Pulmonary hypertension in interstitial lung disease: Limitations of echocardiography compared to cardiac catheterization

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Summary at a glance:

In a large ILD cohort, all of whom had undergone right heart catheterization (RHC), the recent European Society of Cardiology/European Respiratory Society echocardiography screening recommendations correctly classified the majority of patients with PH. However, 40% of patients were misclassified as 'low probability' of PH, when PH was confirmed on subsequent RHC.

ABSTRACT

Background and objectives:

In interstitial lung disease (ILD), pulmonary hypertension (PH) is a major adverse prognostic determinant. Transthoracic echocardiography (TTE) is the most widely used tool when screening for PH, although discordance between TTE and right heart catheter (RHC) measured pulmonary haemodynamics is increasingly recognised. We evaluated the predictive utility of the updated European Society of Cardiology/European Respiratory Society (ESC/ERS) TTE screening recommendations against RHC testing in a large, well-characterised ILD cohort.

Methods:

Two hundred and sixty five consecutive patients with ILD and suspected PH underwent comprehensive assessment, including RHC, between 2006 and 2012. ESC/ERS recommended tricuspid regurgitation (TR) velocity thresholds for assigning high (>3.4 m/s), intermediate (2.9-3.4 m/s) and low (<2.8 m/s) probabilities of PH were evaluated against RHC testing.

Results:

RHC testing confirmed PH in 86% of subjects with a peak TR velocity > 3.4 m/sec, and excluded PH in 60% of ILD subjects with a TR velocity < 2.8 m/sec. Thus, the ESC/ERS guidelines misclassified 40% of subjects as 'low probability' of PH, when PH was confirmed on subsequent RHC. Evaluating alternative TR velocity thresholds for assigning a 'low probability' of PH did not significantly improve the ability of TR velocity to exclude a diagnosis of PH.

Conclusion:

In patients with ILD and suspected PH, currently recommended ESC/ERS TR velocity screening thresholds were associated with a high positive predictive value (86%) for confirming PH, but were of limited value in excluding PH, with 40% of patients misclassified as 'low probability' when PH was confirmed at subsequent RHC.

Key words: interstitial lung disease, pulmonary hypertension

Short title: Pulmonary hypertension in ILD

INTRODUCTION

In many interstitial lung diseases (ILDs), the presence of pulmonary hypertension (PH) is a major adverse prognostic determinant associated with increased morbidity and mortality (**1, 2**). Measures of pulmonary vascular disease are strongly predictive of early mortality across a spectrum of ILDs, irrespective of histopathologic subtype, or severity of underlying interstitial disease (**3, 4**). While right heart catheter (RHC) testing remains the gold standard diagnostic investigation for PH, selecting whom to refer for this invasive and resource-limited procedure can be challenging.

Transthoracic echocardiography (TTE) is the most widely utilised screening test for PH, providing a non-invasive estimation of the pulmonary artery systolic pressure (PASP), and crucial information about right ventricular (RV) size and function. While TTE_{PASP} (estimated from Doppler measured tricuspid transvalvular gradient via the modified Bernoulli equation) correlates strongly with directly measured RHC_{PASP} under controlled study conditions (**5-7**), discrepancies between these measures have been reported in 'real world' screening populations (**8-10**), including ILD patients, with differences between RHC_{PASP} and TTE_{PASP} of 10 mmHg or more reported in up to 50% of patients (**11, 12**).

The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines for the diagnosis and treatment of pulmonary hypertension (**13**) recommend Doppler measurement of peak tricuspid regurgitation (TR) velocity (rather than the traditionally used TTE_{PASP}) as the primary screening metric for assessing the likelihood of PH. Specific TR velocity thresholds (coupled with ancillary TTE findings when required) have been recommended to assign high, intermediate and low probabilities of PH. In the current study, the largest ILD-PH cohort yet reported, we evaluated the utility of these ESC/ERS TR thresholds for predicting the presence of PH (compared against RHC testing), and assessed

alternative thresholds which may provide improved discrimination between the presence and absence of PH in our cohort. .

METHODS

Patient selection

Consecutive patients with ILD and suspected PH who completed clinical and haemodynamic assessment (including RHC testing) between 2006 and 2012 were evaluated. Importantly, only patients with clinically suspected PH following review by an expert PH physician (with integration of all relevant information including physical examination, TTE, pulmonary function tests (PFTs) and other tests where available) proceeded to RHC testing. All patients were under follow-up with the Royal Brompton ILD Unit, , and this research was conducted in accordance with the amended Declaration of Helsinki. Institutional ethics review board approval was in place for the study (Royal Brompton, Harefield & NHLI REC reference 01-246).

