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Prognostic Value of Main Pulmonary Artery Diameter in Pulmonary Arterial Hypertension

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Running Title

Prognostic value of main pulmonary artery diameter in PAH

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Acknowledgements & Contributions

JYC – study conception and design, data collection, data analysis, data interpretation, manuscript preparation
RA – data collection, data interpretation, manuscript preparation
NW – data collection, data interpretation, manuscript preparation
NO – data analysis, data interpretation, manuscript preparation
KK – study conception and design, data interpretation, manuscript preparation
KW – study conception and design, data interpretation, manuscript preparation
EL – study conception and design, data interpretation, manuscript preparation
DC – study conception and design, data interpretation, manuscript preparation
EK – study conception and design, data interpretation, manuscript preparation

RC – study conception and design, data interpretation, manuscript preparation

Disclosures

There are no financial disclosures.

Conflicts of Interest

There are no conflicts of interest for any of the authors.

Key words: pulmonary artery diameter; pulmonary arterial hypertension; risk stratification.

Abbreviations: MRI = magnetic resonance imaging. CT = computed tomography. CTD = connective tissue disease. CTEPH = chronic thromboembolic pulmonary hypertension. ESC/ERS = European Society of Cardiology/European Respiratory Society. MPA = main pulmonary artery. PAH = pulmonary arterial hypertension. REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management. ROC = receiver operator characteristic.

Abstract

Background. Accurate risk stratification is critical aspect of pulmonary arterial hypertension (PAH) management. It is unclear whether main pulmonary artery (MPA) enlargement offers additional prognostic value to validated risk scores.

Research Question. Is MPA diameter prognostic in PAH, independent of the existing risk scores.

Study Design and Methods. A retrospective review of PAH patients from two large referral centres was conducted. Baseline REVEAL 2.0, REVEAL Lite 2 and ESC/ERS scores were calculated. The primary endpoint was composite death, lung transplantation and right heart failure hospitalisation. Cox proportional hazards models were used for time-to-event analyses. Receiver-operator characteristic and net reclassification improvement analyses additionally assessed the prognostic value of MPA diameter.

Results. 351 patients were included. Baseline MPA diameter was 35.3 ± 7.1 mm. MPA grew by 0.4 ± 1.1 mm/year (1.1% baseline diameter). Over mean 4.0 ± 3.4 years follow up, 190 primary events occurred, and MPA diameter was a predictor (HR 1.06 per mm, 95% CI 1.04-1.07, p<0.001). MPA diameter remained an independent predictor after multivariable adjustments for the three risk scores, and their individual components. MPA growth rate also predicted the outcome (HR 1.79 per mm/year, 95% CI 1.52-2.11, p<0.001), independent of baseline MPA diameter. Area under the receiver-operator characteristic curve for the risk of the primary endpoint at one year was similar for MPA alone (0.72) compared to the three risk scores (0.72-0.75). Furthermore, using MPA in addition to REVEAL 2.0 resulted in risk reclassification in 23% of patients, mostly due to appropriate risk downgrading.

Interpretation. MPA diameter is a significant independent predictor of adverse clinical events in PAH patients without congenital heart disease. It may potentially be a novel prognostic marker in addition to the existing risk scores.

Pulmonary arterial hypertension (PAH) is a progressive, life-threatening condition characterised by elevated pulmonary vascular resistance and pulmonary arterial pressures. Despite advances in medical therapy, the prognosis for patients with PAH remains poor, and accurate risk stratification is crucial for guiding treatment decisions and improving outcomes [1,2]. Currently, risk stratification in PAH relies on a combination of clinical, biochemical, echocardiographic and invasive haemodynamic parameters, which are incorporated into various scoring systems as described in the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines [3]. These models provide valuable insights into a patient's prognosis but require multiple parameters, some of which may be difficult to obtain. Therefore, there is ongoing need for non-invasive and accessible parameters to prognosticate clinical outcomes.

The main pulmonary artery (MPA) diameter is one such parameter that has garnered increasing attention. Enlargement of the MPA is frequently observed in PAH and may reflect the cumulative effects of elevated pulmonary pressures and vascular remodelling. Existing data on the prognostic value of MPA diameter in PAH have been conflicting [4-8], although the cohorts have been heterogeneous or limited in size. Therefore, the present study has two aims – firstly to comprehensively characterise the size and growth of MPA in PAH patients without congenital heart disease; and secondly to evaluate its prognostic value especially in the context of existing risk stratification scores.

Study Design and Methods

We retrospectively analysed all patients with PAH without congenital heart disease from two large pulmonary hypertension referral centres in Sydney, Australia. Patients with PAH and congenital heart disease were excluded as pulmonary enlargement in certain congenital lesions can result from volume overload, which differs in mechanism to the other subgroups of PAH. Those with concurrent chronic thromboembolic pulmonary hypertension (CTEPH) were also excluded due to the impact of reflected waves on pulmonary vascular remodelling. Finally, those with documented history of vasculitis involving the pulmonary circulation were excluded.

PAH was diagnosed according to the 2015 ESC guidelines [9]. The PAH subgroups were defined according to the World Health Organisation classification [10].

Patients were included if they had at least one pulmonary artery imaging between January 2010 to December 2021. In those with multiple imaging, we took the earliest imaging available within the study period. The Sydney Local Health District Institutional Review Board approved the study.

<u>Baseline Clinical Variables & Outcomes</u>

Baseline data were extracted through retrospective electronic medical record review. To be included, data points had to be within 12 months of baseline MPA imaging. The specific baseline variables collected are described in the Supplementary Method. These variables were used to calculate the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) 2.0 [11], REVEAL Lite 2 [12], and ESC/ERS scores [3] (e-Fig. 1). REVEAL 2.0 score was calculated if there were at least seven parameters available. REVEAL Lite 2 score was calculated if there were at least three parameters available including at least two of WHO functional class, 6MWD or NT-proBNP. ESC/ERS score was calculated if there were at least three parameters available.

The primary outcome was a composite of all-cause mortality, lung transplantation (including combined heart and lung transplantation), and hospitalisation for right heart failure. Right heart failure hospitalisation was defined according to available discharge summaries, and in the majority of cases included significant peripheral oedema or ascites requiring uptitration of diuretics or intravenous diuretics in hospital. Initiation of intravenous epoprostenol was not included as a primary endpoint component since some patients were already on epoprostenol at baseline MPA imaging, introducing potential bias. There were two secondary outcomes – first a composite of all-cause mortality and lung transplantation, and second a composite of all-cause mortality, lung transplantation, right heart failure hospitalisation and new commencement of intravenous epoprostenol.

MPA Imaging

Two imaging modalities were considered for MPA measurement – computed tomography (CT) with or without contrast and cardiac magnetic resonance imaging (MRI). Transthoracic echocardiogram was not considered given that the scans were not dedicated for MPA measurement. Both ECG gated and non-gated CTs were included. MPA is measured using a previously described method that correlated well with pulmonary pressures [13] (Supplementary Method, e-Fig. 2). The most recent follow-up imaging, where available, was used to evaluate MPA diameter changes. The change between baseline and follow-up MPA diameter was then used to calculate absolute MPA growth (mm/year) and relative MPA growth as a percentage of baseline MPA diameter (%/year).

Statistical Analysis

Baseline categorical data were presented as count and percentage, and continuous data as mean ± standard deviation if normally distributed or median (interquartile range) otherwise. Baseline variables were compared between the three MPA diameter tertiles using chi-squared tests for categorical variables, and ANOVA or

Kruskal-Wallis tests for continuous variables. Predictors of baseline MPA size and growth were evaluated by univariable linear regression.

Survival analysis was performed using the "survival" package (version 3.3.1) in R [14]. Univariable Cox Proportional Hazards models evaluated MPA and other baseline variables as predictors of the primary endpoint. Six multivariable Cox models were pre-specified: five adjusted for REVEAL 2.0, REVEAL Lite 2, ESC/ERS, and their components, while the sixth was empirical, including baseline variables associated with the endpoint at $p<0.2$. Thereafter, predictors on the multivariable model with the highest *p* value were removed in a stepwise manner until all predictors had $p<0.2$. In all multivariable models, only factors with adjusted variance inflation factor < 3 were included to minimise collinearity, and this was performed prior to stepwise variable selection for the sixth model. Subgroup analyses evaluated PAH subgroups, ECG gating, and timing of MPA imaging relative to diagnosis.

Time-dependent ROC analysis for the primary endpoint at one year was performed using the "survivalROC" package (version 1.0.3.1) in R [15]. The MPA ROC curve was visually and statistically compared to the three scores using DeLong's test. Net reclassification improvement analysis evaluated adding MPA diameter to REVEAL 2.0 for one-year primary outcome risk prediction using risk categories <5%, 5-20%, and >20%.

All analyses used R version 4.2.1 (R Core Team, 2024), with $p<0.05$ considered significant.

Results

There were 449 PAH patients without congenital heart disease followed at two centres, with 95 excluded (e-Fig. 3), leaving 351 for analysis. This comprised 244 (70%) contrast-enhanced CTs, 95 (27%) non-contrast enhanced CTs and 12 (3%) MRIs.

Baseline variables are shown in Table 1. The most common PAH subgroup was connective tissue disease (CTD)-related (49%), followed by idiopathic PAH (30%) and portopulmonary hypertension (5%). Baseline mean pulmonary artery pressure (MPAP) was 43±13 mmHg, and pulmonary vascular resistance was 7.8±5.1 Wood units. Right ventricular function on echocardiography was normal in 55%, mildly impaired in 17%, moderately impaired in 12%, and severely impaired in 15%. Pericardial effusion was seen in 18%.

The REVEAL 2.0, REVEAL Lite 2, and ESC/ERS scores were calculated for 90%, 84%, and 92% of the cohort, respectively. The cohort was intermediate risk: 8.2±3.2

on REVEAL 2.0, 6.5±2.5 on REVEAL Lite 2, and 1.9±0.5 on ESC/ERS score (e-Fig. 4).

