

Word Count 2500/2500

Abstract 236/250

Right Ventricle to Left Ventricle ratio at CTPA predicts mortality in Interstitial Lung Disease

Authors, e-mails and affiliations

Simon Bax ^{1,2,3} S.bax@nhs.net

Joseph Jacob ^{4,5} j.jacob@ucl.ac.uk

Riaz Ahmed² Riazeahmed@nhs.net

Charlene Bredy ^{1,10} Charlenebredy@hotmail.com

Konstantinos Dimopoulos ^{1,3} k.dimopoulos02@gmail.com

Aleksander Kempny ¹ A.Kempny@rbht.nhs.uk

Maria Kokosi ⁶ M. Kokosi@rbht.nhs.uk

Gregory Kier ⁷ Gregory.Keir@health.qld.gov.au

Elisabetta Renzoni ⁶ E.Renzoni@rbht.nhs.uk

Philip L Molyneaux ^{6,8} p.molyneaux@imperial.ac.uk

Felix Chua ⁶ F.Chua@rbht.nhs.uk

Vasilis Kouranos ⁶ V.Kouranos@rbht.nhs.uk

Peter George ^{3,6} P.George@rbht.nhs.uk

Colm McCabe ¹ C.McCabe2@rbht.nhs.uk

Michael Wilde ² Michael.Wilde@SASH.nhs.uk

Anand Devaraj ⁹ A. Devaraj@rbht.nhs.uk

Athol Wells ⁶ RBHILD@rbht.nhs.uk

S John Wort ^{* 1,3} S.Wort@rbht.nhs.uk

Laura C Price ^{* 1} Laura.Price@rbht.nhs.uk

* Joint final authors

Affiliations

1. National Pulmonary Hypertension Service, Royal Brompton and Harefield NHS Trust
2. Surrey and Sussex Hospital, Redhill, Canada Ave, Redhill, Surrey, UK
3. National Heart and Lung Institute, Imperial College, London, UK.
4. Department of Respiratory Medicine, University College London, London, UK
5. Centre for Medical Image Computing, University College London, London, UK.
6. Department of Interstitial Lung Diseases, Royal Brompton and Harefield NHS Trust
7. Princess Alexandra Hospital, Department of Respiratory Medicine, Woolloongabba, Australia
8. Fibrosis Research Group, National Heart and Lung Institute, Imperial College, London, UK.
9. Department of Radiology, Royal Brompton and Harefield NHS Trust
10. CHU Arnaud de Villeneuve, Montpellier, France

Corresponding Author

Dr Simon Bax

Consultant Respiratory Physician

Surrey and Sussex Hospital

Redhill, Canada Avenue

Surrey, RH1 5RH

Email: S.Bax@nhs.net

Conflict of Interest

Simon Bax - No conflict of interest

Joseph Jacob – reports receiving personal fees from Boehringer Ingelheim and Roche, outside the submitted work, and was supported by a Wellcome Trust Clinical Research Career Development Fellowship (209553/Z/17/Z).

Riaz Ahmed - No conflict of interest

Charlene Bredy - No conflict of interest

Konstantinos Dimopoulos - reports receiving unrestricted educational grants and has acted as a consultant for Actelion, GSK, Pfizer and Bayer, outside the submitted work.

Aleksander Kempny - reports receiving grants from Actelion Global, outside the submitted work.

Maria Kokosi - No conflict of interest

Gregory Kier - No conflict of interest

Elisabetta Renzoni - reports personal fees from Roche, Boehringer Ingelheim outside the submitted work.

Philip L Molyneaux - reports personal fees from Roche and Boehringer Ingelheim, outside the submitted work.

Felix Chua - reports personal fees from Roche and Boehringer Ingelheim, outside the submitted work.

Vasilis Kouranos - No conflict of interest

Peter George - reports personal fees from Roche, Boehringer Ingelheim and Teva outside the submitted work.

Colm McCabe - No conflict of interest

Michael Wilde - No conflict of interest

Anand Devaraj - reports personal fees from Roche, GSK and Boehringer Ingelheim, outside the submitted work.

Athol Wells - reports receiving personal fees from Intermune, Boehringer Ingelheim, Gilead, MSD, Roche, Bayer and Chiesi, outside the submitted work.

S John Wort - reports receiving grants from Actelion, GSK, Pfizer and Bayer, outside the submitted work.

Laura Price - reports educational grants from Actelion and GSK, during the conduct of the study.

Abbreviations list

Ao	Aorta
AUC	Area under the curve
BNP	Brain natriuretic peptide
CI	Confidence interval
CO	Cardiac output
CT	Computerised tomography
CTPA	Computerised tomography pulmonary angiogram
FVC	Forced vital capacity
HR	Hazard ratio
HRCT	High resolution computerised tomography
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
ILD-PH	Interstitial lung disease associated pulmonary hypertension
KCO _c	Gas transfer co-efficient
LA	Left atrium
LV	Left ventricle
MPA	Main pulmonary artery
MPA:Ao	Main pulmonary artery to Aorta ratio
mPAP	Mean pulmonary arterial pressure
PH	Pulmonary Hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart catheter
RA	Right atrium
RV	Right ventricle
RVSP	Right ventricular systolic pressure
TLCO _c	Gas transfer
RV:LV	Right ventricle to left ventricle ratio

Introduction

Patients with interstitial lung disease (ILD) may develop pulmonary hypertension (PH), often disproportionate to ILD severity. Right ventricle to left ventricle diameter ratio (RV:LV) measured at CT pulmonary angiography (CTPA), has been shown to provide valuable information in pulmonary arterial hypertension patients and to predict death or deterioration in acute pulmonary embolism.

