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Diagnostic delay in pulmonary arterial hypertension: Insights from the Australian and New Zealand pulmonary hypertension registry

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Summary at a Glance

We examined diagnostic delay in a large binational cohort of pulmonary arterial hypertension patients. Mean and median diagnostic intervals were 2.5 ± 4.1 years and 1.2 (IQR: 0.6-2.7) years, respectively. Age, cardiovascular and respiratory comorbidities were associated with longer diagnostic interval. Mortality was increased in patients with greater diagnostic interval.

Abstract

Background and objective

Early diagnosis of PAH is clinically challenging. Patterns of diagnostic delay in Australian and New Zealand PAH populations have not been explored in large-scale studies. We aimed to evaluate the magnitude, risk factors and survival impact of diagnostic delay in Australian and New Zealand PAH patients.

Methods

Cohort study of PAH patients from the Pulmonary Hypertension Society of Australia and New Zealand Registry, diagnosed from 2004-2017. Diagnostic interval was the time from symptom onset to diagnostic right heart catheterisation as recorded in the Registry. Factors associated with diagnostic delay were analysed in a multivariate logistic regression model. Survival rates were compared across patients based on time to diagnosis, using Kaplan Meier method and Cox regression.

Results

2,044 patients were included in analysis. At diagnosis, median age was 58 years (IQR: 43-69), female to male ratio was 2.8:1, and majority of patients were in New York Heart Association Functional Class III-IV (82%). Median diagnostic interval was 1.2 years (IQR: 0.6-2.7). Age, congenital heart disease-associated PAH, obstructive sleep apnoea and peripheral vascular disease were independently associated with diagnostic interval of ≥1 year. No improvement in diagnostic interval was seen during the study period. Longer diagnostic interval was associated with decreased 5-year survival.

Conclusion

PAH patients experience significant diagnostic interval, which has not improved despite increased community awareness. Age, cardiovascular and respiratory comorbidities are significantly associated with longer time to diagnosis. Mortality rates appear higher in patients who experience longer diagnostic interval.

Key Words

Cohort studies, delayed diagnosis, mortality, pulmonary hypertension, survival analysis.

Short Title

Diagnostic delay in PAH.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease affecting the small arteries of the pulmonary circulation. Without therapy, PAH is associated with a continual increase in pulmonary vascular resistance, resulting in right heart failure and death. Rapid advances in PAH treatment over the last few decades have given rise to a multitude of available therapies.[1-5] While survival has improved with the development of targeted therapy, overall survival rates remain unsatisfactory with 3-year survival estimates ranging from 58-77%.[6-11]

Timely diagnosis of PAH can be challenging due to the non-specific nature of early symptoms, which include exertional dyspnoea and lethargy.[12-14] Patients diagnosed in later stages may have more severe, irreversible pathological changes and right ventricular failure, leading to poorer prognosis.[2,3,5,10,15,16] International registry studies have consistently found a significant delay between symptom onset and definitive diagnosis in PAH patients.[13,17-22] Moreover, time to diagnosis has not improved over the past few decades. In the USA-based REVEAL registry, median time to diagnosis was 1.3 years, with 21% of patients experiencing a delay of over 2 years.[18,23] More recently, a small Australian cohort study on idiopathic PAH (IPAH) patients using specific interview questions found a median diagnostic interval of 3.7 years.[22]

The diagnostic delay associated with PAH is concerning, given the variety of treatments now available to patients. However, existing research provides limited information about the magnitude and predictors of diagnostic delay in Australian and New Zealand. Greater insights into the subject may lead to more timely PAH diagnosis, particularly for patients at highest risk of delayed diagnosis. Our study objective was to determine the time from symptom onset to PAH diagnosis in Australia and New Zealand patients, and identify factors associated with delayed definitive diagnosis. In addition, we aimed to examine the effects of delayed diagnosis on mortality.

METHODS

Study Population

We performed a cohort study on adult and paediatric patients enrolled in the Pulmonary Hypertension Registry of Australia and New Zealand (PHSANZ Binational Registry). The registry contains data on patients diagnosed with PAH from 21 specialist centres across Australia and New Zealand. Data were retrospectively entered from medical records between January 2004 and December 2011, and prospectively collected from December 2011 onwards. All data were entered into a centralised Registry database (Spot On Software) after undergoing final review against source documents. Patients undergoing diagnostic right heart catheterisation (RHC) between January 2004 and December 2017 and classified as PAH in the registry were included in the study (Figure 1). Haemodynamic

criteria for PAH was mean pulmonary artery pressure (mPAP) ≥25 mmHg and pulmonary artery wedge pressure (PAWP) ≤15 mmHg. Diagnostic interval was calculated as the period between symptom onset attributable to PAH and diagnosis by RHC. Estimated date of symptom onset was routinely entered in the registry by the treating physician. Patients were excluded if recorded dates of diagnosis or symptom onset were not clearly documented.

