Early View

Original research article

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Causes and Outcomes of ICU Hospitalizations in Patients with Pulmonary Arterial Hypertension

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Take home message

PAH continues to have limited survival despite improvements in therapy. ICU and one-year mortality risk factors include hyponatremia, elevated proBNP, hyperbilirubinemia, and need for vasopressors/inotropes and mechanical ventilation.

Abstract

Rationale: Pulmonary arterial hypertension (PAH) is a rare disease characterized by limited survival despite remarkable improvements in therapy. The causes, clinical burden, and outcomes of patients admitted to the intensive care unit (ICU) remain poorly characterized.

Objectives: To describe patient characteristics, causes of ICU hospitalization, and risk factors for ICU and one-year mortality.

Methods: Data from patients enrolled in the Johns Hopkins Pulmonary Hypertension Registry were analyzed for the period between January 2010 to December 2020. Clinical, functional, hemodynamic, and laboratory data were collected.

Measurements and Main Results: 102 adult patients with 155 consecutive ICU hospitalizations were included. The leading causes for admission were right heart failure (RHF, 53.3%), infection (17.4%), and arrhythmia (11.0%). ICU mortality was 27.1%. Mortality risk factors included Na < 136 mEq/mL (OR: 3.10, 95% CI: 1.41 – 6.82), elevated proBNP (OR: 1.75, 95% CI: 1.03 – 2.98), hyperbilirubinemia (OR: 1.40, 95% CI: 1.09 – 1.80), hyperlactemia (OR: 1.42, 95% CI: 1.05 – 1.93), and need for vasopressors/inotropes (OR: 5.29, 95% CI: 2.28 – 12.28), mechanical ventilation (OR: 3.76, 95% CI: 1.63 – 8.76), and renal replacement therapy (OR: 5.57, 95% CI: 1.25 – 24.76). Mortality rates at 3, 6 and 12 months were 17.5%, 27.6%, and 39.0%, respectively. Connective tissue disease-associated

PAH has lower 1-year survival compared to idiopathic PAH (51.4% vs. 79.8%, log-rank test p=0.019).

Conclusions: RHF is the most common cause for ICU admission. In-hospital and one-year mortality remain exceedingly high despite improved ICU care. Recognizing specific risk factors on admission can help identifying patients at risk for poor outcomes.

Abstract word count: 250

Keywords: Pulmonary arterial hypertension, hospitalization, intensive care unit, mortality, right heart failure.

Introduction

Pulmonary arterial hypertension (PAH) remains a disease with significant morbidity and mortality despite a plethora of modern medications which have improved general outcomes [1-3]. It is a complex disorder of the pulmonary vasculature leading to progressive adaptive and maladaptive morphological and functional changes of the right ventricle (RV), with RV failure being the single most important determinant of survival [4, 5].

The clinical course of PAH is characterized, in part, by a high risk of hospitalization. Data from recent large multicenter trials and observational studies have identified right heart failure (RHF) as the primary cause of hospital admission and mortality in PAH patients [6-10]. However, patient characteristics and co-morbidities, causes of admission, and mortality risk factors of patients admitted to the intensive care unit (ICU) remain poorly defined, perhaps explaining the limited number of targeted clinical trials and therapeutic recommendations or guidelines from scientific societies for the management of critically ill PAH patients [11, 12].

The aims of this study were to analyze the causes, clinical characteristics, outcomes, and mortality risk factors of PAH patients needing admission to the medical ICU, and to assess the 3, 6, and 12 month mortality rates and associated risk factors upon hospital discharge.

Patients and Methods

Patient Population

From January 2010 to December 2020, data of adult PAH patients enrolled in the Johns Hopkins Pulmonary Hypertension Registry and hospitalized at the Johns Hopkins Hospital

Medical ICU, were collected. The diagnosis of PAH, group 1 pulmonary hypertension (PH), was confirmed by a mean pulmonary artery pressure (mPAP) greater than 20 mmHg at rest, a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and a pulmonary vascular resistance (PVR) ≥ 3 Wood units [13]. Within group 1 PH, we limited our analysis to idiopathic PAH (IPAH), PAH due to connective tissue diseases (CTD-PAH), congenital heart diseases-PAH (CHD-PAH), portopulmonary hypertension-PAH (PoPH-PAH), and HIV-associated PAH (HIV-PAH). Other causes of group 1 PH were excluded due to a low number of subjects. This study was approved by the Johns Hopkins University Institutional Review Board.

Demographic data, including medical history, PAH characteristics at diagnosis, and ICU admission and discharge information, were retrieved from electronic records. Charlson comorbidity index was calculated from the medical history [14]. Anemia was defined as hemoglobin < 13 g/dL for males and < 12 g/dL for females [15]. Hyponatremia was defined as a Na serum concentration ≤ 136 mEq/L [6]. Estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet in Renal Disease equation [16]. RHF was defined by symptoms and physical evidence of volume overload [17, 18].

Risk factors for in-hospital ICU mortality included demographics, underlying PAH diagnosis, World Health Organization functional class (WHO FC) at the latest outpatient assessment, physical signs and laboratory parameters on ICU admission, and ever need for vasopressors/inotropes, mechanical ventilation, and renal replacement therapy during the ICU stay. These variables were selected based on prior studies that have addressed mortality related to hospital and ICU admissions in PAH patients [1, 6, 12, 19-21]. Among

survivors, mortality at 3, 6, and 12 months was analyzed from the index hospitalization. Risk factors for mortality after discharge included similar variables. The latest clinic visit or contact with the patient was considered as censoring time for living patients. Death after discharge was determined from hospital records up to December 31, 2020.