Methods

Demographics, ILD subtype, echocardiography and detailed CTPA measurements were collected in consecutive patients undergoing both CTPA and right heart catheterisation (RHC) at the Royal Brompton Hospital between 2005 and 2015. Fibrosis severity was formally scored using CT criteria. RV:LV ratio at CTPA was evaluated by three different methods. Cox-proportional hazard analysis was used to assess the relation of CTPA-derived parameters to predict death or lung transplantation.

Results

92 patients were included: 64% male, mean age 65 ± 11 years, with FVC $57 \pm 20\%$ (predicted), $TLCO_c$ $22 \pm 8\%$ (predicted) and KCO_c $51 \pm 17\%$ (predicted). PH was confirmed at RHC in 78%. Of all CTPA-derived measures, an RV:LV ratio ≥ 1.0 strongly predicted mortality or transplantation at univariate analysis (HR 3.26, 95%CI:1.49-7.13, $p=0.003$), whereas invasive haemodynamic data did not. The RV:LV ratio remained an independent predictor at multivariate analysis (HR: 3.19, CI:1.44-7.10, $p=0.004$), adjusting for an ILD diagnosis of IPF and CT derived ILD severity.

Conclusion

An increased RV:LV ratio measured at CTPA provides a simple, non-invasive method of risk stratification in patients with suspected ILD-PH. This should prompt closer follow up, more aggressive treatment and consideration of lung transplantation.

Introduction

Pulmonary hypertension (PH) is common in interstitial lung disease (ILD) and impacts adversely on outcome, which is independent of the subtype of interstitial lung disease¹. Clinical signs of PH are difficult to detect, and physicians rely on the integration of pre-test probability and non-invasive investigations, such as echocardiography, brain natriuretic peptide (BNP), six-minute walk data and ancillary signs afforded by CT evaluation. Invasive right heart catheterisation (RHC) remains essential for confirming the diagnosis of PH². In patients with PH due to lung disease and/or hypoxia (group 3 PH), RHC is usually reserved for patients worked-up for lung transplantation or in whom PH appears disproportionate to the severity of the ILD. Patients considered to have a “pulmonary vascular phenotype”, should be investigated further and may be enrolled in studies using pulmonary arterial hypertension therapies².

Echocardiographic variables such as right ventricular systolic pressure (RVSP) predict both the presence of PH and mortality with varying degrees of accuracy³⁻⁷. However, suitable echocardiographic windows are often difficult to attain in ILD patients. Several studies have evaluated the ability of the CT-derived main pulmonary artery (MPA) diameter and MPA to aorta (Ao) diameter ratio (MPA:Ao) to predict the presence of PH in ILD. Although useful predictors of PH in other conditions⁸, studies differ in patients with ILD, with some demonstrating that MPA dilatation occurs in the absence of PH^{9,10}. However a recent study found that MPA diameter was reliable in detecting PH in patients with ILD¹¹. Recently, the MPA:Ao was shown to be an independent predictor of survival or transplantation in a large cohort of unselected patients with idiopathic pulmonary fibrosis (IPF)¹².

Right ventricular (RV) to left ventricular (LV) ratio measured on CT (RV:LV) has been shown to predict the presence of PH in patients with pulmonary arterial hypertension^{13,14}. In addition, studies have shown that the CT-derived RV:LV ratio predicts 30-day mortality in patients following acute pulmonary embolism¹⁵. We hypothesized that patients with ILD associated PH (ILD-PH) would have a larger RV:LV ratio, and an increased RV:LV ratio would predict PH and be associated with a worse prognosis.

Methods

Consecutive ILD patients with suspected PH referred to the Royal Brompton Hospital National Pulmonary Hypertension Service between 2005 and 2015 were reviewed. Patients were included if a CTPA had been performed within 6 months of the baseline diagnostic right heart catheterisation (RHC) study. To reflect a pure 'group 3' PH cohort, those with an ILD diagnosis of an idiopathic interstitial pneumonia or chronic hypersensitivity pneumonitis were included^{16,17}, whereas those with sarcoidosis or a connective tissue disease were excluded, as were those with co-existent acute and/or chronic pulmonary thromboembolism detected on CTPA. This study had institutional review board approval (Royal Brompton, Harefield reference 2016PH002B).

Right heart catheterisation

RHC was performed using standard techniques² with haemodynamic measurements obtained at rest. PH was defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg. Cardiac output (CO) was measured using the indirect Fick method with oxygen consumption estimated using the LaFarge equation. Pulmonary vascular resistance (PVR) was calculated as $PVR = (mPAP - \text{pulmonary capillary wedge pressure}) / CO$.

CTPA acquisition

CT was performed at full inspiration. A continuous scale of ILD severity was produced using volumetric HRCT images scored independently by an experienced radiologist (JJ). Lobar extents of reticulation or honeycombing were scored to the nearest 5% to create a lobar fibrosis score. Lobar scores of fibrosis were summed and divided by 6 to create an overall fibrosis score per patient¹⁸. All CTPA examinations were performed at the discretion of the PH team at the time of the PH assessment. Intravenous administration of contrast medium

was performed with standard intravenous access, using automated administrator injection equipment. Bolus tracking was used to trigger the start of the acquisition of images. Electrocardiogram gating of image acquisition was not performed. We analysed the RV:LV ratio using a threshold of 1.0 to define RV dilatation.

