Pulmonary arterial hypertension with below threshold pulmonary vascular resistance

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ABSTRACT Pulmonary vascular resistance (PVR) >3 Wood units is a criterion of the haemodynamic definition of pulmonary arterial hypertension (PAH). However, this cut-off is conservative and arbitrarily defined. Data is lacking on the natural history, response to therapy and survival of patients diagnosed with precapillary pulmonary hypertension (PH) with mild or borderline elevation of PVR.

In Australia, PAH therapy could be prescribed solely on mean pulmonary arterial pressure (PAP) and pulmonary arterial wedge pressure (PAWP) criteria. Using the Australian and New Zealand Pulmonary Hypertension Registry, we aimed to study a population diagnosed with PAH between January 2004 and December 2017 with the pre-defined haemodynamic characteristics of mean PAP ⩾25 mmHg, PAWP ⩽15 mmHg and PVR <3 Wood units.

Eighty-two patients met the pre-defined haemodynamic inclusion criteria (mean age 63±11 years; 67 females). Underlying aetiologies included idiopathic disease (n=39), connective tissue disease (CTD; n=42) and HIV infection (n=1). At diagnosis, mean PAP was 27 mmHg (interquartile range (IQR) 25–30 mmHg), PAWP 13 mmHg (IQR 11–14 mmHg) and PVR 2.2 Wood units (IQR 1.9–2.7 Wood units). Baseline 6-min walk distance (6MWD) was 352 m (IQR 280–416 m) and 77% of subjects were in New York Heart Association (NYHA) functional class 3 or 4. All patients were commenced on initial monotherapy with an endothelin receptor antagonist (ERA; n=66) or phosphodiesterase type-5 inhibitor (PDE5i; n=16). At first re-evaluation, 6MWD increased by 46 m (IQR 7–96 m) and 35% of subjects demonstrated improvement in NYHA functional class. After a median follow-up of 65 months (IQR 32–101 months), 18 out of 82 subjects (22.0%) had died, with estimated 1-year and 5-year survival rates of 98% and 84%, respectively. Death attributed to PAH occurred in six out of these 18 patients (33.3%, 7% of total cohort).

Patients with precapillary PH and "borderline" PVR falling outside the current definition have adverse outcomes. Such patients appear to respond to PAH therapy; however, this requires further study in randomised trials.

Introduction

Pulmonary arterial hypertension (PAH) is a haemodynamic consequence of obstructive remodelling of the small pulmonary arteries and patients can progress to right-heart failure and death [1]. A form of precapillary pulmonary hypertension (PH), PAH is traditionally defined by mean pulmonary arterial pressure (PAP) $\geqslant$25 mmHg, pulmonary arterial wedge pressure (PAWP) $\leqslant$15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units on right-heart catheterisation (RHC) [2].

Our increasing understanding of the normal ranges of pulmonary haemodynamics has resulted in a recent revision of the definition of PH. At the 6th World Symposium on Pulmonary Hypertension (2018, Nice, France), it was recognised that the original haemodynamic definition of PAH was arbitrary and that the mean PAP threshold should be lowered to 20 mmHg, whilst the cut-off values of PAWP $\leqslant$15 mmHg and PVR >3 Wood units remained unchanged [3]. Indeed, invasive RHC studies have shown that in healthy subjects normal mean PAP averages 14 mmHg with an upper limit of approximately 20 mmHg [4]. There is also increasing evidence that patients with mildly elevated mean PAP, between 21 mmHg and 24 mmHg, experience functional limitation and poorer outcomes compared to those with strictly normal mean PAP $\leqslant$20 mmHg [5–7]. Recent data from large cohorts have confirmed the prognostic significance of mean PAP in the 21–24 mmHg range based on RHC or estimated from transthoracic echocardiography [8, 9].

Despite the amended mean PAP value for diagnosis of PAH, the current PVR threshold of 3 Wood units is not based on evidence regarding the normal upper limit for PVR. A meta-analysis of all published data on healthy controls showed that normal PVR remained below 2 Wood units, although the upper limit for elderly patients is less clear due to scarce normative data [4]. Indeed, the limitation of the current PVR threshold was acknowledged at the recent 6th World Symposium [3]. A threshold of 3 Wood units was considered "conservative" but allowed a "safety gap" which would only include patients with clear pulmonary vascular disease [3, 10].