Baseline MPA Diameter and Growth

The median age of baseline MPA imaging was 62 (49-73) years. The median time of imaging post-PAH diagnosis was 0.5 (0-3.0) years, with 200 (57%) within one year. Intraclass correlation between the two blinded raters was high at 0.93 (95% CI 0.87-0.96).

Mean clinical follow up post-baseline imaging was 4.0±3.4 years. The mean baseline MPA diameter was 35.3±7.1 mm and the MPA-to-aorta ratio was 1.2±0.3 (Fig. 1). The mean MPA diameter did not differ according to mode of imaging (contrast CT: 35.4±7.1 mm; non-contrast CT: 35.1±7.0 mm; MRI: 35.6±8.9 mm, p=0.91). 33 (9%) scans were ECG-gated and 318 (91%) were not. The mean MPA diameter not differ depending on the use of gating (gated: 35.5±7.1 mm; non-gated: 34.1±7.7 mm, p=0.33). MPA diameter ranged from 17 to 75 mm and was divided into three tertiles (tertile 1: 17-32 mm; tertile 2: 33-38 mm; tertile 3: 39-75 mm). Baseline MPA diameter was associated with various factors, including PAH subgroup, elevated pulmonary pressures, right ventricular function, and body surface area (e-Table 1).

Serial imaging was available for 170 patients at a median 3.8 (2.3-6.9) years, with 111 using the same modality. The indications for follow up imaging were not well captured. Those with follow up imaging, however, were at lower risk of the primary endpoint (HR 0.63, 95% CI 0.47-0.84; p=0.002). Between those with and without follow-up imaging, the REVEAL 2.0 (7.9±3.1 versus 8.5±3.2, p=0.12), REVEAL Lite 2 (6.2±2.4 versus 6.8±2.5, p=0.07) and ESC/ERS (1.9±0.5 versus 2.0±0.5, p = 0.15) scores were comparable.

Between imaging, MPA grew in 56% of patients, remained unchanged in 31%, and shrank in 13%. Mean growth was 0.4±1.1 mm/year (1.1±2.9%/year). Idiopathic PAH patients had minimal growth compared to CTD-related PAH (0.04±0.98 mm/year vs. 0.49±1.04 mm/year, p=0.02). Larger baseline MPA diameter predicted faster growth, independent of body surface area. Baseline risk scores predicted growth, but haemodynamic and echocardiographic parameters did not consistently do so (e-Table 1).

Prognostic Value of MPA Diameter and Growth

Over the follow up of the study, 190 patients reached the primary composite endpoint. The first event was death in 82 patients, lung transplantation in 11 patients and right heart failure hospitalisation in 97 patients. The proportional hazards assumption was tested using Schoenfeld residuals for baseline MPA diameter and

the global model. The findings suggest that the assumption holds for the Cox proportional hazards model (MPA p=0.6, global p=0.6). Baseline MPA diameter was a significant predictor of the primary endpoint (HR 1.06 per mm, 95% CI 1.04-1.07, p<0.001). In turn, every 5 mm larger baseline MPA was associated with a 31% (95% CI 22-41%) increased hazard. This association remained when the analysis was restricted to CT imaging (HR 1.06 per mm, 95% CI 1.04-1.07, p<0.001). When divided by tertiles, the medium and largest MPA tertile, compared to the smallest tertile, was associated with 2.6- (95% CI 1.7-3.8) and 3.5-times (95% CI 2.4-5.2) increased hazard (p<0.001. Fig. 2).

The three pre-specified subgroup analyses revealed consistent results. When grouped by PAH subgroup, MPA was a predictor of the primary endpoint in both PAH-CTD (HR 1.10 per mm, 95% CI 1.07-1.13, p<0.001) and idiopathic PAH (HR 1.07 per mm, 95% CI 1.03-1.11, p<0.001). When grouped by the presence of ECG gating, MPA remained a predictor in both gated (HR 1.13, 95% CI 1.03-1.25, p=0.015) and non-gated groups (HR 1.05, 95% CI 1.04-1.07, p<0.001) with no significant interaction between the groups (interaction p=0.23). When grouped by timing of initial MPA imaging, 200 patients had MPA imaging within one year of PAH diagnosis, and 149 patients more than one year after diagnosis. MPA diameter was prognostic in both groups (within one year: HR 1.08, 95% CI 1.05-1.11, p<0.001; more than one year after: HR 1.04, 95% CI 1.02-1.06, p<0.001) .

Various other baseline variables, including the REVEAL 2.0, REVEAL Lite 2 and ESC/ERS scores, were associated with increased hazard of the primary endpoint (Table 2). On multivariable analysis, baseline MPA measurement remained a significant independent predictor of the primary outcome in the empirical model (Table 2) as well as models that adjusted for 1) REVEAL 2.0 score; 2) REVEAL Lite 2 score; 3) ESC/ERS score; 4) components of REVEAL 2.0 score; and 5) components of ESC/ERS score (Table 3). In all models, the adjusted hazard ratio as predicted by the baseline MPA diameter remained comparable to the unadjusted value. In all the five models including the three with composite scores and two with score components, adding MPA diameter produced a statistically significant increase in the C-statistic and reduction in Bayesian information criterion suggestive of a better fit model (Table 3).

The secondary outcome of death or lung transplantation occurred in 165 patients (148 deaths, 17 transplantations). Baseline MPA diameter was a significant predictor (HR 1.05, 95% CI 1.03-1.07, p<0.001). The secondary outcome of death, lung transplantation, right heart failure hospitalisation and new commencement of intravenous epoprostenol occurred in 195 patients. Baseline MPA diameter was also a significant predictor (HR 1.06, 95% CI 1.04-1.07, p<0.001). MPA remained a predictor after adjustment for baseline risk scores (e-Table 2 and 3).

MPA growth was a predictor of the primary endpoint, with every 1 mm/year conferring a 79% increased hazard (HR 1.79, 95% CI 1.52-2.11, p<0.001). This remained significant after adjusting for baseline MPA diameter (HR 1.61, 95% CI 1.33-1.95, p<0.001), as well as for baseline REVEAL 2.0 (HR 1.53 per mm/year growth, 95% CI 1.28-1.84, p<0.001), REVEAL Lite 2 (HR 1.59 per mm/year growth, 95% CI 1.33-1.90, p<0.001) and ESC/ERS score (HR 1.59 per mm/year growth, 95% CI 1.34-1.89, p<0.001). Notably, event rate was 28 % in those who had unchanged or shrinking of the MPA between imaging, whereas it was 83 % in those who had growth ≥ 2mm/year (Fig. 3).

Time-dependent ROC analysis was performed for the 1-year risk of the primary outcome with the predictors being baseline MPA diameter alone and the 3 risk scores (Fig. 4). The AUC for MPA alone was 0.72 (95% CI 0.66-0.77). This was comparable to the AUC for REVEAL Lite 2, REVEAL 2.0 and ESC/ERS scores by DeLong's test and visually. The sensitivity and specificity values at different MPA cutoffs are shown in e-Table 4.

When MPA diameter was added to REVEAL 2.0, this resulted in risk reclassification in 23% of patients (95% CI 13-34%, p<0.05). This was primary driven by reclassification of non-events (20%), that is more appropriately lowering the risk of those classified into a higher risk category by the REVEAL 2.0 score.

Discussion

The current study aimed to characterise MPA growth in PAH patients without congenital heart disease and evaluate its prognostic value alongside established risk stratification scores. Our findings highlight several clinically relevant insights. First, MPA enlargement is frequent in PAH, with progressive growth being the norm. While we identified several clinical and haemodynamic variables associated with baseline MPA enlargement, fewer predicted growth. Second, MPA diameter was independently associated with increased risk of mortality, lung transplantation, or hospitalisation for right heart failure, a relationship that remained robust after adjusting for multiple PAH risk scores (REVEAL 2.0, REVEAL Lite 2, ESC/ERS Guidelines) and their components. Third, the rate of MPA growth served as an additional risk modifier, predicting outcomes independent of baseline diameter. Finally, MPA diameter alone demonstrated modest predictive value for 1-year risk of the primary endpoint, performing comparably to existing risk scores.

In our cohort, the mean MPA diameter was 35 mm, with over 90% of patients exceeding sex-specific thresholds (29 mm for men, 27 mm for women) from the Framingham Heart Study [16]. Approximately half had serial imaging, allowing us to characterise MPA changes over time, a less-explored aspect in the literature. Most patients showed progressive MPA enlargement or stability, with an average growth of

0.4 mm/year, equivalent to 1.1%/year of baseline diameter. The MPA growth rate is similar to that of aortic root/ascending aorta aneurysms in contemporary series [17,18].

Importantly, our findings suggest that baseline MPA diameter and MPA growth rate are robust predictors of adverse clinical outcomes, independent of existing risk models. This may underscore the complex interplay of haemodynamics, vascular biology and genetic predisposition leading to pulmonary vascular remodelling that is not predicted by traditional risk factors [19,20]. In our cohort, every 5 mm increase in baseline MPA diameter was associated with a 31% higher risk of death, transplantation, or right heart failure hospitalisation. When stratified by tertiles, 1-year event-free survival rates were 92%, 76%, and 64% for the smallest, medium, and largest MPA tertiles, respectively. Likewise, our receiver-operatory characteristics analyses noted a specificity of 80% for one-year risk of the primary endpoint in those with MPA larger than 39.5 mm. Such information is pertinent for weighing up the risks and benefits of transplant and determining timing of transplant listing.

