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Original Article

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Insights Into Differences in Pulmonary Hemodynamics in Hispanic Patients With Pulmonary Arterial Hypertension

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Abstract

Background: Emerging data suggest that Hispanic patients with pulmonary arterial hypertension (PAH) exhibit improved survival rates compared to individuals of other ethnicities with similar baseline hemodynamics. However, the underlying reasons for this survival advantage remain unclear. This study focused on comparing pulmonary hemodynamics in Hispanic and non-Hispanic PAH patients and how these differences may contribute to varied clinical outcomes.

Methods: A retrospective analysis of right heart catheterization data was conducted on a treatment-naive PAH patient cohort from a single center.

Results: Over a 10-year period, a total of 226 PAH patients were identified, of which 138 (61%) were Hispanic and 88 (39%) were non-Hispanic. Hispanic patients presented with lower pulmonary artery pressures, lower pulmonary vascular resistance, and exhibited significantly higher pulmonary arterial compliance (PAc). Hispanic patients had better 5-year survival rates.

Conclusions: This study highlights the importance of exploring phenotypic differences in ethnically diverse PAH cohorts.

Keywords: Pulmonary arterial hemodynamics; Hispanic; Pulmonary arterial hypertension; Phenotypes

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Introduction

Pulmonary arterial hypertension (PAH) is a vascular remodeling syndrome that results in increased right ventricular (RV) afterload and ultimately leads to right heart failure. Adaptation of the RV to an increasing afterload is a crucial determinant of outcomes in PAH [1, 2]. Recently, various PAH vascular phenotypes have been identified, with variations in hemodynamic profiles and differences in the contribution of left heart and lung disease [3]. Additionally, RV structure and function are known to vary by age, sex, and ethnicity [4, 5]. Studies have shown that Hispanics free of known cardiovascular disease have a higher RV mass and RV end-diastolic volume at baseline than other ethnicities [6]. Moreover, Hispanic patients with PAH appear to have a survival benefit compared to other PAH ethnicities [7, 8]. However, the extent, validity, and potential reasons for this survival advantage remain unclear. There is a scarcity of detailed studies on right heart hemodynamics in Hispanic patients. One study found that Hispanic patients had higher mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR) than African-American and non-Hispanic white patients [7]. Conversely, another study involving 98 Hispanic and 585 non-Hispanic patients did not find significant differences in right heart hemodynamics, although Hispanic patients exhibited improved unadjusted survival rates [9].

The purpose of the current study was to examine potential baseline hemodynamic differences in treatment-naive Hispanic and non-Hispanic patients with PAH in a single-center patient cohort and to assess whether these differences have any implications on mortality.

Materials and Methods

Patient cohort

This was a single-center retrospective study conducted in a large referral center, University Medical Center (UMC) at the American-Mexican border with access to all advanced PAH-targeted therapies. Of 226 total patients with PAH, 138 Hispanic PAH patients who met the inclusion criteria and were

consecutively managed at the University Center between January 2012 and December 2022 were included. Patients were enrolled in this registry as inpatients with outpatient follow-up or as outpatients only. We chose only patients who met the following criteria based on previous and most recent guidelines [10]: 1) treatment-naive with newly diagnosed PAH; 2) initiation of PAH-targeted therapies within 6 months after diagnosis; 3) mPAP > 25 mm Hg (> 20 mm Hg after 2019), pulmonary artery wedge pressure < 15 and pulmonary vascular resistance (PVR) > 3 Wood Units (PVR > 2 after 2019); and 4) exclusion of World Health Organization (WHO)-group 2, 3, and 4 pulmonary hypertension (PH) based on past medical history, echocardiography, high-resolution chest imaging, pulmonary function testing, and ventilation perfusion scans. PAH-targeted therapies were reported within 3 months after diagnosis of PAH. Ethnicity was self-reported and extracted from patients' medical records.

Hemodynamic measurements

Pressure measurements were recorded at end-expiration at rest. Cardiac output (CO) was measured by thermodilution. Pulmonary pressures, pulmonary capillary wedge pressure (PCWP), CO, cardiac index (CI), and PVR were extracted from medical records after the catheterization report was completed. Stroke volume (SV) index was calculated based on heart rate, CO and body surface area (BSA). Pulmonary arterial compliance (PAc) was calculated as SV divided by pulmonary artery pulse pressure. Resistance-compliance (RC) time (s) was calculated as the product of PVR (mm Hg × s/mL) and PAc (mL/mm Hg).