CTPA measurements

All measurements were performed on standard axial imaging. All scans were anonymised, and the reviewer blinded to all clinical and haemodynamic data (SB). The following measurements (for full details of measurements see Figure 1 and supplementary material) were performed:

- The main pulmonary artery (MPA) and aortic (Ao) diameter were measured and the MPA:Ao ratio calculated¹⁹.
- The RV was said to be “larger” or “smaller” than the LV using a subjective evaluation of RV and LV size where no measurements were performed, and the reviewer could evaluate the entire scan²⁰.
- RV and LV diameter were measured at their widest point²¹ at the mid-ventricular level, (Figure 1, panel 1), on the same CT axial image, and the RV:LV ratio calculated (RV:LV_{axial}).
- The RV and LV diameters were also measured at their widest point²² at mid ventricular level (Figure 1, panel 2 and 3), and the RV:LV ratio calculated (RV:LV_{largest}).
- The right atrium (RA) diameter was measured (Figure 1, panel 4) in the longitudinal plane (RA_{longitudinal}) and in the transverse plane (RA_{transverse}).

- Reflux of contrast media into the inferior vena cava was scored as absent or present (Figure 1, panel 5).
- The left atrium (LA) diameter was measured (Figure 1, panel 6).
- Ventricular septal bowing was scored as present or absent (Figure 1, panel 7 and 8).

Echocardiography

Images were acquired using a 3MHz frequency harmonic phased-array transducer. Doppler echocardiography was performed as per the American Society of Echocardiography recommendations^{23,24}. The 2D-echo datasets were interpreted by a cardiologist with advanced echocardiography training.

Statistical analysis

All statistical analyses were performed using R version 3.3.1 (R Foundation for Statistical Computing). Data were summarised as number (percentage) for categorical variables and mean \pm SD or median [interquartile range] for continuous variables as appropriate. Continuous variables were compared using t-test, Wilcoxon Rank-Sum test and categorical data was compared with Chi-squared test. Continuous measurements were compared using Bland and Altman analysis. Survival analysis was performed using Cox-proportional hazard modelling, with the date of the CTPA as the start of follow up and patients followed over 5 years. Kaplan Meier plots were used to estimate outcome. Receiver operating characteristic analysis was performed to evaluate the ability of the RV:LV ratio to detect PH. The primary end-point was death or lung transplantation, and all other patients were censored at the last date of clinical contact. Backwards selection of variables in multivariate models was used, including severity of fibrosis measured at CT, ILD subtype (IPF versus non-IPF), and the RV:LV_{largest} ratio.

Results

Patient demographics

92 patients were included in the study, with a mean age of 62 ± 11 years; 64% male. The time between RHC and CTPA was 0.1 ± 1.1 months. Most patients had IPF ($n=58$, 63%, Table 1), with FVC $57\pm 20\%$ predicted, $TLCO_c$ $22\pm 8\%$ predicted and KCO_c $51\pm 17\%$ predicted. Pulmonary hypertension ($mPAP\geq 25$ mmHg) was confirmed at RHC in 72/92 (78%) patients; 31/92 (34%) had severe PH ($mPAP\geq 35$ mmHg) (Table 2).

CTPA measured RV:LV measurements

The mean *RVaxial* diameter was 45.3 ± 9.0 mm, and mean *RVlargest* diameter was 52.1 ± 8.7 mm. The RV was deemed to be subjectively larger than the LV in $n=71$ (77%) patients. The *RV:LVlargest* method produced larger RV (52 ± 0.8 mm versus 45 ± 0.9 mm, $p<0.001$) and LV values (35 ± 0.8 mm versus 39 ± 0.7 mm, $p<0.001$) compared to the *RV:LVaxial* method (Figure 2). Bland-Altman analysis showed that the mean *RVlargest* diameter was 7.0 [5.8-8.1mm] larger than the *RVaxial* method. The *RV:LVaxial* ratio (1.38 ± 0.5) did not differ when compared to the *RV:LVlargest* ratio (1.39 ± 0.4 , $p=0.9$, although, RV enlargement frequently occurred inferiorly and was missed by the *RV:LVaxial* method (figure 2). Use of the *RV:LVlargest* method resulted in the reclassification of 6 (32%) patients with a *RV:LVaxial* ratio of <1.0 into the ≥ 1.0 category.

Use of RV:LV ratio at CT to predict the presence of PH

RV:LVaxial ratio predicted the presence of PH with an area under the curve (AUC) of 69.4%. An *RVaxial* >1.0 identified PH with a sensitivity of 83.9%, and specificity of 50.0%. The AUC of *RV:LVlargest* ratio for predicting the presence of PH was 59.3%. An *RV:LVlargest* >1.0 identified PH with a sensitivity of 90.4%, and specificity of 34.8%.

Comparison of patients stratified by the RV:LVlargest ratio

PH was present in n=9 (69%) patients with an RV:LVlargest <1.0, and in n=63 (80%) of patients with an RV:LVlargest ≥1.0. PVR was significantly higher in patients with an RV:LVlargest ≥1.0 (5.8±3.3 versus 3.9±2.0 Wood units, p=0.01, Table 2). Patients with an RV:LVlargest ≥1.0 had a larger MPA diameter (p=0.01), larger transverse (p<0.001) and longitudinal RA (p=0.05) diameter measured at CT, larger RA area measured at echocardiogram (p=0.03), higher RVSP (p=0.04), higher BNP (p=0.03) and larger inferior vena cava diameter (p=0.02). Ventricular septal bowing only occurred when the RV:LVlargest ratio was >1.0. Spirometry was not different between groups, although measures of gas transfer and gas transfer co-efficient were lower in patients with an RV:LVlargest ≥1.0 (p=0.01 for TLco_c and p=0.003 for Kco_c) (Table 2). The fibrosis score measured at CT was not different between groups (p=0.3).

