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# Pulmonary arterial hypertension with below threshold pulmonary vascular resistance

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**Take home messages:** Selected patients with precapillary PH and “borderline” PVR who fail to meet the current threshold of 3WU have functional limitation, adverse outcomes and potentially benefit from PAH therapy.

**Key words:** pulmonary hypertension, pulmonary arterial hypertension, pulmonary vascular resistance, pulmonary artery pressure

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**ABSTRACT**

Pulmonary vascular resistance (PVR)>3 WU 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 with mild or borderline elevation of PVR.

In Australia, PAH therapy could be prescribed solely on mean pulmonary artery pressure (mPAP) and pulmonary artery wedge pressure (PAWP) criteria. Using the Australian and New Zealand Pulmonary Hypertension Registry, we aimed to study a population diagnosed with PAH between Jan 2004-Dec 2017 with the pre-defined haemodynamic characteristics of mPAP≥25 mmHg, PAWP≤15mmHg and PVR<3WU.

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(n=42) and HIV infection(n=1). At diagnosis, mPAP was 27mmHg(IQR25-30), PAWP 13mmHg(IQR11-14) and PVR 2.2WU(IQR1.9-2.7). Baseline 6MWD was 352m(IQR280-416) and 77% were in NYHA 3 or 4 functional class. All patients were commenced on initial monotherapy with an endothelin receptor antagonist(n=66) or phosphodiesterase-5 inhibitor(n=16). At first re-evaluation, 6MWD increased by 46m(IQR7-96) and 35% demonstrated improvement in NYHA functional class. After a median follow-up of 65 months(IQR32-101), 18/82(22.0%) had died, with estimated 1-yr and 5-yr survivals of 98% and 84%,

respectively. Death attributed to PAH occurred in 6/18(33.3%) of these patients (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.

Pulmonary arterial hypertension (PAH) is haemodynamic consequence of obstructive remodeling of the small pulmonary arteries, and patients can progress to right heart failure and death[1]. PAH (a form of precapillary pulmonary hypertension) is defined traditionally by a mean pulmonary artery pressure (mPAP) ≥25mmHg, pulmonary artery wedge pressure (PAWP) ≤15mmHg and PVR >3WU at 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 pulmonary hypertension. At the recent 6$^{th}$ World Symposium on Pulmonary Hypertension (Nice, 2018), it was recognised that the original haemodynamic definition of PAH was arbitrary and that the mPAP threshold should be lowered to 20 mmHg, whilst the cut-off values of pulmonary artery wedge (PAWP) ≤15 mmHg and PVR >3 WU remained unchanged[3]. Indeed, invasive right heart catheter studies have shown that in healthy subjects, normal mPAP averages 14 mmHg with an upper limit of approximately 20 mmHg[4]. There is also increasing evidence that patients with mildly elevated mPAP between 21-24 mmHg experience functional limitation and poorer outcomes, compared to those with strictly normal mPAP ≤20 mmHg[5-7]. Recent data from large

cohorts have confirmed the prognostic significance of mPAP 21-24 mmHg based on right heart catheterisation or estimated from transthoracic echocardiography[8, 9].

Despite the amended mPAP value for diagnosis of PAH, the current PVR threshold of 3 WU for diagnosis of PAH 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 WU, 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 WU 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 pulmonary hypertension 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 3WU.

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 pulmonary hypertension. 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 mPAP ≥25 mmHg, PAWP ≤15 mmHg and PVR <3 WU.

**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 pulmonary hypertension, the largest population is Group 1 PAH[15]. Data for patients diagnosed prior to December 2011 were entered retrospectively; data for incident cases and follow up data were entered prospectively using a dedicated software platform. The PHSANZ Registry records demographics, detailed data of investigations (invasive haemodynamic, pulmonary function tests and echocardiographic data), functional capacity (NYHA functional class, six-minute walk distance 6MWD), treatment 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 (mPAP ≥25 mmHg, PAWP ≤15 mmHg

and PVR <3 WU) were included in the present study. It is important to note that the old haemodynamic definition of PAH (mPAP ≥25 mmHg and PAWP ≤15 mmHg *without* the PVR >3 WU criterion) was used for the PHSANZ Registry, as data collection began prior to the official inclusion of PVR >3 WU into the haemodynamic definition of PAH at the 5th World Symposium on PH 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 pulmonary hypertension deemed to be caused by left to right cardiac shunts, congenital heart disease, chronic liver disease, lung disease and left heart disease, and 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 type of PAH therapy administered. Mortality and last follow-up were censored at 1 March 2017. The PHSANZ Registry protocol was approved by the human ethical committee at St Vincent's Hospital Sydney (HREC: LNR/11/SVH/178).

Variables were expressed as mean and standard deviation (SD), or median and 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. 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 3-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]. Cox model was used to determine baseline variables predictive of survival. For all

analyses, a two-tailed p-value of <0.05 was deemed to be significant. Statistical analyses were conducted using STATA v15.1 (StataCorp, 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 (mPAP ≥25 mmHg, PAWP ≤15 mmHg and PVR < 3WU). However, 8 of these were excluded as their PH was due to congenital heart disease with left to right shunt (n=4), left heart or pulmonary disease (n=4) **(Figure 1).**

Thus, 82 patients were included in the present study with mean age 63 ± 11 years and 67 (82%) were female. Baseline characteristics are summarised in **Table 1**. Underlying diagnoses included 40 with non-connective tissue disease PAH (idiopathic [n=39] and human immunodeficiency disease [n=1]), and 42 with connective tissue disease associated PAH (systemic sclerosis spectrum disease [n=39], rheumatoid arthritis [n=2], and systemic lupus erythematosus [n=1]). At diagnosis, baseline haemodynamics showed mild pulmonary hypertension with mPAP 27 mmHg (IQR 25-30), PAWP 13 mmHg (IQR 11-14) and PVR 2.2 WU (IQR 1.9-2.7). The median 6-minute walk distance (6MWD) at baseline was 352m (IQR 280-416). The majority of patients had significant functional limitation at diagnosis as demonstrated by NYHA FC 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-connective tissue disease and connective tissue

disease groups were broadly similar apart from a higher prevalence of diabetes, lower 6MWD and more severe NYHA FC in the non-connective tissue disease group (**Supplementary Table 1**).

*PAH therapy*

All patients were commenced on initial monotherapy. The mean time between confirmation of diagnosis by right heart catheterisation 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 (PDE5 inhibitor) at the discretion of the treating physician. Of the patients commenced on an ERA, 50 were commenced on bosentan, 7 on sitaxsentan, 5 on macitentan and 4 on ambrisentan. The majority of patients started on PDE5 inhibitors were started on sildenafil (15), with 1 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%) escalated to combination therapy with PDE5 and 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 2**.