Statistical Methods

Group comparisons were made using the Chi-squared and Fisher exact tests as appropriate for categorical variables and ANOVA test for continuous variables. Patients were grouped as IPAH, CTD-PAH, and other-PAH (including CHD-PAH, PoPH-PAH, and HIV-PAH) for optimal statistical analysis and result presentation. Correlation analyses were performed to identify significant variables to be considered for regression analysis. The identification of prognostic factors for ICU mortality was performed using logistic regression with robust adjustment of the variance for repeated measurements to handle patients with multiple hospitalizations. Risk factors were adjusted for age and underlying PAH diagnosis in a multivariable model. Mortality after ICU discharge was assessed using the Kaplan–Meier method. Comparisons between groups were performed by log-rank test. Risk factors for mortality at 1-year were assessed via Cox proportional hazards models. Computations were completed using the Stata statistical software (version 16.1; Stata, College Station, TX, USA). A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

From January 2010 to December 2020, 102 PAH patients were admitted to the Johns

Hopkins Hospital Medical ICU. The general characteristics of the patient population are

presented in **Table 1.** Twenty-nine patients had IPAH, 57 patients CTD-PAH, and 16 patients

had other-PAH (CHD-PAH (3), PoPH-PAH (6), and HIV-PAH (7)). Compared to IPAH,

patients with CTD-PAH were older (63.5 ± 11.9 vs. 53.7 ± 13.5 years; p<0.001), had a lower

proportion of females (89.5% vs. 93.1%; p<0.001), included a higher proportion of White

(63.1% vs. 55.2%; p=0.05) and a lower proportion of African American (35.1% vs. 41.4%;

p=0.05), presented with a higher Charlson comorbidity index ≥ 3, (77.2% vs. 37.9%;

p<0.001), and were more likely to have a history of cerebrovascular disease, peripheral

vascular disease, and depression.

WHO FC, assessed during the last clinical encounter before admission, showed an overall

high proportion of patients with functional limitation (WHO FC II: 23.5%, III: 57.9%, IV:

18.6%).

Hemodynamic data obtained at the time of PAH diagnosis indicated severe PAH across all

groups, with a right atrial pressure (RAP) of 11 ± 6 mmHg, mPAP of 45 ± 14 mmHg, cardiac

output (CO) of 4.7 ± 1.9 L/min, cardiac index (CI) 2.19 ± 0.64 L/min/m^2, and PVR of 7.7 Wood

units (IQR: 4.8 – 11.8). Patients with CTD-PAH had significantly lower mPAP compared with

IPAH and other-PAH patients (39 vs. 54 vs. 50 mmHg; p<0.001), as well as a lower PVR (6.7

vs. 10.0 vs. 9.4 Wood units; p=0.008). Other hemodynamic parameters such as CO, CI or RAP were similar between groups. The median time from PAH diagnosis to first ICU admission was 38.9 months (IQR: 12.4 - 92.3) and was significantly lower in CTD-PAH compared to IPAH patients (39.5 vs. 64.5 months; p=0.002).

Characteristics of ICU hospitalizations

A total of 155 ICU hospitalizations in 102 patients were identified. The characteristics of the patients and hospitalizations, and differences between groups, are shown in **Table 2**. The underlying diagnoses were IPAH (45 hospitalizations), CTD-PAH (85 hospitalizations), and other-PAH (25 hospitalizations, including CHD-PAH (3), PoPH-PAH (11), and HIV-PAH (11)). The most common causes for ICU admission were RHF (83; 53.5%), infection (27; 17.4%), arrhythmia (17; 11.0%), syncope (13; 8.4%), and bleeding disorders (8; 5.2%). Among infections, those related to pneumonia were the most frequent (15; 55.6%), followed by skin and soft tissue infections (6; 22.2%), urinary tract infections (4; 14.8%), and central line bloodstream infections (2; 7.4%).

Upon admission, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, blood urea nitrogen (BUN), lactate, hemoglobin, and pro-B-type natriuretic peptide (pro-BNP) were not significantly different across groups. In contrast, creatinine was higher among other-PAH patients compared to IPAH and CTD-PAH (2.6 vs. 1.8 vs. 1.5 mg/dL; p=0.006). CTD-PAH patients had worse renal function overall based on eGFR less than 60 ml/min/1.73 m^2 (p=0.009). IPAH presented the lowest proportion of patients with serum sodium concentrations < 136 mEq/mL (17; 37.8%). Patients with other-PAH had the highest mean

levels of total bilirubin (2.5 mg/dL ± 2.0; p<0.001). During their ICU stay, 75 patients (48.4%) received vasopressors or inotropes, 32 (20.1%) received mechanical ventilation, and 9 (5.8%) received renal replacement therapy. Among patients who received vasopressors or inotropes, norepinephrine was the most common vasopressor (55.8%), followed by dopamine (31.2%), with the latter including patients who only received low-dose dopamine to assist diuresis. Vasopressin was used in 21 patients (27.3%) and dobutamine in 12 patients (15.7%), usually as adjunct therapies to norepinephrine.

