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Magnetic resonance imaging in the prognostic evaluation of patients with pulmonary arterial hypertension

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Author contributions

AS and DK conceived the idea for the study. AS, SR, AR, MC, and DK participated in the study design. AS, DC, CJ, RC, CE, AL and SR acquired the MRI data. Image analysis was performed by AS, DC and SR. AS, JW, AR, AL, JW, NH and DGK analysed and interpreted the MR data. AS, SR, AR, AL, NH, JH, DC, JW and DK drafted the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Rationale Prognostication is important when counselling patients and defining treatment strategies in pulmonary arterial hypertension (PAH). Current biomarkers including MRI have been shown to predict mortality. However, their relative prognostic significance remains unclear.

Objective To determine the value of MRI metrics for prediction of mortality in PAH.

Methods Consecutive patients with PAH undergoing MRI were identified from the ASPIRE-Pulmonary-Hypertension-Registry. Multivariate Cox proportional hazards and receiver operating curve analysis (ROC) were used to determine the prognostic value of MRI in patients with PAH.

Measurements and main results During the follow-up period of 32±20 months 576 patients were studied and 221 (38%) died. A derivation cohort (n=288, 115 deaths) and validation cohort (n=288, 106 deaths) were identified. On multivariate Cox regression analysis: RV-end-systolic-volume-index percent predicted by age and sex (RVESVI%pred) and pulmonary artery relative area change independently predicted mortality ($p<0.01$). A model of MRI and clinical data was accurate for predicting mortality at 1 and 3 years in the validation cohort, AUC 0.741 and AUC 0.815, respectively. The model was highly accurate in patients with IPAH, at 1 and 3 years in the validation cohort, AUC 0.803 and AUC 0.872.

Conclusion MRI measurements reflecting both RV structure and stiffness of the proximal pulmonary vasculature are independent predictors of outcome in PAH. In combination with clinical data MRI allows accurate prognostic evaluation in PAH, especially in IPAH.

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INTRODUCTION

Over the last 2 decades there has been significant progress in the treatment of pulmonary arterial hypertension (PAH) but despite this it remains a progressive life shortening condition. Assessment of disease severity and estimating life expectancy is an important part of patient evaluation. It aids selection of treatment strategy, timing of transplantation and counselling of patients (1).

Changes in the pulmonary vasculature in PAH cause an increase in right ventricular afterload, a reduction in cardiac output resulting in increasing breathlessness and a fall in exercise capacity (2). A number of measurements have been used to assess disease severity and estimate prognosis and include parameters reflecting symptomatic limitation (WHO function class (3)), impairment of right ventricular function (elevated right atrial pressure (3-5), reduced cardiac output (4-6) and reduced mixed venous oxygen saturation (5)) and measurements of exercise capacity (6 minute walk test distance (6MWT) (5, 6), and maximal oxygen uptake measured using cardiopulmonary exercise testing (7)). In addition, multiparametric equations have been developed in attempts to improve the assessment of disease severity and aid prognostication (8, 9). All of these approaches are limited in part by inherent problems with reproducibility, subjective interpretation and the invasive nature of investigations such as cardiac catheterisation.

Magnetic resonance imaging (MRI) provides accurate and reproducible information on cardiac morphology and function (10-12) and in addition also has sensitivity to changes in the pulmonary vasculature (13-16). Recently a number of studies have evaluated MRI as a tool to assess for the presence of PAH (14, 15, 17-21). Additionally studies have evaluated the prognostic value of MRI measurements; RV (right ventricular) end-diastolic and end-systolic volumes, RV ejection fraction, and more recently RV-pulmonary artery (PA) coupling metrics and PA relative area change (13, 16, 22-25)

have all been shown to have predictive value in patients with PAH. However, these studies have often been performed in relatively small numbers of patients and have concentrated on a limited number of parameters. The aim of this study was to investigate the prognostic value of cardiopulmonary MRI metrics in a large PAH registry.

METHODS

Patients

Consecutive patients diagnosed with PAH, at a pulmonary hypertension referral centre, who underwent MRI, were identified from January 2008 to February 2015. Patients referred with suspected pulmonary hypertension underwent systematic evaluation as previously described in the ASPIRE registry (26), including lung function, exercise testing, high resolution computed tomography (CT) and CT pulmonary angiography, MRI and right heart catheterisation. Data was also retrieved for treatment at the time of census or death and was recorded as oral monotherapy (phosphodiesterase 5 inhibitor or endothelin receptor antagonist), oral combination therapy (phosphodiesterase 5 inhibitor and endothelin receptor antagonist), prostanoid therapy or calcium channel blocker therapy. Ethical approval for this analysis of imaging techniques and routinely collected data was granted by our institutional review board, ref c06/Q2308/8.

MR image acquisition

MR imaging was performed using an 8 channel cardiac coil on a GE HDx (GE Healthcare, Milwaukee, USA) whole body scanner at 1.5T. Short axis cine images were acquired using a cardiac gated multi-slice balanced SSFP sequence (20 frames per cardiac cycle, slice thickness 8mm, FOV 48, matrix 256 x 256, BW 125 KHz/pixel, TR/TE 3.7/1.6 ms). A stack of images in the short axis plane with slice thickness of 8 mm (2mm inter-slice gap) were acquired fully covering both ventricles from base to apex. End-systole was considered to be the smallest cavity area. End-diastole was defined as the first cine phase of the R-wave triggered acquisition or largest volume. Through plane phase contrast imaging was performed orthogonal to the main pulmonary trunk. Phase contrast imaging parameters were as follows: repetition time, TR 5.6 ms; echo time, TE 2.7 ms; slice thickness, 10 mm; field of view, 48 cm, bandwidth, 62.5 kHz; matrix, 256 x 128; 20 reconstructed cardiac phases; and velocity encoding of flow, 150 cm/s. Patients were

in the supine position with a surface coil and with retrospective ECG gating.

