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Pulmonary Hypertension as a Prognostic Indicator at the Initial Evaluation in Idiopathic Pulmonary Fibrosis

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For editorial comment see p. 452

Key Words
Idiopathic pulmonary fibrosis · Mortality · Pulmonary hypertension

Abstract
Background: The impact of pulmonary hypertension (PH) on survival has been demonstrated in severe cases with idiopathic pulmonary fibrosis (IPF) who were referred for transplantation. However, whether PH is a predictor of survival remains unclear in milder cases. ***Objectives:*** To evaluate the survival impact of pulmonary artery pressure measured during the initial evaluation in patients with IPF. ***Methods:*** We retrospectively analyzed the initial evaluation data of 101 consecutive IPF patients undergoing right heart catheterization. Patients evaluated with supplemental oxygen were excluded. Predictors of 5-year survival were analyzed using the Cox proportional model. ***Results:*** The mean forced vital capacity (FVC) % predicted, diffusing capacity of the lung for carbon monoxide (DLCO) % predicted, and mean pulmonary artery pressure (MPAP) were 70.2 ± 20.1%, 47.9 ± 19.5%, and 19.2 ± 6.5 mm Hg, respectively. A univariate Cox proportional hazard model showed that the body mass index, %FVC, %DLCO, baseline Pa_{O_2}, modified Medical Research Council score, 6-min walk distance, and lowest Sp_{O_2} of the 6-min walk test were significantly predictive of survival. The MPAP and pulmonary vascular resistance of right heart catheterization were also significant. With stepwise, multivariate Cox proportional analysis, MPAP (HR = 1.064; 95% CI 1.015–1.116, p = 0.010) and %FVC (HR = 0.965, 95% CI 0.949–0.982, $p < 0.001$) were independent determinants of survival. Analysis of the receiver operating curve revealed MPAP >20 mm Hg to be optimal for predicting the prognosis. ***Conclusions:*** Higher MPAP and lower %FVC at the initial evaluation were significant independent prognostic factors of IPF. The current results suggested the importance of the initial evaluation of PH for patients with IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and devastating disease with a median survival of 3–5 years [1, 2]. Previous studies have reported several poor prognostic factors, including decreased forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO), modified Medical Research Council

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(MMRC) scale, and degree of desaturation during the 6-min walk test (6MWT) [3–10].

Pulmonary hypertension (PH) is often observed in the clinical course of IPF patients with advanced disease [11–17]. In a retrospective study, Lettieri et al. [13] reported poor outcomes in IPF patients who were listed for lung transplantation with PH [mean pulmonary artery pressure (MPAP) >25 mm Hg] identified by right heart catheterization (RHC). In their study, a significant difference in outcomes was demonstrated with 1-year mortality.

Since PH does not always correlate with the restrictive impairment or the extent of fibrosis, the question of whether PH in less severe cases predicts mortality is interesting. Only one study, however, has reported mild or early cases. Hamada et al. [18] demonstrated the importance of PH in IPF patients at their initial workup using another cutoff point (MPAP >17 mm Hg) by RHC. However, when they performed a stepwise regression analysis, MPAP was not confirmed as an independent prognostic factor after adjusting for some parameters.

Moreover, in recent studies [11, 13, 15, 16, 18, 19] PH was evaluated in patients including those treated with supplemental oxygen, which could improve hypoxemic vasoconstriction and influence MPAP. No study has targeted IPF patients without supplemental oxygen at the initial evaluation by RHC.

In the current definition [20], the class of patients with MPAP 21–24 mm Hg remains undetermined. For example, in patients with chronic obstructive pulmonary disease (COPD), the cutoff point of PH has been defined as MPAP >20 mm Hg or >25 mm Hg [21]. However, in IPF, the optimal cutoff point has not been sufficiently discussed.

The aim of this study was to evaluate whether MPAP predicts survival in IPF patients who could be evaluated based on the background, pulmonary function test, 6MWT, and RHC at the initial evaluation in milder cases, and to evaluate the optimal cutoff point of MPAP.

