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Impact of race on survival in pulmonary arterial hypertension: Results from the REVEAL registry

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BACKGROUND: Prior research has suggested that the prevalence and outcomes of pulmonary arterial hypertension (PAH) may vary by race or ethnicity. However, these studies have been limited by small sample size or methodological techniques relying on epidemiologic data. The purpose of this study is to evaluate the relationship between race/ethnicity and survival in a large U.S.-based prospective multicenter registry.

METHODS: Patients in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL), a 5-year observational study of Group 1 PAH, were categorized by race/ethnicity. Baseline hemodynamic characteristics, clinical characteristics, and medication use was described. The relationship between race/ethnicity and outcome was evaluated by Kaplan−Meier and Cox proportional hazards modeling techniques. Left-truncation analysis, which adjusted for time from diagnosis to study enrollment, was used to minimize the effect of survivor bias.

RESULTS: This analysis included 3,046 patients; 2,202 identified as white, 393 as black, 263 as Hispanic, 100 as Asian or Pacific Islander, and 88 as other. Unadjusted Kaplan−Meier survival analysis indicated that white patients had the lowest survival rates. After adjusting for variables of prognostic impact, race/ethnicity was no longer significantly associated with survival. Other results showed that black patients were more likely to have connective tissue disease−associated PAH, Hispanic patients were more likely to have portopulmonary hypertension, and Asian patients were more likely to have congenital heart disease−associated PAH.

CONCLUSIONS: Analysis of the REVEAL registry did not find race/ethnicity to be a significant predictor of mortality. This is the largest analysis to date evaluating the role of race/ethnicity on outcomes in PAH.

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Pulmonary arterial hypertension (PAH) is a progressive and severe disease that, if left untreated, leads to right-sided heart failure and death.[1] With the introduction of multiple new therapies for this disease in the past 15 years, the choice of which medication to use for a given patient has become increasingly complex.[2,3] Unlike other cardiovascular diseases such as congestive heart failure and systemic hypertension, there are no specific treatment recommendations for PAH medical treatment based on race or ethnicity.[4,5] Furthermore, it is unclear if different races or ethnicities have differing prognoses after receiving a diagnosis of PAH.[6]

Prior studies have suggested that there may be differences in outcome in PAH based on race/ethnicity, but these studies have limitations prohibiting generalizability. Epidemiologic studies using large US-based databases that

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encoded data based on International Classification of Diseases diagnoses have suggested that black, non-Hispanic patients had increased mortality compared with other races/ethnicities.[7–9] Given the poor performance of International Classification of Diseases coding in identifying patients with pulmonary hypertension and classifying them according to accepted schema, it is difficult to know the significance of these results.[10] Other studies evaluating the role of race/ethnicity on outcomes have been single- or dual-center studies.[11–13] One study showed that the effect of race/ethnicity on survival did not persist after adjusting for insurance status,[13] and another looked at all subtypes of pulmonary hypertension and not solely PAH.[12]

The Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) is a multicenter observational US-based registry that enrolled 3,515 patients. Prior work describing the baseline demographics of the registry showed that there was a relative over-representation of black patients and a relative under-representation of Hispanic and Asian and/or Pacific islanders when compared with the overall makeup of the population of the United States based on census data.[14] Overall, the enrollment of patients with diverse backgrounds was encouraging, given that many clinical trials in PAH have had insufficient enrollment of ethnic minorities.[6] Other work using the REVEAL registry showed that race/ethnicity was not associated with a delay in disease recognition of PAH.[15] Surprisingly, unadjusted analysis of 5-year outcomes of PAH showed that white patients had worse survival than other races/ethnicities.[16]

Given these conflicting findings regarding the role of race/ethnicity in outcomes in the REVEAL registry, we pursued additional analysis adjusting for known factors that affect mortality in PAH to examine whether race/ethnicity remained a significant predictor of outcome.

Methods

Study design and setting

The REVEAL registry is a US-based observational prospective registry that enrolled patients with an expanded definition of World Health Organization (WHO) Group 1 PAH according to the 2003 Third World Symposium classification.[17,18] From 55 university-affiliated and community centers were enrolled 3,515 patients. Approximately 3,000 newly and previously diagnosed patients were enrolled between March 2006 and September 2007. Between September 2007 and December 2009, another approximately 500 newly diagnosed patients were enrolled.[19] All patients were followed up for a minimum of 5 years. The REVEAL registry was overseen by an independent steering committee, and the study protocol was approved by the institutional review board of each participating center.[20] Study design, objective, and enrollment criteria have been described previously.[17,19]

Patients

All enrolled patients had WHO Group 1 PAH and met specific hemodynamic criteria on the basis of right heart catheterization (RHC).[17] Patients were designated as newly diagnosed if the qualifying RHC was performed within the 3 months preceding enrollment and as previously diagnosed if the qualifying RHC was performed >3 months before enrollment.[19] In the REVEAL registry, race was self-identified by the patients. Study personnel classified these designated races into pre-printed categories including white, black, Hispanic, Asian or Pacific Islander, Native American or Native Alaskan, unknown, and others.[14] The REVEAL registry included patients aged ≥3 months and hemodynamically confirmed WHO Group 1 PAH, defined as mean pulmonary arterial pressure of ≥25 mm Hg at rest, pulmonary vascular resistance of ≥3 Woods units, and a mean pulmonary capillary wedge pressure of ≤18 mm Hg. In this analysis, patients with elevated pulmonary capillary wedge pressure (>15) or who met criteria for PAH only with exercise were excluded. Only patients with a diagnosis of PAH according to the clinical investigator's judgment were included; this did allow for inclusion of patients with comorbidities such as sleep apnea and chronic obstructive pulmonary disease, as long as the enrolling physician felt that the associated comorbidities were not the cause of the PAH.[17] Eligible patients were required to provide written informed consent in accordance with the Health Insurance Portability and Accountability Act.

