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Non-invasive Screening for Pulmonary Hypertension in Idiopathic Pulmonary Fibrosis

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Abstract

Background—Pulmonary hypertension (PH) is a common complication of idiopathic pulmonary fibrosis (IPF) that is associated with poor prognosis. Noninvasive screening for PH in IPF patients is challenging and a combination of several noninvasive determinations can improve discrimination.

Methods—We included 235 IPF patients who underwent right heart catheterization (RHC) as part of the lung transplant evaluation. We measured electrocardiographic (ECG) and echocardiographic variables as well as the pulmonary artery (PA) and ascending aorta (AA) diameters on chest CT. We recorded results of arterial blood gases (ABG), pulmonary function (PFT) and 6-min walk tests (6MWT).

Results—Several variables were predictors of PH in IPF patients in univariable models including a lower arterial oxygenation and 6MWT distance; worse right ventricular (RV) function, rightward deviation of the QRS axis and a higher FVC/DLCOc ratio, PA/AA diameter ratio, and estimated RV systolic pressure. In multivariable analysis, a worse RV function and higher PA/AA ratio remained predictors of PH (c-index 0.75 (0.65–0.84)). Similarly, a worse RV function, a higher PA/AA ratio and a rightward QRS axis deviation were independent predictors of precapillary PH (c-index 0.86 (0.76–0.92)). A combination of PA/AA diameter ratio <1.1, a QRS axis <90° and normal RV function showed a negative predictive value of 85% for precapillary PH.

Conclusions—There are significant differences in ECG, echocardiographic, chest CT, PFT and ABG parameters between IPF patients with and without PH. However, these noninvasive tests alone or combination have limited discrimination ability for PH screening in IPF.

Keywords

Idiopathic pulmonary fibrosis; pulmonary hypertension; echocardiography; electrocardiogram; computed tomography scan

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive fibrotic disease that can lead to respiratory failure and death. Patients with IPF have a mean survival from diagnosis of about 3 years[1,2]. Pulmonary hypertension (PH) commonly occurs in advanced stages of IPF and this association has negative prognostic implications[3–6]. The prevalence of PH in patients with IPF varies between 14 % and 85 %[3,7,8], mostly influenced by the severity of the parenchymal lung disease. Nathan et al. showed that the prevalence of PH increased from 33 to 85% as the IPF progressed[7].

Pulmonary hypertension in IPF can lead to a decrease in the functional capacity and increase in oxygen requirements during rest and exercise[8,9]. The presence of PH in patients with advanced IPF may influence the decision to perform single versus bilateral lung transplant or use cardiopulmonary bypass[10,11]. More importantly, higher pulmonary artery pressures during right heart catheterization (RHC) were associated with higher mortality[3,4]. In fact, patients with IPF who developed PH had a 1-year mortality rate of 28 % compared to 6 % in those without PH[9]. Given these important implications, screening for PH in patients with IPF is of distinct importance.

Noninvasive screening for PH in IPF patients is challenging because the main methodology used for this purpose[3], i.e. Doppler echocardiography, has important limitations due to the poor acoustic window[12,13]. In fact, several studies showed that the right ventricular systolic pressure (RVSP) estimated by echocardiography does not provide an accurate reflection of the measured values during RHC[13–15]. Interestingly, the accuracy of echocardiography slightly improved when the measures are combined with pulse oximetry (SpO_2), pulmonary function (PFT) and six-minute walk (6MWT) tests[13,15].

We hypothesized that a combination of certain determinations including 12-lead electrocardiogram (ECG)[16–20], computed tomography (CT) of the chest[21–24], 6MWT[25], PFT[26,27], arterial blood gases (ABG) and echocardiography improves the noninvasive screening for PH in patients with IPF. In the presented exploratory study, we tested whether an approach that incorporates results of several non-invasive investigations can better predict the presence of PH (diagnosed by RHC) in patients with IPF evaluated for lung transplant.

Methods

This retrospective study was approved by the Cleveland Clinic Institutional Review Board (study number 12-045). Written informed consent was waived. We included IPF patients[28] evaluated for lung transplantation between March 2005 and January 2012. Patients were identified using the Cleveland Clinic Lung Transplantation Registry (EDIT). Data extracted from the EDIT database included demographics, lung allocation score (LAS) at the time of transplant[29], PFT and RHC results. The patients' electronic medical records provided any additional information. All the echocardiograms obtained during the lung transplant evaluation were reviewed. Measurements acquired included the estimated RVSP, visual right ventricular (RV) function, trans-annular plane systolic excursion (TAPSE) as well as the basal, mid and longitudinal RV dimensions[30]. PFT measurements included forced expiratory

volume in the first second (FEV_1 % predicted), forced vital capacity (FVC % predicted), FEV_1/FVC, total lung capacity (TLC % predicted), corrected diffusion capacity for carbon monoxide (DLCOc % predicted), and the ratio of FVC/DLCO. We also gathered the results of the ABG analysis while breathing room air (arterial saturation (SaO_2) and partial pressure of O_2 (PaO_2) and CO_2 ($PaCO_2$)).

We reviewed the chest CT scans and measured the pulmonary artery (PA) and ascending aorta (AA) diameters at the level of PA bifurcation. We calculated the ratio between these two measurements (PA/AA). We collected data on the 6MWT including distance walked in meters (6MWD), heart rate at the start and the end of the test, and heart rate recovery (HRR) at 1 minute[31].