In accordance with current ESC/ERS recommendations (**13**), peak TR velocity thresholds for assessing the probability of PH were evaluated. Peak TR velocities of >3.4 m/s and ≤2.8 m/s (or not measurable) are recommended thresholds associated with a high and low probability of PH respectively, while TR velocities of 2.9-3.4 m/s are associated with an intermediate probability of PH, and ancillary TTE features should be incorporated into the screening algorithm (table 1). Given the retrospective nature of the study, not all ancillary features were available, so an *a priori* decision was made to use the presence of RV dilatation and/or dysfunction on TTE as a surrogate in lieu of the ancillary features recommended by the ESC/ERS guidelines. Thus, strictly speaking, we assessed 'modified' ESC/ERS criteria for predicting the presence or absence of PH in our cohort.

Measurements

RHC was performed using standard techniques (**14**), with mean pulmonary artery pressure (mPAP) measured at rest in all patients. PH was defined as mPAP ≥ 25 mmHg (**13**). Two-dimensional TTE using Doppler colour flow imaging was performed, including measurement of the peak TR velocity. TTE_{PASP} was calculated using the modified Bernoulli equation ($PASP=4 \times TR^2$ + right atrial pressure) (**7**), with right atrial pressure (RAP) estimated on the basis of inferior vena cava size and movement with respiration (**15**). RV size was assessed using the mid and/or basal chamber end diastolic dimensions, while RV function was measured using tricuspid annular plane systolic excursion and/or tissue Doppler imaging (**16**).

All patients underwent thoracic computed tomography (CT), performed in the supine position at full inspiration, with scans anonymized by an independent investigator not involved in subsequent scoring. The presence and extent of ILD on CT was assessed independently by two radiologists (SLFW and JJ), blinded to clinical and haemodynamic data. In order to determine whether measures of tricuspid regurgitation were influenced by the severity of ILD, extent of ILD on CT was classified as limited (<20%), extensive (>20%) or indeterminate, as previously described (**17**). Where CT ILD extent was judged as indeterminate, forced vital capacity percent predicted (FVC%) using a threshold of 70% was used to classify limited or extensive ILD. PFTs were performed (Jaeger Masterscreen; Cardinal Health UK 240 Ltd), with predicted values calculated according to ATS/ERS guidelines (**18-21**).

Statistical Analysis

All analyses were performed using STATA statistical software (version 14.0; Stata Corp., College Station, TX, USA). Data were expressed as means with standard deviation (for normally distributed data) or medians with ranges (for non-normally distributed data). Group comparisons were made using the Student t test, Wilcoxon rank-sum test, and χ^2 statistics where appropriate. ROC curve analysis was performed to assess the discriminatory ability of the currently recommended TR thresholds (coupled with RV characteristics on TTE) to distinguish

between the presence and absence of PH, with an area under the curve (AUC) of 1.0 indicating perfect discrimination between patients with and without PH, while a value of 0.5 indicates no discriminatory value from the test.

RESULTS

Baseline characteristics

Two hundred and sixty five consecutive patients (mean age 60.8±11.6 years; 143 females) with ILD and suspected PH who underwent RHC were evaluated. ILD clinical diagnoses included connective tissue disease (CTD) associated ILD (n=94; 35%), idiopathic pulmonary fibrosis (IPF: 63; 24%), sarcoidosis (38; 14%), other idiopathic interstitial pneumonias (IIP; including idiopathic non-specific interstitial pneumonia and cryptogenic organising pneumonia) (31; 12%), and other ILDs (including chronic hypersensitivity pneumonitis, drug induced ILD, and unclassifiable ILD) (39; 15%). The majority of ILD diagnoses were confirmed at multidisciplinary team review. ILD was classified as extensive in 199 patients (75%) and limited in 66 (25%), with good agreement between radiologists (kappa 64.0%; $p<0.01$). There was no correlation between ILD severity (as determined by FVC% predicted) and mPAP ($r=0.00$; $p=0.70$) (figure 1). Baseline characteristics are presented in table 2.

