HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2019 October 03.

Published in final edited form as:

J Pediatr. 2019 August ; 211: 63–71.e6. doi:10.1016/j.jpeds.2019.04.046.

Racial and ethnic differences in pediatric pulmonary hypertension: An analysis of the Pediatric Pulmonary Hypertension Network Registry (PPHNet)

Mei-Sing Ong, PhD[1,2], Steve Abman, MD[3], Eric D. Austin, MD[4], Jeffrey A. Feinstein, MD, MPH[5], Rachel K. Hopper, MD[5], Usha S. Krishnan, MD[6], Mary P. Mullen, MD, PhD[7], Marc D. Natter, MD[2], J. Usha Raj, MD[8], Erika B. Rosenzweig, MD[6], Kenneth D. Mandl, MD, MPH[2] on behalf of Pediatric Pulmonary Hypertension Network and National Heart, Lung, and Blood Institute Pediatric Pulmonary Vascular Disease Outcomes Bioinformatics Clinical Coordinating Center Investigators.

[1]Department of Population Medicine, Harvard Medical School & Harvard Pilgrim Health Care Institute, Boston MA.

[2]Computational Health Informatics Program, Harvard Medical School & Boston Children's Hospital, Boston MA.

[3]Department of Pediatric Pulmonary Medicine, Children's Hospital Colorado, University of Colorado School of Medicine, Denver CO.

[4]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, TN.

[5]Department of Pediatrics (Cardiology); Vera Moulton Wall Center for Pulmonary Vascular Disease, Stanford University School of Medicine, Palo Alto, CA.

[6]Department of Pediatrics (Pediatric Cardiology), Columbia University Medical Center, New York-Presbyterian Children's Hospital, NY, NY.

[7]Department of Cardiology, Harvard Medical School, Boston Children's Hospital, Boston MA.

[8]Department of Pediatrics, University of Illinois, Chicago, IL.

Abstract

Objective—To investigate racial and ethnic differences in pulmonary hypertension (PH) subtypes and survival differences in the pediatric population.

Study design—A retrospective analysis of a cohort of PH patients (aged ≤ 18 years) enrolled in the Pediatric Pulmonary Hypertension Network (PPHNet) registry between years 2014 and 2018, comprising subjects at eight Pediatric PH Centers throughout North America (n=1,417).

Results—Among children diagnosed after the neonatal period, pulmonary arterial hypertension (PAH) was more prevalent among Asians (OR 1.83; 95% CI 1.21 – 2.79; p=0.0045), lung disease-associated PH among Blacks (OR 2.09; 95% CI 1.48 – 2.95; p<0.0001), idiopathic PAH among

Address correspondence to: Mei-Sing Ong, PhD, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, 401 Park Drive, Suite 401E, Boston MA 02115, Mei-Sing_Ong@hms.harvard.edu, **T** 617-867-4552, **F** 617-867-4276.

Whites (OR 1.58; 95% CI 1.06 – 2.41; p=0.0289); pulmonary veno-occlusive disease among Hispanics (OR 6.11; 95% CI 1.34 – 31.3; p=0.0184). Among neonates, persistent pulmonary hypertension of the newborn (OR 4.07; 95% CI 1.54 – 10.0; p=0.0029) and bronchopulmonary dysplasia (OR 8.11; 95% CI 3.28 – 19.8; p<0.0001) were more prevalent among Blacks, and congenital diaphragmatic hernia was more prevalent among Whites (OR 2.29; 95% CI 1.25 – 4.18; p=0.0070). Increased mortality risk was observed among Blacks (HR, 1.99; 95% CI 1.03 – 3.84; p=0.0396), driven primarily by the heightened mortality risk among those with lung disease-associated PH (HR 2.84; 95% CI 1.15 – 7.04; p=0.0241).

Conclusions—Our study demonstrated significant racial variability in the prevalence of PH subtypes and survival outcomes among children with PH. Given the substantial burden of the disease, further studies to validate the observed phenotypic differences and to understand the underlying causes of survival disparities between racial and ethnic groups are warranted.

Introduction

In adults with pulmonary hypertension (PH), several studies have documented racial and ethnic differences in survival, with increased mortality reported among racial and ethnic minorities when compared with non-Hispanic White patients [1–4]. Other studies have documented racial and ethnic variability within PH subtypes, including a higher incidence of connective tissue disease (CTD) and sickle cell disease-associated PH among Black subjects [5–10], familial and idiopathic PH among White patients [5,11], and congenital heart disease (CHD)-associated PH among Hispanic patients has been reported [5]. Historically, racial and ethnic minority populations are disproportionately affected by poor access to health care services and treatment disparities may have resulted in poorer survival outcomes [5]. Heterogeneity in clinical phenotypes and underlying genotypes may also have contributed to the observed survival disparities among minority races with PH, as disease progression and availability of treatment vary substantially by PH subtypes.

There are currently no published data examining racial and ethnic differences among children with PH, and understanding racial and ethnic differences in PH manifestations and outcomes are crucial for disease diagnosis and management. By leveraging the Pediatric Pulmonary Hypertension Network (PPHNet) registry, that includes subjects enrolled from established interdisciplinary PH programs at eight Pediatric PH Centers throughout North America [12], we conducted the first study investigating racial and ethnic differences in PH subtypes and outcomes in the pediatric population.

Methods

Study design and cohort

This is a retrospective analysis of the PPHNet registry – a multicenter registry enrolling at eight pediatric PH clinical programs in North America. The study protocol was approved by the institutional review boards of all participating centers and all study participants signed informed consent. The cohort included 1,417 incident and prevalent children (≤18 years old) enrolled in the registry between 2014 and 2018. Demographics (including age, sex, race, ethnicity), PH subtypes, and survival outcomes were extracted. To examine the potential

impact of socioeconomic status on survival outcomes, we linked patients' zip code of residence to the 2016 US Census Bureau Small Area Income and Poverty Estimates to derive a neighborhood socioeconomic indicator quantifying the percentage of children aged below 18 living in poverty at the county level, as defined by the Census Bureau [13].