Other studies evaluating the prognostic value of MPA diameter have yielded conflicting results. In a cohort of adults with suspected pulmonary hypertension of various aetiologies, Truong *et al*. noted a four-fold increased risk of death per log MPA diameter [7]. However, given heterogeneity in pathophysiological mechanisms between pulmonary hypertension subgroups, extrapolation of these results to PAH was unclear. In PAH patients and PAH-CTD patients only, Tonelli *et al.* [4] and Li *et al* [8], respectively, found worse survival with bigger MPA, but due to limited covariate adjustment, the value of MPA in the context of existing risk scores was not evaluated. In a cohort of patients with PAH or CTEPH, Zylkowska *et al*. found higher risk of unexpected death in those with bigger MPA, raising concerns about risk of pulmonary artery rupture or left main coronary artery compression with MPA dilatation [6]. In contrast, Rajaram et al. found no association between the MPA-to-aorta ratio and all-cause mortality in a treatment-naïve PAH cohort, possibly due to a large proportion of congenital heart disease patients, who may experience MPA enlargement independent of pulmonary pressures [5]. To our knowledge, the current study is the largest to evaluate MPA diameter as a prognostic marker in a non-congenital heart disease PAH cohort, and explore its value in the context of existing risk scores.

In addition to its independent prognostic value, we demonstrated that MPA diameter alone offers similar predictive power as existing risk stratification scores. Given the increasing use of cross-sectional imaging for other indications, MPA diameter may serve as a simple and readily accessible alternative to the multi-parametric risk scores. Our ROC analyses showed comparable area under the curve values for MPA diameter alone to REVEAL 2.0, REVEAL Lite 2, and ESC/ERS guidelines. Furthermore, MPA diameter may offer incremental risk stratification value. The net reclassification improvement analysis highlighted that one in five patients would be

more appropriately classified into a lower risk category if MPA diameter was used in addition to the REVEAL 2.0 score.

This study has several limitations. First, its retrospective design meant that not all patients had appropriate MPA imaging or complete baseline data. Therefore, external validation in a prospective cohort is necessary to confirm the prognostic value of MPA diameter before clinical implementation. Second, we lacked data on the causes of mortality, which would be crucial in understanding the risks of pulmonary artery dissection and left main coronary artery compression and in determining appropriate screening strategies and surgical timing. Third, most imaging was not ECG-gated, potentially introducing variability in measurements, although this reflects the range of imaging modalities used in clinical practice. Nevertheless, we have highlighted comparable mean MPA measurements between gated and non-gated images and no difference in the prognostic value of MPA between the two modalities. Fourth, the incompleteness of the follow up imaging may have introduced bias into our analyses. Despite similar risk scores, those with follow-up imaging were at lower risk of the primary endpoint, which could be driven by unmeasured risk factors, thus necessitating prospective validation. Finally, we weren't able to capture the impact of pulmonary vasodilators on MPA diameter and its prognostic value. Nevertheless, MPA diameter remained prognostic in both those with MPA imaging within one year of PAH diagnosis and those with imaging more than one year after diagnosis.

Interpretation

Our study demonstrated that MPA diameter is a clinically significant predictor of adverse outcomes in patients with non-congenital heart disease PAH. It is additionally robust to adjustment for existing risk scores. It may serve as a readily accessible marker that offers incremental risk stratification values when added to existing risk stratification scores. Prospective validation is necessary before this novel parameter can be integrated into clinical practice.

References

1. Chin KM, Gaine SP, Gerges C, et al. Treatment algorithm for pulmonary arterial hypertension. *Eur Respir J.* 2024.
2. Dardi F, Boucly A, Benza R, et al. Risk stratification and treatment goals in pulmonary arterial hypertension. *Eur Respir J.* 2024.
3. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J.* 2022;43(38):3618-3731.
4. Tonelli AR, Johnson S, Alkukhun L, Yadav R, Dweik RA. Changes in main pulmonary artery diameter during follow-up have prognostic implications in pulmonary arterial hypertension. *Respirology.* 2017;22(8):1649-1655.
5. Rajaram S, Swift AJ, Condliffe R, et al. CT features of pulmonary arterial hypertension and its major subtypes: a systematic CT evaluation of 292 patients from the ASPIRE Registry. *Thorax.* 2015;70(4):382-387.
6. Zylkowska J, Kurzyna M, Florczyk M, et al. Pulmonary artery dilatation correlates with the risk of unexpected death in chronic arterial or thromboembolic pulmonary hypertension. *Chest.* 2012;142(6):1406-1416.
7. Truong QA, Bhatia HS, Szymonifka J, et al. A four-tier classification system of pulmonary artery metrics on computed tomography for the diagnosis and prognosis of pulmonary hypertension. *J Cardiovasc Comput Tomogr.* 2018;12(1):60-66.
8. Li X, Zhang C, Sun X, et al. Prognostic factors of pulmonary hypertension associated with connective tissue disease: pulmonary artery size measured by chest CT. *Rheumatology (Oxford).* 2020;59(11):3221-3228.
9. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37(1):67-119.
10. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(25 Suppl):D34-41.
11. Benza RL, Gomberg-Maitland M, Elliott CG, et al. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. *Chest.* 2019;156(2):323-337.
12. Benza RL, Kanwar MK, Raina A, et al. Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension. *Chest.* 2021;159(1):337-346.
13. Mahammedi A, Oshmyansky A, Hassoun PM, Thiemann DR, Siegelman SS. Pulmonary artery measurements in pulmonary hypertension: the role of computed tomography. *J Thorac Imaging.* 2013;28(2):96-103.
14. Therneau TM. A Package for Survival Analysis in R. 2022.
15. Heagerty PJ, by Paramita Saha-Chaudhuri P. survivalROC: Time-Dependent ROC Curve Estimation from Censored Survival Data. 2022.

16. Truong QA, Massaro JM, Rogers IS, et al. Reference values for normal pulmonary artery dimensions by noncontrast cardiac computed tomography: the Framingham Heart Study. *Circ Cardiovasc Imaging.* 2012;5(1):147-154.
17. Elefteriades JA, Ziganshin BA, Rizzo JA, et al. Indications and imaging for aortic surgery: size and other matters. *J Thorac Cardiovasc Surg.* 2015;149(2 Suppl):S10-13.
18. Gagné-Loranger M, Dumont É, Voisine P, Mohammadi S, Dagenais F. Natural history of 40–50 mm root/ascending aortic aneurysms in the current era of dedicated thoracic aortic clinics †. *European Journal of Cardio-Thoracic Surgery.* 2016;50(3):562-566.
19. Raymond TE, Khabbaza JE, Yadav R, Tonelli AR. Significance of main pulmonary artery dilation on imaging studies. *Ann Am Thorac Soc.* 2014;11(10):1623-1632.
20. Boerrigter B, Mauritz GJ, Marcus JT, et al. Progressive dilatation of the main pulmonary artery is a characteristic of pulmonary arterial hypertension and is not related to changes in pressure. *Chest.* 2010;138(6):1395-1401.

Take Home Points

- Study question – what is the prognostic role of main pulmonary artery diameter in pulmonary arterial hypertension?
- Results – pulmonary artery diameter and rate of growth are adversely prognostic, independent of existing risk scores.
- Interpretation – pulmonary artery diameter may be an accessible and independent prognosticator in pulmonary arterial hypertension, but external validation is required.

Figure Legend

Figure 1. Histograms of baseline MPA diameter (A), MPA-to-aorta ratio (B), MPA growth rate per year (C) and MPA growth rate per year as a percentage of baseline MPA diameter (D). The red vertical dashed lines in A represent the cutoff for the three MPA diameter tertiles. The red vertical dashed line in B represents the value 0.9, which is a previously defined threshold for MPA enlargement. MPA = main pulmonary artery.

Figure 2. Event-free survival according the tertiles of baseline MPA diameter.

Figure 3. Risk of the primary event during follow up according to rate of MPA growth per year.

Figure 4. Receiver-operator characteristic analyses comparing MPA size alone as a predictor of the 1-year risk of the primary outcome versus the other three risk stratification scores. ESC/ERS = European Society of Cardiology/European Respiratory Society. MPA = main pulmonary artery. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0.

e-Figure Legend

e-Figure 1. The REVEAL 2.0 (A), REVEAL Lite 2 (B) and ESC/ERS (C) scores. ESC/ERS = European Society of Cardiology/European Respiratory Society. MPA = main pulmonary artery. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0. *Source: PAH Initiative. https://www.pahinitiative.com/hcp/risk-assessment/calculators*

e-Figure 2. Example of MPA diameter measurement. MPA = main pulmonary artery.

e-Figure 3. Flowchart of patients. PAH = pulmonary arterial hypertension.

e-Figure 4. Distribution of risk across the ESC/ERS, REVEAL 2.0 and REVEAL Lite 2 scores. ESC/ERS = European Society of Cardiology/European Respiratory Society. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0.