All 12-lead ECG (10-second recording) performed during the lung transplant evaluation were reviewed. The ECG were read by two investigators (M.B and L.A). In cases of irregular cardiac rhythm such as atrial fibrillation or flutter with variable atrioventricular conduction, we averaged at least 3 beats for each ECG determination. We excluded the ECG if the patient was on ventricular pacemaker at the time of recording or had a left bundle branch block. QT interval was corrected for heart rate by Bazett's formula (QTc)[32]. We assessed whether the QRS morphology in lead V_1 showed complete (RBBB) or incomplete right bundle branch block (IRBBB), qR or QS patterns. Right heart catheterization was performed following standard protocols and keeping the SpO_2 at 90 % or above. Pulmonary hypertension was defined as a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg[3]. Hemodynamic determinations were obtained at end-expiration. Pulmonary vascular resistance (PVR) was calculated by dividing the trans-pulmonary gradient (mean PAP – pulmonary artery wedge pressure) over the cardiac output obtained by thermodilution. The investigators that reviewed the echocardiograms, CT and ECG were blinded to the clinical and hemodynamic data.

Statistical Analysis

Continuous variables were summarized using mean ± standard deviation or median and interquartile range (IQR) when appropriate. We compared numerical variables using t-test and categorical variables with Chi-square test. Agreement was tested with Bland-Altman plot and expressed as mean difference with 95% limit of agreement[33].

We used binary logistic regression (forward- variable selection) to test the variables that either alone or in combination could predict the presence of PH (mean PAP ≥ 25 mmHg) or precapillary PH (PH with PVR > 3 Wood units)[34]. For the univariable analysis we used the demographic, functional (6MWT), gasometric, spirometric, electrocardiographic, echocardiographic and radiographic variables presented in table 1 to 3. Results are given as odds ratio (OR) with 95% confidence interval. We performed correlation analyses and tested variance inflation factor (VIF) of the predictors to prevent collinearity and multicollinearity, respectively. We excluded variables that showed p values ≥ 0.10 in univariable logistic regression. We also excluded variables with VIF higher than 5, correlation value ≥ 0.8 or that measured similar effects (e.g. PaO_2 and SaO_2, 6MWD in meters and percentage of predicted, PA diameter or PA/AA ratio, etc). In the latter situation we kept the variables with the OR that departed the furthest from 1. Linearity assumption for logistic regression was

met. We also explored non-linear relationships and reported the model accuracy and c-index when appropriate. Accuracy represents the proportion of the total number of model predictions that were correct. The c-index (concordance index) examines how well the models discriminate between groups of interest. For our binary outcomes (presence of PH or precapillary PH) the c-index represents the probability that a measure is higher or lower for a case than for a non-case[35]. For instance, in our data we found a probability of 64% that a PA/AA ratio is higher in IPF patient with PH than those without PH (c-index 0.64). In general, c-index values of 0.7 to 0.8, 0.8 and 0.9 and ≥ 0.9 indicate acceptable, excellent and outstanding discrimination, respectively[36].

We developed models using CART (classification and regression tree) binary recursive partitioning[37] in which the parent nodes are split into two nodes in a recursive manner until each terminal node is assigned to a class outcome. CART looks at all possible splits for all variables included in the analysis. The chosen split is based on maximizing classification and minimizing error. Splitting stops when a node has few cases or all cases belong to one group. Once a maximal tree is grown, smaller trees are examined by pruning away branches. We included categorical and continuous data in the CART models. The whole cohort was used to build the trees presented.

V-fold cross-validation[38] with 10 partitions was used to estimate the error rate of a sub-tree, in where the total sample is divided 9/10 for learning and 1/10 for testing. This is repeated 10 times, an in each iteration a unique 1/10 of the total sample is used for testing and the remaining 9/10 for learning. There is no overlap in the testing samples, but there is considerable overlap in the learning samples. When summed, the test partitions are equal to the entire original training data. Importantly, each sub-tree has the same distribution of patients with and without the condition of interest (e.g. PH and no PH). Random forest, a nonparametric tree-based ensemble machine learning tool, was used to rank variables that best discriminate between groups[39].

All the p values were reported as two tailed. A p value of <0.05 was pre-specified as indicative of statistical significance. The statistical analyses were performed using the statistical package SPSS version 17 (IBM; Armonk, N.Y., USA), MedCalc version 14.10.2 (MedCalc Software bvba, Ostend, Belgium) and CART version 7.0 (Salford Systems, California, USA).

Results

a) Patient characteristics

We included 235 IPF patients with a mean age of 60 ± 9 years. One hundred and sixty-seven (71 %) were male. Pulmonary hypertension was present in 119 patients (51 %). Patients with PH had similar gender, were slightly younger and had higher LAS than patients without PH. In PH patients, mean PAP and PVR were 35 ± 10 mmHg and 4.6 ± 2.8 Woods units, respectively. Three quarters of the patients (n=185) had an echocardiogram performed around the time of RHC. The median (IQR) time difference in weeks between RHC and ECG, PFT, chest CT, ABG, 6MWT and echocardiogram were 0 (−1, +14), −3 (−6, −1), −2 (−6, 0), −3 (−6, 0) and −3 (−45, 17), respectively.

Echocardiography showed RV dysfunction (mild to severe) in 22 (25%) IPF patients without PH and 52 (54%) with PH (p<0.001) (Table 1). The RV size appears larger in patients with PH (Table 1). TAPSE was decreased in IPF patients both with and without PH. Using Bland-Altman analysis the agreement (95% limit of agreement) between the systolic PAP measured during RHC and the RVSP estimated with echocardiogram was −3.9 mmHg (+34.6 and −42.3 mmHg).

b) Comparison between IPF patients with and without PH

Most of the patients had normal sinus rhythm (98%). In IPF patients with PH, we noticed a rightward deviation in both the P and QRS axes and leftward deflection of the T wave axis. Significant differences were noticed in other electrocardiographic signs as shown in Table 2.