Haemodynamic assessment

Following RHC, PH was confirmed in 194 patients (73%; average mPAP 37.2±9.2 mmHg), with an elevated pulmonary capillary wedge pressure (>15 mmHg) in 54 patients (28%) in this group. TTE results were available for review in all patients, with TR able to be measured in 215 (81%) patients, and RV size and function documented in 250 (94%). There was a moderate correlation between peak TR velocity and RHC measured mPAP ($r=0.48$; $p<0.01$) (figure 2). As reflected by ROC curve analysis, peak TR velocity provided moderate discriminatory value

in distinguishing between the presence and absence of PH in our cohort (AUC 0.73; 95% confidence interval 0.68 to 0.79; p<0.01) (figure 3).

On TTE, 138 patients had a peak TR velocity of >3.4 m/s, with PH confirmed on subsequent RHC in 118 patients (yielding a sensitivity of 61%, and PPV of 86%) (table 3a). The combination of a TR velocity of >3.4 m/s coupled with the presence of RV dilatation and/or dysfunction improved sensitivity and PPV to 85% and 90% respectively. Peak TR velocity was ≤2.8 m/s (or not measurable) in 78 patients, with normal RV size and function in 43 (55%). In this group of 43 patients classified as 'low probability' of PH by the modified ESC/ERS criteria,17 (40%) had PH present on subsequent RHC, while in the remainder (26 patients; 60%) PH was excluded on RHC. Therefore in our cohort, the modified ESC/ERS criteria for assigning a 'low probability' of PH were associated with a sensitivity and positive predictive value for excluding PH of 74% and 60% respectively (table 3a). Comparing the correctly classified (n=26) and misclassified (n=17) 'low probability' cohorts revealed a lower FEV_1 and FVC % predicted in the misclassified cohort, but there were no other significant differences in demographic or clinical data to explain the relatively high misclassification rate (table 4). In patients with a TR velocity of <2.8 m/s (or not measurable) and RV dilatation or dysfunction on TTE, the majority (25/35; 71%) had PH confirmed on subsequent RHC.

In 49 patients, TR velocity was between 2.9-3.4 m/s. PH was confirmed on RHC in 34 patients (69%), in whom 17 (50%) had RV dilation and/or dysfunction on TTE. Fifteen patients (31%) had PH excluded at RHC, eight (53%) of whom had normal RV size and function on TTE. In our cohort with an intermediate probability of PH based on TR velocity, the presence of RV dilatation and/or dysfunction was of limited value in further refining the probability of PH (table 3a).

Alternative TR velocity thresholds in assessing for PH

Evaluating alternative TR thresholds for assigning PH probabilities resulted in the expected 'trade offs' between sensitivity and specificity. Using a TR velocity threshold of 3.2 m/s by which to define a 'high probability' of PH improved sensitivity, but reduced the specificity due to an increased number of false positive cases (table 3b). Importantly, using a lower TR velocity (eg 2.4 m/s) for assigning 'low probability' of PH still resulted in approximately 30% of patients with RHC proven PH being misclassified as low probability by TR velocity thresholds alone (table 3b).

DISCUSSION

Pulmonary hypertension occurring in association with ILD is an ominous development, with measures of pulmonary vascular disease predictive of early mortality (**3, 4**). Despite this morbidity and mortality burden, accurate ILD-PH prevalence data remains elusive, in part due to the confounding effects of ILD on conventional PH screening measures. Our study, the largest ILD-PH cohort yet reported and the first to evaluate the recent ESC/ERS TTE screening recommendations (albeit with several important modifications), highlights strengths and limitations of the current screening approach. While the modified ESC/ERS criteria correctly identified PH in the majority of patients, a significant minority (40%) were misclassified as 'low probability' of PH, when PH was confirmed on subsequent RHC. Assessing alternative TR thresholds by which to more accurately define 'low probability' of PH did not yield significantly better cut-offs, with up to 30% of patients in our cohort still misclassified as 'low probability' even at very low TR velocity thresholds (eg <2.4 m/s). Our results suggest that in the setting of clinically suspected ILD-PH, TR velocity (even in the presence of normal RV size and function), may not be sufficiently robust to confidently exclude a diagnosis of PH.