Despite the above considerations, it is widely accepted that early treatment of PAH is associated with improved outcomes [11–13].This has led to the recommendation that at-risk groups, such as those with systemic sclerosis or carriers of a *BMPR2* mutation, should undergo regular screening for PAH [2]. On the other hand, randomised controlled trials of treatments for PAH have universally included patients with moderate to severe elevation of PVR [2, 14]. Hence, there is little or no published data on patients with precapillary PH with only "borderline" or mild elevation of PVR. The natural history and long-term prognosis of these patients are unclear but important, as they may represent a substantial group of symptomatic patients. Furthermore, it is unknown whether these patients respond to targeted PAH therapy and this question will be difficult to answer in the current era where treatments are only recommended if PVR exceeds 3 Wood units.

Using data from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) Registry, the aim of the present study was to describe the clinical characteristics, treatment response to PAH therapy and long-term outcomes of patients with "early" precapillary PH. This was facilitated by examining a group of patients in Australia and New Zealand where PVR was not part of the haemodynamic definition required for treatment initiation in our region. We thus prospectively defined this group of interest with the haemodynamic characteristics of mean PAP $\geqslant$25 mmHg, PAWP $\leqslant$15 mmHg and PVR <3 Wood units.

Methods

We performed a retrospective observational study using the PHSANZ Registry (which commenced in December 2011 and currently has 21 participating centres across Australia and New Zealand). Although the PHSANZ Registry enrolls patients with all groups of PH, the largest population is Group 1 PAH [15]. Data for patients diagnosed prior to December 2011 were entered retrospectively, whilst data for incident cases and follow-up data were entered prospectively using a dedicated software platform (FileMaker Pro 17, Claris, Santa Clara, USA). The PHSANZ Registry records demographics, detailed data of investigations (invasive haemodynamic tests, pulmonary function tests (PFTs) and echocardiographic data), functional

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capacity (New York Heart Association (NYHA) functional class and six-min walk distance (6MWD)), treatment data and outcome data. Data was collected at time of enrolment and at subsequent periodic reviews determined by the treating physician (typically every 3–6 months).

Using the PHSANZ Registry, patients with physician diagnosed Group 1 PAH fulfilling the following haemodynamic characteristics (mean PAP ⩾25 mmHg, PAWP ⩽15 mmHg and PVR <3 Wood units) were included in the present study. It is important to note that the old haemodynamic definition of PAH (mean PAP ⩾25 mmHg and PAWP ⩽15 mmHg without the PVR >3 Wood units criterion) was used for the PHSANZ Registry, as data collection began prior to the official inclusion of PVR >3 Wood units into the haemodynamic definition of PAH at the 5th World Symposium on Pulmonary Hypertension in 2013. The diagnosis of Group 1 PAH was made by the treating physician at each centre after the integration of all clinical, radiological and haemodynamic data. Patients with PH deemed to be caused by left to right cardiac shunt, congenital heart disease, chronic liver disease, lung disease and left-heart disease, as well as chronic thromboembolic disease, were excluded from the analysis. Baseline demographics, disease aetiology, comorbidities, NYHA functional class, 6MWD, lung function tests and invasive haemodynamics were recorded, as well as the type of PAH therapy administered. Mortality and last follow-up were censored at March 01, 2017. The PHSANZ Registry protocol was approved by the human ethical committee at St. Vincent's Hospital, Sydney, Australia (HREC: LNR/11/SVH/178).

Variables were expressed as mean±standard deviation (SD) or median (interquartile range (IQR)) if their distribution was non-parametric. All-cause mortality data was determined from the database and patients were censored at the date of last follow-up. Mortality status was updated to the PHSANZ Registry at each clinical follow-up. The Kaplan–Meier method was use to estimate survival, with censoring at the date of last follow-up. Risk assessment was performed using the REVEAL 2.0 Risk Score and the modified three tier low, intermediate and high risk strata [16]. This REVEAL 2.0 Risk Score has recently been validated in the PHSANZ PAH population [16, 17]. The Cox model was used to determine baseline variables predictive of survival. For all analyses, a two-tailed p-value of less than 0.05 was deemed to be significant. Statistical analyses were conducted using STATA version 15.1 (StataCorp LLC, College Station, TX, USA).