Variable	Total N = 351	Tertile 1 (17-32 mm) N = 126	Tertile 2 (33-38 mm) N = 122	Tertile 3 (39-75 mm) N = 103	P Value
MPA Imaging					
MPA diameter – mm	35.3 ± 7.1	28.6 ± 3.3	35.4 ± 1.8	43.5 ± 5.9	<0.001
MPA/BSA – mm/m^2	20.0 ± 4.4	16.8 ± 2.7	20.1 ± 3.0	24.1 ± 4.2	<0.001
MPA/Aorta	1.2 ± 0.3	1.0 ± 0.2	1.2 ± 0.2	1.4 ± 0.3	<0.001
MPA growth – mm/year	0.4 ± 1.1	0.2 ± 0.8	0.4 ± 1.4	0.8 ± 0.9	0.01
MPA growth – % baseline/year	1.1 ± 2.9	0.5 ± 2.8	1.2 ± 3.7	1.7 ± 2.0	0.09
Clinical					
Baseline age – yr	61.8 ± 23.9	65.7 ± 20.8	61.1 ± 25.9	59.8 ± 22.7	0.09
Last follow up age – yr	64.4 ± 15.2	67.4 ± 14.9	62.5 ± 16.1	63.2 ± 14.3	0.025
Male sex – no. (%)	93 (26.5)	30 (23.8)	32 (26.2)	31 (30.1)	0.561
Body surface area – m^2	1.8 ± 0.2	1.7 ± 0.2	1.8 ± 0.2	1.8 ± 0.3	0.002
PAH subgroup – no. (%)					0.288
Idiopathic	104 (29.6)	30 (23.8)	44 (36.1)	30 (29.1)	
CTD	172 (49.0)	71 (56.3)	57 (46.7)	44 (42.7)	
Drug	10 (2.8)	4 (3.2)	3 (2.5)	3 (2.9)	
PoPH	18 (5.1)	6 (4.8)	4 (3.3)	8 (7.8)	
Other	47 (13.4)	15 (11.9)	14 (11.5)	18 (17.5)	
WHO functional class – no. (%)					0.817
I	2 (0.6)	1 (0.8)	0 (0.0)	1 (1.0)	
II	148 (42.2)	57 (45.2)	51 (41.8)	40 (38.8)	
III	176 (50.1)	61 (48.4)	61 (50.0)	54 (52.4)	
IV	17 (4.8)	5 (4.0)	8 (6.6)	4 (3.9)	
Invasive Haemodynamics					
MPAP – mmHg	42.9 ± 13.4	36.1 ± 11.5	43.9 ± 11.8	50.6 ± 13.2	<0.001
PVR – WU	7.8 ± 5.1	6.0 ± 4.1	8.6 ± 5.3	9.3 ± 5.5	<0.001
RAP – mmHg	9.2 ± 4.6	8.4 ± 3.7	9.0 ± 5.0	10.7 ± 4.9	0.003
PAWP – mmHg	10.9 ± 4.5	10.6 ± 3.4	10.3 ± 4.4	11.9 ± 5.8	0.053
CO – L/min	4.7 ± 1.6	4.8 ± 1.4	4.7 ± 1.6	4.7 ± 1.7	0.756

CI – L/min/m^2	2.7 ± 0.8	2.8 ± 0.8	2.6 ± 0.8	2.5 ± 0.7	0.086
Biochemistry					
eGFR – mL/min/1.73 m^2	73 ± 34	73.5 ± 33.8	76 ± 34	73 ± 35	0.67
NT-proBNP – pg/mL	527 ± 1535	308 ± 690	776 ± 1442	795 ± 2698	0.01
Echocardiography					
RV size – no. (%)					< 0.001
Normal	102 (31)	58 (49.6)	28 (24.8)	16 (16.2)	
Mildly dilated	72 (21.9)	23 (19.7)	23 (20.4)	26 (26.3)	
Moderately dilated	73 (25.2)	24 (20.5)	34 (31.1)	25 (25.2)	
Severely dilated	72 (21.9)	12 (10.3)	28 (24.8)	32 (32.3)	
RV systolic function – no. (%)					< 0.001
Normal	180 (55.0)	83 (72.8)	54 947.4)	43 (43.4)	
Mildly impaired	57 (17.4)	13 (11.4)	20 (17.5)	24 (24.2)	
Moderately impaired	40 (12.2)	8 (7.0)	19 (16.7)	13 (13.1)	
Severely impaired	50 (15.3)	10 (8.8)	21 (18.4)	19 (19.2)	
Pericardial effusion – no. (%)	55 (15.7)	15 (11.9)	19 (15.6)	21 (20.4)	0.236
TAPSE – mm	19.5 ± 4.9	20.0 ± 4.3	19.3 ± 5.0	19.1 ± 5.6	0.501
TAPSE/PASP – mm/mmHg	0.4 ± 0.3	0.5 ± 0.3	0.4 ± 0.4	0.3 ± 0.2	0.026
Other					
Six minute walk distance – m	336.1 ± 143.5	344.8 ± 141.6	332.5 ± 146.7	330.2 ± 142.9	0.753
DLCO – % predicted	45.0 ± 20.1	45.3 ± 19.9	42.8 ± 19.0	47.5 ± 21.8	0.426
Scores					
REVEAL 2.0	8.2 ± 3.5	7.4 ± 3.2	8.3 ± 3.2	9.3 ± 4.0	0.011
Low – no. (%)	100 (31.5)	43 (39.1)	34 (29.8)	23 (24.7)	
Intermediate – no. (%)	71 (22.4)	22 (20.0)	30 (26.3)	19 (20.4)	
High – no. (%)	146(46.1)	45 (40.9)	50 (43.9)	51 (54.8)	
REVEAL Lite 2	6.4 ± 2.9	5.8 ± 2.7	6.6 ± 2.7	7.0 ± 3.2	0.109
Low – no. (%)	114 (38.5)	46 (44.7)	37 (33.9)	31 (36.9)	
Intermediate – no. (%)	68 (23.0)	26 (25.2)	27 (24.8)	15 (17.9)	
High – no. (%)	114 (38.5)	31 (30.1)	45 (41.3)	38 (45.2)	
ESC/ERS	1.9 ± 0.5	1.8 ± 0.4	2.0 ± 0.5	2.1 ± 0.5	<0.001
Low – no. (%)	56 (17.3)	25 (22.1)	20 (17.5)	11 (11.5)	

Intermediate – no. (%) High – no. (%)	215 (66.6) 52 (16.1)	77 (68.1) 11 (9.7)	74 (64.9) 20 (17.5)	64 (66.7) 21 (21.9)	

Table 1. Baseline variables according to tertiles of MPA size. BSA = body surface area. CI = cardiac index. CO = cardiac output. CTD = connective tissue disease. DLCO = diffusing capacity of the lungs for carbon monoxide. eGFR = estimated glomerular filtration rate. ESC/ERS = European Society of Cardiology/European Respiratory Society. MPA = main pulmonary artery. MPAP = mean pulmonary arterial pressure. NT-proBNP = N-terminal pro b-type natriuretic peptide. PAH = pulmonary arterial hypertension. PAWP = pulmonary artery wedge pressure. PASP = pulmonary artery systolic pressure. PAH = pulmonary arterial hypertension. PoPH = portopulmonary hypertension. PVR = pulmonary vascular resistance. RAP = right atrial pressure. RV = right ventricle. TAPSE = tricuspid annular plane systolic excursion. WHO = World Health Organization. WU = Wood units.

Variable	HR (95% CI)	P Value	HR (95% CI)	P Value
MPA Imaging				
MPA diameter – per mm	1.06 (1.04-1.07)	< 0.001	1.07 (1.03-1.11)	0.001
MPA/BSA – per mm/m^2	1.13 (1.10-1.16)	< 0.001		
MPA/Aorta – per unit	2.66 (1.74-4.07)	< 0.001		
MPA growth – per mm/year	1.79 (1.52-2.11)	< 0.001		
MPA growth – per % baseline/year	1.26 (1.18-1.34)	< 0.001		
Clinical				
Baseline age – per yr	1.03 (1.02-1.04)	< 0.001	1.02 (1.00-1.04)	0.018
Male sex – ref. female	1.16 (0.85-1.59)	0.356		
Body surface area – per m^2	0.60 (0.32-1.13)	0.111		
PAH subgroup – ref. PAH-CTD				
Idiopathic	0.52 (0.36-0.74)	< 0.001		
Drug	0.57 (0.22-1.59)	0.295		
PoPH	1.18 (0.66-2.09)	0.354		
Other	0.81 (0.52-1.25)	0.582		
WHO class – ref. class I				
II	0.46 (0.06-3.34)	0.442		
III	1.12 (0.16-8.02)	0.913		
IV	2.48 (0.33-18.92)	0.380		
Hospitalisation ≤ 6 mo	1.64 (1.23-2.18)	< 0.001	2.12 (1.29-3.49)	0.003
Invasive Haemodynamics				
Systolic blood pressure – per 10 mmHg	0.96 (0.88-1.04)	0.273		
Heart rate – per 10 bpm	1.16 (1.03-1.30)	0.012	1.25 (1.05-1.49)	0.012
MPAP – per mmHg	1.02 (1.01-1.03)	< 0.001		
PVR – per WU	1.05 (1.02-1.07)	0.001		
RAP – per mmHg	1.08 (1.04-1.11)	< 0.001	1.07 (1.01-1.13)	0.016
PAWP – per mmHg	1.02 (0.98-1.06)	0.248		
CO – per L/min	0.90 (0.80-1.00)	0.053		
Biochemistry				