Statistical analysis

Data are presented as absolute numbers, percentage, mean (standard deviation), or median (interquartile range). Differences in baseline variables were assessed using Spearman rank correlation, Chi-square, or *t*-test. All statistical analyses were performed using SPSS 29 and GraphPad Prism 8.0 software. Kaplan-Meier survival analysis was used to assess the 5-year survival rates in both patient populations, while adjusting for age, gender, and WHO functional classification (WHO-FC).

Written informed consent was not required for this study and it was performed in accordance with Texas Tech University Institutional Review Board.

Results

After assessing eligibility criteria, a total of 226 patients with PAH, 138 Hispanic patients and 88 non-Hispanic patients, were included in this study, between 2012 and 2022. The study cohort consisted predominantly of females (74.3%) with a mean age of 56.3 years. The baseline characteristics, including WHO-FC, body mass index (BMI), 6-min walking distance (6MWD), and hemodynamic variables are shown in Table 1. Hispanic patients had a higher 6MWD (352 ± 121 vs. 320 ± 109, P = 0.047), but similar WHO-FC (3.0 ± 0.5 vs. 3.0 ± 0.4, P = 0.506). Compared to the non-Hispanic cohort, mPAP (43.2 ± 11.8 vs. 50.6 ± 12.1, P = 0.001), systolic pulmonary artery pressure (SPAP) (71.5 ± 18.7 vs. 81.7 ± 21.0, P = 0.004), PVR (9.9 ± 6.8 vs. 11.7 ± 5.2, P = 0.024), and pulse pressure (PP) (42.6 ± 13.0 vs. 58.6 ± 14.3, P = 0.001) were significantly lower in Hispanic patients. However, there were no significant differences in diastolic pulmonary artery pressure (DPAP), PCWP, SV, and CI between the two groups. Notably, PAc was significantly higher in Hispanic patients (1.36 ± 0.64 vs. 1.0 ± 0.48, P = 0.020) as shown in Table 1 and Figure 1. The RC time for the entire cohort was 0.66 s and longer in Hispanic patients (0.7 s) compared to non-Hispanic patients (0.61 s, P = 0.004). These differences remained in a subgroup analysis excluding patients with congenital heart disease (CHD)-PAH (Supplementary Material 1, www.cardiologyres.org). Hispanic patients had a significantly higher adjusted 5-year survival rate compared to the non-Hispanic cohort (Fig. 2). This survival benefit remained after removing patients with CHD-PAH from the cohort (Supplementary Material 2, www.cardiologyres.org). A reduced PAc was associated with poor outcomes in both cohorts. Hispanic patients with a PAc below the mean for the Hispanic cohort (1.36 mL/mm Hg) had a significantly higher 5-year mortality (estimated median survival 4.6 versus 4.0 years, P < 0.001, Fig. 2b). Non-Hispanic patients with a PAc below the mean for the non-Hispanic cohort (1.0 mL/mm Hg) had a significantly higher 5-year mortality (estimate mean survival 4.6 versus 4.5 years, P < 0.001, Fig. 2c). There were no significant differences in the intensity of PAH-targeted therapies (mono- double- or triple therapy) in Hispanic and non-Hispanic patients (Supplementary Material 1, www.cardiologyres.org) at the end of the study.

Discussion

This study has three main findings. 1) Despite similar age, gender, and WHO-FC, Hispanic patients present with a favorable hemodynamic profile at baseline, characterized by lower PAPs, PVR, and higher PAc. 2) Hispanic patients have a higher baseline functional capacity. 3) Hispanic patients have improved 5-year survival rates compared to non-Hispanic patients.