Study Outcomes

The primary variables of interest were racial/ethnic variability in PH subtypes and survival. Race was classified into six categories: American Indian/Alaska Native, Asian, Black, Native Hawaiian/other Pacific Islander, White, or multiracial. Ethnicity was categorized as Hispanic/Latino and non-Hispanic/Latino. Because PH in the first four weeks of life may be transient, we conducted separate analyses comparing patients diagnosed in the first four weeks of life with those diagnosed beyond the neonatal period.

We performed survival analysis on the overall study population, as well as for specific PH subtypes, with a focus on lung disease-associated PH and PAH – the subtypes with the largest sample size in our cohort. Recognizing the registry included patients enrolled at different stages of disease progression and to ameliorate potential survival bias (patients who survived longer were more likely to be enrolled in the study), survival analysis was limited to an "incident cohort," defined as patients enrolled in the registry within 180 days of disease diagnosis. We further conducted sensitivity analyses to assess survival outcomes in both the prevalent and incident cohorts for the overall study population, as well as for a subset of patients with PH subtypes that present in the neonatal period, including congenital diaphragmatic hernia (CDH) and persistent pulmonary hypertension of the newborn (PPHN). In the sensitivity analysis involving patients with CDH and PPHN, survival time was measured from the date of birth to the date of death.

Statistical analyses

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between racial/ethnic subgroups and PH subtypes. Kaplan-Meier estimates and Cox regression models were used to examine racial and ethnic variability in all-cause mortality. We examined the unadjusted mortality risk of individual racial and ethnic subgroup, as well as mortality risk adjusted for patients' age at diagnosis, sex, and socioeconomic status (i.e. county-level childhood poverty rate). Survival time was defined as the time elapsed between the date of diagnosis and date of death. Patients still alive on February 22, 2019 (i.e. date of registry data extraction) and those lost to follow-up prior to this date were censored on February 22, 2019 and the last day of enrollment, respectively. Patients without a self-identified race were excluded from analyses examining racial variability in PH subtypes and survival outcome, and patients without a self-identified ethnicity were excluded from analyses comparing ethnic subgroups.

Results

A total of 1,417 patients enrolled in the PPHNet registry were included in the analysis. Of the subjects, 60.1% self-identified as White, 13.1% Black, 9.1% Asian, 1.6% multiracial, 1.0% American Indian or Alaska Native, and 0.7% Native Hawaiian or other Pacific

Islander. Hispanic or Latino ethnicity comprised 16.0% of the study cohort (Table 1). The mean and median follow-up duration of the study cohort were 943.7 and 995 days, respectively. Approximately one in four of those included (n=340, 24.0%) were diagnosed with PH within the first four weeks of life (Figure 1; online), the majority of whom were male (59.1%) and White (67.1%). The most common PH subtypes among neonates were CDH (72.9%), PPHN (10.9%), and BPD (10.0%). Compared with other racial and ethnic subgroups, Black (OR 1.10; 95% CI 1.07–1.13; p<0.0001) and Hispanic (OR 1.03; 95% CI 1.01 – 1.06; p=0.013) children were more likely to live in counties with high childhood poverty rate, while Asian (OR 0.95; 95% CI 0.91 – 0.98; p=0.007) and White (OR 0.97; 95% CI 0.95 – 0.99; p=0.002) children were less likely to live in counties with high childhood poverty rate.

Racial and ethnic differences in PH subtypes

Lung-disease associated PH and PAH comprised nearly 90.2% of the cohort (n=688, 48.6%; n=591, 41.7% respectively) (Table 1). Lung-disease associated PH was the most common subtype among Black, White, and multiracial patients, while PAH was most common among Asian, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander patients (Table 2). Among Hispanic patients, lung-disease associated PH and PAH were the most common PH subtypes.

Bivariate analysis revealed associations between race/ethnicity and several PH subtypes (Table 3). Notably, Asian patients were more likely to have PAH (OR 2.04; 1.41 – 2.97; p=0.0002) and less likely to develop lung disease-associated PH (OR 0.51; 0.34 – 0.74; p=0.0005); Black patients were less likely to have PAH (OR 0.57; 0.40 – 0.79; p=0.0009). A higher incidence of chronic thromboembolic pulmonary hypertension (CTEPH) was observed among Black patients (OR 5.60; 1.03 – 30.5; p=0.0357). To examine if the association between CTEPH and Black patients was driven by a higher incidence of hematological disease-associated PH among Black individuals, we examined the number of patients co-diagnosed with CTEPH and hematological-associated PH. There were no patients in our study cohort with a co-diagnosis of CTEPH and hematological-associated PH. However, given the small number of patients with CTEPH (n=7) and the lack of association between CTEPH and Black patients when neonates were excluded from the analysis (Table 3), this finding should be interpreted with caution.

We further observed a higher risk of lung disease-associated PH among Black children who were diagnosed beyond the neonatal period (OR 2.09; 95% CI 1.48 – 2.95; p<0.0001); however, this relationship was not observed among those diagnosed in the neonatal period (Table 3). To investigate this inconsistency, we further examined separately the risk of CDH and BPD – the two most common causes of lung disease-associated PH among neonates. The analysis showed that Black neonates were significantly more likely to develop BPD (OR 8.20; 95% CI 3.18 – 20.8; p<0.0001) but were less likely to have CDH (OR 0.13; 95% CI 0.05 – 0.30; p<0.0001). The heightened risk of BPD in Black children persisted when we extended the analysis to include children diagnosed beyond the neonatal period (OR 3.21; 95% CI 2.32 – 4.45; p<0.0001). Among White children diagnosed in the neonatal period, an increased risk of lung disease-associated PH was observed (OR 3.06; 95% CI 1.64 – 5.73;

p=0.0004); subgroup analysis of CDH and BPD showed an increased risk of CDH (OR 2.56; 95% CI 1.38 – 4.78; p=0.0029) and a reduced risk of BPD (OR 0.37; 95% CI 0.16 – 0.90; p=0.0226) among White children (Table 3). The reduced risk of BPD among White patients persisted when we extended the analysis to include children diagnosed beyond the neonatal period (OR 0.46; 95% CI 0.35 – 0.61; p<0.0001). Among neonates, a higher risk of PPHN was also observed among Black children (OR 4.63; 95% CI 1.73 – 11.7; p=0.0015), and a lower risk of PPHN was observed among White children (OR 0.30; 95% CI 0.13 – 0.68; p=0.0033).