Regarding therapy, 91 (89.2%) patients were already receiving PAH-specific therapy. The most commonly used medications included phosphodiesterase-5 inhibitors (PDE5-i) (78), followed by endothelin receptor antagonists (53) and prostanoids (35). Patients not receiving targeted therapy, included patients with a recent PAH diagnosis and who required immediate hospital admission.

The median length of ICU stay for all groups was 5 days (IQR: 2 - 9). Overall, ICU mortality was 27.1% (42 patients), and 42.7% and 50% among patients who required vasopressor/inotropes or mechanical ventilation, respectively. The in-hospital mortality was 31.3% for patients admitted for RHF, and 22.2% for those admitted due to infection.

Risk factors for in-hospital mortality during ICU hospitalizations

Significant risk factors for in-hospital mortality are shown in **Table 3**. Several variables were shown by univariable logistic regression models to be potential risk factors. After adjusting for age and underlying PAH diagnosis, risk factors were Na <136 mEq/mL (OR 3.10; p=0.005),

elevated pro-BNP (OR 1.75; p=0.03), hyperbilirubinemia (OR 1.40; p=0.009), hyperlactemia (OR 1.42; p=0.023), use of vasopressors or inotropes (OR 5.29; p<0.001), mechanical ventilation (OR 3.76; p=0.002), and renal replacement therapy (OR 5.57; p=0.024). Although eGFR <60 ml/min/1.73 m^2 was not statistically significant in the multivariable logistic regression model, its unadjusted significance is noteworthy (OR 5.27; p=0.04).

Outcomes after ICU discharge

Among 77 patients who survived their first ICU admission, 2 patients underwent a lung transplant. Thus, outcomes were assessed in 75 patients. At the time of discharge from the ICU, 66 of these patients were on PAH-specific treatment, including 25 patients on monotherapy, 28 on dual therapy, and 13 on triple therapy. Patients who were not started on targeted therapy, or therapy was not escalated, by the time they left the ICU, were kept clinically and hemodynamically optimized before hospital discharge while awaiting initiation, or escalation, of PAH targeted therapy or pending insurance approval. Furthermore, the monotherapy cohort included patients with a long history of the disease who had remained stable on their respective regimen up until admission. The late mortality rates among hospital survivors at 3, 6 and 12 months were 17.5%, 27.6%, and 39.0%, respectively (**Figure 1**). When 1-year survival was compared across the three PAH groups, IPAH survival was 79.8% vs. CTD-PAH 51.4% vs. Other-PAH 59.7% (log-rank test p=0.06). Furthermore, the difference in survival was statically significant when comparing the two largest groups, IPAH vs. CTD-PAH (log-rank test p=0.019) (**Figure 2**).

Risk factors for 1-year mortality

Univariable and multivariable Cox proportional hazards models for one-year mortality are presented in **Table 4**. Several variables were identified by univariable Cox models to be potential risk factors. After adjusting for age and underlying PAH diagnosis, risk factors were Na <136 mEq/mL (HR 1.71; p=0.021), elevated pro-BNP (HR 1.35; p=0.04), hyperbilirubinemia (HR 1.19; p=0.006), and use of vasopressors or inotropes (HR 2.57; p<0.001) and mechanical ventilation (HR 2.06; p=0.005). After adjusting for age, CTD-PAH patients had a higher risk of death compared to IPAH patients (HR 1.89; p=0.05).

Discussion

This study identified specific features related to PAH patients requiring ICU admission. First, RHF continues to be the single most common reason for hospitalization to an ICU setting. Second, common risk factors for ICU and one-year mortality after discharge include hyponatremia, elevated pro-BNP, hyperbilirubinemia, and need for vasopressors or inotropes and mechanical ventilation. Third, among all PAH subgroups, CTD-PAH is associated with worse outcomes and survival. Finally, in-hospital and one-year mortality remain exceedingly high despite a general improvement in clinical management and targeted therapeutics for PAH.

The Johns Hopkins Hospital Medical ICU is a closed unit with standardized protocols designed to provide optimal evidence-based patient care, particularly related to the use of intravenous diuretics, vasopressors or inotropes, mechanical ventilation, and renal

replacement therapy as clinically indicated [11, 22, 23]. The Johns Hopkins PH specialists are directly involved in the care of PAH patients admitted to the ICU to provide multidisciplinary management along with the ICU providers. Therefore, the goal of this study was to explore the clinical characteristics, causes of ICU admission, general practices and determinants of survival, and to assess improvement in care and survival, if any, compared to our experience from a decade ago [6] and other recent studies.

In 2010, Sztrymf and colleagues reported findings in a PAH population of 46 patients admitted to an ICU setting. Mortality was 41%, however, no significant differences were found between survivors and non-survivors across demographics, clinical features, and hemodynamic data collected on admission. SBP, pro-BNP, C-reactive protein, Na, and creatinine correlated significantly with survival [21]. In contrast, Campo et al. and Haddad et al. described statistically significant differences across PAH groups regarding demographics, outcomes and survival of patients admitted to the hospital due to RHF, however, only 25% and 17% of these admissions required ICU care, for each study respectively [6, 12]. More recently, Ambroz et al. reported predictors of survival in 70 PH patients (59 PAH and 11 chronic thromboembolic pulmonary hypertension (CTEPH)) admitted with RHF. Their cohort included 96 admissions to cardiology wards and 21 to the ICU, with overall hospital and ICU mortality rates of 12.8% and 52.4%, respectively. Hyponatremia, younger age, CTD-PAH and need for PAH combination therapy were described as in-hospital mortality risk factors [24]. Moreover, Bauchmuller and colleagues recently published a retrospective observational study based on the ASPIRE registry. They included 242 critical care PH admissions involving 206 patients (162 PAH admissions, including 96 IPAH and 40 CTD-PAH). Hospital survival

