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# Outcomes of Hospitalization for Right Heart Failure in Pulmonary Arterial Hypertension

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**Running title:** Outcomes of RHF hospitalization in PAH

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**Abstract**

**Question of study**: To examine the causes and outcomes of hospitalization in patients with pulmonary arterial hypertension (PAH).

**Patients and Methods**: 205 consecutive hospitalizations from 2000 to 2009 in 90 PAH patients.

**Results**: The leading causes for hospitalization were right heart failure (RHF) (56%), infection (16%), and bleeding disorders (8%). For patients with RHF, in-hospital mortality was 14% overall, 46% for patients receiving inotropes, and 48% for those admitted to the ICU. The predictors for in-hospital mortality were the presence of connective tissue disease (CTD) (OR 4.92;*P*=0.03), systolic blood pressure<100 (OR 4.32;*P*=0.01) and Na<=136 (OR 4.29;*P*=0.02). Mortality after discharge was 13%, 26% and 35% at 3, 6 and 12 months. WHO functional class prior to admission, renal dysfunction, Charlson comorbidity index, and the presence of CTD were all predictors of mortality after discharge.

**Conclusions**: Hyponatremia and low systolic blood pressure upon admission, and underlying CTD are the main prognostic factors for in-hospital mortality in patients with PAH admitted for RHF. The short term outcomes after discharge are poor and remarkably worse in patients with underlying CTD or renal impairment. Early recognition of these factors may guide decision regarding more aggressive therapy including consideration for lung transplantation.

**Word count: 196**

**Key words**: Connective tissue diseases; Heart failure; Hospital mortality; Scleroderma, systemic; Ventricular dysfunction, right

## Introduction

Pulmonary arterial hypertension (PAH) remains a disease with high morbidity and mortality rates despite recent advances in therapy and overall improved survival. PAH is usually progressive, with right ventricular dysfunction being the leading cause of death. Patients often require hospitalization during the course of their disease, typically for bouts of right heart failure (RHF). In addition, complications related to treatment itself, including PAH specific therapy, anticoagulation, and long-standing indwelling catheters, constitute other potential causes of hospitalization.

In contrast with left heart failure (LHF), the course and outcomes of acute or decompensated RHF have been seldom described[1 2]. Several features differentiate RHF secondary to severe PAH from LHF and make management of RHF particularly challenging. While in both LHF and RHF aggressive diuresis is usually required, the large increase in transpulmonary gradient due to a fixed resistance in the pulmonary vasculature in PAH complicates the treatment of RHF. In addition, right ventricular-left ventricular (LV) interdependence often leads to LV dysfunction with low cardiac output and consequent systemic hypotension in RHF, which may require the use of vasopressor and inotropic agents. These hemodynamic perturbations may be further complicated by decreased myocardial perfusion from compromised coronary flow due to right ventricle overload. Ultimately, these processes can lead to distal organ dysfunction and irreversible hemodynamic collapse.

The causes, clinical burden, and outcomes of hospitalization for RHF, have been poorly characterized and their impact on overall clinical course is unknown. Thus our study aims were to analyze the causes, clinical characteristics and outcomes of hospitalization, as well as prognostic factors for mortality, in a cohort of PAH patients closely followed at a specialized pulmonary hypertension clinic. Some of the results of this study have been previously reported in abstract form[3].

## PATIENTS AND METHODS

### Patient Population

This study was approved by the Johns Hopkins University Institutional Review Board. Adult patients with PAH evaluated at the Johns Hopkins Pulmonary Hypertension Program were prospectively included in the Hopkins Pulmonary Hypertension Registry. Data from hospitalizations occurring at Johns Hopkins Hospital and its affiliate Johns Hopkins Bayview Medical Center from January 2000 to March 2009 were analyzed.

The diagnosis of PAH (WHO Group 1) was established by hemodynamic criteria (mean pulmonary artery pressure ≥25 mmHg, pulmonary capillary wedge pressure ≤15 mmHg, and pulmonary vascular resistance >3 Wood units) and exclusion of other potential causes of PH (WHO Groups 2-5)[4]. Within WHO Group 1, we limited our analysis to patients with idiopathic PAH (IPAH), and PAH associated with drugs/toxins (AiPAH) and connective tissue diseases (CTD-PAH), thus excluding other causes of WHO Group 1 PAH such as portopulmonary hypertension, hemoglobinopathies, or HIV. The decision to exclude these conditions was based

on the high prevalence of co-morbidities in these patients that lead to hospitalization unrelated to PAH. Although co-morbid conditions are also common in CTD-PAH, we included these patients because of our long interest in their outcomes[5 6 7 8] and the fact that they represent the bulk of referral to our Pulmonary Hypertension program. Patients with significant interstitial lung disease (ILD) as previously defined (TLC<60% or TLC 60-70% with significant interstitial radiological changes)[6 7 8] were excluded.

Electronic records and file charts were reviewed to obtain the demographic information, past medical history, findings on admission and at discharge, therapy during hospitalization, and medications prescribed at discharge. Charlson comorbidity index was calculated from the medical history[9]. Anemia was defined by hemoglobin <13 g/dL for men and <12 g/dL for women[10]. The estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the Modified Diet in Renal Disease equation[11]. Hyponatremia was defined as serum Na ≤ 136 mEq/L based on previous literature on PAH[5] and LHF [17 12].