Results
Study population
At the time of data extraction, there were 3292 patients in the PHSANZ registry. Of these, 2378 were diagnosed as having Group 1 PAH. Of these, 90 patients met the haemodynamic criteria for inclusion (mean PAP ⩾25 mmHg, PAWP ⩽15 mmHg and PVR <3 Wood units). However, eight of these were excluded as their PH was due to congenital heart disease with left to right shunt (n=4), left heart disease or pulmonary disease (n=4) (figure 1).

Thus, 82 patients were included in the present study, with a mean age of 63±11 years, of which 67 (82%) were female. Baseline characteristics are summarised in table 1. Underlying diagnoses included 40 patients
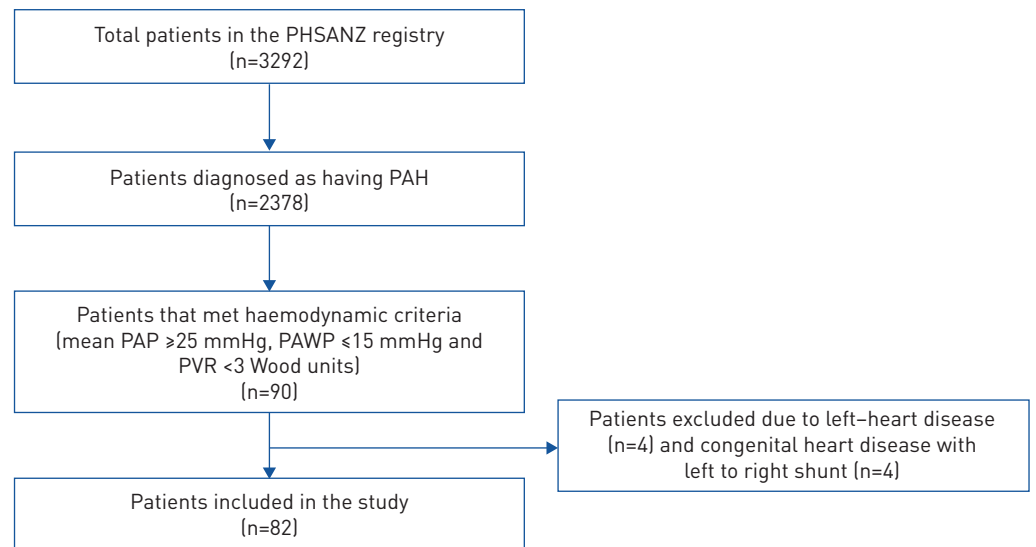

FIGURE 1 Flow diagram of the study population from the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) registry. PAH: pulmonary arterial hypertension; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance.

TABLE 1 Baseline characteristics of the study population

Characteristic	Result
Age years	63±11
Female gender %	82
BMI kg·m^{-2}	31.4±7.8
Aetiology	
Non-CTD associated PAH	40
Idiopathic	39
HIV associated	1
CTD associated PAH	42
Systemic sclerosis spectrum	39
Rheumatoid arthritis	2
Systemic lupus erythematosus	1
Comorbidities	
Diabetes mellitus	20 (24)
Hypertension	45 (55)
Dyslipidaemia	36 (44)
Ischaemic heart disease	22 (27)
Peripheral vascular disease	5 (6)
Current smoker	3 (4)
Ex-smoker	26 (32)
OSA	20 (24)
Baseline haemodynamics	
Mean PAP mmHg	27 (25–30)
PAWP mmHg	13 (11–14)
PVR Wood units	2.2 (1.9–2.7)
Cardiac output L·min^{-1}	6.7 (5.8–7.9)
Cardiac index L·min^{-1}·m^{-2}	3.55 (3.1–4.2)
RAP mmHg	8.0 (5.2–10.0)
Mean SAP mmHg	98 (83–106)
SVR dynes·sec·cm^{-5}	1078 (852–1240)
HR beats·min^{-1}	72 (67–87)
Baseline 6MWD m	352 (280–416)
PFT	
FEV$_1$ % predicted	91 (75–96)
FVC % predicted	90 (81–105)
TLC % predicted	93 (80–98)
D_{LCO} % predicted	53 (45–62)
NYHA functional class	
1	1 (1)
2	19 (23)
3	60 (73)
4	2 (3)