Patients with IPF and PH have higher FVC and TLC, but lower DLCOc; therefore the ratio of FVC/DLCOc was higher in this subgroup of patients. IPF patients with PH had more hypoxemia and a larger diameter of PA and ratio between the PA / AA. Furthermore, IPF patients with PH covered less distance during 6MWT than patients without PH (Table 3).

c) Univariable and multivariable analyses to predict PH

Several variables were predictors of PH in univariable logistic regression models (Table 4). The discriminatory ability of the tested variables was modest and similar for PaO_2, SaO_2, FVC/DLCOc ratio, PA/AA diameter ratio, 6MWD, QRS axis and RVSP (Table 4). In multivariable analysis, not including echocardiographic variables, only SaO_2 (OR for every 10% increase: 0.35, 95% CI: 0.18–0.69, p=0.002) and PA/AA diameter ratio (OR for every 0.1 increase: 1.38, 95% CI: 1.04–1.83, p=0.03) remained significant predictors of PH, with a c-index of 0.71 (95% CI: 0.63–0.79) and accuracy of 64.2%. When including echocardiographic determinations, RV function (OR for every unit of worsening: 2.79, 95% CI: 1.38–5.64, p=0.004) and PA/AA ratio (OR for every 0.1 increase: 1.45, 95% CI: 1.04–2.03, p=0.03) remained predictors of PH with a c-index of 0.75 (95% CI: 0.65–0.84) and accuracy of 71.4%.

d) Univariable and multivariable analyses to predict patients with precapillary PH (PVR > 3 Wood units)

Several variables were predictors of precapillary PH in univariable analyses (Table 5). The variables that provided the best discrimination were SaO_2, FVC/DLCOc ratio, PA/AA diameter ratio, 6MWD, QRS axis and RVSP (Table 5). In a multivariable analysis, not including echocardiographic variables, SaO_2 (OR every 10% increase: 0.50, 95% CI: 0.25–0.99, p=0.04), PA/AA diameter ratio (OR every 0.1 increase: 1.76, 95% CI: 1.27–2.46, p< 0.001) and QRS axis (OR every 10° increase: 1.19, 95%: 1.06–1.34, p=0.004) remained significant predictors of precapillary PH (c-index 0.83 (95% CI: 0.75–0.89), accuracy of 80.9 %).

In a multivariable analysis that included echocardiographic variables, PA/AA (OR every 0.1 increase: 2.01, 95% CI: 1.30–3.12, p=0.002), QRS axis (OR every 10° increase: 1.22, 95% CI: 1.04–1.42, p=0.02) and RV function (OR for every unit of worsening: 2.36, 95% CI: 1.04–5.39, p=0.04) were independent predictors of precapillary PH (c-index 0.86 (95% CI:

0.76–0.92), accuracy of 84.2%). Interestingly, a combination of PA/AA diameter ratio < 1.1, a QRS axis < 90° and a normal RV function encompassed 57% of the patients and had a sensitivity of 73%, specificity of 70% and negative predictive value of 85% for the presence of precapillary PH. The cut-offs selected for PA/AA diameter ratio and QRS axis were a priori-planned and based on the literature[20,24,40].

e) Classification and regression tree analyses

Random forests analysis identified DLCOc, P axis, QRS axis and PA/AA ratio as the variables with the highest importance for adequate discrimination between IPF patients with and without PH. CART analysis is shown in Figure 1. In the testing sample, the model misclassified 58 out of 119 (48.7%) PH subjects and 47 out of 116 (40.5%) non PH patients, with an overall adequate discrimination of 55.3%. Receiver operating characteristics (ROC) for the testing cohort showed an area under the curve of 0.56. When echocardiographic data were allowed in the model, RV function and RVSP were used in distal nodes, but they minimally improved the overall discrimination and made the overall model more complex.

The variables with the highest importance to discriminate IPF patients with and without precapillary PH (PVR <3 Wood units) were QRS axis and RVSP. The CART analysis is shown in Figure 2. In the testing sample, the percentages of misclassification were 20.1 % and 53.9% in the PVR ≤ 3 and PVR > 3 Wood unit groups, with an overall prediction success of 70.1 % and ROC area under the curve of 0.64.

Discussion

The identification of PH is of great importance in IPF; however, the traditional noninvasive tools used for PH screening have limitations particularly in patients with parenchymal lung diseases. We tested whether a distinct non-invasive methodology or a combination of tests is particularly useful in discriminating IPF patients with or without PH. We found that a large number of non-invasive variables derived from ABG, ECG, chest CT, PFT and echocardiography were significant predictors of PH. However, none of these tests either alone or in combination correctly classified PH patients with a percentage higher than 71 %.

Echocardiography is commonly used in screening of PH. However, this test has limited accuracy in the setting of IPF[12,13,15]. In fact, Arcasoy et al. showed that 48% of IPF patients were misclassified as having PH; moreover, echocardiography was unable to estimate the RVSP in 44% of patients due to poor acoustic window[12]. We found that the echocardiographic determinations that included RVSP, TAPSE and RV dimensions were of limited value in discriminating IPF patients with and without PH. Similarly to results reported by other authors, we found a limited utility in combining non-invasive investigations to increase the ability of detecting PH in IPF[13,26,27]. Interestingly, 22 out of 88 (25%) IPF patients without PH by RHC had some degree of RV dysfunction by echocardiography, both by visual estimation and TAPSE. Fourteen of the 22 patients with RV dysfunction underwent lung transplantation and in all the RV function returned to normal. The origin of the RV dysfunction in the absence of PH during RHC is unclear but likely represents and early involvement of the RV function in IPF due to systemic

inflammation, endothelial dysfunction and the result of small increases in mean PAP (below 25 mmHg)[41].

