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Publication Date

2020-03-01

DOI

10.1016/j.rmed.2020.105891

Peer reviewed

HHS Public Access

Author manuscript

Respir Med. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Respir Med. 2020 March ; 163: 105891. doi:10.1016/j.rmed.2020.105891.

Pulmonary arterial capacitance predicts outcomes in patients with pulmonary hypertension independent of race/ethnicity, sex, and etiology

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Abstract

Background: Pulmonary arterial capacitance (PAC) is a strong hemodynamic predictor of outcomes in patients with pulmonary hypertension (PH). Its value across subgroups of race/ethnicity, sex, and PH etiologies is unclear. We hypothesized that the association of PAC with outcomes would not vary across World Health Organization (WHO) PH group, race/ethnicity, or sex.

Methods: We performed a retrospective study in patients (n = 270) with PH diagnosed and managed at the Pulmonary Hypertension Comprehensive Care Center of a tertiary care hospital. Demographic, diagnostic, treatment, and outcome data were extracted from the electronic medical record. Cox proportional hazards models were used to model time from right heart catheterization to event in univariate and multivariable models. Our primary outcome was all-cause mortality and our secondary outcome was PH hospitalization.

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Jacob J Mayfield: Conceptualization, Methodology, Formal Analysis, Writing – Original Draft, Writing-Review & Editing, Visualization. **Alexander Papolos**: Conceptualization, Methodology, Validation, Writing-Review & Editing. **Elena Vasti**: Investigation, Data Curation, Writing-Review & Editing. **Teresa De Marco**: Conceptualzation, Methodology, Writing-Review & Editing, Supervision. **Geoffrey H Tison**: Conceptualization, Methodology, Software, Formal Analysis, Validation, Writing-Original Draft, Writing-Review & Editing, Supervision, Project administration.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Results: The median age of the cohort was 56 years (±14.6), and 67% were female. In multivariable Cox models adjusted for significant covariates, decreased PAC remained independently and significantly associated with both all-cause mortality (p=0.029) and hospitalization for PH (p=0.010). No significant interactions were observed between PAC and race, sex, or WHO group. Hispanic patients exhibited a significant independent association with increased hospitalizations (p=0.030), and there was a trend toward increased all-cause mortality in African Americans. WHO group 2 PH was associated with more frequent hospitalization (p=0.004).

Conclusions: Decreased PAC is significantly associated with mortality and hospitalization in PH patients independent of race, sex, and PH subgroups. Further investigation is required to characterize the effects and determinants of racial disparities in PH.

Keywords

Pulmonary hypertension; pulmonary arterial capacitance; health disparities; prognosis

Introduction

Pulmonary hypertension (PH) is a clinically diverse condition that results in significant morbidity, mortality, and economic burden.[1-5] Pulmonary arterial capacitance (PAC), defined as the right ventricular stroke volume divided by the pulmonary arterial pulse pressure, has been recognized as a strong hemodynamic measure of disease severity, prognosis, and response to treatment in patients with PH due to various etiologies.[6-10] PAC is a powerful prognostic tool because it is a quantitative marker of right ventricular (RV)-pulmonary arterial (PA) coupling. In patients with PH, increased PA pressures result in increased pulsatile RV workload culminating in RV-PA uncoupling and ultimately RV dysfunction.[11]

Membership in racial and ethnic subgroups is known to affect the diagnosis, management, and outcomes of many cardiovascular diseases, including PH.[12-15] While genetic mechanisms may underlie some of these differences, the primary driver is suspected to be disparities in social and economic determinants of health driven by structural inequity.[15-24] Whether PAC is uniformly associated with PH outcomes across racial subpopulations has not been studied. And, while the utility of PAC is established in World Health Organization (WHO) Group 1,[7,9,10,25] Group 2,[6,8,26,27] and Group 4[28] PH, it has not been studied in a mixed population of patients with WHO Groups 1-5 PH with a diverse racial composition.

To better understand the generalizability and prognostic value of PAC across different populations, we aimed to study the interaction between PAC with outcomes across subgroups of racial/ethnic, sex, and PH etiology. Since the prognostic value of PAC is thought to be related to RV coupling with the pulmonary vasculature, we hypothesized that the association of PAC with outcomes would not vary by race/ethnicity, sex, or WHO PH Group.

