Echocardiographic and Hemodynamic Predictors of Mortality in Idiopathic Pulmonary Fibrosis

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Background: Idiopathic pulmonary fibrosis (IPF) can lead to the development of pulmonary hypertension, which is associated with an increased risk of death. In pulmonary arterial hypertension, survival is directly related to the capacity of the right ventricle to adapt to elevated pulmonary vascular load. The relative importance of right ventricular function in IPF is not well understood. Our objective was to evaluate right ventricular echocardiographic and hemodynamic predictors of mortality in a cohort of patients with IPF referred for lung transplant evaluation.

Methods: We performed a retrospective cohort study of 135 patients who met 2011 American Thoracic Society/European Respiratory Society criteria for IPF and who were evaluated for lung transplantation at the Hospital of the University of Pennsylvania.

Results: Right ventricle:left ventricle diameter ratio (hazard ratio [HR], 4.5; 95% CI, 1.7-11.9), moderate to severe right atrial and right ventricular dilation (HR, 2.9; 95% CI, 1.4-5.9; and HR, 2.7; 95% CI, 1.4-5.4, respectively) and right ventricular dysfunction (HR, 5.5; 95% CI, 2.6-11.5) were associated with an increased risk of death. Higher pulmonary vascular resistance was also associated with increased mortality (HR per 1 Wood unit, 1.3; 95% CI, 1.1-1.5). These risk factors were independent of age, sex, race, height, weight, FVC, and lung transplantation status. Other hemodynamic indices, such as mean pulmonary artery pressure and cardiac index, were not associated with outcome.

Conclusions: Right-sided heart size and right ventricular dysfunction measured by echocardiography and higher pulmonary vascular resistance by invasive hemodynamic assessment predict mortality in patients with IPF evaluated for lung transplantation. *CHEST 2013; 144(2):564-570*

Abbreviations: HR = hazard ratio; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; LV = left ventricle; mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RA = right atrium; RHC = right-sided heart catheterization; RV = right ventricle; RV:LV = right ventricle:left ventricle diameter ratio; RVOT VTI = right ventricular outflow tract velocity time integral; RVSP = right ventricular systolic pressure; TAPSE = tricuspid annular plane systolic excursion; WU = Wood units

Idiopathic pulmonary fibrosis (IPF) is a fatal disease with a variable natural history. Pulmonary hypertension (PH) is frequently found in patients with IPF and is associated with an almost threefold increase in the risk of death.^{1,2} In pulmonary arterial hypertension (PAH), outcome is directly related to the capacity of the right ventricle (RV) to adapt to elevated afterload.³ However, the role of RV function is not clearly understood in pulmonary vascular disease related to IPF.

Although right-sided heart catheterization (RHC) is the gold standard modality for hemodynamic assessment, Doppler echocardiogram is a complementary

method of assessing RV function. While Doppler echocardiogram measurement of the right ventricular systolic pressure (RVSP) has limited accuracy in advanced lung disease,^{4,5} several echocardiographic measurements of the RV have been associated with outcomes in PH. Such measurements include tricuspid annular plane systolic excursion (TAPSE) as a measure of RV ejection fraction,⁶⁻⁸ RV outflow tract velocity-time integral (RVOT VTI) as a surrogate for stroke volume, and the presence of “notching” in the Doppler flow velocity envelope obtained from the RVOT, indicating elevated pulmonary vascular resistance (PVR).^{9,10} We

hypothesized that these and other echocardiographic measurements of the RV would be associated with outcomes in patients with IPF.

MATERIALS AND METHODS

We performed a retrospective cohort study of patients with IPF evaluated for lung transplantation at the Hospital of the University of Pennsylvania between 2005 and 2010. The study was approved by the University of Pennsylvania Institutional Review Board (Review Board No. 4, protocol 813174).