Outcomes

Patients were grouped according to self-identified race. Baseline characteristics including demographic data, medical comorbidities, hemodynamic parameters, 6-minute walking distance (6MWD), REVEAL risk score,[21] laboratory values including N-terminal pro-brain natriuretic peptide (BNP) levels, WHO subclassification, New York Heart Association (NYHA) functional class, and medication use were collected. Analysis of baseline characteristics was done for (1) all patients, (2) previously diagnosed patients, and (3) newly diagnosed patients. Information on medication use by class (including phosphodiesterase-5 inhibitors, endothelin receptor antagonists [ERAs], and prostacyclin) over the last 6 months of enrollment was collected. Five-year survival data was collected.

Statistical analysis

This analysis was based on the final REVEAL database locked on February 4, 2013. Patients who were ≥18 years of age with WHO Group 1 PAH and resting pulmonary capillary wedge pressure ≤15 mm Hg at the time of diagnosis were included in the analysis. Descriptive statistics were used to evaluate the differences in baseline data. Categorical data are presented as a percentage analyzed with chi-square tests and continuous data as mean ± standard deviation or percentile analyzed using Student's *t*-test. Survival was estimated from the time of diagnostic RHC using the Kaplan–Meier method, accounting for left truncation as has been described in prior REVEAL publications.[22] Patients who were alive at the end of the study were censored at date of their last assessment. Cox proportional hazards modeling was also used to determine whether ethnicity was a significant predictor of outcome. Left truncation for time between diagnosis and the study enrollment and adjustment for other covariates known to impact outcomes in PAH was performed. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Table 1 Baseline Demographics and Disease Characteristics in the REVEAL Registry

Variable		White $n = 2,202$	Black $n = 393$	Hispanic $n = 263$	Asian $n = 100$	Other $n = 88$
Age at enrollment, years	Mean (SD)	54.6 (14.5)	**50.7 (13.9)**	**43.6 (12.4)**	**43.3 (13.8)**	**47.7 (15.8)**
	p-value		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Gender, male	*n* (%)	507 (23.0%)	60 (15.3%)	37 (14.1%)	19 (19%)	19 (21.6%)
	p-value		0.1130	0.0516	0.8382	0.3495
BMI, kg/m^2	*n*, mean (SD)	2,080 28.4 (6.9)	369 29.1 (7.4)	245 27.8 (6.5)	**99 23.3 (4.9)**	76 28.5 (7.7)
	p-value		0.2835	0.7788	**<0.0001**	1.0000
Time from diagnosis to enrollment, months	Mean (SD)	33.6 (45.6)	25.7 (32.4)	36.2 (44.3)	43.1 (55.9)	22.9 (31.8)
	Median (Q1, Q3)	18.3 (2.7, 46.6)	13.5 (1.7, 37.5)	23.7 (3.0, 51.9)	29.1 (4.2, 61.9)	5.7 (1.6, 33.9)
	p-value		0.01	0.8884	0.2132	0.165
Diagnostic status	Newly diagnosed, *n* (%)	588 (26.7%)	120 (30.5%)	65 (24.7%)	23 (23.0%)	34 (38.6%)
	Previously diagnosed, *n* (%)	1,614 (73.3%)	273 (69.5%)	198 (75.3%)	77 (77.0%)	54 (61.4%)
	p-value		0.3701	0.1533	0.1512	0.1512
WHO Group I diagnosis at enrollment	IPAH, *n* (%)	1,046 (47.5%)	182 (46.3%)	109 (41.4%)	48 (48.0%)	40 (45.5%)
	FPAH, *n* (%)	70 (3.2%)	3 (0.8%)	6 (2.3%)	1 (1.0%)	2 (2.3%)
	APAH—CTD, *n* (%)	565 (25.7%)	**136 (34.6%)**	58 (22.1%)	24 (24.0%)	27 (30.7%)
	APAH—CHD, *n* (%)	217 (9.9%)	13 (3.3%)	39 (14.8%)	**22 (22.0%)**	6 (6.8%)
	APAH—drugs and toxins; *n* (%)	127 (5.8%)	11 (2.8%)	15 (5.7%)	3 (3.0%)	8 (9.1%)
	APAH—HIV; *n* (%)	20 (0.9%)	23 (5.9%)	11 (4.2%)	0	0
	APAH—other; *n* (%)	19 (0.9%)	14 (3.6%)	2 (0.8%)	1 (1.0%)	1 (1.1%)
	APAH—portal hypertension; *n* (%)	138 (6.3%)	11 (2.8%)	23 (8.7%)	1 (1.0%)	4 (4.5%)
	p-value		<0.0001	<0.0001	0.0028	0.6862

APAH, associated pulmonary arterial hypertension; BMI, body mass index; CHD, congenital heart disease; CTD, connective tissue disease; FPAH, familial pulmonary arterial hypertension; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; Q, quintile; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SD, standard deviation; WHO, World Health Organization.

p-values were from comparisons between each race and white by using chi-square test for categorical variables and *t*-test for continuous variables.

