overall study group. Adjusted Kaplan-Meier curves with the IPTW KM method and cox proportional hazards models were adjusted for sex, center, diagnosis decade, BMI, SPP, PAPP, mPAP and PVR, in addition to the presence of systemic hypertension as diagnosed by the respective referral center. Center was additionally included as a clustering variable. In analyses restricted to patients with PAH, treatment with PAH-specific drugs was additionally included as a covariate.

B) Hazard ratios for patients with systemic hypertension defined by hemodynamics upon registry entry (sSAP >140 or dSAP >90) in GoDeep-UK PH and PAH patients and in UK&ASPIRE PH and PAH patients. Hazard ratios and 95% confidence intervals are displayed for each subgroup: GoDeep-UK PH, GoDeep-UK PAH, validation cohort PH, and validation

cohort PAH. The validation cohort consists of patients from the National Cohort Study of Idiopathic and Heritable PAH and ASPIRE. To ensure that no patient was represented in both the GoDeep and validation cohorts, all patients from the United Kingdom were excluded from the GoDeep dataset for this analysis. Cox proportional hazards models were adjusted for sex, center, diagnosis decade, BMI, mPAP and PVR, in addition to the presence of systemic hypertension as defined above. In analyses restricted to patients with PAH, treatment with PAH-specific drugs was additionally included as a covariate.

PH = pulmonary hypertension; BMI = body mass index; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; PAH = pulmonary artery hypertension; HR = Hazard Ratio; RHC = right heart catheterization; sSAP = systolic systemic arterial pressure; dSAP = diastolic systemic arterial pressure; UK = National Cohort Study of Idiopathic and Heritable PAH; ASPIRE = Assessing the Spectrum of Pulmonary Hypertension In a REferral Centre.

Figure 2. Association Between sSAP, mPAP and Heart Rate and Mortality of A) PAH and B) PH patients

a) sSAP dependency of hazard ratios (mean and 95% confidence bands) relative to a reference patient with sSAP of A) 126 mmHg or B) 128 mmHg (PAH and PH sample median, respectively) (i), for the sample split by PVR, with patients with a PVR ≤5 WU used as reference group (ii), and patient numbers by sSAP (light pink: all patients, dark pink: patients who died within 5 years after diagnosis), (iii). The models are adjusted for age at diagnosis, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, and stratified for center, sex, and diagnosis decade. Center was additionally included as a clustering variable. In the analysis for patients with PAH, P(A)H treatment was additionally added as a covariable.

b) mPAP dependency of hazard ratios (mean and 95% confidence intervals) relative to a reference patient with a mPAP of A) 46 mmHg or B) 38 mmHg (PAH and PH sample median,

respectively), for the overall cohort (i). In (ii), mPAP dependency of the hazard ratio is given for each sSAP quartile: Q1 (PAH mean sSAP = 103 mmHg; PH mean sSAP = 101 mmHg), Q2 (PAH mean sSAP = 120 mmHg; mean sSAP = 121 mmHg), Q3 (PAH mean sSAP = 134 mmHg; PH mean sSAP = 136 mmHg), and Q4 (PAH mean sSAP = 159 mmHg; PH mean sSAP = 164 mmHg). (iii) Patient numbers by mPAP (light pink: all patients, dark pink: patients who died within 5 years after diagnosis). The models are adjusted for age at diagnosis, sSAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, and stratified for center, sex, and diagnosis decade. Center was additionally included as a clustering variable. In the analysis for patients with PAH, P(A)H treatment was additionally added as a covariable.

c) Heart rate dependency of hazard ratios (mean and 95% confidence bands) relative to a reference patient with a heart rate of A) 79 bpm or B) 77 bpm (PAH and PH sample median, respectively) for the overall study group with reported heart rate (i) and for the sample split by PVR (ii), with patients with a PVR ≤5 WU used as reference group. (iii) Patient numbers by heart rate (light pink: all patients, dark pink: patients who died within 5 years after diagnosis). The models are adjusted for age at diagnosis, sSAP, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, and stratified for center, sex, and diagnosis decade. Center was additionally included as a clustering variable. In the analysis for patients with PAH, P(A)H treatment was additionally added as a covariable. All hemodynamic values were collected during the initial right heart catheterization upon registry entry.

sSAP = systolic systemic arterial pressure; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; BMI = body mass index; RHC = right heart catheterization.

Figure 3. Association Between A) sSAP and Mortality as well as B) Heart Rate and Mortality in patients with i) PAH, ii) IPAH and iii) PH.

A) Forest plots show hazard ratios (HR) with 95% confidence intervals for mortality stratified by sSAP (<110 mmHg, 110-140 mmHg and >140 mmHg), using the reference group of sSAP 110–140 mmHg. HRs, corresponding 95% confidence intervals, and P values are reported for each subgroup. The vertical dashed line indicates HR = 1.0. The models are adjusted for age at diagnosis, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, stratified for center, sex, and diagnosis decade and center as cluster. In the analysis for patients with PAH and IPAH, P(A)H treatment was additionally added as a covariable.
B) Forest plots show hazard ratios (HR) with 95% confidence intervals for mortality stratified by heat rate (<60 bpm, 60-100 bpm and >100 bpm), using the reference group of heart rate 77 bpm. HRs, corresponding 95% confidence intervals, and P values are reported for each subgroup. The vertical dashed line indicates HR = 1.0. The models are adjusted for age at diagnosis, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, stratified for center, sex, and diagnosis decade and center as cluster. In the analysis for patients with PAH and IPAH, P(A)H treatment was additionally added as a covariable.
sSAP = systemic arterial pressure; PAH = pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; PH = pulmonary hypertension; mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; BMI = body mass index; RHC = right heart catheterization.