A higher incidence of schistosomiasis-associated PH was detected among American Indians/Alaska Native and Native Hawaiians/other Pacific Islander patients; however, given the small number of patients with schistosomiasis, this finding should be interpreted with caution.

Racial and ethnic disparities in PH survival

During the period of follow-up, 105 (7.4%) patients died, on average 1,220 days from the time of PH diagnosis. To define an “incident cohort,” we identified patients who were diagnosed within 180 days of study enrollment. A total of 528 patients comprised this cohort, 57 (10.8%) of whom died, on average 802.8 days from the time of PH diagnosis. Of the 119 neonates in the incident cohort, 18 (15.1%) died during the study period. In comparison, of the 409 incident cases diagnosed after the neonatal period, 39 (9.5%) died during the study period. Younger age at diagnosis was associated with poorer survival outcome (HR 0.91; 95% CI 0.83 – 0.99; p=0.0311). Survival outcome was not associated with specific PH subtypes, sex, and county-level childhood poverty rate.

Variability in survival outcomes was observed across racial and ethnic subgroups (Table 4). Among those diagnosed after the neonatal period, increased mortality risk was observed among Black patients (HR, 2.46; 95% CI 1.17 – 5.17; p=0.0176) (Figure 2; online), and the risk remained significant after adjusting for age at diagnosis, sex, and county-level poverty rate (HR 2.42; 95% CI 1.12 – 5.23; p=0.0243). Poorer survival outcome was also observed among Native Hawaiian/other Pacific Islander children diagnosed beyond the neonatal period (HR 4.50; 95% CI 1.08 – 18.8; p=0.0393), and mortality risk remained significant after adjusting for age at diagnosis, sex, and county-level poverty rate (HR 4.97; 95% CI 1.16 – 21.3; p=0.0308). No significant racial and ethnic variability in mortality risk was observed among children diagnosed during the first four weeks of life. The majority of neonatal deaths (n=11) comprised infants with CDH (n=9). In sensitivity analyses including both prevalent and incident cases, increased mortality risk was observed among Black children and reduced mortality risk was observed among White children in both adjusted and unadjusted models (Table 7; online).

We further evaluated separately the survival outcomes of patients with lung disease-associated PH and PAH. Survival analysis of the incident cohort of patients with lung disease-associated PH showed that Black patients experienced poorer survival outcomes compared with White patients (Figure 3; online), and this association remained significant after excluding neonates and adjusting for age at diagnosis, sex, and county-level childhood poverty rate (HR 2.91; 95% CI 1.01 – 8.42; p=0.0489) (Table 4). However, subgroup

analysis of neonates with lung disease-associated PH did not reveal statistically significant racial and ethnic differences in survival. We further performed a sensitivity analysis that included prevalent and incident cases of patients with CDH and PPHN, whereby survival time was measured from the date of birth to the date of death; poorer survival outcome was observed among Native Hawaiian/other Pacific Islander children in both the unadjusted and adjusted models (Table 8; online). Survival analysis of an incident cohort of patients with PAH showed increased mortality risk among Native Hawaiian/other Pacific Islander children, and the risk persisted following adjustment for age at diagnosis, sex, and county-level childhood poverty rate (Table 4).

Discussion

In this analysis of the largest pediatric-focused PH registry to date, we found significant variability in the prevalence of PH subtypes and survival outcomes among children of different racial and ethnic backgrounds. Notably, among children diagnosed after the neonatal period, Asian patients were more likely to have a diagnosis of PAH and less likely to develop lung disease-associated PH; Black patients were more likely to have a diagnosis of lung disease-associated PH and less likely to have PAH; White patients were more likely to have a diagnosis of idiopathic PAH; Hispanic patients were more likely to have a diagnosis of PVOD. With the exception of the higher incidence of idiopathic PAH among White patients, which has been documented in published studies on the adult population, these relationships have not been previously reported. We further observed that PVOD was over-represented among Native Hawaiian/other Pacific Islander patients, and schistosomiasis-associated PH was over-represented among American Indian/Alaska Native and Native Hawaiian/other Pacific Islander children. However, since American Indian/Alaska Native and Native Hawaiian/other Pacific Islander children represent less than 2% of the study cohort, study findings pertaining to these racial subgroups should be interpreted with caution. Among neonates, we observed an increased risk of PPHN and BPD among Black children, and an increased risk of CDH among White children.

The relationship between lung disease-associated PH and specific racial subgroups (i.e. reduced risk among Asian children and elevated risk among Black children) may be mediated by differences in preterm birth rates – a known risk factor for lung disease-associated PH in children. Historically, Asian infants have the lowest preterm birth rate in the US, while Black infants have the highest [15]. The increased risk of PPHN and BPD among Black infants observed in our analysis has also been documented in several studies [17–19], thus highlighting the need to address this disparity. Recent studies reported that inhaled nitric oxide (iNO) improves survival and reduces the risk of BPD in preterm Black infants but not White infants [20–21] and genetic variability may contribute to the differential response [21]. These findings provide a rationale for considering iNO therapy for preterm Black infants with severe early respiratory failure who are at high risk of developing BPD.