Bold values indicate $p < 0.01$.

Results

Baseline characteristics

A total of 3,515 consecutive patients were enrolled in REVEAL, 3,046 of whom met the inclusion criteria for this analysis. There were 830 newly diagnosed and 2,216 previously diagnosed patients in this cohort. Baseline demographic characteristics of all patients are reported in Table 1 (with additional information in Supplementary Table S1, available online at www.jhltonline.org). White patients were significantly older than other races/ethnicities. At the time of PAH diagnosis, the median age in white patients was 57.6 years old vs 51.3 years of age in black patients, 44.5 in Hispanic patients, and 37.6 in Asian. Black patients had more frequent connective tissue disease (CTD)-associated PAH, more Asian and Hispanic patients had congenital heart disease–associated PAH, and Hispanics had slightly more portopulmonary hypertension (PoPH).

Analysis of other baseline characteristics was divided into newly diagnosed and previously diagnosed with PAH as defined earlier. Among newly diagnosed patients, there were no significant differences by race/ethnicity in NYHA functional class, REVEAL risk score, 6MWD, or BNP level. Hispanics had a higher pulmonary vascular resistance (PVR) than other races/ethnicities, but there were no differences in other hemodynamic parameters (Table 2). There were no differences in cardiopulmonary comorbidities (Supplementary Table S2 online).

Among the previously diagnosed patients, black patients had a lower 6MWD and a lower mean pulmonary artery pressure at diagnosis. Asian patients had a higher PVR (Table 3). Black patients were more likely to have chronic obstructive pulmonary disease, and Asian patients were less likely to have sleep apnea (Supplementary Table S3 online).

Medication use

PAH therapies within 6 months before death (for deceased patients) or within the last 6 months of study follow-up (for living patients) are summarized in Table 4. Analysis showed a lower use of ERAs in Hispanic patients who had died. There was also lower phosphodiesterase-5 inhibitor use in living and deceased black patients.

Medication use at the time of enrollment was also evaluated. Of the previously diagnosed patients, black patients were less likely to be on a phosphodiesterase-5 inhibitor (Supplementary Table S3 online). Out of the newly diagnosed patients, there was no difference in medication use by subclass (Supplementary Table S2 online).

Table 2 Clinical Characteristics of Newly Diagnosed Patients at Enrollment

Variable		White $n = 588$	Black $n = 120$	Hispanic $n = 65$	Asian $n = 23$	Other $n = 34$
Six-minute walk distance, m	Mean (SD)	308.1 (131.7)	295.2(120.5)	302.1(91.3)	376.2(107.0)	329.7(125.5)
	p-value		0.9309	0.9985	0.1166	0.9505
BNP value, pg/ml	Mean (SD)	512.1 (857.6)	499.9 (1,151.5)	353.4 (495.7)	201.3 (169.3)	350.3 (451.5)
	p-value		1.0000	0.8911	0.8843	0.9822
REVEAL risk score	Mean (SD)	8.4 (2.2)	8.4 (2.0)	8.3 (1.9)	8.0 (1.5)	8.1 (2.4)
	p-value		0.9995	0.9891	0.9382	0.9480
NYHA class, *n* (%)	Unknown	113 (19.2%)	18 (15.0%)	7 (10.8%)	3 (13.0%)	6 (17.6%)
	I	17 (2.9%)	6 (5.0%)	1 (1.5%)	—	—
	II	83 (14.1%)	20 (16.7%)	17 (26.2%)	5 (21.7%)	5 (14.7%)
	III	289 (49.1%)	58 (48.3%)	32 (49.2%)	11 (47.8%)	14 (41.2%)
	IV	86 (14.6%)	18 (15.0%)	8 (12.3%)	4 (17.4%)	9 (26.5%)
	p-value		0.4153	0.0944	0.9480	0.0675
mPAP	Mean (SD)	49.7 (12.8)	46.9 (12.3)	53.6 (14.2)	51.4 (16.4)	48.9 (12.8)
	p-value		0.2000	0.1395	0.9714	0.9961
Mean RAP	Mean (SD)	9.7 (6.0)	10.9 (6.2)	10.0 (5.8)	8.3 (5.6)	9.5 (5.6)
			0.3214	0.9957	0.8313	0.9997
Mixed venous O_2 saturation	Mean (SD)	61.8 (10.6)	61.9 (10.6)	59.8 (10.9)	60.7 (7.6)	58.7 (12.8)
			1.0000	0.7570	0.9949	0.7175
Cardiac index, liter/min/m^2	Mean (SD)	2.3 (0.8)	2.2 (0.9)	2.2 (0.8)	2.3 (0.6)	2.1 (0.7)
	p-value		0.9992	0.9466	0.9974	0.7762
PVR, Wood units	Mean (SD)	10.8 (5.8)	9.8 (5.7)	13.1 (6.8)	13.1 (8.5)	12.2 (6.0)
	p-value		0.5243	0.0365	0.3776	0.7097
PCWP at rest, mm Hg	Mean (SD)	9.5 (3.7)	10.4 (3.2)	8.7 (3.8)	8.1 (3.6)	9.2 (3.5)
	p-value		0.1289	0.5253	0.4003	0.9908

BNP, brain natriuretic peptide; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SD, standard deviation.

p-values were from comparisons between each race and white by using chi-square test for categorical variables and *t*-test for continuous variables. Some patients may have missing values in some variables.