Figure 4. Association Between sSAP and Mortality of PH Patients in Dependence of Drug Administration in Pulmonary Hypertension
A) sSAP dependency of hazard ratios (mean and 95% confidence bands), relative to a reference patient with a sSAP of 128 mmHg (overall sample median) for patients never receiving (i) any systemic hypertension medication, (ii) ACE inhibitors and/or ARBs or (iii) β-blockers during the entire observation period. Patients included are only from centers from which systemic hypertension medication reporting was available. The models are adjusted for

age at diagnosis, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, and stratified for center, sex, and diagnosis decade. Cluster was additionally added as center. In the analysis for patients with PAH, P(A)H treatment was additionally added as a covariable.
B) sSAP dependency of hazard ratios (mean and 95% confidence bands), relative to a reference patient with a sSAP of 128 mmHg (overall sample median) for patients (i) never receiving treatment with PAH targeting drugs or (ii) being treated with PAH drugs. The models are adjusted for age at diagnosis, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, and stratified for center, sex, and diagnosis decade.
C) sSAP dependency of hazard ratios (mean and 95% confidence bands), relative to a reference patient with a sSAP of 128 mmHg (overall sample median) for patients never receiving treatment with calcium channel antagonists. The models are adjusted for age at diagnosis, mPAP, PVR and BMI as restrictive cubic splines with 3 degrees of freedom, and stratified for center, sex, and diagnosis decade. Cluster was additionally added as center. In the analysis for patients with PAH, P(A)H treatment was additionally added as a covariable.
D) Correlation between sSAP and both cardiac index (orange) and BNP (green) in the overall PH population, based on available cardiac index and BNP data. The plot displays sSAP on the x-axis and either cardiac index or BNP on the y-axis, along with a 95% confidence interval.
All hemodynamic values as well as BNP were collected during the initial right heart catheterization upon registry entry. PH = pulmonary hypertension; PAH = pulmonary arterial hypertension; sSAP = systolic systemic arterial pressure; ACE = Angiotensin-Converting Enzyme; ARBs = Angiotensin II receptor blockers; SH = systemic hypertension; No. = number of, BNP = B-Type Natriuretic Peptide.

Table 1. Baseline Characteristics of the GoDeep PAH group and overall PH group entered into the analysis.

PH = Pulmonary Hypertension; PAH = Pulmonary Arterial Hypertension; WHO FC = WHO functional class; BMI = body mass index; BNP = B-type natriuretic peptide; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; mSAP = mean systemic arterial pressure; sSAP = systolic systemic arterial pressure; CI = cardiac index; PVR = pulmonary vascular resistance; WU = Wood Units.

	PAH	Overall
N	3595	12771
Age at diagnosis (years)		
Median [Q1, Q3]	60 [47, 70]	65 [53, 73]
Missing	0 (0%)	0 (0%)
Sex		
male	1120 (31%)	5399 (42%)
Missing	0 (0%)	0 (0%)
WHO FC		
I	63 (2%)	202 (2.1%)
II	492 (16%)	1544 (16%)
III	2122 (68%)	6373 (68%)
IV	448 (14%)	1314 (14%)
Missing	470 (13%)	3338 (26%)
BMI (kg/m²)		
Median [Q1, Q3]	27 [23, 31]	28 [24, 33]
Missing	0 (0%)	0 (0%)
BNP (pg/mL)		
Median [Q1, Q3]	170 [63, 420]	210 [72, 520]
Missing	1846 (51%)	6531 (51%)
mPAP (mmHg)		
Median [Q1, Q3]	46 [36, 55]	39 [30, 49]
Missing	0 (0%)	0 (0%)
PAWP (mmHg)		
Median [Q1, Q3]	9 [7, 12]	12 [8.3, 17]

	PAH	Overall
Missing	0 (0%)	0 (0%)
CI (L/(min·m²))		
Median [Q1, Q3]	2.3 [1.8, 2.8]	2.4 [1.9, 2.9]
Missing	0 (0%)	0 (0%)
PVR (WU)		
Median [Q1, Q3]	8.8 [5.6, 13]	5.3 [3, 9.3]
Missing	0 (0%)	0 (0%)
sSAP (mmHg)		
Median [Q1, Q3]	130 [110, 140]	130 [120, 150]
Missing	0 (0%)	0 (0%)
mSAP (mmHg)		
Median [Q1, Q3]	93 [83, 100]	93 [83, 100]
Missing	0 (0%)	0 (0%)
dSAP (mmHg)		
Median [Q1, Q3]	75 [67, 84]	74 [65, 83]
Missing	80 (2.2%)	206 (1.6%)
Heart rate (beats/min)		
Median [Q1, Q3]	79 [70, 89]	77 [67, 87]
Missing	0 (0%)	0 (0%)
PAPP (mmHg)		
Median [Q1, Q3]	44 [32, 54]	34 [24, 48]
Missing	196 (5.5%)	621 (4.9%)
SPP (mmHg)		
Median [Q1, Q3]	52 [41, 66]	56 [43, 71]
Missing	82 (2.3%)	211 (1.7%)
Transplantation		
yes	63 (1.8%)	160 (1.3%)
Missing	0 (0%)	0 (0%)
One or more PH drugs		
treated	3102 (86%)	6875 (54%)
Missing	0 (0%)	0 (0%)

Conflict of interests

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