High geographic prevalence of pulmonary artery hypertension: associations with ethnicity, drug use, and altitude

Jason Dubroff[1], Lana Melendres[2], Yan Lin[3], Daniel Raley Beene[3] and Loren Ketai[4]

[1]Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA; [2]Department of Internal Medicine, University of New Mexico, Albuquerque, NM, USA; [3]Department of Geography and Environmental Studies, University of New Mexico, Albuquerque, NM, USA; [4]Department of Radiology, University of New Mexico, Albuquerque, NM, USA

Abstract

While estimates of pulmonary arterial hypertension incidence and prevalence commonly range from 1–3/million and 15–25/million, respectively, clinical experience at our institution suggested much higher rates. We sought to describe the disease burden of pulmonary arterial hypertension in the geographic area served by our Pulmonary Hypertension Clinic and compare it to the REVEAL registry. Our secondary objectives were to document pulmonary arterial hypertension prevalence in minorities under-represented in REVEAL (Hispanics and Native Americans) and to address the association of pulmonary arterial hypertension with exposure to drugs and moderately increased residential altitude in this population. Retrospective review of pulmonary arterial hypertension clinic patients alive during 2016 identified 154 patients. Hispanic patients made up 35.7% of the cohort, a much greater percentage than REVEAL, $p < .001$ but smaller than the percentage of Hispanic patients (48.4%) in geographic area served by the clinic. Pulmonary arterial hypertension due to drug exposure was more common and idiopathic pulmonary arterial hypertension was less common than in REVEAL ($p < .001$). Overall, pulmonary arterial hypertension incidence was 14 cases per million, greater than the REVEAL registry, odds ratio 6.3 (95% CI: 4.2–9.5), ($p < .001$). Annual period prevalence of pulmonary arterial hypertension was 93 cases per million, also greater than the REVEAL, odds ratio = 7.5 (95% CI: 6.4–8.8) and remained greater when the clinic cohort was constrained to patients with hemodynamic severity comparable to REVEAL, odds ratio = 3.8 (95% CI: 3.0–4.6), ($p < .001$). There was a strong association between pulmonary arterial hypertension prevalence and residence at altitude > 4000 ft, odds ratio = 26.6 (95% CI: 8.5–83.5), $p < .001$; however, this was potentially confounded by pulmonary arterial hypertension treatment referral patterns. These findings document a much higher local pulmonary arterial hypertension incidence and prevalence than previously reported in REVEAL. While population ethnicity differed markedly from REVEAL, the disease burden was not driven by these differences. The possible association of moderately increased residential altitude with pulmonary arterial hypertension warrants further evaluation.

Introduction

Pulmonary arterial hypertension (PAH), or Group 1 Pulmonary Hypertension (PH) in the World Health Organization (WHO) classification, is a rare disease that can be caused by a variety of etiologies including congenital heart disease, connective tissue diseases (CTD), and exposure to drugs and toxins.[1] Since the 1980s several registries of patients with PAH have characterized its population, etiologies, and demographics.[2,3] These, PAH registries have served as a foundation that informs clinical trials of current and future treatments. Estimates of PAH incidence and prevalence vary between registries and populations.

Corresponding author:
Loren Ketai, Department of Radiology, University of New Mexico, MSC10 5530, Albuquerque, NM 87131, USA.
Email: lketai@unm.edu

The French registry describes an incidence of 2.4 cases and prevalence of 15 cases per million adults. Based upon hospitalization records, the Scottish registry estimated annual incidence as 7.1 and prevalence as high as 52 cases per million.[4,5] In the US, the largest registry of PH patients, Registry to Evaluate Early and Long-term PAH (REVEAL), utilized inclusion criteria dependent on catheterization data and estimated incidence and prevalence of PAH in adults as 2.3 and 12.4 cases per million, respectively.[6]

Clinical experience at our institution suggested disease prevalence greater than these previous population-level descriptions of PAH. The primary aim of this retrospective chart review is to describe a cohort of adult PAH patients at an academic medical institution in the southwestern United States with a large geographic catchment area and compare this cohort's PAH disease burden with previously published descriptions. In doing so, this study also aims to provide PAH epidemiologic data relevant to minorities, Hispanics, and Native Americans, which are underrepresented in the REVEAL registry.[7,8]

The secondary aim is to address the association of PAH with known drugs and toxins and with regional altitude for this population. Methamphetamine has recently been classified as a definite cause of PAH, and recent epidemiologic study has supported this classification.[9–11] Public health data from our state indicates exposure rates to methamphetamine above the US national average, raising the possibility of its contribution to PAH in our patient cohort.[12] The mean elevation of our state is approximately 5700 ft (or 1700 m), an altitude accompanied by a decrease in sea level ambient oxygen saturation of 20.9% to approximately 17%. This altitude, however, falls short of the threshold of 2500 m, above which Group 3 PH from chronic hypoxia is generally diagnosed.[13] We sought to determine if among our cohort there was an apparent lower altitude threshold, above which PAH was more likely to be observed.

