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A scoring system to predict the elevation of mean pulmonary arterial pressure in idiopathic pulmonary fibrosis

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A simple scoring system comprising three variables can predict the likelihood of elevation of MPAP in IPF http://ow.ly/kZjA30haKvo

ABSTRACT Elevated mean pulmonary arterial pressure (MPAP; $\geqslant$21 mmHg) is sometimes seen in patients with idiopathic pulmonary fibrosis (IPF) and has an adverse impact upon survival. Although early diagnosis is crucial, there is no established screening tool that uses a combination of noninvasive examinations.

We retrospectively analysed IPF patients at initial evaluation from April 2007 to July 2015 and, using logistic regression analysis, created a screening tool to identify elevated MPAP. Internal validation was also assessed for external validity using a bootstrap method.

Using right-heart catheterisation (RHC), elevation of MPAP was determined to be present in 55 out of 273 patients. Multivariate models demonstrated that % predicted diffusing capacity of the lung for carbon monoxide (D_{LCO}) <50%, ratio of pulmonary artery diameter to aorta diameter (PA/Ao) on computed tomography (CT) $\geqslant$0.9 and arterial oxygen tension (P_{aO_2}) <80 Torr were independent predictors. When we assigned a single point to each variable, the prevalence of elevation of MPAP with a score of zero, one, two or three points was 6.7%, 16.0%, 29.1% and 65.4%, respectively. The area under curve (AUC) for the receiver operating characteristic (ROC) curve was good at 0.757 (95% CI 0.682–0.833).

A simple clinical scoring system consisting of % predicted D_{LCO}, PA/Ao ratio on CT and P_{aO_2} can easily predict elevation of MPAP in patients with IPF.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic lung disease of unknown aetiology [1]. Following diagnosis, the median survival time is approximately 2–3 years and treatment options are limited [1]. Pulmonary hypertension (PH), defined as an elevation of resting mean pulmonary arterial pressure (MPAP) to $\geqslant$25 mmHg, is a well-recognised complication in advanced IPF which is associated with higher mortality rates [2–5]. While the upper level of normal for MPAP is 20 mmHg, the significance of MPAP levels between 21 and 24 mmHg remains unclear in terms of their prognostic and therapeutic implications [6, 7]. However, KIMURA et al. [8] have demonstrated that, in patients with IPF, even elevation of MPAP ($\geqslant$21 mmHg) at initial evaluation indicated a higher mortality rate. TERAMACHI et al. [9] have also revealed that MPAP gradually progresses (the annual change in their patients was 1.8 mmHg per year) and that at initial evaluation MPAP was a significant predictor of mortality. Thus, early detection of elevated MPAP ($\geqslant$21 mmHg) is important.

However, the equivocal clinical findings on elevated MPAP in IPF pose a challenge, as symptoms (such as dyspnoea on exertion) are common in both PH and IPF [7]. Thoracic echocardiography is a noninvasive screening tool for PH but it does not show favourable accuracy in IPF [10, 11]. Alternatively, the ratio of pulmonary artery diameter (PA) to ascending aorta diameter (Ao) on computed tomography (CT) of the chest is a useful indicator of PH [11] and is reportedly a predictor of higher mortality [12]. Other noninvasive predictors of PH have been reported; however, they have limited discriminative ability for PH in IPF [10, 13–16]. Thus, there is a need for reliable criteria to determine when right heart catheterisation (RHC) should be performed in suitable patients.

With this in mind, ALKUKHUN et al. [11] have attempted to create a noninvasive screening tool for PH based on the PA/Ao ratio from chest CT in 235 patients with IPF who underwent RHC as part of a lung transplant evaluation. ZISMAN et al. [17] have also proposed a noninvasive screening tool for PH using standard lung function measurements; however, these tools are complicated and difficult to use in clinical practice and the study populations include only advanced patients. Therefore, the aim of the present study is to predict elevated MPAP ($\geqslant$21 mmHg) in patients with IPF at initial evaluation using a combination of noninvasive examinations.