was 59.3%, 94% and 92% for patients admitted for medical, surgical, or obstetric reasons, respectively. Higher APACHE II (Acute Physiology and Chronic Health Evaluation) score, age, and lactate, and lower oxygen saturation, platelet count and sodium levels were identified as independent predictors of hospital mortality [25], similar to risk factors described in our study.

Observational studies and registry data have demonstrated RHF to be the leading cause of hospitalization in PAH patients, which is associated with a shorter time to clinical worsening after discharge, including PAH-related readmissions, deterioration in FC or decrease in 6-minute walk test distance by 20% from baseline, need for interventional procedures (i.e., lung transplantation, atrial septostomy); and increased mortality rates [6, 19, 21, 24, 26]. Respiratory failure frequently complicates the hospitalization course with hypoxia, acidosis, and hypercapnia contributing to worsening pulmonary vasoconstriction and increased RV afterload [27]. The latter is also increased by the effect of positive pressure from mechanical ventilation. [28]. In this study, significant predictors of poor outcomes included the use of vasopressors or inotropes and mechanical ventilation. In particular, we observed that 42.7% of patients treated with either vasopressors or inotropes, and 50% of patients who needed mechanical ventilation died during their hospitalization, compared to 45.7% and 100% as we previously reported, respectively [6]. This improvement of outcomes in PAH patients receiving mechanical ventilation may derive from recent advances in evidence-based practices focused on addressing pathophysiological pathways with emphasis on low tidal volume ventilation [29], appropriate sedation, early mobilization [30], and the implementation of ICU care bundles [31]. Furthermore, a multidisciplinary team-based approach between

PAH providers and cardiac anesthesia at our institution [32], may have contributed to the education and awareness among ICU and anesthesia providers regarding the specific challenges surrounding induction and intubation, and other invasive procedures in the ICU.

Several metabolic and electrolyte derangements were identified as ICU mortality risk factors. Aside from hyponatremia, elevated proBNP, hyperbilirubinemia, and hyperlactemia; the need for renal replacement therapy was a strong risk factor for ICU adverse outcomes. Renal dysfunction has been associated with abnormal cardiopulmonary hemodynamics, increased in-hospital mortality, and poor survival in PAH patients enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL). Participants with a ≥10% decline in eGFR from baseline over ≥1 year had a significantly increased risk of death (HR 1.66; $p < 0.0001$) and the composite of all-cause hospitalization and death (HR 1.33; $p = 0.002$) [33]. In the present study, renal dysfunction, defined as eGFR <60 ml/min/1.73 m^2 at the time of ICU admission, was a significant risk factor for ICU mortality (OR 5.3; $p=0.04$) and highlights the significance of the cardiorenal axis. The primary mechanism through which PH leads to renal dysfunction is due to increased central venous pressure (CVP) and consequent renovascular congestion, mediated by RV dysfunction [34]. This results in decreased effective renal perfusion due to reduced trans-glomerular pressure gradients. Furthermore, a cascade of myogenic and neural reflexes, baroreceptor stimulation, activation of the renin-angiotensin-aldosterone system (RAAS), and pro-inflammatory pathways lead to a rapid decline in the glomerular fraction rate. The activation of the RASS and production of angiotensin-II has been shown to activate NADPH oxidase, leading presumably to progressive oxidative kidney injury [35]. In this context, as renal function declines and diuretics become ineffective, renal

replacement therapy is the only available option for fluid removal. Hence, we found that patients requiring renal replacement therapy had a poor prognosis and increased mortality (OR 5.6; p=0.024).

Overall in-hospital mortality in PAH patients who required ICU care was lower in this study compared with previous reports (27.1% vs. 38% [12] vs. 41% [21]). It is noteworthy that admission for RHF portends a worse prognosis (31.3% present study vs. 48% [6] vs. 52.4% [24] ICU mortality) relative to left heart failure (LHF) (4% - 17%) [20, 36, 37]. Compared with patients with LHF, patients with PAH are younger, are more often women, and have a higher prevalence of connective tissue disease. Comorbid conditions, such as systemic hypertension, diabetes mellitus, or peripheral vascular disease, are also less common. Despite high in-hospital mortality rates, we noted a remarkable improvement compared to our previous experience between 2000 to 2009. The cohort then included 61 patients with 115 hospitalizations, including 25.2% ICU admissions [6]. Of the latter group, 48.3% of patients admitted with RHF died compared to 31.3% patients in the present study. Within the largest subgroups of this population, IPAH (45 hospitalizations) and CTD-PAH (85 hospitalizations), in-hospital mortality was 22.2% and 25.9%, respectively, which is considerably lower compared to rates from the prior epoch (30% and 57.9%, respectively) [6]. This important trend in outcomes could be the reflection of a better understanding of the disease and improved overall care.