Data are presented as n, n (%), mean±SD or median (IQR), unless otherwise stated. BMI: body mass index; CTD: connective tissue disease; PAH: pulmonary arterial hypertension; OSA: obstructive sleep apnoea; PAP: pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; RAP: right-atrial pressure; SAP: systemic arterial pressure; SVR: systemic vascular resistance; HR: heart rate; 6MWD: 6-min walk distance; PFT: pulmonary function test; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; NYHA: New York Heart Association.

with non-connective tissue disease (CTD)-associated PAH (idiopathic (n=39) and human immunodeficiency disease (n=1)) and 42 patients with CTD-associated PAH (systemic sclerosis spectrum disease (n=39), rheumatoid arthritis (n=2) and systemic lupus erythematosus (n=1)). At diagnosis, baseline haemodynamics showed mild PH with mean PAP 27 mmHg (IQR 25–30 mmHg), PAWP 13 mmHg (IQR 11–14 mmHg) and PVR 2.2 Wood units (IQR 1.9–2.7 Wood units). The median 6MWD at baseline was 352 m (IQR 280–416 m). The majority of patients had significant functional limitation at diagnosis as demonstrated by NYHA functional class status. Using the Reveal 2.0 risk score, 61% of the cohort was low-risk, 35% were intermediate risk and 4% were high-risk at diagnosis. Baseline characteristics of the non-CTD and CTD groups were broadly similar apart from a higher prevalence of diabetes, lower 6MWD and more severe NYHA functional class in the non-CTD group (supplementary table S1).

Pulmonary arterial hypertension therapy

All patients were commenced on initial monotherapy. The mean time between confirmation of diagnosis by RHC and commencement of PAH treatment was 30±38 days. Sixty-six patients were commenced on an endothelin receptor antagonist (ERA) and 16 were commenced on a phosphodiesterase type-5 inhibitor (PDE5i) at the discretion of the treating physician. Of the patients commenced on an ERA, 50 were commenced on bosentan, seven on sitaxsentan, five on macitentan and four on ambrisentan. The majority of patients started on PDE5i's were started on sildenafil (n=15), with one patient commenced on tadalafil. All patients commenced on sitaxsentan were switched to alternate endothelin antagonist medications when this drug was taken off the market in Australia. There were 14 patients (17%) who were escalated to combination therapy with both a PDE5i and an ERA during the follow up period. There were no treatment interruptions due to side effects and all patients remained on treatment until the end of the follow-up period. Types of PAH treatment administered are summarised in table 2. Treatment stratified by underlying aetiology can be found in supplementary table S2.

Treatment response

Treatment response was assessed at least 3 months after treatment commencement. Median time of first post-treatment evaluation was 5 months (IQR 4–12 months). In the overall population, 6MWD increased by 46 m (IQR 7–96 m) (p=0.01) and 35% of patients demonstrated improvement in NYHA functional class status (figures 2a and 2b). Using the REVEAL 2.0 risk score, PAH therapy increased the proportion of patients in the low-risk category from 61% to 72% (figure 3).

Treatment response stratified by underlying aetiology showed that patients with non-CTD-associated PAH demonstrated a change in 6MWD of 65 m (IQR 14–104 m) (p=0.03), whereas the CTD group changed by 41 m (IQR 8–85 m) (p=0.15) (supplementary figure S1). Similarly, 34% of patients with non-CTD-associated PAH showed improvement in NYHA functional class *versus* 20% for CTD-associated PAH (supplementary figures S2a and S2b). Using the REVEAL 2.0 risk score, PAH therapy resulted in a similar proportion of improvement into the lower-risk category at time of first follow-up when stratified by aetiology (supplementary figures S3a and S3b).

Long term follow-up

Median follow-up after diagnosis was 65 months (IQR 32–101 months) for the entire cohort. Follow-up RHC was not mandated by the PHSANZ Registry but was performed at the discretion of the treating

TABLE 2 Therapy at diagnosis and last follow-up

Strategy	n (%)
Initial treatment	
Medication class	
ERA	66 (80)
PDE5i	16 (20)
Specific medications	
Bosentan	50 (61)
Sitaxsentan	7 (9)
Macitentan	5 (6)
Ambrisentan	4 (5)
Sildenafil	15 (18)
Tadalafil	1 (1)
Treatment at last follow-up	
Monotherapy	68 (83)
Bosentan	38 (46)
Sitaxsentan	1 (1)
Macitentan	8 (10)
Ambrisentan	4 (5)
Sildenafil	14 (17)
Tadalafil	3 (4)
Combination therapy	14 (17)
Ambrisentan+sildenafil	8 (10)
Ambrisentan+tadalafil	1 (1)
Macitentan+sildenafil	4 (5)
Sitaxsentan+sildenafil	1 (1)