Materials and Methods

Study design and patients.

We performed a retrospective cohort study of patients who carried a diagnosis of PH and received care at the Pulmonary Hypertension Comprehensive Care Center of a single tertiary referral center. Subjects were eligible for inclusion if they had at least one encounter at our institution and had previously undergone right heart catheterization (RHC) within two months of a transthoracic echocardiogram. This was to ensure RHC and echocardiogram data were collected under relatively similar clinical conditions. Exclusion criteria included missing hemodynamic or demographic data and lack of formal diagnosis of PH.

Demographic, diagnostic, treatment, and outcome data were extracted manually from the electronic medical record. Race and ethnicity data were self-reported on presentation to our center. Patients who declined to self-identify or reported a race/ethnicity categorized as “other” were excluded. The primary outcome was all-cause mortality and the secondary outcome was hospitalization for which decompensated PH was the primary diagnosis. Hospitalization for intravenous line infections related to PH therapy were not included in the secondary outcome. Outcomes were adjudicated by manual chart review (JJM, AP, and EV). The Institutional Review Board of the University of California, San Francisco (UCSF) approved this study and approved a waiver of consent.

Diagnostic Testing.

Right heart catherization (RHC) and transthoracic echocardiography were performed according to routine clinical care at the UCSF cardiac catheterization laboratory and the UCSF echocardiography laboratory, respectively (UCSF, San Francisco, CA, USA). Hemodynamic data were extracted from RHC reports including right atrial pressure; systolic, diastolic, and mean pulmonary arterial pressures; pulmonary capillary wedge pressure; and Fick cardiac output and index. Stroke volume, pulmonary vascular resistance, and PAC were calculated per standard practice. Echocardiographic data were extracted from computerized reports.

Statistical Analysis.

Continuous variables are summarized as means and/or medians ± standard deviations (SD). Cox proportional hazards modeling was used to perform time to event analysis in univariate and multivariable models. Interaction terms were created to ascertain whether racial group membership, sex, or WHO PH Group 2 diagnosis modified the effect of PAC. Follow-up began at the time of the first RHC that met inclusion criteria. The censor date was the date of last documented contact between the patient and our health system or date of death. Covariates were selected for inclusion in multivariable models if they were of clinical interest or if the p-value in the respective univariate analysis was less than 0.20. Schoenfeld residuals were used to test the proportional hazards assumption.[29] A two-sided p-value threshold of 0.05 was used to establish statistical significance. Data were analyzed using Stata 15.1 (StataCorp LP, College Station, TX).

Results

Of 750 charts reviewed, 301 subjects were eligible for inclusion. 31 subjects were excluded for missing hemodynamic data, ethnicity data or lack of PH diagnosis. A total of 270 patients were included in this analysis. Median age in the cohort was 56 (±14.6), and 67% were female. Baseline cohort demographics, racial/ethnic, etiologic and hemodynamic characteristics are summarized in Tables 1-2. The total time at risk was 788.3 years and there were 57 deaths and 48 hospitalizations for PH during the follow up period.

Univariate analysis (Table 3) revealed decreased PAC, a diagnosis of heart failure reduced ejection fraction (HFrEF), and a history of smoking to be statistically significantly associated with the primary outcome of all-cause mortality, while low PAC and Hispanic ethnicity were associated with increased risk of hospitalization. Older age at RHC was associated with decreased hospitalizations.

The multivariable adjusted Cox model for the primary outcome included age, sex, race/ethnicity, diagnosis of Group 2 PH, smoking status, and prior diagnosis of atrial fibrillation or flutter as covariates (Table 4A). HFrEF was excluded from multivariable models since it is on the same causal pathway as Group 2 PH. Adjusted for all other covariates in the multivariable model, lower PAC was independently associated with higher risk of death in time to event analysis (HR 0.70, CI: 0.50 - 0.96, p = 0.029). The Kaplan-Meier survival curve (Figure 1), created by stratifying our cohort by the median PAC, demonstrates this effect. None of the other covariates were statistically significant.

We examined interactions between PAC and race/ethnicity for the primary outcome. There were no significant interactions observed by racial subgroups: Asian American (HR 1.63, CI: 0.50 - 5.32, p = 0.419), African American (HR 0.50, CI: 0.17 - 1.40, p = 0.185), or Hispanic (HR 1.08, CI: 0.45 - 2.60, p = 0.861) patients. There were no significant interactions between a diagnosis of Group 2 PH and PAC (HR 1.57, 0.73 - 3.40, p = 0.252) or sex and PAC (HR 1.26, CI 0.67 - 2.37, p = 0.474). The primary outcome model satisfied the proportional hazards assumption as assessed by Schoenfeld residuals.

The multivariable model for the secondary outcome initially included age, sex, race/ethnicity, diagnosis of Group 2 PH, diabetes mellitus, and obesity as covariates (Table 4B). While it satisfied the proportional hazards assumption globally by Schoenfeld residuals, sex alone was found to violate the assumption. Thus, the final model was stratified by sex. Adjusting for these covariates in the multivariable model, lower PAC was independently associated with higher risk of hospitalization (HR 0.60, CI: 0.40 - 0.88, p = 0.010; Figure 2). Hispanic ethnicity (HR 2.23, CI: 1.08 - 4.59, p = 0.030), Group 2 PH (HR 4.38, CI: 1.61 - 11.92, p = 0.004), and obesity (HR 0.36, 0.15 - 0.86, p = 0.021) were also significantly independently associated with hospitalization. Significant interactions between PAC and race/ethnicity were not observed in Asian American (HR 0.57, CI: 0.10 - 3.34, p = 0.535), African American (HR 2.35, CI: 0.65 - 8.51, p = 0.193), or Hispanic (HR 1.22, CI: 0.50 - 2.96, p = 0.656) patients. Group 2 PH diagnosis also did not significantly interact with PAC (HR 0.42, 0.13 - 1.40, p = 0.159).

In our models each 1 mL/mmHg reduction in PAC was associated with an increased risk of death of approximately 30% and increased risk of hospitalization of approximately 40%.

Discussion

In this study we demonstrate that PAC is significantly associated with mortality and hospitalization independent of other traditional risk factors in a diverse cohort of PH patients of varying race/ethnicity and WHO subgroups. We did not find significant interactions between PAC and race/ethnicity, sex, or WHO Group 2 etiology, which supports PAC as the strongest prognostic marker of PH outcomes in all-comers with PH, regardless of race/ethnicity and comorbidities.

PAC has previously been shown in Group 1 PH to be the best hemodynamic predictor of outcomes[7,9,10] and measure of response to treatment.[27] Similarly, it has been repeatedly shown to be a strong prognostic marker in patients with Group 2 PH,[6,8,30] even in the absence of elevated pulmonary vascular resistance.[31] Our results build on these findings, validating the application of PAC across hemodynamic phenotypes in a diverse referral population. In our cohort, a 1 mL/mmHg increase in PAC conferred and 30% decrease in the risk of death and a 40% decrease in risk of hospitalization for PH. In light of a standard deviation of 1.18 mL/mmHg, relatively small changes in PAC are PAC is associated with significant differences in outcomes, further supporting the practical clinical significance of PAC.

In our study, Hispanic patients had significant association with hospitalization independent of other covariates. However, we found no significant interaction between ethnicity and PAC for either mortality or hospitalization. This suggests an alternative mechanism of effect for the positive association between Hispanic ethnicity and hospitalization, possibly including socioeconomic factors. This interpretation is consistent with the burgeoning scientific consensus that vast majority of variation in health outcomes by race/ethnicity is the result of socioeconomic disparity resulting from structural inequality rather than genetic differences between culturally-designated racial groups.[32-36] The same could be true of our observation of a trend toward increased mortality in African American patients. Further research is necessary to understand socioeconomic determinants and mechanisms of worse outcomes in people of color with PH.

Women are known to be at greater risk for developing Group 1 PH, while men (especially those >60 years of age) appear to be at greater risk for all-cause mortality.[37-39] The mechanism behind these associations is not well understood, but is suspected to be related to differences in circulating hormone levels. We did not observe any association between sex and outcomes in our univariate or primary multivariable models. It is possible that our sample size was insufficiently large to detect these differences. Alternatively, the protective effect of female sex may not extend to Group 2-5 PH.