In-hospital mortality was analyzed for general and RHF hospitalizations after exclusion of 45 elective admissions in stable patients (i.e. patients requiring initiation of treatment, elective surgery, or change of central infusion catheter). Mortality at 3, 6, and 12 months after discharge was analyzed for patients with a first hospitalization due to RHF. The diagnosis of RHF was considered in the presence of symptoms and physical evidence of volume overload (increased dyspnea and weight gain, peripheral edema or ascites, increased jugular venous pressure, and audible S3 gallop on auscultation) and inclusion of the diagnosis on the discharge report and/or billing code sheet (acute cor pulmonale, volume overload, or RHF). Death after discharge was

determined from the hospital records as well as the Social Security Death Index up to September 25, 2009. The latest clinic visit or contact with the patient up to that date was considered as censoring time for living patients. Lung transplantation was considered as a failure event in survival analysis, thus lung transplant recipients were excluded from further analysis after transplantation.

The analysis of risk factors for in-hospital mortality included demographics, underlying PAH disease, Charlson index, WHO functional class (WHO FC) at the latest outpatient assessment, physical signs, laboratory parameters on admission, and previous hospitalization for RHF. Risk factors for mortality after discharge included all factors mentioned above in addition to laboratory parameters at discharge.

**Statistical Methods**

Group comparisons were made using $\chi^2$ test and Fisher exact test as appropriate for categorical variables and Student's *t* test or Mann-Whitney test as appropriate for continuous variables. Systolic blood pressure (SBP) was considered for analysis both as a continuous and a dichotomized variable (SBP > or ≤ 100 mmHg)[17]. Correlation analyses (Spearman Rho) were performed to identify significant correlations between variables considered for regression analysis. The identification of prognostic factors for in-hospital mortality was performed using logistic regression with robust adjustment of the variance for repeated measurements in order to handle patients with multiple hospitalizations[13]. Mortality and readmission after discharge were assessed using the Kaplan-Meier method and Cox proportional hazards models. Risk factors were adjusted for age and underlying PAH type in multivariate analysis. Comparisons between

groups were assessed by Log-Rank Test. All computations were performed using Stata statistical software (version 10.1, Stata, College Station, TX). A *P* value <0.05 was considered as statistically significant.

## RESULTS

### Characteristics of patients and hospitalizations

After the exclusion of 45 admissions for elective causes, 205 hospitalizations in 90 patients were identified. The underlying diagnosis were IPAH (61 hospitalizations; 29.8%), Anorexigen-induced PAH (26; 12.6%), Systemic sclerosis (SSc) (113; 55.1%) and Connective tissue disease not including SSc (5; 2.4%). The most common causes for non-elective admissions were RHF (115; 56.1%), infection (32; 15.6%), bleeding (17; 8.3%), arrhythmia (13; 6.3%), and syncope (12; 5.8%). Among infections, those related to indwelling catheter were the most frequent (14 admissions; 43.8%), followed by pneumonia (7 admissions; 21.9%). Bleeding disorders included gastrointestinal (GI) bleeding (7 hospitalizations; 41.2%) and hemoptysis (6; 35.3%). GI bleeding occurred exclusively in 6 patients with scleroderma. Atrial fibrillation on admission was present in a minority of patients (7.3%). ICU hospitalization was required in 16.1% of hospitalizations, and overall in-hospital mortality was 8.8%.

### Hospitalizations for RHF

One hundred and fifteen hospitalizations due to RHF were identified in 61 patients. The characteristics of the patients and hospitalizations, and differences between patients with or without CTD are shown in Tables 1 and 2, respectively. Hemodynamic data obtained at the time of PAH diagnosis indicated severe PAH with a mean mPAP of 49 mmHg, CI of 2.22 L/min/$m^2$,

and PVR of 10.8 Wood Units. At the time of PAH diagnosis, patients with CTD-PAH had significantly lower mPAP compared to IPAH/AiPAH patients but other hemodynamic parameters such as CI or PVR were similar between the two groups. The median time from PAH diagnosis to first RHF admission was 11 months for all patients and not significantly different between the IPAH/AiPAH and CTD-PAH groups.

In-hospital mortality was 14% overall, and 48%, 46% and 100% when ICU admission, use of inotropes/vasopressors or mechanical ventilation were required, respectively. The causes of mortality were progressive RHF in 13 (81.3%), sepsis in 2 (12.5%), and gastrointestinal bleeding in 1 (6.2%).

***Demographics***. As shown in Table 1, compared to IPAH/AiPAH, patients with CTD-PAH were older, had a lower proportion of women, higher Charlson comorbidity index, and were more likely to have a history of depression, but had similar functional impairment as assessed by WHO FC. On admission, patients with CTD-PAH demonstrated lower heart rate, and had poorer renal function as assessed by serum creatinine, blood urea nitrogen (BUN) levels or eGFR. Serum proBNP level on admission was available in 41 patients and was higher in the patients with CTD-PAH.