*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). In the overall population, 6MWD increased by 46 m (IQR 7-96, p=0.01) and 35% demonstrated improvement in NYHA FC status **(Figures 2A and 2B).** Using

the REVEAL 2.0 Risk Score, PAH therapy increased the proportion of patients in low-risk category from 61% to 72% (**Figure 3).**

Treatment response stratified by underlying aetiology showed that patients with non-connective disease associated with PAH demonstrated a change in 6MWD of 65m (IQR 14-104, p=0.03) whereas connective tissue disease group changed by 41m (IQR 8-85, p=0.15) (**Supplementary Figure 1**). Similarly, 34% of patients with non-connective tissue disease associated PAH showed improvement in NYHA FC versus 20% for connective tissue disease associated PAH (**Supplementary Figure 2A and 2B)**. Using the REVEAL 2.0 Risk Score, PAH therapy resulted in a similar proportion of improvement into lower risk categories at time of first follow-up when stratified by aetiology **(Supplementary Figure 3A and 3B).**

*Long term follow-up*

Median follow-up after diagnosis was 65 months (IQR 32-101) for the entire cohort. Follow up RHC was not mandated by the PHSANZ Registry but was performed at the discretion of the treating physician. In order to evaluate long-term progression of PAH, we only included follow-up RHC which were performed at least one year after initial diagnosis. Twenty-six of 82 subjects (connective tissue disease group [n=18] and non-connective tissue disease group [n=8]) had long-term follow-up RHC available at a median follow-up time of 48 months (IQR 32-58). Overall, there were no significant changes in mPAP and PVR between RHC at diagnosis and at long term follow-up (**Supplementary Table 3**). Of note, 7 of 26 (26.9%) patients developed PVR >3 WU at follow-up RHC. In these patients PVR increased from 2.6 (IQR 2.3 – 2.8) to 3.4 WU (IQR 3.2-4.6).

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

There were 18 (22%) deaths during the study period. PAH was identified as the likely cause of death (sudden cardiac death or right ventricular failure) in 6 (33%) patients. The 3 patients who died from right ventricular failure had repeated hospitalisations for PAH prior to death. Of the remaining 12 deaths, 3 were unknown, and 9 attributed to causes unrelated to PAH (**Table 4**). Kaplan-Meier survival estimates of 1-yr, 3-yr and 5-yr survivals were 99% (95%CI 0.92-1.00), 89% (95%CI 0.79-0.94), 84% (95%CI 0.73-0.91), respectively **(Figure 4A).** There was no significant difference in survival between non-connective tissue disease group versus connective tissue disease group (p=0.85) (**Figure 4B**). On univariate cox model, the presence of co-morbidities (ischaemic heart disease, diabetes, hypertension and obesity) were not predictive of survival (all p>0.15).

**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 “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 under 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 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 WU, 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 of PH recommended that a PVR cut off >3 WU should remain for the haemodynamic diagnosis of PAH. However, prior studies have demonstrated that PVR remains <2 WU in healthy subjects[4, 19]. Thus, the current PVR >3 WU 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 mPAP $\geq$25 mmHg has recently been modified to 20 mmHg, which is aligned with what is known regarding the upper limit of normal mPAP. Furthermore, the impetus for lowering the mPAP threshold is supported by recent studies showing that patients with systemic sclerosis and mildly elevated mPAP (21-24 mmHg) have more functional limitation and increased risk of disease progression compared to those with mPAP <20 mmHg[5, 20, 21]. In addition, large population-based RHC studies have found that patients with mPAP 21-24 mmHg have excess mortality and

hospitalisations compared to those with lower ranges of mPAP[9]. Therefore, it can be argued that the current PVR threshold of 3WU 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 hemodynamic impairment in the group studied, most patients presented with advanced NYHA functional class. Co-morbidity status may impact on this tendency towards more advanced functional class. Our population displayed a high proportion of cardiometabolic risk factors such as ischaemic heart disease, hypertension, diabetes and obesity. Thus, it is possible that the poor functional capacity may have other contributor 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 pulmonary artery pressure 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 pulmonary arterial wedge pressures (median 13mmHg) but did not have overt left heart disease as deemed by their treating physician. However, we cannot fully exclude the possibility that some of these patients had occult left heart disease, but the PAWP in all subjects remained below 15 mmHg which is in line with the current haemodynamics classification of precapillary pulmonary hypertension. 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 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 rates of 77% reported from the PHSANZ registry in 2018[27], although the latter figure included only those with idiopathic, heritable and drug-induced PAH only. The better survival seen in our study population is not unexpected in a population with a lesser degree of haemodynamic abnormality at diagnosis. However, 6 out of 18 (33%) patients 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 assessment. 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 “at risk” populations such as those with systemic sclerosis[28].

Only a small proportion (26 of 82) of patients had follow-up RHC at long term follow-up, since RHC was not mandated by the Registry and 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 mPAP 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 7 of 26 patients with follow-up RHC crossed the threshold of PVR>3 WU 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 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 <3WU) with PAH patients from the PHSANZ registry with PVR 3-4, mPAP ≥25mmHg, PAWP ≤15mmHg. There was no significant difference in survival between the two groups (**Supplementary Figure 4),** which provides some reassurance that an excess harmful signal was present when PAH therapy were administered in our study population. It is important to emphasise that all our patients were diagnosed with PAH and commenced on PAH therapy by clinicians experienced in the management of pulmonary hypertension. The findings of the present study cannot be extrapolated to all patients with this haemodynamic profile where pulmonary hypertension could be due other causes such as lung disease, chronic thromboembolic disease or left heart disease.

There are several limitations to this study. This was an observational study in a relatively small number of patients with the majority of patients having underlying

connective tissue disease, 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 profile where PAH therapy was not administered. Provocative testing with fluid or exercise challenge were not performed during diagnostic RHC, which would have provided additional insights in the haemodynamic phenotyping of this population. Diuretic therapy was not captured in the registry so we were unable to comment whether diuretic therapy accounted, in part, for the improvement demonstrated at first follow-up evaluation. 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 determine possible risks factors that predict progression. 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 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 3WU may have adverse clinical outcomes and may potentially benefit from PAH therapy. Survival data shows a significant proportion of patient died of a PAH-related cause during follow up, highlighting that this 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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## Figure Legend

**Figure 1.** Flow Diagram of Study Population from the PHSANZ Registry.

**Figure 2.** (A) Six-minute walk distance at baseline and at first follow up after initial treatment initiation. The median improvement was 46m (IQR7-96, p=0.01). (B) New York Heart Association Functional Class at baseline and at first follow up, showing 35% patients had an improvement in functional class status.

**Figure 3.** REVEAL 2.0 modified risk assessment at baseline and first follow-up after initial treatment initiation showing an increase in the proportion of patients in low-risk category from 61% 72%.

**Figure 4.** (A) Kaplan-Meier survival estimates of entire study cohort showing 1-yr, 3-yr and 5-yr survivals of 99% (95%CI 0.92-1.00), 89% (95%CI 0.79-0.94), 84% (95%CI 0.73-0.91). (B) Kaplan-Meier survival estimates of connective tissue disease related PAH and non-connective tissue disease related PAH.