Previous studies on the adult population documented a higher burden of PH among Black patients with CTD [7,22]; this relationship, however, has not been consistently demonstrated [23]. In our study cohort, Black children were indeed over-represented among those with

CTD-associated PAH; two of seven children with CTD-associated PAH were Black. However, risk analysis did not reach statistical significance. Published studies on the adult population have also reported a higher risk of familial PAH among White individuals [5,11] and a higher prevalence of CHD-associated PAH among Hispanic individuals [5]. These relationships were not observed in our study cohort. Sampling bias, inadequate sample size, and differences between childhood-onset and adult-onset PH may explain some of the observed inconsistencies.

Importantly, our study demonstrates a two-fold increased risk of mortality among Black children with lung disease-associated PH. These findings are consistent with previous studies that reported poorer prognosis among Black adults with PH [1–4, 24]. One study reported a three-fold increased risk of death among African American adults with ILD-associated PH, compared with White patients [24]. A number of factors may have contributed to the observed disparities. Historically, racial and ethnic minority populations are disproportionately affected by poor access to health care services. Treatment disparities among racial minorities with PH have been reported in a number of studies [5,25]. Because the prognosis of PH is dependent on early diagnosis and treatment, poor access to care likely results in worse outcomes. In our study, we attempted to account for the impact of socioeconomic status by examining the childhood poverty rate in the county where patients reside. While Black and Hispanic patients in our study cohort were more likely to live in counties with higher poverty rate, county-level childhood poverty rate did not appear to be associated with survival outcome. Further studies are needed to investigate other socioeconomic determinants that may contribute to survival disparities not currently captured in our data source, including the type of insurance coverage and treatment access.

Racial differences in clinical expression of disease and treatment response may also affect survival outcomes. A pooled analysis of six randomized controlled trials of endothelin-receptor antagonists showed that White patients experienced a greater treatment benefit than Black patients, highlighting racial heterogeneity in treatment-response to PAH medications that remains poorly understood and understudied [26]. Further studies are needed to explore the underlying causes of survival disparities among black children with PH. The young age of disease presentation in a substantial proportion of patients in our study cohort further highlights opportunities to investigate genetic causes of PH among different racial and ethnic subgroups.

Contrary to published evidence documenting higher mortality rate among Black and Hispanic preterm infants, our study did not detect disparities in PH survival outcome among Black and Hispanic neonates. Several factors may have contributed to this inconsistency. Firstly, survival outcome for different PH subtypes vary substantially. Given the small number of neonates in our dataset, who were predominantly White patients with CDH, our analysis was not adequately powered to examine survival disparities in individual subtypes. Secondly, our analysis did not account for the full range of clinical variables (e.g. birth weight, prematurity, treatment, family history) known to affect survival outcomes in neonates. We were also unable to ascertain cases of transient PH in this population. Efforts are currently underway to collect these data elements in the registry. Finally, studies have shown that racial and ethnic disparities in neonatal mortality is often driven by systemic

factors. Minority populations tend to be served by health care facilities that are under-resourced and unable to provide high quality care [27–29]. A recent study reported that Black and Hispanic infants are more likely to be born in hospitals with higher risk-adjusted neonatal morbidity and mortality rates than White infants [27]. Because our study is limited to eight academic centers, our analysis could not have adequately captured variability in care quality contributing to the observed survival disparities among minority infants in the US.

Our analysis also showed an increased mortality risk among Native Hawaiian/other Pacific Islander children in both the overall cohort and patients with PAH. However, the limited sample size prohibits generalization of the findings. Larger studies are needed to investigate the extent and causes of survival disparities. Contrary to published data reporting survival disparities among Hispanic patients with PH, we did not detect ethnic differences in survival outcome in our study cohort.

There are several limitations of this study that may influence the generalizability of the results. First, the study subjects were referred to one of eight tertiary referral centers, and thus may not be generalizable to the US population at large. Because racial and ethnic minorities are historically an underserved population, they are likely to be under-represented in our study cohort. To investigate the extent of referral bias, we compared the racial/ethnic distribution of patients at the referral centers under study (by querying the Pediatric Health Information System database [30]) and the population at the counties where the referral centers were located (quantified based on the U.S. Census data [31]). Race and ethnicity data were available for four of the eight referral centers and the extent to which the study cohort is representative of the general population varies by race/ethnicity and center – Asian individuals were under-represented at all four centers; black and Hispanic individuals were under-represented at two centers (Table 8), indicating that referral bias may be present. Despite this limitation, our study cohort is the largest pediatric PH cohort to date, providing a unique opportunity to characterize these patients.

Another limitation is that race and ethnicity were self-reported, limited to broad categories that may not adequately capture biological variability among racial subgroups, and were incomplete. Furthermore, the limited sample size of certain patient subgroups and PH subtypes prohibits comprehensive analysis of survival disparities. In addition to referral bias, there may be enrollment bias within each referral center whereby patients enrolled in the registry may not truly reflect the pediatric PH population at each center. Future studies that leverage electronic medical records to further characterize racial and ethnic variability in childhood-onset PH will be important. It should also be noted that some of the PH subtypes, such as schistosomiasis-associated PH, are rare; thus, caution should be taken in the interpretation of the risk analysis. Finally, while we attempted to control for duration of disease using the date of first diagnosis, it is possible that true duration of disease prior to the diagnosis of PH varied and thus may have skewed the survival analysis.

In summary, our study demonstrates significant racial variability in the prevalence of PH subtypes and survival outcomes among children with PH, and highlights the reduced survival among Black children with lung disease-associated PH. Given the substantial

burden of the disease, further studies to validate the observed phenotypic differences and to understand the underlying causes survival disparities are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

We thank Michelle Heinz, Deborah Batson, and Lynn Sleeper for their assistance in extracting and cleaning the study dataset.

Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number U01HL121518. We have no conflicts of interest to declare.

Abbreviations and Acronyms

BPD	Bronchopulmonary dysplasia
CDH	Congenital diaphragmatic hernia
CHD	Congenital heart disease
CTD	Connective tissue disease
CTEPH	chronic thromboembolic pulmonary hypertension
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
PPHNet	Pediatric Pulmonary Hypertension Network

References

1. Kawut SM, Horn EM, Berekashvili KK, Garofano RP, Goldsmith RL, Widlitz AC, et al. New predictors of outcome in idiopathic pulmonary arterial hypertension. Am J Cardiol. 2005;95:199–203. [PubMed: 15642552]
2. Lilienfeld DE, Rubin LJ. Mortality from primary pulmonary hypertension in the United States, 1979–1996. Chest. 2000;117:796–800. [PubMed: 10713009]
3. Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA. Pulmonary hypertension surveillance – United States, 1980–2002. MMWR Surveill Summ. 2005;54:1–28.
4. George MG, Schieb LJ, Ayala C, Talwalkar A, Levant S. Pulmonary hypertension surveillance: United States, 2001 to 2010. Chest. 2014; 146:476–495. [PubMed: 24700091]
5. Al-Naamani N, Paulus JK, Roberts KE, Pauciulo MW, Lutz K, Nichols WC, et al. Racial and ethnic differences in pulmonary arterial hypertension. Pulm Circ. 2017;7:1–4..
6. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Resp Crit Care Med. 2009;179:151–7. [PubMed: 18931333]
7. Beall AD, Nietert PJ, Taylor MH, Mitchell HC, Shaftman SR, Silver RM, et al. Ethnic disparities among patients with pulmonary hypertension associated with systemic sclerosis. J Rheumatol. 2007;34:277–82.

8. Parikh KS, Stackhouse KA, Hart SA, Bashore TM, Krasuski RA. Health insurance and racial disparities in pulmonary hypertension outcomes. Am J Manag Care. 2017;23:474–480. [PubMed: 29087147]
9. Ataga KI, Sood N, De Gent G, Kelly E, Henderson AG, Jones S, et al. Pulmonary hypertension in sickle cell disease. Am J Med. 2004;117:665–9. [PubMed: 15501204]
10. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. Am J Med. 2006;119:897.e7–11.
11. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest. 2010;138:1383–94. [PubMed: 20507945]
12. Abman SH, Raj U. Towards improving the care of children with pulmonary hypertension: the rationale for developing a Pediatric Pulmonary Hypertension Network. Prog Pediatr Cardiol. 2009;1:3–6.
13. United States Census Bureau. Small area income and poverty estimates (SAIPE) program. https://www.census.gov/programs-surveys/saipe.html (last accessed March 8th, 2019).
14. Berg N Non-response bias. Encyclopedia of Social Measurement. Kempf-Leonard K, ed., London, Academic Press 2005;2:865–873.
15. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P, Division of Vital Statistics. Births: final data for 2016. National Vital Statistics Report. 2018;67.
16. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. Am J Med. 2006;119:897.e7–11.
17. Hernández-Díaz S, Van Marter LJ, Werler MM, Louik C, Mitchell AA. Risk factors for persistent pulmonary hypertension of the newborn. Pediatrics. 2007;120:e272–82. [PubMed: 17671038]
18. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent pulmonary hypertension of the newborn in late preterm and term infants in California. Pediatrics 2017;139:e20161165. [PubMed: 27940508]
19. Janevic T, Zeitlin J, Auger N, Egorova NN, Hebert P, Balbierz, et al. Association of race/ethnicity with very preterm neonatal morbidities. JAMA Pediatr. 2018;172:1061–1069. [PubMed: 30208467]
20. Askie LM, Davies LC, Schreiber MD, Hibbs AM, Ballard PL, Ballard RA. Race effects of inhaled nitric oxide in preterm infants: an individual participant data meta-analysis. J Pediatr. 2018;193:34–39. [PubMed: 29241680]
21. Torgeson DG, Ballard PL, Keller RL, Oh SS, Huntsman S, Hu D, et al. Ancestry and genetic associations with bronchopulmonary dysplasia in preterm infants. Am J Physiol Lung Cell Mol Physiol. 2018 11 1;315:L858–L869. [PubMed: 30113228]
22. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Resp Crit Care Med. 2009;179:151–7. [PubMed: 18931333]
23. Gelber AC, Manno RL, Shah AA, Woods A, Le EN, Boin F, et al. Race and association with disease manifestations and mortality in scleroderma. Medicine. 2013;92:191–205. [PubMed: 23793108]
24. Matthai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, et al. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases. Arthritis Rheum. 2009;60:567–77.
25. Parikh KS, Stackhouse KA, Hart SA, Bashore TM, Krasuski RA. Health insurance and racial disparities in pulmonary hypertension outcomes. Am J Manag Care. 2017;23:474–480. [PubMed: 29087147]
26. Gabler NB, French B, Strom BL, Liu Z, Palevsky HI, Taichman DB, et al. Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. Chest. 2012;141:20–26. [PubMed: 21940766]
27. Howell EA, Janevic T, Hebert PL, Egorova NN, Balbierz A, Zeitlin J. Differences in morbidity and mortality rates in Black, White, and Hispanic very preterm infants among New York City hospitals. JAMA Pediatr. 2018;172:269–277. [PubMed: 29297054]

28. Howell EA, Hebert P, Chatterjee S, Kleinman LC, Chassin MR. Black/white differences in very low birth weight neonatal mortality rates among New York City hospitals. Pediatrics. 2008;121:e407–e415. [PubMed: 18267978]

29. Morales LS, Staiger D, Horbar JD, Carpenter J, Kenny M, Geppert J, et al. Mortality among very low-birthweight infants in hospitals serving minority populations. Am J Public Health. 2005;95:2206–2212. [PubMed: 16304133]

30. Pediatric Health Information System. https://www.childrenshospitals.org/phis (accessed on October 3, 2018).

31. United States Census Bureau: https://www.census.gov/ (accessed on October 3, 2018).

Table 1.