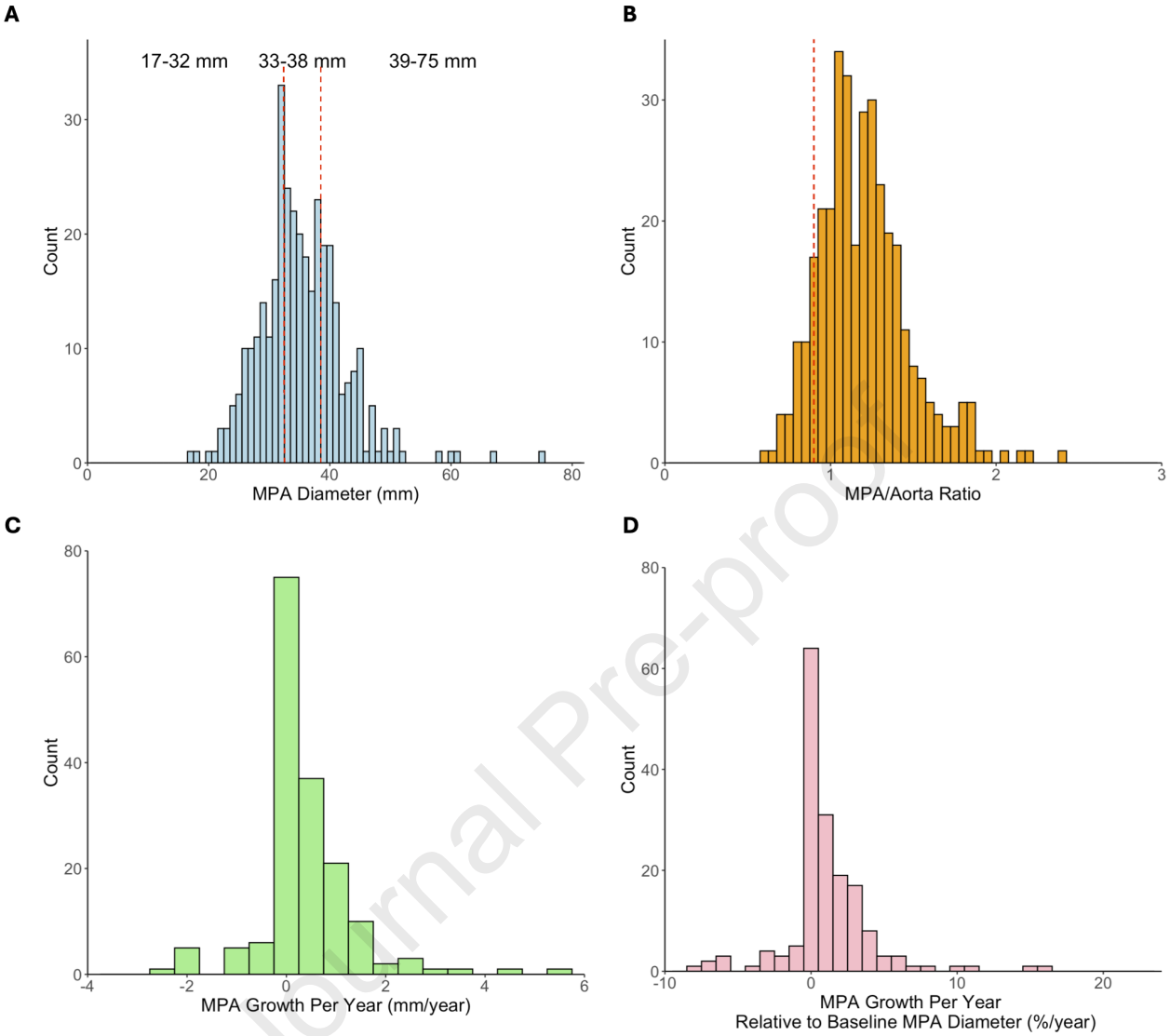
eGFR – per mL/min/1.73 m^2	0.98 (0.97-0.99)	< 0.001		
NT-proBNP – per 100pg/mL	1.003 (1.002-1.005)	< 0.001		
Echocardiography				
RV size – ref. normal				
Mildly dilated	1.86 (1.19-2.90)	0.007		
Moderately dilated	2.21 (1.46-3.34)	< 0.001		
Severely dilated	2.89 (1.89-4.43)	< 0.001		
RV systolic function – ref. normal				
Mildly impaired	1.61 (1.07-2.42)	0.022	1.06 (0.56-2.00)	0.853
Moderately impaired	1.97 (1.27-3.06)	0.002	0.65 (0.29-1.45)	0.291
Severely impaired	1.80 (1.18-2.74)	0.006	0.35 (0.14-0.89)	0.028
Pericardial effusion	1.84 (1.27-2.69)	0.001	1.58 (0.91-2.76)	0.105
TAPSE – per mm	0.95 (0.92-0.98)	0.003		
TAPSE/PASP – per mm/mmHg	0.15 (0.06-0.39)	< 0.001		
Right atrial area – per cm^2	1.08 (1.06-1.10)	< 0.001	1.08 (1.03-1.11)	< 0.001
Other				
Six minute walk distance – per 100m	0.66 (0.59-0.75)	< 0.001		
DLCO – per 10% predicted	0.66 (0.58-0.75)	< 0.001	0.64 (0.54-0.76)	< 0.001
Scores				
REVEAL 2.0 – per score	1.28 (1.21-1.35)	< 0.001		
REVEAL Lite 2 – per score	1.33 (1.23-1.43)	< 0.001		
ESC/ERS – per score	3.72 (2.70-5.13)	< 0.001		

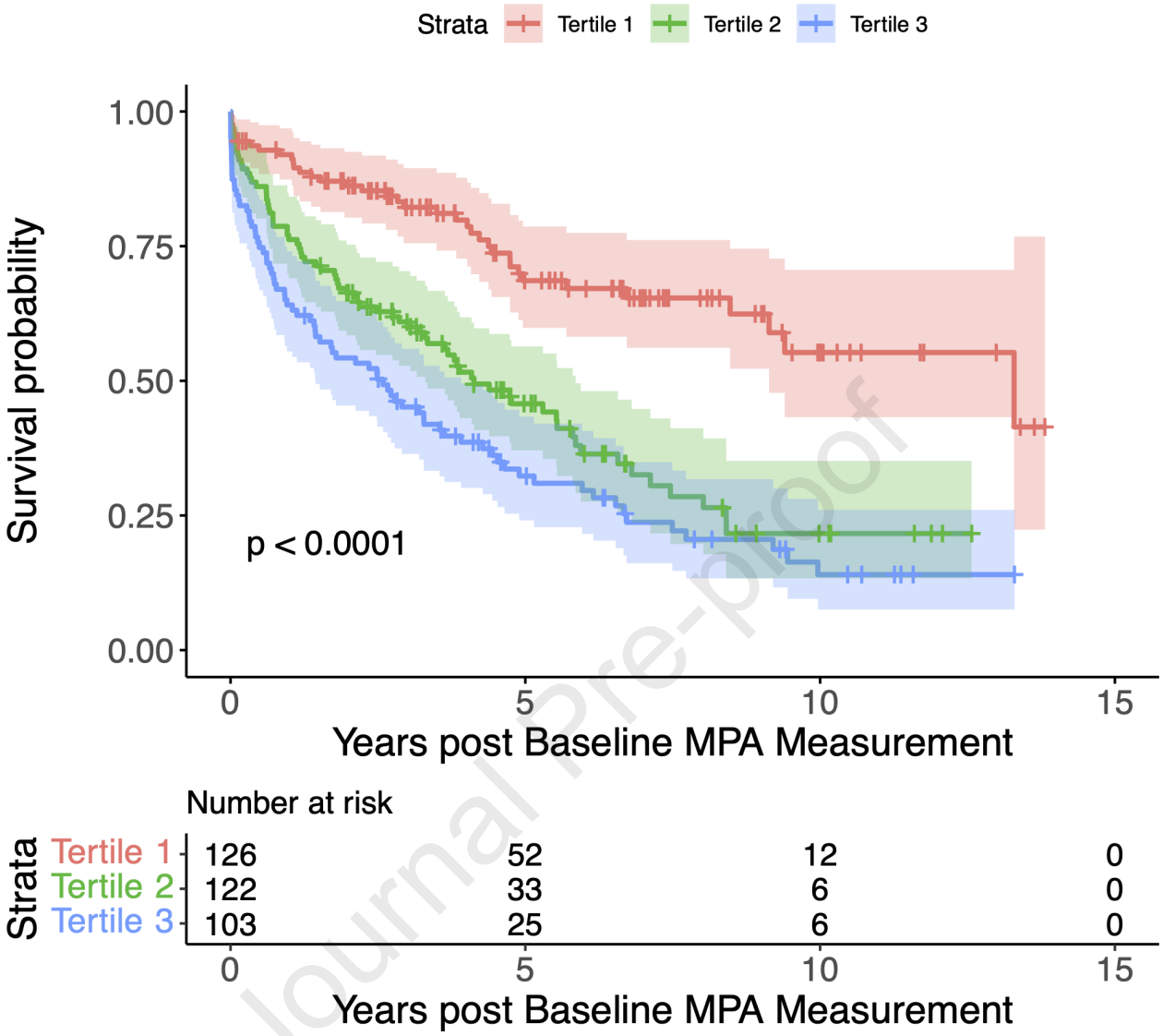
Table 2. Univariable and multivariable Cox Proportional Hazards model for the primary endpoint (death, transplantation or hospitalisation for right heart failure). Multivariable models were chosen based on univariable analysis with $p < 0.2$ provided the adjusted variance inflation factor is < 3. The predictors with the highest p values were then removed stepwise until all predictors in the multivariable model had $p < 0.2$. CO = cardiac output. CTD = connective tissue disease. DLCO = diffusing capacity of the lung for carbon monoxide. eGFR = estimated glomerular filtration rate. ESC/ERS = European Society of Cardiology/European