**Table 1. Baseline characteristics of study population**

| | |
|---|---|
| Age, years | 63 ± 11 |
| Gender, Female% | 82% |
| BMI, kg/$m^2$ | 31.4 ± 7.8 |
| **Aetiology, n** | |
| Non-connective tissue disease associated PAH | 40 |
| Idiopathic | 39 |
| HIV associated | 1 |
| Connective tissue disease associated PAH | 42 |
| Systemic sclerosis spectrum | 39 |
| Rheumatoid arthritis | 2 |
| Systemic lupus erythematous | 1 |
| **Co-morbidities, n (%)** | |
| Diabetes mellitus | 20 (24%) |
| Hypertension | 45 (55%) |
| Dyslipidaemia | 36 (44%) |
| Ischemic heart disease | 22 (27%) |
| Peripheral vascular disease | 5 (6%) |
| Current smoker | 3 (4%) |
| Ex-smoker | 26 (32%) |
| Obstructive sleep apnoea | 20 (24%) |
| | |
| **Baseline haemodynamics** | |
| mPAP, mmHg | 27 (IQR 25-30) |
| PAWP, mmHg | 13 (IQR 11-14) |
| PVR, WU | 2.2 (IQR 1.9-2.7) |
| CO, L/min | 6.7 (IQR 5.8-7.9) |
| CI, L/min/$m^2$ | 3.55 (IQR 3.1-4.2) |
| RAP, mmHg | 8.0 (IQR 5.2 – 10.0) |
| MAP, mmHg | 98 (IQR83-106) |
| SVR, dynes.sec/$cm^5$ | 1078 (IQR 852 – 1240) |

| | |
|---|---|
| HR, bpm | 72 (IQR 67 – 87) |
| **Baseline 6MWD, m** | 352 (IQR 280-416) |
| **Pulmonary Function Tests** | |
| FEV1, % predicted | 91 (IQR 75-96) |
| FVC, % predicted | 90 (IQR 81-105) |
| TLC, % predicted | 93 (IQR 80-98) |
| DLCO, % predicted | 53 (IQR 45-62) |
| **NYHA Functional class, n (%)** | |
| I | 1 (1%) |
| II | 19 (23%) |
| III | 60 (73%) |
| IV | 2 (3%) |

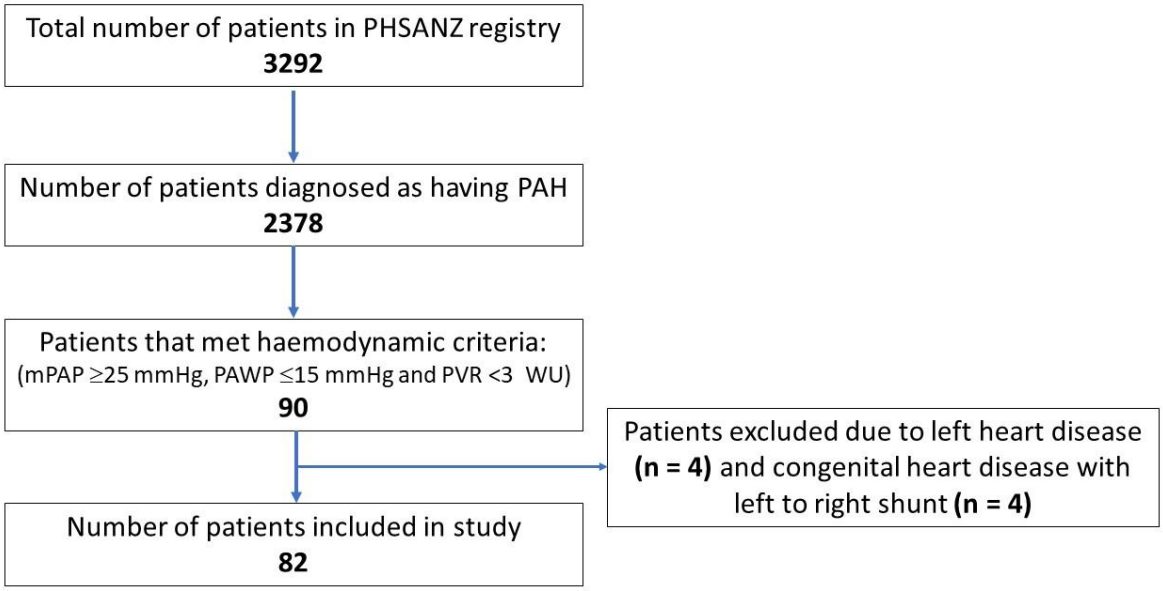
Data expressed as mean +/- SD unless otherwise stated. BMI – body mass index, mPAP – mean pulmonary artery pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, CO – cardiac output, CI – cardiac index, RAP – right atrial pressure, MAP – mean arterial pressure, SVR – systemic vascular resistance, NYHA – New York Heart Association, 6MWD – 6 minute walk distance, DLCO – diffusing capacity for carbon monoxide, FEV1 – forced expiratory volume in 1 sec, FVC – forced vital capacity, TLC – total lung capacity.