Material and methods

Study subjects

We retrospectively analysed medical records from 302 consecutive patients with IPF who underwent initial systemic evaluation between April 2007 and July 2015 at Tosei General Hospital (Aichi, Japan). The diagnosis of IPF was made according to the 2011 international consensus guidelines. For patients who initially presented before 2010, the diagnoses were confirmed in May 2015 [1]. Of these 302 patients the following were excluded: 18 patients who declined RHC; four patients who had already been prescribed medication for IPF or PH (*i.e.* antifibrotic drugs, corticosteroids, immunosuppressants, or drugs for the treatment of PH), or had already undergone long-term oxygen therapy, who might thus exhibit treatment bias; and seven patients who had a pulmonary arterial wedge pressure (PAWP) of >15 mmHg following RHC, indicative of left-heart disease. Consequently, we examined 273 patients with IPF in a derivation cohort and this study was approved by the Tosei General Hospital institutional review board (IRB number 584). The requirement for informed consent was waived other than the initial informed consent for physical examination as part of regular clinical practice.

Data collection

Clinical data were collected retrospectively by medical chart review. Eligible patients underwent physical examination and assessment of physiological function, exercise capacity (by 6-min walk test (6MWT) and desaturation just after the 6MWT), and RHC at the initial evaluation, as usual for assessment for interstitial pneumonia.

All patients completed pulmonary function tests by spirometry (CHESTAC-55V; Chest, Tokyo, Japan) according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria [18]. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) was also measured (CHESTAC-55V) [19]. The 6MWT was performed according to the ATS/ERS criteria [20] while the RHC procedure was performed according to the most recent international guidelines [6]. A high-resolution computed tomography (HRCT) chest scan, performed within the 3-month window prior to the RHC procedure, was reviewed in a blinded, independent fashion by two of the authors (T. Furukawa and M. Yagi). The diameter of the pulmonary artery (PA) on HRCT was measured at its bifurcation, the largest diameter of the ascending aorta (Ao) was measured at the corresponding level and the PA/Ao ratio was calculated from these measurements. The intra-class correlation coefficient was used to determine the level of agreement between the two readers for the continuous variables of PA, Ao and the PA/Ao ratio. The extent of

fibrosis and of the low attenuation area (LAA) were scored by a thoracic radiologist with 28 years of experience. Combined pulmonary fibrosis and emphysema (CPFE) was defined as having ⩾10% LAA in the upper zone on the chest HRCT (supplementary material).

Statistical analysis

All analyses were performed using IBM SPSS Statistics v. 24 (IBM Corp., Armonk, NY, USA) and R statistical software (The R Project for Statistical Computing, www.r-project.org/). Continuous data were presented as mean±SD or median (range) as appropriate, while categorical variables were reported as frequency (%). Between-group differences were assessed using a two-sided t-test, Mann–Whitney U-test or Chi-squared test as appropriate, while the results of the regression analyses were presented in terms of the estimated odds ratios with corresponding 95% confidence intervals.

Predictor variables that were statistically significant were included in a multiple regression model to determine those that could appropriately predict the elevation of MPAP. The use of predictors as continuous variables showed similar statistical significance both before and after categorisation (supplementary table S1). We believe that categorisation of predictor variables can facilitate the application of the score in daily clinical practice. To determine the threshold of a categorical variable to be included in the score, we divided each continuous variable into a binary variable considering the prior literature, the ROC curve analysis for predicting the elevation of MPAP, and the ease-of-use in daily practice. Finally, we selected a threshold for each predictor variable (data not shown) as follows: P_{aO_2} >80 Torr [8], forced vital capacity (FVC) >75% predicted, D_{LCO} >50% predicted [16, 21], 6-min walk distance (6MWD) >540 m [14], lowest arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) during the 6MWD >80%, PA/Ao ratio ⩾0.9 [12], and estimated right-ventricular systolic pressure (RVSP) using echocardiography >30 mmHg [14, 22]. LAA ⩾10% in the upper zone was taken as being indicative of the presence of CPFE. Multivariable logistic regression analysis was performed using forward model selection to create a model that best predicted MPAP ⩾21 mmHg. To avoid multicollinearity, one part of the highly correlated variables (Pearson's correlation coefficient >0.7) was excluded in the multivariate analysis. The ROC curve was determined to estimate the AUC of the simplified score. The bootstrap method was used to internally validate this score by sampling with replacement for 1000 iterations (p-values <0.05 were considered statistically significant).