***Hyponatremia***. Hyponatremia (Na≤136 mEq/L) on admission was present in 52 (45.2%) patients, and was moderate or severe (Na<130 mEq/L) in 11 (9.6%). Patients with hyponatremia compared with those with normal sodium levels had similar age (*P*=0.20), WHO FC prior to admission (P=0.26), and frequency of renal impairment (52% vs. 44%; *P*=0.42), but presented

with significantly lower SBP on admission (103 vs. 120 mmHg; $P<0.01$), higher heart rate (99 vs. 91 bpm; $P=0.01$), and more elevated serum BUN (32 vs. 24 mg/dL; $P<0.01$) and proBNP (11099 vs. 5088 pg/mL; $P=0.04$) levels. These patients also had a longer median length of stay (9 vs. 6 days; $P=0.02$), more commonly required inotropes (48.1% vs. 15.9%; $P<0.01$) or ICU admission (38.5% vs. 14.3%; $P<0.01$), and were more likely to die in-hospital (23.1% vs. 6.3%; $P=0.01$). There was a significant correlation between natremia and SBP on admission (Spearman Rho 0.55 ($P<0.01$)). There was not a significant correlation between eGFR and natremia.

***Renal dysfunction***. Renal dysfunction defined by eGFR<60 mL/min/1.73m$^2$ was present on admission in 55 patients (48%); these patients had a longer length of stay (8 vs. 6 days, $P=0.03$), required more frequent ICU admission (33% vs. 13%; $P=0.01$) or inotropes (40% vs. 20%; $P=0.02$), and their in-hospital mortality tended to be higher (20% vs. 8%, $P=0.10$).

**Treatment characteristics during hospitalization for RHF**

On admission, 95 (82.6%) out of the 115 patients admitted with RHF were already receiving PAH specific therapy: 43 (45.3%) were on monotherapy, and 52 (54.7%) on combined treatment. The most commonly used drugs were phosphodiesterase-5 inhibitors (PDE5-i) (58 patients) followed by endothelin receptor antagonists (ERA) (50 patients), and prostanoids (49 patients).

During hospitalization for RHF, patients received standard treatment based on their status severity and decisions of the attending physician. Inotropes or vasopressors were administered in 30.4% of patients, with dopamine being the most common drug choice (29.6%), followed by

norepinephrine (11.3%). Dopamine was used in combination with other vasoactive drugs in 18 of 34 patients. Three patients required hemodialysis or hemofiltration. One atrial septostomy was performed in a patient who eventually died during the hospitalization.

At discharge, loop diuretics were prescribed in 97 patients (98%), with a median dose for furosemide of 160 mg a day (range 5-500 mg). Aldosterone antagonists were prescribed in 81.8%, digoxin in 15.1%, calcium channel blockers in 16.5% and angiotensin inhibitors in 12.1%.

**Risk factors for in-hospital mortality after RHF admission**

Significant risk factors for in-hospital mortality are shown in Table 3. After adjusting for age, the presence of underlying CTD portended an OR for mortality of 4.9 [P=0.03]. After adjusting for age and underlying diagnosis, the independent risk factors were SBP<100 mmHg on admission (OR 4.32; *P*=0.01) and Na≤136 (OR 4.29; *P*=0.02).

**Outcomes after discharge**

Of the 61 patients with a first admission for RHF at our center, 7 died during hospitalization. Thus, outcomes after discharge where assessed in 54 patients. At discharge, 48 of these patients were on PAH specific treatment: 25 patients were on monotherapy (10 prostanoids, 5 ERA, 7 PDE5-i, and 3 high dose calcium channel blockers), and 23 patients on combined therapy. The baseline hemodynamic data of survivors of first RHF admission were not different between the CTD-PAH and IPAH/AiPAH groups (results not shown). In total, 15 patients were receiving intravenous prostacyclin, 3 subcutaneous treprostinil and 1 intravenous treprostinil at the time of discharge. The use of intravenous prostacyclin was higher in IPAH/AiPAH: 10 (50%) patients

with IPAH/AiPAH were discharged on intravenous prostacyclin compared to only 5 (14.7%) patients with CTD-PAH ($P$<0.01). Median survival after discharge for patients with CTD-PAH and IPAH/AiPAH receiving intravenous prostacyclin was 5.3 months and 18 months respectively ($P$<0.01). However, for those patients on prostacyclin, baseline hemodynamic data were significantly worse in the CTD-PAH compared to the IPAH/AiPAH subgroup (mean PAP 54 vs. 53 mmHg; $P$=0.85; PVR of 16.5 vs. 9.6 U.W.; $P$=0.02; and CI of 1.6 vs. 2.4 L/min/m$^2$; $P$=0.03).

During the first year of follow up, 18 patients (33%) died, and 3 patients with IPAH received lung transplantation. The mortality rates at 3, 6, and 12 months were 13%, 26% and 35% (Figure 1A). The causes of death after discharge were RHF (12 patients), sudden cardiac death (1 patient), massive hemoptysis (1 patient), sepsis (1 patient) and unknown (3 patients). Only 2 patients were censored before completing 12 months of follow-up. The median survival since PAH diagnosis was 4.2 years for patients with IPAH/AiPAH and 3.1 for patients with CTD-PAH ($P$=0.03). At the end of follow-up only 15.4% of CTD-PAH patients were alive compared to 59.1% of IPAH/AiPAH patients ($P$ < 0.01).

**Risk factors for mortality**

Univariable and multivariable analysis for mortality or lung transplantation after discharge are shown in Table 4. After adjusting for age and underlying diagnosis, the independent risk factors were WHO-FC prior to admission (Hazard Ratio (HR) 3.58; $P$<0.01), Charlson comorbidity index ≥2 (HR 2.98; $P$=0.03), and eGFR<60 at discharge (HR 5.84; $P$=0.02). After adjusting for age and Charlson comorbidity index, the presence of CTD conferred a HR of 15.3 [95%CI: 1.77

to 133] *P*=0.01). Regarding parameters obtained upon admission, only eGFR<60 was a significant risk factor for discharge mortality (Adjusted HR 5.93 [95%CI: 1.68 to 20.9] *P*<0.01).