Methods

Patient identification

A retrospective chart review was performed of patients seen in PAH specialty clinic between 1 January 2016 and 31 December 2016. The University of New Mexico Human Research Protection Office waived the need for informed consent. Patients included in this cohort met PAH hemodynamic criteria: mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg, pulmonary vascular resistance (PVR) > 3 Wood units, and a pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg as documented via right-heart catheterization performed during or prior to 2016. Patients also had PAH attributed to etiologies consistent with WHO Group 1 categorization during the time of study.[1] Prevalent cases were included for analysis if the patient was alive during the 2016 calendar year, which yielded an annual period prevalence. Incident cases were

included for analysis if patients received a new diagnosis of PAH confirmed by right heart catheterization over the same time period. The 2016 U.S. Census American Community Survey was used to determine both incidence and prevalence population at risk by summing the total adult population within our state in addition to the population in ZIP codes outside the state in which clinic PAH patients resided.[14] The ethnic composition of each of these ZIP codes was determined from the same database.

Patient charts were reviewed using a standardized form to assess for characteristics including age, sex, race/ethnicity, current substance abuse (within last 12 months), history of substance abuse (any past use of at least three months duration), body mass index, and hemodynamic findings. Drug and toxins were categorized into the following groups based upon known PAH exposure risks; definite (aminorex, fenfluramine, amphetamines, methamphetamines, etc.), possible (cocaine, chemotherapy agents, etc.), and unlikely (estrogen, tobacco smoke, etc.).[1,11] Etiologies associated with WHO group I PAH were determined from PAH clinical records as well as other specialty clinical encounters, when relevant. Specifically, patients with CTD had been documented with appropriate laboratory testing and a final diagnosis from a rheumatologist. Similarly, patients were designated as portal hypertension-associated PAH when the diagnosis of portal hypertension had been made by a gastroenterologist. Etiology of PAH was considered mutually exclusive for patients with multiple associated PAH diagnoses, according to the hierarchy used in the REVEAL registry: congenital heart disease (CHD) > collagen vascular disease/CTD > portal hypertension (HTN) > drugs/toxins > HIV and other.[15] Patients with obstructive sleep apnea (OSA) were only included in the cohort if PAH was documented despite ongoing treatment with continuous positive airway pressure or bi-level positive airway pressure devices. All OSA patients had been formally evaluated by a sleep physician and adequately titrated on positive pressure ventilation with compliance assessed through the sleep clinic for a minimum of six months of sleep disorder treatment. Whenever questions arose regarding compliance or the need for changes to positive pressure ventilation regimen patients were at a minimum reassessed with overnight oximetry.

Geographic analysis

The elevation at which patients resided was determined based on patient's ZIP codes in the electronic medical record. To better approximate elevations associated with patient residences, Geographic Information Systems (GIS) was used to calculate mean elevation by ZIP code and adjusted to exclude areas of low population density, defined as a population density $\leq$ 1 person per square mile in census block groups. Based on the distribution of PAH cases in relation to these ZIP codes, an empiric altitude threshold associated with increased risk of PAH was chosen
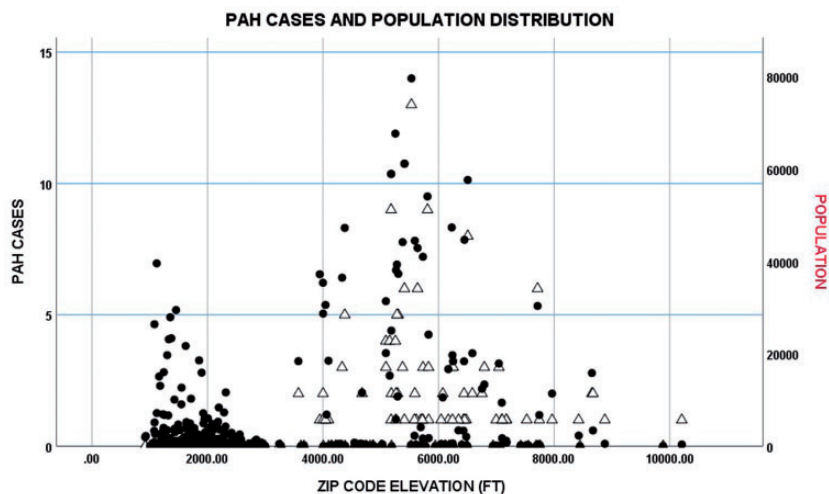
Fig. 1. Scatterplot showing the distribution of PAH cases in the cohort (open triangles) and ZIP code populations (filled circles) as a function of adjusted ZIP code altitude in feet.

(see Statistics section). Because our referral center is located above 5000 ft, we recognized that altitude and distance from our site could co-vary. If lower elevation ZIP codes were also more distant from our institution, patients in those ZIP codes might be referred to other PAH centers, lowering the apparent prevalence of PAH in those ZIP codes. Accordingly, we also analyzed altitude and PAH prevalence as a function of proximity to referral center. ZIP codes from the population at risk were allocated to the study's home institution or to one of three other regional hospitals with PAH specialty care, based on GIS calculation of projected shortest patient travel time.[16] When compared to allocation based on Health Referral Regions determined by Centers for Medicare and Medicaid (CMS), allocation of populations based on travel times slightly increased the estimated population served by other centers. The latter was analyzed to avoid underestimating the confounding effect of referral patterns.