Image analysis

Image analysis was performed on a GE Advantage Workstation 4.1 with the observer blinded to the patient clinical information, and cardiac catheter parameters. Right and left endocardial and epicardial surfaces were manually traced from the stack of short-axis cine images, using proprietary MR workstation software to obtain RV end-diastolic (RVEDV) and end-systolic (RVESV), and LV end-diastolic (LVEDV) and end-systolic volumes (LVESV). From end-diastolic and end-systolic volumes, RV and LV ejection fraction (RVEF and LVEF) and RV and LV stroke volume were calculated. With the exception of RVEF and LVEF, these measurements were indexed for BSA. Based on previous work, stroke volume (SV) was considered to be the most accurate from LV volumetry (27) and was used for MRI estimation of RV-PA coupling. For calculation of ventricular mass the interventricular septum was considered as part of the LV. Right ventricular end-diastolic mass (RV mass) and left ventricular end-diastolic mass were derived (LV mass). Ventricular mass index (VMI) was defined as RV mass divided by LV mass, as previously described (18). Maximal and minimal PA areas were measured, and relative area change was defined by the following equation: RAC= (maximum area-minimum area)/minimum area (14, 28). See **Figure 1.** Inter-observer reproducibility was tested in 30 randomly selected cases.

Right heart catheterisation and clinical assessment

Right heart catheterisation was performed using a balloon-tipped 7.5 Fr thermodilution catheter (Becton-Dickinson, USA). Right heart catheterisation was usually performed via the internal jugular vein using a Swan-Ganz catheter. Features at right heart catheterisation required to define PAH were mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest with a pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg (29). Pulmonary vascular resistance (PVR) was determined as follows: PVR = (mPAP -

PAWP)/Cardiac output (CO). CO was measured by thermodilution technique. Diagnostic classification of the form of PAH was made using standard criteria following multiprofessional assessment (26). To be included in the study patients were also required to have received treatment with PAH therapy during the study period.

Coupling measurements

As previously described, right ventricular elastance (Ees) was estimated as mPAP divided by RVESV index (30). Pulmonary arterial elastance (Ea) was estimated using mPAP-PCWP divided by SV index. Therefore, Ees/Ea by a combined right heart catheterisation and MRI approach was defined as follows (mPAP/RVESV index)/(mPAP-PCWP)/SV index). MRI estimated Ees/Ea was defined by SV/RVESV (24, 30-32). **Table 1** summarises the coupling measurements and pulmonary arterial relative area change metrics.

Statistics

The interval from evaluation with MRI until all cause death or census was regarded as the follow-up period. Individual analyses of mortality, at 1 and 3 years were also performed. A census was performed on the 15th of July 2016. Log-log plots were produced for each variable to assess proportional hazards; continuous variables were dichotomised for this analysis. CMR volumetric measurements indexed for BSA were corrected for age and gender and presented as percentage (%) predicted as per prior data by Maceira et al (33) and Kawut et al (34). The prognostic value of MRI derived biventricular volume, mass and function, PA measurements, mPAP, mean right atrial pressure (mRAP), CI, PVR, mixed venous oxygen saturation (SvO2), RV-PA coupling indices and patient age, sex and WHO functional class were assessed using univariate Cox proportional hazards regression analysis. Variable scaling was performed to allow direct comparison of hazard ratios of all continuous variables by dividing individual values by the standard deviation of the variable. In addition, Bonferroni correction was performed on univariate predictors. Highly correlated variables ($r>0.8$) that were significant at univariate Cox analysis were entered separately into the model. Multivariate analysis with a forward stepwise approach was performed for demographic,

CMR and right heart catheterisation data significant at univariate analysis ($p<0.2$). IPAH, the largest diagnostic population, was used as the reference category for multivariate analysis and combination therapy, being the largest therapy group was used as the reference category for multivariate analysis. Derivation and validation cohorts were constructed to develop models encompassing MRI data alone and MRI and clinical data combined. In the derivation cohort variables significant at $p<0.2$ were entered into a Cox proportional hazards regression model. The model was tested in the validation cohort. Kaplan-Meier analysis was used to assess the prognostic value of MRI volumetric measurements using median threshold values. Groups were compared using the log-rank (Mantel-Cox) test. Receiver operating characteristic (ROC) analysis and the Mann-Whitney U test were employed to assess prognostic significance of candidate predictors of mortality with area under the curve data presented for mortality at 1 and 3 years. The derivation cohort was utilized to develop predictive thresholds for CMR parameters. Statistical analysis was performed using SPSS 19 (SPSS, Chicago, Ill) and for presentation of the data GraphPad Prism 6.04 (GraphPad Software, San Diego, Calif) software was used. A p-value < 0.05 was considered statistically significant.

RESULTS

Five hundred and seventy six patients with PAH were identified. Three hundred and ninety eight patients were incident and treatment naïve, and one hundred and seventy eight patients were prevalent PAH patients on PAH therapy, see **Figure 2**. **Table 2** shows the demographic, MRI and right heart catheterisation data for i) the total study cohort, ii) incident patients with PAH who were treatment naïve and iii) prevalent patients with PAH on PAH treatment. The study group included 260 patients with idiopathic pulmonary arterial hypertension (IPAH), 195 patients with PAH associated with connective tissue disease, 63 patients with congenital heart disease, 58 patients with PAH associated with HIV, portal hypertension or drugs and toxins. **Table 3** summarises the baseline characteristics of incident treatment naïve patients with IPAH and PAH-CTD.

Survival analyses

Full cohort

During the follow-up period 221 patients (38%) died (mean follow up was 32 (SD 20) months). **Table 4** presents the univariate cox proportional hazards regression analysis data for demographic, hemodynamic and MRI data. MRI measures of RV size and function: RVEDV %pred ($p=0.003$), RVESV %pred ($p<0.0001$), RVEF %pred ($p<0.0001$) and invasive and non-invasive MRI derived Ees/Ea ($p<0.001$) predicted mortality at univariate Cox regression analysis. Both pulmonary artery relative area change (RAC) and pulmonary arterial distensibility ($p<0.0001$) predicted mortality at univariate Cox regression analysis following Bonferroni correction. Age>50, WHO functional class IV and SvO2 (all $p<0.0001$) were also predictive of mortality, all remaining significant following Bonferroni correction. At multivariate analysis increased RVESVI %pred ($p=0.005$) reduced PA relative area change ($p=0.008$), age >50 ($p<0.0001$), the presence of CTD

(p=0.039), and decreased SvO_2 (p=0.006) and oral monotheray as compared to combination oral therapy (p=0.006) were associated with worse outcome. **Figure 3** shows Kaplan Meier plots for RVESVI %pred and PA relative area change above and below median thresholds.