Univariate and Multivariate predictors of mortality

Median follow up was 18.8 months [8.3 – 31.6 months]; 74 patients died (80.4%) and 6 (6.5%) underwent transplantation over the 5-year follow up period. Univariate Cox regression analysis results are shown in Table 3. At univariate assessment, the following were associated with an increased risk of mortality: a diagnosis of IPF (hazard ratio (HR) 1.94, 95% confidence interval (CI) 1.21-3.10, p=0.006); subjectively larger RV than LV at CT (HR: 2.08, CI: 1.16-3.74, p=0.01); an RV:LVaxial ≥1.0 (HR: 2.17, CI:1.19-3.97,p=0.01) and an RV:LVlargest ratio ≥1.0 (HR: 3.26, CI: 1.49-7.15, p=0.003) (Figure 3). Fibrosis score measured at CT was associated with mortality (HR: 1.37, CI: 1.15-1.63, p<0.001) per 10% increase in fibrosis score. Neither haemodynamic or echocardiographic variables predicted mortality at univariate assessment. Neither MPA diameter nor MPA:Ao diameter predicted mortality (Table 3).

At multivariate analysis, after adjustment for the fibrosis score at HRCT and a diagnosis of IPF, an RV:LVlargest ≥ 1.0 remained an independent predictor of mortality / lung transplant (HR: 3.19, CI: 1.44-7.10, p=0.004) (Table 4).

Discussion

This study demonstrates that CTPA is a useful method of risk stratification in patients with ILD who are suspected of having PH. The RV:LV_{largest} ratio was superior to invasive haemodynamics and echocardiography in terms of predicting outcome. An RV:LV_{largest} ratio ≥ 1.0 (HR: 3.26, CI: 1.49-7.15, $p=0.003$) was strongly associated with mortality, as well as higher PVR, and remained an independent predictor of mortality, after adjusting for ILD severity and a diagnosis of IPF. The RV:LV ratio had poor specificity in detecting PH at RHC however, suggesting that the RV:LV ratio at CT cannot be relied upon to exclude PH.

In our cohort, a high proportion of patients had PH (78%). Of 80 patients with an RV:LV_{largest} ≥ 1.0 , 16 (20%) had borderline PH (mPAP of 21[16-23] mmHg, and PVR 2.8[1.8-3.1] Wood units). This may relate to the impact of exercise on the RV in these patients, or the time taken to develop PH and the relative compliance of the pulmonary circulation. PH can progress rapidly in IPF patients awaiting transplant: of 44 patients included in the study by Nathan et al., 38.6% had PH at initial transplant workup RHC, which rapidly increased to 86.4% at the time of transplantation²⁵. The factors leading to the development of PH in patients with ILD remain poorly understood and include fibrosis-induced destruction of pulmonary vessels, and excessive pulmonary vascular remodelling. It is likely that patients with borderline haemodynamics progress and develop PH, in part related to acute exacerbations, which are more common in those awaiting lung transplant²⁶. A sub-group of patients seem to develop RV dilatation even without PH at RHC, and are at an increased risk of mortality, hence haemodynamic assessment following exercise is likely to be an important future component of assessment²⁷. It seems probable in ILD patients that RV diameter and the MPAD serve somewhat as barometers for current and prior disease trends being influenced by progressive interstitial lung disease (be it either slow progression or dramatic deterioration as occurs

during acute exacerbations), pulmonary vascular remodelling, and hypoxia. An RV:LV>1 may be seen as a tipping point in favour of worse prognosis. The only other study in patients with PH, evaluating the prognostic role of RV/LV ratio at CTPA, is in patients with chronic thromboembolic PH and supports our findings²⁸.

Previous studies have differed in their findings that haemodynamics predict outcome in IL- PH. For example, studies that evaluated PH at initial IPF diagnosis using RHC (when the prevalence of PH = 8.1%) found that the best mPAP threshold to predict outcome was 17mmHg²⁹. Another study again in early stage IPF (PH prevalence = 14.9%) found that a mPAP of 20mmHg was the best threshold to predict mortality³⁰. In contrast, in 135 patients with IPF undergoing lung transplant evaluation (PH prevalence = 29%), mPAP did not predict mortality, however PVR did⁴. Similarly, in a mixed ILD cohort of 66 patients with a high prevalence of PH (75.7%), mPAP did not predict mortality, however PVR predicted short-term mortality³¹. Another factor to consider is pulmonary vasodilator treatment (HR:0.62, CI:0.40-0.97, p=0.04) which suggests a beneficial effect in our cohort. Although, the decision to treat was closely linked to ILD subtype and PH severity and strongly limits inference of vasodilator benefits.

The finding that RV:LV ratio measured at CTPA predicted mortality, whereas haemodynamic assessment did not, challenges previously held beliefs regarding the diagnosis of IL- PH and risk stratification. Perhaps it is time to re-evaluate whether RHC is the best way to predict risk in IL- PH, and whether the standard definition of PH (mPAP \geq 25mmHg) should be used which disregards patients with borderline PH in whom important changes in RV morphology may occur. Indeed, a positive treatment effect with sildenafil has been suggested in IPF patients with right ventricular dysfunction on echocardiography³², reinforcing the importance of RV assessment in this setting.