Table 3 Clinical Characteristics of Previously Diagnosed Patients at Enrollment

Variable		White $n = 1,614$	Black $n = 273$	Hispanic $n = 198$	Asian $n = 77$	Other $n = 54$
Six-minute walk distance, m	Mean (SD)	378.7 (127.4)	**335.9 (121.5)**	376.6 (106.5)	417.3 (101.4)	346.0 (145.0)
	p-value		**<0.0001**	0.9995	0.0887	0.4728
BNP value, pg/ml	Mean (SD)	268.8 (504.7)	327.1 (472.3)	240.3 (386.1)	354.1 (776.4)	205.2 (281.5)
	p-value		0.7289	0.9848	0.8666	0.9838
REVEAL risk score	Mean (SD)	7.3 (2.4)	7.4 (2.3)	7.4 (1.9)	6.8 (1.9)	7.0 (2.2)
	p-value		0.9203	0.9994	0.3525	0.9098
NYHA class	Unknown	490 (30.4%)	63 (23.1%)	67 (33.8%)	15 (19.5%)	17 (31.5%)
	I	40 (2.5%)	6 (2.2%)	2 (1.0%)	2 (2.6%)	1 (1.9%)
	II	276 (17.1%)	40 (14.7%)	28 (14.1%)	18 (23.4%)	8 (14.8%)
	III	696 (43.1%)	126 (46.2%)	90 (45.5%)	36 (46.8%)	23 (42.6%)
	IV	112 (6.9%)	38 (13.9%)	11 (5.6%)	6 (7.8%)	5 (9.3%)
	p-value		0.0207	0.9763	0.1752	0.7158
mPAP, mm Hg	Mean (SD)	51.4 (13.7)	47.6 (12.8)	53.3 (15.1)	56.2 (14.9)	52.7 (16.3)
	p-value		0.0003	0.3320	0.0245	0.9630
Mean RAP, mm Hg	Mean (SD)	9.2 (5.4)	9.6 (5.6)	8.5 (5.5)	8.6 (5.4)	9.5 (5.6)
			0.7385	0.5059	0.8925	0.9967
Mixed venous O_2 saturation, %	Mean (SD)	63.3 (9.8)	62.7 (11.4)	62.9 (10.3)	62.9 (10.0)	60.3 (11.4)
			0.9610	0.9865	0.9980	0.4011
Cardiac index, liter/min/m^2	Mean (SD)	2.5 (0.8)	2.5 (0.8)	2.6 (0.9)	2.5 (0.7)	2.5 (1.0)
	p-value		0.9961	0.9454	0.9754	0.9799
PVR, Wood unit	Mean (SD)	9.9 (7.2)	9.1 (5.4)	11.4 (7.1)	13.4 (9.3)	10.8 (6.0)
	p-value		0.4581	0.0588	0.0006	0.4581
PCWP at rest, mm Hg	Mean (SD)	10.0 (4.2)	9.8 (3.8)	9.7 (4.0)	9.6 (3.9)	9.6 (4.1)
	p-value		0.9729	0.9185	0.9465	0.9672

BNP, brain natriuretic peptide; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SD, standard deviation.

p-values were from comparisons between each race and white by using chi-square test for categorical variables and *t*-test for continuous variables. Some patients may have missing values in some variables.

Survival analysis

Figure 1 shows the unadjusted survival analysis among different races. Asian, black, and Hispanic patients had a lower risk of death than white patients. Figure 2 shows survival analysis performed accounting for left truncation and limiting the analysis to ages 60 or younger. Restricting analysis to a younger age group was performed because an age of greater than 60 is associated with an increased risk of death.[21] Results of this analysis showed that there was no difference in survival by race/ethnicity among these patients ($p > 0.05$). Because prior work with the REVEAL registry has shown that the PAH subgroups of PoPH, CTD-associated PAH, and familial PAH have worse outcomes,[21] adjustments were made for these prognostic factors. Restricting analysis to only the lower-risk subtypes of PAH further showed that survival was consistent across various races and ethnicities (Supplementary Figure S1 online). Survival analysis using Cox proportional hazards modeling was also performed. This model was adjusted for age as a continuous variable and WHO Group 1 subgroup diagnosis at enrollment (with patients with CTD, familial PAH, and PoPH assessed as being at higher risk for death, based on prior work). Left truncation was accounted for by calculating survival time from diagnosis to account for survival bias. Results of this analysis did not show any significant difference in survival based on race/ethnicity (Table 5).

Discussion

This is the largest reported analysis of the impact of race on survival in PAH. Contrary to the results from other studies,[7–9,11,12] this analysis shows that self-identified race/ethnicity does not play an important role in outcome after adjusting for age, disease subtype, and time to diagnosis. Evaluation of patients in the REVEAL registry offers benefits over other cohorts for multiple reasons. In comparison with epidemiological data suggesting that black patients, and particularly black women, may have worsened survival,[7–9] the diagnosis of PAH is verified for all patients within the REVEAL cohort by strict hemodynamic parameters. This is of critical importance because of the significant limitations of classifying patients as having pulmonary hypertension based on diagnostic coding alone.[10,23] Compared with other smaller studies evaluating the role of race/ethnicity in outcomes in PAH, REVEAL has extensive clinical data regarding disease characteristics at the time of presentation, as well as 5-year follow-up data and information on medication use.[11–13] Data from REVEAL also offered the ability to evaluate both patients who were newly