Incident and prevalent cases

Incident treatment naïve patients were older (p<0.0001) and had worse outcome at Cox regression analysis (hazard ratio 2.338 (1.603 to 3.408) (p<0.0001) than prevalent patients with PAH on therapy. Incident patients had more severe haemodynamic impairment with lower SvO_2 (p=0.003) and CI (p<0.0001) and on MRI had evidence of more severe disease with higher RVESVI (%pred) (p<0.0001) and lower RVEF (%pred), LVEDV (%pred) (p<0.0001) and PA relative area change (p<0.0001), **Table 2**. At multivariate Cox regression analysis of incident patients the same predictors were significant as in the full cohort inclusive of incident and prevalent cases; age >50, lower SvO_2 and lower PA relative area change were independent indicators of adverse outcome, lower RVESVI %pred and combination oral therapy predicted improved survival, **Table 5.**

Subgroup analysis –IPAH and PAH-CTD

In incident treatment naïve patients with IPAH there were a number of independent variables that predicted outcome at multivariate analysis: RVESVI %pred (p=0.001), Ees (p=0.035), low SvO2 (p=0.002), age>50 (p=0.010) and male sex (p=0.029), **Table 5.** At ROC analysis, RVESVI %pred was predictive of mortality in patients with IPAH at 1 and 3 years, AUC=0.716 and 0.735 respectively.

In incident treatment naïve patients with PAH-CTD, PA stiffness measured by PA relative area change (p=0.003) and Ees/Ea (combined invasive/non-invasive metric) (p=0.010) and treatment (oral monotherapy as compared to combination therapy, p=0.019) were independent predictors of outcome at multivariate analaysis, **Table 5.** In PAH-CTD PA

relative area change was predictive of mortality at 1 and 3 years, AUC 0.640 and AUC 0.696, respectively.

Prognostic model and validation

A derivation cohort (n=288, 115 deaths) and validation cohort (n=288, 106 deaths) were identified. There was no significant difference in age, sex, WHO functional class, MRI data, right heart catheter hemodynamics, time to death or census, or the proportion of CTD, IPAH or congenital heart disease or male patients between the validation and derivation cohorts (all p>0.05). In the derivation cohort the following model was derived from multivariate Cox regression analysis of MRI and clinical data: Prognostic score = (RVESVI (%pred) x 0.208) – (PA relative area change x 0.208) + (WHO FC X 0.458) + (Age x 0.031) – (male = 0.488 or female = 0.976) + (0.304 if CTD). In the validation cohort the model showed the following accuracy, AUC 0.741 and AUC=0.815 at 1 and 3 years. A model based on MRI parameters alone (RVESVI (%pred) x 0.325 - PA relative area change x 0.295) demonstrated the following prognostic accuracy at 3 years in all PAH (AUC=0.741), in IPAH AUC=0.820 (**Figure 4)** and in PAH-CTD, AUC=0.690.

Optimal thresholds at ROC analysis, were identified in the derivation cohort for RVESVI (%pred): 180%, the MRI model: 0.13 units and the model including MRI and clinical data: 3.0 units. **Table 6** presents the sensitivity, specificity, positive and negative predictive value data for these optimal thresholds for 3 year mortality. There was no significant difference at ROC analysis for predicting mortality, between current methods of correcting MRI data for age, sex and body size (Maceira et al (33) and Kawut et al (34)), RVEDV (p=0.955), RVEF (p=0.236) and RVEDM (p=0.635).

Reproducibility of MR indices

Excellent inter-observer reproducibility was identified for RV end-diastolic and end-systolic volume measurements; with high intra- class correlation coefficients demonstrated ICC 0.959 and 0.991 respectively. The agreement was found to be

marginally weaker for RV ejection fraction and stroke volume measurements 0.957 and 0.928 respectively. MRI estimated Ees/Ea was highly reproducible, ICC 0.977 (CI 0.953 to 0.989). PA relative area change was reproducible, ICC 0.891 (0.655 to 0.957). Intra-observer agreement was also high for LV volume measurements (ICC 0.973 to 0.986) and similarly high intra-observer agreement for RV volume measurements was shown (ICC 0.940 to 0.996).

DISCUSSION

This study confirms the independent prognostic value, of MRI measurements reflecting RV volume and stiffness of the proximal pulmonary vasculature, in a large cohort of patients with PAH. In addition, a model including MRI measurements of RV end-systolic volume (%pred) and PA relative area change in combination with clinical data, age, sex, WHO FC and the presence or absence of an underlying connective tissue disease, improves prognostication in pulmonary arterial hypertension.

Many indices of RV size and function have been proposed as prognostic markers in the assessment of patients with pulmonary hypertension, however, previous studies have often been performed in relatively small and selected cohorts of patients. Given the large number of patients in the current study and number of deaths during the follow-up period it has provided an opportunity to assess the clinical utility and relative value of a number of candidate MRI prognostic markers in clinical practice. This study confirms the prognostic value of RV volumes and ejection fraction measured at MRI shown in previous studies (23, 25). Although in clinical practice physicians have traditionally favoured single measurements such as RV ejection fraction, this study demonstrates the added prognostic value of combining a measure of the RV (RVESVI %pred) and a measure of changes in the pulmonary vasculature (pulmonary artery relative area change).

A criticism of relatively simple measures thought to reflect right ventricular function such as volumes and ejection fraction is that these metrics are not load independent (35). Recently more complex measurements reflecting RV-PA coupling, described by the simultaneous relationship between two load independent metrics, RV contractility (Ees) and afterload (Ea) (35) have been proposed as superior to volumetric measurements. Previous work has shown that parameters such as Ees and Ea can be estimated from standard data collected from right heart catheterisation and MRI (30), rather than using conductance catheters not typically used in routine clinical practice. In addition a

completely non-invasive MR based approach and techniques using gated blood pool scintingraphy, can yield measures of RV-PA coupling acknowledging previously described limitations (24, 30-32, 36). A recent study has shown the superior prognostic significance of an MRI derived estimate of right ventricular-arterial coupling Ees/Ea over other invasive and non-invasive measures of RV function (24). In the present study, although MRI estimated Ees/Ea and combined MRI and RHC Ees/Ea, were prognostic at univariate analysis they were not found to be independently prognostic in the full cohort. However, in the subgroup analysis in patients with PAH-CTD in contrast to IPAH combined MRI and RHC Ees/Ea was independently predictive of mortality.