Statistics

Data were analyzed using descriptive statistics. Prevalence and incidence of PAH were compared to the REVEAL data using two by two contingency tables. An altitude threshold of 4000 ft was selected based on visual inspection (Fig. 1) and the association of this threshold with the prevalence of PAH was assessed in a similar fashion. Distribution of race/ethnicity, PAH etiologies, and prevalence of OSA were compared to previously published REVEAL data and to the population at risk's demographic data using contingency tables. Post hoc analysis of standardized residuals was used to identify statistically significant differences in specific etiologies and race/ethnicity.[8,17] Adjusted residuals were used to calculate specific p values for each contingency table cell, the level of significance subjected to a Bonferroni correction.[18] The distribution of functional classes in the study cohort was compared to REVEAL data in a similar fashion. Hemodynamic data from the current cohort was compared to published REVEAL data using independent t-tests.[15] Data analysis was performed with SPSS version 2.5.

Results

Based on the above inclusion criteria, 154 patients diagnosed with WHO group I PAH were included for analysis. Mean patient age was 58.3 ± 16.3 years. The majority of patients were aged ≤ 64 years (60.4%) (Table 1). Patients in this cohort were predominantly female with a 2.4:1 female to male ratio. Thirty-nine percent of the cohort was obese and OSA was documented in 23% of the total study cohort and in 28% of patients with idiopathic pulmonary arterial hypertension (IPAH), compared to 22% and 23%, respectively, in the REVEAL cohort (Table 2).[15] These differences from the REVEAL cohort were not statistically significant ($p = 0.4$ and 0.7). Analysis of racial and ethnic distribution revealed that slightly less than half of the patients were white (48.7%) (Table 1). Hispanics were the next most frequently represented racial/ethnic group (35.7%), followed by Native Americans (10.4%) (Table 1). Contingency table for race/ethnicity indicated significant differences ($p < 0.001$) in distribution between the REVEAL registry and this cohort.[13] Post hoc analysis revealed that our cohort contained significantly more Hispanic and fewer white ($p < 0.0001$) and fewer black patients ($p < 0.005$) than the REVEAL cohort. Despite the greater representation of Hispanic patients compared to the REVEAL registry, the percentage of Hispanic patients in this PAH cohort was significantly lower relative to the total at risk population, 48.4% ($p < 0.005$). Since data specific to Native Americans in not available in the published REVEAL data, Native Americans ($n = 16$) and

Table 1. Demographic factors and characteristics of PAH patients in New Mexico 2016 ($n = 154$).

Characteristics	All patients	IPAH	CHD	CTD	Portal HTN	Drugs/toxins
Patients, No. (%)	154 (100)	46 (29.63)	10 (6.49)	53 (34.41)	13 (8.64)	32 (20.7)
Age						
Mean ± SD	58.3 ± 16.3	61.77 ± 17.62	50.00 ± 19.78	61.87 ± 16.77	55.85 ± 7.77	51.21 ± 12.29
≤64, No. (%)	93 (60.4)	20 (43.5)	8 (80)	25 (47.2)	12 (92.3)	28 (90.65)
65–74, No. (%)	36 (23.4)	15 (32.6.)	1 (10)	18 (34)	1 (7.7)	3 (9.37)
≥75, No. (%)	25 (16.2)	11 (23.9)	1 (10)	10 (18.8)	0 (0)	1 (3.03)
Gender						
Female	109 (70.8)	29 (64.58)	6 (60)	47 (88.67)	5 (38.4)	22 (68.75)
Male	45 (29.2)	17 (35.42)	4 (40)	6 (11.32)	8 (61.53)	10 (31.30)
Race and ethnicity						
White	75 (48.7)	25 (54.34)	2 (20)	25 (47.16)	5 (38.4)	18 (56.25)
Hispanic	55 (35.7)	13 (28.26)	6 (60)	20 (37.72)	6 (46.1)	10 (32.25)
Native American	16 (10.4)	7 (15.21)	0 (0)	7 (13.21)	1 (7.69)	1 (3.13)
Black	7 (4.5)	1 (1.89)	1 (10)	1 (1.88)	1 (7.69)	3 (9.38)
Asian	1 (0.7)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
BMI						
Mean ± SD	29.26 ± 7.54	30.21 ± 7.57	26.90 ± 5.47	26.97 ± 6.99	26.55 ± 4.47	32.91 ± 8.53
Elevation						
Mean ± SD, feet	5779 ± 1135	6030.70 ± 1087.29	5893.74 ± 1439.77	5708.85 ± 1416.09	5947.26 ± 1012.33	5239.17 ± 901.09
Diagnostic right heart catheterization, mean ± SD						
mPAP, mmHg	42.8 ± 14.0	43.9 ± 15.5	52.8 ± 19.7	38.4 ± 10.7	43.4 ± 16.6	45.2 ± 11.7
PCWP, mmHg	10.23 ± 4.7	9.6 ± 3.8	9.4 ± 2.7	9.8 ± 3.5	8.9 ± 3.9	10.3 ± 4.81
PVR, Woods units	8.1 ± 4.45	8.3 ± 4.7	9.1 ± 4.9	7.6 ± 3.4	6.9 ± 4.5	8.8 ± 5.3
NYHA functional class, No. (%)						
I	30 (19.4)	8 (17.4)	3 (30.00)	12 (22.65)	1 (14.29)	6 (18.75)
II	62 (40.2)	20 (43.5)	4 (40.00)	19 (35.85)	7 (50.00)	12 (37.50)
III	52 (33.8)	16 (34.8)	3 (30.00)	15 (28.30)	5 (35.71)	13 (40.62)
IV	10 (6.5)	2 (4.3)	0 (0)	7 (13.20)	0 (0)	1 (3.13)

Case 126, Row 150.
CTD: connective tissue diseases: BMI: body mass index; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; NYHA: New York Heart Association.

