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Racial and ethnic differences in pulmonary arterial hypertension

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Abstract

This study explores the racial and ethnic differences in presentation, severity, and treatment of patients with pulmonary arterial hypertension (PAH) in a large multicenter registry. African American and Hispanic patients are more likely to present with associated PAH compared to non-Hispanic whites. Hispanic patients with PAH were less likely to be treated with PAH-specific medications compared to non-Hispanic whites.

Keywords

pulmonary arterial hypertension, race, ethnicity, epidemiology

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Racial differences in the manifestations of respiratory diseases have been well-documented and, in some instances, lead to healthcare disparities, defined as healthcare variations not attributable to patient characteristics, preferences, or disease severity that result in adverse health consequences.[1] Racial differences in treatment of pulmonary arterial hypertension (PAH) have not been explored, but differences in response to a specific medication class, endothelin receptor antagonist, among patients with PAH have been documented.[2–4] While PAH was historically considered a disease of young white women,[5] a contemporary large PAH registry, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL), showed that 27% of patients with PAH were from minority groups.[6] In a small, single-center, retrospective cohort, non-white patients with PAH had worse outcomes than white patients with PAH.[3] In two studies using national registries of death certificate data, African American (AA) women had the highest mortality rates among patients with PAH.[2,7]

The past two decades have witnessed the development of several PAH therapies with improvement in outcomes for patients with PAH including improved functional class and exercise capacity, increased time to clinical worsening, and decreased hospitalization.[8–11] Whether racial differences in utilization of different classes of PAH-specific medications exist has not been explored. Race and ethnicity may contribute to such differences in utilization due to varying cultural expectations, socioeconomic status, site of medical care, and effectiveness.[4]

We aimed to describe (1) the racial and ethnic distribution of PAH subtypes and (2) the racial and ethnic PAH-specific treatment patterns in a large cohort of patients with PAH enrolled in the National Biological Sample and Data Repository for PAH (PAH Biobank).

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Methods

The PAH Biobank is an ongoing NIH-funded convenience sample of PAH patients enrolled from 34 US centers with clinical data, banked biological samples, and genetic data. The study protocol was approved by the institutional review boards of all participating centers and all study participants signed informed consent. White and AA patients with WHO Group 1 PAH were included in this analysis if they were aged ≥ 18 years, had complete data on ethnicity, had a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. Patients of other races were excluded from this analysis because sample sizes were too small to allow for meaningful assessments.

Data on demographics (including age, sex, race, and ethnicity), body mass index, PAH subtype, 6-minute walk distance (6MWD), and hemodynamics from the diagnostic right heart catheterization were collected. Participants were classified as incident if their date of diagnostic right heart catheterization was within three months of enrollment in PAH Biobank. The Biobank captured information on PAH-specific medication history including medications that were discontinued or switched to a different compound. We defined treatment with any PAH-specific medication as having ever received a prostacyclin, endothelin receptor antagonist, phosphodiesterase inhibitor, riociguat, or selexipag.

Differences between groups were compared using Fisher's exact tests, ANOVA, and Kruskal–Wallis tests, as appropriate. Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between race/ethnicity (independent variable) and treatment with PAH-specific medication (dependent variable). Models were then adjusted for variables thought to be possible confounders based on prior literature or clinical experience (age, sex, right atrial pressure [RAP], cardiac index [CI], and 6MWD). Multiple imputation was used to handle missing data (3% missing for RAP, 2% missing for CI, and 51% for 6MWD) in the multivariate models. These analyses were repeated after stratification by PAH subtype and with adjustment for calcium channel blockers.

Results

A total of 2279 patients were enrolled in the PAH Biobank, of whom 1837 (81%) met the inclusion criteria and were included in the analysis. Seventy-nine percent were non-Hispanic white (NHW), 11% were AA, and 10% were Hispanic (who were 99% white) (Table 1). The majority of patients enrolled were prevalent PAH cases. Hispanic and AA patients were younger and more commonly women than NHWs. AA patients were more likely to have connective tissue disease-related PAH (CTD) and less likely to have portopulmonary hypertension (POPH) compared to other groups. Hispanic patients more commonly had congenital heart disease whereas NHWs had more familial PAH and PAH associated with drugs and toxins. AA patients had a lower mPAP, lower pulmonary vascular resistance (PVR), and shorter 6MWD compared to Hispanics and NHWs, but other hemodynamic parameters were similar.

PAH treatment varied by race ($P < 0.001$), with 78% of AA, 70% of NHW, and 57% of Hispanics receiving PAH-specific medications. However, among those who received PAH-specific therapy, there were no differences between the classes of drugs used. After adjustment for age, sex, RAP, CI, disease sub-type and center volume, Hispanics were less commonly treated (OR = 0.55; 95% CI = 0.40–0.77) compared to NHWs. AA patients were more likely to be treated with PAH-specific medications as compared to NHWs although this did not reach statistical significance (OR = 1.20; 95% CI = 0.84–1.73). These results were similar after stratified analysis in idiopathic and CTD-associated PAH and after adjustment for calcium channel blockers.

Discussion

In this study, we demonstrate racial and ethnic differences in PAH disease subtypes and severity as well as racial and ethnic differences in treatment with PAH-specific medications. Although it was known that AA patients bear a higher burden of certain PAH-associated clinical diseases such as CTD, human immunodeficiency virus (HIV), and liver disease,[12–15] the racial distribution of patients among PAH subtypes has not been reported. While our study did not follow individuals longitudinally to determine incidence of PAH among different racial groups, in this large multicenter registry we found significant differences in the prevalence of PAH subtypes among racial and ethnic groups. AA patients were 2.5 times more likely to have a diagnosis of CTD-associated PAH compared to NHWs and Hispanics. Moreover, Hispanics were twice as likely to have PAH associated with congenital heart disease compared to NHWs.