Demographics (n=1,417)

Race/ethnicity	N (%)
Age at diagnosis (years)	
1st quartile	0.0
Median	1.0
Mean	2.7
3rd quartile	4.0
Range	0 to 18
Sex	
Female	690 (48.7)
Male	727 (51.3)
Race	
American Indian/Alaska Native	14 (1.0)
Asian	129 (9.1)
Black	186 (13.1)
Native Hawaiian/other Pacific Islander	10 (0.7)
White	852 (60.1)
Multiracial	23 (1.6)
Not specified	203 (14.3)
Ethnicity	
Hispanic/Latino	227 (16.0)
Non-Hispanic/Latino	1056 (74.5)
Not specified	134 (9.5)
PH subtypes	
PAH	591 (41.7)
Idiopathic	163 (11.5)
Heritable	26 (1.8)
Drugs/toxins	2 (0.1)
Associated PAH	403 (28.4)
Connective tissue disease (CTD)	7 (0.5)
HIV	0
Portal hypertension	6 (0.4)
Congenital heart disease (CHD)	390 (27.5)
Schistosomiasis	4 (0.3)
PVOD	9 (0.6)
Persistent PH of the newborn (PPHN)	46 (3.2)
Left-heart disease	49 (3.5)
Lung disease	688 (48.6)

Race/ethnicity	**N (%)**
CTEPH	7 (0.5)
Unclear mechanisms	31 (2.2)
Hematological	8 (0.6)
Systemic disorders	7 (0.5)
Metabolic disorders	3 (0.2)
Segmental PH	3 (0.2)
Others	3 (0.2)
Neighborhood socioeconomic indicator	
Percentage of children living in poverty at the county level	
1st quartile	8.3
Median	11.1
Mean	12.5
3rd quartile	15.3
Range	3.0 to 36.2

Table 2.

PH subtypes by race and ethnicity

PH subtypes	Race							Ethnicity		
	American Indian / Alaska Native (n=14)	Asian (n=129)	Black (n=187)	Native Hawaiian / other Pacific Islander (n=10)	White (n=852)	Multi-racial (n=23)	Not specified (n=203)	Hispanic (n=227)	Non-Hispanic (n=1056)	Unknown (n=134)
PAH	8 (57.1)	75 (58.1)	58 (31.2)	6 (60.0)	361 (42.4)	6 (26.1)	77 (37.9)	101 (44.5)	440 (41.7)	50 (37.3)
Idiopathic	1 (7.1)	20 (15.5)	10 (5.4)	2 (20.0)	109 (12.8)	4 (17.4)	17 (8.4)	26 (11.5)	125 (11.8)	12 (9.0)
Heritable	0	5 (3.9)	2 (1.1)	0	14 (1.6)	1 (4.3)	4 (2.0)	4 (1.8)	19 (1.8)	3 (2.2)
Drugs/toxins	0	0	0	0	0	0	2 (1.0)	1 (0.4)	0	1 (0.7)
Associated PAH	7 (50.0)	50 (38.8)	46 (24.7)	4 (40.0)	241 (28.3)	1 (4.3)	54 (26.6)	70 (30.8)	299 (28.3)	34 (25.4)
CTD	0	0	2 (1.1)	0	2 (0.2)	0	3 (1.5)	0	3 (0.3)	4 (3.0)
HIV	0	0	0	0	0	0	0	0	0	0
Portal hypertension	0	1 (0.8)	1 (0.5)	0	3 (0.4)	0	1 (0.5)	2 (0.9)	4 (0.4)	0
CHD	7 (50.0)	49 (38.0)	41 (22.0)	4 (40.0)	238 (27.9)	1 (4.3)	50 (24.6)	68 (30.0)	292 (27.7)	30 (22.4)
Schistosomiasis	1 (7.1)	0	0	1 (10.0)	2 (0.2)	0	0	1 (0.4)	3 (0.3)	0
PVOD	0	0	3 (1.6)	1 (10.0)	2 (0.2)	1 (4.3)	2 (1.0)	4 (1.8)	5 (0.5)	0
PPHN	0	5 (3.9)	9 (4.8)	0	22 (2.6)	1 (4.3)	9 (4.4)	7 (3.1)	32 (3.0)	7 (5.2)
Left-heart disease	0	3 (2.3)	4 (2.2)	1 (10.0)	32 (3.8)	1 (4.3)	8 (3.9)	7 (3.1)	34 (3.2)	8 (6.0)
Lung disease	6 (42.9)	43 (33.3)	100 (53.8)	2 (20.0)	417 (48.9)	14 (60.9)	106 (52.2)	105 (46.3)	516 (48.9)	67 (50.0)
CTEPH	0	0	3 (1.6)	0	3 (0.4)	0	1 (0.5)	1 (0.4)	6 (0.6)	0
Unclear mechanisms	0	3 (2.3)	10 (5.4)	0	17 (2.0)	0	1 (0.5)	5 (2.2)	24 (2.3)	2 (1.5)
Hematological	0	2 (1.6)	3 (1.6)	0	3 (0.4)	0	0	0	7 (0.7)	1 (0.7)
Systemic disorders	0	0	2 (1.1)	0	5 (0.6)	0	0	2 (0.9)	5 (0.5)	0
Metabolic disorders	0	0	1 (0.5)	0	1 (0.1)	0	1 (0.5)	2 (0.9)	1 (0.1)	0
Segmental PH	0	1 (0.8)	0	0	2 (0.2)	0	0	0	2 (0.2)	1 (0.7)
Others	0	0	1 (0.5)	0	2 (0.2)	0	0	1 (0.4)	2 (0.2)	0

Table 3.