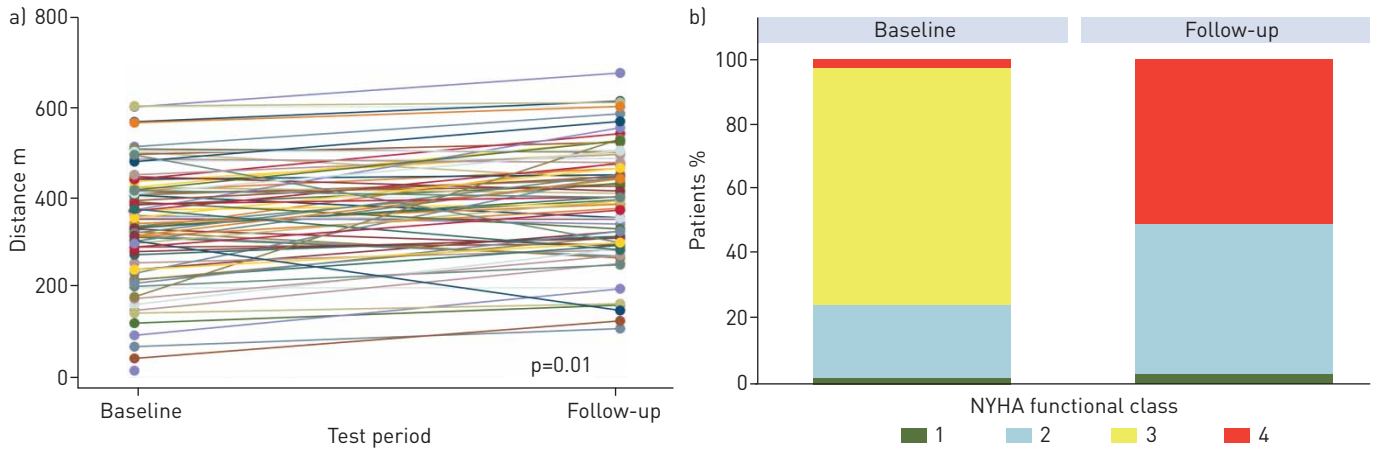ERA: endothelin receptor antagonist; PDE5i: phosphodiesterase type-5 inhibitor.

FIGURE 2 (a) Change in 6-min walk distance (6MWD) between baseline and first follow-up after initial treatment initiation (median improvement was 46 m (IQR 7–96 m); p=0.01). (b) Change in New York Heart Association (NYHA) functional class between baseline and first follow-up (35% of patients had an improvement in functional class status). IQR: interquartile range.

physician. In order to evaluate long-term progression of PAH, we only included follow-up RHCs which were performed at least 1 year after initial diagnosis. Twenty-six out of 82 subjects (CTD group (n=18) and non-CTD group (n=8)) had long-term follow-up RHC available at a median follow-up time of 48 months (IQR 32–58 months). Overall, there were no significant changes in mean PAP and PVR between RHC at diagnosis and at long-term follow-up (supplementary table S3). Of note, seven out of 26 patients (26.9%) developed PVR >3 Wood units at follow-up RHC. In these patients, PVR increased from 2.6 Wood units (IQR 2.3–2.8 Wood units) to 3.4 Wood units (IQR 3.2–4.6 Wood units).

There were 29 individual hospitalisations related to management of PAH in our cohort, which correlated to a hospitalisation rate of 6.3% per year. Six patients had recurrent hospitalisations during the follow-up period.

There were 18 deaths (22%) during the study period and PAH was identified as the likely cause of death (sudden cardiac death or right-ventricular failure) in six patients (33%). The three patients who died from right-ventricular failure had repeated hospitalisations for PAH prior to death. Of the remaining 12 deaths, three were from unknown causes and nine were attributed to causes unrelated to PAH (table 3). Kaplan–Meier estimates of 1-year, 3-year and 5-year survival were 0.99 (95% confidence interval (CI) 0.92–1.00), 0.89 (95% CI 0.79–0.94) and 0.84 (95% CI 0.73–0.91), respectively (figure 4a). There was no significant difference in survival between the non-CTD group *versus* the CTD group (p=0.85) (figure 4b). On use of a univariate Cox model, the presence of comorbidities (ischaemic heart disease, diabetes, hypertension and obesity) were not predictive of survival (p>0.15 for all).