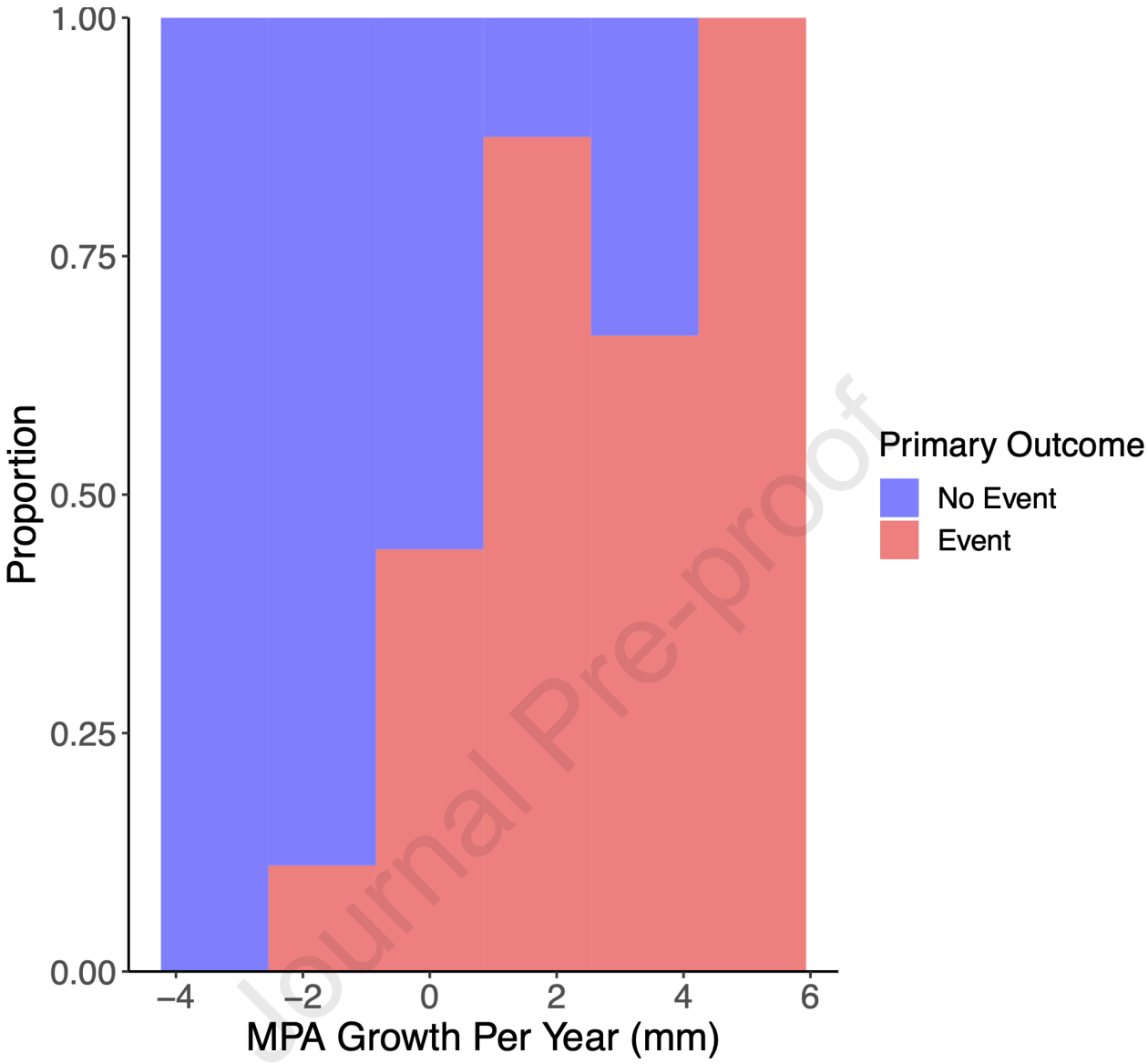
Respiratory Society. MPA = main pulmonary artery. MPAP = mean pulmonary artery pressure. NT-proBNP = N-terminal pro B-type natriuretic peptide. PAH = pulmonary arterial hypertension. PASP = pulmonary artery systolic pressure. PAWP = pulmonary artery wedge pressure. PoPH = portopulmonary hypertension. PVR = pulmonary vascular resistance. RAP = right atrial pressure. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0. TAPSE = tricuspid annular plane systolic excursion. WHO = World Health Organization.

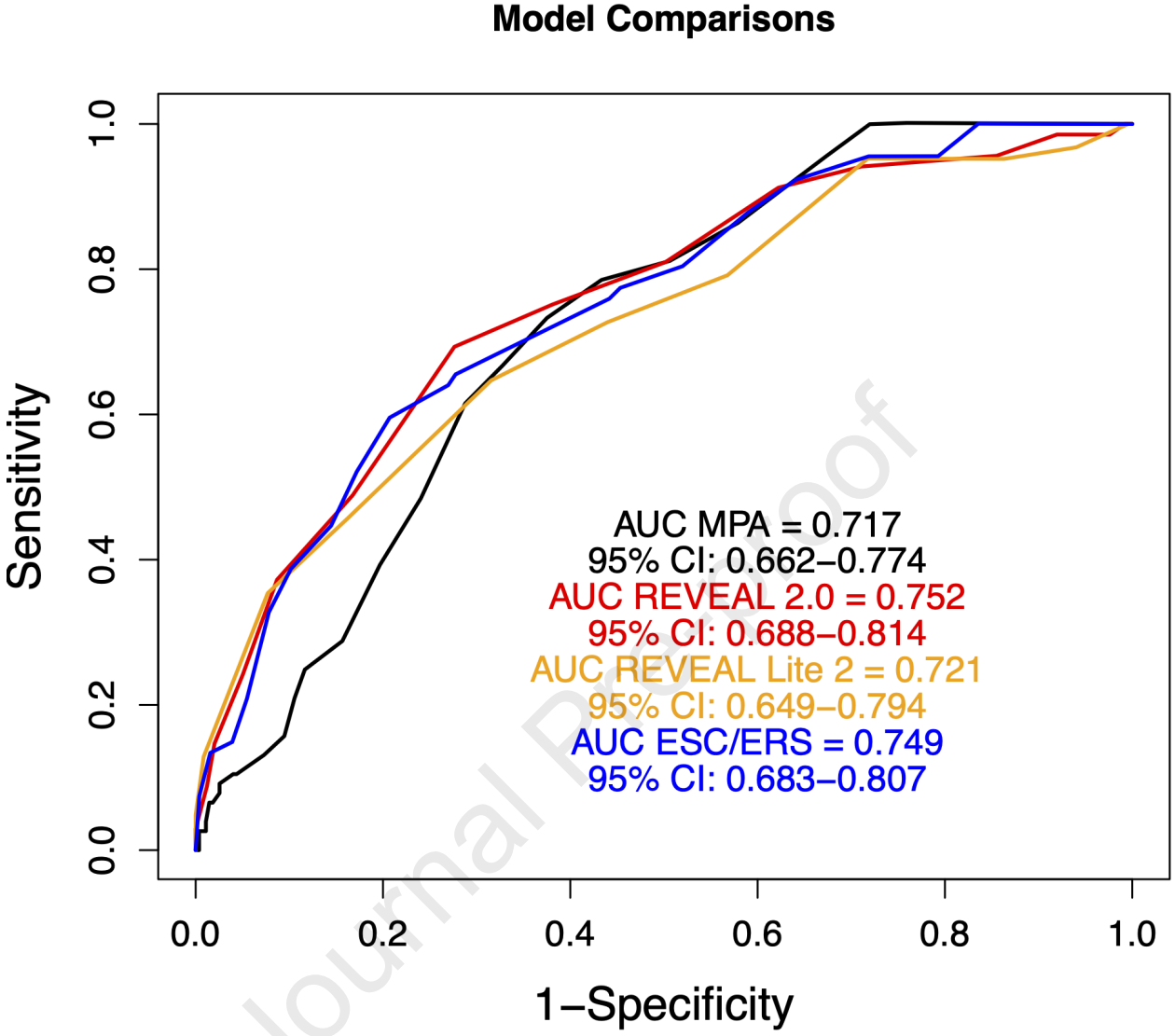
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**
MPA HR (95% CI) – per mm	1.05 (1.03-1.06)	1.06 (1.04-1.08)	1.06 (1.04-1.07)	1.08 (1.02-1.15)	1.05 (1.01-1.08)
MPA p value	< 0.001	< 0.001	< 0.001	0.007	0.01
Risk score HR (95% CI)	1.24 (1.18-1.31)	1.30 (1.21-1.40)	3.29 (2.38-4.53)		
Risk score p value	< 0.001	< 0.001	< 0.001		
C-statistic of the multivariable model	0.74	0.72	0.73	0.82	0.75
∆ C-statistic of the multivariable model	+ 0.03	+ 0.04	+ 0.04	+ 0.03	+ 0.02
∆ Bayesian information criterion	-15	-28	-25	-4	-2

Table 3. Multivariable Cox Proportional Hazards models for the primary endpoint (death, transplantation or hospitalisation for right heart failure). The hazard ratios for MPA and the three risk scores (Model 1: REVEAL 2.0; Model 2: REVEAL Lite 2; Model 3: ESC/ERS) are presented. Model 4 includes MPA and components of REVEAL 2.0. Model 5 includes MPA and components of the ESC/ERS score. The additive value of MPA is evaluated by the change in C-statistic and Bayesian information criterion when MPA is added to the existing risk scores or score components. ESC/ERS = European Society of Cardiology/European Respiratory Society. HR = hazard ratio. MPA = main pulmonary artery. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0.









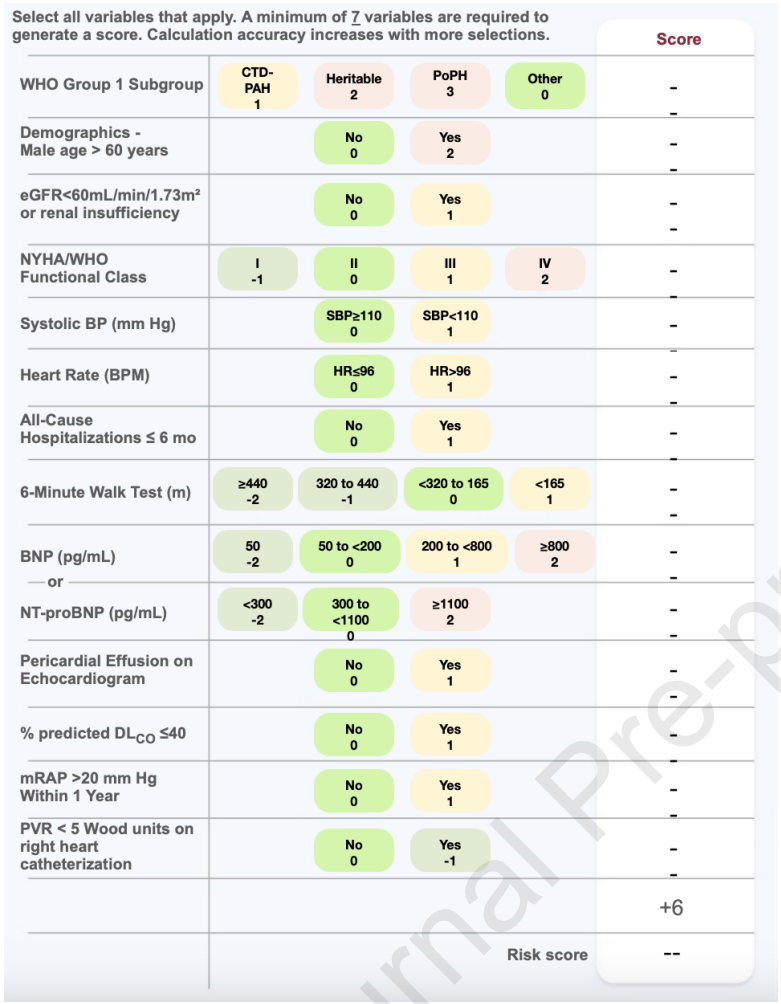
Take Home Points

- Study question – what is the prognostic role of main pulmonary artery diameter in pulmonary arterial hypertension?
- Results – pulmonary artery diameter and rate of growth are adversely prognostic, independent of existing risk scores.
- Interpretation – pulmonary artery diameter may be an accessible and independent prognosticator in pulmonary arterial hypertension, but external validation is required.