RV failure is a complex process that is incompletely understood and not all aspects of RV function and dysfunction are captured by right heart catheterization. However, the adaptation of the RV to an increasing afterload from pulmonary vascular remodeling is a major determinant of outcomes in PAH and a drop in afterload can improve survival [11, 12]. Favorable hemodynamics at baseline in Hispanic patients are therefore likely related to improved 5-year survival in this cohort. The afterload of the RV is characterized by a static component (PVR) and a pulsatile component (PAc). A striking difference in our cohort was the higher PAc in Hispanic patients with a longer RC-time, compared to non-Hispanic patients. There is debate if both parameters reflect the same functional and anatomic vascular bed and truly provide independent prognostic information beyond other hemodynamic variables, especially PVR [13-22]. However, more recently, PAc has been shown to

Table 1. Baseline Characteristics of All Cohort

	All (n = 226)	Hispanic (n = 138)	Non-Hispanic (n = 88)	P
Age	56.3 (14.7)	57.7 (14.6)	54.0 (14.5)	0.064
Gender (%)	74.3	76.1	71.6	0.597
BMI	26.4 (6.9)	27.5 (8.5)	25.4 (3.9)	0.002*
WHO-group				0.043*
IPAH	149 (65.9%)	83 (60.1%)	66 (75%)	
CTD-PAH	41 (18.1%)	28 (20.3%)	13 (14.8%)	
CHD-PAH	30 (13.3%)	25 (18.1%)	5 (5.7%)	
PoPAH	5 (2.2%)	1 (0.7%)	4 (4.5%)	
HIV	1 (0.4%)	1 (0.7%)	0	
WHO-FC	3.0 (0.5)	3.0 (0.5)	3.0 (0.4)	0.506
6MWD (m)	340 (117)	352 (121)	320 (109)	0.047*
SPAP	77.6 (20.9)	71.5 (18.7)	81.7 (21.0)	0.004*
DPAP	29.7 (9.7)	28.9 (10.6)	31.1 (8.4)	0.062
mPAP	45.7 (12.5)	43.2 (11.8)	49.8 (12.1)	0.001*
PP (mm Hg)	48.9 (15.6)	42.6 (13.0)	58.6 (14.3)	0.001*
PCWP	9.5 (2.7)	9.0 (2.9)	11.4 (2.8)	0.150
CI (mL/min/m^2)	2.3 (0.7)	2.4 (0.8)	2.2 (0.7)	0.094
PVR (WU)	11.5 (6.3)	9.9 (6.8)	11.7 (5.2)	0.024*
SV (mL)	53.9 (10.3)	53.3 (14)	54.9 (18)	0.058
PAc (mL/mm Hg)	1.23 (0.61)	1.36 (0.64)	1.0 (0.48)	0.020*
RC time (s)	0.68 (0.24)	0.73 (0.21)	0.61 (0.18)	0.011*

Data are shown as mean (standard deviation), except for gender (%). P-values for continuous variables were calculated by Spearman rank correlation, Chi-square test for gender, and *t*-test for WHO-FC. *Statistically significant. BMI: body mass index; IPAH: idiopathic pulmonary arterial hypertension; CTD: connective tissue disease; CHD: congenital heart disease; PoPAH: porto-pulmonary arterial hypertension; WHO-FC: World Health Organization Functional Classification; mPAP: mean pulmonary artery pressure; SPAP: systolic pulmonary artery pressure; DPAP: diastolic pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PP: pulse pressure; PA: pulmonary arterial; CI: cardiac index; PVR: pulmonary vascular resistance; SV: stroke volume; 6MWD: 6-min walking distance.

be an independent predictor of survival and a predictor of RV functional recovery [23-26].

Our study confirms the well-established inverse hyperbolic relation of PAc and PVR with a relative maximum of pulmonary artery stiffness at higher resistance values (Supplementary Materials 1-4, www.cardiologyres.org) [21]. The understanding of the pathophysiologic relationship between increasing PVR and decreasing compliance in PAH has evolved over time [27]. With a stable CO and PCWP, an increase in mPAP will lead to an increase in PVR and a decrease in PAc due to the non-linear compliance of the PA [13, 14, 28]. A compliant pulmonary vascular bed accumulates blood during systole and releases this volume during diastole, resulting in a continuous peripheral flow during the complete cardiac cycle. The product of PVR and PAc is expressed as the RC time which characterizes the decay of DPAP. In this study, both cohorts had similar heart rates, PCWP, and patients with non-WHO 1 PH were excluded. Therefore, the RC time was narrowly constraint in both cohorts (0.73 ± 0.21, 0.61 ± 0.18), similar to previous reports [21, 22]. However, this finding is not supported by other studies [29, 30]. Differences in data acquisition and analysis, variations heart rate, elevation in left atrial pressure in different PAH subtypes might be potential contributors for RC time scatter [22, 31].