Methods

Subjects

Patients who underwent systematic evaluations were registered in our database, which we retrospectively analyzed. Four hundred eighty-nine patients with interstitial pneumonia were enrolled at Tosei General Hospital between April 2001 and February 2009. One hundred seventy-seven patients were diagnosed with IPF and 76 patients were excluded for the following reasons: (1) they did not consent to RHC, (2) RHC was not performed within 3 months, (3) they suffered from unstable disease, such as acute exacerbation, infection, or heart failure, (4) there were other obvious causes of PH, for example chronic thromboembolic PH, (5) evaluation was done with supplemental oxygen, and (6) RHC was performed, but the pulmonary capillary wedge pressure (PCWP) was over 15 mm Hg. Finally, we reviewed 101 stable IPF patients who underwent RHC for the initial evaluation in this period (fig. 1).

This study was approved by the Tosei General Hospital Institutional Review Board (IRB No. 219). The IRB did not require the patients' approval or informed consent for the retrospective review of their records and images.

The diagnosis of IPF was made in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) statement [1], using the following major criteria: (1) exclusion of other known causes of interstitial lung disease, (2) abnormal pulmonary function with restriction and impaired gas exchange, (3) bibasilar reticular abnormalities on high-resolution computed tomography (HRCT), and (4) transbronchial lung biopsy or bronchoalveolar lavage showing no features to support an alternative diagnosis. Minor criteria included: (1) age >50 years, (2) insidious onset of otherwise unexplained dyspnea, (3) duration of illness >3 months, and (4) bibasilar inspiratory crackles. All of the major criteria and at least 3 of the 4 minor criteria had to be satisfied. For those with a surgical lung biopsy specimen showing usual interstitial pneumonia, only the major criteria were considered relevant.

Measurements

We recorded patients' characteristics, pulmonary function tests, Pa_{O_2}, 6MWT, and hemodynamics, retrospectively. All patients underwent spirometry (CHESTAC-55V; Chest, Tokyo, Japan), according to the method described in the ATS 1994 update [22]. Single-breath D_{LCO} was also measured (CHESTAC-55V). The values for FVC and D_{LCO} were related to % predicted values [23]. 6MWT was conducted in all patients who participated in the study, according to the ATS statement [24]. Briefly, all patients were tested under standardized conditions by trained technicians. Baseline blood pressure, heart rate, and oxygen saturation were measured. Patients were instructed to walk as far as possible in 6 min. The distance that patients could walk was recorded. Oxygen saturation was also measured by pulse oximetry at rest for 5 min prior to and immediately after the test. All patients underwent the tests twice to minimize the training effects. The MMRC scale includes 5 grades (0–4) of various physiological activities that provoke dyspnea [10, 25]. After the patients had read the descriptive phrases, they selected the number that best corresponded to their level of dyspnea in daily living.

RHC was performed using a Swan-Ganz catheter percutaneously via either the cubital vein or the femoral vein.

Statistical Analysis

All data were based in February 2011. Continuous variables were expressed as means ± SD. Categorical variables were summarized by frequency. The MMRC score was analyzed as a continuous variable. Distribution of continuous variables was evaluated using the Shapiro-Wilk test. If both variables had a normal distribution, correlations were calculated using Pearson's correlation test. If either variable had a nonnormal distribution, correlations were calculated using Spearman's correlation test.

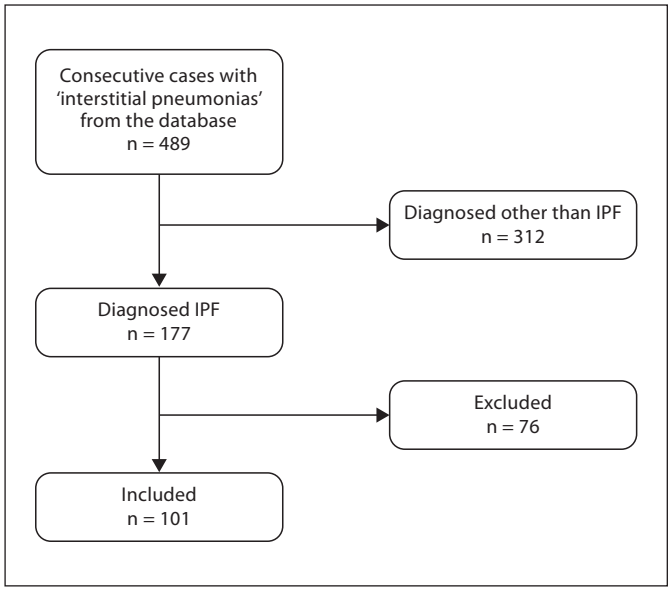

Fig. 1. Screening and inclusion process for patients in the study.