Scleroderma associated PAH (SSc-PAH) was the most common cause of PAH in our cohort due to referral bias, and the second most commonly identified PAH etiology in most PH

registries. It is the leading cause of death in SSc [5, 38, 39]. Dual upfront combination therapy has certainly been a significant therapeutic advance in this disease and offers new hopes for this population [7, 40]. The current CTD-PAH cohort included 46 (81%) SSc-PAH patients, who were older and had a higher prevalence of comorbidities compared to other groups, which is similar to prior observations [41]. Most patients had a Charlson comorbidity index ≥ 2 (89.5%), suggesting that the presence of numerous comorbidities carries a higher in-hospital mortality risk, although this association was not statistically significant. After discharge, CTD-PAH patients had the worst one-year survival (48.6% mortality), followed by other-PAH (40.3%) and IPAH (20.2%). Similar risk factors predicted 1-year mortality, including hyponatremia, elevated proBNP, and hyperbilirubinemia, as well as the need for vasopressors or inotropes and mechanical ventilation during the initial ICU admission. Carrying a diagnosis of CTD-PAH compared to IPAH is by itself a strong mortality risk factor. This difference in outcomes in CTD-PAH patients can be attributed to a complex interaction between older age, higher prevalence of comorbidities, and more refractory PAH [41-43]. In addition, we have previously identified profound sarcomere dysfunction (i.e., depressed RV contractility and contractile reserve) in SSc-PAH compared to IPAH [44], which could potentially be a major contributory factor to RHF, and hence worse clinical outcomes.

Some limitations of this study must be noted. First, we analyzed the predictive value of clinical and laboratory parameters on admission, but not the effect of their changes during the ICU stay. Second, given that we only included patients cared for at a single center, and considering the high proportion of patients with CTD-PAH, our findings cannot be generalized to other centers where PAH subgroups may differ.

Conclusion

In summary, in-hospital mortality for PAH patients remains unacceptably high, and when patients need advanced care in the ICU, outcomes can be devastating. This trend is carried over after discharge, and despite a plethora of new therapeutics, short-term survival remains dismal. These findings are especially concerning for CTD-PAH patients, suggesting that the need for ICU hospitalization itself portends a poor prognosis. Common risk factors for ICU and one-year mortality include hyponatremia, elevated proBNP, and total bilirubin, and the need for vasopressors/inotropes and mechanical ventilation. Abnormal renal function or need for renal replacement also convey a poor prognosis. Improvements in long-term outcomes of stable PAH patients are now reflected in a considerable, but still far from acceptable, decrease of in-hospital and post-discharge mortality rates. Strategies aimed at identifying patients at higher risk early in the hospitalization course should help guide management and optimize treatment.

acquisition, analysis, and interpretation. All authors listed have been involved in revising the manuscript for important intellectual content, approved the final version submitted for publication, and are in agreement with the accuracy and integrity of the submitted work.

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Table 1. Characteristics of PAH patients admitted to the ICU

	All n=102	IPAH n=29	CTD-PAH n=57*	Other-PAH n=16**	p-value
Age upon first admission, years, mean	58.7 ± 13.6	53.7 ± 13.5	63.5 ± 11.9	50.6 ± 12.8	<0.001
Female, n (%)	86 (84.3)	27 (93.1)	51 (89.5)	8 (50.0)	<0.001
Race, White/AA/Hispanic/Others, n	59/39/2/2	16/12/0/1	36/20/0/1	7/7/2/0	0.05
WHO FC pre-admission (II/III/IV), n	24/59/19	10/15/4	12/36/9	2/8/6	0.002
Median time since PAH diagnosis to first ICU admission, months, median (IQR)	38.9 (12.4-92.3)	64.5 (25.9-147.3)	39.5 (11.8-92.1)	24.6 (9.7-33.9)	0.002
Hemodynamics at PAH diagnosis					
RAP, mmHg, mean	11 ± 6	12 ± 6	9 ± 6	12 ± 7	0.14
mPAP, mmHg, mean	45 ± 14	54 ± 14	39 ± 12	50 ± 15	<0.001
PCWP, mmHg, mean	10 ± 4	10 ± 3	11 ± 4	11 ± 4	0.97
CO, L/min, mean	4.7 ± 1.9	4.6 ± 2.0	4.8 ± 1.8	4.6 ± 2.1	0.85
CI, L/min/m², mean	2.19 ± 0.64	2.11 ± 0.53	2.23 ± 0.69	2.12 ± 0.58	0.61
PVR, Wood units, median (IQR)	7.7 (4.8-11.8)	10.0 (7.6-14.6)	6.7 (3.0-9.6)	9.4 (5.-14.0)	0.008
Comorbidities					
Coronary artery disease, n (%)	10 (9.8)	4 (13.8)	4 (7.2)	2 (13.0)	0.56
Systemic hypertension, n (%)	23 (22.6)	8 (27.6)	14 (24.6)	1 (6.3)	0.22
Diabetes mellitus, n (%)	14 (13.7)	9 (31.0)	3 (5.3)	2 (12.5)	0.005
Peripheral vascular disease, n (%)	3 (2.9)	0(0)	2 (3.5)	1 (6.3)	0.45
Cerebrovascular disease, n (%)	3 (2.9)	0(0)	2 (3.5)	1 (6.3)	0.45
History of depression, n (%)	9 (8.8)	1 (3.5)	5 (8.8)	3 (18.8)	0.68
Charlson comorbidity index					
0, n (%)	9 (8.8)	8 (27.6)	0(0)	1 (6.3)	
1, n (%)	10 (9.8)	4 (13.8)	6 (10.4)	0(0)	<0.001
2, n (%)	15 (14.7)	6 (20.7)	7 (12.3)	2 (12.5)	
≥3, n (%)	68 (66.7)	11 (37.9)	44 (77.2)	13 (81.2)	