Limitations

The studies retrospective design leads to selection bias. All patients studied had a high pre-test probability of PH or were being assessed for lung transplantation. This bias may overestimate the prevalence of RV dilatation in ILD but is unlikely to have influenced its relation to outcome. CTPA was performed at PH assessment and therefore did not factor in the decision to refer to PH services. In addition, the lack of electrocardiographic gating at CTPA acquisition may reduce the accuracy of RV:LV measurement but makes the findings of this study reproducible in everyday clinical practice. Finally, it was not possible to adjust for treatment of the underlying ILD or the use of advanced pulmonary vasodilator therapies in this analysis due to the heterogeneity of the treatment regimens.

We used an “ILD fibrosis score” to record the extent of disease. However, our results were unchanged if we substituted FVC or CPI as measures of disease severity (supplementary material). The ILD fibrosis score was not different between patients with dilated and non-dilated RV at CTPA, which replicates previous study findings suggesting that ILD severity is not the sole cause of PH / RV dilatation in this group of patients^{33,34}.

Conclusion

The RV:LV ratio measured at CTPA is a useful non-invasive screening tool to identify high risk patients with suspected ILD-PH including the impact of borderline PH on the RV. It is a strong prognostic marker in this population and is superior to invasive haemodynamic assessment.

Acknowledgments

SB performed all CTPA measurements and had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

JJ scored ILD severity and contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

CB undertook echocardiographic measurements and contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

KD, AK, MK, GK, ER, PM, FC, VK, PG, CM, MW, AD and AW contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

SW and LP (joint final authors) had full access to all the data and contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript

Table 1: Interstitial lung disease diagnoses

ILD diagnosis	CTPA Cohort (n=92)
Idiopathic pulmonary fibrosis	58
Chronic hypersensitivity pneumonitis	13
Idiopathic non-specific interstitial pneumonitis	13
Smoking related ILD	3
Unclassifiable ILD	3
Fibrotic cryptogenic organising pneumonia	1
Pleuro-parenchymal fibroelastosis	1

Table 1: Interstitial lung disease diagnoses

Abbreviations: ILD Interstitial lung disease

Table 2: Invasive and non-invasive variables stratified by RV:LVlargest ratio

	Entire Cohort (n=92)	RV:LV <1.0 (n=13)	RV:LV ≥1.0 (n=79)	p value
Age	65±11	63±8	66±12	0.6
Male gender n (%)	59 (64)	6 (46)	53 (67)	0.2
Functional class, (II/III/IV) (%)	(2/80/18)	(0/85/15)	(3/78/19)	0.8
Long term oxygen therapy n (%)	77 (83%)	11 (85)	66 (83)	0.9
Treatment with PH therapies, n (%)	40 (43)	3 (23)	37 (47)	0.2
<i>Pulmonary function tests</i>				
FEV ₁ (% predicted)	58±18	51±17	59±18	0.1
FVC (% predicted)	57±20	52±18	58±20	0.3
TLco _c (% predicted)	22±8	29±8	21±7	0.01
Kco _c (% predicted)	51±17	67±17	48±16	0.003
Composite physiological Index	66±9	62±9	66±9	0.1
<i>Echocardiography</i>				
Tricuspid regurgitant velocity (m/s)	3.79±0.6	3.57±0.4	3.82±0.6	0.1
RVSP (mmHg)	67±19	59±11	68±20	0.04
Right atrial area (cm ²)	20±7	15±6	20±7	0.03
Pulmonary acceleration time (ms)	76±17	81±20	75±16	0.3
RV:LVecho	0.77[0.6-1.1]	0.58[0.5-0.6]	0.8[0.6-1.0]	0.01
TAPSE (mm)	1.8±0.5	1.9±0.5	1.8±0.5	0.5
RV Fractional area change (%)	37±8	37±6	37±8	0.9
BNP (ng/L)	82[42-270]	48[29-84]	90[44-355]	0.03
<i>Right heart catheter haemodynamics</i>				
mPAP (mmHg)	31±9	28±7	32±9	0.06
mPAP ≥25mmHg, n (%)	72 (78)	9 (69)	63 (80)	0.6
PVR (Wood units)	5.5±3.2	3.9±2.0	5.8±3.3	0.01
Cardiac Output (litres/minute)	4.4±1.3	4.3±0.9	4.4±1.3	0.7
<i>CT Variables</i>				
Fibrosis score (%)	46±14	43±12	46±14	0.3
Main pulmonary artery diameter (mm)	34±5	30±5	35±4	0.01
MPADiameter:Aorta ratio	1.1[0.9-1.2]	1.0[0.9-1.1]	1.1[1.0-1.2]	0.2
RAlongitudinal diameter (mm)	50±9	45±9	50±9	0.05
RAtransverse diameter (mm)	60±12	49±6	62±12	<0.001
LA diameter (mm)	38±9	38±10	38±9	0.9
Ventricular septal bowing n (%)	35 (38)	0 (0)	35 (44)	0.002
IVC diameter (mm)	26±6	21±6	27±6	0.02
IVC reflux, n (%)	62 (67)	7 (54)	55 (69)	0.3

Table 2: Invasive and non-invasive variables stratified by RV:LVlargest ratio

Patients were stratified by the RV:LVlargest ratio of 1.0.