Table 4 Summary of PAH Medications during the Last 6 Months of Follow-Up

Race	PAH medication	Alive	Died
White	Total	1,298	681
	CCB	157 (12.1%)	44 (6.5%)
	ERA	759 (58.5%)	373 (54.8%)
	PDI	868 (66.9%)	493 (72.4%)
	Prostacyclin	608 (46.8%)	438 (64.3%)
	No ERA, PDI, Prostacyclin, or CCB	21 (1.6%)	6 (0.9%)
Black	Total	250	98
	CCB	24 (9.6%)	7 (7.1%)
	ERA	139 (55.6%)	54 (55.1%)
	PDI	155 (62.0%)*	60 (61.2%)*
	Prostacyclin	108 (43.2%)	61 (62.2%)
	No ERA, PDI, Prostacyclin, or CCB	10 (4.0%)	0
Hispanic	Total	179	67
	CCB	17 (9.5%)	3 (4.5%)
	ERA	114 (63.7%)	30 (44.8%)*
	PDI	131 (73.2%)	49 (73.1%)
	Prostacyclin	91 (50.8%)	41 (61.2%)
	No ERA, PDI, Prostacyclin, or CCB	3 (1.7%)	3 (4.5%)
Asian	Total	71	21
	CCB	10 (14.1%)	0
	ERA	45 (63.4%)	12 (57.1%)
	PDI	52 (73.2%)	14 (66.7%)
	Prostacyclin	35 (49.3%)	14 (66.7%)
	No ERA, PDI, Prostacyclin, or CCB	1 (1.4%)	1 (4.8%)
Other	Total	58	21
	CCB	4 (6.9%)	0
	ERA	30 (51.7%)	14 (66.7%)
	PDI	43 (74.1%)	11 (52.4%)
	Prostacyclin	26 (44.8%)	12 (57.1%)
	No ERA, PDI, Prostacyclin, or CCB	1 (1.7%)	1 (4.8%)

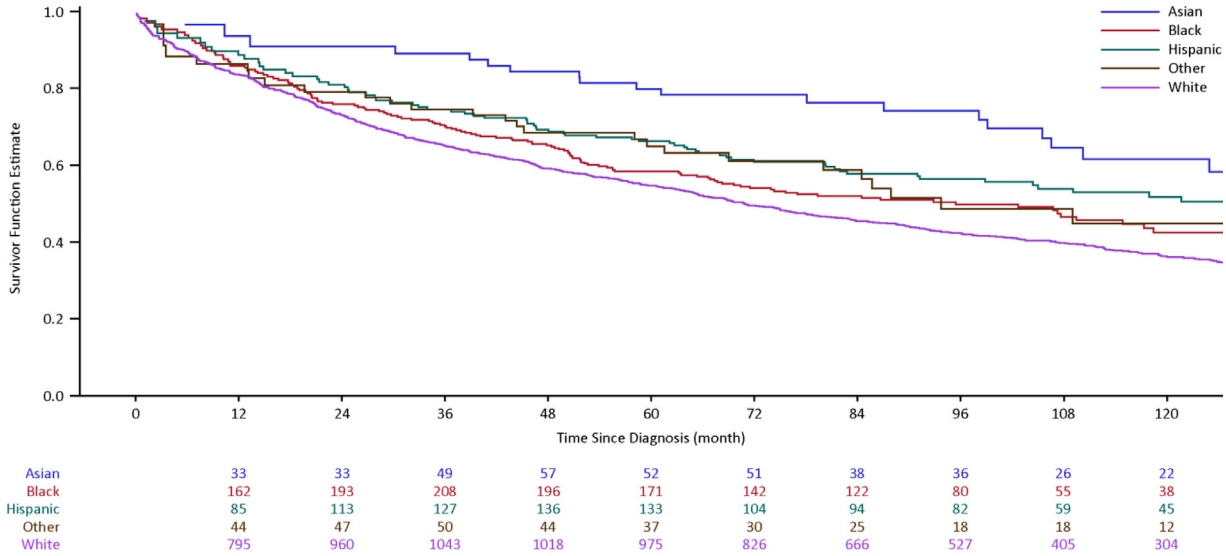
CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDI, phosphodiesterase inhibitor.
Clinically meaningful difference defined as a 10-percentage point difference between groups.

diagnosed with PAH and previously diagnosed with PAH. Accounting for left truncation as undertaken in this analysis allowed us to address any possible survivor bias in a rigorous statistical manner.

Our analysis showed that there are differences in the distributions of PAH subtypes based on race/ethnicity. Black patients were more likely to have CTD-associated PAH, Hispanic patients were more likely to have PoPH, and Asian patients were more likely to have congenital heart disease−associated PAH. Data from the National Biological Sample and Data Repository for PAH (PAH biobank) also showed that black patients were more likely to have CTD-associated PAH.[24] This study also showed that Hispanic patients were more likely to have congenital heart disease. This study only included 3 categories of race/ethnicity including white, non-Hispanic white (79%); Hispanic (10%); and African-American (11%). It did not separately identify Asian patients.