Information in the registry includes patient demographics (PAH subtype, age, gender, race, country and location of residence), medical comorbidities (peripheral vascular disease, diabetes, ischaemic heart disease, essential hypertension, obstructive sleep apnoea, obesity), pulmonary function indices at diagnosis (six minute walk distance (6MWD), diffusing capacity for carbon monoxide (DLCO), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC)), haemodynamic characteristics, and follow-up information (mortality status, mortality date, date of last follow-up).

The PHSANZ Registry protocol was approved by the lead site St Vincent's Hospital (HREC: LNR/11/SVH/178). Permission to use de-identified registry data was sought, and local ethics approval for the research protocol was obtained from participating centres.

Statistical analysis

Continuous variables were reported as medians (± 25th and 75th interquartile range [IQR]) or means (± standard deviation), as appropriate. Haemodynamic and functional variables

were summarised in two subgroups based on diagnostic interval (<1 year, ≥1 year). The cut-off of 1 year was chosen as an easily interpretable value close to the median diagnostic interval, similar to methods used previously.[18] Diagnostic intervals were compared across clinical, demographic and geographic features using Kruskal-Wallis and Mann-Whitney tests.

Potential predictors of diagnostic delay were screened using univariate logistic regression analysis, where the outcome was diagnostic interval ≥1 year. Variables satisfying p≤0.20 were included in adjusted regression analysis and subjected to stepwise model selection.

For survival analysis, patient follow-up was from the date of PAH diagnosis until the last clinical visit or death. Patients undergoing pulmonary transplantation were censored at transplant date. Crude mortality rates were calculated based on stratification into the following diagnostic intervals (≤1 year, 1-2 years, >2 years), by dividing number of deaths by total follow-up time. Mortality differences between groups were described using a Kaplan-Meier survival curve, and analysed with a log-rank test for linear trend. Mortality ratios were also calculated across diagnostic interval using Cox regression, adjusting for age, sex and PAH subtype. To account for nonlinearity, associations were described using multivariate fractional polynomial models.[24]

A p-value of ≤0.05 was deemed significant for all analyses. Data was analysed using Stata version 15 (Stata Corporation, College Station, TX, USA).

RESULTS

Patient Demographics

In total, 2,044 patients were included in the analysis from 3,260 patients in the PHSANZ Binational Registry diagnosed between January 2004 and December 2017 (Figure 1). As of 31 December 2017, 1,201 patients (59%) remained alive and 843 (41%) had died. At diagnosis, the median age was 58 years (IQR: 43-69), female-to-male ratio 2.8:1, and majority of patients were in New York Heart Association Functional Class (NYHA FC) III-IV (82%) (Table 1). The most common PAH subtypes were IPAH (39%), connective tissue disease-associated PAH (CTD-PAH) (36%) and congenital heart disease-associated PAH (CHD-PAH) (11%). Of those with CTD-PAH, 75% had systemic sclerosis-associated PAH (SSc-PAH). The majority (61%) of Australian patients with postcode data lived in major cities of Australia, while 1% lived in remote/very remote Australia. Haemodynamic variables were least severe in CTD-PAH compared to IPAH at diagnosis, while baseline mPAP was highest in CHD-PAH patients.

Diagnostic interval

The median interval from symptom onset to diagnostic RHC was 1.2 years (IQR: 0.6-2.7), while mean diagnostic interval was 2.5 ± 4.1 years. Overall, 42%, 23%, and 35% of patients were diagnosed after <1 year, 1-2 years, and >2 years respectively

(Supplementary Figure S1). Table 2 summarises pulmonary function, haemodynamic variables and functional capacity of patients stratified by diagnostic interval. At diagnosis, patients with a diagnostic interval of ≥1 year had shorter 6MWD (313.4 vs 328.9 m), lower DLCO (49 vs 52% predicted), lower FEV1 (78% vs 82% predicted) and lower FVC (84% vs 89%). However, haemodynamic variables and functional class were similar across diagnostic interval strata.