Discussion

To the best of our knowledge, this is the first study to examine the characteristics, treatment outcomes and survival of a PAH population with borderline elevation of PVR. This was possible because of a historical
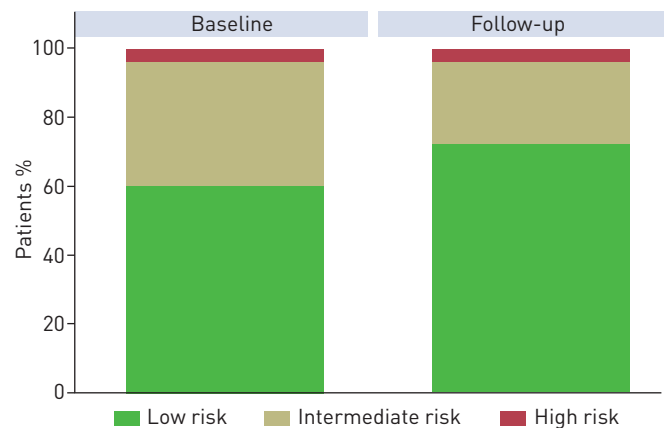

FIGURE 3 REVEAL 2.0 modified risk assessment at baseline and first follow-up after initial treatment initiation (the proportion of patients in the low risk category increased from 61% to 72%).

TABLE 3 Cause of death during follow-up

Cause	n (%)
Total deaths	18 (100)
Deaths attributed to PAH	6 (33)
Right-ventricular failure	3 (17)
Sudden cardiac event	3 (17)
Deaths not directly attributed to PAH	9 (50)
Respiratory failure	2 (11)
Acute respiratory infection	3 (17)
Malignancy	3 (17)
Other	1 (6)
Unknown	3 (17)

PAH: pulmonary arterial hypertension.

"gap" (prior to 2013) in which there was no accepted PVR criterion required for the definition of PAH and hence the PHSANZ Registry enrolled patients with sub-criterion PVR values. These patients, with precapillary PH but PVR <3 Wood Units, displayed significant functional limitation at baseline and appeared to respond to PAH therapy with both an improvement in walk distance, NYHA functional class and global risk assessment. Despite this apparently favourable treatment response mortality during follow-up was significant, with an estimated 5-year survival rate of 84%; whereas age and gender matched subjects from the general adult population in Australia would have an expected life-expectancy of 85 years [18]. Furthermore, progressive PAH was the cause of death in 33% of patients who died during the follow-up period, suggesting that this is not a benign condition despite only mild elevation of PVR at diagnosis. The current haemodynamic definition of PAH, which requires PVR >3 Wood units, may potentially "miss" patients with clinically important pulmonary vascular disease who are at increased risk of adverse outcomes and who may benefit from early PAH therapy.