Markers of disease severity measured at the time of enrollment were compared between different races/ethnicities. Among newly diagnosed patients, PVR was significantly higher in Hispanic patients than other races/ethnicities. No other markers of disease severity such as 6MWD, NYHA functional class, other hemodynamic parameters, BNP level, or the verified composite of all these variables (i.e., REVEAL risk score)[21] showed significant differences. This is an important observation as it suggests that all patients irrespective of race present and are diagnosed at similar clinical and symptomatic levels of dysfunction and that similar subsequent survival is not a function of differences in disease severity at enrollment. Despite the finding that PVR was higher in newly diagnosed Hispanic patients, it was not higher in previously diagnosed Hispanic patients. In the previously diagnosed group, black patients had a shorter 6MWD and a lower mean pulmonary artery pressure. This was consistent with the PAH biobank analysis showing a lower walk distance in black patients.[24] Although previously diagnosed black patients showed some markers of greater disease severity, the composite REVEAL risk score was not different; possible explanations for the observed differences might include differences in treatment or differences in disease progression. However, this was not supported by the outcomes analysis.

Patterns of medication use also showed some variations by race/ethnicity. Phosphodiesterase-5 inhibitor use was lower in black patients than those of other races/ethnicities in surviving and non-surviving patients. Without further analysis, it is difficult to comment on why surviving black



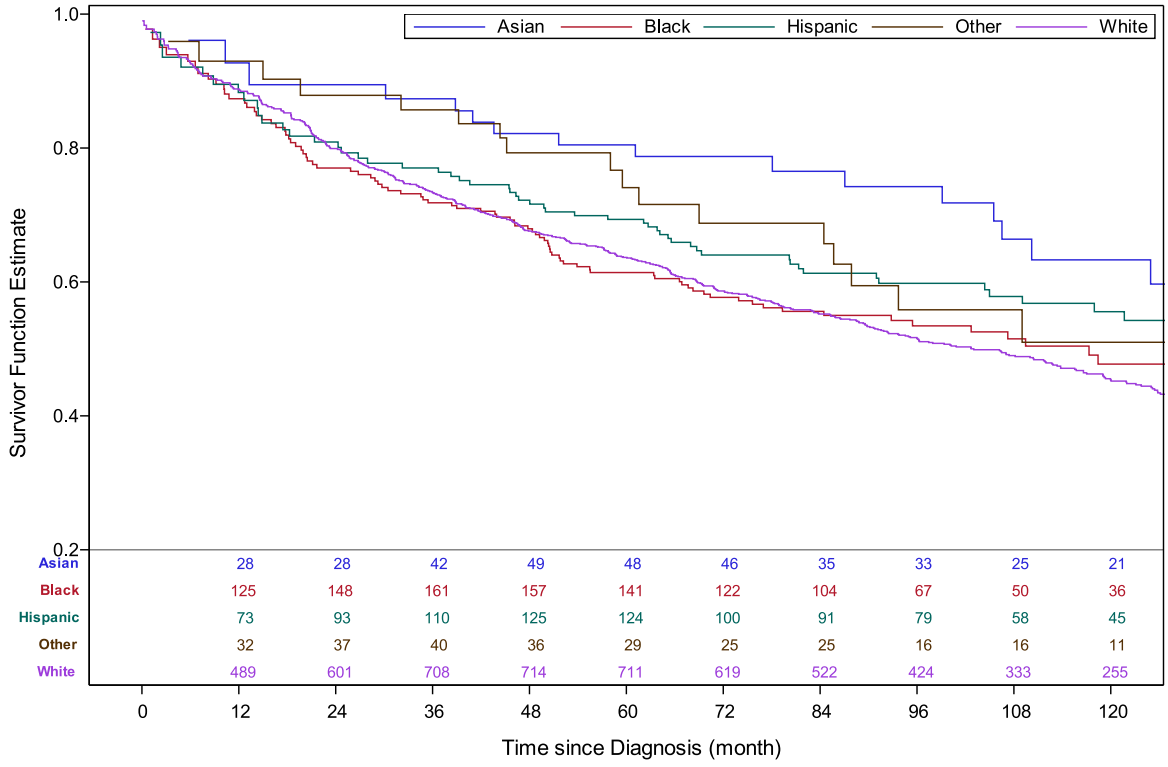
Race	n	HR (95% CI) vs white patients	P value
Asian	100	0.541 (0.358–0.819)	0.0037
Black	393	0.813 (0.672–0.982)	0.0319
Hispanic	263	0.709 (0.560–0.897)	0.0041
Other	88	0.788 (0.541–1.149)	0.2157
White	2202	—	—

Figure 1 **Unadjusted survival analysis.** Unadjusted Cox model; only left truncation for time since diagnosis was included. HR, hazard ratio.

patients were less likely to be prescribed this class of medication. However, this observation was also noted in black patients with PAH who died; hypothetically, most patients with PAH should be on therapy with all medication classes at the time of death. Multiple reasons may exist for not using this medication class including lack of tolerance, lack of patient acceptance, lack of medical coverage, or transition to hospice care.[25] It is possible that there may be physiological reasons why this drug class was underutilized. Other reasons may include contra-indications because of concomitant medications, such as antiretroviral agents or alpha agonists, or use of riociguat near the end of the study period. Non-surviving Hispanic patients had a reduced use of ERA therapy. One hypothesis for this finding may be the higher prevalence of PoPH within this group; at the time of REVEAL, ERAs had been neither tested nor approved for use in PoPH.. Work from the PAH biobank did not show significant differences in classes of drugs used based on race/ethnicity but did show that Hispanic patients were less commonly treated with PAH-specific medications in general.[24] At time of diagnosis, white patients were much older than other races, especially Hispanics and Asians, though again the principle composite marker of disease severity, the REVEAL risk score, was not different.