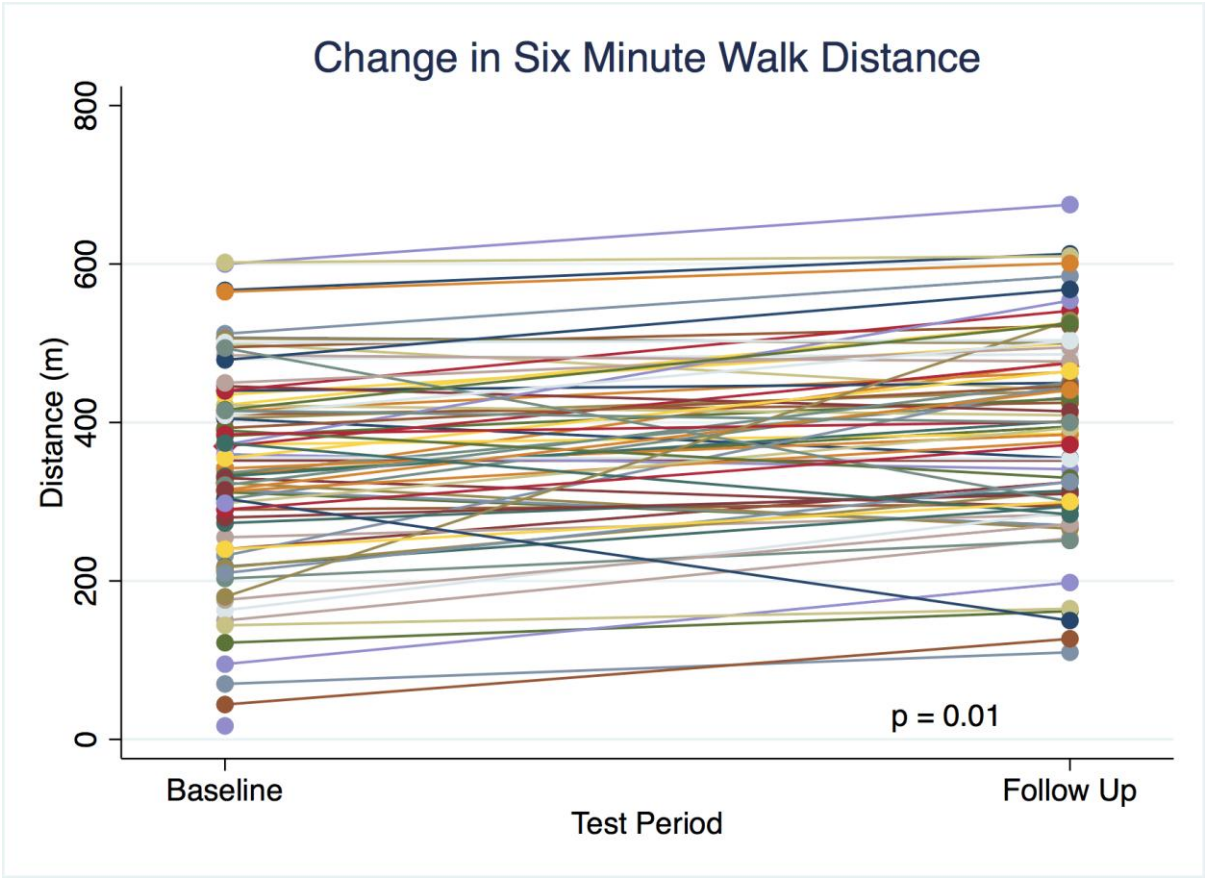
**Table 2. Therapy at diagnosis and last follow-up**

| | |
|---|---|
| **Initial treatment strategy** | |
| *Medication class (%)* | |
| Endothelin receptor antagonists | 66 (80%) |
| Phosphodiesterase type 5 inhibitors | 16 (20%) |
| *Specific medications (%)* | |
| Bosentan | 50 (61%) |
| Sitaxsentan | 7 (9%) |
| Macitentan | 5 (6%) |
| Ambrisentan | 4 (5%) |
| Sildenafil | 15 (18%) |
| Tadalafil | 1(1%) |
| | |
| **Treatment strategy 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%) |

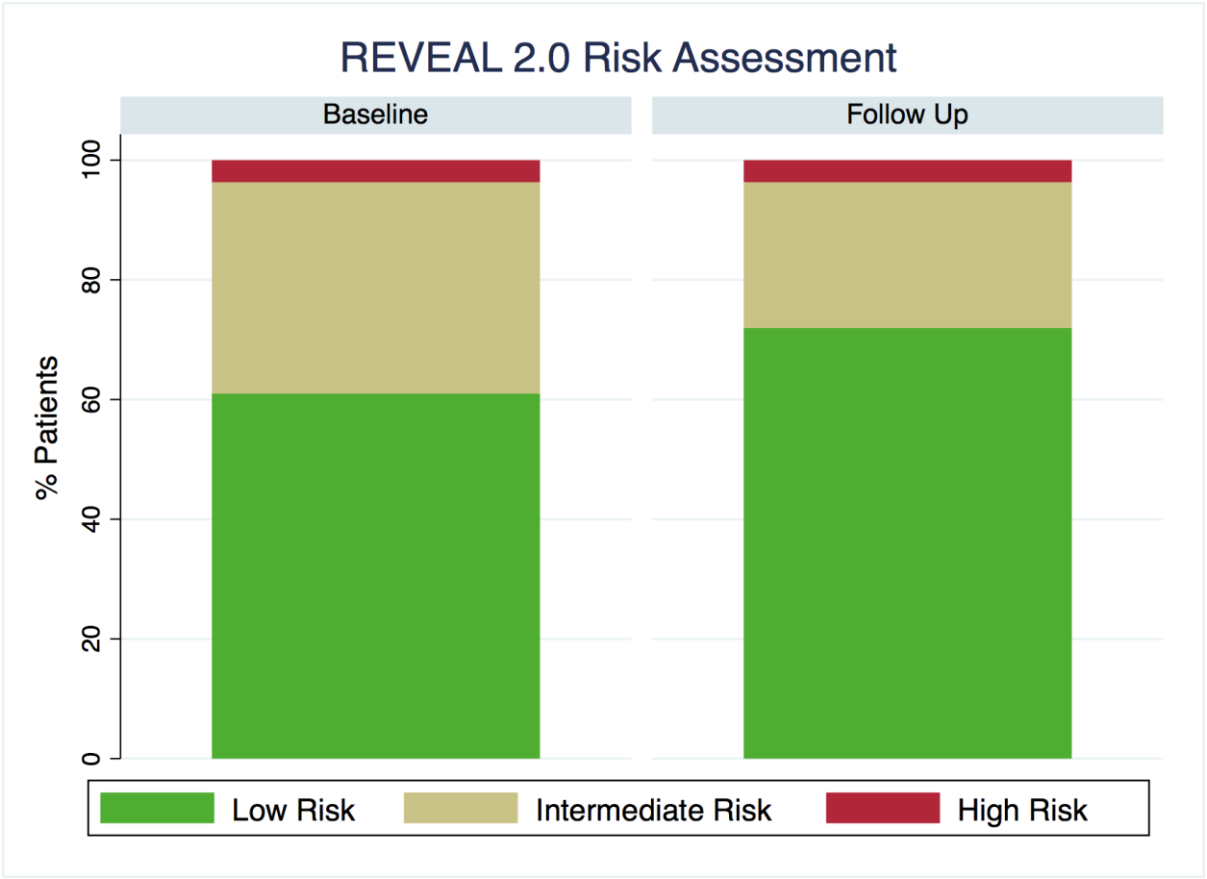
**Table 3. Cause of death during follow-up**