In the present study, we found several ECG variables associated with PH. These include larger P wave amplitude in DII and rightward deflection of both the QRS and P axes because of right atrial and ventricular dilation. Other studies showed that P wave amplitude, QRS and P axes were significantly different in PH patients and they correlated with worse prognosis[18,42,43]. Ahearn, et al. found that QRS axis deviation was the ECG sign that correlated best with hemodynamic parameters and right ventricular size in PH[16]. We have previously reported that the QRS axis deviates to the right from the time between PAH diagnosis and death[20].

On chest CT the PA and PA/AA diameter ratio were significantly larger in patients with PH[24]. These CT scan measurements usually predict PH with good sensitivity and specificity[44,45]. However, in pulmonary fibrosis, the predictive value of these CT measurements is inadequate[23,24,46,47]. In a prospective study, Alhamad, et al. found a poor correlation between mPAP and PA diameter in patients with IPF[21]. It has been proposed that pulmonary fibrotic changes cause traction and dilation of the pulmonary artery wall, thus, blunting the relationship between dilated PA and PH[24].

In our study we found that SaO_2 was an independent predictor of PH and precapillary PH in IPF patients. Several determinations obtained from ABG and PFT have been associated with the presence of PH in IPF[9,26,27,48,49]. Patients with IPF and PH have a lower DLCO that the one expected for their degree of parenchymal lung disease[26,27,48]. Lettieri, et al. noted that a DLCO < 40 % of predicted was a strong predictor of PH in IPF patients[9]. Since FVC/DLCO ratio and SaO_2 were significantly associated with PH[26,27], a formula that uses these two variables was proposed for estimating the mean PAP in IPF patients[26,27]. In our study, DLCOc was lower in PH patients but the FVC/DLCOc was higher. FVC/DCLOc showed one of the highest c-index to predict PH in univariable analysis; however this variable was not selected in multivariable analyses.

In the 6MWT, we showed that a shorter distance walked was associated with the presence of PH in IPF patients. Heart rate recovery (HRR) in 1 minute[50] was not significantly different between patients with and without PH, possibly because all the patients had advanced IPF and in this context, HRR might lose its predictive ability. In other studies, HRR was predictive of mortality and the development of PH in IPF patients[25,51].

None of the investigations tested, including echocardiography, was good enough either alone or in combination to accurately screen IPF patients for the presence of PH. A quarter of IPF patients were misclassified, even when combining the information provided by several non-invasive tests. Therefore, RHC remains necessary to confirm the diagnosis of PH in IPF. Nevertheless, the combination of a low PA/AA diameter ratio, a normal QRS axis and good RV function has a high negative predictive value for the presence of precapillary PH, which has evolved as a useful parameter in predicting mortality in parenchymal lung diseases[52,53].

Our study has limitations: a) all of the patients had advanced IPF evaluated for lung transplantation; therefore our results might not apply to the milder forms of IPF or other

interstitial lung diseases, b) given the retrospective nature of our study, external validation of our results is necessary. Nevertheless, we included a large number of IPF patients who underwent RHC and several non-invasive determinations which are traditionally used for PH screening. Overall, this study highlights the challenges of diagnosing PH by noninvasive methodologies in patients with IPF.

Conclusion

There are significant differences in ECG, echocardiographic chest CT, PFT and ABG parameters between IPF patients with and without PH. However, these noninvasive tests alone or combination are not accurate enough for PH screening in IPF patients.

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Abbreviations

6MWT	six minute walk test
ABG	arterial blood gases
AA	ascending aorta
AUC	area under curve
CART	classification and regression tree
CI	confidence interval
CT	computed tomography
DLCOc	corrected diffusion lung capacity of carbon monoxide
ECG	electrocardiography
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
IPF	idiopathic pulmonary fibrosis
IQR	inter-quartile range
IRBBB	incomplete right bundle branch block
HR	heart rate
HRR	heart rate recovery
LAS	lung allocation score

mPAP	mean pulmonary artery pressure
PA	pulmonary artery
$PaCO_2$	partial arterial pressure of CO_2 in arterial blood
PaO_2	partial arterial pressure of O_2 in arterial blood
PAWP	pulmonary artery wedge pressure
PAP	pulmonary artery pressure
PFT	pulmonary function test
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
RBBB	right bundle branch block
RHC	right heart catheterization
RV	right ventricle
RVSP	right ventricular systolic pressure
SaO2	pulse oximetry
TAPSE	tricuspid annular plane systolic excursion

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- Recognition of pulmonary hypertension (PH) is important in idiopathic pulmonary fibrosis (IPF)
- We found that several non-invasive determinations are predictors of PH or precapillary PH in IPF
- Worse right ventricular (RV) function and higher pulmonary artery to aorta ratio predict PH
- The value to detect PH of non-invasive determinations either alone or in combination was limited
- A combination of certain determinations and cut-offs provides adequate negative predictive value