Table 2. Comorbid conditions of PAH patients in New Mexico, 2016.

Comorbid conditions	All patients	IPAH	CHD	CTD	Portal HTN	Drugs/toxins
No.	154	46	10	53	13	32
Systemic sclerosis—limited	22 (14.2)	0	0	22 (42.5)	0	0
Systemic sclerosis—diffuse	7 (4.5)	0	0	7 (13.2)	0	0
Mixed CTD	11 (7.1)	0	0	11 (20.7)	0	0
Other CTDs	13 (8.4)	0	0	8 (24.5)	0	0
Obese (BMI ≥ 30 mg/kg^2)	56 (36.4)	17 (37.0)	1 (10)	17 (32.1)	3 (23.1)	18 (56.3)
Obstructive sleep apnea	36 (23.4)	13 (28.2)	1 (10)	8 (15.3)	2 (15.3)	12 (37.5)
Drug exposure	38 (24.6)	0	2 (20.0)	2 (3.7)	2 (15.3)	32 (100)

CTD: connective tissue diseases; BMI: body mass index.

Asians ($n = 1$) were combined to correspond with the previously published racial/ethnic group: "other."[8] The percentage of patients designated as "other" trended greater than in the REVEAL registry ($p < .05$) but the significance did not survive Bonferroni correction.

Analysis of PAH etiologies identified CTDs as the most common PAH-associated condition, affecting 34.4% of the cohort (Table 1). This was most commonly associated with limited systemic sclerosis (Table 2). IPAH was the next most common etiology in our cohort, followed by exposure to
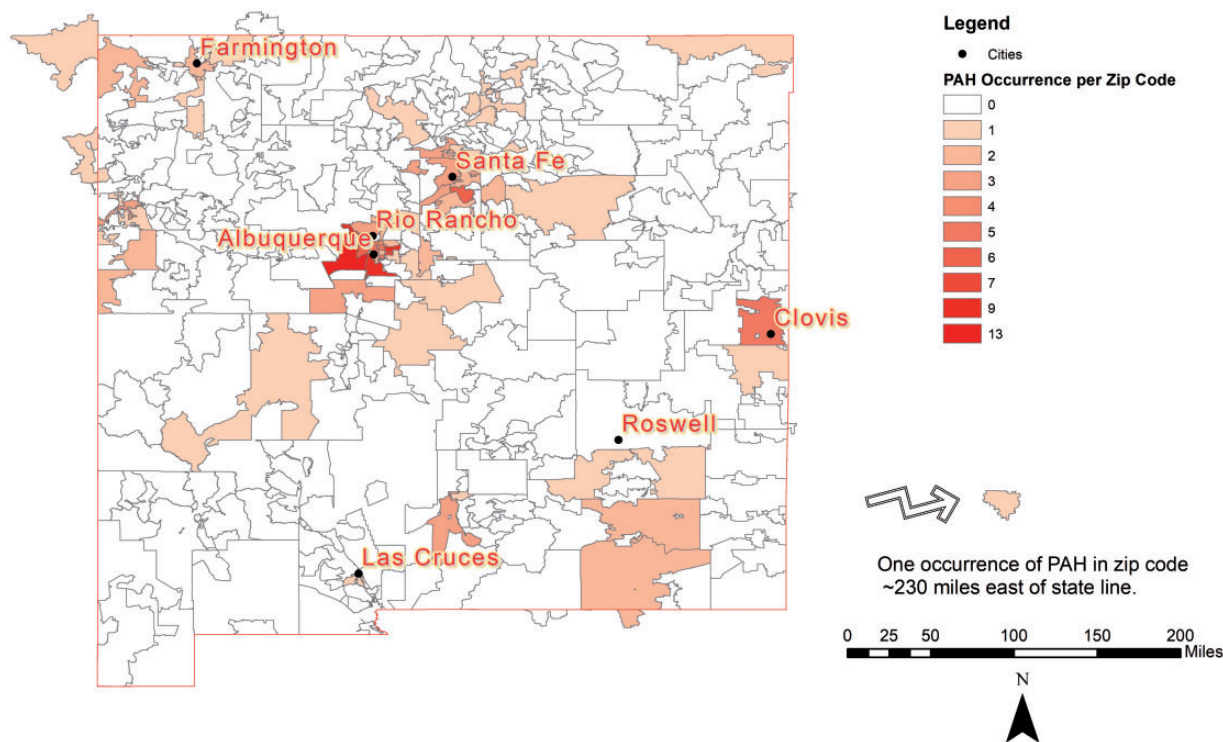
Fig. 2. Geographic distribution residences of PAH patients seen at the study sites PAH specialty clinic during 2016. Although distribution in general clustered around population centers, few cases were seen in the vicinity of Las Cruces, the state's second largest city, which contains ZIP codes with elevation < 4000 ft above sea level (see Fig. 3).
PAH: pulmonary arterial hypertension.