The observation that white patients presented at an older age is interesting. Some minor findings from this analysis may partly explain this result. Asian patients were more likely to have congenital heart disease−associated PAH, which may be diagnosed at an earlier age (Table 1). When evaluating all patients enrolled in the registry, black patients had a significantly shorter time from diagnosis to enrollment ($p = 0.01$, Supplementary Table S1). However, it is unlikely that these findings would explain the magnitude of the difference in age in presentation between different races/ethnicities. There are multiple genetic mutations implicated in the development of PAH, and although there is no notable data regarding the distribution of these mutations by race/ethnicity, it is plausible that differences may exist.[26] The incomplete penetrance of these mutations suggests that epigenetic or environmental factors play a role in disease risk, and these factors may differ by race/ethnicity.[27]

One important consideration when evaluating the relationship between race/ethnicity and outcome in PAH is whether variations in socioeconomic status might have a confounding influence.[28] Previous authors have suggested that lower socioeconomic status is associated with worse outcomes in PAH.[29,30] A single-center study showed a negative relationship between socioeconomic status and the severity of disease on presentation.[29] The REVEAL registry



Race	n	HR (95% CI) vs white patients	*P* value
Asian	91	0.654 (0.418–1.023)	0.0630
Black	313	0.881 (0.700–1.110)	0.2827
Hispanic	239	0.782 (0.600–1.019)	0.0683
Other	68	0.841 (0.531–1.331)	0.4587
White	1506	—	—

Figure 2 **Survival analysis limited to patients aged ≤ 60 years, using left truncation analysis.** Unadjusted Cox model; only left truncation for time since diagnosis was included.

did not collect information on socioeconomic status. However, each enrolled patient has a recorded ZIP code, which corresponds to a geographic region with an average population of 7,500 people. Review of U.S. Census data can provide a median household income for that region. Previously reported data from the REVEAL registry did not show any variations in prostanoid use based on ZIP code.[31] ZIP code was not significantly predictive of 1-year outcomes within the REVEAL PAH cohort.[21] There was no association between ZIP code and a delay in the time to diagnosis of PAH.[15] Given the lack of clear association between ZIP code analysis and outcomes within the REVEAL registry, this piece of data was not evaluated in our study. It is likely that ZIP code is not a sufficiently sophisticated tool to assess income and hence health care status. It only provides a median income that may not accurately reflect the enrolled patient's actual household income.

Regardless, prior analysis using ZIP code analysis within the REVEAL registry showed that lower income groups had a longer time to disease recognition and that there were more functional class 3–4 patients in lower income groups at the time of diagnosis.[32] Black and Hispanic races were reported at a higher frequency in the lower 2 income categories compared with the higher 2 income categories.[32] Although these findings might suggest that outcomes should be worse in the black and Hispanic groups, this was not borne out in this analysis. It is unclear that adjusting for socioeconomic status

Table 5 Adjusted Cox Model

Race	*n*	Hazard ratio (95% CI) (vs. white group)	*p*-value
Asian	100	0.778 (0.512-1.183)	0.241
Black	393	0.931 (0.767-1.130)	0.469
Hispanic	263	0.969 (0.758-1.239)	0.802
Other	88	0.943 (0.637-1.397)	0.770

CTD, connective tissue disease, FPAH, familial pulmonary arterial hypertension; WHO, World Health Organization.

Cox model adjusted for age (as a continuous variable) and WHO Group I diagnosis at enrollment (CTD, portal hypertension/FPAH, vs. Other). Time from diagnosis was adjusted for using left truncation.

would have mitigated the apparent lack of impact on outcomes by race/ethnicity as described in this analysis. The interplay between socioeconomic status, race/ethnicity, and outcomes merits future prospective evaluation.

This study was limited in that it is a retrospective analysis of a prospectively collected cohort of patients enrolled between 2006 and 2009. Race or ethnicity was not evaluated genetically but was self-reported. In addition, the methodology of classifying race/ethnicity differed from the 1997 recommendations by the United States Office of Management and Budget, which established 5 categories of race (including white, Asian, black, American Indian/Alaska Native, and Native Hawaiian or other Pacific Islander) and 2 categories of ethnicities (Hispanic or Latino and not Hispanic or Latino).[33] The differences in the REVEAL definitions and the Office of Management and Budget recommendations may result in some misclassification. For example, it is possible that some patients who identify as Hispanic ethnicity and African American race would be classified as black instead of Hispanic. According to 2010 U.S. Census Data, only 2.5% of Hispanic and Latino patients identified their race as black.[34] Therefore we estimate that the effect of misclassification on our results would be minimal.

In conclusion, this analysis of 5-year outcomes of patients enrolled in a large US-based PAH registry does not show any difference in mortality associated with race or ethnicity. Although prior analysis suggested worsened survival in white patients, this effect did not persist after adjusting for age, PAH subtype, and time from diagnosis. The role of socioeconomic status and access to care on outcomes in PAH remains unclear and warrants further study. Observations from this analysis regarding disparate PAH-specific medication usage between ethnic/racial groups merit further examination.