Several covariates including HFrEF, obesity, and age were significant in univariate and multivariable models and merit discussion. PH is a relatively common complication of HFrEF[40] and portends worse outcomes in these patients as compared to those with HFrEF

without PH.[41-43] Therefore, our findings of increased risk of death associated with HFrEF in univariate analysis and more frequent hospitalization associated with Group 2 PH in multivariable models are consistent with these prior reports.

Despite its negative impact on survival in the general population, obesity appears to be protective in patients with both acute and chronic heart failure, leading some authors to label this association the "obesity paradox."[44-47] This relationship has not been confirmed in Group 1 PH–in fact, obesity may actually be associated with worse outcomes in young people with pulmonary arterial hypertension (PAH).[48] Recent data from The Pulmonary Hypertension Association Registry suggest that obesity is also associated with worse quality of life in Group 1 PH.[49] Our finding of a protective association between obesity and hospitalization may reflect the fact that our cohort is drawn from patients with Groups 2-5 PH as well as Group 1.

Our results also suggest a significant negative association between older age at diagnosis and subsequent PH hospitalization. The mechanism behind this association is unclear but may reflect the fact that more severe PH may present earlier or that different PH etiologies exhibit varied prevalence in different age groups. Hospitalization data from large mixed-etiology PH cohorts are not currently available for comparison.[50] Further research is necessary to better understand these relationships between covariates and PH outcomes.

Limitations

Our study is best understood in the context of its limitations. By design, this was a retrospective, single-center design, which may limit generalizability of findings to other institutions. Another limitation is the relatively small sample size of our study cohort. This is especially pertinent for interaction analyses within the racial and hemodynamic subpopulations, which may have limited our ability to identify significant interactions. However, in general there is a lack of large, mixed-etiology PH cohorts in the literature that report race/ethnicity data and our study represents among the largest currently available. It is possible that a larger sample size could reveal significant interactions between certain race/ethnicities and PAC, for PH outcomes.

Conclusions

Decreased pulmonary arterial capacitance is significantly associated with mortality and hospitalization outcomes in PH patients independent of race/ethnicity, sex, and PH etiology subgroups.

Acknowledgements

The authors would like to thank Beth Cohen MD, MA for her assistance with statistical analysis and the members of the UCSF Program in Residency Investigation Methods and Epidemiology (PRIME)[51] for their assistance with editing the manuscript. Dr. Tison received support from the National Institutes of Health (NHLBI K23HL135274).

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Highlights

- Pulmonary arterial capacitance (PAC) predictors outcomes in pulmonary hypertension
- Univariate predictors of mortality included PAC, heart failure and smoking
- Univariate predictors of hospitalization included PAC, age and Hispanic ethnicity
- Adjusted for other covariates, PAC significantly predicted mortality
- There were no significant interactions observed between PAC and race for mortality
- A 1 mL/mmHg reduction in PAC was associated with 30% increased risk of death