Data are expressed as mean ± standard deviation, absolute number (percentage), median (interquartile range, IQR) unless otherwise indicated. **Definitions of abbreviations:** PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD-PAH, connective tissue PAH; ICU, intensive care unit; AA, African American; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; PVR, pulmonary vascular resistance.
*CTD-PAH includes: 46 scleroderma associated PAH (SSc-PAH) patients and 11 patients with other CTD-associated PAH conditions.
**Other-PAH includes: CHD-PAH (3), PoPH-PAH (6), and HIV-PAH (7) patients.

Table 2. Characteristics of ICU admissions

	All n=155	IPAH n=45	CTD-PAH n=85	Other-PAH n=25*	p-value
Causes of ICU admission					
Right heart failure, n (%)	83 (53.5)	27 (60.0)	45 (52.9)	11 (44.0)	0.27
Infection, n (%)	27 (17.4)	6 (13.3)	16 (18.8)	5 (20.0)	0.54
Arrhythmia, n (%)	17 (11.0)	5 (11.1)	11 (12.9)	1 (4.0)	0.61
Syncope, n (%)	13 (8.4)	1 (2.2)	8 (9.4)	4 (16.0)	0.09
Bleeding disorder, n (%)	8 (5.2)	2 (4.4)	3 (3.5)	3 (12.0)	0.19
Others, n (%)	7 (4.5)	4 (8.9)	2 (2.4)	1 (4.0)	0.37
Admission data					
Systolic BP, mmHg, mean	105.9 ± 22.1	105.3 ± 15.5	106.8 ± 24.3	103.6 ± 26.6	0.85
Diastolic BP, mmHg, mean	62.4 ± 12.9	63.2 ± 9.0	62.9 ± 15.0	58.3 ± 9.9	0.37
Heart rate, bpm, mean	93.7 ± 17.7	94.9 ± 15.1	93.7 ± 18.7	91.1 ± 19.8	0.75
Creatinine, mg/dL, mean	1.8 ± 1.4	1.8 ± 1.3	1.5 ± 1.2	2.6 ± 2.0	0.006
eGFR <60 ml/min/1.73 m^2, n (%)	97 (62.6)	26 (57.8)	52 (61.2)	19 (76.0)	0.009
BUN, mg/dL, mean	34.5 ± 22.3	33.0 ± 21.3	36.2 ± 23.1	31.7 ± 22.0	0.57
Na, mEq/mL, mean	135.7 ± 6.1	135.2 ± 6.8	136.5 ± 5.9	134.1 ± 4.7	0.16
Na < 136 mEq/mL, n (%)	74 (47.7)	17 (37.8)	37 (43.5)	20 (80.0)	0.002
Bilirubin, total, mg/dL, mean	1.5 ± 1.6	1.7 ± 2.0	1.0 ± 0.9	2.5 ± 2.0	<0.001
Lactate, mmol/L, mean	2.6 ± 3.1	2.4 ± 2.9	2.6 ± 3.3	3.1 ± 2.9	0.72
Hemoglobin, g/dL, mean	11.0 ± 2.4	11.6 ± 2.9	10.9 ± 2.1	10.6 ± 2.5	0.15
Anemia, n (%)	115 (74.2)	31 (68.9)	63 (74.1)	21 (84.0)	0.38
ProBNP, pg/mL, median (IQR)	3851 (2229-7000)	3192 (1533-6874)	4727 (2302-6945)	4209 (921-8518)	0.63
ICU support					
Vasopressors/Inotropes, n (%)	75 (48.4)	19 (42.2)	43 (50.6)	13 (52.0)	0.61
Mechanical ventilation, n (%)	32 (20.1)	9 (20.0)	17 (20.0)	6 (24.0)	0.90
Renal replacement therapy, n (%)	9 (5.8)	2 (4.4)	2 (2.4)	5 (20.0)	0.004
Length of ICU stay, days, median (IQR)	5 (2-9)	5 (2-8)	5 (3-10)	5 (3-8)	0.60
ICU mortality, n (%)	42 (27.1)	10 (22.2)	22 (25.9)	10 (40.0)	0.25
Right heart failure, mortality, n (%)	26 (31.3)	9 (90.0)	12 (54.5)	5 (50.0)	0.31
Infections, mortality, n (%)	6 (22.2)	0 (0)	5 (22.7)	1 (10.0)	0.76
Vasopressors/Inotropes, mortality n (%)	32 (42.7)	8 (80.0)	15 (68.2)	9 (90.0)	<0.001
Mechanical ventilation, mortality n (%)	16 (50.0)	5 (50.0)	7 (31.8)	4 (40.0)	0.001

Data are expressed as mean ± standard deviation, absolute number (percentage), median (interquartile range, IQR) unless otherwise indicated.
Definitions of abbreviations: PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD-PAH, connective tissue PAH; ICU, intensive care unit; BP, blood pressure; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Na, sodium; proBNP, pro-b-type natriuretic peptide.
*Other-PAH includes: CHD-PAH (3), PoPH-PAH (11), and HIV-PAH (11) admissions.