Table 3 summarises diagnostic interval according to demographic characteristics, PAH aetiology and comorbidities. Diagnostic interval increased in older age groups. In terms of PAH aetiology, patients with CHD-PAH had the longest diagnostic interval (median 1.8 years, IQR: 0.7-4.5) whereas heritable PAH (HPAH) was associated with the shortest interval (median 0.4 years, IQR: 0.2-1.1). There were no significant differences in diagnostic interval across subtypes of CHD-PAH (Supplementary Table S1).

When stratified by the year of diagnosis, there was no improvement in diagnostic interval across the study period. Subpopulations of SSc-PAH and HPAH also demonstrated no improvement in diagnostic interval over time (Supplementary Table S2 and Supplementary Figure S2). Co-morbid obstructive sleep apnoea, ischaemic heart disease, peripheral vascular disease and essential hypertension were associated with longer diagnostic interval in univariate analyses (all $p<0.05$).

Table 4 describes the variables associated with diagnostic delay of ≥1 year in unadjusted and adjusted logistic regression. In the adjusted model, age (OR 1.014, 95% CI: 1.009-1.019), CHD-PAH (OR 2.12, 95% CI: 1.55-2.91), peripheral vascular disease (OR 1.80, 95% CI: 1.16-2.78) and obstructive sleep apnoea (OR 1.50, 95% CI: 1.17-1.93) remained significant variables associated with diagnostic interval ≥1 year.

Survival analysis

In total, there were 10,467 person-years (pys) of follow-up. The overall crude mortality rate was 82.1 deaths/1000 pys. Longer diagnostic interval was associated with decreased 5-year survival (70% ≤1 years, 66% 1-2 years, and 61% >2 years, p<0.001) (Figure 2). Crude mortality rates increased from 73.5 (95% CI: 65.8-82.0)/1000 pys in patients diagnosed in ≤1 year to 95.7 (95% CI: 85.9-106.6)/1000 pys in patients diagnosed in >2 years. After adjustment for age, gender and PAH subtype, a diagnostic delay of 2 years increased mortality rates by 11% (95% CI: 5%-17%), while a delay of 5 years increased mortality by 29% (95% CI: 12%-47%) (Figure 2).

DISCUSSION

This binational study included 2,044 patients and 10,467 pys of follow-up to evaluate diagnostic interval of PAH in Australia and New Zealand. We found a median diagnostic interval of 1.2 years (mean 2.5 years) between symptom onset and RHC. Longer diagnostic interval was found to be associated with poorer long term survival, 6MWD and pulmonary function. Age, CHD-PAH, peripheral vascular disease and obstructive sleep apnoea were independent predictors of longer diagnostic interval. The strengths of this study include the large multi-centre sample, representing the largest Australian and New Zealand study to investigate diagnostic interval in PAH to date.

Our mean diagnostic interval of 2.5 years is consistent with data from USA,[9] Europe[7,17,20] and China,[21] with international mean estimates of diagnostic interval ranging from 2.2 to 3.7 years. A previous Australian study by Strange et al. investigating diagnostic delay in patients with IPAH (diagnosed in 2007-2008) found a mean interval of 47 ± 34 months (median 44; IQR: 21-65) months.[18] Although our study suggests a shorter diagnostic interval compared to Strange et al, firm conclusions cannot be drawn since the methodology of estimating diagnostic interval differed significantly between studies. Our study relied on physician-determined estimation of symptom onset as part of routine clinical assessment, whereas Strange et al. used standardised interview questions with the interviewer blinded to the patient's medical history.

Interestingly, diagnostic interval in our study did not improve from 2004 to 2017. This was a surprising result considering there has been greater general awareness of PAH in the community, and greater emphasis on screening in SSc-PAH and HPAH. While HPAH had the shortest diagnostic interval among PAH subtypes, patients with SSc-PAH had a similar diagnostic interval compared to other CTD-PAH patients. Due to the registry's design, we were unable to determine what proportion of SSc-PAH or HPAH was diagnosed through a screening programme. We suspect very few patients are diagnosed by screening alone, given the low proportion of NYHA FC I patients (1%) in CTD-PAH and HPAH groups. Moreover, many SSc-PAH patients have background interstitial lung disease or musculoskeletal disease, which make assessment of symptoms attributable to PAH difficult to define and hence result in longer apparent diagnostic interval.

Patients with CHD-PAH had significantly longer diagnostic interval compared to other PAH subtypes. A previous study of 360 CHD-PAH patients from Australia and New Zealand found a median interval of 2.2 years (mean 6.5 years) between symptom onset and diagnosis.[25] The lengthy diagnostic delay in CHD-PAH is surprising, given that these patients are typically followed up in specialised centres. However, many CHD patients are lost to follow-up during transition from paediatric to adult care.[26] This may explain, in part, the surprisingly long diagnostic interval in this group. Furthermore, patients with CHD-PAH may display a longer diagnostic interval given that pre-existing symptoms may be attributed to underlying congenital heart disease rather than PAH per se.

We found that older age groups experienced a longer interval to disease recognition, independently of other risk factors. This is consistent with findings from a previous Australian IPAH cohort.[22] Several other factors may contribute to delayed PAH recognition in older individuals. The insidious onset of non-specific symptoms, such as breathlessness and fatigue, may be misattributed to age-related functional decline in older populations.[27] Presentation to health professionals may therefore occur later in the course of the disease. Furthermore, dyspnoea may be initially misdiagnosed more commonly in older patients due to higher burden of cardiovascular and respiratory disease. Conversely, the smaller number of differential diagnoses and more rapid progression of PAH in young patients may lead to earlier referral and disease recognition.

The presence of comorbid cardiovascular and respiratory conditions may mask the onset of PAH, resulting in later disease recognition. We found that peripheral vascular disease and obstructive sleep apnoea were independent predictors of longer diagnostic interval, while patients with comorbid ischaemic heart disease and essential hypertension experienced longer diagnostic interval only in univariate analysis. Diagnostic interval of ≥1 year was also associated with poorer 6MWD and lung function at diagnosis, which cannot be explained by comorbid peripheral vascular disease or obstructive sleep apnoea alone. It is unclear whether this decline reflects the presence of longstanding respiratory comorbidities, or disease progression associated with worsening right ventricular function and physical deconditioning. The REVEAL Registry found similar associations between

respiratory comorbidities and diagnostic delay,[18] while cardiovascular and metabolic comorbidities were not investigated.

To our knowledge, this is the first study to establish a link between length of diagnostic interval and increased mortality, independent of age, gender and PAH aetiology. In a condition like PAH where disease progression can be rapid, timely recognition and treatment may have significant prognostic benefits. PAH survival has improved substantially over the past few decades with the availability of targeted therapy.[23,28,29] However, 82% of patients in our entire cohort were classified as NYHA FC III-IV at diagnosis, corresponding to marked functional impairment. Interestingly, the severity of pulmonary haemodynamic and NYHA FC status were not associated with diagnostic interval. It is possible that despite similar NYHA FC and haemodynamics at diagnosis, patients with longer diagnostic interval may be less responsive to medical therapy, but this remains speculative.

Several limitations need to be acknowledged. Diagnostic delay was defined using symptom onset date, which was estimated by each patient's physician at time of registry enrolment based on history and review of medical records where necessary. Although the same methodology has been used in other registry studies,[18] accuracy may be suboptimal and subject to recall bias. The survival analysis introduces possible lead-time bias, as longer diagnostic interval shortens the survival period and increases observed mortality rates. Co-morbidities were captured in dichotomous variables and the severity of each co-

morbidity was not known. In the setting of background cardiorespiratory co-morbidities, obesity and musculoskeletal disorders, it is not possible to confirm precisely that the date of symptom onset was attributable to the onset of PAH.

In summary, we show that there remains significant diagnostic delay of PAH in Australia and New Zealand, which has not improved in the more recent era. This is concerning given that PAH can be a rapidly fatal disease and highly efficacious therapies are now available. Our study also demonstrates that longer diagnostic interval is associated with poorer long-term survival, reinforcing that early diagnosis and timely treatment are paramount to achieve best outcomes. Further efforts are needed to actively screen patients at risk for developing PAH (such as systemic sclerosis and CHD patients), and to raise awareness in primary and secondary care physicians to investigate for alternative causes of dyspnoea when symptoms are progressive or fail to respond to initial treatment. Increasing public awareness that breathlessness needs thorough investigation and the creation of symptom-based breathlessness clinics may play a role in expediting patient referral to tertiary PAH centres.

Data availability statement:

Specific data requests can be considered on a case-by-case basis for a period of 12 months following article publication online, conditional on approval of the PHSANZ board, the owner of the registry. Access of data will only be allowed for research purposes, and not for financial use.

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Abbreviations:

PAH, pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PHSANZ, Pulmonary Hypertension Society of Australia and New Zealand; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; RHC, right heart catheterisation; IQR, interquartile range; NYHA FC, New York Heart Association Functional Class; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; CHD-PAH, congenital heart disease-associated pulmonary arterial hypertension; SSc-PAH, systemic sclerosis-associated PAH; OR, odds ratio; 95% CI, 95% confidence interval; USA, United States of America; DPAH, drug-induced pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; 6MWD, six minute walk distance; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HIV, human immunodeficiency virus.

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Table 1. Baseline characteristics of study population.

	All	IPAH/DPAH/HPAH	CTD-PAH	CHD-PAH
Number (%)*	2,044 (100%)	861 (42%)	741 (36%)	227 (11%)
Age, years	55.1 ± 18.9	54.5 ± 20.2	60.1 ± 13.7	36.9 ± 19.8
Gender, female:male	2.8:1	2.6:1	5.2:1	2.5:1
Body mass index, kg-m^{-2}	27.9 ± 9.1	29.5 ± 11.2	27.1 ± 7.2	24.6 ± 7.2
Haemodynamics at diagnosis				
mPAP, mmHg	43.8 ± 16.0	46.3 ± 15.4	36.9 ± 13.2	55.8 ± 20.3
RAP, mmHg	9.2 ± 5.0	9.8 ± 5.1	8.4 ± 4.8	8.5 ± 4.7
PAWP, mmHg	11.4 ± 5.6	11.2 ± 5.0	10.8 ± 5.3	11.9 ± 7.4
CI, L-min^{-1}-m^{-2}	2.6 ± 0.8	2.4 ± 0.8	2.7 ± 0.8	3.1 ± 1.1
PVR, dynes-s-cm^{-5}	648.7 ± 444.7	731.6 ± 473.1	528.9 ± 365.2	797.7 ± 580.8
NYHA functional class (n, %)‡				

1	20	(1%)	10	(1%)	6	(1%)	2	(1%)
2	293	(16%)	99	(13%)	133	(21%)	38	(21%)
3	1,262	(71%)	568	(74%)	437	(68%)	132	(72%)
4	204	(11%)	92	(12%)	70	(11%)	11	(6%)
6MWD, m	319.8	± 137.2	316.4	± 141.2	321.1	± 131.8	363.5	± 134.2

IPAH, idiopathic pulmonary arterial hypertension; DPAH, drug-induced pulmonary arterial hypertension; HPAH, heritable pulmonary arterial hypertension; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; CHD-PAH, congenital heart disease-associated pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; NYHA, New York Heart Association; 6MWD, six minute walk distance.

*Row percentages; ‡column percentages. All continuous variables are expressed as mean ± standard deviation.

Table 2. Functional and haemodynamic characteristics at diagnosis, stratified by diagnostic interval.

Characteristics	Time to Diagnosis (years)	Mean	95% CI	p-value*
6MWD (m)	<1	328.9	[319.3,338.5]	**0.02**
	≥1	313.4	[305.3,321.4]	
DLCO (% predicted)	<1	52	[50,54]	**0.02**
	≥1	49	[47,51]	
FEV1 (% predicted)	<1	82	[80,83]	**<0.001**
	≥1	78	[76,79]	
FVC (% predicted)	<1	89	[87,91]	**<0.001**
	≥1	84	[83,86]	
FEV1/FVC	<1	0.75	[0.74,0.76]	0.97
	≥1	0.75	[0.74,0.76]	
	<1	2.59	[2.52,2.66]	0.59

Cardiac Index (L-min^{-1}-m^{-2})	≥1	2.62 [2.56,2.68]	
RAP (mmHg)	<1	9.4 [9.0,9.7]	0.32
	≥1	9.1 [8.8,9.4]	
MPAP (mmHg)	<1	43.3 [42.1,44.4]	0.23
	≥1	44.2 [43.2,45.1]	
PAWP (mmHg)	<1	11.4 [11.0,11.8]	0.40
	≥1	11.3 [11.0,11.7]	
PVR (dynes-s-cm^{-5})	<1	658 [619,696]	0.53
	≥1	642 [613,672]	

		Class I	Class II	Class III	Class IV	
NYHA Functional Class (n, %)	<1	11 (1)	136 (18)	525 (70)	74 (10)	0.09‡
	≥1	9 (1)	157 (15)	737 (71)	130 (13)	

95% CI, 95% confidence interval; 6MWD, 6 minute walk distance; DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RAP, right atrial pressure; MPAP, mean pulmonary arterial pressure; PAWP,

pulmonary artery wedge pressure; PVR, peripheral vascular resistance; NYHA, New York Heart Association.

*p-values calculated using two sample t-test; ‡p-value calculated using chi-squared test.

Table 3. Diagnostic interval stratified by demographic features, pulmonary arterial hypertension subtypes, and period of diagnosis.

Demographics	n	(%)	Time to Diagnosis (years) Median	IQR	p-value*
Total	2044	(100)	1.19	[0.56,2.73]	
Age group					<0.001
≤15	82	(4)	0.48	[0.04,2.48]	
16-29	144	(7)	1.07	[0.34,2.63]	
30-44	304	(15)	1.06	[0.45,2.26]	
45-59	547	(27)	1.13	[0.64,2.58]	
60-74	663	(32)	1.40	[0.65,2.93]	

≥75	304	(15)	1.44	[0.60,3.00]	
Gender					0.72
Male	542	(27)	1.21	[0.53,2.86]	
Female	1502	(73)	1.19	[0.57,2.72]	
Race					0.46
Caucasian	1637	(80)	1.19	[0.55,2.67]	
Asian	95	(5)	1.16	[0.29,2.86]	
Pacific Islander	59	(3)	1.16	[0.65,3.44]	
Indigenous Australian	26	(1)	1.20	[0.34,2.12]	
Other	74	(4)	1.27	[0.69,2.86]	
Year of Diagnosis					0.26
2004-2008	737	(36)	1.18	[0.55,2.54]	
2009-2013	884	(43)	1.25	[0.58,3.03]	
2014-2017	423	(21)	1.13	[0.53,2.72]	
PAH Subtype					<0.001
Idiopathic PAH	790	(39)	1.13	[0.57,2.41]	
CTD-PAH	741	(36)	1.27	[0.59,2.94]	
Systemic sclerosis-associated PAH‡	558	(27)	1.31	[0.61,2.93]	
CHD-PAH	227	(11)	1.79	[0.71,4.49]	
Multifactorial mechanisms	124	(6)	1.09	[0.46,2.18]	
Portal hypertension	61	(3)	1.00	[0.47,2.24]	

Heritable PAH	44	(2)	0.39	[0.22,1.13]	
Drugs or toxins	27	(1)	1.11	[0.38,2.19]	
HIV infection	12	(1)	1.05	[0.38,2.01]	
Geographical Remoteness[§]					0.35
Major cities of Australia	954	(47)	1.19	[0.57,2.79]	
Inner regional Australia	428	(21)	1.22	[0.55,2.59]	
Outer regional Australia	157	(8)	1.03	[0.47,2.32]	
Remote/very remote Australia	22	(1)	0.97	[0.42,2.19]	
Comorbidities					
Smoker (current)					0.15
Yes	122	(6)	1.16	[0.48,2.11]	
No	1922	(94)	1.20	[0.56,2.81]	
Smoker (ever)					0.46
Yes	727	(36)	1.26	[0.60,2.66]	
No	1317	(64)	1.16	[0.52,2.80]	
Obstructive sleep apnoea					<0.001
Yes	335	(16)	1.61	[0.79,3.35]	
No	1709	(84)	1.14	[0.53,2.58]	
Ischaemic heart disease					0.003
Yes	383	(19)	1.48	[0.67,2.88]	
No	1661	(81)	1.14	[0.53,2.66]	

Peripheral vascular disease					<0.001
Yes	111	(5)	2.06	[0.80,3.67]	
No	1933	(95)	1.17	[0.55,2.66]	
Essential hypertension					0.003
Yes	759	(37)	1.38	[0.63,2.87]	
No	1285	(63)	1.11	[0.49,2.61]	
Diabetes					0.66
Yes	306	(15)	1.28	[0.58,2.66]	
No	1738	(85)	1.19	[0.55,2.77]	
Obesity					0.46
Yes	1002	(49)	1.25	[0.61,2.66]	
No	1042	(51)	1.13	[0.53,2.83]	

IQR, interquartile range; PAH, pulmonary arterial hypertension; CTD-PAH, connective tissue disease-associated pulmonary arterial hypertension; CHD-PAH, congenital heart disease-associated pulmonary arterial hypertension; HIV, human immunodeficiency virus.

*p-values calculated using overall Mann-Whitney test, or Kruskal-Wallis test where more than two groups; ‡Included in CTD-PAH subgroup; §Determined using Australian Statistical Geographical Standard remoteness structure, includes Australian patients only.

Table 4. Unadjusted and adjusted logistic regression of variables associated with diagnostic interval of ≥1 year.

Characteristics	Unadjusted Model*			Adjusted Model§		
	OR (95% CI)		p-value‡	OR (95% CI)		p-value‡
Age	1.011	(1.006, 1.016)	<0.001	1.014	(1.009,1.019)	<0.001
CHD-PAH	1.53	(1.14,2.05)	0.004	2.12	(1.55,2.91)	<0.001
Peripheral vascular disease	2.01	(1.31,3.09)	0.001	1.80	(1.16,2.78)	0.01
Ischaemic heart disease	1.35	(1.07,1.70)	0.01		-	
Essential hypertension	1.28	(1.07,1.54)	0.007		-	
Obstructive sleep apnoea	1.58	(1.24,2.03)	<0.001	1.50	(1.17,1.93)	0.001
Obesity	1.22	(1.02,1.45)	0.03		-	

OR, odds ratio; CI, confidence interval; CHD-PAH, congenital heart disease-associated pulmonary arterial hypertension.

*Variables with p>0.20 on univariate regression: sex, race, year of diagnosis, idiopathic pulmonary arterial hypertension, connective tissue disease-associated pulmonary arterial hypertension, smoking status, diabetes; ‡p-values obtained from Wald χ^2 test; §Adjusted model contains the following variates: age, CHD-PAH, peripheral vascular disease, and obstructive sleep apnoea**.**

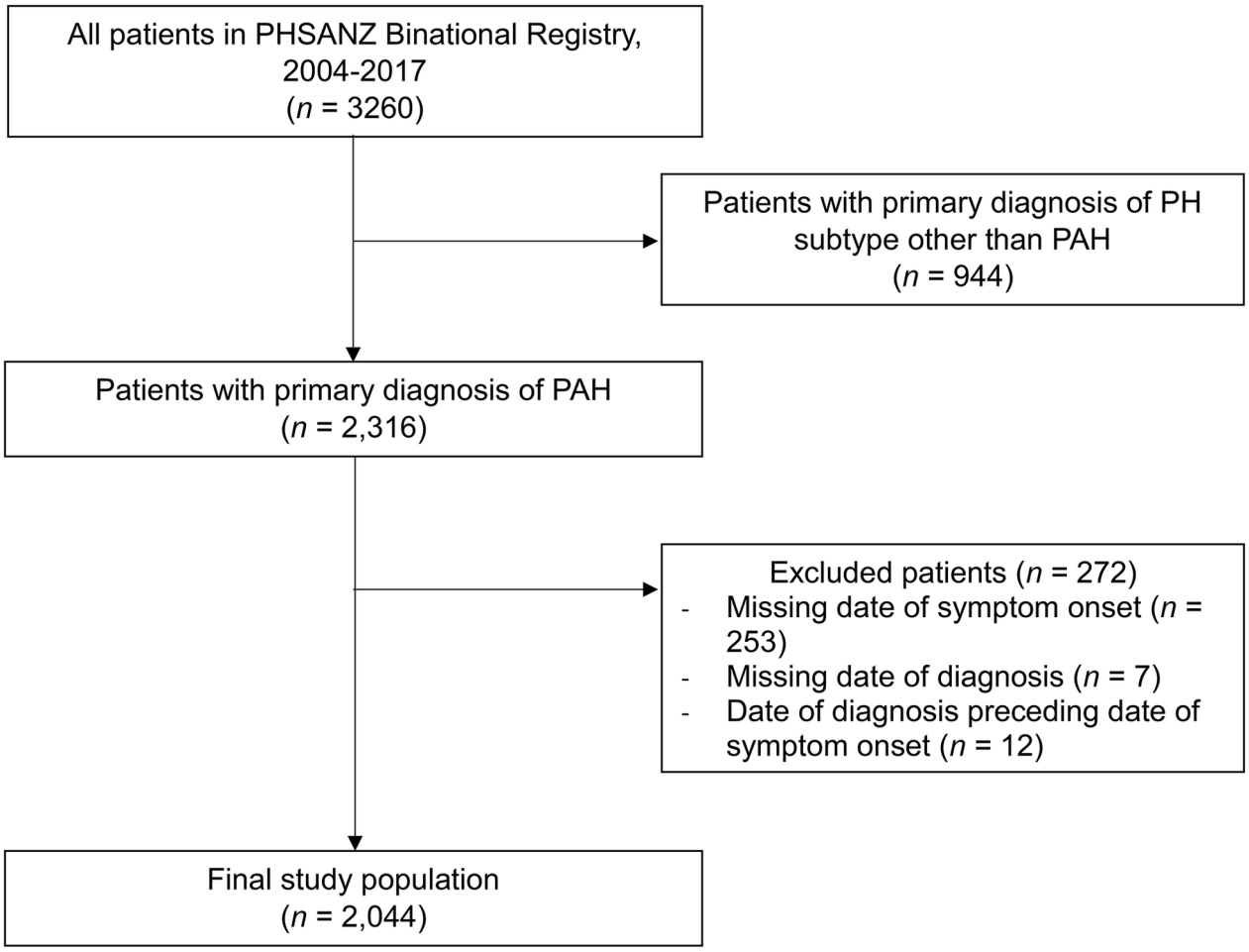
Figure Legends

Figure 1. Patient flow chart of inclusion into analysis.

PHSANZ, Pulmonary Hypertension Society of Australia and New Zealand; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension.

Figure 2. A) Kaplan-Meier curve of survival, stratified by time to diagnosis; B) Mortality ratio against time to diagnosis, with 95% confidence interval.

*Data were adjusted for age, sex and PAH subtype. The graph is based on fractional polynomials with powers 3 and 1. Shaded area indicates 95% confidence intervals.



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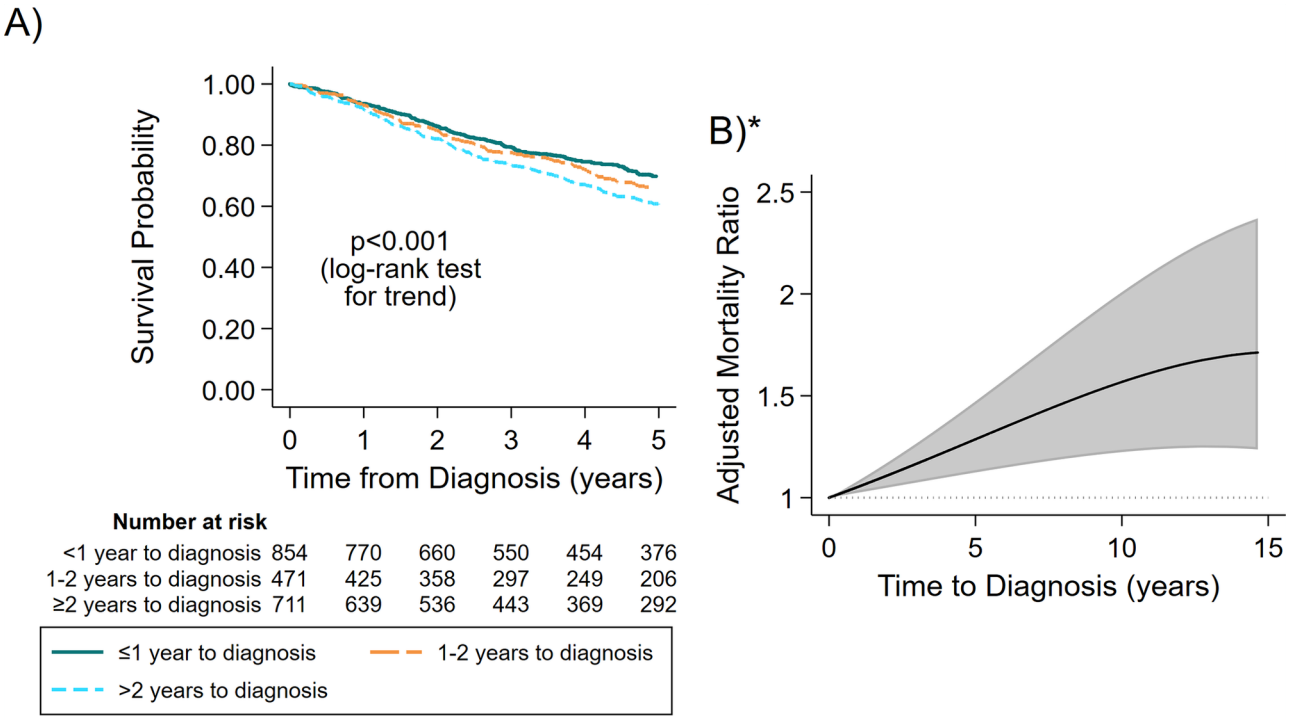

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