PH subtypes significantly associated with specific racial and ethnic subgroups

Race/Ethnicity	PH subtype	OR (95% CI)	p-value
Analysis including all patients			
American Indian/Alaska Native	Schistosomiasis	30.7 (1.47 – 258.6)	0.0034
Asian	PAH	2.04 (1.41 – 2.97)	0.0002
	APAH	1.66 (1.13 – 2.42)	0.0084
	PAH-CHD	1.67 (1.14 – 2.44)	0.0152
	PH-Lung	0.51 (0.34 – 0.74)	0.0005
Black	PAH	0.57 (0.40 – 0.79)	0.0009
	Idiopathic PAH	0.37 (0.18 – 0.69)	0.0035
	CTEPH	5.60 (1.03 – 30.5)	0.0357
	Unknown	2.86 (1.27 – 6.09)	0.0079
Native Hawaiian/other Pacific Islander	PVOD	22.2 (1.12 – 149.9)	0.0061
	Schistosomiasis	44.5 (2.09 – 388.1)	0.0016
White	PVOD	0.17 (0.02 – 0.78)	0.0335
Multiracial	APAH	0.11 (0.01 – 0.53)	0.0312
	PAH-CHD	0.11 (0.01 – 0.55)	0.0342
Analysis including only patients diagnosed after the neonatal period			
American Indian/Alaska Native	Schistosomiasis	45.8 (2.03 – 517.9)	0.0025
Asian	PAH	1.83 (1.21 – 2.79)	0.0045
	PH-Lung	0.61 (0.39 – 0.93)	0.0236
Black	PAH	0.44 (0.30 – 0.62)	<0.0001
	Idiopathic PAH	0.29 (0.14 – 0.56)	0.0006
	APAH	0.67 (0.45 – 0.97)	0.0393
	PAH-CHD	0.62 (0.42 – 0.91)	0.0164
	Lung disease	2.09 (1.48 – 2.95)	<0.0001
Native Hawaiian/other Pacific Islander	PVOD	42.8 (1.57 – 260.7)	0.0031
	Schistosomiasis	65.6 (2.86 – 769.5)	0.0011
White	Idiopathic PAH	1.58 (1.06 – 2.41)	0.0289
Multiracial	APAH	0.10 (0.01 – 0.47)	0.0238
	PAH-CHD	0.10 (0.01 – 0.49)	0.0259
	PH-Lung	2.77 (1.12 – 7.43)	0.0316
Hispanic	PVOD	6.11 (1.34 – 31.3)	0.0184
Analysis including only patients diagnosed during the neonatal period			
Black	PPHN	4.07 (1.54 – 10.0)	0.0029
	PH-Lung	0.25 (0.11 – 0.56)	0.0008
	BPD	8.11 (3.28 – 19.8)	<0.0001
	CDH	0.16 (0.06 – 0.36)	<0.0001
White	PPHN	0.29 (0.13 – 0.65)	0.0020

Race/Ethnicity	PH subtype	OR (95% CI)	p-value
	PH-Lung	3.51 (1.92 – 6.45)	<0.0001
	BPD	0.38 (0.17 – 0.88)	0.0190
	CDH	2.29 (1.25 – 4.18)	0.0070

Table 4.

Cox regression analysis of survival outcome by race and ethnicity

Variable	Unadjusted		Adjusted*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Analysis including all PH subtypes				
All incident cases				
Race				
American Indian/Alaska Native	1.73 (0.24 – 12.6)	0.5860	1.43 (0.20 – 10.4)	0.7256
Asian	0.65 (0.23 – 1.82)	0.4132	0.75 (0.27 – 2.09)	0.5826
Black	1.99 (1.03 – 3.84)	0.0396*	1.93 (0.98 – 3.78)	0.0934
Multiracial	1.09 (0.26 – 4.49)	0.9059	1.17 (0.28 – 4.85)	0.8300
Native Hawaiian/other Pacific Islander	3.23 (0.78 – 13.3)	0.1047	3.36 (0.80 – 14.1)	0.0969
White	0.63 (0.35 – 1.12)	0.1142	0.61 (0.34 – 1.08)	0.0896
Ethnicity				
Hispanic	0.45 (0.16 – 1.26)	0.1289	0.45 (0.16 – 1.27)	0.1329
Incident cases diagnosed after the neonatal period				
Race				
American Indian/Alaska Native	2.51 (0.34 – 18.4)	0.3652	2.13 (0.29 – 15.9)	0.4600
Asian	0.65 (0.20 – 2.13)	0.4763	0.80 (0.24 – 2.64)	0.7120
Black	2.46 (1.17 – 5.17)	0.0176*	2.42 (1.12 – 5.23)	0.0243*
Multiracial	1.43 (0.34 – 5.99)	0.6228	1.57 (0.37 – 6.64)	0.5420
Native Hawaiian/other Pacific Islander	4.50 (1.08 – 18.8)	0.0393*	4.97 (1.16 – 21.3)	0.0308*
White	0.46 (0.23 – 0.90)	0.0244*	0.42 (0.21 – 0.83)	0.0134*
Ethnicity				
Hispanic	0.47 (0.14 – 1.54)	0.2135	0.50 (0.15 – 1.64)	0.2547
Incident cases diagnosed during the neonatal period				
Race				
American Indian/Alaska Native	0.00 (0.00 - Inf)	0.9983	0.00 (0.00 - Inf)	0.9980
Asian	0.76 (0.10 – 5.83)	0.7937	0.60 (0.07 – 4.89)	0.6330
Black	1.08 (0.24 – 4.83)	0.9203	1.04 (0.23 – 4.69)	0.9600
Multiracial	0.00 (0.00 - Inf)	0.9983	0.00 (0.00 - Inf)	0.9983
Native Hawaiian/other Pacific Islander	0.00 (0.00 - Inf)	0.9983	0.00 (0.00 - Inf)	0.9980
White	1.40 (0.39 – 5.01)	0.6087	1.68 (0.44 – 6.31)	0.4460
Ethnicity				
Hispanic	0.43 (0.06 – 3.25)	0.4102	0.32 (0.04 – 2.56)	0.2810
Subgroup analysis of patients with lung disease-associated PH				
All incident cases				
Race				
American Indian/Alaska Native	0.00 (0.00 - Inf)	0.9979	0.00 (0.00 - Inf)	0.9979