drugs and toxins, which accounted for 29.6% of all patients. Most had been exposed to drugs/toxins categorized as definite causes of PAH ($n = 26$, 16.8%), most commonly amphetamines and methamphetamines ($n = 22$). Fewer patients had documented drug exposures categorized as possible ($n = 6$, 3.8%). Active drug use was less prevalent than drug exposure and was confined to six patients (3.5%) documented to be currently using amphetamines or methamphetamines. In an additional six patients with significant drug exposures, PAH was attributed to an alternative etiology (Table 2). HIV infection was uncommon among this cohort, affecting only two patients (1.2%) and was not classified as causal based on the hierarchy of etiologies described above. The distribution of PAH etiologies among this cohort significantly differed ($p < 0.001$) from the distribution of etiologies previously described in the REVEAL registry.[8] Analysis of standardized residuals from the contingency tables indicated that in our cohort, PAH related to drug/toxins was significantly more common than seen in the REVEAL registry, while idiopathic PAH was significantly less common (both p values < 0.001). Although the frequency of CTD-associated PAH trended higher than in the REVEAL study, this difference did not reach statistical significance ($p = 0.057$).

The total population within ZIP Codes in which one or more PAH cases occurred (New Mexico plus two adjacent ZIP Codes in Arizona and one in Texas) was 1,516,715. An additional 701,059 individuals lived within New Mexico in ZIP Codes without cases of PAH, yielding a total population of 2,217,774 (Fig. 2). During this time, approximately 74.8% of the New Mexico population was 18 years or older, yielding an estimated adult population of 1,658,895. This population was used as the denominator in order to best mirror the REVEAL registry (which used the total adult US population as denominator).[5,6] Using this denominator, our registry demonstrated a prevalence of 93 cases per million, significantly greater than the REVEAL registry, odds ratio = 7.5 (95% CI: 6.4–8.8), ($p < 0.001$). Over the same time-period, 24 patients (Table 3) were newly diagnosed with PAH via right heart catheterization yielding an incidence of 14 cases per million, also significantly greater than observed in the REVEAL registry, odds ratio = 6.3 (95% CI: 4.2–9.5), ($p < 0.001$).

Significant differences existed between this study cohort's hemodynamics and the REVEAL data. The mPAP and mean PVR were both lower in the current cohort than in the REVEAL registry ($p < 0.001$). The distribution of functional classes also differed from the REVEAL registry ($p < 0.001$), the largest group of patients characterized as functional class II, rather than functional class III as in the REVEAL registry. When PAH severity in our cohort were stratified by mPAP, the aggregate of the top two quartiles manifested a mean mPAP of 52.5 ± 11.4 mmHg and a mean PVR of 10.5 ± 4.5 Woods units. These hemodynamics

did not differ significantly from the REVEAL registry (Table 3). When our PAH cohort is constrained to only those patients in these two top quartiles, prevalence of PAH in our population remains significantly higher than that in the REVEAL registry, odds ratio 3.8 (95% CI: 3.0–4.6), ($p < 0.001$).

Baseline characteristics and hemodynamics for incident cases are more similar to newly diagnosed PAH in the REVEAL registry and are detailed in Table 4. mPAPs and PVR in this group did not differ significantly from that in newly diagnosed patients in the REVEAL registry (PVR was unavailable for two cohort incident patients). Neither did the distribution of New York Heart Association functional classes differ significantly from REVEAL incident cases.

Review of the distribution of PAH cases with respect to altitude demonstrated 152 cases of PAH from ZIP Codes with mean altitudes greater than 4000 ft (Figs. 2 and 3), odds ratio $= 26.6$ (95% CI: 8.5–83.5), ($p < 0.001$). Only 4 of these 152 patients resided at very high altitude, above 2500 m. Of the 574,052 adult individuals residing below 4000 ft, however, over 60% would have shorter driving times to alternative PAH centers (Fig. 4). The observed prevalence of PAH for the 515,715 adults residing nearer other centers was much lower than the prevalence among adults nearest the study center, odds ratio 0.28 (95% CI: 0.46–0.17), ($p < 0.01$). The population nearer other centers accounted for only 17 of the 154 PAH patients. Fourteen of these 17 PAH patients with shorter travel times to other centers, however, resided above 4000 ft.

Table 3. Patients by mean pulmonary artery pressure (mPAP) Quartiles ($n = 154$).

Quartile	Number	Age	Mean PAP	PVR	% NYHA class 3/4
First	38	61.9 ± 17.1	28 ± 2.1	4.8 ± 1.8	25.8
Second	39	64 ± 15.7	35.5 ± 2.4	6.4 ± 3.1	38.4
Third	38	55.5 ± 17.7	45.2 ± 3.3	8.5 ± 3.2	39.5
Fourth	39	51.9 ± 11.6	62.3 ± 10.2	12.6 ± 4.6	53.9

PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance.

Table 4. Baseline characteristics and hemodynamics of newly diagnosed patients meeting Group I criteria.