Table 3. Risk factors for in-hospital mortality in PAH patients admitted to the ICU

	Unadjusted OR (95% CI)	p-value	Adjusted for PAH diagnosis and age OR (95% CI)	p-value
Age per year	1.01 (0.98-1.03)	0.67	NA	NA
Female vs. male	0.47 (0.20-1.10)	0.08	0.57 (0.23-1.40)	0.22
CTD-PAH v. IPAH	1.27 (0.52-2.90)	0.64	1.11 (0.44-2.80)*	0.83
WHO FC pre-admission (III & IV)	4.05 (0.56-29.27)	0.16	3.46 (0.41-26.10)	0.26
Charlson index ≥2	1.94 (0.12-31.89)	0.64	1.30 (0.22-7.80)	0.29
Data on admission				
Systolic BP per mmHg decrease	0.99 (0.97-1.01)	0.36	0.99 (0.97-1.01)	0.28
Systolic BP <100 mmHg	1.05 (0.51-2.16)	0.88	1.06 (0.51-2.20)	0.87
Anemia	0.70 (0.32-1.54)	0.37	0.64 (0.29-1.43)	0.28
eGFR <60 ml/min/1.73 m^2	5.27 (1.05-26.60)	0.04	4.65 (0.86-25.10)	0.07
Na < 136 mEq/mL	3.37 (1.58-7.19)	0.002	3.10 (1.41-6.82)	0.005
ProBNP, pg/mL (log transformed)	1.74 (1.04-2.93)	0.036	1.75 (1.03-2.98)	0.03
Bilirubin, total, mg/dL	1.39 (1.08-1.78)	0.01	1.40 (1.09-1.80)	0.009
Lactate, mmol/L	1.40 (0.98-2.02)	0.06	1.42 (1.05-1.93)	0.023
Previous hospitalization	1.10 (0.52-2.31)	0.89	1.09 (0.52-2.31)	0.81
In-hospital support				
Need for vasopressors/inotropes	5.21 (2.32-11.68)	<0.001	5.29 (2.28-12.28)	<0.001
Need for mechanical ventilation	3.73 (1.64-8.47)	0.002	3.76 (1.63-8.67)	0.002
Need for renal replacement therapy	6.11 (1.45-25.81)	0.014	5.57 (1.25-24.76)	0.024

Definitions of abbreviations: PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD-PAH, connective tissue PAH; ICU, intensive care unit; WHO FC, World Health Organization functional class; BP, blood pressure; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Na, sodium; proBNP, pro-b-type natriuretic peptide.
*adjusted only for age

**Table 4. Risk factors for mortality within the first year after discharge in PAH patients admitted to the ICU**

	Unadjusted HR (95% CI)	p-value	Adjusted for PAH diagnosis and age HR (95% CI)	p-value
Age per year	1.02 (1.01-1.04)	0.01	NA	NA
Female vs. male	0.89 (0.49-1.62)	0.70	0.98 (0.53-1.81)	0.93
CTD-PAH v. IPAH	2.31 (1.28-4.16)	0.005	1.89 (1.01-3.59)*	0.05
WHO FC pre-admission (III & IV)	3.24 (0.95-11.02)	0.06	2.99 (0.84-10.63)	0.09
Charlson index ≥2	4.41 (0.53-36.67)	0.17	1.25 (0.35-4.52)	0.72
Data on admission				
Systolic BP <100 mmHg	1.08 (0.70-1.68)	0.72	1.06 (0.69-1.64)	0.78
Anemia	0.91 (0.55-1.49)	0.70	0.86 (0.53-1.40)	0.55
eGFR <60 ml/min/1.73 m^2	1.91 (0.76-4.78)	0.16	1.52 (0.59-3.92)	0.38
Na < 136 mEq/mL	1.87 (1.21-2.89)	0.005	1.71 (1.08-2.69)	0.021
ProBNP, pg/mL (log transformed)	1.48 (1.10-1.98)	0.009	1.35 (1.01-1.83)	0.04
Bilirubin, total, mg/dL	1.12 (1.00-1.26)	0.06	1.19 (1.05-1.34)	0.006
In-hospital support				
Need for vasopressors/inotropes	2.73 (1.73-4.30)	<0.001	2.57 (1.62-4.08)	<0.001
Need for mechanical ventilation	2.05 (1.24-3.38)	0.005	2.06 (1.25-3.40)	0.005
Need for renal replacement therapy	1.80 (0.68-4.76)	0.23	1.91 (0.68-5.38)	0.21