Independent prognostic markers differed between IPAH and PAH-CTD. In IPAH measures of RV size and function, RV end systolic volume and Ees were independently prognostic, in addition to age, sex and SvO_2. Whereas, independent prognostic markers in PAH-CTD were pulmonary arterial relative area change and Ees/Ea (combined invasive/MRI). These differences are likely to reflect the individual pathophysiology and therapy responsiveness of PAH subgroups and reinforces that subgroups have differing prognostic markers.

Pulmonary artery relative area change was found to be an independent prognostic marker in the full cohort, and our data suggests that the stiffness of the pulmonary vasculature has independent prognostic value in addition to baseline measurements reflecting RV function. The present study shows comparable univariate prognostic value of non-invasive PA relative area change and PA distensibility, and no significant difference at ROC analysis between the two measures. This may reflect the close correlation between these two metrics ($r=0.88$).

Patient age has been shown to strongly predict mortality in several PAH cohorts (37, 38). These studies have also demonstrated that the range and average age of patients has risen significantly over the last decade making adjustments for age and sex more

relevant in the current era for accurate individual risk stratification (39). RV end-systolic volume corrected for age, sex and body surface was a significantly stronger predictor of mortality than when adjusted for body surface area alone, highlighting the need to adjust volumetric measurements for individual patients. We have corrected our data using data by Maceira et al (33) due to similarity in RV analysis technique for the main analyses, however, other normative RV data, such as Kawut et al (34), is available and demonstrated similar prognostic value in our cohort of patients. In the present study RVESVI%pred rather than RVEDV%pred was independently prognostic; increased RVESV implies enlargement of the RV in addition to a loss of systolic function and may explain the greater prognostic importance. This finding mirrors data in chronic heart failure, in which increasing RVESV has been shown to be an independent predictor of mortality (40).

Interestingly, in the present study patients on combination therapy with a phosphodiesterase inhibitor and endothelin receptor antagonist had a better outcome than patients on phosphodiesterase inhibitor or endothelin receptor antagonist alone. This is consistent with a prospective double-blinded study, which showed the benefit of combination therapy over monotherapy in patients with PAH (41) in reducing clinical worsening and a MRI focused study of combination therapy in systemic sclerosis which demonstrated improvements in RV function(42).

In clinical practice assessments are based on integrating available information and there has been a move towards developing scoring systems to aid prognostication. ROC curves are frequently used to assess the value of diagnostic tests, however, there is only limited data on assessing the prognostic value of candidate prognostic markers in PAH using ROC analysis. The prognostic value of a single MRI measurement was improved by combining MRI metrics and further improved by incorporating additional clinical data, obtaining ROC values equal to or better than previous studies in cardiac disease (43) and PAH (44).

Limitations

This is a single centre study. There are limitations to estimating RV-PA coupling non-invasively as previously described. Race has been shown to have an independent effect on RV volumes; however, the demographic of our population does not allow direct comparison with the published reference data (34) and we have not adjusted MRI data for race in this study.

Conclusions

MRI measurements of RV structure and function are highly reproducible and have prognostic value. Combining MRI measures of RV function and pulmonary artery stiffness with clinical data further improves prognostication in patients with pulmonary arterial hypertension.

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Table 1 Description of and coupling measurements and PA stiffness metric and pulmonary arterial relative area change

Key metrics	Measurement description	Equation
Ea (mmHg/ml/m^2)	Arterial elastance	(mPAP-PAWP)/stroke volume index
Ees (mmHg/ml/m^2)	Right Ventricular elastance	mPAP/RV end systolic volume index
Ees/Ea (ratio)	PA-RV coupling metric	(mPAP/RV end systolic volume)/[(mPAP-PAWP)/stroke volume]
MRI Ees/Ea (ratio)	Non-invasive PA-RV coupling metric	Stroke volume/RV end systolic volume
PA relative area change (%)	Non-invasive measurement of PA stiffness	(Maximal pulmonary arterial area-minimal pulmonary arterial area)/minimal pulmonary arterial area
Distensibility (%/PP)	Measurement of PA stiffness	PA relative area change/pulse pressure

mPAP=mean pulmonary artery pressure, PAWP=pulmonary arterial wedge pressure, RV=right ventricle, PA=pulmonary artery, MRI=magnetic resonance imaging, PP=pulse pressure

Table 2 Baseline demographic, MRI and right heart catheterisation (RHC) data.

N=576	All patients	Incident patients N=398	Prevalent patients N=178	P value
Demographics				
Age (yrs)	57 (16)	60 (15)	52 (17)	<0.0001
Gender (female %) M/F	182/394	132/266	50/128	0.264
WHO functional class				
I	5	2	3	
II	50	32	17	
III	451	308	141	
IV	70	56	14	
Subgroup				
IPAH	260	179	80	0.946
CTD	195	147	48	0.022
Congenital	63	31	32	<0.0001
Other (portal, HIV and drugs)	58	41	18	0.883
PAH therapy				
Monotherapy oral	155	126	29	<0.0001
Combination oral	308	205	104	0.138
Prostanoid	107	62	45	0.005
RHC				
mPAP (mmHg)	48 (13)	48 (13)	45 (14)	0.090
mRAP (mmHg)	10 (6)	10 (3)	10 (5)	0.369
PAWP (mmHg)	10 (3)	10 (3)	11 (3)	0.046
Svo2 (%)	64 (10)	63 (9)	67 (10)	0.003
CI ($L.min^{-1}.m^{-2}$)	2.8 (0.9)	2.7 (0.8)	3.3 (1.1)	<0.0001
PVRI (Wood units*m^2)	16 (8.1)	15.7 (7.9)	14.0 (9.5)	0.206
Cardiac MR indices				
RVEDVI (ml/m2)	94 (35)	94 (33)	94 (40)	0.978
RVEDVI %pred	128 (47)	129 (45)	124 (52)	0.233
RVESVI (ml/m2)	59 (29)	62 (28)	54 (30)	0.005
RVESVI %pred	246 (125)	262 (126)	210 (117)	<0.0001
RVEF (%)	39 (14)	36 (14)	44 (13)	<0.0001
RVEF %pred	58 (22)	54 (21)	67 (20)	<0.0001
RVSVI (ml/m2)	35 (16)	33 (14)	40 (19)	<0.0001
RVSVI %pred	71 (33)	67 (30)	20 (19)	<0.0001
LVEDVI (ml/m2)	54 (19)	50 (16)	61 (23)	<0.0001
LVEDVI %pred	69 (24)	66 (21)	79 (30)	<0.0001
LVESVI (ml/m2)	18 (9)	17 (8)	20 (11)	0.001
LVESVI %pred	73 (38)	70 (35)	79 (46)	0.049
LVEF (%)	67 (11)	66 (11)	68 (9)	0.036
LVEF %pred	98 (15)	97 (16)	101 (14)	0.008
LVSVI (ml/m2)	26 (14)	23 (12)	12 (16)	<00001
LVSVI %pred	52 (28)	47 (24)	65 (32)	<0.0001
RVEDMI	35 (20)	36 (20)	34 (21)	0.330
RVEDMI %pred	124 (70)	127 (70)	114 (70)	0.120
PA forward flow index (l/min/m2) #	3.2 (1.4)	3.0 (1.3)	3.6 (1.5)	<0.0001
PA stiffness metrics				
PA relative area change#	12 (8)	11 (7)	14 (9)	<0.0001
PA distensibility*	0.28 (0.31)	0.25 (0.30)	0.37 (0.31)	0.003
RV PA coupling metrics				
Ea (mmHg/ml/m^2)*	2.0 (1.4)	2.2 (1.4)	1.4 (1.2)	<0.0001
Ees (mmHg/ml/m^2)*	0.95 (0.246)	0.9 (0.5)	1.0 (0.5)	0.024
Ees /Ea (ratio)*	0.80 (0.83)	0.7 (0.7)	1.3 (1.2)	<0.0001
MRI Ees /Ea (ratio)	0.74 (0.47)	0.7 (0.4)	0.9 (0.5)	<0.0001