Expert consensus from the recent 6th World Symposium on Pulmonary Hypertension recommended that a PVR cut-off >3 Wood units should remain for the haemodynamic diagnosis of PAH. However, prior studies have demonstrated that PVR remains <2 Wood units in healthy subjects [4, 19]. Thus, the current PVR >3 Wood units cut-off is intended to allow greater specificity for the diagnosis of PAH but at the expense of sensitivity, particularly in the younger population. It is noteworthy that the traditional definition of PH requiring mean PAP ⩾25 mmHg has recently been modified to 20 mmHg, which is aligned with what is known regarding the upper limit of normal mean PAP. Furthermore, the impetus for lowering the mean PAP threshold is supported by recent studies showing that patients with systemic
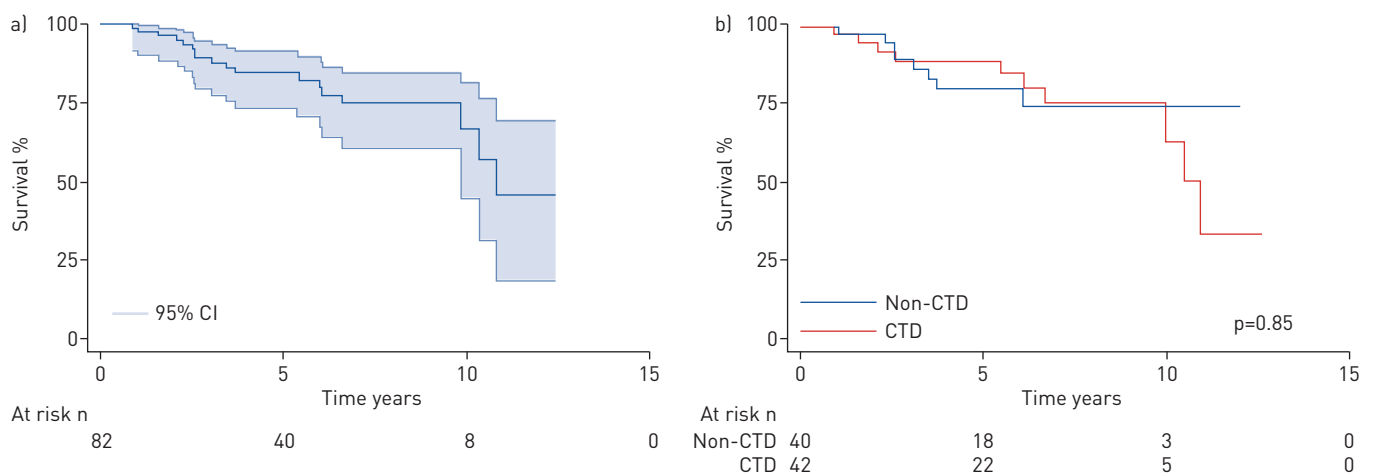

FIGURE 4 (a) Kaplan–Meier survival estimates from time of pulmonary arterial hypertension (PAH) diagnosis for the entire study cohort (1-year, 3-year and 5-year survival estimates were 0.99 (95% CI 0.92–1.00), 0.89 (95% CI 0.79–0.94) and 0.84 (95% CI 0.73–0.91), respectively). (b) Kaplan–Meier survival estimates from time of PAH diagnosis stratified by aetiology (connective tissue disease (CTD) related PAH and non-CTD related PAH). CI: confidence interval.

sclerosis and mildly elevated mean PAP (21–24 mmHg) have more functional limitation and increased risk of disease progression compared to those with mean PAP <20 mmHg [5, 20, 21]. In addition, large population-based RHC studies have found that patients with mean PAP in the 21–24 mmHg range have excess mortality and hospitalisations compared to those with lower ranges of mean PAP [9]. Therefore, it can be argued that the current PVR threshold of 3 Wood units is not based on available evidence and does not represent the normal upper limit of PVR in healthy subjects [4]. Further studies are required to determine the threshold of PVR elevation that is associated with increased risk of adverse outcomes.

Despite relatively mild haemodynamic impairment in the group studied, most patients presented with an advanced NYHA functional class, although comorbidity status may impact on this tendency towards more advanced functional class. For example, our population displayed a high proportion of cardiometabolic risk factors, such as ischaemic heart disease, hypertension, diabetes and obesity. Thus, it is possible that poor functional capacity may have other contributory factors beyond pulmonary haemodynamics and right-heart function. Invasive exercise haemodynamics were not performed and it is unknown whether these patients developed a brisk rise in PAP during exercise, which could account for the advanced functional disability experienced despite mild resting haemodynamic derangement [22].

The patients in our cohort had high normal PAWP values (median 13 mmHg) but did not have overt left-heart disease (as deemed by their treating physician). While we cannot fully exclude the possibility that some of these patients had occult left-heart disease, the PAWP in all subjects remained below 15 mmHg which is in line with the current haemodynamic classification of precapillary PH. Assessment of left-heart filling pressure following fluid loading or exercise challenge would have allowed greater confidence in excluding left-heart disease in our subjects [23, 24]. Reassuringly, none of these patients had PAH treatment withdrawn due to worsening symptoms, which can commonly occur in the setting of left-heart disease [25]. Our cohort highlights the real-world diagnostic challenge of differentiating occult left-heart disease (especially heart failure with preserved ejection fraction) from PAH.