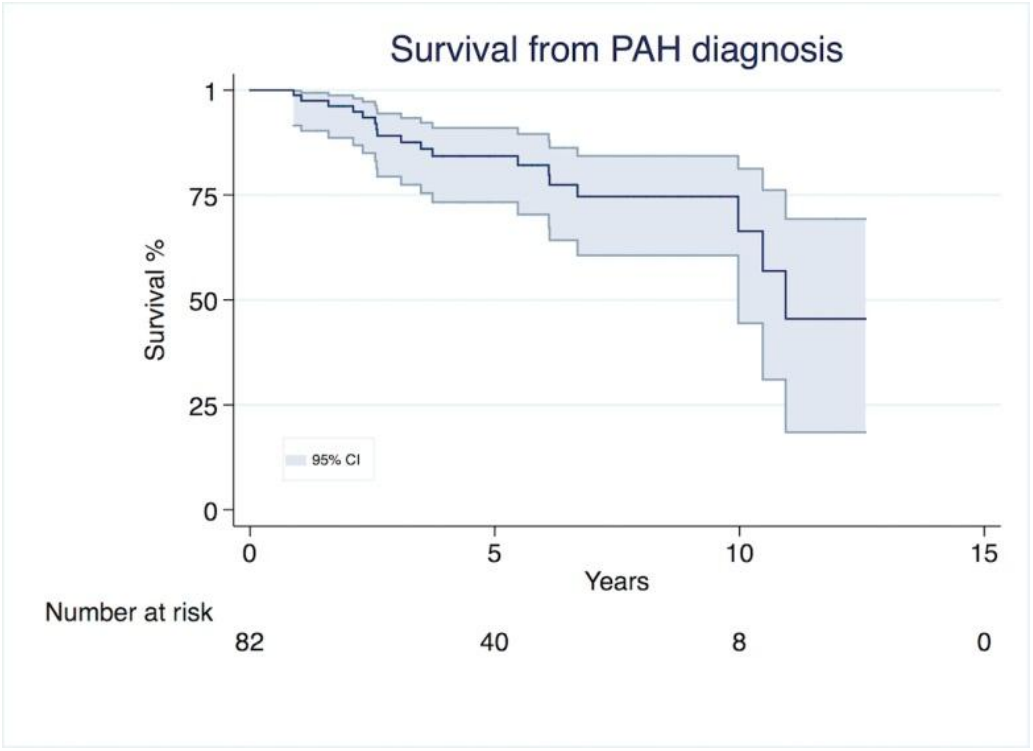
| | N (%) |
|---|---|
| **Total deaths** | **18** |
| **Death attributed to PAH** | **6 (33%)** |
| Right ventricular failure | 3 (11%) |
| Sudden cardiac events | 3 (17%) |
| **Deaths not directly attributed to PAH** | **9 (50%)** |
| Respiratory failure | 2 (11%) |
| Acute respiratory infections | 3 (17%) |
| Malignancy | 3 (17%) |
| Other | 1 (6%) |
| **Unknown** | **3 (17%)** |


Total number of patients in PHSANZ registry
3292
Number of patients diagnosed as having PAH
2378
Patients that met haemodynamic criteria:
(mPAP ≥25 mmHg, PAWP ≤15 mmHg and PVR <3 WU)
90
Patients excluded due to left heart disease (n = 4) and congenital heart disease with left to right shunt (n = 4)
Number of patients included in study
82


Change in Six Minute Walk Distance
Distance (m)
0
200
400
600
800
p = 0.01
Baseline
Follow Up
Test Period


Change in Functional Class
Baseline
Follow Up
% Patients
0
20
40
60
80
100
New York Heart Association Functional Class
1
2
3
4


REVEAL 2.0 Risk Assessment
Baseline
Follow Up
% Patients
0
20
40
60
80
100
Low Risk
Intermediate Risk
High Risk


Survival from PAH diagnosis
Survival %
1
75
50
25
0
95% CI
0
5
10
15
Years
Number at risk
82
40
8
0

## Supplementary Figure Legend

**Supplementary Figure 1.** Six-minute walk distance at baseline and at first follow up after initial treatment initiation stratified by aetiology. Non-CTD PAH group (left panel) showed median improvement of 65m (IQR14-104 p= 0.03) and CTD PAH group (right panel) showed median improvement of 41m (IQR 8-85 p=0.15).

**Supplementary Figure 2.** New York Heart Association Functional Class at baseline and at first follow up after treatment initiation in patients with non-CTD disease related PAH (A) and CTD PAH (B). In the non-CTD PAH group, 34% displayed improvement in FC compared to 20% in CTD-PAH group.

**Supplementary figure 3:** RVEAL 2.0 modified risk assessment at baseline and first follow-up after initial treatment initiation in patients with non-CTD PAH (A) and CTD PAH (B). Proportion of patients in the low risk category increased from 68% to 78% in non-CTD PAH group and from 54% to 64% in CTD PAH group.

**Supplementary Figure 4.** Kaplan-Meier survival estimates of study cohort with PVR <3WU (total = 82) compared to a reference PSHANZ cohort with PVR 3-4 WU (n=107). There was no significant difference in median survival (log rank, p=0.48).

**Supplementary Table 1. Baseline characteristics of patients stratified by aetiology**

| | Connective tissue disease related PAH (n=42) | Non-Connective tissue disease PAH (n=40) | P value |
|---|---|---|---|
| Age, years | 62 ± 10 | 63 ± 11 | 0.93 |
| Gender, Female % | 88% | 73% | 0.38 |
| BMI, kg/m$^2$ | 30.2 ± 8 | 32.8 ± 7 | 0.75 |
| **Co-morbidities, n (%)** | | | |
| Diabetes mellitus | 6 (14%) | 15 (38%) | 0.05 |
| Hypertension | 21 (50%) | 24 (60%) | 0.65 |
| Dyslipidemia | 19 (45%) | 17 (43%) | 0.74 |
| Ischemic heart disease | 14 (33%) | 8 (20%) | 0.20 |
| Peripheral vascular disease | 4 (10%) | 1 (3%) | 0.18 |
| Current smoker | 1 (2%) | 2 (5%) | 0.56 |
| Ex-smoker | 14 (33%) | 12 (30%) | 0.69 |
| Obstructive sleep apnoea | 9 (21%) | 11 (28%) | 0.65 |

| | | | |
|---|---|---|---|
| **Baseline haemodynamics:** | | | |
| mPAP, mmHg | 27 (IQR 26-29) | 27 (IQR 25-30) | 1 |
| PAWP, mmHg | 13 (IQR 11-14) | 13 (IQR 12-14) | 1 |
| PVR, WU | 2.2 (IQR 1.9-2.6) | 2.3 (IQR 1.9-2.7) | 0.96 |
| CO, L/min | 6.6 (IQR 5.8-7.5) | 7 (IQR 6.0-7.5) | 0.91 |
| CI, L/min/$m^2$ | 3.6 (IQR 3.2-4.2) | 3.6 (IQR 3.1-4.3) | 1 |
| RAP, mmHg | 7.0 (IQR 5.0 – 10.0) | 8 (IQR 6-11) | 0.79 |
| MAP, mmHg | 93 (IQR 82-102) | 104 (IQR 97-109) | 0.43 |
| SVR, dynes.sec/$cm^5$ | 1076 (IQR 848-1229)76 | 1078 (IQR 914-1272) | 0.97 |
| HR, bpm | (IQR 69 – 87) | 70 (IQR 66-79) | 0.62 |
| **Baseline 6MWD, m** | 390 (IQR314-436) | 323 (IQR 215-384) | 0.01 |
| **NYHA Functional class, n** | | | |
| I | 0 | 1 | 0.009 |
| II | 16 | 3 | |
| III | 25 | 35 | |
| IV | 1 | 1 | |

Data expressed as mean +/- SD unless otherwise stated. BMI – body mass index, mPAP – mean pulmonary artery pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, CO – cardiac output, CI – cardiac index, RAP – right atrial pressure, NYHA – New York Heart Association, 6MWD – 6 minute walk distance, MAP – mean arterial pressure, SVR – systemic vascular resistance, NYHA – New York Heart Association, 6MWD – 6 minute walk distance, DLCO – diffusing capacity for carbon monoxide, FEV1 – forced expiratory volume in 1 sec, FVC – forced vital capacity, TLC – total lung capacity.