Abbreviations: PH pulmonary hypertension, FEV₁ Forced expiratory volume in one second, FVC Forced vital capacity, TLCO_c corrected transfer factor, KCO_c corrected transfer coefficient , RVSP Right ventricular systolic pressure, RV Right ventricle, LV Left ventricle, TAPSE Transannular plane systolic excursion, BNP Brain natriuretic peptide, mPAP mean pulmonary pressure at right heart catheterisation, PVR pulmonary vascular resistance, ILD, Interstitial lung disease, MPA Main pulmonary artery, RA Right atrium, LA Left atrium, IVC Inferior vena cava. Data are mean±standard deviation or median [interquartile range].

Table 3: Univariate assessment of invasive and non-invasive variables

	Hazard ratio (95% CI)	Univariate p-value
Age	1.01 (0.98-1.03)	0.6
Composite physiological index	1.06 (1.03-1.09)	<0.001
Male gender	1.51 (0.95-2.38)	0.08
Diagnosis of Idiopathic pulmonary fibrosis	1.94 (1.21-3.10)	0.006
Fibrosis score (Increase by 10%)	1.37 (1.15-1.63)	<0.001
Vasodilator treatment	0.62 (0.40-0.97)	0.04
Right heart catheter haemodynamics		
Mean pulmonary artery pressure	1.00 (0.98-1.03)	0.7
Mean pulmonary artery pressure \geq25mmHg	1.15 (0.68-1.97)	0.6
Pulmonary vascular resistance	1.03 (0.96-1.10)	0.4
Cardiac Output	0.88 (0.73-1.01)	0.2
Echocardiography		
Right ventricular systolic pressure	1.01 (0.99-1.01)	0.3
Right atrial area	1.00 (0.97-1.04)	0.8
Pulmonary acceleration time	1.00 (0.99-1.02)	0.7
RV:LV_{echo}	1.07 (0.71-1.60)	0.7
Transannular plane systolic excursion	0.97 (0.93-1.02)	0.3
RV Fractional area change	1.01 (0.98-1.04)	0.5
CT Pulmonary Angiography		
MPA diameter (per 1mm increase)	1.01 (0.96-1.06)	0.7
MPA diameter (>32mm)	1.50 (0.93-2.43)	0.1
MPADiameter:Aorta ratio	0.97 (0.84-1.13)	0.7
RV subjectively larger than LV	2.08 (1.16-3.74)	0.01
RV:LV_{axial} ratio	1.04 (0.99-1.07)	0.1
RV:LV_{axial} ratio \geq 1.0	2.17 (1.19-3.97)	0.01
RV:LV_{largest} ratio	1.06 (1.01-1.11)	0.02
RV:LV_{largest} ratio \geq 1.0	3.26 (1.49-7.15)	0.003
Ventricular septal bowing	1.30 (0.81-1.96)	0.3
RA_{transverse}	1.01 (0.99-1.03)	0.3
RA_{longitudinal}	1.02 (0.99-1.05)	0.09

Table 3: Univariate assessment of invasive and non-invasive variables

Abbreviations: As per table 2.

Table 4: Multivariate adjustment of the RV:LV ratio

	Hazard ratio	Confidence interval	P value
Fibrosis score at CT (per 10% increase)	1.32	1.11-1.56	0.004‡
IPF diagnosis	1.91	1.17-3.14	0.001‡
RV:LV_{largest} ratio >1.0	3.19	1.44-7.10	0.004‡

Table 4: Multivariate adjustment of the RV:LV ratio

Abbreviations: IPF idiopathic pulmonary fibrosis, RV Right ventricle, LV Left ventricle.