Results

A total of 273 patients were enrolled in the study and the overall prevalence of elevated MPAP and PH confirmed by RHC was 20.1% (n=55) and 6.6% (n=18), respectively (figure 1). Patient demographics and other clinical data are given in table 1. In comparison to the lower MPAP group (MPAP <21 mmHg), the higher group (MPAP ⩾21 mmHg) was characterised by lower P_{aO_2}, FVC (% predicted), forced expiratory volume in 1 s (FEV1; % predicted), D_{LCO} (% predicted) and 6MWD, as well as the lowest S_{pO_2} during the 6MWT. Moreover, the higher MPAP group showed a greater extent of LAA, greater presence of CPFE, and greater PA, PA/Ao ratio and estimated RVSP. As there were high degrees of correlation between FVC (% predicted) and FEV1 (% predicted) (Pearson correlation coefficient 0.82, p<0.001) and between PA and the PA/Ao ratio (Pearson correlation coefficient 0.72, p<0.001), we selected FVC (% predicted) and the PA/Ao ratio as candidate variables for multivariate analysis. In the CT findings, the inter-rater reliability of
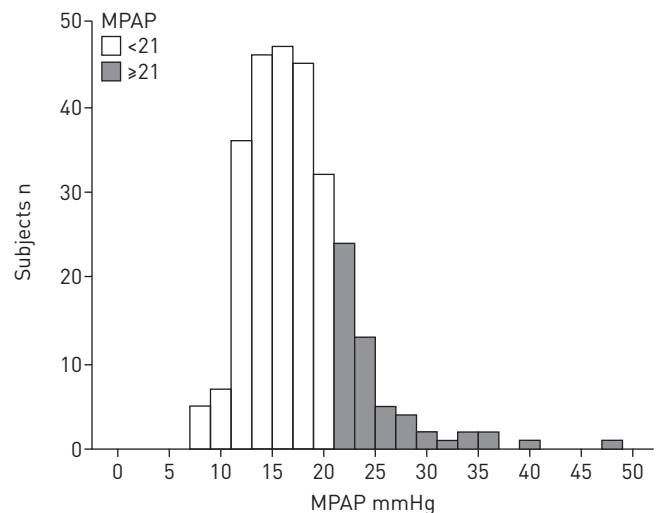

FIGURE 1 Distribution of resting mean pulmonary arterial pressure (MPAP) in the study population that underwent right heart catheterisation. Dark vertical bars indicate elevation of MPAP (⩾21 mmHg).

TABLE 1 Baseline characteristics of the study population

Characteristic	MPAP ⩾21 mmHg	MPAP <21 mmHg	p-value
Subjects[#]	55	218	
Age years	64.5±6.8	66.7±7.8	0.06
Male	44 (80.0)	183 (83.9)	0.49
BMI kg·m^{-2}	24.7±4.0	23.6±3.2	0.05
pack-years	43.1±37.4	34.7±33.5	0.10
mMRC dyspnoea scale			<0.001
Level 0	7	72	
Level 1	21	96	
Level 2	14	37	
Level 3	10	11	
Level 4	3	2	
P_{aO_2} mmHg	74.5±12.1	83.5±11.3	<0.001
BNP pg·mL^{-1}	20.7 (10.8–34.9)	17.2 (9.7–30.9)	0.23
FVC % predicted	75.4±20.8	82±19.2	0.03
FEV1 % predicted	85.4±20.0	94.3±19.9	0.003
FEV1/FVC	85.7±8.8	85.1±7.8	0.60
D_{LCO} % predicted	46.9±18.3	64.3±20.9	<0.001
6MWD m	508±124	585±135	<0.001
Lowest S_{pO_2} %	77.5±10.5	84.3±8.2	<0.001
HRCT findings			
PA mm	28.7±3.6	26.6±3.8	<0.001
Ao mm	32.6±3.6	33.4±3.6	0.11
PA/Ao	0.89±0.12	0.80±0.11	<0.001
Fibrosis %	35.0 (24.2–46.7)	31.7 (22.5–41.7)	0.11
LAA %	1.7 (0.0–11.7)	0.0 (0.0–3.3)	0.02
⩾10% in upper zone	22 (40.0)	54 (24.8)	0.02
⩾25% in upper zone	8 (14.5)	12 (5.5)	0.03
Echocardiograph findings			
Ejection fraction %	0.65±0.12	0.68±0.06	0.14
E/A	0.47±0.43	0.65±0.98	0.18
Estimated RVSP mmHg	29.6±20.6	22.8±16.4	0.01
RHC findings			
MPAP mmHg	24.9±5.3	15.0±2.9	<0.001
PVR Wood units	3.0±1.8	1.7±0.7	<0.001
Cardiac index L·min^{-1}·m^{-2}	3.0±0.6	3.0±0.5	0.96
PAWP mmHg	10.7±3.4	6.6±3.0	<0.001