Despite its limitations, TTE remains the most widely used screening test for suspected PH. While several studies have demonstrated excellent correlation between TTE_{PASP} and RHC_{PASP} (**5-7**), a number of contemporary studies have questioned the strength of this relationship, particularly when applied to 'real world' screening populations (**7-9**). Several authors have reported a discordance between TTE_{PASP} and RHC_{PASP} of ≥10 mmHg in approximately 50% of patients (**7-9**), including patients with IPF and other ILDs (**11, 12).** In the setting of advanced lung disease, Arcasoy reported estimation of TTE_{PASP} to be possible in only a minority of patients (44%), and even then, TTE_{PASP} was accurate (within 10 mmHg of RHC_{PASP}) in only half of patients (**11**). In an IPF population, Nathan reported similar results, with TTE_{PASP} accurately reflecting RHC_{PASP} in only 40% of patients (**12**).

In our cohort, a peak TR velocity of >3.4 m/s correctly predicted PH in almost 90% of patients; a diagnostic yield significantly greater than many previous studies. This higher positive predictive value may be explained, at least in part, by differences in patient recruitment, in particular the importance of expert clinical assessment in identifying patients with a high pre-test probability of PH. Previous ILD-PH studies have typically included patients undergoing lung transplant assessment where the decision to perform RHC was part of standardised clinical protocol. In contrast, we included patients in whom expert clinical assessment judged the likelihood of PH to be high enough to warrant proceeding to RHC, and as such, the PH prevalence in our cohort was significantly higher (73%) compared to previous studies (with prevalence ranges of 25-51%) (**11, 12, 25**). Through this application of Bayesian principles, we were able to identify a population with a high pre-test probability for PH, and thus enable more appropriate triaging for invasive and resource limited right heart catheterisation.

Despite impressive results for TTE in accurately predicting PH in a majority of patients, 40% of our cohort classified as 'low probability' of PH by the ESC/ERS guidelines had PH confirmed on subsequent RHC, and the reason for this remains difficult to explain. . Anatomic changes in chest wall configuration and cardiac orientation (with resultant poor acoustic windowing of the TR jet) may explain the limitations of TTE in assessing pulmonary pressures in chronic obstructive pulmonary disease (**26, 27**), but whether these same factors apply in ILD is not known. In our cohort, , the ILD extent was similar in the correctly and incorrectly classified 'low probability' groups (despite a greater reduction in FEV_1 and FVC % predicted in the incorrectly classified subgroup; table 4), suggesting that ILD extent may not have influenced TR interpretation. Whether the presence of co-existent emphysema impacted the accuracy of TTE warrants further evaluation.

Our findings expand on previously reported data in two important areas. Firstly, there was a relatively high prevalence (28%) of raised pulmonary capillary wedge pressure on RHC testing, suggesting a component of 'post capillary' PH which may be amenable to therapies directed at optimising left heart function and improving symptoms. Our results also demonstrate the poor

correlation between ILD extent and pulmonary haemodynamics, reflecting the frequent 'uncoupling' of interstitial and pulmonary vascular disease processes. PH was present in 1/3 of our cohort with 'milder' ILD (defined as a FVC >70% predicted), and these findings should further discount the outdated perception that PH occurs only in the setting of advanced ILD. Finally, the incorporation of additional non-invasive investigations (such as brain natriuretic peptide, PFTs, and vascular dimensions on thoracic CT imaging), has shown some promise in better defining the presence of ILD-PH (particularly in the setting of IPF), and warrants more detailed evaluation (**28-31**).

Inherent in the retrospective design of this study are limitations involved with respect to selecting patients to undergo RHC. We aimed to mirror real world clinical practice where patients are selected for RHC testing based on clinically suspected PH (including TTE findings) following expert PH physician review. While the decision to proceed with invasive testing will inevitably vary between institutions, we sought to minimise bias by evaluating consecutive patients with a range of ILD diagnoses following comprehensive assessment. Finally, we did not strictly adopt ESC/ERS ancillary TTE findings, in part due to the retrospective nature of the study as not all these TTE findings were consistently reported. We elected instead to adopt a pragmatic approach of incorporating the presence of RV dysfunction and/or dilatation, as these data are generally readily available and well understood.

In conclusion, our study highlights the need for readily accessible, accurate screening tools to assess for ILD-PH, and the continued pivotal role for RHC in confirming the diagnosis. In a large heterogeneous ILD population, currently recommended TTE screening thresholds performed strongly in confirming a diagnosis of PH, although were associated with a significant misclassification rate when used in isolation to exclude PH.

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Table 1. Echocardiographic probability of pulmonary hypertension (PH) in symptomatic patients with a suspicion of PH, as recommended by the 2015 European Society of

Cardiology/European Respiratory Society Guidelines for the diagnosis and treatment of PH (**13**).