Definitions of abbreviations: PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD-PAH, connective tissue PAH ICU; ICU, intensive care unit; WHO FC, World Health Organization functional class; BP, blood pressure; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Na, sodium; proBNP, pro-b-type natriuretic peptide.
*adjusted only for age
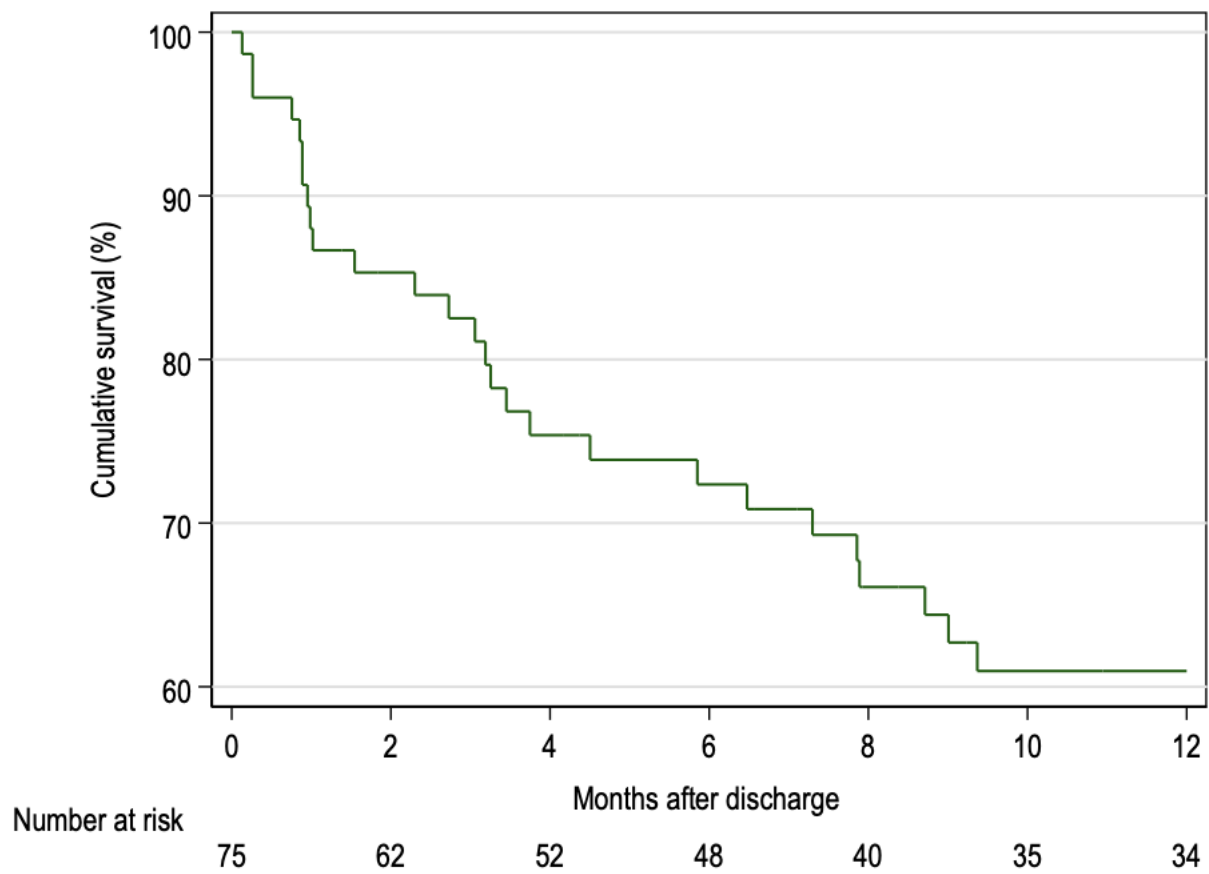
Figure 1. Cumulative survival after discharge at 3, 6, and 12 months of PAH patients admitted to the ICU.
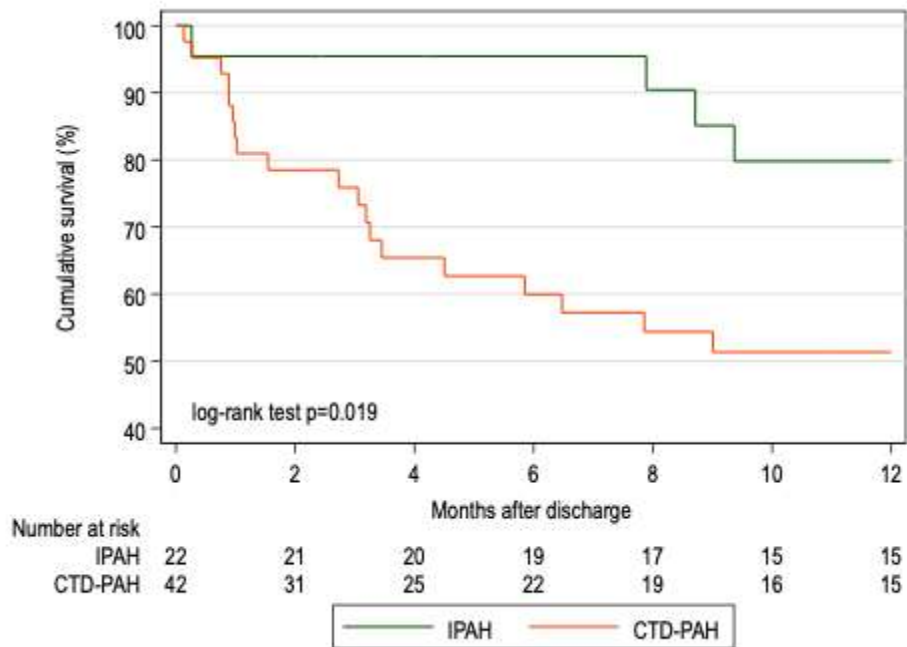
Figure 2. Kaplan-Meier curve of 1-year survival after discharge of PAH patients admitted to the ICU by underlying diagnosis (IPAH vs. CTD-PAH).