Due to its inverse hyperbolic relationship, at high PVR, a significant decrease of such is needed (> 7 WU) to improve compliance [22, 32]. Hispanic patients had a slower diastolic pressure decay, shown by an increased RC time, compared to non-Hispanic patients despite similar CO, SV and PCWP resulting in a steeper RC time curve (Supplementary Materials 1-4, www.cardiologyres.org). A steeper RC time curve in Hispanic patients could imply more improvement of PAc for each unit the PVR is lowered, potentially translating into a favorable response to PAH-targeted therapies and survival.

Several alternative explanations may account for the relationship between improved baseline hemodynamics in PAH and better survival outcomes. A lower PAP and PVR and increased PAc can be associated with a decrease in RV pulsatile workload, leading to decreased wall-stress, oxygen consumption, and a lower risk for RV-PA uncoupling [33, 34]. However, it should be noted that our study does not provide data on RV anatomy and therefore any comments on RV adaptation in these cohorts remain speculative. Nonetheless, our findings are in line with previous studies showing that PAc is a strong predictor of mortality in different patient cohorts with various forms of PH [23, 35-38].

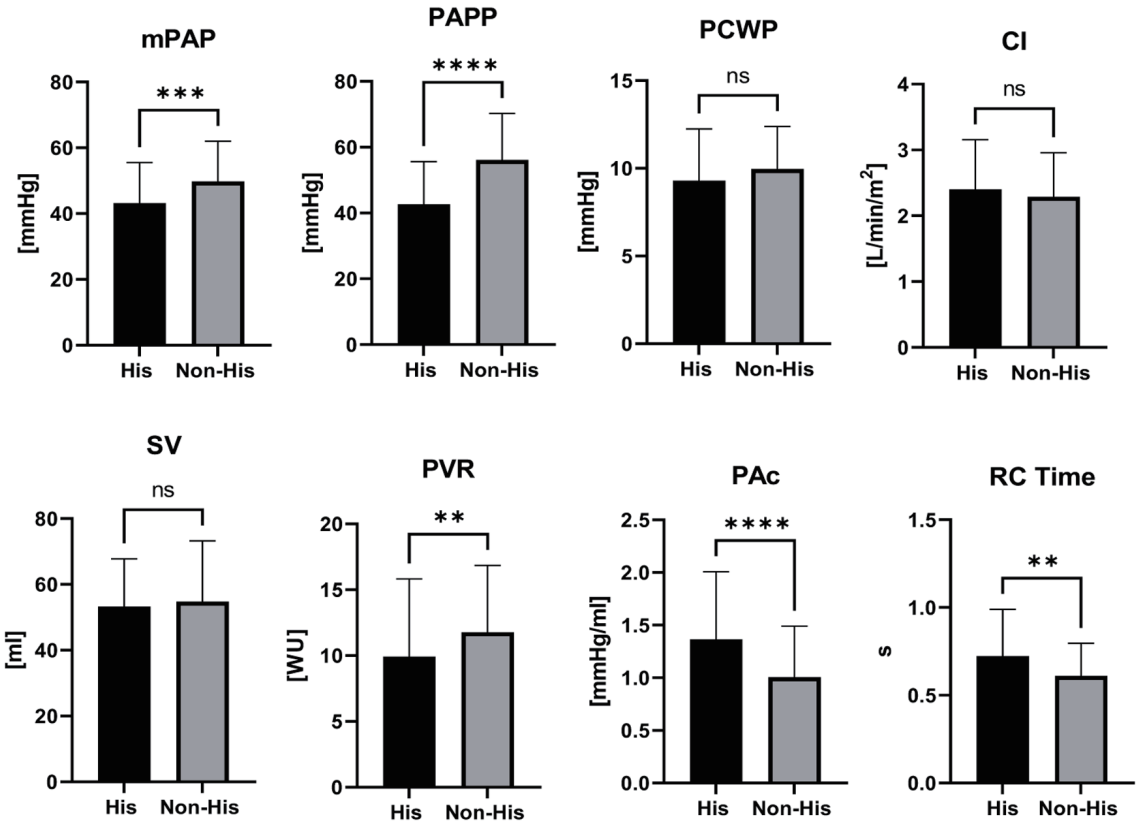

Figure 1. Relationship of baseline hemodynamic profiles between Hispanic and non-Hispanic patients, with mean pulmonary artery pressure (mPAP), pulmonary arterial pulse pressure (PAPP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), stroke volume (SV), peripheral vascular resistance (PVR), pulmonary arterial compliance (PAc), and resistance-compliance (RC) time significantly different between both groups. All values are recorded as mean ± standard deviation.