## DISCUSSION

Our study reveals several important findings relative to patients with PAH who require hospital admission after diagnosis of their disease: 1) RHF is by far the most common reason for hospital admission, and the need for ICU care is not infrequent; 2) in-hospital mortality and mortality after discharge are exceedingly high; and 3) the main prognostic factors of poor outcomes related to RHF hospitalization include admission hyponatremia and hypotension, underlying CTD and presence of renal dysfunction.

### Course and outcomes for RHF hospitalization

This study demonstrates a high mortality for patients with RHF requiring hospitalization, with rates of 14% during hospital admission, and 13%, 26% and 35% at 3, 6 and 12 months after discharge. These results are in stark contrast with studies of left heart failure indicating rates of inpatient mortality mostly in the order of 3-5%[14 15 16 17 18 19] , although higher rates of 7%[20] and 9%[21] have been occasionally reported. Mortality after discharge for LHF has been reported at 10.7% at 30 days[21], 10.3% at 60 days[19] and 8.6% at 60-90 days[16].

The clinical characteristics of our patients with PAH were remarkably different from those described in LHF patients. PAH patients are younger and predominantly women, whereas LHF affects men and women equally[17]. PAH patients suffer less frequently from comorbid conditions common in LHF, such as atrial fibrillation, diabetes or systemic hypertension[14 17 18 20 21]. Additionally, the burden of hospital admission appears higher in RHF compared to studies on acute LHF done in the United States, with longer length of stay[14 17 18], and more frequent ICU admissions[14].

**Hyponatremia and hypotension on admission are significant prognostic factors for mortality during RHF hospitalization**

Similar to LHF[18 21 22], hyponatremia and low SBP were strong predictors of mortality during admission. Hyponatremia portended a 4-fold risk of in-hospital mortality. Patients with hyponatremia were also characterized by other severity indices such as lower SBP, increased heart rate and BUN levels, higher requirement for inotropes or ICU admission and a longer length of stay. Hyponatremia is a well established prognostic factor in LHF[18 21 22], and has been attributed to neurohormonal activation mediated mostly by vasopressin and causing water retention. We have previously demonstrated that hyponatremia is a strong indicator of poor long-term survival in patients with PAH[5]. In the current cohort, hyponatremia was strongly associated with low SBP, which was itself a significant predictor for in-hospital mortality, suggesting mediation by neurohormonal activation in the context of low cardiac output. Increased sympathetic activation has recently been demonstrated in PAH and is thought to correlate with disease severity and impact hemodynamics similar to LHF[23].

Low SBP portended a 4-fold increase in in-hospital mortality for patients with SBP <100 mmHg upon admission. Most patients requiring pressure support received dopamine, generally at low dose to ensure renal perfusion, and reflecting a team preference at our institution for this particular vasopressor in the case of RHF. Although no standardized treatment has yet been established for RHF, dopamine has been traditionally used in acute RHF[1 24], and recommended for non tachycardic patients with hypotension[24], since dobutamine is more likely to cause systemic hypotension. However, dobutamine with or without the addition of norepinephrine has

recently been proposed for inotropic support for RHF secondary to PAH[2 25] due to its ability to restore RV-pulmonary arterial coupling and cardiac output with less tachycardic effect[26]. Further studies are warranted to assess the impact of specific vasopressor protocols on altering this particular outcome.

**Impact of CTD and renal dysfunction on survival**

Patients with CTD-PAH had a 5-fold increment in in-hospital mortality, and up to 5.6-fold increased risk of death after discharge compared to IPAH/AiPAH, conferring a 50% mortality at 12 months for CTD-PAH patients. It is now well established that patients with CTD, in particular patients with systemic sclerosis, have a poorer long-term prognosis than patients with IPAH[6 27]. It has been hypothesized that a particularly inadequate RV adaptation to an increased afterload contributes to rapidly progressive RHF and death[6 28]. However, the higher prevalence of renal impairment might have conferred an increased risk in patients with CTD-PAH in this study as we have previously demonstrated in stable CTD-PAH patients[7].

Renal dysfunction defined by eGFR<60 is a common condition in LHF hospitalizations[15 16 17 21], with a prevalence reported in different series between 29% and 64%[29 30 31], and is also prevalent in stable patients with PAH (16.7% in a cohort of heterogeneous PAH patients)[32], conferring a higher risk for mortality[32 33]. In our cohort, renal dysfunction was remarkably high in CTD patients (72%), but also surprisingly common in IPAH/AiPAH (20%). Multiple factors may contribute to renal impairment in PAH such as low cardiac output, venous congestion, activation of the renin-angiotensin-aldosterone system, hypoxia, and the use of diuretics. Recent studies have demonstrated the contribution of venous congestion, in patients with cardiac dysfunction, to

a significant degree of renal impairment[34], and its correlation with right atrial pressure[19]. Thus, the higher prevalence of renal impairment in PAH patients admitted to the hospital with RHF may not be too surprising. In addition to older age, other factors may account for a higher prevalence of renal impairment in SSc-PAH patients in the absence of scleroderma renal crisis. The prevalence of renal dysfunction in patients with SSc has been reported at 3%[35], however, renal functional reserve is impaired in 75% of patients with SSc with normal creatinine levels[36], conferring an increased risk for renal dysfunction in this group.