*N=379 #N=555. Values presented as mean (standard deviation) unless otherwise stated. WHO= world health organisation, IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index, Svo2= mixed venous oxygen saturations, RVEDVI=right ventricular end-diastolic volume index, RVESVI=right ventricular end-systolic volume index, RVEF=right ventricular ejection fraction, LVEDVI=left ventricular end-diastolic volume index, LVESVI=left ventricular end-systolic volume index, LVEF=left ventricular ejection fraction, LVSVI=left ventricular stroke volume index, VMI=ventricular mass index, E_a = arterial load and E_{max} = RV elastance.

Table 3 Demographics and comparison of incident treatment naïve patients IPAH and PAH-CTD.

	IPAH n=179	PAH-CTD n=147	P value
Demographics			
Age (yrs)	60 (16)	63 (13)	0.093
Gender M/F	73/106	31/116	<0.0001
WHO functional class			
I	0	1	
II	14	9	
III	128	121	
IV	137	16	
PAH therapy			
Monotherapy oral	61	49	0.888
Combination oral	82	82	0.074
Prostanoid	36	16	0.024
RHC			
mPAP (mmHg)	52 (11)	43 (12)	<0.0001
mRAP (mmHg)	11 (5)	10 (6)	0.061
PAWP (mmHg)	10 (3)	10 (3)	0.207
Svo2 (%)	61 (9)	65 (8)	<0.0001
CI ($L.min^{-1}.m^{-2}$)	2.5 (0.8)	2.9 (0.8)	<0.0001
PVRI (Wood units*m^2)	18.1 (7.5)	13.1 (8.2)	<0.0001
Cardiac MR indices			
RVEDVI %pred	134 (43)	117 (37)	<0.0001
RVESVI %pred	286 (126)	235 (116)	<0.0001
RVEF %pred	48 (18)	57 (22)	<0.0001
RVSVI %pred	63 (19)	64 (23)	0.758
LVEDVI %pred	63 (19)	67 (18)	0.095
LVESVI %pred	72 (38)	67 (18)	0.136
LVEF %pred	93 (16)	101 (15)	<0.0001
LVSVI %pred	41 (21)	51 (25)	<0.0001
RVEDMI %pred	215 (119)	166 (93)	<0.0001
PA forward flow index (l/min/m2)	2.6 (1.0)	3.0 (0.9)	<0.0001
PA stiffness metrics			
PA relative area change	10 (6)	11 (8)	0.089
PA distensibility	0.18 (0.15)	0.31 (0.35)	0.001
RV PA coupling metrics			
Ea (mmHg/ml/m^2	1.8 (1.9)	1.3 (1.3)	0.003
Ees (mmHg/ml/m^2)	0.89 (0.34)	0.98 (0.43)	0.047
Ees /Ea (ratio)	0.45 (0.34)	0.95 (0.84)	<0.0001
MRI Ees /Ea (ratio)	0.54 (0.31)	0.75 (0.47)	<0.0001

Values presented as mean (standard deviation) unless otherwise stated. WHO= world health organisation, IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index, Svo2= mixed venous oxygen saturations, RVEDVI=right ventricular end-diastolic volume index, RVESVI=right ventricular end-systolic volume index, RVEF=right ventricular ejection fraction, LVEDVI=left ventricular end-diastolic volume index, LVESVI=left ventricular end-systolic volume index, LVEF=left ventricular ejection fraction, LVSVI=left ventricular stroke volume index, VMI=ventricular mass index, E_a = arterial load and E_{max} = RV elastance.

Table 4 Univariate Cox proportional hazards regression analysis showing prognostic significance of demographic, right heart catheterisation (RHC) and MRI data for the full cohort