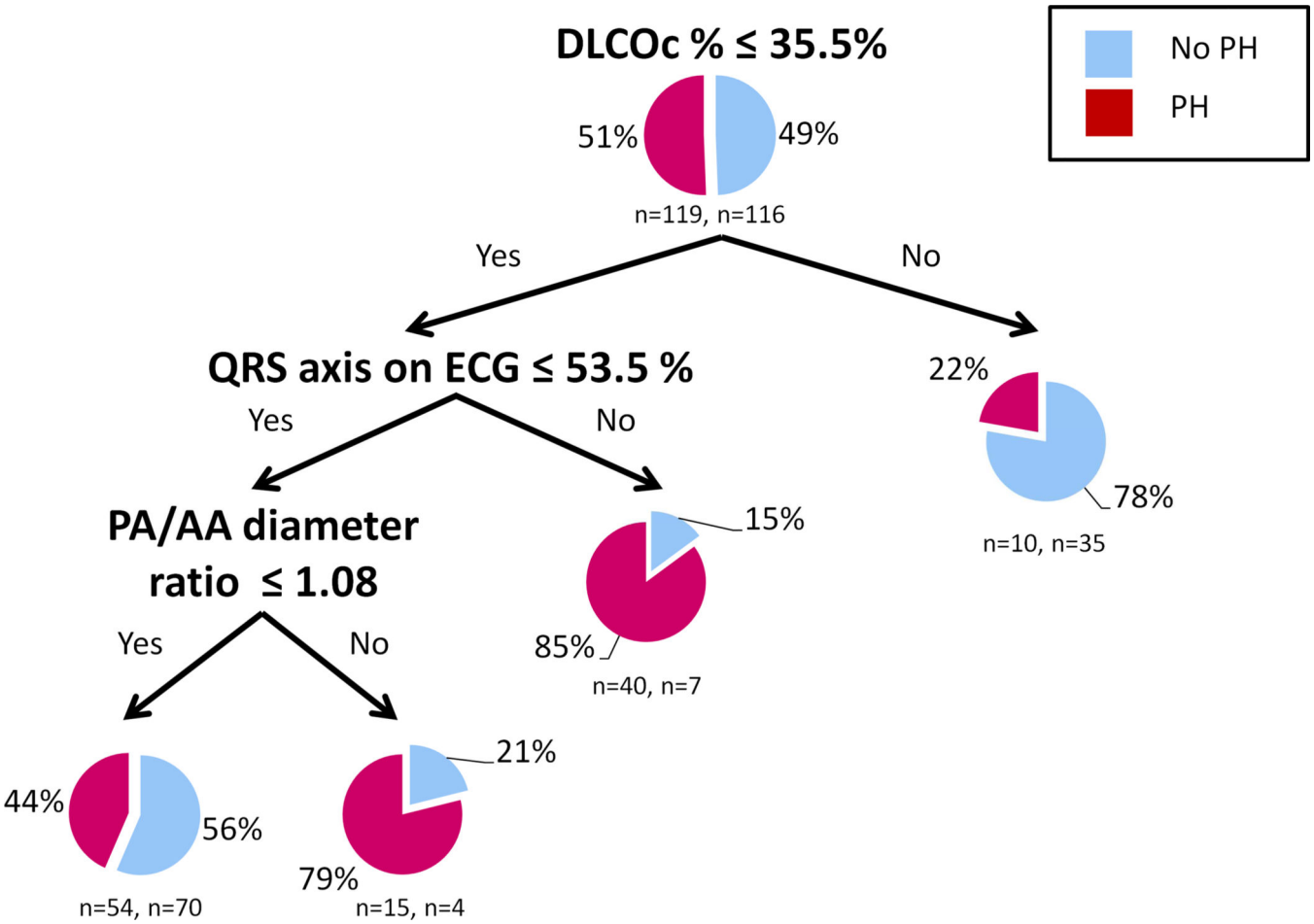

Figure 1. CART analysis to discriminate between IPF patients with and without PH

Each terminal node provides a pie chart with the percentage of IPF patients with PH (mean PAP ≥ 25 mmHg) and without PH (mean PAP < 25 mmHg). The number of patient with and without PH is provided below the pie chart.