**Supplementary Table 2. Therapy at diagnosis and last follow-up**

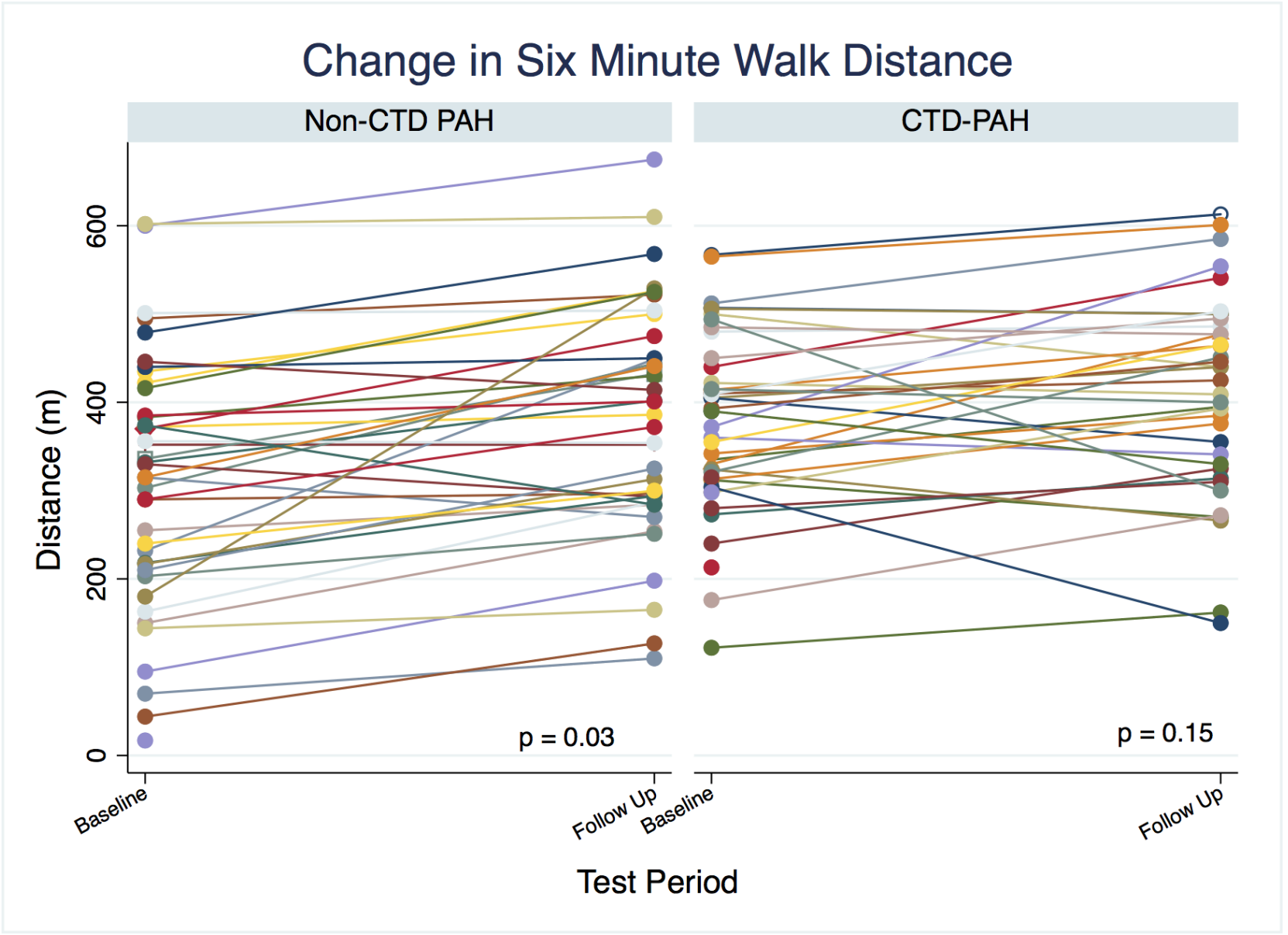
| | Connective tissue disease related PAH | Non-Connective tissue disease |
|---|---|---|
| **Number (%)** | 42 (100%) | 40 (100%) |
| **Initial treatment strategy** | | |
| *Medication class (%)* | | |
| Endothelin receptor antagonists | 32 (76%) | 34 (85%) |
| Phosphodiesterase type 5 inhibitors | 10 (24%) | 6 (15%) |
| *Specific medications (%)* | | |
| Bosentan | 23 (55%) | 27 (68%) |
| Sitaxsentan | 4 (10%) | 3 (8%) |
| Macitentan | 3 (7%) | 2 (5%) |
| Ambrisentan | 2 (5%) | 2 (5%) |
| Sildenafil | 10 (24%) | 5 (13%) |
| Tadalafil | 0 (0%) | 1 (3%) |
| **Treatment strategy at last follow up** | | |