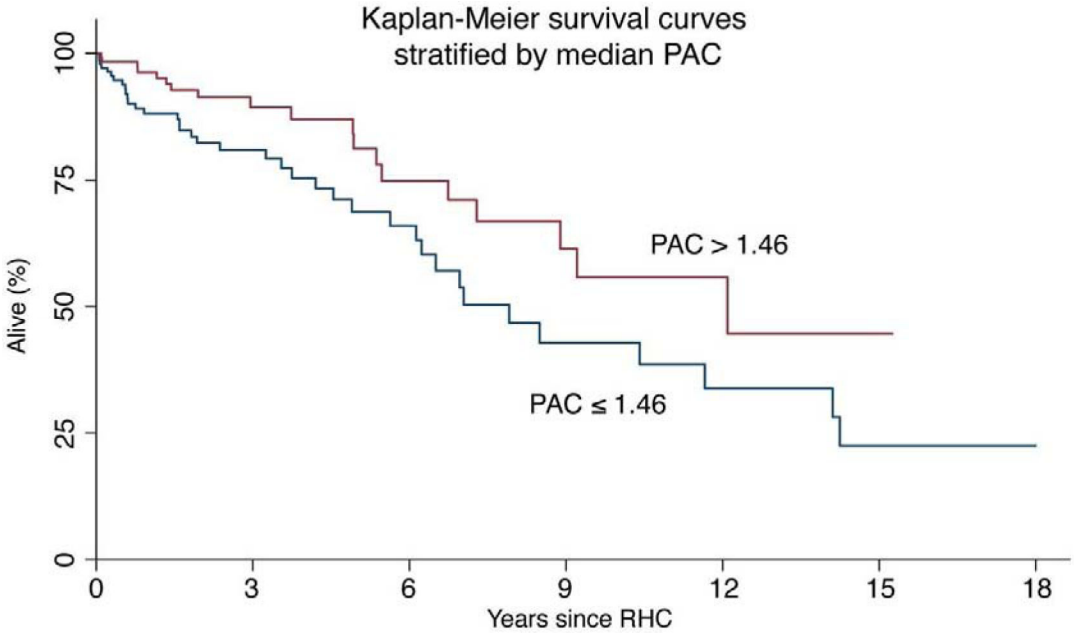

Figure 1.
Kaplan-Meier survival curve stratified by median PAC (1.46).

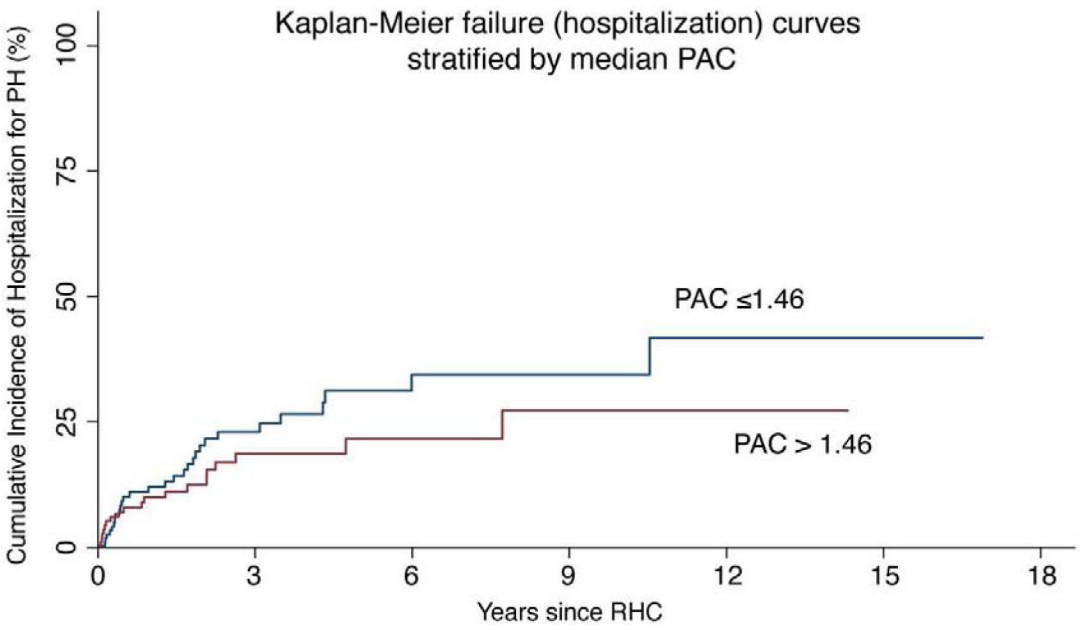

Figure 2.
Kaplan-Meier cumulative hospitalization curve stratified by median PAC (1.46).

Table 1.

Primary etiology of pulmonary hypertension in the study cohort.