Characteristics	All patients	IPAH	CHD	CTD	Portal HTN	Drugs/toxins
Patients, No. (%)	24 (100)	5 (20.83)	1 (4.17)	7 (29.16)	2 (8.33)	9 (37.50)
Age						
Mean ± SD	60.08 ± 13.21	71.6 ± 8.44	58 ± 0	63.71 ± 14.43	55.50 ± 3.54	51.33 ± 11.75
≤64, No. (%)	14 (56.00)	1 (20.00)	1 (50.00)	2 (28.57)	2 (100)	8 (88.89)
65–74, No. (%)	7 (29.16)	2 (40.00)	0 (0)	4 (57.14)	0 (0)	1 (11.11)
≥75, No. (%)	3 (12.00)	2 (40.00)	0 (0)	1 (14.29)	0 (0)	0 (0)
Gender						
Female	15 (64.00)	2 (12.50)	1 (100)	7 (100.00)	1 (50.00)	4 (44.44)
Male	9 (36.00)	3 (33.33)	0 (0)	0 (0)	1 (50.00)	5 (55.56)
Race and ethnicity						
White	14 (48.33)	5 (100.00)	0 (0)	3 (14.29)	1 (50.00)	5 (44.44)
Hispanic	8 (33.33)	0 (0)	1 (50.00)	4 (42.86)	1 (50.00)	2 (22.22)
Native American	1 (4.17)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11.11)
Black	1 (4.17)	0 (0)	0 (0)	0 (42.86)	0 (0)	1 (22.22)
BMI						
Mean ± SD	26.34 ± 4.03	24.80 ± 2.65	21.4 ± 0	26.34 ± 4.82	27.65 ± 0.35	27.69 ± 4.04
Diagnostic right heart catheterization, mean ± SD						
mPAP, mmHg	45.16 ± 13.18	51.00 ± 14.51	42 ± 0	33.71 ± 7.54	61.00 ± 12.73	49.11 ± 10.68
PCWP, mmHg	9.76 ± 3.46	9.00 ± 2.35	9 ± 0	8.42 ± 3.10	9.5 ± 3.54	10.67 ± 4.06
PVR, Woods units	9.88 ± 3.97	9.23 ± 2.74	13.7 ± 0	8.19 ± 3.47	9.46 ± 7.41	11.76 ± 4.14
NYHA functional class, No. (%)						
I	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
II	9 (40.00)	3 (60.00)	0 (0)	3 (42.86)	1 (50.00)	2 (22.22)
III	13 (52.00)	2 (40.00)	1 (100.00)	3 (42.86)	1 (50.00)	6 (66.67)
IV	2 (8.00)	0 (0)	0 (0)	1 (14.29)	0 (0)	1 (11.11)

CTD: connective tissue diseases; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; NYHA: New York Heart Association.

Discussion

The disease burden of PAH presented in this southwestern US population is much higher than previously reported and suggests that major regional differences may exist with the respect to PAH epidemiology. The data may ultimately yield insights into the interplay between ethnicity, age, PAH etiology, and other covariables, such as altitude. Although this study's external validity is limited as patients were drawn from a single clinic site, increasing portions of the US population are likely to share the minority majority demographic described in this population.[16]

The racial and ethnic makeup of the current cohort differs from REVEAL with the respect to Hispanic and Native American patients, the latter group previously absent from any prior PAH registry. Hispanic patients were underrepresented in the REVEAL registry, where they constitute only 8.9% of the patients despite an expected proportion of 11.5%.[7] The percentage of Hispanic PAH patients reported here is much higher (36%). This percentage, however, remains less than the percentage of Hispanic individuals in the at risk population. The smaller percentage of Native American PAH patients in our cohort (10%) closely reflects the percentage of Native Americans in the study population as whole (9%). Neither group demonstrated prevalence greater than among whites, indicating that neither Hispanic nor Native American populations specifically contributed to the overall increased prevalence of PAH in our cohort.

The prevalence and incidence of PAH in our cohort is markedly higher than the REVEAL or other previously reported registries.[2,19] At least a portion of this disparity likely represents underestimate of PAH prevalence and incidence in the REVEAL registry, which did not capture patients with undiagnosed PAH, patients not seen at PAH centers and patients seen at PAH centers not participating in REVEAL. REVEAL study investigators are forthright about these and other limitations.[20]

The increased PAH prevalence and incidence in our cohort is not attributable to broadening of the hemodynamic inclusion criteria, the increases observed despite the use of a more stringent upper limit for PCWPs (15 mmHg) than currently proposed by some investigators.[20] On average, however, patients had less severe hemodynamic impairment than patients in the REVEAL registry, particularly those with CTD-related PAH which comprised 34% of our cohort. Patients with CTD related PAH, in general, respond well to drug therapy and demonstrate long-term survival which can augment prevalence.[21] Other patients with mild PAH from other etiologies might also survive longer and have a similar impact. The older age of our patients in the lowest two quartiles of mPAP could reflect such prolonged survival in patients with mild hemodynamic impairment (Table 2). PAH prevalence in our cohort, however, remains high (approximately 46 per million adults), even if constrained to those patients whose hemodynamic abnormalities are more severe, comparable to patients in the REVEAL registry.