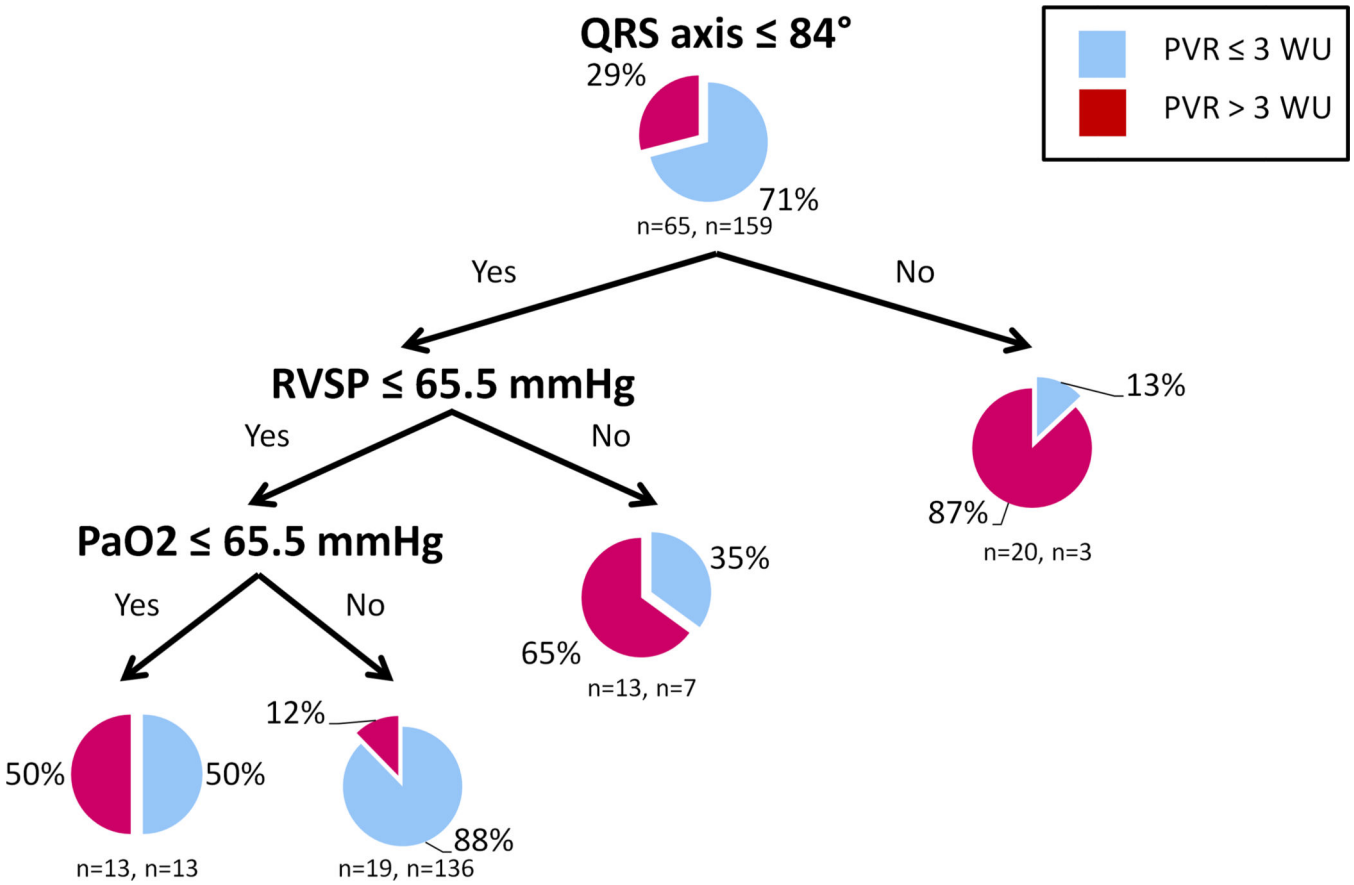

Figure 2. CART analysis to discriminate between IPF patients with and without precapillary PH

Each terminal node provides the number and percentage of IPF patients with precapillary PH (mean PAP ≥ 25 mmHg and PVR >3 Wood units) and without precapillary PH (PVR ≤3 Wood units). The number of patient with and without precapillary PH is provided below the pie chart.

Table 1

Patient characteristics

	All patients Mean ± SD or n (%)	No PH Mean ± SD or n (%)	PH Mean ±SD or n (%)	P (T-test / Fisher's exact test)^
N	235	116 (49.4)	119 (50.6)	
Age (year)	59.3 ± 8.9	60.7 ± 8.5	57.9 ± 9.1	0.02
Male gender	167 (71.1)	79 (68.1)	88 (73.9)	0.32
Lung allocation score[29]	49.3 ± 18.8	44.1 ± 15.2	54.0 ± 20.4	<0.001
Hemodynamic data				
-Systolic ABP (mm Hg)	129.4 ± 19.0	131.1 ± 20.0	128.4 ± 18.7	0.67
-Diastolic ABP (mm Hg)	83.9 ± 17.2	83.4 ± 9.9	84.2 ± 20.7	0.89
-RA pressure (mm Hg)	6.2 ± 4.3	4.4 ± 2.7	7.9 ± 4.6	<0.001
-Systolic PAP (mm Hg)	43.8 ± 16.8	32.6 ± 6.8	54.8 ± 16.4	<0.001
-Diastolic PAP (mm Hg)	17.9 ± 8.6	12.6 ± 4.7	23.1 ± 8.4	<0.001
-Mean PAP (mm Hg)	27.1 ± 10.8	19.2 ± 4.0	34.7 ± 9.7	<0.001
-PAWP (mm Hg)	10.7 ± 6.0	8.6 ± 4.4	12.8 ± 6.6	<0.001
-CO (L/min)	5.4 ± 1.5	5.3 ± 1.4	5.5 ± 1.6	0.33
-CI (L/min/m2)	2.8 ± 0.7	2.9 ± 0.7	2.8 ± 0.7	0.44
-PVR (Wood Units)	3.4 ± 2.4	2.2 ± 1.1	4.6 ± 2.8	<0.001
Echocardiographic data				
Left ventricular EF (%)	56.4 ± 10.5	56.8 ± 6.3	57.5 ± 6.5	0.93
RVSP (mmHg) *	49.1 ± 20.4	43.8 ± 15.0	54.1 ±23.5	0.001
TAPSE (cm) ¶	1.4 ± 0.4	1.40 ± 0.4	1.3 ± 0.4	0.31
RV diameter (cm) ‡				
-Basal	4.1 ± 0.8	3.9 ± 0.7	4.2 ± 0.8	0.01
-Mid	3.7 ± 0.8	3.5 ± 0.7	3.8 ± 0.9	0.02
-Longitudinal	7.0 ± 1.1	6.8 ± 1.1	7.1 ± 1.1	0.04
RV dysfunction				
-Not available	50 (21.3)			
-Normal	111 (47.2)	66 (75.0)	45 (46.4)	
-Mild	34 (14.5)	13 (14.8)	21 (21.6)	<0.001
-Moderate	18 (7.7)	6 (6.8)	12 (12.4)	
-Severe	22 (9.4)	3 (3.4)	19 (19.6)	

Abbreviations: ABP: arterial blood pressure, CI: cardiac index, CO: cardiac output, EF: ejection fraction, PAWP: pulmonary artery wedge pressure, PAP: pulmonary artery pressure, PVR: pulmonary vascular resistance, RA: right atrium, RV: right ventricle, RVSP: right ventricular systolic pressure, TAPSE: tricuspid annular plane systolic excursion.

* Data available in 159 patients.

¶ Data available in 166 patients.

≠Data available in 159 patients.