Data are presented as n, n (%), mean±SD or median (interquartile range), unless otherwise indicated. [#]: the total number of subjects (N) was 273. MPAP: mean pulmonary arterial pressure; BMI: body mass index; mMRC: modified Medical Research Council; P_{aO_2}: arterial oxygen tension; BNP: brain natriuretic peptide; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWD: 6-min walk distance; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; HRCT: high-resolution computed tomography; PA: pulmonary artery diameter; Ao: ascending aorta diameter; LAA: low attenuation area; E: peak velocity flow in early diastole (E-wave); A: peak velocity flow in late diastole (A-wave); RVSP: right-ventricular systolic pressure; RHC: right heart catheterisation; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure.

TABLE 2 Multivariate logistic regression analysis for elevation of mean pulmonary arterial pressure (MPAP)

Variables[#]	OR (95% CI)	p-value	Points
D_{LCO} (% predicted) <50%	3.624 (1.763–7.449)	<0.001	1
P_{aO_2} <80 Torr	2.653 (1.242–5.665)	0.012	1
PA/Ao >0.9	2.245 (1.083–4.656)	0.030	1

[#]: C-index 0.772 (95% CI 0.699–0.845; p<0.001). D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{aO_2}: arterial oxygen tension; PA: pulmonary artery diameter; Ao: ascending aorta diameter.

PA, Ao and the PA/Ao ratio was almost perfect, with discrimination of greater than 0.9 in the PA/Ao ratio being substantial (supplementary table S2).

Development of the risk tool

Based on multivariable analysis (table 2), the candidate variables found to be significantly associated with the elevation of MPAP were D_{LCO} (% predicted) $\leqslant$50% (*versus* >50%), PA/Ao ratio $\geqslant$0.9 (*versus* <0.9) and P_{aO_2} <80 Torr (*versus* $\geqslant$80 Torr) (C-index 0.772, 95% CI 0.699–0.845; p<0.001). Based on the β-regression coefficients of the covariates in the final multivariable models, we assigned a score of one point to each covariate depending on the proximity of the coefficient to the nearest whole number, as this would facilitate easy interpretation by clinicians. The individual covariate scores were totalled to obtain an individual risk score ranging from zero to three.

Accuracy and validation of the risk tool

We created a cumulative graph (figure 2) and plotted the risk scores using the ROC curve (figure 3). In the simplified scores, a score of three points indicated an elevation of MPAP by about 65% and was associated with an approximately 26-fold probability of elevated MPAP (table 3). A score of zero had a specificity of 54.2% and a sensitivity of 13.2%, with a positive-predictive value (PPV) of 6.7% for the elevation of MPAP. By contrast, a score of three had a specificity of 95.8% and a sensitivity of 32.1%, with a PPV of 65.4% for the elevation of MPAP (table 4). The AUC of the model was good (0.757, 95% CI 0.682–0.833) and the Hosmer–Lemeshow goodness-of-fit test for the derivation cohort was nonsignificant (p=0.58), indicating that the model had a good fit. After internal validation by the bootstrap method, the AUC of the simplified score was 0.756 (95% CI 0.687–0.825).

Discussion

We developed a simple, noninvasive screening tool based on P_{aO_2}, D_{LCO} (% predicted) and the PA/Ao ratio derived from HRCT. This tool might be useful in clinical settings because it allows simple, noninvasive selection of patients with elevated MPAP, in whom RHC should be performed, especially those achieving three points in the present scoring system.

A few screening tools have already been developed and ZISMAN *et al.* [17, 23] have developed and validated equation 1, which considers room air resting pulse oximetry and the FVC/D_{LCO} ratio, and demonstrated its relatively high negative predictive value (NPV) for PH in advanced IPF patients.

$$MPAP = -11.9 + 0.272 \times S_{pO_2} + 0.0659 \times (100 - S_{pO_2})^2 + 3.06 \times (\%FVC/\%D_{LCO}) \qquad (1)$$

Furthermore, ALKUKHUN *et al.* [11] have attempted to create a noninvasive screening tool for PH in IPF as part of the evaluation for lung transplantation; however, they have concluded that noninvasive tests, alone or in combination, are not accurate enough for PH screening in IPF patients. In comparison with these