Conflict of Interest

All the authors have no conflict of interest to declare for the submitted project.

A.



Select all variables that apply. A minimum of 7 variables are required to generate a score. Calculation accuracy increases with more selections.

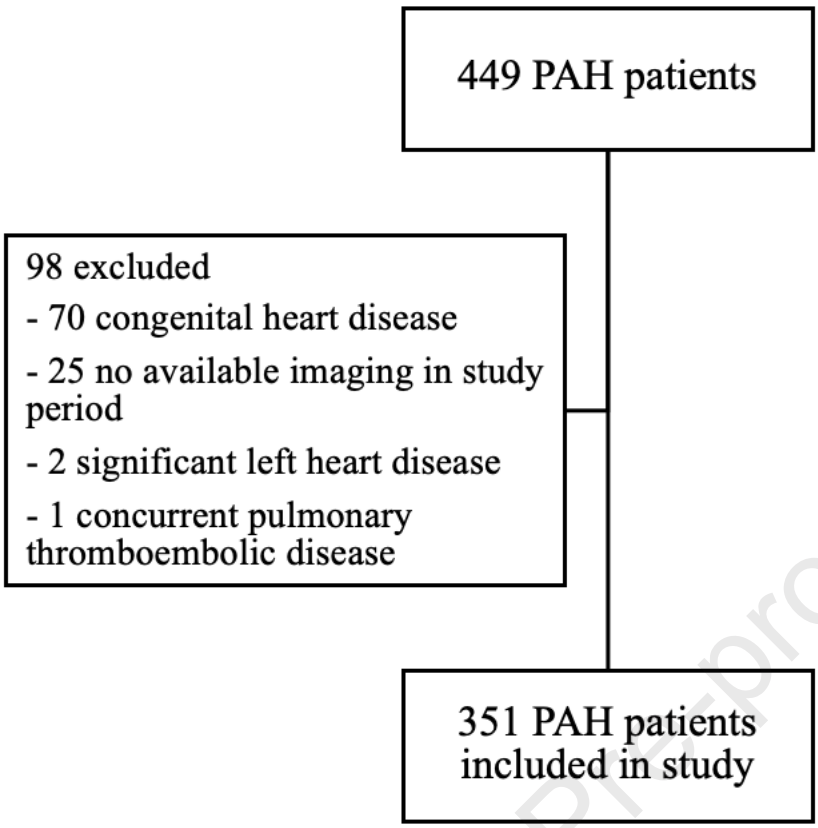
					Score
WHO Group 1 Subgroup	CTD-PAH 1	Heritable 2	PoPH 3	Other 0	-
Demographics - Male age > 60 years		No 0	Yes 2		-
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		-
NYHA/WHO Functional Class	I -1	II 0	III 1	IV 2	-
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		-
Heart Rate (BPM)		HR≤96 0	HR>96 1		-
All-Cause Hospitalizations ≤ 6 mo		No 0	Yes 1		-
6-Minute Walk Test (m)	≥440 -2	320 to 440 -1	<320 to 165 0	<165 1	-
BNP (pg/mL)	50 -2	50 to <200 0	200 to <800 1	≥800 2	-
or					
NT-proBNP (pg/mL)	<300 -2	300 to <1100 0	≥1100 2		-
Pericardial Effusion on Echocardiogram		No 0	Yes 1		-
% predicted DL_{CO} ≤40		No 0	Yes 1		-
mRAP >20 mm Hg Within 1 Year		No 0	Yes 1		-
PVR < 5 Wood units on right heart catheterization		No 0	Yes -1		-
					+6
				Risk score	--

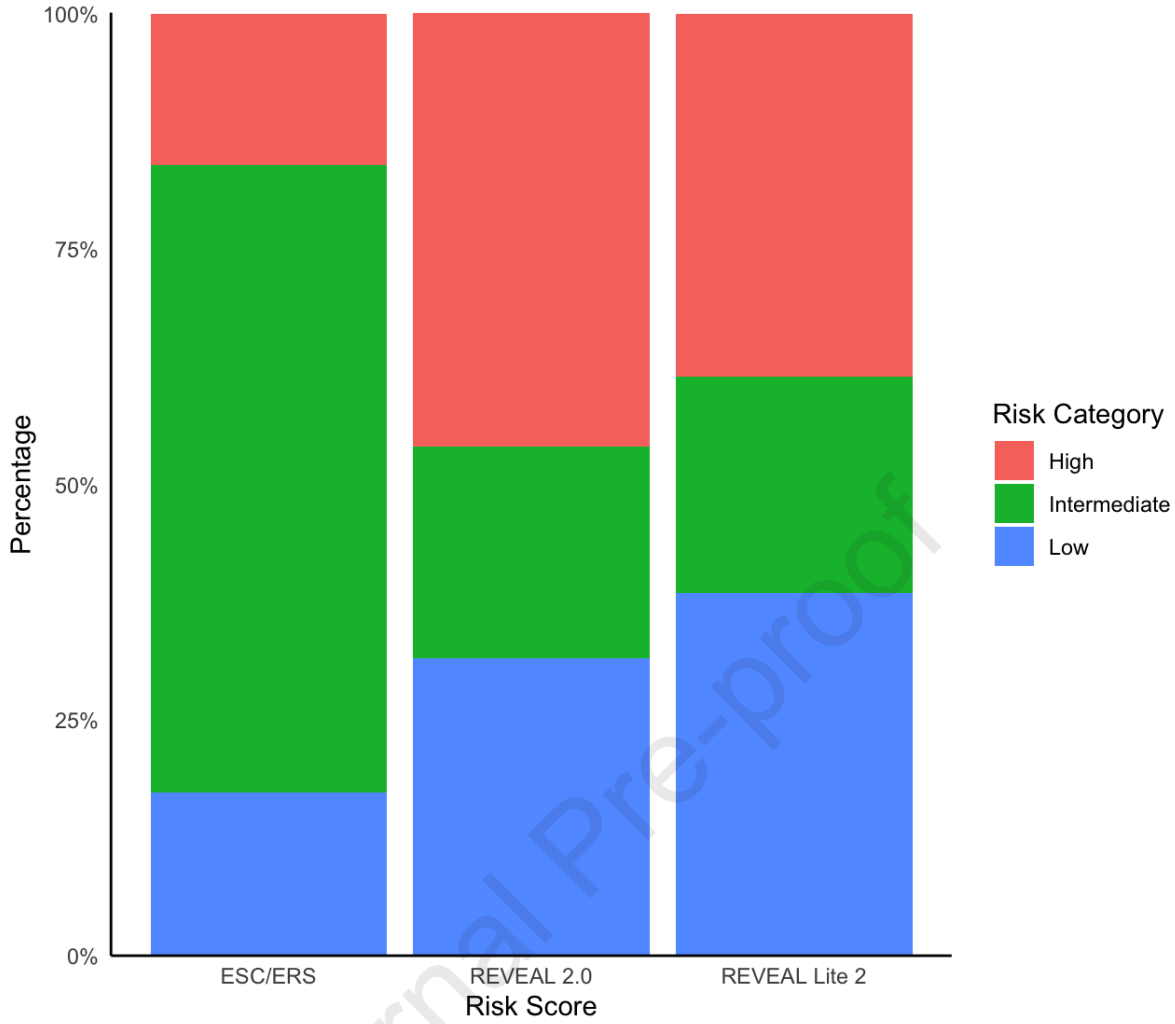
B.

Select all variables that apply. A minimum of 3 variables are required to generate a score where at least 2 are of the most predictive variables - denoted **.					Score
BNP (pg/mL)**	<50 -2	50 to <200 0	200 to <800 1	≥800 2	-
or					-
NT-proBNP (pg/mL)**	<300 -2	300 to <1100 0	≥1100 2		-
6-Minute Walk Test (m)**	≥440 -2	320 to 440 -1	<320 to 165 0	<165 1	-
NYHA/WHO Functional Class**	I -1	II 0	III 1	IV 2	-
Systolic BP (mm Hg)		SBP≥110 0	SBP<110 1		-
Heart Rate (BPM)		HR≤96 0	HR>96 1		-
eGFR<60mL/min/1.73m² or renal insufficiency		No 0	Yes 1		-
					+6
				Risk score	--

C.