The high rate of drug exposures in our population could contribute to both PAH prevalence and incidence in our
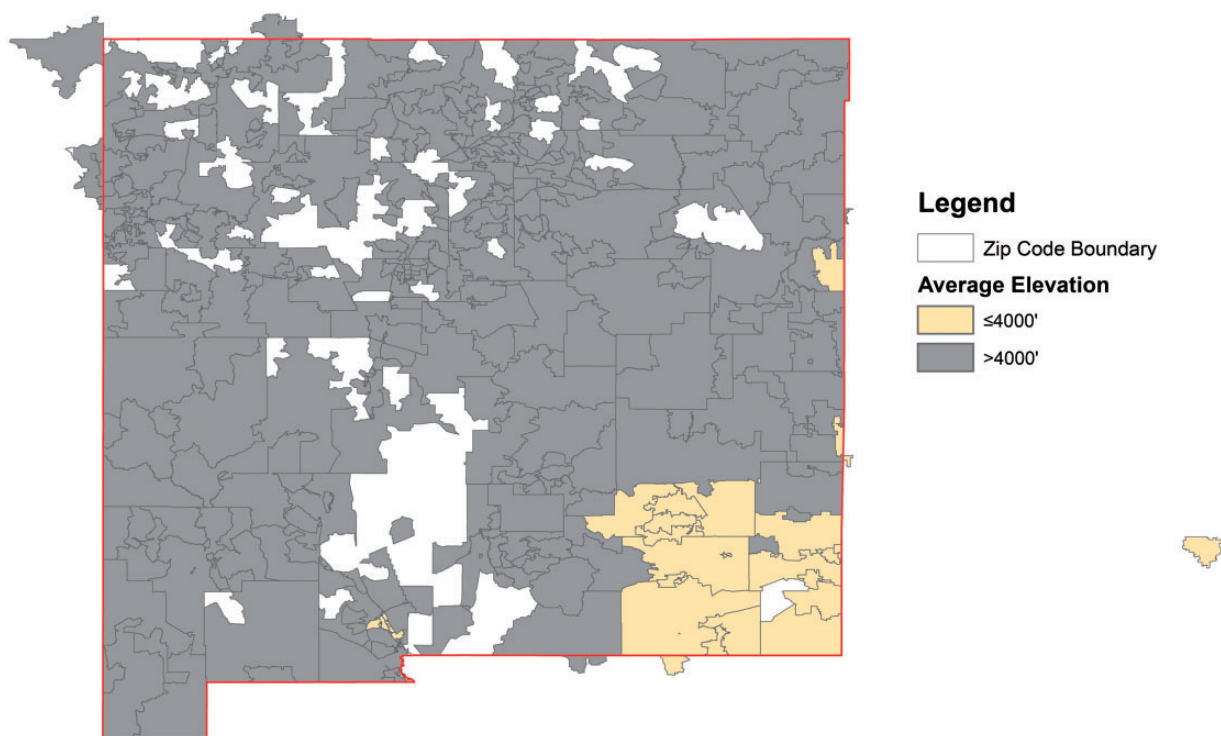

Fig. 3. Map demonstrating a binary distribution of ZIP codes either ≤ 4000 ft or > 4000 ft in elevation. Areas without ZIP codes (white spaces), generally represent public lands such as wilderness areas or national monuments.
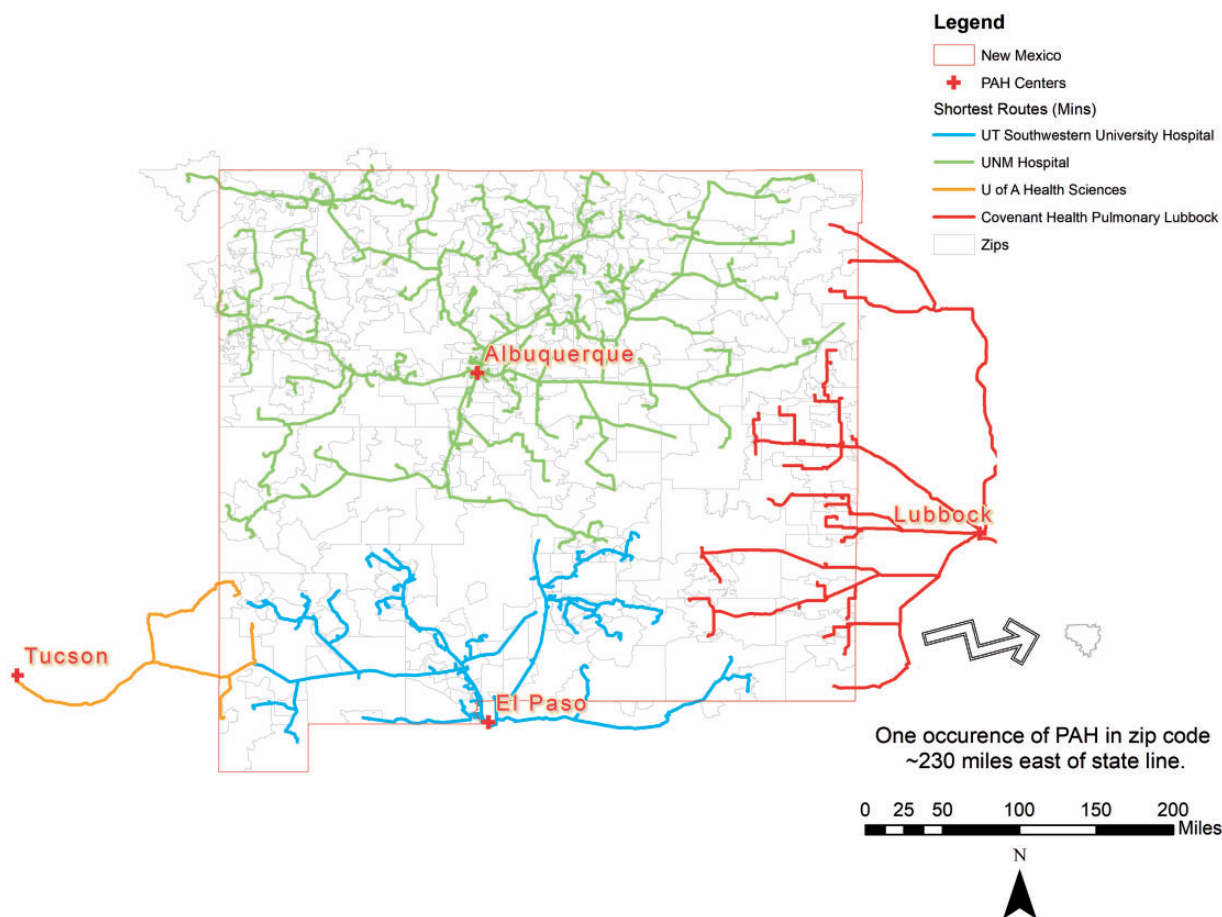
Fig. 4. Map linking driving distances from individual ZIP Codes to the closest PAH referral center. Colored coded lines attach ZIP Codes to PAH centers with the shortest travel times based on the ArcGIS Online service, which determines a route along road networks according to the cost in travel time between origins (population centers) and destinations (PAH treatment facilities) based on average speed values calculated from the historical traffic data. This distribution also approximated the allocation of patients to Health Referral Regions determined by CMS. PAH: pulmonary arterial hypertension.