**Other potential factors affecting prognosis**

Other clinical differences between IPAH/AiPAH and CTD-PAH are worth noting. The use of intravenous prostacyclin was higher in IPAH/AiPAH: 10 (50%) patients with IPAH/AiPAH were discharged on intravenous prostacyclin, compared to only 5 (14.7%) patients with CTD ($P<0.01$). While the hemodynamic data were not significantly different between the CTD-PAH and IPAH/AiPAH cohorts at baseline, patients in the former group receiving intravenous prostacyclins had more altered hemodynamics compared to their counterpart IPAH/AiPAH patients. Thus, we cannot discard lack of a more intensive therapy approach as a contributing factor for worse prognosis in CTD-PAH patients. Difficulty in handling administration of intravenous treatment due to frequently associated musculoskeletal impairment[37] and older age have been the underlying reasons for our center's preference for oral therapy in SSc-PAH patients. In view of these patients' poor prognosis, use of prostacyclin analogues (including subcutaneous route) should perhaps be considered more carefully in this group. Finally, patients with CTD were less likely than IPAH patients to be suitable candidates for lung transplant due to older age and associated comorbidities. However, even when considering transplantation as a

failure outcome, the differences in outcomes persisted (Figure 1B). Our data support the notion that once there is clinical evidence of RV failure, the prognosis for CTD-PAH patients is extremely poor. Whether this is compounded by renal impairment cannot be ascertained given the high prevalence of renal impairment found in this cohort of SSc-PAH patients.

**Limitations**

Some limitations of this study must be noted. First, we were unable to analyze the effect of treatment on outcomes due to lack of specific treatment protocol. Second, we analyzed the prognostic value of blood pressure and laboratory parameters on admission, but not their evolution during hospital stay. Third, due to the high proportion of patients with CTD included in the study, the poor outcomes noted during and after hospitalization cannot be generalized to other PAH groups. However, both hyponatremia and low SBP were high predictors for in-hospital mortality after adjusting for PAH diagnosis, and may potentially be applicable to other PAH populations. We were not able to assess these prediction factors in subgroups of PAH due to the limited number of deaths in each group. Renal dysfunction was a predictor for mortality after discharge, but since very few IPAH patients died and renal impairment was less common, we cannot infer any association of renal dysfunction and outcomes for this group. Finally, since the study included hospitalizations at a single center, generalizability of the results to other institutions or protocols cannot be inferred.

**Conclusions**

In conclusion, hyponatremia and low SBP on admission are the main prognostic factors for in-hospital mortality in patients with PAH admitted for RHF. The short term outcomes after

discharge are poor and remarkably worse in patients with underlying CTD, suggesting that the need for hospitalization constitutes in itself a poor prognosis in this group. Renal dysfunction may be of particular importance in these patients, perhaps requiring specific attention (e.g., kidney protective management with avoidance of nephrotoxic drugs, controlled use of diuretics, or initiation of angiotensin inhibitors) and warranting further studies. Recognition of these ominous factors of mortality in hospitalized PAH patients should alert the clinician and maybe guide therapeutic decisions to avoid emergence of RHF and prompt consideration of timely lung transplantation in appropriate patients. Further studies are also warranted to assess the efficacy of specific therapeutic protocols in patients thus deemed to be at higher risk for mortality.

**Table 1. Characteristics of patients admitted with right heart failure**

| | **All** | **IPAH/AiPAH** | **CTD-PAH** | ***P* value** |
|---|---|---|---|---|
| | **n = 61** | **n = 22** | **n = 39** | |
| Age upon first admission | 55 ± 14 | 46 ± 13 | 60 ± 11 | < 0.01 |
| Female (%) | 56 (91.8%) | 22 (100%) | 34 (87.2%) | 0.15 |
| Ethnicity/race | | | | |
| Caucasian/Black/Hispanic/Asian/Others | 47/11/2/0/1 | 16/4/1/1 | 31/7/1/0 | 0.61 |
| Underlying diagnosis | | | | NA |
| IPAH | 15 (24.6%) | 15 (68.2%) | | |
| Anorexigen induced PAH | 7 (11.5%) | 7 (31.8%) | | |
| SSc | 37 (60.7%) | | 37 (94.9%) | |
| Diffuse SSc | 3 (8.1%) | | | |
| Other CTD | 2 (3.3%) | | 2 (5.1%) | |
| Median time since PAH diagnosis to first RHF admission, months (IQR) | 11.1 (0; 25.2) | 13.9 (1; 25) | 11 (1; 28) | 0.98 |
| Right heart catheterization at PAH diagnosis | | | | |
| RAP, mmHg | 10 ± 5 | 10 ± 6 | 10 ± 5 | 0.95 |
| mPAP, mmHg | 49 ± 13 | 55 ± 14 | 45 ± 10 | <0.01 |
| CI, L/min/m2 | 2.22 ± 0.68 | 2.14 ± 0.57 | 2.26 ± 0.73 | 0.54 |
| PCWP, mmHg | 10 ± 3 | 10 ± 4 | 10 ± 3 | 0.87 |
| PVR, Wood Units | 10.8 ± 5.6 | 12 ± 5 | 10 ± 6 | 0.43 |
| Comorbidities | | | | |
| Coronary artery disease | 3 (5.1%) | 0 | 3 (7.9%) | 0.55 |
| Systemic hypertension | 17 (27.9%) | 9 (40.9%) | 8 (20.5%) | 0.14 |
| Diabetes mellitus | 4 (6.6%) | 1 (4.5%) | 3 (7.7%) | 1 |
| Peripheral vascular disease | 9 (14.8%) | 0 | 9 (23.1%) | 0.02 |
| Cerebrovascular disease | 2 (3.3%) | 2 (9%) | 0 | 0.13 |
| History of depression | 11 (18.1%) | 1 (4.5%) | 10 (25.6%) | 0.04 |
| Charlson comorbidity index | | | | <0.01 |
| 0 | 19 | 19 | 0 | |
| 1 | 20 | 2 | 18 | |
| 2 | 12 | 0 | 12 | |
| $3^{+}$ | 10 | 1 | 9 | |