N=576, 221 deaths	Univariate Hazard ratio	Scaled univariate Hazard ratio	P value
Demographics			
Age (dichotomised <50 and ≥50)	4.092 (2.697 to 6.208)		<0.0001+
Gender (female %)	0.794 (0.600 to 1.049)		0.105
WHO FC			
I&II vs III&IV	1.876 (1.126 to 3.125)		0.016
I-III vs IV	2.636 (1.912 to 3.634)		<0.0001+
IPAH	0.873 (0.669 to 1.140)		0.319
CTD	1.572 (1.202 to 2.056)		0.001
Congenital	0.389 (0.212 to 0.713)		0.002
Other	0.971 (0.625 to 1.509)		0.897
PAH therapy			
Monotherapy oral	1.658 (1.281 to 2.239)		<0.0001
Combination oral	0.684 (0.524 to 0.892)		0.005
Prostanoid	0.946 (0.679 to 1.317)		0.742
RHC			
mPAP (mmHg)	0.997 (0.987 to 1.008)	0.968 (0.842 to 1.112)	0.643
mRAP (mmHg)	1.019 (0.994 to 1.045)	1.112 (0.967 to 1.279)	0.137
PAWP (mmHg)	0.978 (0.938 to 1.019)	0.926 (0.804 to 1.067)	0.291
Svo2 (%)	0.969 (0.955 to 0.983)	0.738 (0.644 to 0.847)	<0.0001+
CI ($L.min^{-1}.m^{-2}$)	0.826 (0.698 to 0.979)	0.840 (0.720 to 0.981)	0.027
PVRI ($dyn.s.cm^{-3}$)	1.008 (0.991 to 1.025)	1.065 (0.931 to 1.218)	0.359
Cardiac MR indices			
RVEDVI %pred	1.005 (1.002 to 1.007)	1.244 (1.107 to 1.399)	<0.0001+
RVESVI %pred	1.003 (1.002 to 1.004)	1.403 (1.256 to 1.567)	<0.0001+
RVEF %pred	0.987 (0.981 to 0.993)	0.754 (0.662 to 0.860)	<0.0001+
RVSVI %pred	0.999 (0.995 to 1.003)	0.956 (0.838 to 1.091)	0.506
LVEDVI %pred	0.990 (0.984 to 0.996)	0.998 (0.996 to 0.999)	0.002
LVESVI %pred	0.998 (0.994 to 1.002)	0.999 (0.998 to 1.001)	0.359
LVEF %pred	0.993 (0.985 to 1.001)	0.898 (0.790 to 1.022)	0.103
LVSVI %pred	0.990 (0.983 to 0.996)	0.744 (0.619 to 0.896)	0.002
RV EDM %pred	1.001 (1.000 to 1.002)	1.149 (1.009 to 1.308)	0.036
PA forward flow index (l/min/m2) #	0.851 (0.761 to 0.951)	0.797 (0.682 to 0.932)	0.004
PA stiffness metrics			
PA relative area change#	0.951 (0.932 to 0.971)	0.672 (0.569 to 0.794)	<0.0001+
PA distensibility*	0.134 (0.045 to 0.401)	0.536 (0.381 to 0.754)	<0.0001+
RV PA coupling metrics			
Ea ($mmHg/ml/m^2$)*	1.036 (0.942 to 1.140)	1.051 (0.920 to 1.201)	0.462
Ees ($mmHg/ml/m^2$)*	0.921 (0.831 to 1.020)	0.793 (0.667 to 0.944)	0.112
Ees /Ea (ratio)*	0.549 (0.401 to 0.753)	0.777 (0.673 to 0.896)	0.001+
MRI Ees /Ea (ratio)	0.525 (0.375 to 0.736)	0.739 (0.621 to 0.866)	<0.0001+

*N=379 #N=555. +Significant after Bonferonni correction. WHO= world health organisation, IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index, Svo2= mixed venous oxygen saturations, RVEDVI=right ventricular end-diastolic volume index, RVESVI=right ventricular end-systolic volume index, RVEF=right ventricular ejection fraction, LVEDVI=left ventricular end-diastolic volume index, LVESVI=left ventricular end-systolic volume index, LVEF=left ventricular ejection fraction, LVSVI=left ventricular stroke volume index, VMI=ventricular mass index, Ea = arterial load and Ees = RV elastance.

Table 5 Multivariate analyses showing independent predictors of outcome in the whole PAH cohort, all incident patients with PAH and incident patients with IPAH and CTD

	Multivariate Hazard ratio	P value
Full cohort		
Age >50	2.787 (1.691 to 4.592)	<0.0001
Presence of CTD	1.421 (1.017 to 1.984)	0.039
Monotherapy vs Combination therapy	1.700 (1.200 to 2.409)	0.003
SvO2 (scaled)	0.792 (0.672 to 0.934)	0.006
RV ESV %pred (scaled)	1.217 (1.061 to 1.539)	0.005
PA RAC (scaled)	0.762 (0.623 to 0.932)	0.008
Incident cases		
Age >50	2.324 (1.380 to 3.915)	0.002
Monotherapy vs Combination therapy	1.571 (1.087 to 2.270)	0.016
SvO2 (scaled)	0.790 (0.661 to 0.944)	0.009
RV ESV %pred (scaled)	1.186 (1.015 to 1.385)	0.032
PA RAC (scaled)	0.741 (0.589 to 0.932)	0.010
Incident IPAH		
Age >50	2.837 (1.200 to 6.708)	0.010
Female	0.583 (0.360 to 0.945)	0.029
SvO2 (scaled)	0.652 (0.495 to 0.858)	0.002
Ees (scaled)	0.781 (0.621 to 0.983)	0.035
RV ESV %pred (scaled)	1.408 (1.147 to 1.729)	0.001
Incident CTD		
Monotherapy vs Combination therapy	2.182 (1.282 to 3.714)	0.004
Ees/Ea (scaled)	0.757 (0.642 to 0.892)	0.001
PA RAC (scaled)	0.653 (0.496 to 0.859)	0.002

CTD = connective tissue disease, Svo2= mixed venous oxygen saturations, RVESVI=right ventricular end-systolic volume index, PA RAC= Pulmonary artery relative area change, Ea = arterial load and Ees = RV elastance.

Table 6 MRI and demographics model

	Sens	Spec	PPV	NPV	LHR	**p-value**
Full cohort						
Prognostic model 3 years						
RV end-systolic volume (%pred) (1.8)	61	63	43	78	1.64	0.0002
MRI model (0.13)	71	63	47	83	1.91	<0.0001
MRI and demographic model (3.0)	77	73	56	87	2.78	<0.0001

Sens = sensitivity, Spec= specificity, PPV=positive predictive value, NPV=negative predictive value and LHR=likelihood ratio.