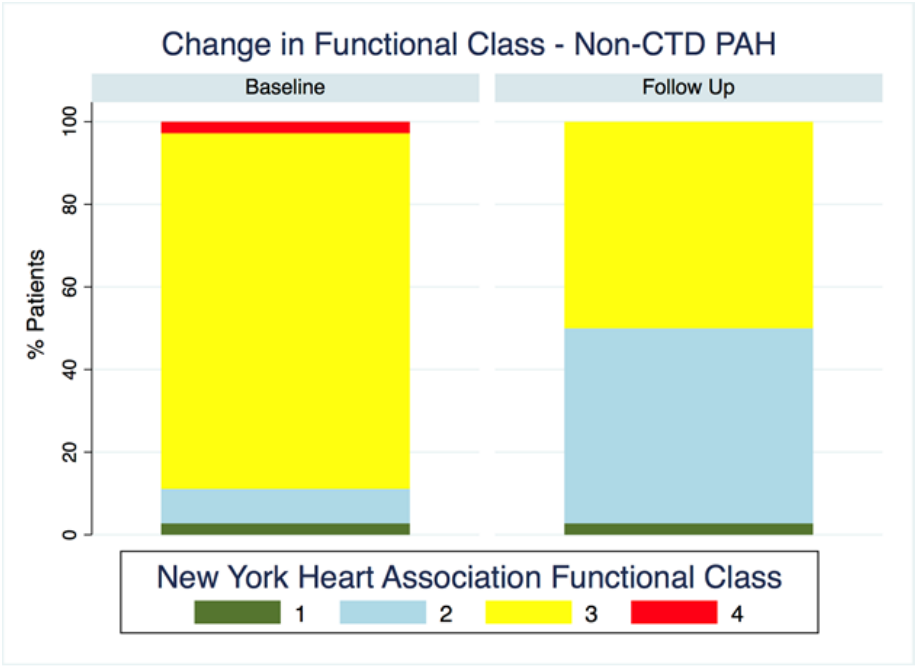
| | | |
|---|---|---|
| *Monotherapy (%)* | 31 (74%) | 37 (93%) |
| Bosentan | 16 (38%) | 22 (55%) |
| Sitaxsentan | 1 (2%) | 0 (0%) |
| Macitentan | 3 (7%) | 5 (13%) |
| Ambrisentan | 1 (2%) | 3 (7%) |
| Sildenafil | 10 (24%) | 4 (10%) |
| Tadalafil | 0 (0%) | 3 (8%) |
| *Combination therapy (%)* | 11 (26%) | 3 (8%) |
| Ambrisentan + sildenafil | 7 (17%) | 1 (2%) |
| Ambrisentan + tadalafil | 1 (2%) | 0 (0%) |
| Macitentan + sildenafil | 3 (7%) | 1 (2%) |
| Sitaxsentan + sildenafil | 0 (0%) | 1 (2%) |

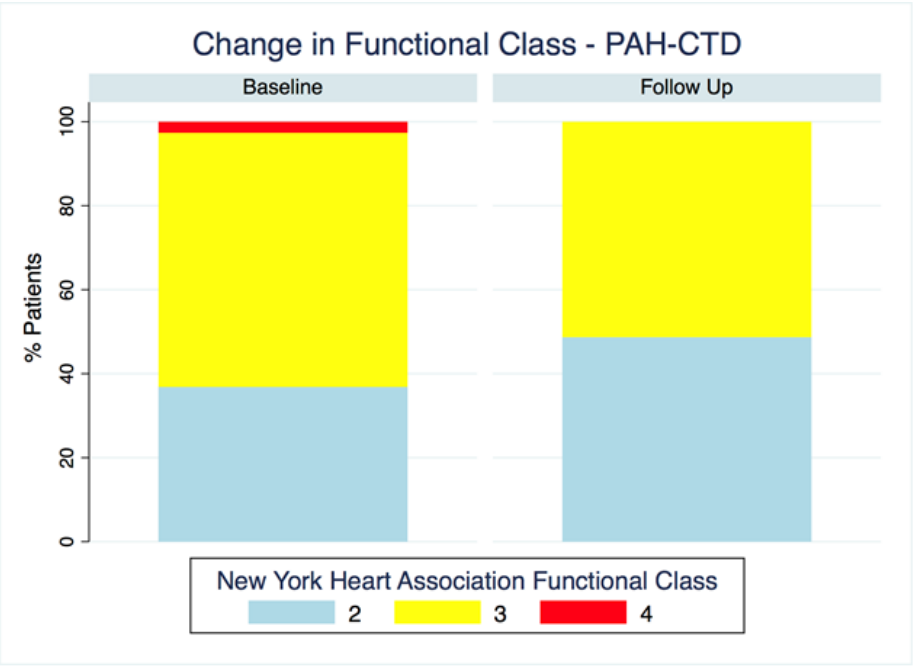
**Supplementary Table 3. Right heart catheterisation hemodynamics at baseline and follow up**

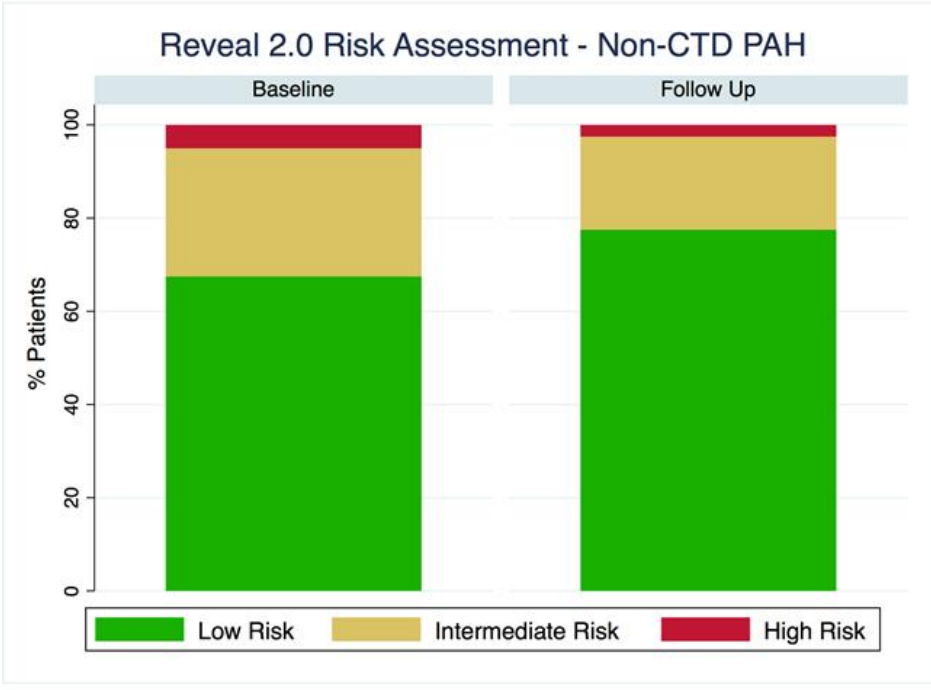
| | Baseline RHC | Repeat RHC | P value |
|---|---|---|---|
| mPAP, mmHg | 27 (IQR 26-28) | 25 (IQR 23-29) | 0.65 |
| PAWP, mmHg | 13 (IQR 11-14) | 12 (IQR 10-15) | 0.51 |
| PVR, WU | 2.3 (IQR 1.8 – 2.7) | 2.1 (IQR 1.7-3.0) | 0.37 |
| CO, L/min | 6.0 (IQR 5.8-6.9) | 5.6 (IQR 4.9-6.0) | 0.04 |
| CI, L/min/$m^2$ | 3.3 (IQR 3.1-3.5) | 3.1 (IQR 3.0-3.4) | 0.16 |
| RAP, mmHg | 7.0 (IQR 5.0 – 10.0) | 8.5 (IQR 6.8-10.0) | 0.35 |