The higher pulmonary compliance observed in Hispanic patients may provide insights into the phenomenon known as the "Hispanic paradox" [17]. This phenomenon suggests that Hispanic patients exhibit better survival after cardiovascular events despite having worse comorbidities and cardiovascular risk factors. While the precise mechanisms behind this paradox remain elusive, our findings align with the hypothesis that inherently higher vascular compliance in Hispanic patients may be related to a favorable survival, despite the presence of other risk factors and comorbidities. A prominent feature of pulmonary vascular remodeling in PAH is the thickening of the smooth muscles cell layer in the pulmonary artery, leading to an increase in PVR [39]. In addition, vascular remolding of the adventitia with a decrease in elastin content and an increase in collagen, fibronectin, glycosaminoglycans, and tenascin-C deposition is linked to a decrease in PAc. It is interesting to note that in preclinical PH models, extracellular matrix changes in the pulmonary artery precede pulmonary artery smooth muscle cell hypertrophy [40-46]. Similarly in humans, patients with exercise-induced PH can have normal mPAP and a decrease in PAc [13, 14], indicating that low PAc could contribute to the progression of PAH. Furthermore, there is cumulating evidence that the majority of PAc is located in distal arteries, indicating that resistance vessels are the same as compliance vessels [20, 27, 47]. It is possible that Hispanic patients may have a different pulmonary vascular or RV genotype that leads to an altered molecular and cellular response to pulmonary vascular remodeling, associated with less pulmonary vascular stiffening, leading to advantageous baseline hemodynamics, a possible favorable response to PAH-targeted therapies, and potentially better clinical outcomes. Combination PAH-targeted therapies can improve outcomes [48, 49]; however, in our cohort, we did not detect differences in the use of combination therapy. Given that this was a single-center retrospective analysis, patients received fairly homogenous care and it is therefore less likely that differences in PAH therapy contributed to differences in outcomes.

The adaptation of the RV to an increase in afterload is different in different forms of PAH. For instance, patients with post-tricuspid ventricular defects have a more favorable RV adaptation to the same afterload, and improved survival, compared to patients with idiopathic PAH (IPAH) or systemic sclerosis-associated PAH (SSc-PAH) [50, 51]. It is important to note that 18% of the Hispanic patients carried a diagnosis of CHD, compared to 5.7% of the non-Hispanic cohort. In subgroup analyses, excluding patients with CHD-PAH, we could not find significant differences in baseline hemodynamics or adjusted 5-year survival. It is therefore less likely that the sur-