ETIOLOGY	WHITE	ASIAN AMERICAN & PACIFIC ISLANDER	AFRICAN AMERICAN	HISPANIC	TOTAL
Group 1 – Pulmonary arterial hypertension	**96 (52.7%)**	**18 (9.9%)**	**17 (9.3%)**	**51 (28%)**	**182**
Idiopathic (1.1)	18 (48.6%)	5 (13.5%)	6 (16.2%)	8 (21.6%)	37
Heritable (1.2)	3 (100%)	0 (0%)	0 (0%)	0 (0%)	3
Drug and toxin induced (1.3)	37 (69.8%)	1 (1.9%)	2 (3.8%)	13 (24.5%)	53
Connective tissue disease associated (1.4.1)	24 (63.2%)	3 (7.9%)	4 (10.5%)	7 (18.4%)	38
HIV associated (1.4.2)	3 (50%)	0 (0%)	2 (33.3%)	1 (16.7%)	6
Portal hypertension associated (1.4.3)	10 (37%)	4 (14.8%)	3 (11.1%)	10 (37%)	27
Congenital heart disease associated (1.4.4)	1 (5.6%)	5 (27.8%)	0 (0%)	12 (66.7%)	18
Group 2 – PH due to left heart disease	**24 (55.8%)**	**7 (16.3%)**	**7 (16.3%)**	**5 (11.6%)**	**43**
HFpEF (2.1)	15 (60%)	5 (20%)	3 (12%)	2 (8%)	25
HFrEF (2.2)	7 (50%)	2 (14.3%)	4 (28.6%)	1 (7.1%)	14
Valvular disease (2.3)	2 (50%)	0 (0%)	0 (0%)	2 (50%)	4
Group 3 – PH due to lung diseases and/or hypoxia	**15 (68.2%)**	**3 (13.6%)**	**2 (9.1%)**	**2 (9.1%)**	**22**
Obstructive lung disease (3.1)	1 (50%)	0 (0%)	1 (50%)	0 (0%)	2
Restrictive lung disease (3.2)	9 (69.2%)	2 (15.4%)	0 (0%)	2 (15.4%)	13
Mixed restrictive and obstructive diseases (3.3)	2 (50%)	1 (25%)	1 (25%)	0 (0%)	4
Hypoxia without lung disease (3.4)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2
Developmental lung disorders (3.7)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1
Group 4 – Chronic thromboembolic PH	**12 (80%)**	**1 (6.7%)**	**2 (13.3%)**	**0 (0%)**	**15**
Group 5 – PH with unclear multifactorial mechanisms	**3 (37.5%)**	**2 (25%)**	**2 (25%)**	**1 (12.5%)**	**8**
Hematologic disorders (5.1)	1 (33.3%)	1 (33.3%)	0 (0%)	1 (33.3%)	3
Systemic and metabolic disorders (5.2)	1 (33.3%)	0 (0%)	2 (66.7%)	0 (0%)	3
Others (5.3)	1 (50%)	1 (50%)	0 (0%)	0 (0%)	2
Total	**150 (37.5%)**	**31 (25%)**	**30 (25%)**	**59 (12.5%)**	**270**

Pulmonary hypertension etiology according to the 6th World Symposium classification[52] of PH tabulated by race/ethnicity. Some etiologic categories are not displayed as no patients included in our study met the diagnostic criteria. (HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; PAC = pulmonary arterial capacitance)

Table 2.

Cohort demographics and characteristics.

Trait	n/median/mean (%/SD)
Female	181 (67%)
HFpEF	48 (18%)
HFrEF	27 (10%)
CAD	45 (17%)
Hypertension	122 (45%)
Hyperlipidemia	71 (26%)
CKD	61 (23%)
Diabetes mellitus	47 (17%)
Obese	59 (22%)
AF or AFL	49 (18%)
OSA	74 (27%)
Smoking	112 (41%)
COPD	38 (14%)
WHO Functional Class I	14 (5%)
WHO Class II	56 (21%)
WHO Class III	115 (43%)
WHO Class IV	43 (16%)
Unknown WHO Class	42 (16%)
Median Age	56 (±14.6)
Mean RA Pressure (mmHg)	8.8 (±5.7)
Mean PA Pressure (mmHg)	44.3 (±13.0)
Mean Cardiac Output (Fick, L/min)	4.68 (±1.87)
Mean Cardiac Index (Fick, L/min/m^2)	2.71 (±2.43)
Mean Pulmonary vascular resistance (dynes·s/cm^{-5})	8.31 (±5.33)
Mean PCWP (mm Hg)	11.4 (±5.9)
Median PAC (ml/mm Hg)	1.46 (±1.18)
Mean PAC (ml/mm Hg)	1.74 (±1.18)
Mean Heart rate (BPM)	77.6 (±15.9)
Mean Left ventricular ejection fraction (%)	64.4 (±9.7)
Mean PASP, TTE (mmHg)	70.0 (±23.1)

(HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; CAD = coronary artery disease; CKD = chronic kidney disease; AF = atrial fibrillation; AFL = atrial flutter; COPD = chronic obstructive pulmonary disease; RA = right atrial; PA = pulmonary artery; PCWP = pulmonary capillary wedge pressure; PASP = pulmonary artery systolic pressure; TTE = transthoracic echocardiogram)

Table 3.