Disclosure statement

S.M. does not have any disclosures. C.Z. is an employee of Actelion Pharmaceuticals US, Inc, a Janssen Pharmaceutical Company of Johnson & Johnson, and holds stock in Johnson & Johnson. S.S. serves on speaker panel for Actelion, Bayer, and United Therapeutics and has received honoraria from these entities. Additionally, S.S. has accepted consultancy fees for Bayer and Actelion and has received lodging support from Actelion for presenting scientific data in a conference. M.S. is a full-time employee of Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson, and holds stock in Johnson & Johnson. A.E.F. has received honoraria from Actelion, Bayer, and United Therapeutics for speaking; has consulted for Actelion and United Therapeutics; and has participated in endpoint adjudication committees for United Therapeutics and Complexa.

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Part of this data has been presented at the International Society of Heart and Lung Transplantation Annual Meeting 2019, Orlando, FL, USA. (Medrek S, *et al. JHLT* 38(4): S96)

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2019.11.024.

References

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
2. Galiè N, Channick RN, Frantz RP, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53:1801889.
3. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST guideline and Expert Panel Report. Chest 2019;155:565-86.
4. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049-57.
5. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
6. Medrek SK, Sahay S. Ethnicity in pulmonary arterial hypertension: possibilities for novel phenotypes in the age of personalized medicine. Chest 2018;153:310-20.
7. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. Chest 2014;146:476-95.
8. Lilienfeld DE, Rubin LJ. Mortality from primary pulmonary hypertension in the United States, 1979-1996. Chest 2000;117:796-800.
9. Davis KK, Lilienfeld DE, Doyle RL. Increased mortality in African Americans with idiopathic pulmonary arterial hypertension. J Natl Med Assoc 2008;100:69-72.
10. Gillmeyer KR, Lee MM, Link AP, Klings ES, Rinne ST, Wiener RS. Accuracy of algorithms to identify pulmonary arterial hypertension in administrative data: a systematic review. Chest 2019;155:680-8.
11. Kawut SM, Horn EM, Berekashvili KK, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol 2005;95:199-203.
12. Yang BQ, Assad TR, O'Leary JM, et al. Racial differences in patients referred for right heart catheterization and risk of pulmonary hypertension. Pulm Circ 2018;8:2045894018764273.
13. Parikh KS, Stackhouse KA, Hart SA, Bashore TM, Krasuski RA. Health insurance and racial disparities in pulmonary hypertension outcomes. Am J Manag Care 2017;23:474-80.
14. Frost AE, Badesch DB, Barst RJ, et al. The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US Contemporary Registries. Chest 2011;139:128-37.
15. Brown LM, Chen H, Halpern S, et al. Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry. Chest 2011;140:19-26.
16. Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the REVEAL Registry. Chest 2015;148:1043-54.
17. McGoon MD, Krichman A, Farber HW, et al. Design of the REVEAL registry for US patients with pulmonary arterial hypertension. Mayo Clin Proc 2008;83:923-31.
18. Simonneau G, Galiè N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43(12 Suppl S):5S-12S.
19. McGoon MD, Miller DP. REVEAL: a contemporary US pulmonary arterial hypertension registry. Eur Respir Rev 2012;21:8-18.
20. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. Chest 2010;137:376-87.
21. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to

Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164-72.
22. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012; 142:448-56.
23. Mathai SC, Ryan Hemnes A, Manaker S, et al. Identifying patients with pulmonary arterial hypertension (PAH) using administrative claims algorithms. Ann Am Thorac Soc 2019;16:797-806.
24. Al-Naamani N, Paulus JK, Roberts KE, et al. Racial and ethnic differences in pulmonary arterial hypertension. Pulm Circ 2017;7:793-6.
25. Farber HW, Miller DP, Meltzer LA, McGoon MD. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. J Heart Lung Transplant 2013;32:1114-22.
26. Ma L, Chung WK. The role of genetics in pulmonary arterial hypertension. J Pathol 2017;241:273-80.
27. Morrell NW, Aldred MA, Chung WK, et al. Genetics and genomics of pulmonary arterial hypertension. Eur Respir J 2019;53:1801899.
28. Minai OA, Yan T, Mascha E, Stoller JK. Race as an independent prognostic factor in patients with idiopathic pulmonary arterial hypertension. Am J Cardiol 2005;96:740.
29. Talwar A, Sahni S, Talwar A, Kohn N, Klinger JR. Socioeconomic status affects pulmonary hypertension disease severity at time of first evaluation. Pulm Circ 2016;6:191-5.
30. McLaughlin VV, Langer A, Tan M, et al. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. Chest 2013;143:324-32.
31. Frantz RP, Barst RJ, Turner M, Watson P, McGoon MD. Regional heterogeneity in prostanoid usage for pulmonary arterial hypertension in the United States. Am J Respir Crit Care Med 2009;179:A3360.. Available at: https://doi.org/10.1164/ajrccm-conference.2009.179.1_MeetingAbstracts.A3350.
32. Talwar A, Garcia JGN, Tsai H, et al. Health disparities in patients with pulmonary arterial hypertension: A blueprint for action. An Official American Thoracic Society Statement. Am J Respir Crit Care Med 2017;196:e32-47.
33. Office of Management and Budget (US). Revisions to the standards for the classification of federal data on race and ethnicity. Fed Regist 1997. Available at: https://obamawhitehouse.archives.gov/omb/fedreg_1997-standards.
34. Humes KR, JN RRR.Overview of race and Hispanic origin. 2010 Census Briefs. Available at: https://web.archive.org/web/20110429214029/http://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf.