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ORIGINAL ARTICLE

Pulmonary Hypertension in Central Australia: A Community-Based Cohort Study

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Background The burden of pulmonary hypertension (PHT) in Central Australia has not been previously studied. Our aim is to characterise the prevalence, clinical classification, and long-term survival of individuals with PHT in Central Australia.

Methods A community-based cohort study of all individuals diagnosed with PHT in Central Australia between 2005 and 2016 was undertaken. We estimated PHT prevalence using population data, describe clinical PHT classification, and characterised long-term survival using Kaplan-Meier approaches.

Results A total of 183 patients were identified (mean age 52 ± 16 years, 63% female). Of these individuals, 149 (81.4%) were of Aboriginal and Torres Strait Islander (ATSI) descent. The prevalence per 100,000 of any PHT was significantly higher In ATSI (723 [95% CI 608–839] compared to non-ATSI individuals (126 [95% CI 84–168], $p < 0.001$). Furthermore, ATSI individuals were diagnosed at younger ages compared to non-ATSI individuals (49 ± 15 vs 64 ± 16 years, $p < 0.001$). Median estimated pulmonary artery systolic pressure (ePASP) was higher in patients with pulmonary arterial hypertension (PAH) compared to other causes (62 [IQR 54–69] vs 50 [IQR 44–58] mmHg, $p < 0.01$). The median survival rate from

Abbreviations: PHT, Pulmonary hypertension; ATSI, Aboriginal and Torres Strait Islanders; CVD, Cardiovascular disease; RHC, Right heart catheterisation; PAP, Pulmonary artery pressure; ePASP, estimated Pulmonary Artery Systolic Pressure; TRV, Tricuspid regurgitant velocity; RVSP, Right ventricular systolic pressure; PAH, Pulmonary arterial hypertension; PAPm, Mean pulmonary artery pressure; PLHD, Pulmonary hypertension due to left heart disease; RPHT, Respiratory-associated pulmonary hypertension; CTEPH, Chronic thromboembolic pulmonary hypertension; UPHT, Pulmonary hypertension of unknown cause

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diagnosis was 9 years (IQR 7.2–13.2). Age and ePASP were significant predictors of mortality (HR 1.05 [95% CI 1.02–1.07] and HR 1.56 [95% 1.00–2.42] respectively).

Conclusions In this community based study, we found a high burden of PHT in Central Australia. The prevalence of PHT is greater in ATSI individuals and is diagnosed at younger ages compared to non-ATSI individuals. Together with other cardiovascular diseases, PHT may be in-part contributing to the gap in life expectancy between ATSI and non-ATSI individuals.

Keywords Pulmonary hypertension • Echocardiography • Indigenous Health

Introduction

Aboriginal and Torres Strait Islander (ATSI) people continue to experience a greater burden of ill health than non-Indigenous Australians, facing greater mortality, morbidity, and reduced quality of life [1]. It is well established that ATSI individuals have a high prevalence of cardio metabolic conditions such as hypertension, diabetes, heart failure, and atrial fibrillation, furthermore, cardiovascular disease (CVD) is the major cause of premature death experienced by ATSI individuals [2,3]. However, the burden of less common CVD conditions such as pulmonary hypertension [PHT] remains yet to be characterised.

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure (PAPm) ≥25 mmHg at rest as assessed by right heart catheterisation (RHC) [4–6]. Although RHC remains the gold-standard investigation for confirming the diagnosis of PHT, echocardiography continues to be the most important non-invasive screening tool to assess the possibility of PHT. Furthermore, echocardiography can also be helpful in detecting the cause of suspected or confirmed PHT. PHT is characterised by progressive dyspnoea, functional limitation and if untreated, right ventricular failure and death [4–8]. Given the rarity of the disease, most data on PHT is obtained from registries, and these often focus on pulmonary arterial hypertension (PAH) [9,10]. To the best of our knowledge, there are no previous studies on the burden of PHT and its classification in ATSI individuals, and community-based data on the prevalence and subtypes of pulmonary hypertension is scant, despite the morbidity and mortality from this malignant condition [11,12].

In the present study, we thus sought to characterise the prevalence and burden of each subclass of pulmonary hypertension in Central Australia, a region with high proportion (44%) of ATSI individuals [13].

Methods and Material

Population, Study Setting and Cohort

In the very heart of the Australia is the Central Australia Region, covering some 830,000 square kilometres. Central Australia shares borders with South Australia, Queensland and Western Australia. The Central Australia Region has a population of 46,315, of which 44% identify as ATSI (2007), which is the largest percentage of Indigenous Australians in any region of Australia. Approximately 28,000 live in the largest centre of Alice Springs. The remainder of the population reside in the 47 remote communities and out-stations [13]. Although the ATSI population is dynamic, travelling and often without a single primary residence, all cardiovascular care is coordinated from Alice Springs Hospital. As a result of this geographic isolation and the provision of cardiovascular services by a single provider, community-based epidemiological research is very feasible in Central Australia [14].

We analysed the characteristics and outcomes of individuals diagnosed with PHT in Central Australia between August 2005 and November 2016; in this period there were 19,125 transthoracic echo cardiograms performed on 9,044 patients. An initial cohort were identified via echocardiography and the diagnosis of PHT was made if estimated Pulmonary Artery Systolic Pressure (ePASP) ≥40 mmHg. Patients with an insufficient tricuspid regurgitation preventing ePASP estimation were excluded. Mortality status and time of death was established from the Central Australian Department of Health Database. The study was approved by Central Australian Human Research Ethics Committee.

Echocardiography

Echocardiograms were performed by experienced sonographers using a GE Vivid Q, GE Vivid i (GE Vingmed Ultrasound AS, Horten, Norway), or a Philips EPIQ 7 (Philips, Seattle, WA, USA) cardiac ultrasound machine. Images were stored digitally and sent to the Royal Darwin Hospital where they were reported by senior cardiologists in accordance with American Society of Echocardiography (ASE) guidelines [15]. A local protocol was used to perform a full two dimensional (2D) transthoracic echocardiography and Doppler measurements according to ASE criteria [16]. ePASP was assessed by imaging the peak velocity of the tricuspid regurgitant jet (TRV) of the systolic difference of pressures between the right ventricle and the right atrium and applying the simplified Bernoulli equation right ventricular systolic pressure (RVSP) [17]. To minimise error, a right atrial pressure of 10 mmHg was assumed for all patients. Although there can be some disagreement between echocardiographic estimates of ePASP and invasive measurement at right-side heart catheterisation, these two methods are sufficiently correlated to warrant the use of Doppler to screen for PHT [18,19].

Table 1 **Baseline Characteristics.**

	All (n = 183)	ATSI (n = 149)	Non-ATSI (n = 33)	P-value
Age, y ± SD	52 ± 16	49 ± 15	64 ± 16	<0.001
Female, n (%)	116 (63)	96 (64)	20 (61)	0.69
ePASP, mmHg (IQR)	50 (44-58)	50 (44-58)	48 (43-58)	0.42
Chronic lung disease, n (%)	42 (23)	35 (24)	7 (21)	1.00
Left-sided heart disease and valvular disease, n (%)	128 (70)	106 (71)	22 (67)	0.67
Obstructive sleep apnoea, n (%)	21 (11)	16 (11)	5 (15)	0.55

Abbreviations: y, years; SD, standard deviation; n, number; IQR, interquartile range; ePASP, estimated pulmonary artery systolic pressure; ATSI, Aboriginal and Torres Strait Islanders.

Definition of Pulmonary Hypertension With Sub-Groups and Follow-Up

All patients aged older than 16 with an ePASP >40 mmHg were included. Patients with insufficient tricuspid regurgitation to estimate ePASP were not included. Patients with PHT were separated into three groups: mild PHT (ePASP 40–50 mmHg), moderate PHT (51–60 mmHg) and severe PHT (>60 mmHg). Pulmonary hypertension causality was defined using criteria and subclasses of the most recent American College of Cardiology (ACC) working group classifications; group 1: PAH, group; 2: PHT in association with left heart disease; group 3: PHT in association with hypoxic respiratory disease; group 4: PHT due to chronic thrombotic and/or embolic disease and group 5: miscellaneous [4]. Comprehensive echocardiography and other investigations were used wherever possible to determine the cause of PHT. To identify causes for pulmonary hypertension, investigations (lung function test, computed tomography pulmonary angiogram, ventilation-perfusion scan, and sleep studies) were done in Alice Springs Hospital. Patients requiring and consenting to RHC were sent to Royal Darwin Hospital, Royal Adelaide Hospital or Flinders Medical Centre. Identified cases of PAH were thoroughly investigated to identify the cause of PHT, including lung function tests, sleep studies, high-resolution CT scan, VQ scan, CT pulmonary angiogram and RHC. If the underlying aetiology was not clear from these data, the cause of the PHT was deemed to be 'unknown'. In patients with two or more known causes of PHT, the dominant cause was classified.

Continuous variables are reported as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate, and categorical variables reported as frequency and percentage. Study population characteristics were compared using unpaired Student t tests, Kruskal-Wallis tests with post-hoc Dunn's test, or ANOVA as appropriate. Pulmonary hypertension prevalence was estimated using Central Australian population data from the Australian Bureau of Statistics, and presented as rates per 100,000 persons with 95% confidence intervals (CI). Kaplan Meier and Cox proportional hazard regression methods were employed to study the univariate and multivariate relationship between PHT class, ePASP, other patient characteristics, and mortality. Statistical tests were performed using Stata 14.0 (Stata Corporation) and a two-tailed value of $p < 0.05$ was considered significant.

Results

Patient Demographics

Between August 2005 and November 2016, we identified 183 patients with PHT. Baseline characteristics of the study population are outlined in Table 1. The mean age at diagnosis of all PHT classes was 52 ± 16 years. The majority of our cohort was female (63%) and of Aboriginal and Torres Strait Islander (ATSI) background (81%). ATSI individuals were significantly younger than non-ATSI individuals (49 ± 15 vs 64 ± 16 years, $p < 0.001$).

Prevalence

The estimated overall prevalence of any PHT in Central Australia was 385 (95% CI 329–440) per 100,000. The prevalence rate per 100,000 of any PHT was significantly higher in ATSI (723 [95% CI 608–839] compared to non-ATSI individuals (126 [95% CI 84–168], $p < 0.001$); Figure 1). The majority

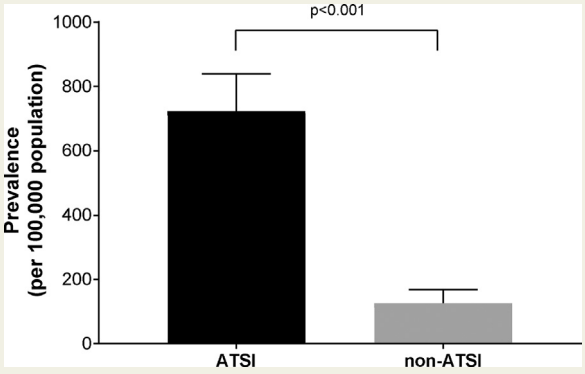

Figure 1 Graph showing the race-specific prevalence of pulmonary hypertension from all causes in Indigenous and non-Indigenous Central Australian cohort.

of ATSI individuals were diagnosed under 60 years of age compared to a minority of non-ATSI individuals (73% vs 35%, $p < 0.001$).

The estimated prevalence rate per 100,000 of Class I patients with PAH was 27 (95% CI 12–42), the majority (more than 90%) of whom were prescribed disease-specific treatment. The estimated prevalence of Class II, III and IV patients was 244 (95% CI 199–288), 63 (95% CI 40–96), and two (95% CI 0-6) per 100,000 respectively. There were no cases of PHT unclear multifactorial mechanisms. The prevalence of PHT patients without an identified cause was 63 (95% CI 19–53) per 100,000 population.

PHT Classification

Study population characteristics according to PHT classification are shown in Table 2. Of the 183 individuals with elevated ePASP, 116 (63%) patients had PHT due to left heart disease (PLHD), 30 (16%) had PHT due to lung disease (RPHT), 13 (7%) had pulmonary arterial hypertension (PAH), and one (0.54%) patient had chronic thromboembolic pulmonary hypertension (CTEPH). Twenty-three (23) (12%) patients had PHT of unknown cause (UPHT). As mentioned above, there were no cases of PHT with unclear multifactorial mechanisms. No significant age differences were observed between groups (Table 2).

Statistically significant differences between ePASP were seen between groups (Figure 2). The median ePASP was significantly higher in patients with PAH compared to PLHD ($p = 0.002$), RPHT ($p = 0.03$), and UPHT ($p = 0.006$). There were no significant differences in ePASP according to gender or ATSI status (p = NS for both).

Survival

The median overall survival rate of patients with PHT in our study population was 9 years (IQR 7.2–13.2). We observed a statistically significant difference in survival according to PHT classification ($p = 0.002$; Figure 3). However, after accounting for other potential confounders in multivariate models, this relationship was no longer statistically significant (Table 3). There was a statistically significant relationship between increasing ePASP and mortality (Figure 4) that remained significant in multivariable models, with a 60% increased hazard of death for each increase in ePASP category (Table 3). As expected, there was also a statistically significant relationship between increasing age and mortality, with a 5% increased hazard of death for each year (Table 3). Gender and ATSI status were not significant predictors of mortality in univariate or multivariate models.

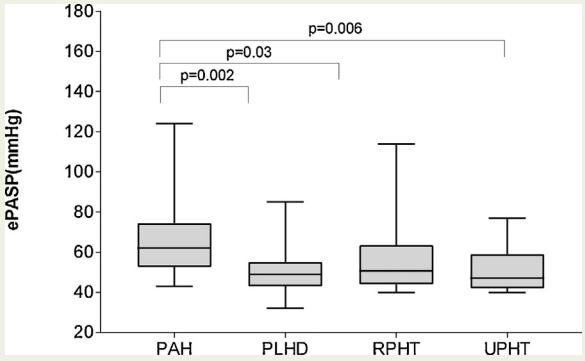

Figure 2 ePASP distribution in different classes of PHT $p < 0.05$.
Abbreviations: PAH, pulmonary arterial hypertension; PLHD, pulmonary hypertension secondary to left heart disease; RPHT, respiratory-associated pulmonary hypertension; UPHT, pulmonary hypertension of unknown cause.

Discussion

In this community-based cohort study, we characterised the prevalence, clinical classification, and long-term survival of PHT in Central Australia. Notably, our cohort demonstrated PHT at strikingly young ages. Furthermore, there is a high burden of this malignant disease in Central Australia amongst the ATSI community, comprising 81% of diagnosed individuals despite the ATSI community representing only 40% of the Central Australian population.

There are few community-based studies that have previously characterised the prevalence of PHT in Australia. In one report from Armadale in Western Australia, investigators describe an overall prevalence of 326 per 100,000 [11]. In comparison, the overall prevalence of PHT observed in the present study was significantly greater, and seemed to reflect increases in all PHT subgroups. Furthermore, the average age of our cohort was 52 years, suggesting that PHT is diagnosed almost two decades earlier in Central Australia compared to other community cohorts [11,14]. ATSI individuals were significantly younger

Table 2 Pulmonary Hypertension Classification.