Factors associated with mortality and hospitalization in univariate Cox proportional hazards models.

	PRIMARY (MORTALITY) OUTCOME		SECONDARY (HOSPITALIZATION) OUTCOME	
Covariate	**Hazard Ratio (CI)**	**p-value**	**Hazard Ratio (CI)**	**p-value**
PAC	0.70 (0.52 – 0.94)	**0.019**	0.63 (0.44 - 0.90)	**0.012**
Age	1.01 (0.99 - 1.03)	0.371	0.98 (0.96 - 0.996)	**0.021**
WHO PH Group (Group 1 ref.)				
Group 2	1.65 (0.79 - 3.46)	0.182	1.12 (0.50 - 2.54)	0.779
Group 3	1.90 (0.80 - 4.55)	0.148	1.09 (0.38 - 3.07)	0.878
Group 4	0.94 (0.22 - 3.94)	0.933	0.75 (0.18 - 3.14)	0.696
Group 5	0.75 (0.10 - 5.50)	0.78	0.81 (0.11 - 5.89)	0.832
HFpEF	1.34 (0.65 - 2.75)	0.425	1.40 (0.68 - 2.89)	0.366
HFrEF	2.54 (1.26 - 5.13)	**0.009**	2.03 (0.95 - 4.36)	0.069
CAD	1.10 (0.55 - 2.18)	0.789	0.75 (0.32 - 1.77)	0.514
Hypertension	1.30 (0.76 - 2.24)	0.337	1.22 (0.69 - 2.16)	0.496
CKD	1.11 (0.60 - 2.03)	0.744	1.25 (0.66 - 2.36)	0.500
Diabetes Mellitus	0.89 (0.46 - 1.72)	0.731	0.57 (0.24 - 1.33)	0.193
Obesity	1.12 (0.61 - 2.06)	0.714	0.46 (0.19 - 1.08)	0.073
Atrial fibrillation or flutter	1.84 (0.97 - 3.48)	0.059	0.86 (0.39 - 1.92)	0.715
OSA	1.21 (0.69 - 2.16)	0.500	0.74 (0.38 - 1.45)	0.374
Smoking	1.78 (1.03 - 3.09)	**0.040**	1.37 (0.77 - 2.44)	0.277
COPD	1.39 (0.65 - 2.96)	0.394	0.90 (0.36 - 2.27)	0.820
Male sex	0.77 (0.43 - 1.37)	0.367	1.15 (0.63 - 2.07)	0.651
Race/Ethnicity (white ref.)				
Asian American	0.38 (0.12 - 1.25)	0.111	0.76 (0.26 - 2.19)	0.605
African American	1.84 (0.92 - 3.69)	0.086	0.66 (0.20 - 2.21)	0.506
Hispanic	1.06 (0.55 - 2.03)	0.869	2.14 (1.15 - 3.97)	**0.016**

Table 4A.

Factors predicting mortality in multivariable time to event Cox modeling.

Covariate	Hazard Ratio (CI)	p-value
PAC	0.70 (0.50 - 0.96)	**0.029**
Age	0.997 (0.974 - 1.02)	0.780
Male sex	0.70 (0.38 - 1.30)	0.261
Race/Ethnicity (White ref.)		
Asian American	0.45 (0.12 - 1.65)	0.227
African American	1.92 (0.94 - 3.90)	0.071
Hispanic	1.08 (0.53 - 2.19)	0.835
Group 2 PH	1.60 (0.67 - 3.85)	0.291
Smoking	1.63 (0.92 - 2.87)	0.092
AF or AFL	1.34 (0.66 - 2.73)	0.422

Table 4B.

Factors predicting hospitalization in multivariable time to event Cox modeling.

Covariate	Hazard Ratio (CI)	p-value
PAC	0.60 (0.40 - 0.88)	**0.010**
Age	0.97 (0.95 - 0.999)	0.046
Race/Ethnicity (White ref.)		
Asian American	0.51 (0.15 - 1.71)	0.275
African American	0.50 (0.15 - 1.69)	0.263
Hispanic	2.23 (1.08 - 4.59)	**0.030**
Group 2 PH	4.38 (1.61 - 11.92)	**0.004**
Diabetes Mellitus	0.53 (0.21 - 1.29)	0.162
Obesity	0.36 (0.15 - 0.86)	**0.021**