Subjects

During the study period, 787 patients were evaluated for lung transplantation at our center. Of these, 315 carried a diagnosis of IPF, pulmonary fibrosis, or interstitial lung disease. One hundred and fifty-three met “definite” usual interstitial pneumonia criteria by high-resolution CT scanning or “possible” usual interstitial pneumonia criteria by CT scanning with “definite or probable” histopathologic criteria using the 2011 American Thoracic Society/European Respiratory Society guidelines (reviewed by BRL).¹¹ We excluded patients with other forms of diffuse parenchymal lung disease or coexisting rheumatologic disease. Of the 153 patients, 18 were missing Doppler echocardiogram or RHC data, leaving 135 patients in the final study sample.

Hemodynamics

All patients underwent a standard resting RHC (Swan-Ganz catheter; Edwards Lifesciences Corp). We reviewed the tracings in a subset of the cohort (68%), blinded to clinical and echocardiographic data (B. N. R.-L.), and compared the results to those from the clinical interpretation that was used for this analysis.

Echocardiography

All patients underwent resting transthoracic Doppler echocardiogram, which was interpreted by a researcher blinded to clinical

information and RHC tracings (B. N. R.-L.) (Prosolv Cardio-Vascular, FUJIFILM Holdings America Corp). Thirty percent of the echocardiograms were evaluated by a second physician (P. R. F.) blinded to the first read, to assess interobserver reliability. Additional echocardiographic and hemodynamic method details are provided in e-Appendix 1.

Follow-up

Vital status was determined for all patients using the US Social Security Death Index until June 2011. No patients were lost to follow-up.

Statistical Analysis

Continuous variables were summarized by the mean $\pm$ SD or median (interquartile range), as appropriate. Categorical variables were summarized by frequency and percentage. Rank-sum tests and *t* tests were used as appropriate. Cox proportional hazards regression models were used to identify echocardiographic and hemodynamic predictors of mortality with adjustment for lung transplantation status as a time-varying covariate and with censoring at transplant. Adjusting for transplant has two benefits: (1) It accounts for the effects of this procedure on outcomes and (2) allows for the consideration of overall survival, the definitive end point of the fatal disease of IPF. Pearson or Spearman rank-correlation tests were used as appropriate, as were simple and multivariate linear regression. Interclass correlation coefficients and kappas were used to quantify interobserver reliability. All analyses used available data and no imputation was performed. STATA software version 12 (StataCorp LP) was used for all analyses. A *P* value $< .05$ was considered significant. Additional statistical analysis details are provided in e-Appendix 1.

RESULTS

Subject characteristics are presented in Table 1. The average age was 58 ± 7 years, 73% of patients were men, and 82% were non-Hispanic white. The mean FVC % predicted was $51\% \pm 15\%$, diffusing capacity for carbon monoxide % predicted (DLCO%) was $39\% \pm 14\%$, and 6-min walk distance was 379 ± 128 m. The general characteristics and disease severity of the 18 excluded patients were not substantially different from the patients who were included in the sample (data not shown).

A second physician (S. M. K.) independently reviewed 32 of the 315 patients (10%) who carried a clinical diagnosis of pulmonary fibrosis, with an interobserver κ of 1.0 for a diagnosis of IPF. The interclass correlation coefficients for hemodynamic parameters ranged from 0.95 to 0.99 in the 92 (68%) of the RHCs blindly reinterpreted and compared with the clinical reports. The interclass correlation coefficients for the echocardiographic parameters ranged from 0.70 to 0.90 in the 41 (30%) of the Doppler echocardiograms reinterpreted blindly by a second physician.