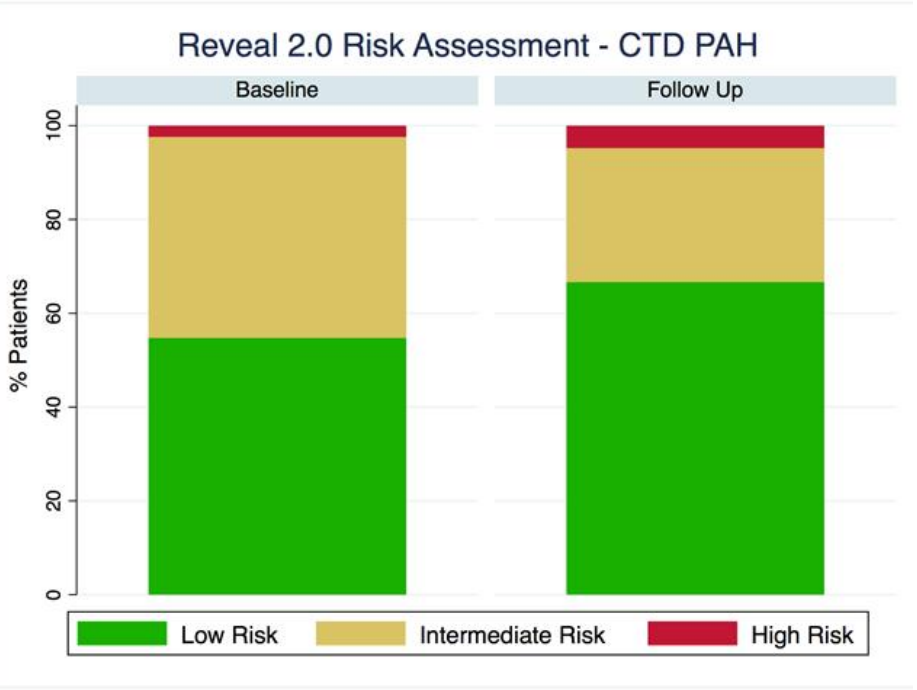
Data expressed as median (IQR). mPAP – mean pulmonary artery pressure, PAWP – pulmonary arterial wedge pressure, PVR – pulmonary vascular resistance, CO – cardiac output, CI – cardiac index, RAP – right atrial pressure

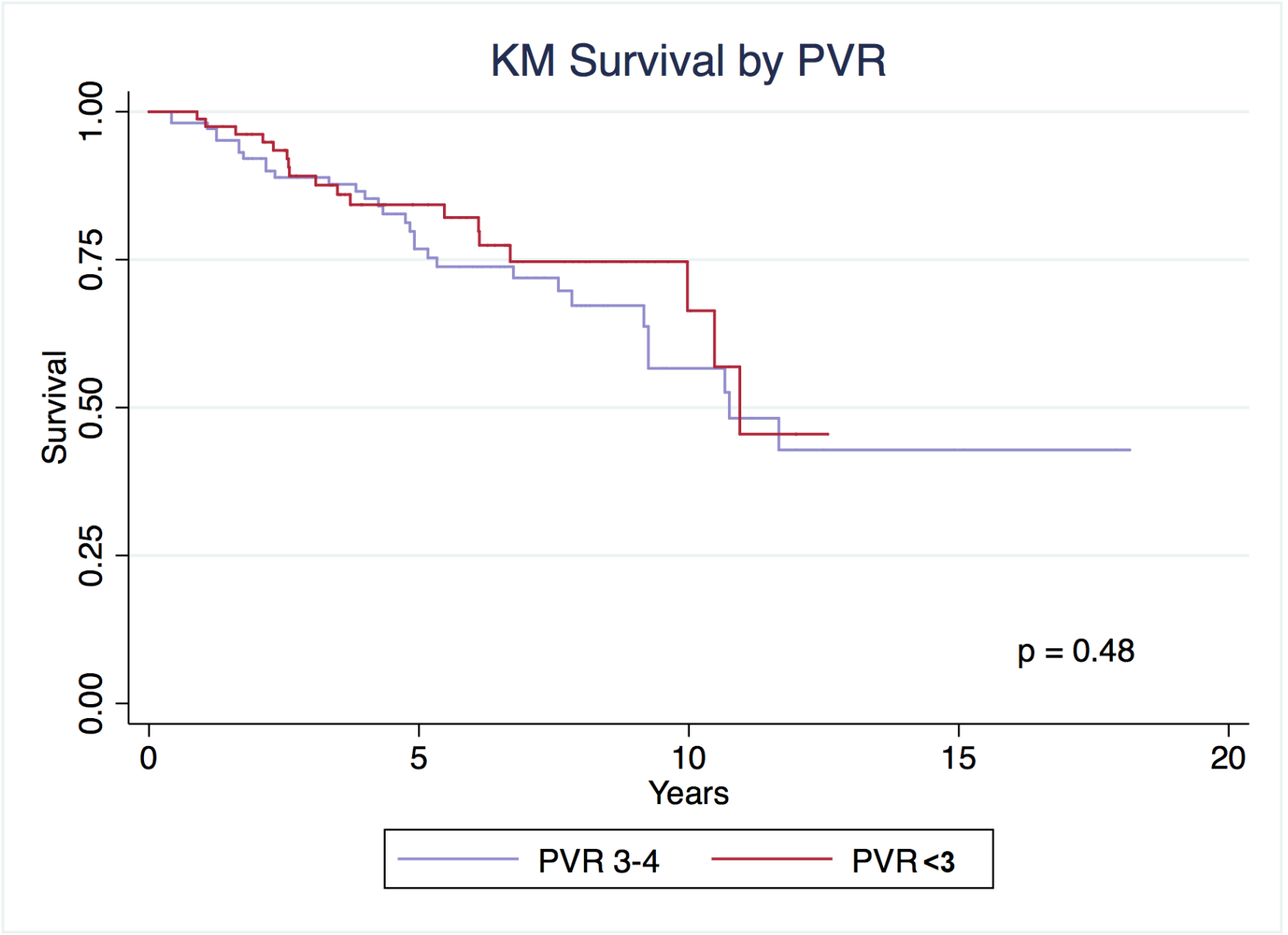

Change in Six Minute Walk Distance
Non-CTD PAH
CTD-PAH
Distance (m)
0
200
400
600
p = 0.03
p = 0.15
Baseline
Follow Up
Baseline
Follow Up
Test Period


Change in Functional Class - Non-CTD PAH
Baseline
Follow Up
% Patients
0
20
40
60
80
100
New York Heart Association Functional Class
1
2
3
4


Change in Functional Class - PAH-CTD
Baseline
Follow Up
% Patients
0
20
40
60
80
100
New York Heart Association Functional Class
2
3
4


Reveal 2.0 Risk Assessment - Non-CTD PAH
Baseline
Follow Up
% Patients
0
20
40
60
80
100
Low Risk
Intermediate Risk
High Risk


Reveal 2.0 Risk Assessment - CTD PAH
Baseline
Follow Up
% Patients
0
20
40
60
80
100
Low Risk
Intermediate Risk
High Risk


KM Survival by PVR
Survival
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
Years
p = 0.48
PVR 3-4
PVR<3