	All PHT (n = 183)	PAH (n = 13)	PLHD (n = 116)	RPHT (n = 30)	CTEPH (n = 1)	UPHT (n = 23)
Age, y ± SD	52 ± 16	46 ± 15	50 ± 16	58 ± 17	51	55 ± 14
Female, n (%)	116 (63%)	12 (92%)	72 (62%)	15 (50%)	0	17 (62%)
ePASP mmHg (IQR)	50 (44-58)	62 (54-69)	49 (43-55)	51 (44-63)	64	47 (42-59)

Abbreviations: PHT, pulmonary hypertension; PAH, pulmonary arterial hypertension; PLHD, pulmonary hypertension due to left heart disease; RPHT, respiratory-associated pulmonary hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; UPHT, pulmonary hypertension of unknown cause.

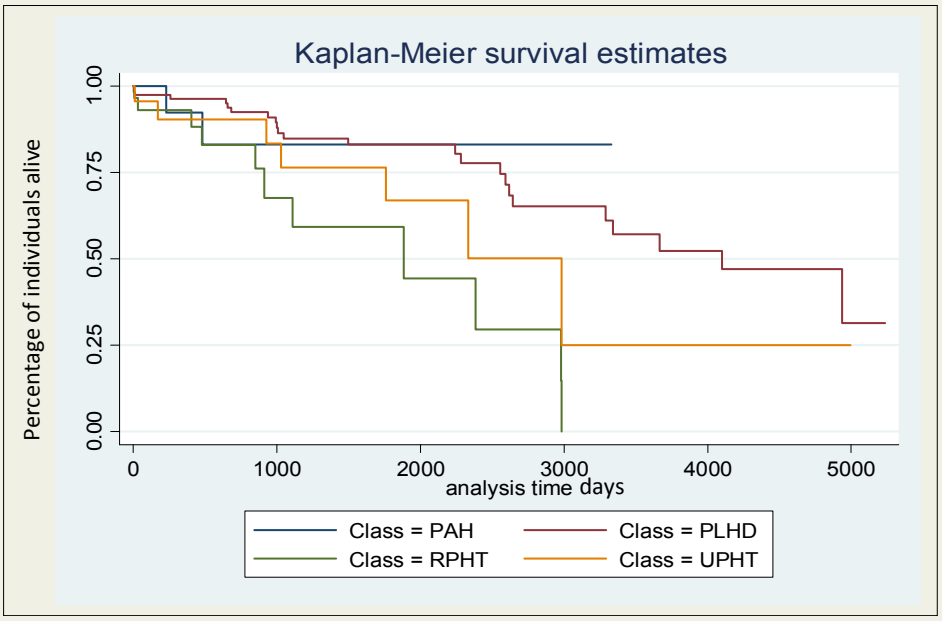

Figure 3 Kaplan-Meier Survival curve according to PHT subclass.
Abbreviations: PAH, pulmonary arterial hypertension; PLHD, pulmonary hypertension secondary to left heart disease; RPHT, respiratory-associated pulmonary hypertension; UPHT, pulmonary hypertension of unknown cause.
p = 0.002 for difference between PHT subclasses.

than non-ATSI individuals. While a similarly early onset and high prevalence of other cardiovascular diseases such as high blood pressure, coronary artery disease, and heart failure have been reported in amongst ATSI populations, we are not aware that PHT has previously been studied to the best of our knowledge [1,20–22]

Class I PAH is rare and previous prevalence estimates have varied throughout the literature. Contemporary reports have ranged from as low as 15 cases per million in a French registry [9], to 26 cases per million in a Scottish registry [23], and to as high as 151 per million in a community study in Australia [11]. Earlier data have described even lower numbers; for example, in 1991 the incidence of 'primary' PAH was estimated at one to two cases per million in the USA [24].

Table 3 Multivariate Predictors of Survival.