Table 2 summarizes the hemodynamic and echocardiographic variables. The median time between RHC and Doppler echocardiogram was 24 h (interquartile range, 24–48 h). Thirty-nine patients (29%)

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Table 1—Characteristics of the Cohort

Subject Characteristics (n = 135)	Value
Age, y	58 ± 7
Male sex	98 (73)
Race/ethnicity	
White	111 (82)
Black	10 (7)
Hispanic	9 (7)
Other	5 (4)
BMI, kg/m ²	29 ± 5
Past smokers	98 (73)
Pack-y	33 ± 25
Supplemental oxygen, L (n = 100)	4 ± 2
Lung biopsy	84 (62)
Vasodilator therapy	
None	124 (92)
Prostacyclin analogs	1 (1)
PDE5 inhibitors	2 (1)
Endothelin receptor antagonists	8 (6)
Pulmonary function tests	
FVC, % predicted	51 ± 15
FEV ₁ , % predicted	56 ± 16
FEV ₁ /FVC ratio	0.85 ± 0.08
TLC, % predicted (n = 129)	58 ± 12
DLCO, % predicted (n = 109)	39 ± 14
6-min walk test (n = 130)	
Total distance, m	379 ± 128
Supplemental oxygen during walk test, L	7 ± 7

Data given as mean ± SD or No. (%). DLCO = diffusing capacity of the lung for carbon monoxide; PDE5 = phosphodiesterase type 5 inhibitor; TLC = total lung capacity.

had PH-IPF (defined by mean pulmonary artery pressure [mPAP] ≥ 25 mm Hg and pulmonary capillary wedge pressure [PCWP] < 15 mm Hg). Of those with PH-IPF, the mean mPAP was 31 ± 6 mm Hg, the PVR was 5 ± 2 Wood units (WU), and the PCWP was 9 ± 4 mm Hg. Fourteen patients (11%) in the entire cohort had moderate to severe RV dysfunction; these patients had a significantly lower TAPSE (1.8 cm vs 2.1 cm; $P = .01$), higher mPAP (34 mm Hg vs 24 mm Hg; $P < .001$) and higher PVR (6.3 WU vs 3.3 WU; $P < .001$) compared with those with normal or mild RV dysfunction.

The median follow-up time was 2.5 years. Sixty-eight patients (50%) underwent transplantation. Fifty-eight patients died during the study period, 26 of whom (45%) died after lung transplantation. The post-transplant 1-year survival was 78% and the 5-year survival was 52%. Additional results are provided in e-Appendix 2 and e-Figure 1.

Echocardiographic Predictors of Mortality

Table 3 shows the associations of echocardiographic predictors with survival in unadjusted and adjusted models. In unadjusted models, right ventricle:left ventricle diameter ratio (RV:LV), TAPSE < 1.6 cm (lowest quartile), and moderate to severe right atrial (RA) or

RV dilation and RV dysfunction were associated with an increased risk of death. Figures 1 and 2 show that patients with TAPSE < 1.6 cm and RV:LV ≥ 1, respectively, had a significantly increased risk of death after adjustment for transplant status.

Each predictor was then adjusted for age, sex, race, height, weight, FVC, and lung transplant status in multivariate models. Larger RV:LV was still associated with an increased risk of death, and moderate to severe RA and RV dilation and RV dysfunction were all associated with a more than doubling in the risk. TAPSE < 1.6 cm was possibly associated with an increased risk of death, but did not reach statistical significance ($P = .06$). RVSP did predict outcome in those in whom it was measureable.

When we additionally adjusted for PVR or for the presence of PH-IPF, moderate to severe RV dysfunction remained significantly associated with outcome (adjusted hazard ratio [HR], 3.7; 95% CI, 1.5-9.1; $P = .004$; and HR, 5.4; 95% CI, 2.6-11.5; $P < .001$, respectively). Similarly, moderate to severe RV dysfunction was the only variable that remained significant after adjustment for the other echocardiographic