Online supplement tables

Table a Univariate Cox proportional hazards regression analysis showing prognostic significance of demographic, right heart catheterisation (RHC) and MRI data for incident treatment naïve patients with PAH

N=398, 189 deaths	Univariate Hazard ratio	Scaled Univariate Hazard ratio	P value
Demographics			
Age (dichotomised <50 and ≥50)	2.852 (1.827 to 4.450)		<0.0001 +
Gender (female %)	0.905 (0.668 to 1.226)		0.519
WHO FC			
I&II vs III&IV	1.708 (0.989 to 2.950)		0.055
I-III vs IV			
IPAH	0.955 (0.717 to 1.274)		0.756
CTD	1.271 (0.950 to 1.701)		0.107
Congenital	0.595 (0.314 to 1.125)		0.110
Other	0.879 (0.541 to 1.430)		0.604
PAH therapy			
Monotherapy oral	1.447 (1.074 to 1.949)		0.009
Combination oral	0.731 (0.549 to 0.974)		0.033
Prostanoid	0.987 (0.677 to 1.438)		0.945
RHC			
mPAP (mmHg)	0.997 (0.985 to 1.008)	0.958 (0.825 to 1.112)	0.572
mRAP (mmHg)	1.017 (0.991 to 1.044)	1.097 (0.949 to 1.269)	0.209
PAWP (mmHg)	0.980 (0.938 to 1.025)	0.935 (0.804 to 1.088)	0.384
Svo2 (%)	0.969 (0.954 to 0.984)	0.738 (0.637 to 0.856)	<0.0001 +
CI ($L.min^{-1}.m^{-2}$)	0.797 (0.658 to 0.966)	0.813 (0.682 to 0.969)	0.021
PVRI ($dyn.s.cm^{-3}$)	1.008 (0.991 to 1.027)	1.070 (0.926 to 1.237)	0.358
Cardiac MR indices			
RVEDVI %pred	1.005 (1.002 to 1.007)	1.240 (1.085 to 1.416)	0.002
RVESVI %pred	1.002 (1.001 to 1.003)	1.326 (1.172 to 1.499)	<0.0001 +
RVEF %pred	0.991 (0.985 to 0.998)	0.828 (0.717 to 0.956)	0.010
RVSVI %pred	1.000 (0.996 to 1.005)	1.008 (0.869 to 1.169)	0.915
LVEDVI %pred	0.994 (0.987 to 1.002)	0.999 (0.997 to 1.000)	0.141
LVESVI %pred	1.000 (0.996 to 1.005)	1.000 (0.988 to 1.002)	0.892
LVEF %pred	0.994 (0.986 to 1.003)	0.917 (0.801 to 1.049)	0.206
LVSVI %pred	0.996 (0.989 to 1.004)	0.897 (0.729 to 1.104)	0.306
RV EDM %pred	1.001 (1.000 to 1.002)	1.137 (0.987 to 1.310)	0.076
PA forward flow index (l/min/m2) #	0.942 (0.838 to 1.058)	0.919 (0.780 to 1.083)	0.313
PA stiffness metrics			
PA relative area change#	0.948 (0.926 to 0.972)	0.657 (0.543 to 0.795)	<0.0001 +
PA distensibility*	0.088 (0.022 to 0.360)	0.467 (0.303 to 0.721)	0.001+
RV PA coupling metrics			
Ea ($mmHg/ml/m^2$)*	1.014 (0.913 to 1.121)	1.017 (0.881 to 1.174)	0.819
Ees ($mmHg/ml/m^2$)*	0.892 (0.799 to 0.996)	0.873 (0.766 to 0.995)	0.042
Ees /Ea (ratio)*	0.702 (0.566 to 0.872)	0.786 (0.678 to 0.911)	0.001+
MRI Ees /Ea (ratio)	0.592 (0.407 to 0.862)	0.811 (0.698 to 0.943)	0.006

*N=325 #N=385. +Significant after Bonferonni correction. WHO= world health organisation, IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index, Svo2= mixed venous oxygen saturations, RVEDVI=right ventricular end-diastolic volume index, RVESVI=right ventricular end-systolic volume index, RVEF=right ventricular ejection fraction, LVEDVI=left ventricular end-diastolic volume index, LVESVI=left ventricular end-systolic volume index,

LVEF=left ventricular ejection fraction, LVSVI=left ventricular stroke volume index, VMI=ventricular mass index, Ea = arterial load and Ees = RV elastance.

Table b Univariate Cox proportional hazards regression analysis showing prognostic significance of demographic, right heart catheterisation (RHC) and MRI data for incident treatment naïve patients with IPAH

N=179, 84 deaths	Univariate Hazard ratio	Scaled univariate Hazard ratio (variable/SD)	P value
Demographics			
Age (dichotomised <50 and ≥50)	3.881 (1.872 to 8.045)		<0.0001⁺
Gender (female %)	0.649 (0.422 to 0.997)		0.048
WHO FC			
I&II vs III&IV	2.431 90.978 to 6.043)		0.056
I-III vs IV	2.618 (0.650 to 4.155)		<0.0001⁺
PAH therapy			
Monotherapy oral	1.103 (0.703 to 1.730)		0.670
Combination oral	1.106 (0.717 to 1.706)		0.649
Prostanoid	0.763 (0.446 to 1.306)		0.325
RHC			
mPAP (mmHg)	0.979 (0.959 to 1.000)	0.765 (0.587 to 0.996)	0.046
mRAP (mmHg)	1.031 (0.989 to 1.075)	1.186 (0.940 to 1.497)	0.150
PAWP (mmHg)	0.982 (0.914 to 1.055)	0.941 (0.738 to 1.199)	0.621
Svo2 (%)	0.960 (0.937 to 0.985)	0.680 (0.534 to 0.865)	0.002
CI ($L.min^{-1}.m^{-2}$)	0.781 (0.573 to 1.064)	0.798 (0.602 to 1.058)	0.117
PVRI ($dyn.s.cm^{-3}$)	0.984 (0.950 to 1.019)	0.874 (0.659 to 1.161)	0.354
Cardiac MR indices			
RVEDVI %pred	1.007 (1.003 to 1.011)	1.383 (1.133 to 1.688)	0.001⁺
RVESVI %pred	1.003 (1.001 to 1.004)	1.392 (1.173 to 1.651)	<0.0001⁺
RVEF %pred	0.991 (0.980 to 1.002)	0.828 (0.651 to 1.053)	0.123
RVSVI %pred	1.004 (0.997 to 1.011)	1.136 (0.909 to 1.420)	0.261
LVEDVI %pred	0.998 (0.986 to 1.010)	1.000 (0.997 to 1.003)	0.779
LVESVI %pred	1.308 (0.633 to 2.702)	1.001 (0.988 to 1.004)	0.515
LVEF %pred	0.992 (0.979 to 1.004)	0.878 (0.721 to 1.068)	0.193
LVSVI %pred	1.002 (0.991 to 1.014)	1.072 (0.778 to 1.477)	0.673
RV EDM %pred	1.003 (0.999 to 1.006)	1.203 (0.955 to 1.515)	0.117
PA forward flow index (l/min/m2) #	0.863 (0.687 to 1.083)	0.813 (0.591 to 1.119)	0.204
PA stiffness metrics			
PA relative area change#	0.951 (0.915 to 0.990)	0.673 (0.492 to 0.921)	0.013
PA distensibility*	0.044 (0.004 to 0.438)	0.380 (0.186 to 0.774)	0.008
RV PA coupling metrics			
Ea ($mmHg/ml/m^2$)*	0.823 (0.679 to 0.997)	0.925 (0.743 to 1.150)	0.482
Ees ($mmHg/ml/m^2$)*	0.328 (0.157 to 0.684)	0.573 (0.396 to 0.827)	0.003
Ees /Ea (ratio)*	0.477 (0.235 to 0.966)	0.603 (0.372 to 0.977)	0.040
MRI Ees /Ea (ratio)	0.540 (0.260 to 1.124)	0.749 (0531 to 1.056)	0.100