^p values are given for reference only and have not been adjusted for multiple comparison.

Table 2

Electrocardiographic determinations.

	All patients Mean ± SD or n (%)	No PH Mean ± SD or n (%)	PH Mean ± SD or n (%)	P (T-test / Fisher's exact test)
N	228	111	117	
Rhythm				0.62
-Sinus	222 (97.8)	110 (99.1)	112 (96.6)	
-Atrial Fibrillation	1 (0.4)	0 (0)	1 (0.9)	
-Nodal	4 (1.8)	1 (0.9)	3 (2.6)	
Heart rate (bpm)	81.5 ± 16.6	80.5 ± 15.5	82.5 ± 17.5	0.35
P wave axis (degrees)	+38.8 ± 19.0	+34.8 ± 18.9	+42.7 ± 18.5	0.002
P wave amplitude V_1 (mA)	0.14 ± 0.06	0.13 ± 0.06	0.14 ± 0.07	0.11
P wave amplitude lead II (mA)	0.14 ± 0.06	0.13 ± 0.05	0.15 ± 0.06	0.02
PR interval (ms)	152.2 ± 24.0	153.3 ± 22.7	151.1 ± 25.3	0.51
QRS complex (ms)	92.2 ± 16.2	90.9 ± 14.7	93.4 ± 17.4	0.24
QRS axis (degrees)	+23.2 ± 46.2	+10.5 ± 30.9	+35.2 ± 54.4	<0.001
R wave lead V_1 (mA)	0.29 ± 0.26	0.26 ± 0.21	0.32 ± 0.29	0.13
S wave lead V_1 (mA)	0.81 ± 0.47	0.87 ± 0.45	0.75 ± 0.48	0.07
R/S ratio lead V_1	0.59 ± 1.2	0.48 ± 1.0	0.71 ± 1.3	0.15
QTc interval (ms)	442.7 ± 38.5	439.1 ± 35.4	446.2 ± 41.1	0.17
T wave axis (degrees)	+23.8 ± 34.6	+28.9 ± 29.5	+18.9 ± 38.4	0.03
RBBB	10 (4.4)	4 (3.6)	6 (5.1)	0.75
IRBBB	34 (14.9)	10 (9.0)	24 (20.5)	0.02
qR complex in lead V_1	6 (2.6)	0 (0)	6 (5.1)	0.03
QS complex in lead V_1	6 (2.6)	1 (0.9)	5 (4.3)	0.02
Negative T wave in V_1–V_3	140 (61.4)	64 (57.7)	76 (65.0)	0.28
Negative T wave in inferior leads	113 (49.6)	50 (45.0)	63 (53.8)	0.19
ST segment depression in V_1–V_3	27 (11.8)	7 (6.3)	20 (17.1)	0.01
ST segment depression in inferior leads	5 (2.2)	0 (0)	5 (4.3)	0.06

Abbreviations: bpm: beats-per-minute, IRBBB: incomplete right bundle branch block, RBBB: right bundle branch block, RHC: right heart catheterization.

Table 3

PFT, ABG and chest CT determinations.

	All patients Mean ± SD or n (%)	No PH Mean ± SD or n (%)	PH Mean ±SD or n (%)	P (t-test) (T-test)
Spirometry (n=225)				
FVC (% of predicted)	47.5 ± 16.2	45.2 ± 13.8	49.8 ± 18.0	0.03
FEV_1 (% of predicted)	51.5 ± 14.8	50.5 ± 14.4	52.3 ± 15.4	0.37
FEV_1/FVC	0.84 ± 0.10	0.85 ± 0.11	0.83 ± 0.1	0.09
TLC (% of predicted)	54.5 ± 14.0	52.1 ± 10.9	56.8 ± 16.1	0.02
DLCOc (% of predicted)	27.3 ± 10.4	28.9 ± 11.3	25.1 ± 9.0	0.004
FVC / DLCOc	2.1 ± 1.0	1.8 ± 0.8	2.3 ± 1.1	0.002
Six-minute walk test (n=199)				
Baseline HR (bpm)	87.8 ± 15.6	88.1 ± 15.0	87.5 ± 16.1	0.79
Distance walked (m)	318.8 ± 101.2	342.6 ± 107.9	295.3 ± 88.5	0.001
Distance walked (% predicted)	60.7 ± 21.1	66.8 ± 21.6	54.0 ± 18.4	<0.001
HRR (1 min)	14.2 ± 9.2	13.6 ± 9.3	14.7 ± 9.2	0.51
Arterial blood gases on room air (n=205)				
PaO_2 (mmHg)	56.9 ± 13.1	60.4 ± 12.1	53.5 ± 13.2	<0.001
$PaCO_2$ (mmHg)	39.5 ± 5.8	40.3 ± 4.8	39.0 ± 6.5	0.11
Computed tomography (n=189)				
Aortic diameter (mm)	34.7 ± 3.8	34.9 ± 4.0	34.5 ± 3.6	0.46
PA diameter in (mm)	32.2 ± 5.2	31.0 ± 4.8	33.2 ± 5.3	0.003
Ratio of PA/AA diameters	0.93 ± 0.15	0.89 ± 0.14	0.97 ± 0.16	0.001

Abbreviations: AA: ascending aorta, DLCOc: corrected carbon monoxide diffusion capacity, FEV_1: forced expiratory volume in 1 sec, FVC: forced-vital capacity, HR: heart rate, HRR: heart rate recovery, PA: pulmonary artery, PaO_2: partial arterial pressure of O_2, $PaCO_2$: partial arterial pressure of CO_2, TLC: total lung capacity.