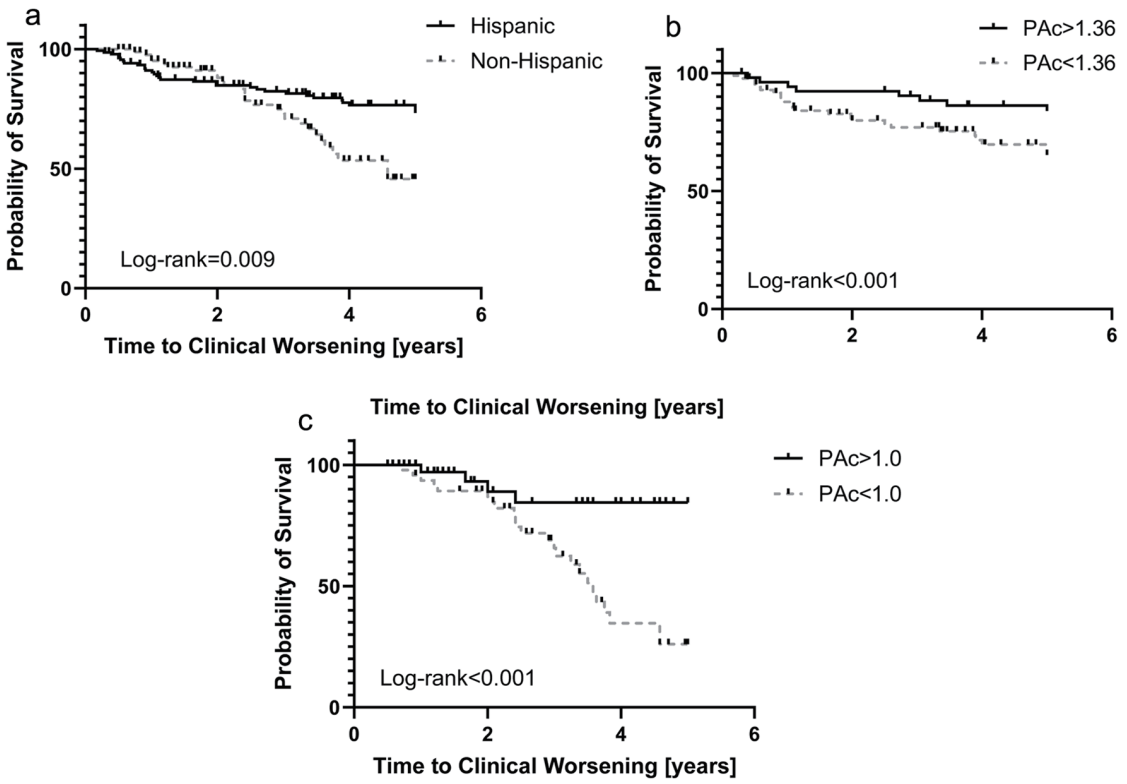

Figure 2. Kaplan-Meier survival estimate: 5-year survival in (a) Hispanic and non-Hispanic patients; (b) Hispanic patients with pulmonary arterial compliance (PAc) of 1.36 mL/mm Hg; c) non-Hispanic patients with PAc of 1.0 mL/mm Hg.

vival benefit observed in this study is explained by a favorable RV phenotype from CHD-PAH patients [52].

Limitations

This study has several limitations, mainly based on its single-center cohort, retrospective design, and lack of hemodynamic follow-up. The methodology of PAc and RC time measurements represents simplified equations to calculate resistance, compliance, and the RC time, which may not reflect true physiologic values [29, 47]. All variables investigated here are mathematically coupled and accurate interpretation of the functional relationship necessitates caution. Furthermore, this study lacks insight into RV performance measured by volumetric assessment or derived pressure volume loops. Therefore, the results of this study need to be interpreted critically and larger, more sophisticated studies are needed to confirm our results and expand on these findings. It is important to note that even though we recruited patients from one predominantly Hispanic region, such groups are potentially genetically diverse, carrying varying degrees of different ancestries [9].

Conclusion

In conclusion, our study presents compelling evidence supporting a favorable hemodynamic profile in Hispanic patients with PAH compared to non-Hispanic patients, which appears to be linked to improved clinical outcomes independent of PAH-targeted therapies or PAH subgroups. Our findings indicate that Hispanic PAH patients demonstrate significantly lower mPAP, PVR, and higher PAc in comparison to non-Hispanic patients, potentially contributing to enhanced RV function. However, further investigation is necessary to understand the specific factors driving this difference in PAc and RV adaptation to elucidate the underlying pathobiological mechanisms. Prospective studies incorporating larger sample sizes, a more detailed anatomic and functional assessment of the RV, and diverse populations are crucial to validate our findings and explore the potential implications of PAc as a predictor of mortality outcomes in PAH. Of note, Hispanics are not a homogeneous ethnic group, as there is great genetic diversity and socioeconomic, educational, and demographic variation among them and future studies with disaggregated data may provide even greater insight into PAH pathophysiology in different ethnic groups. By uncovering the mechanisms and factors influencing variations in pulmonary vascular compliance among different ethnicities, novel therapeutic interventions and strategies to improve patient outcomes in PAH may be identified.

Supplementary Material

Suppl 1. PAH-Targeted Medications.

Suppl 2. Kaplan-Meier curves without CHD-PAH.

Suppl 3. Patient Cohorts Without CHD-PAH.

Suppl 4. Scatterplot with nonlinear regression line delineating the relationship between pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAc).

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Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Written informed consent was not required for this study.

Author Contributions

Kedzie Arrington, Seyed Khalafi, Michael Brockman, and Kahtan Fadah collected data for this project; Kahtan Fadah and Nils P. Nickel wrote the original manuscript; Debabrata Mukherjee, Haider Alkhateeb, and Hernando Garcia revised the manuscript and provided key feedback and insights. Kahtan Fadah and Nils P. Nickel analyzed and created figures, tables, and supporting information. Nils P. Nickel supervised the project.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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