Peak tricuspid regurgitation velocity (m/s)	Presence of other TTE PH signs[1]	Probability of PH
≤2.8 or not measurable	No	**Low**
≤2.8 or not measurable	Yes	**Intermediate**
2.9-3.4	No	
2.9-3.4	Yes	**High**
>3.4	Not required	

[1] Ancillary TTE signs suggesting PH include: right ventricle (RV)/left ventricle basal diameter ratio >1.0; flattening of the interventricular septum; RV outflow Doppler acceleration time <105 msec and/or midsystolic notching; early diastolic pulmonary regurgitation velocity >2.2 m/sec; pulmonary artery diameter >25 mm; inferior vena cava diameter >21 mm with decreased inspiratory collapse; right atrial area (end-systole) >18 cm^2

Table 2. Baseline clinical and demographic information.

	Entire group (n=265)	PH (n=194)	No PH (n=71)	p value

Age, yr	60.8 (11.6)	61.1 (12.0)	59.9 (10.5)	0.46
Gender, M:F	122:143	89:105	33:38	0.93
Body mass index	28.2 (5.4)	28.5 (3.9)	27.9 (6.6)	0.87
ILD diagnosis				
CTD (n)	94	57	37	
IPF	63	46	17	
Other IIP	31	27	4	
Sarcoid	38	36	2	
Other ILD	39	28	11	
ILD extent				
limited:extensive	66:199	46:148	20:51	0.36
Right heart catheter				
mPAP (mmHg)	32.4 (11.3)	37.2 (9.2)	19.3 (3.6)	<0.01
PVR (Wood Units)	5.7 (4.1)	7.1 (4.1)	2.4 (1.3)	<0.01
CO (L/min/m^2)	4.5 (1.3)	4.3 (1.4)	4.9 (1.2)	0.02
PCWP (mmHg)	9.9 (4.6)	10.3 (4.8)	9.1 (4.1)	0.10
Echocardiography				
TR velocity (m/s)	3.6 (6.4)	3.8 (61.0)	3.2 (5.2)	<0.01
RVSP (mmHg)	62.1 (19.4)	66.7 (18.5)	47.2 (14.0)	<0.01
PacT (ms)	80.7 (25.5)	78.1 (25.0)	88.8 (25.8)	0.02
RV dysfunction	118	104	14	<0.01
RV dilation	135	117	18	<0.01
RA dilation	91	82	9	<0.01
Pulmonary function tests				
FEV1%	60.2 (20.2)	58.0 (18.4)	66.1 (23.6)	<0.01
FVC%	64.1 (22.3)	63.3 (20.4)	66.5 (26.8)	0.31
DLco%	28.6 (12.6)	26.6 (11.2)	34.0 (14.5)	<0.01
Kco%	55.0 (17.5)	52.0 (16.7)	63.2 (17.2)	<0.01
PaO_2 (kPa)	8.3 (2.0)	7.8 (1.7)	9.6 (2.0)	<0.01
Aa gradient	5.5 (2.0)	6.0 (1.7)	4.1 (2.0)	<0.01

Abbreviations: PH=pulmonary hypertension, CTD=connective tissue disease, IPF=idiopathic pulmonary fibrosis, IIP=idiopathic interstitial pneumonia, mPAP=mean pulmonary artery pressure, PVR=pulmonary vascular resistance, CO=cardiac output, PCWP=pulmonary capillary wedge pressure, TR=tricuspid regurgitation, RVSP=right ventricular systolic pressure, PacT=pulmonary acceleration time, RV=right ventricle, RA=right atrium, BNP=brain natriuretic peptide, DLco=diffusing capacity of the lung for carbon monoxide, FEV1=forced expiratory volume in one second, FVC= forced vital capacity, DLco= diffusing capacity of the lung for carbon monoxide, Kco= diffusing capacity corrected for alveolar volume, PaO2=partial pressure of oxygen, Aa gradient=Alveolar-arterial oxygen gradient, PA=pulmonary artery, mm=millimeters, 6MWT=6 minute walk test

Table 3. Sensitivity, specificity, positive and negative predictive values of peak tricuspid regurgitation (TR) thresholds in assigning probabilities of pulmonary hypertension: **a)** as recommended by ESC/ERS guidelines and **b)** evaluation of alternative peak TR velocity thresholds for assigning 'high' and 'low' probabilities of PH in our cohort

a)