Variable	Unadjusted		Adjusted*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Asian	0.52 (0.07 – 3.87)	0.5232	0.52 (0.07 – 3.88)	0.5210
Black	2.84 (1.15 – 7.04)	0.0241*	3.01 (1.18 – 7.65)	0.0207*
Multiracial	0.90 (0.12 – 6.72)	0.9197	0.98 (0.13 – 7.47)	0.9870
Native Hawaiian/other Pacific Islander	0.00 (0.00 - Inf)	0.9979	0.00 (0.00 - Inf)	0.9979
White	0.59 (0.25 – 1.40)	0.2338	0.59 (0.25 – 1.41)	0.2330
Ethnicity				
Hispanic	0.73 (0.17 – 3.12)	0.6683	0.80 (0.19 – 3.45)	0.7650
Incident cases diagnosed after the neonatal period				
Race				
American Indian/Alaska Native	0.00 (0.00 - Inf)	0.9978	0.00 (0.00 - Inf)	0.9978
Asian	0.63 (0.08 – 4.81)	0.6574	0.64 (0.08 – 4.93)	0.6710
Black	2.96 (1.05 – 8.32)	0.0395*	2.91 (1.01 – 8.42)	0.0489*
Multiracial	0.96 (0.13 – 7.32)	0.9703	1.01 (0.13 – 7.91)	0.9960
Native Hawaiian/other Pacific Islander	NA	NA	NA	NA
White	0.50 (0.18 – 1.37)	0.1765	0.50 (0.18 – 1.41)	0.1900
Ethnicity				
Hispanic	1.00 (0.22 – 4.42)	0.9968	1.17 (0.26 – 5.21)	0.8370
Incident cases diagnosed during the neonatal period				
Race				
American Indian/Alaska Native	0.00 (0.00 - Inf)	0.9990	0.00 (0.00 - Inf)	0.9990
Asian	0.00 (0.00 - Inf)	0.9990	0.00 (0.00 - Inf)	0.9990
Black	4.05 (0.47 – 34.7)	0.2014	4.04 (0.47 – 35.1)	0.2050
Multiracial	NA	NA	NA	NA
Native Hawaiian/other Pacific Islander	0.00 (0.00 - Inf)	0.9990	0.00 (0.00 - Inf)	0.9990
White	0.82 (0.10 – 6.99)	0.8531	0.81 (0.09 – 7.58)	0.8500
Ethnicity				
Hispanic	0.00 (0.00 - Inf)	0.9987	0.00 (0.00 - Inf)	0.9987
Subgroup analysis of patients with PAH				
All incident cases				
Race				
American Indian/Alaska Native	3.14 (0.42 – 23.7)	0.2670	2.36 (0.31 – 17.9)	0.4067
Asian	0.86 (0.25 – 2.97)	0.8112	1.17 (0.33 – 4.14)	0.8026
Black	0.96 (0.22 – 4.17)	0.9551	0.69 (0.16 – 3.05)	0.6210
Multiracial	2.20 (0.29 – 16.6)	0.4458	2.83 (0.36 – 22.0)	0.3206
Native Hawaiian/other Pacific Islander	6.15 (1.40 – 26.9)	0.0159*	8.61 (1.81 – 40.8)	0.0067*
White	0.58 (0.23 – 1.47)	0.2538	0.56 (0.22 – 1.42)	0.2187
Ethnicity				
Hispanic	0.47 (0.11 – 2.03)	0.3104	0.31 (0.07 – 1.47)	0.1422

Variable	Unadjusted		Adjusted*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Incident cases diagnosed after the neonatal period				
Race				
American Indian/Alaska Native	3.90 (0.51 – 29.8)	0.1900	2.61 (0.34 – 20.2)	0.3580
Asian	0.74 (0.17 – 3.32)	0.6979	1.10 (0.24 – 5.03)	0.9050
Black	1.32 (0.30 – 5.90)	0.7153	0.98 (0.21 – 4.53)	0.9790
Multiracial	2.49 (0.32 – 19.1)	0.3801	2.62 (0.33 – 20.6)	0.3610
Native Hawaiian/other Pacific Islander	7.00 (1.56 – 31.2)	0.0111*	8.29 (1.67 – 41.2)	0.0097*
White	0.44 (0.15 – 1.26)	0.1248	0.41 (0.14 – 1.20)	0.1045
Ethnicity				
Hispanic	0.30 (0.04 – 2.27)	0.2425	0.24 (0.03 – 1.94)	0.1819
Incident cases diagnosed during the neonatal period				
Race				
American Indian/Alaska Native	NA	NA	NA	NA
Asian	0.99 (0.10 – 9.69)	0.9949	0.75 (0.06 – 9.98)	0.8280
Black	0.00 (0.00 - Inf)	0.9991	0.00 (0.00 - Inf)	0.9991
Multiracial	NA	NA	NA	NA
Native Hawaiian/other Pacific Islander	NA	NA	NA	NA
White	2.50 (0.24 – 26.1)	0.4441	2.08 (0.19 – 22.3)	0.5450
Ethnicity				
Hispanic	0.71 (0.07 – 7.25)	0.7731	0.10 (0.00 – 3.76)	0.2113

*adjusted by age at diagnosis, sex, and county-level childhood poverty rate