Table 2—Hemodynamic and Echocardiographic Characteristics of the Cohort

Characteristics	No.	Value
RAP, mm Hg	133	5 ± 4
mPAP, mm Hg	135	25 ± 8
PCWP, mm Hg	134	10 ± 6
LVEDP, mm Hg	127	12 ± 8
SVR, WU	130	15 ± 4
PVR, WU	131	3.7 ± 1.9
CO, L/min	131	5.6 ± 1.3
Cardiac index, L/min/m ²	131	2.9 ± 0.5
SV, mL	131	74 ± 23
SVI, mL/m ²	131	38 ± 10
Heart rate, bpm	135	78 ± 16
TAPSE, cm	134	2.1 ± 0.5
RVSP, mm Hg	96	47 ± 18
RVOT VTI	125	12.9 ± 3
Notching of RVOT, No. (%)	125	47 (38)
RV:LV	133	0.9 ± 0.3
RVOT AT, ms	107	105 ± 28
Moderate to severe RA dilation, No. (%)	130	17 (13)
Moderate to severe RV dilation, No. (%)	132	25 (19)
Moderate to severe RV dysfunction, No. (%)	133	14 (11)
Left ventricular ejection fraction, %	135	63 ± 9
Diastolic dysfunction, No. (%)	103	71 (53)

Data are given as mean ± SD unless otherwise indicated. bpm = beats per min; CO = cardiac output; LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrium; RAP = mean right atrial pressure; RV = right ventricle; RV:LV = right ventricle:left ventricle diameter ratio; RVOT AT = right ventricular outflow tract-acceleration time; RVOT VTI = right ventricular outflow tract velocity-time integral; RVSP = right ventricular systolic pressure; SV = stroke volume; SVI = stroke volume index; SVR = systemic vascular resistance; TAPSE = tricuspid annular plane systolic excursion; WU = Wood units.

Table 3—Cox Proportional Hazards Models for RV Echocardiographic Predictors of Mortality

Variable	Unadjusted Model			Adjusted Model ^a			Censored at Lung Transplantation ^b		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
RV:LV	3.8	1.5-9.7	.006	4.5	1.7-11.9	.003	5.6	1.6-19.8	.008
TAPSE < 1.6 cm	2.0	1.0-3.7	.05	1.9	1.0-3.7	.06	1.5	.7-3.5	.31
TAPSE (continuous)	.7	.4-1.2	.22	.8	.5-1.5	.56	.8	.3-2.1	.60
Moderate to severe RA dilation	2.4	1.2-4.7	.009	2.9	1.4-5.9	.004	3.0	1.2-7.8	.02
Moderate to severe RV dilation	2.6	1.4-4.6	.001	2.7	1.4-5.4	.004	3.2	1.4-7.8	.008
Moderate to severe RV dysfunction	4.9	2.5-9.6	< .001	5.5	2.6-11.5	< .001	7.5	2.7-20.8	< .001
RVSP, for 5 mm Hg increase	1.1	1.1-1.2	< .001	1.2	1.1-1.3	< .001	1.2	1.1-1.4	.002
RVOT VTI	.9	.9-1.0	.16	.9	.9-1.0	.17	.8	.7-1.0	.01
RVOT AT	1.0	.9-1.0	.46	1.0	.9-1.0	.64	1.0	.9-1.0	.11
Notching of RVOT	1.4	.8-2.3	.27	1.4	.8-2.4	.25	2.4	1.0-5.4	.05

HR = hazard ratio. See Table 2 legend for expansion of other abbreviations.

^aAdjusted for age, sex, race/ethnicity, height, weight, FVC and transplant status.

^bAdjusted for age, sex, race/ethnicity, height, weight, FVC.

parameters (adjusted HR, 4.8; 95% CI, 1.3-18.6; $P = .02$). There were no significant interactions between RV echocardiographic parameters and PVR or PH-IPF and survival (data not shown).

Hemodynamic Predictors of Mortality

Table 4 shows the association between hemodynamics and the risk of death. In unadjusted analyses, a 1-WU increase in PVR was associated with a 25% increase in the risk of death. Higher mPAP was also possibly associated with reduced survival, but did not reach statistical significance ($P = .06$). We then adjusted for age, sex, race, height, weight, FVC, and lung transplant status; inclusion of age, sex, height, and weight in the multivariate models eliminated the need to index the measures from RHC (or spirometry) to body size (eg, using cardiac index, stroke volume index, or FVC % predicted). After adjustment, PVR remained significantly associated with the risk of death, and mPAP was borderline statistically significant. Presence

of PH-IPF was not associated with an increased risk of death in the adjusted model (adjusted HR, 1.1; 95% CI, 0.6-2.0; $P = .79$). Cardiac output and stroke volume were not associated with the risk of death in univariate or multivariate analysis.