Table 4

Univariable logistic regression to predict patients with PH (mPAP ≥25 mmHg)

Variables (incremental change)	OR	95%CI	p	C-index	95%CI
Age (every 10 years)	0.69	0.51–0.94	0.02	0.40	0.33–0.47
PaO_2 (every 10 mmHg)	0.64	0.50–0.81	<0.001	0.33	0.26–0.40
SaO_2 (every 10 %)	0.36	0.22–0.58	<0.001	0.31	0.24–0.38
FVC (every 10 %)	1.20	1.01–1.42	0.04	0.56	0.48–0.63
TLC (every 10 %)	1.29	1.03–1.61	0.03	0.57	0.49–0.65
DLCOc (every 10 %)	0.63	0.45–0.86	0.004	0.37	0.28–0.46
FVC/DLCO ratio (every 0.1)	1.77	1.20–2.61	0.004	0.65	0.56–0.73
PA diameter (every 1 cm)	2.41	1.32–4.39	0.004	0.61	0.53–0.69
PA/AA ratio (every 0.1)	1.42	1.15–1.74	0.001	0.64	0.56–0.72
6MWD (every 10 m)	0.95	0.92–0.98	0.001	0.36	0.28–0.44
6MWD (every 10 %)	0.73	0.61–0.87	0.001	0.33	0.24–0.42
P axis (every 10 degrees)	1.26	1.09–1.46	0.002	0.60	0.53–0.68
P wave in D_2 (every 0.1 mV)	1.73	1.07–2.79	0.03	0.58	0.51–0.66
QRS axis (every 10 degrees)	1.14	1.07–1.22	<0.001	0.62	0.55–0.70
T axis (every 10 degrees)	0.91	0.84–0.99	0.03	0.41	0.33–0.48
V_1–V_3 ST depression (Yes)	3.06	1.24–7.57	0.02		
IRBBB (Yes)	2.61	1.18–5.74	0.02		
RVSP (every 10 mmHg)	1.32	1.10–1.57	0.002	0.63	0.54–0.72
RV dilation (every 1 grade^)	1.96	1.31–2.93	0.001		
RV function (every 1 grade^)	2.24	1.52–3.31	<0.001		
RV basal diameter (per 1 cm)	1.71	1.11–2.64	0.02	0.60	0.51–0.69
RV mid diameter (per 1 cm)	1.59	1.05–2.39	0.03	0.57	0.48–0.66
RV longitudinal dimension (per 1 cm)	1.36	1.01–1.83	0.04	0.59	0.50–0.68

Abbreviations: 6MWD: distance walked in six minute walk test, AA: ascending aorta, DLCOc: corrected diffusion lung capacity of carbon monoxide, FVC: forced vital capacity, IRBBB: incomplete right bundle branch block, PA: pulmonary artery, PaO_2: partial arterial pressure of O_2, RV: right ventricle, RVSP: right ventricular systolic pressure, SaO_2: arterial O_2 saturation.

[^] a change from normal to mild, mild to moderate or moderate to severe.

Table 5

Univariable analysis to predict patients with precapillary PH (PVR > 3 Wood Units)

Variables (incremental change)	OR	95%CI	p	C-index	95%CI
PaO_2 (every 10 mmHg)	0.62	0.47–0.82	0.001	0.32	0.24–0.40
SaO_2 (every 10 %)	0.39	0.25–0.62	<0.001	0.30	0.21–0.38
TLC (every 10 %)	1.32	1.06–1.67	0.02	0.58	0.49–0.68
DLCOc (every 10 %)	0.52	0.35–0.78	0.001	0.34	0.25–0.43
FVC/DLCOc (every 0.1)	2.20	1.47–3.32	<0.001	0.69	0.59–0.78
PA diameter (every 1 cm)	2.84	1.50–5.40	0.001	0.65	0.56–0.74
PA/AA diameter ratio (every 0.1)	1.60	1.27–2.00	<0.001	0.69	0.60–0.77
6MWD (every 10 m)	0.96	0.92–0.99	0.006	0.38	0.29–0.46
6MWD %predicted (every 10 %)	0.70	0.57–0.87	0.001	0.31	0.21–0.41
P axis (every 10 degrees)	1.22	1.03–1.44	0.02	0.60	0.51–0.68
P wave in lead II (every 0.1 mV)	2.26	1.35–3.79	0.002	0.65	0.57–0.73
QRS axis (every 10 degrees)	1.21	1.12–1.30	<0.001	0.69	0.61–0.77
T axis (every 10 degrees)	0.90	0.82–1.00	0.04	0.40	0.32–0.49
V_1–V_3 ST depression (Yes)	3.60	1.58–8.21	0.002		
IRBBB (Yes)	4.19	1.95–9.03	<0.001		
RVSP (every 10 mmHg)	1.46	1.21–1.76	<0.001	0.68	0.58–0.78
RV dilation (every 1 grade^)	2.39	1.59–3.61	<0.001		
RV function (every 1 grade^)	2.85	1.92–4.23	<0.001		
RV basal diameter (per 1 cm)	1.68	1.08–2.60	0.02	0.61	0.52–0.71
RV mid diameter (per 1 cm)	1.81	1.18–2.78	0.007	0.62	0.52–0.72

Abbreviations: 6MWD: distance walked in six minute walk test, AA: ascending aorta, DLCOc: corrected diffusion lung capacity of carbon monoxide, IRBBB: incomplete right bundle branch block, PA: pulmonary artery, PaO_2: pulmonary artery pressure of O_2, PVR: pulmonary vascular resistance, RV: right ventricle, RVSP: right ventricular systolic pressure, SaO_2: arterial O_2 saturation, TLC: total lung capacity.

^ a change from normal to mild, mild to moderate or moderate to severe.