| | | | | |
|---|---|---|---|---|
| Status at the end of follow-up | | | | < 0.01 |
| Alive, not transplanted | 14 (23%) | 8 (36.4%) | 6 (15.4%) | |
| Lung transplant recipients | 5 (8.2%) | 5 (22.7%) | 0 | |
| Dead | 42 (68.8%) | 9 (40.9%) | 33 (84.6%) | |

Definition of abbreviations: CI: Cardiac Index; CTD: Connective tissue disease; IPAH: Idiopathic pulmonary arterial hypertension; IQR: Interquartile range; mPAP: Mean pulmonary arterial pressure; NA: Not applicable; PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; RAP: Right atrial pressure; RHF: Right heart failure; SSc: Systemic sclerosis

**Table 2. Characteristics of RHF hospitalizations**

| | RHF hospitalizations | | | |
|---|---|---|---|---|
| | **All** | **Comparison by diagnosis** | | |
| | **All** | **IPAH/AiPAH** | **CTD-PAH** | ***P* value** |
| | **n = 115** | **n =54** | **n = 61** | |
| Age, years | 55 ± 15 | 45 ± 12 | 63 ± 12 | <0.01 |
| Female (%) | 106 (92%) | 54 (100%) | 52 (85.2%) | <0.01 |
| Charlson comorbidity index | | | | <0.01 |
| < 2 | 74 (64.3%) | 51 (94.4%) | 23 (37.7%) | |
| ≥2 | 41 (35.6%) | 3 (5.6%) | 38 (62.3%) | |
| WHO-FC pre-admission (II/III/IV) | 22/70/21 | 13/34/7 | 9/36/14 | 0.23 |
| Admission | | | | |
| Systolic BP, mmHg (n =112) | 112 ± 20 | 111 ± 21 | 113 ± 19 | 0.76 |
| Diastolic BP, mmHg (n =112) | 68 ± 13 | 71 ± 14 | 66 ± 12 | 0.06 |
| Heart rate, bpm (n =111) | 95 ± 16 | 98 ± 17 | 91 ± 14 | 0.02 |
| Atrial fibrillation on ECG (n =111) | 5 (4.5%) | 2 (3.8%) | 3 (5.1%) | 1 |
| s-Creatinine, mg/dL | 1.31± 0.8 | 1.04 ± 0.5 | 1.54 ± 1.0 | <0.01 |
| eGFR, mL/min/1.73 $m^2$ * | 62 ± 26 | 76 ± 24 | 50 ± 22 | <0.01 |
| eGFR | | | | |
| < 60 mL/min/1.73 $m^2$ | 55 (47.8%) | 11 (20.4%) | 44 (72.1%) | <0.01 |
| < 30 mL/min/1.73 $m^2$ | 14 (12.2%) | 3 (5.6%) | 11 (18%) | 0.05 |
| BUN, mg/dL | 28 ± 16 | 19 ± 11 | 35 ± 16 | <0.01 |
| Na, mEq/mL | 136 ± 5 | 136 ± 5 | 137 ± 5 | 0.47 |
| Na ≤ 136 mEq/mL | 52 (45.2%) | 24 (44.4%) | 28 (45.9%) | 0.87 |
| Hemoglobin. g/dL | 12.2 ± 2.3 | 12.5 ± 2.2 | 12.0 ± 2.3 | 0.17 |
| Hematocrit, % | 38.0 ± 6.2 | 38.8 ± 6.0 | 37.5 ± 6.3 | 0.26 |
| Anemia | 52 (45.2%) | 21 (38.9%) | 31 (50.8%) | 0.20 |
| Median ProBNP, pg/mL (IQR)* | 3602 (4815) | 2260 (1263) | 5919.5 (7164) | <0.01 |
| | n = 41 | n = 17 | n = 24 | |
| ICU admission | 29 (25.2%) | 10 (18.5%) | 19 (31.1%) | 0.12 |
| Inotropes/vasopressors | 35 (30.4%) | 14 (25.9%) | 21 (34.4%) | 0.32 |
| Mechanical ventilation | 9 (7.8%) | 3 (5.6%) | 6 (9.8%) | 0.50 |
| Median weight lost during hospitalization, kg (IQR)* | 3.6 (4.1) (n=91) | 3.5 (4.6) | 3.9 (3.7) | 0.96 |

| | | | | |
|---|---|---|---|---|
| Median length of stay, days (IQR)* | 7 (5) | 6 (9) | 8 (8) | 0.23 |
| In-hospital mortality | | | | |
| All (n=115) | 16 (14.0%) | 4 (7.4%) | 12 (19.7%) | 0.06 |
| ICU (n=29) | 14 (48.3%) | 3 (30%) | 11 (57.9%) | 0.24 |
| Inotropes/Vasopressors (n = 35) | 16 (45.7%) | 4 (28.6%) | 12 (57.1%) | 0.17 |
| Mechanical ventilation (n = 9) | 9 (100%) | 3 (100%) | 6 (100%) | NA |