Sensitivity Analysis

When we censored patients at the time of transplantation, our conclusions regarding the echocardiographic and hemodynamic predictors remained unchanged, with the exception that RVOT VTI (Table 3) and mPAP (Table 4) became predictors of mortality. PH-IPF was associated with an increased risk of death in these models (adjusted HR, 2.8; 95% CI, 1.1-7.0; $P = .03$).

Echocardiographic or hemodynamic predictors of mortality did not change after we excluded the 11 patients who were on vasodilator therapy from the analysis (data not shown). Additional results are presented in the online supplement.

FIGURE 1. Survival curve stratified by TAPSE and adjusted for lung transplant status. TAPSE = tricuspid annular plane systolic excursion.

FIGURE 2. Survival curve stratified by RV:LV and adjusted for transplant status. RV:LV = right ventricle:left ventricle diameter ratio.

Table 4—Cox Proportional Hazards Models for Hemodynamic Predictors of Mortality

Variable	Unadjusted Model			Adjusted Model ^a			Censored at Lung Transplantation ^b		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P Value
RAP, for 1 mm Hg increase	.9	.9-1.0	.34	.9	.9-1.0	.48	1.0	.9-1.1	.74
mPAP, for 10 mm Hg increase	1.3	1.0-1.7	.06	1.3	1.0-1.8	.06	2.4	1.4-3.9	.001
PVR, for 1-WU increase	1.3	1.1-1.4	< .001	1.3	1.1-1.5	.001	1.4	1.2-1.7	< .001
CO, for 1 L/min decrease	1.1	.9-1.4	.31	1.2	.9-1.5	.23	1.4	.9-2.0	.10
SV, for 10 mL decrease	1.1	1.0-1.2	.18	1.1	.9-1.3	.19	1.2	.9-1.5	.09
PCWP, for 1 mm Hg increase	.99	.9-1.0	.75	1.0	1.0-1.1	.96	1.0	.9-1.1	.46

See Table 2 and 3 legends for expansion of abbreviations.

^aAdjusted for age, sex, race/ethnicity, height, weight, FVC and transplant status.

^bAdjusted for age, sex, race/ethnicity, height, weight, FVC.

DISCUSSION

Pulmonary vascular disease in IPF is associated with increased mortality. In this study, we have shown that increasing RV:LV, moderate to severe RA and RV dilation, and moderate to severe RV dysfunction detected by Doppler echocardiogram were associated with an increased risk of death, independent of covariates (including FVC and PVR) in patients with IPF being evaluated for lung transplantation. We also found that higher PVR was associated with an increased risk for overall mortality. Twenty-nine percent of the cohort had PH-IPF, which was associated with an increased risk of death when we censored for transplantation, similar to the results of other studies.^{1,2} Taken together, these data suggest that perturbations in right-sided heart structure and function, via an afterload-dependent mechanism, are potentially important determinants of outcome in these patients. Other hemodynamic measures reflecting ventricular function and advanced RV failure (ie, stroke volume, cardiac output, and RA pressure) were not associated with an increased risk of death in this cohort.

The patients with IPF in this study had relative compensation of right-sided heart function with mild RV dilation and low-normal RV systolic function. Even so, our findings suggest that changes in RV structure and function may be clinically significant. The presence of an increased RV:LV might represent an early anatomic change in response to higher PVR prior to the development of frank RV failure and could directly contribute to adverse outcome. Alternatively, changes in RV structure and dysfunction may not directly increase the risk of death, but may reflect increased RV afterload resulting from more severe vascular or fibrotic lung disease as the causal factors.