The estimated survival rate for this cohort was 84% at 5 years and is thus higher than the 5-year survival rate of 57% reported in the REVEAL registry [26] and the more contemporary 3-year survival rate of 77% reported from the PHSANZ registry in 2018 [27]. It should be noted, however, that the latter figure included only those with idiopathic, heritable and drug-induced PAH. The better survival seen in our study population is not unexpected in a population with a lesser degree of haemodynamic abnormality at diagnosis. However, six out of 18 patients (33%) who died during the follow-up period died from a cause that was attributable to PAH. This is despite the fact that all patients received PAH therapy following diagnosis and showed improvements in 6MWD, NYHA functional class and risk assessment at first follow-up. Whilst these patients did not have repeat RHC close to their death, all patients who died of progressive right-heart failure had recurrent hospitalisations related to PAH. This supports the notion that PAH can be a progressive disease, even when diagnosed at a stage with apparently only mild haemodynamic impairment, and highlights the importance of early diagnosis and screening of "at risk" populations, such as those with systemic sclerosis [28].

Only a small proportion of patients (26 out of 82) had follow-up RHC at long term follow-up, since RHC was not mandated by the Registry and was performed at the discretion of the treating physician. Of those who did have a long-term follow-up RHC, there was no significant change in mean PAP and PVR. However, all patients had received PAH therapy so this data does not strictly inform the natural history of untreated patients with borderline PVR elevation. It is of note that seven out of 26 patients with follow-up RHC crossed the threshold of PVR >3 Wood units at follow-up, supporting the notion that at least a proportion of patients are at risk of progression despite PAH therapy.

Our study characterises a group of patients with borderline PVR elevation who may not fulfil the current haemodynamic definition of PAH but may still experience adverse outcomes. However, lowering of the current PVR threshold can potentially lead to the problem of over-diagnosis, particularly when non-efficacious or potentially harmful therapy is given to patients without true pulmonary vascular disease. As a sensitivity analysis, we compared the survival of the current study cohort (PVR <3 Wood units) with PAH patients from the PHSANZ registry who had PVR 3–4 Wood units, mean PAP ⩾25 mmHg and PAWP ⩽15 mmHg. There was no significant difference in survival between the two groups (supplementary figure S4) and this provides some reassurance that an excess harmful signal was not observed when PAH therapy was administered in our study population. It is important to emphasise that all our patients were diagnosed with PAH and were commenced on PAH therapy by clinicians experienced in the management of PH. The findings of the present study cannot be extrapolated to all patients with this haemodynamic profile, where PH could be due to other causes such as lung disease, chronic thromboembolic disease or occult left-heart disease.

There are several limitations to this study. It was observational in nature and based on a relatively small number of patients, the majority of which had underlying CTD which is a strong risk factor for PAH. The

patients included in the current study were given a diagnosis of PAH by their treating physicians and no central review of diagnosis was required in the PHSANZ Registry. Only patients who were commenced on therapy were included in the PHSANZ registry. Thus, we cannot provide a comparator group with similar haemodynamic profiles where PAH therapy was not administered. Provocative testing with fluid or exercise challenge was not performed during diagnostic RHC and this could have provided additional insights into the haemodynamic phenotyping of this population. Furthermore, diuretic therapy was not captured in the registry, so we were unable to comment on whether diuretic therapy accounted, at least in part, for the improvement demonstrated at first follow-up. Due to the fact that follow-up RHC was not mandated by the PHSANZ Registry, long term follow-up RHC was only available in a minority of patients. Systematic follow-up RHC would have allowed comprehensive evaluation of patients with disease progression and the determination of possible risk factors that predict such progression. Finally, the precise mechanism of death was not known in a proportion of our patients, as our registry was not linked to the national death registry. Although our cohort demonstrated clinical response to PAH therapy, this was only observational in nature. There are currently no randomised, controlled data at present to support treating patients with borderline elevation of PVR.

Conclusions

Certain patients with precapillary PH who fail to meet the PVR threshold of 3 Wood units may have adverse clinical outcomes and may potentially benefit from PAH therapy. Survival data shows a significant proportion of patients died of a PAH-related cause during follow-up, highlighting that this is not a benign condition. Further studies are needed to define the PVR thresholds which impact on long-term prognosis and whether early treatment of patients with borderline elevation of PVR confers beneficial impact on symptoms, exercise capacity and/or adverse clinical events.

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