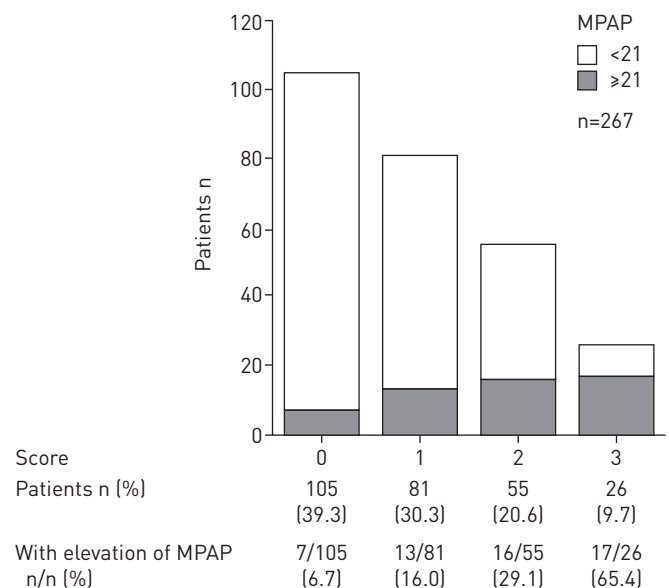| Score	0	1	2	3
Patients n (%)	105 (39.3)	81 (30.3)	55 (20.6)	26 (9.7)
With elevation of MPAP n/n (%)	7/105 (6.7)	13/81 (16.0)	16/55 (29.1)	17/26 (65.4)

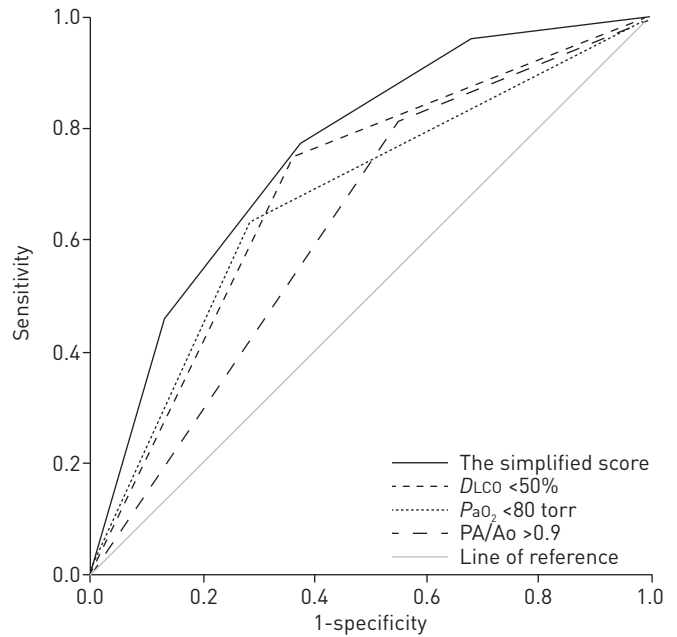FIGURE 2 Simplified scores for elevation of mean pulmonary arterial pressure (MPAP).

FIGURE 3 Receiver operating characteristic (ROC) curve for the simplified score predicting for elevation of mean pulmonary arterial pressure (MPAP).

tests, the screening tool presented in this study is simpler, easier to score without special calculations and more easily applied in clinical settings, as each variable is essential for the clinical assessment of IPF.

Regarding the significance of elevated MPAP ($\geqslant$21 mmHg), KIMURA et al. [8] have demonstrated a similar prognosis with MPAP between 21 and 24 mmHg and MPAP >25 mmHg in IPF patients. YAGI et al. [12] have also demonstrated that elevated MPAP is associated with a poorer prognosis in IPF patients. Elevated MPAP has also been indicated to affect survival in interstitial pneumonias other than IPF [24, 25]. Given these findings, detection of elevated MPAP is an important prognostic indicator. Moreover, IPF is known as a heterogeneous disease [1] and elevated MPAP could be used as a specific spectrum to indicate a poorer prognosis. Its early detection would therefore facilitate future research into its clinical significance and that of early interventions.

We have demonstrated that the prevalence of elevated MPAP for scores of zero, one, two and three points is 6.7%, 16.0%, 29.1% and 65.4%, respectively. Moreover, the group with a score of three points has a specificity of 95.8% for elevated MPAP and, as such, it would be reasonable perform a RHC in patients with such a score. The probability of elevated MPAP in a patient with a score of two points is about 30% and indications for RHC should thus be based on patient preference. We have also shown that there is little value in performing RHC in patients with score of zero because this score has a PPV of only 6.7% for elevation of MPAP. As such, in our cohort, this combination of noninvasive examinations provides for easy selection of patients for RHC.

The development of PH in IPF is caused mainly by chronic hypoxaemic vasoconstriction and destruction of the vascular bed by progressive fibrosis [4], and, although initially reversible, these mechanisms can eventually cause irreversible vascular remodelling. A reduced D_{LCO} (% predicted) measurement, which is reflective of fibrosis, destruction of the vascular bed and perfusion inhomogeneity [26], is well recognised to be associated with a higher mortality rate and the presence of PH in IPF [7, 13, 15–17, 21–23]. In advanced IPF, the optimal cut-off value for predicting PH is reportedly 30% to 45% [15, 16, 21, 27]. As

TABLE 3 Logistic regression analysis for elevation of mean pulmonary arterial pressure (MPAP)

Scores n	OR (95% CI)	p-value
0	Reference	
1	2.676 (1.015–7.057)	0.047
2	5.744 (2.194–15.039)	<0.001
3	26.444 (8.681–80.556)	<0.001

TABLE 4 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for elevation of mean pulmonary arterial pressure

Scores n	Sensitivity %	Specificity %	PPV %	NPV %
0	13.2	54.2	6.7	71.6
1	24.5	68.2	16.0	78.5
2	30.2	81.8	29.1	82.5
3	32.1	95.8	65.4	85.1

such, given we were attempting to predict elevated MPAP at initial evaluation, a value of 50% was selected in consideration of ease-of-use in clinical settings.

A lower PaO$_2$ measurement at rest is also reportedly related to PH in IPF but the optimal cut-off value is unknown [8, 11, 28]. In the present study, we set the cut-off value as 80 Torr (under the normal limit) based on calculations from the ROC analysis. Moreover, PaO$_2$ <80 Torr has been reported as a significant predictor of mortality in IPF patients, giving this value some validity [29].

As for the PA/Ao ratio in IPF, YAGI et al. [12] recently demonstrated that a PA/Ao ratio ⩾0.9 was a predictor for elevated MPAP, while ALKUKHUN et al. [11] demonstrated (in an evaluation for lung transplantation) that a PA/Ao ratio ⩾1.1 was a predictor for PH. Moreover, the PA/Ao ratio was reportedly demonstrated to be a predictor of higher mortality and it is thus an important indicator. In the present study, we aimed to predict elevated MPAP at initial evaluation and so we adopted 0.9 as a reference value.

Our findings differed from previous reports that have evaluated PH in IPF. Echocardiography remains the most widely used noninvasive diagnostic tool for the assessment of PH [7]. Shorter distances and greater desaturation in the 6MWT are reportedly also predictive of underlying PH [16]. However, in the present study, these aspects showed no predictive value of importance. Earlier studies have reported that the accuracy of echocardiography is low [7, 10, 14] and our results are consistent with these previous findings. Another reason for the differences observed is due to patient selection. Our entire study cohort consisted of patients who had not received any treatment for IPF or PH at initial evaluation, whereas the previous literature examined patients with advanced IPF.

The present study has its limitations as, even though the analysis examines internal validation, it was performed in a single centre with patients of a single race. Thus, the results might not be applicable to other general populations and external validation is needed. Moreover, we excluded patients with PAWP >15 mmHg under RHC and we could therefore assume that the scoring system might not perform well in real-world cohorts including such patients. It should be noted, however, that similar findings were obtained when such patients were added to the original cohort (data not shown). Furthermore, the present study was affected by selection bias, as the subjects were treatment-free patients at the time of initial evaluation, which was likely representative of patients on the milder side of the disease spectrum compared to those evaluated in the previous literature.

The latest guidelines show that currently there is no specific therapy for PH associated with lung diseases [7] and no established therapy for patients with elevated MPAP. Further study on when and for whom treatment should be started will be needed. Despite these limitations, this study was the largest single series in IPF with all measurements recorded using RHC, even at initial evaluation, and it presented a means of early detection of elevated MPAP without invasive examination.

We conclude that this simple clinical scoring system comprising DLCO (% predicted), PA/Ao ratio on HRCT scan and PaO$_2$ is able to predict elevated MPAP in patients with IPF. Further multicentre, international studies are necessary.

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