‡ Remained independent after adjustment for PH treatment status. ≠

Figure Legends

Figure 1: CTPA measurements performed

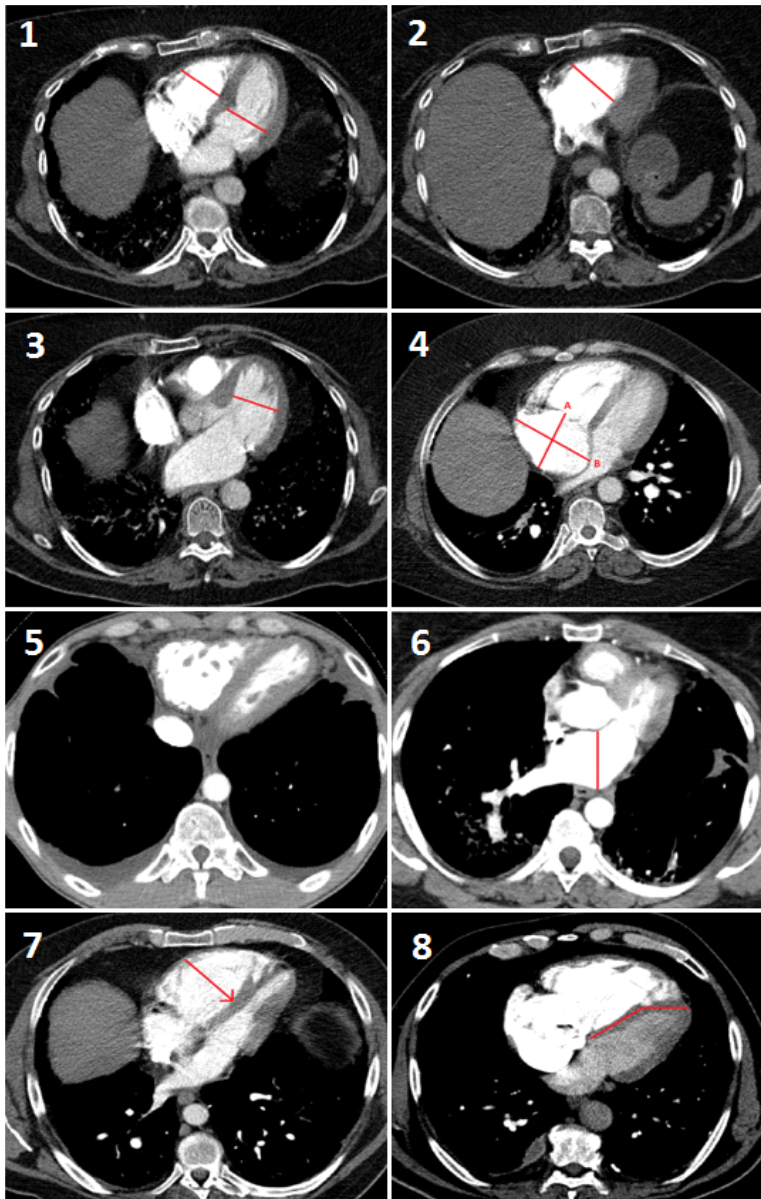


Figure 1: CTPA measurements performed. (1) The largest diameter of the right ventricle (RV) and left ventricle (LV) were measured at the mid-ventricular level at the level which most closely resembled a four-chamber view (and the RV:LV ratio calculated *RV:LV_{axial}*), the largest RV diameter (2) and LV diameter (3) were measured at the mid-ventricular level where it was largest (i.e. on different axial CT slices), and the RV:LV ratio calculated *RV:LV_{largest}*. The right atrium (RA) was measured (4) on both the longitudinal (A, delineated as the posterior border of the RA to the tricuspid annulus), and transverse planes (B, the widest point between RA walls). Reflux of contrast was graded as 0 where no reflux into the IVC was seen, or 1 where reflux into the IVC was present (5). The left atrium was measured (6) from its posterior to anterior border. The septum was said to be “bowed” if either it was deviated into the LV (7), or if the interventricular septum was deviated from its normal orientation (8).

Figure 2: Comparison of RV:LV measurement methodologies



Figure 2: Comparison of RV:LV measurement methodologies. Panel A shows the *RV:LVaxial* measurements. Panel B shows the same patient with the RV measured at the mid-ventricular level at its widest point. Panel C shows the same patient with the LV measured at the mid-ventricular level at its widest point. In our cohort the use of the *RV:LVlargest* method resulted in the reclassification of n=7 (37%) of patients with a *RV:LVaxial* ratio of <1.0 into the ≥ 1.0 category.

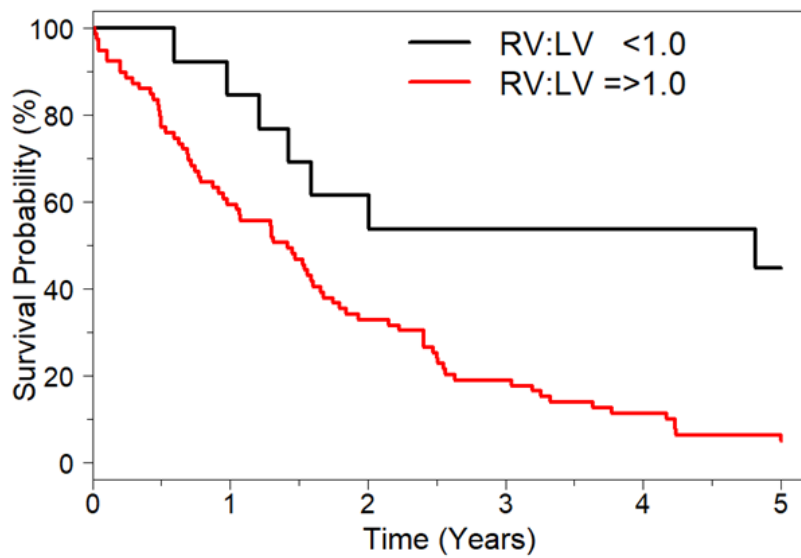


Figure 3: Kaplan Meier survival estimates of patients with ILD stratified by right ventricle to left ventricle ratio (RV:LV) using the *RV:LV_{largest}* ratio

Figure 3: Kaplan Meier survival estimates of patients with ILD stratified by right ventricle to left ventricle ratio (RV:LV) using the *RV:LV_{largest}* method RV:LV<1.0 (n=13), RV:LV≥1.0 (n=80). An *RV:LV_{largest}* ≥1.0 was an adverse predictor of mortality. Hazard ratio=3.26 (CI 1.49-7.15) p=0.003.