Hispanic patients with PAH were less likely to be treated with PAH-specific medications as compared to NHW. Adjusting for disease subtype, exercise capacity and disease severity did not explain differences in treatment among racial and ethnic groups. Socioeconomic factors including access to care and health insurance could contribute to racial/ethnic differences; however, these data were not captured in the parent study.

A strength of this study is the use of a large national PAH registry. Even so, not all racial and ethnic groups were represented and differences in racial and ethnic groups by centers could lead to confounding by center. Race and ethnicity were determined from medical records, leading to possible misclassification error. However, if present, we expect the misclassification to be non-differential which would bias our estimates to the null. The majority of patients in this registry were prevalent cases and enrollment in the registry was voluntary, so there is potential for selection bias. While our analysis attempted to control for potential confounders,

Table 1. Baseline characteristics and medications of patients with PAH enrolled in the PAH Biobank.

	Non-Hispanic white (n = 1439)	African-American (n = 210)	Hispanic (n = 188)	*P* value
Age (years)	53 ± 14	50 ± 14	43 ± 13	<0.001
Female sex (n (%))	1112 (77)	178 (85)	163 (87)	0.001
Body mass index (kg/m^2) (n = 1711)	28.8 (24.5–33.8)	28.8 (24.4–33.1)	28.5 (24.8–33.3)	0.95
Etiology of PAH, (n (%))				<0.001
Idiopathic	664 (46)	80 (38)	82 (44)	
Connective tissue disease*	409 (28)	103 (49)	53 (28)	
Systemic sclerosis (%)	70	35	26	
SLE (%)	10	31	45	
MCTD (%)	8	17	13	
Rheumatoid arthritis (%)	4	10	2	
Other† (%)	8	7	14	
Portal hypertension	90 (6)	5 (2)	11 (6)	
Drug and toxin	78 (5)	5 (2)	6 (3)	
Anorexigen (%)	45	40	33	
Amphetamines (%)	42	60	67	
Other (%)	13	–	–	
Congenital heart disease‡	68 (5)	3 (1)	18 (10)	
Atrial septal defect (%)	59	67	67	
Ventricular septal defect (%)	26	–	22	
PDA (%)	4	–	6	
Other (%)	11	33	5	
Familial‡	64 (4)	1 (<1)	4 (2)	
HIV*	19 (1)	10 (5)	6 (3)	
Incident case (n (%))	60 (4)	11 (5)	8 (4)	0.78
NYHA functional class (%) (n = 1330)				0.31
I	60 (6)	13 (8)	4 (3)	
II	323 (31)	41 (26)	38 (31)	
III	576 (55)	91 (57)	76 (61)	
IV	90 (8)	15 (9)	6 (5)	
Hemodynamics				
RAP (mmHg) (n = 1787)	8 (5–12)	9 (6–13)	8 (5–12)	0.005
mPAP (mmHg)	49 (40–58)	46 (37–55)	50 (42–61)	<0.001
Cardiac output (L/min) (n = 1805)	4.4 (3.5–5.4)	4.4 (3.5–5.6)	4.3 (3.5–5.3)	0.74
PVR (WU) (n = 1805)	9 (6–13)	8 (5–12)	10 (7–13)	0.02
PCWP (mmHg)	10 (7–12)	10 (7–12)	9 (7–12)	0.43
6MWD (m) (n = 894)	338 ± 131	301 ± 107	356 ± 97	0.005
Treated with any PAH (n (%))	1008 (70)	163 (78)	108 (57)	<0.001
Systemic prostacyclin (n (%))				0.41
Epoprostenol (IV)	152 (11)	30 (14)	25 (13)	
Treprostinil (IV or SC)	203 (14)	30 (14)	18 (10)	
Inhaled prostacyclin (n (%))				0.47
Inhaled iloprost	19 (1)	2 (1)	4 (2)	
Inhaled treprostinil	149 (10)	17 (8)	16 (9)	
Oral treprostinil (n (%))	48 (3)	5 (2)	2 (1)	0.21
PD-5 inhibitor (n (%))				0.19
Sildenafil	397 (28)	69 (33)	54 (29)	
Tadalafil	436 (30)	59 (28)	42 (22)	

(continued)

Table 1. Continued

	Non-Hispanic white (n = 1439)	African-American (n = 210)	Hispanic (n = 188)	*P* value
ERA (n (%))				0.45
Bosentan	188 (13)	23 (11)	15 (8)	
Ambrisentan	337 (23)	57 (27)	51 (27)	
Macitentan	112 (8)	14 (7)	5 (3)	
Riociguat (n (%))	18 (1)	1 (<1)	2 (1)	0.79
Mono- vs. combo-therapy (n (%))				<0.001
Monotherapy	343 (34)	77 (47)	35 (32)	
Dual therapy	418 (41)	53 (33)	42 (39)	
Triple therapy	247 (25)	33 (20)	31 (29)	
Calcium channel blocker (n (%))	63 (4)	4 (2)	11 (6)	0.11

Mean ± standard deviation; median (interquartile range).
*$P < 0.001$.
†Other CTD includes Sjogren's syndrome, overlap, and dermatomyositis.
‡$P = 0.008$.
NYHA, New York Heart Association; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; PDA, patent ductus arteriosus; RAP, right atrial pressure; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; PD-5, phosphodiesterase-5; ERA, endothelin receptor antagonist.

there is potential for unmeasured confounding that could have affected our results.

Identification of disparities in PAH is the first step towards eradicating them. Our results highlight the need for a comprehensive assessment of the factors which may contribute to the observed racial and ethnic differences in PAH treatment.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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