Table 1. Baseline characteristics and physiology of patients

Variables	Mean	Range
Sex (M/F)	85/16	
Age, years	65.4 ± 7.6	41–82
BMI	23.4 ± 4.1	13.9–36.1
Smoking status current/former/never	8/71/22	
FVC, % predicted	70.2 ± 20.1	28.3–112.6
DLCO, % predicted	47.9 ± 19.5	7.7–99.7
PaO_2, mm Hg	79.8 ± 12.0	48.8–103.0
MMRC	1.5 ± 1.0	0–4
6MWD, m	526.6 ± 154.0	68–1103
Lowest SpO_2, %	80.8 ± 10.4	46–96
MPAP, mm Hg	19.2 ± 6.5	9–39
PVRI, dyn·s·cm^{-5}·m^2	285.3 ± 151.0	85.6–922.2
Cardiac index, l·min^{-1}·m^{-2}	3.11 ± 0.60	1.51–5.38
PCWP, mm Hg	8.0 ± 3.6	0–15

Data are presented as means ± SD or numbers. n = 101 except for DLCO (n = 96).

When two continuous variables were compared, the t test was used for normal distributions and the Mann-Whitney test was used for nonnormal distributions. When categorical variables were compared, the χ^2 test was used. Univariate Cox's proportional hazard models were used to examine the association of selected variables with survival. Variables that were significant ($p < 0.05$) in the univariate analysis were included in the multivariate model. To avoid multicolinearity, only one of the highly correlated variables (coefficient of correlation ≥ 0.9) was entered in the multivariate model, if present. The stepwise multivariate Cox's proportional hazards model was then used for variables that were revealed to be significant with the univariate model, in order to select more significant variables. To obtain an appropriate cutoff value of MPAP, a receiver operating curve (ROC) analysis was performed. The survival analysis was completed according to the methods of Kaplan-Meier, and the log-rank test was used to compare survival curves. All tests were performed at a significance level of $p < 0.05$. Analyses were completed using IBM SPSS statistics version 19.

Table 2. Results of the univariate Cox proportional hazard model

Variables	HR	95% CI	p value
Sex			
Male	1		
Female	1.076	0.555–2.288	0.829
Age, years	0.998	0.965–1.032	0.911
BMI	0.926	0.863–0.993	0.032
Smoking status			
Never	1		
Former	1.205	0.641–2.266	0.562
Current	1.454	0.514–4.111	0.641
FVC, % predicted	0.960	0.944–0.976	<0.001
DLCO, % predicted	0.980	0.965–0.994	0.005
PaO_2, mm Hg	0.963	0.941–0.985	0.001
MMRC	2.014	1.453–2.790	<0.001
6MWD, m	0.995	0.993–0.997	<0.001
Lowest SpO_2, %	0.965	0.945–0.986	0.001
MPAP, mm Hg	1.082	1.035–1.131	0.001
PVRI, dyn·s·cm^{-5}·m^2	1.003	1.001–1.004	<0.001
Cardiac index, l·min^{-1}·m^{-2}	0.841	0.534–1.322	0.452
PCWP, mm Hg	0.998	0.926–1.077	0.967

Results

The baseline characteristics of 101 patients are summarized in table 1. The mean observation period was 25.1 ± 14.8 months. Twenty-three patients (22.8%) developed acute exacerbation of IPF. In this observation period 60 (59.4%) patients died. Thirty patients (29.7%) died due to respiratory failure, 18 (17.8%) due to acute exacerbation of IPF, 6 (5.9%) due to infection, 2 (2.0%) due to lung cancer, 1 (1.0%) due to acute leukemia, and 3 (3.0%) due to unknown causes. Fourteen patients received therapy for IPF at the initial evaluation. All of them were treated with oral corticosteroids. Ten patients were treated with an immunosuppressive agent. No patients were treated with antithrombotic agents for PH

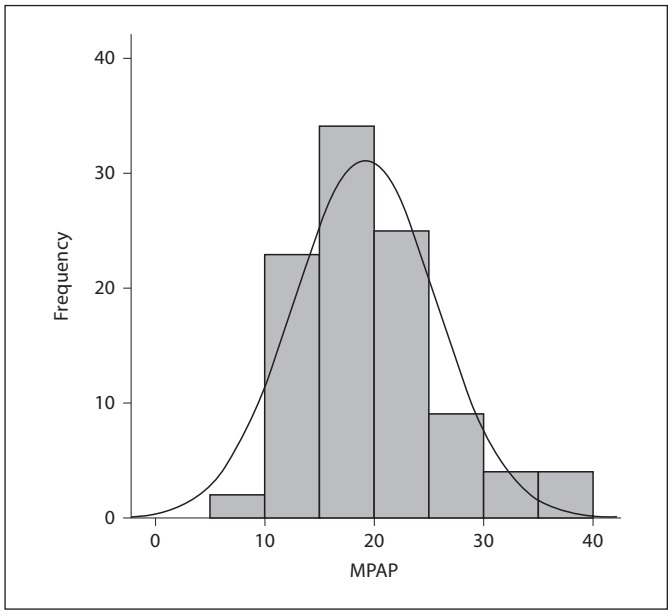

Fig. 2. Histogram of MPAP.

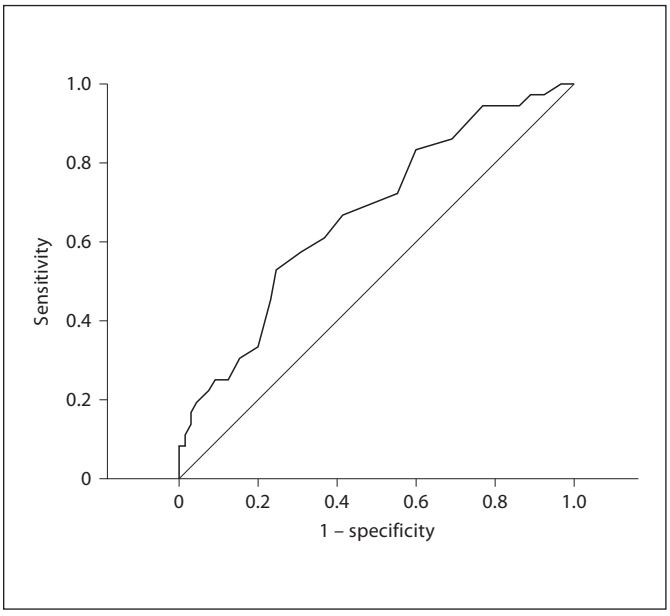

Fig. 3. ROC of pulmonary artery pressure for the prognosis.

Table 3. Results of stepwise multivariate Cox proportional hazards model

Variables	HR	95% CI	p value
FVC, % predicted	0.965	0.949–0.982	<0.001
MPAP, mm Hg	1.064	1.015–1.116	0.010

Adjusted for variables that were significant in univariate analysis (table 2), %FVC and MPAP were independent predictors of 5-year survival. n = 96; DLCO could not be obtained in 5 cases.

and only 6 patients were treated with PH targeted therapy (sildenafil only). The mean MPAP, pulmonary vascular resistance index (PVRI), cardiac index, and PCWP were 19.2 ± 6.5 mm Hg, 285.3 ± 151.0 dyn·s·cm^{-5}·m^2, 3.11 ± 0.60 l·min^{-1}·m^{-2}, and 8.0 ± 3.6 mm Hg, respectively.

A histogram of MPAP is shown in figure 2. Fifteen patients (14.9%) had MPAP >25 mm Hg and only 4 cases were over 35 mm Hg.

The univariate Cox regression model (table 2) demonstrated that MPAP (HR = 1.082; 95% CI 1.035–1.131; p = 0.001) and several variables have a statistically significant impact on survival.

The stepwise multivariate Cox regression model (table 3) demonstrated that MPAP (HR = 1.064; 95% CI 1.015–1.116, p = 0.010) and %FVC (HR = 0.965; 95% CI 0.949–0.982, p < 0.001) have statistically significant impacts on survival.

ROC analysis was performed to obtain an appropriate cutoff value of MPAP. As a result, a value of 20 mm Hg was revealed to be optimal (AUC 0.679, sensitivity 55.0%, specificity 75.4%) (fig. 3).

Table 4 shows the baseline characteristics and physiology of patients using the cutoff point of 20 mm Hg. Thirty-five patients (34.7%) had MPAP >20 mm Hg. Age, %DLCO, Pa_{O_2}, 6-min walk distance (6MWD), and lowest Sp_{O_2} were significantly lower in those with over 20 mm Hg. The rate of smoking history, MMRC, PVRI, and PCWP were significantly higher in those with over 20 mm Hg.

Figure 4 shows a Kaplan-Meier curve that reveals significantly worse survival among patients whose MPAP was >20 mm Hg than among those whose MPAP was ≤20 mm Hg (log-rank test p = 0.001). The median survival estimates were 20.8 and 37.5 months, respectively. In addition, a Kaplan-Meier curve revealed a significant difference in survival between patients whose MPAP was ≤20 mm Hg, 21–25 mm Hg, and >25 mm Hg (log-rank test p = 0.003) (fig. 5).

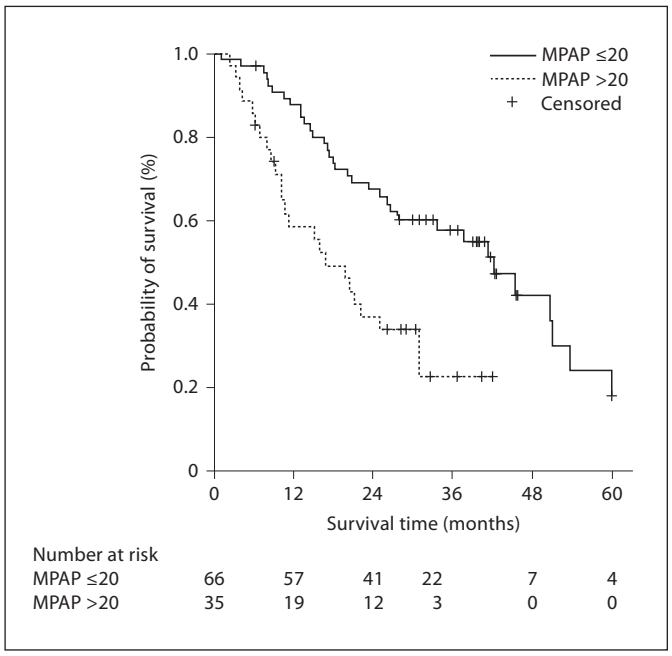

Fig. 4. Kaplan-Meier curves for 5-year survival according to MPAP (p = 0.001). Survival curves were compared with log-rank statistics.

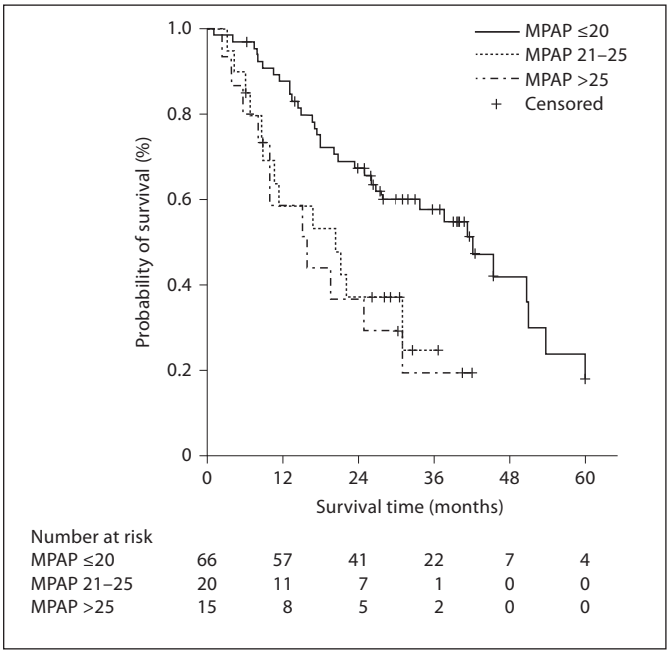

Fig. 5. Kaplan-Meier curves for 5-year survival according to MPAP (p = 0.003). Survival curves were compared with log-rank statistics.

Table 4. Baseline characteristics and physiology of patients with and without high MPAP

Variables	MPAP ≤20 mm Hg (n = 66)	MPAP >20 mm Hg (n = 35)	p value
Sex (M/F)	53/13	32/3	0.145
Age, years	66.6 ± 7.0	63.2 ± 8.3	0.027
BMI	23.1 ± 3.8	24.1 ± 4.6	0.24
Smoking status current/former/never	7/40/19	1/31/3	0.014
FVC, % predicted	71.5 ± 19.7	67.7 ± 20.9	0.373
DLCO, % predicted	52.5 ± 20.5	38.4 ± 13.1	<0.001
PaO_2, mm Hg	83.5 ± 10.0	72.8 ± 12.6	<0.001
MMRC	1.3 ± 0.9	1.9 ± 0.9	0.004
6MWD, m	561.2 ± 150.0	461.2 ± 141.8	0.002
Lowest SpO_2, %	83.8 ± 9.1	75.1 ± 10.6	<0.001
PVRI, dyn·s·cm^{-5}·m^2	225.9 ± 90.7	397.4 ± 177.5	<0.001
Cardiac index, l·min^{-1}·m^{-2}	3.14 ± 0.54	3.06 ± 0.7	0.518
PCWP, mm Hg	6.8 ± 3.3	10.2 ± 3.2	<0.001

Data are presented as means ± SD or numbers. n = 101 except for DLCO (n = 96).

Discussion

This is the first study to confirm by multivariate analysis that a high MPAP at the initial evaluation is an independent predictor of survival in patients with IPF who undergo RHC. In this study, a higher MPAP was an independent prognostic predictor comparable to %FVC, a well-known prognostic factor. The study included patients with milder pulmonary function impairment (mean FVC 70.2%, mean DLCO 47.9%) than subjects of

many previous studies [13, 17, 19], and it excluded patients with left heart failure and those with supplemental oxygen, which may influence hypoxemic vasoconstriction. Therefore, the results are thought to be robust and to demonstrate the importance of PH in IPF at the initial evaluation. The results also support previous reports indicating that PH is not just a result of restrictive impairment in patients with IPF [13, 14, 26].

In advanced patients with IPF who were referred for lung transplantation, PH is reported to be a survival predictor. Lettieri et al. [13] reported that only PH diagnosed by RHC correlated with mortality, and that spirometric measurements did not predict mortality. They included 79 patients with IPF who were listed for lung transplantation. Twenty-five patients (31.6%) met the criteria for PH (MPAP >25 mm Hg), and the mean MPAP was 23.4 mm Hg. Patel et al. [16] found that PH (MPAP >25 mm Hg) was an independent predictor (HR 3.6) in 376 patients with IPF who were referred for lung transplantation. These studies did not include mild cases, so the meaning is different from our cases. However, it is notable that PH is the only prognostic factor in advanced patients with IPF.

On the other hand, Hamada et al. [18] reported the influence of elevated MPAP on the prognosis of 76 IPF patients who were evaluated with RHC in the initial workup. Although they reported that PH defined as MPAP >17 mm Hg was a prognostic factor, DLCO was only one significant parameter when adjusted for certain parameters. The reason for the difference between their study and ours is not apparent. One possibility is a difference in candidates. In their study patients had higher %FVC (76 vs. 70.2%) and there was a lower prevalence of patients whose MPAP was >25 mm Hg (8.1 vs. 14.9%) and a higher rate of patients proved by biopsy (77.4 vs. 41.6%) than in our study. Their cohort may have included milder cases, which might have contributed to the difference in the results.

Recently, Corte et al. [27] reported retrospectively on the prognostic significance of invasive and noninvasive parameters in patients with diffuse fibrotic lung disease and suspected PH. In their study, a raised PVR of >6.23 Wood units was strongly associated with early mortality (OR 1.30; 95% CI 1.11–1.52, p = 0.001) after adjustment for some parameters. Early mortality was not linked to MPAP. In our cases, prognostic early mortality was associated with %FVC and MPAP (data not shown). Their clinical criteria for RHC included echocardiographic right ventricular systolic pressure >40 mm Hg or right ventricular dilation and dyspnea or hypoxemia not explained by the underlying fibrosis. These criteria may have contributed to the difference in results. In fact, our cohort (mean MPAP 19.2 mm Hg, PVRI 285.3 dyn·s·cm^{-5}·m^2, PVR 2.14 Wood units, %FVC 70.2%, and %DLCO 47.9%) was milder than their cohort (mean MPAP 33.5 mm Hg, PVR 5.9 Wood units, %FVC 67.9%, %DLCO 29.6%).

In our initial evaluation for IPF, MPAP >20 mm Hg was revealed to be the optimal cutoff point for predicting the prognosis based on ROC analysis. In the case of PH owing to lung diseases, the optimal cutoff point has not been determined [20]; however, the cutoff point of MPAP >20 mm Hg has been used in COPD. In figure 4, patients with MPAP >20 mm Hg have higher mortality. Additionally, the prognosis seems to be almost the same in patients whose MPAP was 21–25 mm Hg and those whose MPAP was >25 mm Hg (fig. 5). This may suggest that it is a better cutoff point for detecting more patients at risk, who would otherwise not be diagnosed with PH in the present guidelines.

Because no treatment for PH in IPF has been established, a better understanding of the pathogenesis would be meaningful. Previous studies [14, 17, 28–31] have shown the heterogeneity of vascular proliferation in IPF. For example, Judge et al. [30] reported that neovascularization was increased in less fibrotic lesions and decreased in honeycomb lesions in patients with advanced IPF. In addition, it was suggested from another animal model [32] that endothelial apoptosis may be important during early fibrogenesis.

As we showed in table 4, patients with MPAP >20 mm Hg were found to have a higher smoking rate, a lower PaO_2, and a lower SpO_2 during the 6MWT. Recent studies [33, 34] have described the relation between smoking and pulmonary vascular remodeling. Smoking may influence not only parenchymal destruction but also vascular remodeling through various pathways. In addition, it may be speculated that hypoxia induces vascular remodeling through various factors, such as vascular endothelial growth factor and hypoxia-inducible factor 1 alpha [31, 35]. Our results indicate that smoking and a low PaO_2 may play a crucial role in vascular remodeling in mild IPF. Further investigation will be required to determine whether this is the case.

The limitations of this study are as follows. First, the percentage of patients evaluated with biopsy-proven IPF in the previous studies of Lettieri et al. [13] and Hamada et al. [18] was 100 and 74.7%, respectively; however, only 44 (43.6%) patients were diagnosed by surgical lung biopsy in our cases. We suppose our population is closer to

reality because the majority of patients with IPF are diagnosed by clinical criteria in general practice [1]. Secondly, we did not evaluate HRCT findings sufficiently, especially fibrosis and emphysema. Flaherty et al. [4] and Sumikawa et al. [36] reported that the CT fibrotic score was predictive of subsequent mortality. Cottin et al. [37] and Mejia et al. [38] reported the importance of evaluating emphysema. In this study, although we checked the HRCT to diagnose IPF, we did not analyze the relationship between the proportion of fibrosis and emphysema. Further studies are needed to examine this interesting issue. Finally, this is a retrospective study. Collection of additional prospective data is warranted to confirm our findings.

In summary, we demonstrated that higher MPAP and lower %FVC are independent prognostic predictors of IPF. The current results emphasized the importance of evaluating PH for patients with IPF at the initial evaluation. MPAP by RHC is warranted not only for severe IPF patients but also for mild-to-moderate patients with IPF. MPAP >20 mm Hg may be a better cutoff point for detecting more patients at risk among patients with mild IPF.

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Financial Disclosure and Conflicts of Interest

All of the authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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