*N=149 #N=176. ⁺Significant after Bonferonni correction. WHO= world health organisation, IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index, Svo2= mixed venous oxygen saturations, RVEDVI=right ventricular end-diastolic volume index, RVESVI=right ventricular end-systolic volume index, RVEF=right ventricular ejection fraction, LVEDVI=left ventricular end-diastolic volume index, LVESVI=left ventricular end-systolic volume index, LVEF=left ventricular ejection fraction, LVSVI=left ventricular stroke volume index, VMI=ventricular mass index, Ea = arterial load and Ees = RV elastance

Table c Univariate Cox proportional hazards regression analysis showing prognostic significance of demographic, right heart catheterisation (RHC) and MRI data for incident treatment naïve patients with PAH-CTD

N=147, 77 deaths	Univariate Hazard ratio	Univariate Hazard ratio	P value
Demographics			
Age (dichotomised <50 and ≥50)	1.407 (0.675 to 2.929)		0.362
Gender (female %)	0.778 (0.447 to 1.354)		0.374
WHO FC			
I&II vs III&IV	1.416 (0.857 to 2.337)		0.174
I-III vs IV	1.167 (0.881 to 3.168)		0.116
PAH therapy			
Monotherapy oral	1.568 (0.977 to 2.515)		0.062
Combination oral	0.571 (0.364 to 0.896)		0.015
Prostanoid	1.440 (0.776 to 2.673)		0.248
RHC			
mPAP (mmHg)	1.012 (0.995 to 1.030)	1.171 (0.933 to 1.470)	0.174
mRAP (mmHg)	1.000 (0.963 to 1.038)	0.999 (0.809 to 1.234)	0.150
PAWP (mmHg)	0.982 (0.922 to 1.047)	0.941 (0.758 to 1.167)	0.578
Svo2 (%)	0.964 (0.940 to 0.989)	0.707 (0.556 to 0.889)	0.005
CI ($L.min^{-1}.m^{-2}$)	0.766 (0.576 to 1.019)	0.785 (0.605 to 1.017)	0.067
PVRI ($dyn.s.cm^{-3}$)	0.984 (0.950 to 1.019)	1.073 (0869 to 1.326)	0.354
Cardiac MR indices			
RVEDVI %pred	1.004 (0.998 to 1.009)	1.182 (0.897 to 1.558)	0.236
RVESVI %pred	1.002 (1.002 to 1.004)	1.258 (1.005 to 1.574)	0.045
RVEF %pred	0.990 (0.980 to 1.000)	0.798 (0.642 to 0.990)	0.041
RVSVI %pred	0.995 (0.995 to 1.004)	0.844 (0.616 to 1.156)	0.290
LVEDVI %pred	0.362 (0.090 to 1.452)	0.997 (0.994 to 1.000)	0.152
LVESVI %pred	1.242 (0.582 to 2.648)	1.000 (0.997 to 1.002)	0.575
LVEF %pred	0.992 (0.978 to 1.007)	0.886 (0.708 to 1.108)	0.288
LVSVI %pred	0.985 (0.972 to 0.997)	0.644 (0.447 to 0.927)	0.018
RV EDM %pred	1.001 (0.997 to 1.005)	1.055 (0.804 to 1.383)	0.701
PA forward flow index (l/min/m2) #	1.023 (0.804 to 1.300)	1.032 (0.737 to 1.445)	0.855
PA stiffness metrics			
PA relative area change#	0.948 (0.914 to 0.982)	0.652 (0.490 to 0.866)	0.003
PA distensibility*	0.155 (0.034 to 0.700)	0.560 (0.351 to 0.895)	0.015
RV PA coupling metrics			
Ea ($mmHg/ml/m^2$)*	0.984 (0.984 to 1.360)	1.227 (0.978 to 1.538)	0.077
Ees ($mmHg/ml/m^2$)*	0.979 (0.819 to 1.170)	0.975 (0.788 to 1.206)	0.815
Ees /Ea (ratio)*	0.607 (0.425 to 0.867)	0.674 (0.508 to 0.894)	0.006
MRI Ees /Ea (ratio)	0.521 (0.309 to 0.879)	0.770 (0.625 to 0.950)	0.015

*N=134 #N=139. WHO= world health organisation, IPAH = idiopathic pulmonary arterial hypertension, CTD = connective tissue disease, mRAP=mean right atrial pressure, mPAP=mean pulmonary artery pressure, PCWP=pulmonary capillary wedge pressure, PVR=pulmonary vascular resistance, CI=cardiac index, Svo2= mixed venous oxygen saturations, RVEDVI=right ventricular end-diastolic volume index, RVESVI=right ventricular end-systolic volume index, RVEF=right ventricular ejection fraction, LVEDVI=left ventricular end-diastolic volume index, LVESVI=left ventricular end-systolic volume index, LVEF=left ventricular ejection fraction, LVSVI=left ventricular stroke volume index, VMI=ventricular mass index, Ea = arterial load and Ees = RV elastance.

Figure 1

Images detailing PA size and relative area change analysis (A) maximal PA area and (B) minimal PA area and RV volume and mass calculation from end diastolic images (C) and end-systolic images (D).

Figure 2

Study flow diagram

Figure 3

Kaplan-Meier survival curves showing the outcome of PA relative area change and RVESV %pred. Numbers at risk are presented below each plot.

Figure 4

Receiver operating curves for important predictors of mortality in all patients with PAH (a) and incident patients with IPAH (b)