Abbreviations: RV:LV right ventricle to left ventricle ratio

References

1. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest*. 2006;129(3):746-752.
2. Galie 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.
3. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med*. 2003;167(5):735-740.
4. Rivera-Lebron BN, Forfia PR, Kreider M, Lee JC, Holmes JH, Kawut SM. Echocardiographic and hemodynamic predictors of mortality in idiopathic pulmonary fibrosis. *Chest*. 2013;144(2):564-570.
5. Nathan SD, Shlobin OA, Barnett SD, et al. Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. *Respir Med*. 2008;102(9):1305-1310.
6. Amsallem M, Boulate D, Kooreman Z, et al. Investigating the value of right heart echocardiographic metrics for detection of pulmonary hypertension in patients with advanced lung disease. *Int J Cardiovasc Imaging*. 2017.
7. Bax S, Bredy C, Kempny A, et al. A stepwise composite echocardiographic score predicts severe pulmonary hypertension in patients with interstitial lung disease. *ERJ Open Res*. 2018;4(2).
8. Shen Y, Wan C, Tian P, et al. CT-base pulmonary artery measurement in the detection of pulmonary hypertension: a meta-analysis and systematic review. *Medicine*. 2014;93(27):e256.
9. Alhamad EH, Al-Boukai AA, Al-Kassimi FA, et al. Prediction of pulmonary hypertension in patients with or without interstitial lung disease: reliability of CT findings. *Radiology*. 2011;260(3):875-883.
10. Devaraj A, Wells AU, Meister MG, Corte TJ, Hansell DM. The effect of diffuse pulmonary fibrosis on the reliability of CT signs of pulmonary hypertension. *Radiology*. 2008;249(3):1042-1049.
11. Chin M, Johns C, Currie BJ, et al. Pulmonary Artery Size in Interstitial Lung Disease and Pulmonary Hypertension: Association with Interstitial Lung Disease Severity and Diagnostic Utility. *Front Cardiovasc Med*. 2018;5:53.
12. Shin S, King CS, Puri N, et al. Pulmonary artery size as a predictor of outcomes in idiopathic pulmonary fibrosis. *Eur Respir J*. 2016;47(5):1445-1451.
13. Spruijt OA, Bogaard HJ, Heijmans MW, et al. Predicting pulmonary hypertension with standard computed tomography pulmonary angiography. *Int J Cardiovasc Imaging*. 2015;31(4):871-879.
14. Chan AL, Juarez MM, Shelton DK, et al. Novel computed tomographic chest metrics to detect pulmonary hypertension. *BMC Med Imaging*. 2011;11:7.
15. Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. *Eur Respir J*. 2014;43(6):1678-1690.
16. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188(6):733-748.

17. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788-824.
18. Jacob J, Bartholmai BJ, Rajagopalan S, et al. Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures. *Eur Respir J*. 2017;49(1).
19. Devaraj A WA, Meister MG, Corte TJ, Wort SJ, Hansell DM. Detection of pulmonary hypertension with multidetector CT and echocardiography alone and in combination. *Radiology*. 2010;254(2):609-616.
20. Kumamaru KK, Hunsaker AR, Bedayat A, et al. Subjective assessment of right ventricle enlargement from computed tomography pulmonary angiography images. *The International Journal of Cardiovascular Imaging*. 2012;28(4):965-973.
21. Contractor S, Maldjian PD, Sharma VK, Gor DM. Role of helical CT in detecting right ventricular dysfunction secondary to acute pulmonary embolism. *Journal of computer assisted tomography*. 2002;26(4):587-591.
22. Reid JH, Murchison JT. Acute right ventricular dilatation: a new helical CT sign of massive pulmonary embolism. *Clinical radiology*. 1998;53(9):694-698.
23. Douglas PS, DeCara JM, Devereux RB, et al. Echocardiographic imaging in clinical trials: American Society of Echocardiography Standards for echocardiography core laboratories: endorsed by the American College of Cardiology Foundation. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2009;22(7):755-765.
24. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2010;23(7):685-713; quiz 786-688.
25. Nathan SD, Shlobin OA, Ahmad S, et al. Serial development of pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Respiration; international review of thoracic diseases*. 2008;76(3):288-294.
26. Judge EP, Fabre A, Adamali HI, Egan JJ. Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis. *Eur Respir J*. 2012;40(1):93-100.
27. Armstrong HF, Schulze PC, Bacchetta M, Thirapatarapong W, Bartels MN. Impact of pulmonary hypertension on exercise performance in patients with interstitial lung disease undergoing evaluation for lung transplantation. *Respirology*. 2014;19(5):675-682.
28. Ema R, Sugiura T, Kawata N, et al. The dilatation of main pulmonary artery and right ventricle observed by enhanced chest computed tomography predict poor outcome in inoperable chronic thromboembolic pulmonary hypertension. *Eur J Radiol*. 2017;94:70-77.
29. Hamada K, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest*. 2007;131(3):650-656.
30. Kimura M, Taniguchi H, Kondoh Y, et al. Pulmonary hypertension as a prognostic indicator at the initial evaluation in idiopathic pulmonary fibrosis. *Respiration; international review of thoracic diseases*. 2013;85(6):456-463.
31. Corte TJ, Wort SJ, Gatzoulis MA, Macdonald P, Hansell DM, Wells AU. Pulmonary vascular resistance predicts early mortality in patients with diffuse fibrotic lung disease and suspected pulmonary hypertension. *Thorax*. 2009;64(10):883-888.
32. Han MK, Bach DS, Hagan PG, et al. Sildenafil preserves exercise capacity in patients with idiopathic pulmonary fibrosis and right-sided ventricular dysfunction. *Chest*. 2013;143(6):1699-1708.

33. Zisman DA, Karlamangla AS, Ross DJ, et al. High-Resolution Chest Computed Tomography Findings Do Not Predict The Presence of Pulmonary Hypertension in Advanced Idiopathic Pulmonary Fibrosis. *Chest*. 2007;132(3):773-779.
34. Fischer A, Swigris JJ, Bolster MB, et al. Pulmonary hypertension and interstitial lung disease within PHAROS: impact of extent of fibrosis and pulmonary physiology on cardiac haemodynamic parameters. *Clinical and experimental rheumatology*. 2014;32(6 Suppl 86):S-109-114.