	HR	95% CI	P-value
Age	1.04	1.02 - 1.07	0.001
Male	1.38	0.73 - 2.60	0.32
ATSI	1.69	0.71 - 4.-04	0.24
ePASP	1.60	1.05 - 2.45	0.03
PLHD	1.10	0.26 - 4.70	0.90
RPHT	3.358	0.72 - 15.68	0.13
UPHT	1.96	0.40 - 9.57	0.83

Abbreviations: ATSI, Aboriginal and Torres Strait Islanders; ePASP, estimated Pulmonary Artery Systolic Pressure; PLHD, pulmonary hypertension due to left heart disease; RPHT, respiratory-associated pulmonary hypertension; UPHT, pulmonary hypertension of unknown cause.

In the present study, we found a PAH prevalence of 27 per 100,000 (equivalent to 270 per million) a figure that is significantly higher than that described in previous reports. Notably, 85% of PAH cases were in ATSI individuals. The significantly higher prevalence of PAH than in previous reports possibly reflects the community-based nature of this study, the higher numbers of ATSI individuals, and possibly increased diagnosis with echocardiography. Although the greater burden of other cardiovascular diseases can be readily explained by prevalent risk factors, the reasons underlying a greater prevalence of PAH in ATSI individuals is not known.

Pulmonary hypertension (PHT) associated with left heart disease has been hypothesised to be the result of the combination of passive effect of elevated left ventricular end-diastolic pressure backward on the pulmonary venous circulation, and an active vasoreactive process of vasoconstriction and pulmonary arterial remodelling. In the specific case of mitral valve disease, high PASP is driven by an elevation of left atrial pressure, which in turn, leads to pulmonary venous hypertension, and subsequently, pulmonary arterial hypertension. It has been previously shown that PASP is a strong and independent predictor of all-cause death and CV death, independently of other known predictors, including diastolic function measures and brain natriuretic peptide [14]. Not surprisingly, we found a high prevalence of PHT secondary to left heart disease in our cohort (244 per 100,000). These individuals were relatively young (mean age 55 years) and this burden is most likely driven by high prevalence of left heart disease in young Indigenous Australians [1].

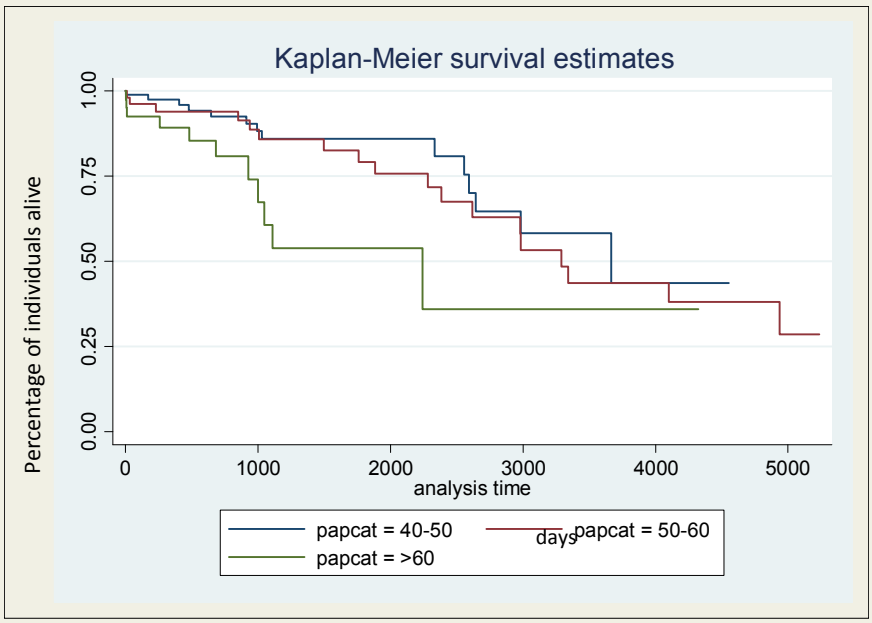

Figure 4 Kaplan-Meier Survival according to severity estimated pulmonary artery systolic pressure for mild, moderate and severe pulmonary hypertension for all causes of pulmonary hypertension during the period of follow-up. $p < 0.001$ for difference between reference range mild (41–50 mmHg) compared with moderate or severe. Abbreviation: ePASP, estimated pulmonary artery systolic pressure.

The prevalence of class III PHT in our study was 63 per 100,000. Pulmonary hypertension secondary to hypoxic lung disease is another important cause of PHT in our population given the high rate of smoking. The rates of smoking is up to 50% in Indigenous Australians and is equally prevalent in males and females[1]. In patient populations with chronic obstructive pulmonary disease, PHT affects a high proportion of patients and is a strong indicator of mortality and a stronger predictor of survival than the forced expiratory volume or gas exchange variables [25–27]. In regards to patients with rare lung diseases, in whom any randomised controlled trial is very unlikely to be undertaken in the near future, registries can provide reliable data about the prevalence of PHT in these populations and provide a framework to evaluate whether observational data supports the possibility that PAH-focussed therapy may be of clinical benefit in this population. Indeed, it has been described that individual responses to treatment with PAH-approved drugs may be possible in some patients with rare hypoxic lung diseases [26].

We describe an overall median survival of 9 years in our PHT cohort, and there was a strong association between increasing PASP and mortality. It seemed that this was partially attributable to the higher median survival of patients with Class II left-sided heart disease. Given our young cohort, it is somewhat reassuring that even these patients with often late stage valvular heart disease can be potentially managed for many years. Although some of these patients with significant valvular heart disease are located in remote communities, the outreach cardiology services from Alice Springs hospital cater for these communities at least 6-monthly, and appropriate patients are referred to a tertiary centre for cardiothoracic input. Our Class III median survival rate of 5.1 years is also comparable to other reported cohorts [11,27]. At the time of final data collection, 11 out of the 13 patients who had class I PAH were alive, which is an improvement compared to previously reported mortality data [11,24]

Pulmonary hyptertension in all its forms is a clinical feature of many diseases and with a variety of implications for treatment and prognosis. Our data highlights the need for increased research in all PHT subtypes in Central Australia and ATSI individuals, and beyond the usual focus on PAH. The present data addresses a current gap in our knowledge and provides data across the complete spectrum PHT in Central Australia. We found a high prevalence of all classes of PHT, and in particular Class I and Class II. The cause for high prevalence of PAH in Indigenous Australians is unknown. Confirmation of our data requires further prospective population-based research. Furthermore, this cohort of PAH patients in Central Australia could be the subject of additional study in the future to further investigate the pathophysiology of PAH in ATSI individuals. While we should be cautious in generalising our conclusions beyond Central Australia, we note that the diversity of communities represented and the results observed are therefore likely to be typical of Indigenous communities in other regions.

Limitations

This study should be interpreted in the context of its limitations. This is a retrospective cohort study and data on minimum indicate prevalence is based on the medical records of one hospital. Although a large, prospective

screening study would potentially provide more accurate data, our results are strengthened by the geographic isolation of resident individuals and provision of cardiovascular services by a single provider in Central Australia. Echocardiography is also not the gold standard investigation for estimating PASP and only correlates modestly with RHC. However, RHC is an invasive investigation that is not available in Central Australia and of limited acceptance to some ATSI individuals. Patients with insufficient tricuspid regurgitation (TR) were also excluded from our cohort, although this would have underestimated the prevalence of PHT. Furthermore, some individuals may not have been diagnosed, further underestimating the true prevalence. These possibilities serve to highlight that the actual burden of PHT in Central Australia may be even higher than we have estimated in the present report.

Conclusion

In this community-based study, we found a high prevalence of PHT in Central Australia and particularly in young ATSI individuals. Although the overall burden was significantly higher, the proportion of PAH and other subclasses was comparable to other community based studies. Our data highlights the need for future research to confirm our findings and identify strategies to mitigate this high burden of disease.

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