cohort, and was driven largely by amphetamine and methamphetamine use. Unfortunately, exposure to these drugs among high school students in our state tracks 50% above the national average.[12] This is of particular concern given recent attention on the long-term effects of childhood insults to the pulmonary vasculature and the development of PAH.[22]

Elevation was considered as a possible contributing factor for the increased burden of disease. The existing PH-related literature has focused exposure to high altitude environments through recreation and on Group 3 PH occurring in individuals residing long-term at very high altitudes, such as in the South American Altiplano.[23–25] In individuals residing above 2500 m, rates of PH range from 5 to 23%.[26,27] Previous research has not evaluated potential effect of altitude on the large populations chronically exposed to less extreme altitudes. In general, pulmonary artery pressures in individuals living below 2500 m falls within normal limits.[28] Cardiovascular changes, however, are observed at these more moderate elevations.

Maximal oxygen consumption during exercise falls linearly above 300 m and statistically significant increases in PVR have been shown in healthy individuals acutely brought to 2250 m (7382 ft).[29,30] Moreover, growing numbers of genetic variations affecting the hypoxia-inducible factor pathway are being recognized, some causing increased sensitivity to hypoxic pulmonary vasoconstriction (HPV).[31–33] It is conceivable that the combination of moderate altitude with genetic predisposition to HPV could contribute to the development of PAH in susceptible individuals.

The association of altitude with PAH in our population is an observation that warrants further study. Although it is notable that very few cases of PAH from this cohort resided in ZIP Codes at < 4000 ft elevation, the role of elevation in the genesis of PAH in this cohort remains speculative. Whether moderate altitude could have chronic effects on the pulmonary vasculature or, alternatively, provoke symptoms in patients with less severe, otherwise indolent and undetected PAH is unknown. Based on proximity to health care, at least some of the population in these lower

altitude ZIP Codes were likely referred to medical centers outside of the University of New Mexico catchment, depressing the apparent prevalence of PAH in those lower-altitude ZIP Codes. Almost all cases of PAH occurring in proximity to other PAH centers, however, occurred in individuals residing above 4000 ft, which argues that referral patterns alone are unlikely to account for the apparent impact of moderate altitude on PAH prevalence on our cohort.

Conclusions

This study was restricted to a single site during a single year and describes a cohort of patients with a much higher prevalence and incidence of PAH than previously reported. PAH is described in previously under-reported race/ethnicities, Hispanics and Native Americans, but neither group is likely to account for the observed increased prevalence in this population. Higher rates of drug exposure and a trend toward increased prevalence of CTDs could play a role.

Finally, our data are insufficient to draw definitive conclusions about the effects of moderate altitude on PAH burden. Other PAH centers located at moderate altitude, some of which participated in REVEAL or are participating in ongoing registries, could provide data for a more powerful GIS analysis.[34] Similarly, GIS could play in an important role in PAH research as the wider scope of pulmonary vascular disease and the contribution of environmental stimuli to its genesis becomes better appreciated.[35]

ORCID iD

Loren Ketai https://orcid.org/0000-0001-7833-8667

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