Corte et al¹² showed that PVR was a predictor of mortality in 66 patients with diffuse fibrotic lung disease; however, several types of idiopathic interstitial pneumonias (IIP) were included. Most epidemiologic studies and clinical trials have focused on IPF as the

most common, and one of the most deadly, IIPs, as combining various forms of IIP with potentially different risks of pulmonary vascular disease and distinct outcomes could lead to confounding. Quantitative echocardiographic assessment of the RV was not performed in this prior study.

Other echocardiographic studies in IPF have focused on RVSP.^{4,13} Nathan et al¹³ found that RVSP was measurable by Doppler echocardiogram in only 55% of their cohort; the accuracy for the diagnosis of PH was 40%. In our study, Doppler-estimated RVSP was associated with an increased risk of death; however, it was unmeasurable in >25% of the cohort. We were able to reliably assess RV parameters in almost all patients and these parameters were associated with differences in long-term outcomes. Moreover, RV:LV and RV dysfunction predicted adverse outcomes independently of the presence of PH-IPF or the level of the PVR. This suggests that right-sided heart structure and function and PVR may provide complementary information in identifying a population of patients with IPF who are at increased risk of death. These findings are consistent with studies in PAH showing that right-sided heart dysfunction and PVR are more strongly associated with outcome than pulmonary artery pressure.³

Some clinical trials of drugs used for PAH have not shown clinical benefits in patients with IPF. Bosentan did not have an effect on pulmonary function or outcome in IPF in two randomized controlled trials.^{14,15} Studies of ambrisentan for IPF, and specifically for PH-IPF, were stopped for futility.¹⁶ Interestingly, a post hoc analysis of a placebo-controlled, randomized clinical trial of sildenafil in IPF showed that the subgroup of patients with RV dysfunction had better preservation of exercise capacity, while subjects without RV dysfunction did not respond to therapy.^{17,18} It may be that subjects with RV dysfunction have a greater degree of circulatory limitation to exercise, and are thus apt to functionally improve in response to RV afterload reducing treatment. Perhaps future studies of PH

therapy for IPF should focus on IPF subgroups with the combination of significantly elevated PVR and RV dysfunction, as these subjects may have greater capacity to benefit, although this is a small subset of the overall IPF population evaluated for lung transplantation.

There were several limitations to our study. This was a retrospective cohort study; however, we reinterpreted all Doppler echocardiograms in a blinded fashion. We did not evaluate the Tei index or RV fractional area of change as measurements of RV function in our study. Although hemodynamic values were derived from the clinical reports, these showed high consistency with our reinterpretation of a subset of the primary tracings. Any nondifferential measurement error in these predictors would bias to the null, so that the associations of echocardiographic variables and PVR with the outcomes may be even stronger than shown. While misclassification in the diagnosis of IPF is possible, there was high interrater reliability in a random sample. We did not have available cause of death for the patients in the cohort; however, cause of death can be notoriously inaccurate. Last, this study included patients with IPF referred for lung transplant evaluation. Results might not apply to patients with mild IPF or with other forms of diffuse parenchymal lung disease.

CONCLUSIONS

RV:LV, moderate to severe RV dysfunction, and PVR are significant predictors of mortality in patients with IPF being evaluated for lung transplantation. Measures of RV structure and function may integrate aspects of IPF not captured by other physiologic measures, including pulmonary artery pressure. Echocardiographic indices of right-sided heart structure and function identify a high-risk population that should be considered for future clinical trials.

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Author contributions: Dr Rivera-Lebron had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Rivera-Lebron: contributed to the study design and data collection, analysis, and interpretation and wrote the first draft and revisions of the manuscript.

Dr Forfia: contributed to the study design and data analysis and interpretation and reviewed and revised the manuscript.

Dr Kreider: contributed to the study design and data interpretation and revised the manuscript.

Dr Lee: contributed to the study design and data interpretation and revised the manuscript.

Dr Holmes: contributed to the study design and data analysis and interpretation and reviewed the manuscript.

Dr Kawut: contributed to the study design and data analysis and interpretation and reviewed the manuscript.

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Additional information: The e-Appendixes and e-Figure can be found in the "Supplemental Materials" area of the online article.

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