TR velocity	**Sensitivity** *(95% CI)*	**Specificity** *(95% CI)*	**PPV** *(95% CI)*	**NPV** *(95% CI)*
<2.8 m/s (or not measurable)*				
-with normal RV size & function	74% (57-88)	60% (44-75)	60% (44-75)	74% (57-88)
2.9-3.4 m/s				
with normal RV size & function *	62% (32-86)	50% (32-68)	32% (15-54)	77% (55-92)
with RV dysfunction &/or dilatation†	50% (32-68)	62% (32-86)	77% (55-92)	32% (15-54)
>3.4 m/s†	61% (54-68)	72% (60-82)	86% (79-91)	40% (32-49)
-with RV dysfunction &/or dilatation	85% (77-91)	42% (20-67)	90% (83-95)	32% (15-54)

b)

TR velocity	**Sensitivity** *(95% CI)*	**Specificity** *(95% CI)*	**PPV** *(95% CI)*	**NPV** *(95% CI)*
<2.4 m/s (or not measurable)*				
-with normal RV size & function	71% (49-87)	58% (39-75)	57% (37-75)	72% (51-88)
>3.2 m/s†	70% (63-76)	65% (53-76)	84% (79-88)	44% (38-51)

* Sensitivity, specificity, positive and negative predictive values in assessing for a diagnosis of 'No pulmonary hypertension'

† Sensitivity, specificity, positive and negative predictive values in assess for a diagnosis of 'pulmonary hypertension'

Abbreviations: TR=tricuspid regurgitation, CI=confidence interval, PPV=positive predictive value, NPV=negative predictive value, RV=right ventricle

Table 4. Comparison of clinical characteristics between patients who were correctly or misclassified as 'low probability' of PH by current ESC/ERS TTE screening recommendations

	Correctly classified (n=26)	Misclassified (n=17)	p value
Age, yr	57.2 (9.4)	51.6 (9.2)	0.08
Gender, M:F	6:20	3:14	0.60
ILD diagnosis			
CTD (n)	20	8	
IPF	3	1	
Other IIP	1	1	
Sarcoid	0	5	
Other ILD	2	2	
ILD extent			
limited:extensive	12:14	5:12	0.23
Right heart catheter			
mPAP (mmHg)	17.4 (3.2)	34.9 (10.6)	<0.01
PVR (Wood Units)	1.9 (0.8)	4.9 (2.1)	<0.01
CO (L/min/m^2)	4.8 (1.2)	4.5 (0.8)	0.40
PCWP (mmHg)	8.9 (3.4)	11.4 (6.8)	0.20
Echocardiography			
TR velocity (m/s)	2.5 (0.3)	2.6 (0.2)	0.60
RVSP (mmHg)	33.4 (7.9)	45.5 (22.6)	0.08
PacT (ms)	104.8 (29.1)	84.8 (20.1)	0.07
RV dysfunction	0	0	
RV dilation	0	0	
RA dilation	0	0	
Pulmonary function tests			
FEV1%	77.4 (20.9)	50.5 (9.8)	<0.01
FVC%	78.5 (24.3)	57.4 (15.2)	<0.01
DLco%	43.6 (16.5)	35.4 (15.8)	0.14
Kco%	68.5 (17.5)	67.3 (12.1)	0.80
PaO_2 (kPa)	11.1 (1.6)	8.5 (1.5)	<0.01
Aa gradient (kPA)	2.6 (1.6)	5.3 (1.5)	<0.01

Abbreviations: PH=pulmonary hypertension, CTD=connective tissue disease, IPF=idiopathic pulmonary fibrosis, IIP=idiopathic interstitial pneumonia, mPAP=mean pulmonary artery pressure, PVR=pulmonary vascular resistance, CO=cardiac output, PCWP=pulmonary capillary wedge pressure, TR=tricuspid regurgitation, RVSP=right ventricular systolic pressure, PacT=pulmonary acceleration time, RV=right ventricle, RA=right atrium, BNP=brain natriuretic peptide, DLco=diffusing capacity of the lung for carbon monoxide, FEV1=forced expiratory volume in one second, FVC= forced vital capacity, DLco= diffusing capacity of the lung for carbon monoxide, Kco= diffusing capacity corrected for alveolar volume, PaO2=partial pressure of oxygen, Aa gradient=Alveolar-arterial oxygen gradient, PA=pulmonary artery, mm=millimeters, 6MWT=6 minute walk test