*Comparison using Mann-Whitney test.
All percentages are referred to episodes of hospitalization.
Definition of abbreviations: AiPAH: Anorexigen induced PAH; BP: Blood pressure; BUN: Blood urea nitrogen; eGFR: Estimated glomerular filtration rate; ICU: Intensive care unit; IQR: Interquartile range; IPAH: Idiopathic PAH; IQR: Interquartile range; PAH: Pulmonary arterial hypertension; ProBNP: Pro Brain natriuretic peptide.
Baseline characteristics are expressed as n (%) or mean ± SD, unless the median value (IQR) is specifically indicated.

**Table 3. Risk factors for in-hospital mortality in RHF hospitalizations**

| | **Unadjusted** | | **Adjusted for underlying diagnosis and age** | |
|---|---|---|---|---|
| | **OR (95%CI)** | ***P* value** | **OR (95% CI)** | ***P* value** |
| Age, per year | 1.0 | 0.67 | NA | |
| | (0.98; 1.03) | | | |
| Male vs. female | 1.88 | 0.38 | 1.17 | 0.81 |
| | (0.46; 7.7) | | (0.32; 4.25) | |
| CTD-PAH vs. IPAH/AiPAH | 3.1 | 0.05 | 4.92* | 0.03 |
| | (1.0; 9.35) | | (1.18; 20.6) | |
| WHO-FC pre-admission | 1.91 | 0.17 | 1.61 | 0.32 |
| | (0.75; 4.85) | | (0.63; 4.09) | |
| Charlson index ≥ 2 | 2.69 | 0.06 | 1.96 | 0.21 |
| | (0.97; 7.46) | | (0.68; 5.61) | |
| **Data on admission** | | | | |
| Systolic BP, per mmHg decrease | 1.05 | <0.01 | 1.06 | <0.01 |
| | (1.02; 1.09) | | (1.02; 1.10) | |
| Systolic BP ≤ 100 mmHg | 3.62 | 0.02 | 4.32 | 0.01 |
| | (1.18; 11.1) | | (1.37; 13.6) | |
| Heart rate, per beat | 1.02 | 0.32 | 1.02 | 0.19 |
| | (0.98; 1.05) | | (0.99; 1.06) | |
| Hematocrit, per % | 0.92 | 0.10 | 0.93 | 0.14 |
| | (0.83; 1.02) | | (0.84; 1.02) | |
| eGFR < 60 mL/min/1.73 $m^2$ | 2.75 | 0.07 | 2.27 | 0.27 |
| | (0.92; 8.23) | | (0.53; 9.77) | |
| Na ≤ 136 mEq/mL | 4.42 | 0.01 | 4.29 | 0.02 |
| | (1.36; 14.4) | | (1.29; 14.7) | |
| ProBNP (pg/mL,log transformed) n = 41 | 65.4 | <0.01 | NA | |
| | (4.5; 946) | | | |
| Previous RHF hospitalization | 1.54 | 0.41 | 2.66 | 0.16 |
| | (0.55; 4.34) | | (0.67; 10.5) | |
| Need for inotropes | 136.2 | <0.01 | NA | |
| | (7.83; 2370) | | | |

| | | | |
|---|---|---|---|
| Need for mechanical ventilation | 252.1 (13.34; 4764) | <0.01 | NA |

* Adjusted only for age

Definition of abbreviations: BP: Blood pressure; BUN: Blood urea nitrogen; eGFR: estimated glomerular filtration rate; NA: Not applicable; OR: Odds ratio; ProBNP: Pro brain natriuretic peptide; WHO FC: World health organization functional class

**Table 4. Risk factors for mortality or lung transplantation within the first year after discharge in patients with first RHF hospitalization.**

| | **Unadjusted HR (95%CI)** | ***P* value** | **Adjusted for underlying diagnosis and age HR (95%CI)** | ***P* value** |
|---|---|---|---|---|
| Age, per year | 0.99 (0.96; 1.02) | 0.40 | NA | |
| Male vs. female | 2.82 (0.82; 9.63) | 0.10 | 3.04 (0.80; 11.5) | 0.10 |
| CTD-PAH vs. IPAH/AIPAH | 3.04 (1.02; 9.05) | 0.04 | 5.66* (1.67; 19.2) | <0.01 |
| WHO-FC preadmission | 4.39 (2.02; 9.53) | <0.01 | 3.58 (1.63; 7.88) | <0.01 |
| Charlson index ≥2 | 3.22 (1.36; 7.63) | <0.01 | 2.98 (0.11; 8.01) | 0.03 |
| Use of Inotropes during admission | 2.63 (1.01; 6.81) | 0.05 | 2.37 (0.9; 6.22) | 0.08 |
| Hematocrit, per % | 1.01 (0.94; 1.08) | 0.76 | 1.04 (0.96, 1.12) | 0.32 |
| Systolic BP ≤ 100 mmHg upon admission | 1.62 (0.54; 4.83) | 0.38 | 1.77 (0.58; 5.44) | 0.32 |
| eGFR<60 mL/min/1.73 $m^2$ upon admission | 3.58 (1.39; 9.25) | <0.01 | 5.93 (1.68; 20.9) | <0.01 |
| Na ≤ 136 mEq/mL upon admission | 2.08 (0.88; 4.91) | 0.09 | 1.72 (0.71; 4.16) | 0.23 |
| eGFR<60 mL/min/1.73 $m^2$ at discharge | 2.75 (1.07; 7.1) | 0.04 | 5.84 (1.27; 26.7) | 0.02 |
| Na ≤ 136 mEq/mL at discharge | 0.82 (0.35; 1.92) | 0.64 | 0.67 (0.26; 1.68) | 0.39 |