Variables Est. 1 Yr Mortality	Low Risk <5%	Intermediate Risk 5%-20%	High Risk >20%	Score
Signs of right HF	Absent	Absent	Present	0
Progression of symptoms	No	Slow	Rapid	0
Syncope	No	Occasional syncope	Repeated syncope	0
WHO-FC	I, II	III	IV	0
6MWD	>440 m	165-440 m	<165 m	0
CPET	Peak VO_2 >15mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11-15mL/min/kg (35-65% pred.) VE/VCO_2 slope 36-44	Peak VO_2 <11mL/min/kg (<35% pred.) VE/VCO_2 slope >44	0
Biomarkers: BNP or NT-proBNP	BNP < 50ng/L NT-proBNP <300ng/L	BNP 50-800ng/L NT-proBNP 300-1100ng/L	BNP >800ng/L NT-proBNP >1100ng/L	0
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No Pericardial Effusion	RA area 18-26 cm^2 TAPSE/sPAP 0.19-0.32 mm/mmHg Minimal Pericardial Effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate-large Pericardial Effusion	0
cMRI	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37-54% SVI 26-40 mL/m^2 RVESVI 42-54 mL/m^2	RVEF <37% SVI >26 mL/m^2 RVESVI >54 mL/m^2	0
Hemodynamics	RAP <8 mm Hg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8-14 mm Hg CI 2-2.4 $L/min/m^2$ SVI 31-38 mL/m^2 SvO_2 60-65%	RAP >14 mm Hg CI <2 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%	0
Total Risk Score	Divide the sum of all variable scores by the number of variables entered and round to the nearest decimal			





	Predictors of Baseline MPA		Predictors of MPA Growth	
Variable	**Estimate**	**P Value**	**Estimate**	**P Value**
Baseline MPA diameter – per mm			0.042	< 0.001
Baseline age – per yr	-0.04	0.083	0.002	0.686
Gender – ref. female	1.43	0.097	0.01	0.972
PAH subgroup – ref. PAH-CTD				
Idiopathic	2.13	0.015	-0.45	0.020
Drug	1.42	0.535	-0.38	0.428
PoPH	6.20	< 0.001	0.57	0.142
Other	2.05	0.077	0.15	0.575
WHO class – ref. class I				
II	-3.39	0.509	-	-
III	-2.13	0.678	-0.08	0.621
IV	-2.53	0.639	1.99	0.001
Body surface area – per m^2	6.55	< 0.001	-0.11	0.757
Aorta size – per mm	0.24	0.007	0.02	0.344
MPAP – per mmHg	0.24	< 0.001	0.01	0.076
SPAP – per mmHg	0.15	< 0.001	0.05	0.322
DPAP – per mmHg	0.27	< 0.001	0.01	0.223
PVR – per WU	0.37	< 0.001	0.01	0.668
RAP – per mmHg	0.27	0.002	0.03	0.139
PAWP – per mmHg	0.14	0.119	0.02	0.349
CO – per L/min	-0.04	0.875	0.02	0.757
CI – per L/min/m^2	-0.91	0.080	0.04	0.781
SVI – per mL	-0.03	0.492	-0.002	0.805
RV size – ref. normal				
Mildly dilated	4.86	< 0.001	0.51	0.027
Moderately dilated	4.89	< 0.001	0.04	0.875
Severely dilated	7.09	< 0.001	0.50	0.033
RV systolic function – ref. normal				
Mildly dilated	3.98	< 0.001	0.18	0.459
Moderately dilated	3.80	< 0.001	0.16	0.588
Severely dilated	4.32	< 0.001	0.27	0.290

TAPSE – per mm	-0.17	0.053	-0.04	0.086
TAPSE/PASP – per mm/mmHg	-6.14	< 0.001	-0.32	0.539
eGFR – per mL/min/1.73 m^2	-0.03	0.170	-0.01	0.198
NT-proBNP – per 100 pg/mL	0.02	0.048	0.01	0.047
Six minute walk distance – per 100m	-0.17	0.563	-0.14	0.048
DLCO – per 10% predicted	0.09	0.703	-0.17	0.007
REVEAL 2.0	0.41	0.001	0.09	0.001
REVEAL Lite 2	0.35	0.041	0.11	0.006
ESC/ERS	3.07	< 0.001	0.54	0.005

e-Table 1. Univariable linear regression evaluating predictors of baseline MPA diameter and MPA growth per year. BSA = body surface area. CI = cardiac index. CO = cardiac output. CTD = connective tissue disease. DLCO = diffusing capacity of the lungs for carbon monoxide. DPAP = diastolic pulmonary arterial pressure. eGFR = estimated glomerular filtration rate. ESC/ERS = European Society of Cardiology/European Respiratory Society. MPAP = mean pulmonary arterial pressure. NT-proBNP = N-terminal pro b-type natriuretic peptide. PAH = pulmonary arterial hypertension. PASP = pulmonary artery systolic pressure. PAWP = pulmonary artery wedge pressure. PVR = pulmonary vascular resistance. RAP = right atrial pressure. RV = right ventricle. SVI = stroke volume index. TAPSE = tricuspid annular plane systolic excursion. WU = Wood units. WHO = World Health Organization.

	Unadjusted HR	Adjusted HR for REVEAL 2.0	Adjusted HR for REVEAL Lite 2	Adjusted HR for ESC/ERS Score
MPA HR (95% CI)	1.05 (1.03-1.07)	1.04 (1.02-1.07)	1.06 (1.04-1.08)	1.05 (1.03-1.07)
MPA p value	< 0.001	< 0.001	< 0.001	< 0.001
Score HR (95% CI)		1.26 (1.19-1.33)	1.31 (1.22-1.42)	3.15 (2.23-4.47)
Score p value		< 0.001	< 0.001	< 0.001

e-Table 2. Cox Proportional Hazards model for the secondary composite endpoint of death and transplantation. Both unadjusted and adjusted models are shown. Adjustment is made for the three existing risk scores – REVEAL 2.0, REVEAL Lite 2 and ESC/ERS score. ESC/ERS = European Society of Cardiology/European Respiratory Society. HR = hazard ratio. MPA = main pulmonary artery. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0.

	Unadjusted HR	Adjusted HR for REVEAL 2.0	Adjusted HR for REVEAL Lite 2	Adjusted HR for ESC/ERS Score
MPA HR (95% CI)	1.06 (1.04-1.07)	1.05 (1.03-1.06)	1.06 (1.04-1.08)	1.06 (1.04-1.08)
MPA p value	< 0.001	< 0.001	< 0.001	< 0.001
Score HR (95% CI)		1.24 (1.18-1.31)	1.31 (1.22-1.41)	3.65 (2.65-5.05)
Score p value		< 0.001	< 0.001	< 0.001

e-Table 3. Cox Proportional Hazards model for the secondary composite endpoint of death, lung transplantation, right heart failure hospitalization and new commencement of intravenous epoprostenol. Both unadjusted and adjusted models are shown. Adjustment is made for the three existing risk scores – REVEAL 2.0, REVEAL Lite 2 and ESC/ERS score. ESC/ERS = European Society of Cardiology/European Respiratory Society. HR = hazard ratio. MPA = main pulmonary artery. REVEAL 2.0 = Risk Evaluation and Assessment of Prognosis in PAH version 2.0.

MPA Diameter (mm)	Sensitivity	Specificity	MPA Diameter (mm)	Sensitivity	Specificity	MPA Diameter (mm)	Sensitivity	Specificity
17	100.0	0.4	44	13.1	92.7	72	0.0	99.9
18	100.0	0.7	45	10.5	95.6	73	0.0	99.9
19	100.0	0.9	46	10.5	96.0	74	0.0	100.0
20	100.0	1.1	47	9.2	97.5	75	0.0	100.0
21	100.0	1.5	48	7.9	97.5			
22	100.0	2.6	49	6.5	98.2			
23	100.0	3.6	50	6.5	98.5			
24	100.0	5.5	51	3.9	98.9			
25	100.0	7.7	52	2.6	98.9			
26	100.0	11.3	53	2.6	99.0			
27	100.0	15.0	54	2.6	99.0			
28	100.0	19.0	55	2.6	99.1			
29	100.0	24.1	56	2.6	99.2			
30	100.0	28.0	57	2.6	99.2			
31	95.6	32.6	58	2.6	99.3			
32	86.4	42.1	59	2.6	99.5			
33	81.1	49.4	60	2.6	99.6			
34	78.5	56.7	61	1.3	99.6			
35	73.3	62.5	62	1.1	99.6			
36	66.7	67.2	63	0.9	99.6			
37	61.5	71.2	64	0.7	99.6			
38	48.4	76.0	65	0.4	99.6			
39	39.3	80.3	66	0.2	99.6			
40	28.8	84.3	67	0.0	99.6			
41	24.9	88.3	68	0.0	99.7			
42	20.9	89.4	69	0.0	99.7			
43	15.7	90.5	70	0.0	99.8			

e-Table 4. Sensitivity and specificity for one-year risk of the primary endpoint at various main pulmonary artery diameter thresholds. MPA = main pulmonary artery.

Supplementary Method

Baseline Variables Collected

These included: 1) serum biochemistry – estimated glomerular filtration rate (eGFR), N-terminal pro b-type natriuretic peptide (NT-proBNP); 2) six minute walk distance (6MWD); 3) Diffusing Capacity of the Lung for Carbon Monoxide (DLCO) and percentage predicted DLCO; 4) invasive haemodynamic parameters on right heart catheterisation; 5) transthoracic echocardiogram parameters; 6) cardiac magnetic resonance imaging (CMRI) parameters.

MPA Measurement

MPA was measured on transverse sections. The slice containing the largest MPA with the walls running parallel was used. MPA was then measured along the line that originates from the centre of the adjacent ascending aorta and passes perpendicular to the long axis of the MPA (Supplementary Fig. 2). In instances where the MPA walls do not run parallel i.e. they diverge, then the diameter was taken at the midpoint between the origin and bifurcation of the MPA. The aorta was measured on the same slice as the MPA and was the average of two perpendicular measurements. In contrast enhanced imaging, the measurements were taken from the edges of the contrast, whereas in non-contrast imaging, the measurements were taken from the tissue borders. 20 randomly chosen scans were chosen from the two sites each, and inter-rater reliability was assessed using intra-class correlation in the “psych” package in R (version 2.4.6.26) [1].

Evaluation of MPA Growth

In those patients with more than one measurement of MPA, the most recent occasion was used as the follow-up measurement to evaluate MPA diameter changes. The change between baseline and follow-up MPA diameter was then used to calculate absolute MPA growth (mm/year) and relative MPA growth as a percentage of baseline MPA diameter (%/year).

Supplementary References

1. William R. psych: Procedures for Psychological, Psychometric, and Personality Research. 2024.