* Adjusted only for age

Definition of abbreviations: AiPAH: Anorexigen induced PAH; BP: Blood Pressure; BUN: Blood urea nitrogen; CTD-PAH: Connective tissue disease associated PAH; eGFR: estimated glomerular filtration rate; HR: Hazard ratio; IPAH: Idiopathic pulmonary arterial hypertension; NA: Not applicable; PAH: Pulmonary arterial hypertension; WHO FC: World health organization functional class

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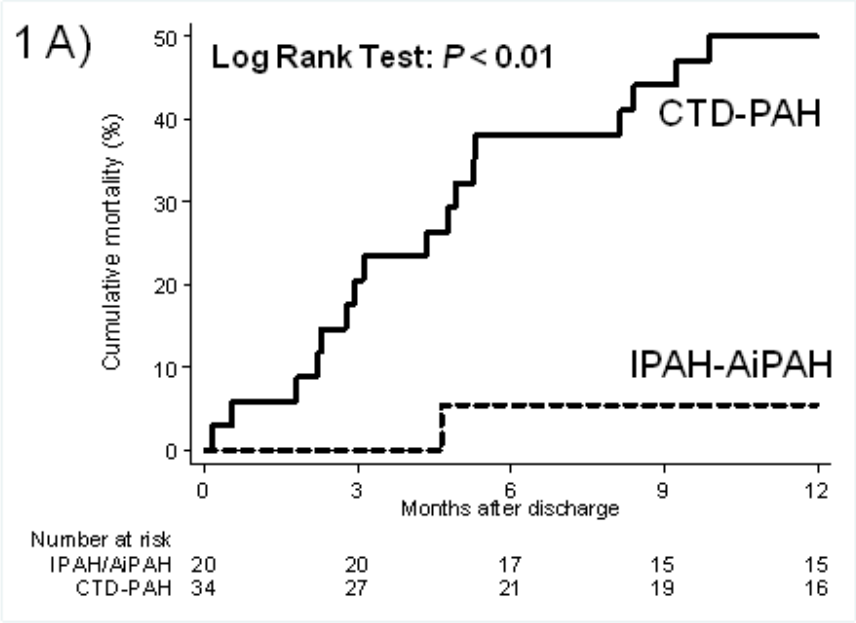
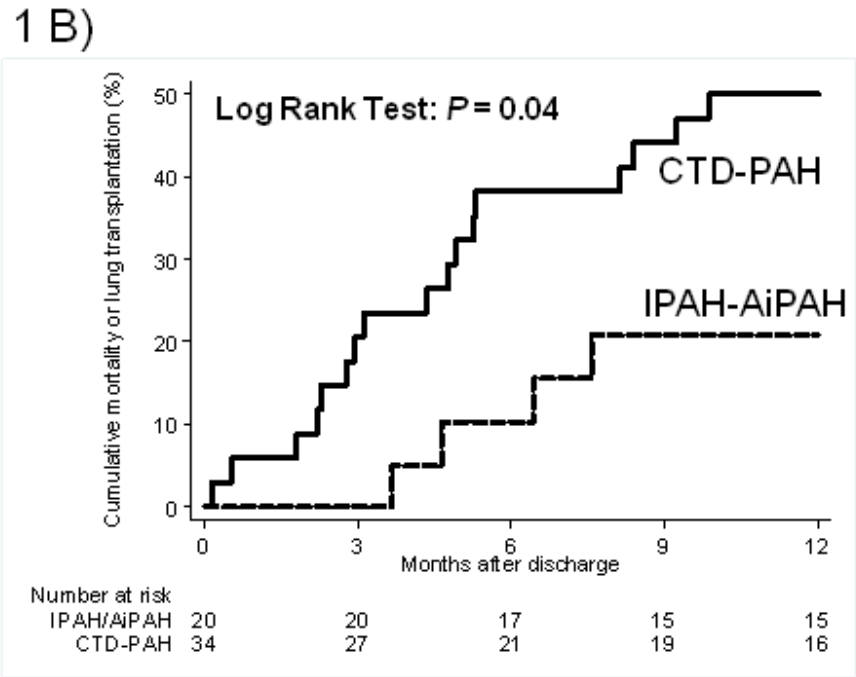
**Figure Legends:**

**Figure 1.** Outcomes after discharge in patients with RHF hospitalization by underlying diagnosis. **1A)** Mortality after discharge by underlying diagnosis. **1B)** Mortality or lung transplantation after discharge by underlying diagnosis.




Footnote:

Definition of abbreviations: CTD-PAH: Connective tissue disease associated PAH. IPAH: Idiopathic PAH. AiPAH: Anorexigen induced PAH.