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Validation of a Method To Screen for Pulmonary Hypertension in Advanced Idiopathic Pulmonary Fibrosis*

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Abstract

Background—We have developed a method to screen for pulmonary hypertension (PH) in idiopathic pulmonary fibrosis (IPF) patients, based on a formula to predict mean pulmonary artery pressure (MPAP) from standard lung function measurements. The objective of this study was to validate this method in a separate group of IPF patients.

Methods—Cross-sectional study of 60 IPF patients from two institutions. The accuracy of the MPAP estimation was assessed by examining the correlation between the predicted and measured MPAPs and the magnitude of the estimation error. The discriminatory ability of the method for PH was assessed using the area under the receiver operating characteristic curve (AUC).

Results—There was strong correlation in the expected direction between the predicted and measured MPAPs ($r = 0.72$; $p < 0.0001$). The estimated MPAP was within 5 mm Hg of the measured MPAP 72% of the time. The AUC for predicting PH was 0.85, and did not differ by institution. A formula-predicted MPAP > 21 mm Hg was associated with a sensitivity, specificity, positive predictive value, and negative predictive value of 95%, 58%, 51%, and 96%, respectively, for PH defined as MPAP from right-heart catheterization > 25 mm Hg.

Conclusions—A prediction formula for MPAP using standard lung function measurements can be used to screen for PH in IPF patients.

Keywords

idiopathic pulmonary fibrosis; prediction; pulmonary fibrosis; pulmonary hypertension

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Pulmonary hypertension (PH) frequently complicates advanced idiopathic pulmonary fibrosis (IPF) and is associated with poor outcome.^{1–7} Currently, right-heart catheterization (RHC) is the only accepted method for the diagnosis of PH in patients with IPF. However, RHC is invasive and expensive. Although echocardiography and CT-determined main pulmonary artery diameter are commonly used tests to screen for PH in patients with IPF, they are not reliable.^{4,8,9} Reliable, noninvasive approaches to the diagnosis of PH in patients with IPF would improve patient safety, reduce costs, and enable the appropriate timing of RHC.

We recently demonstrated that the ratio of the FVC percentage of predicted to diffusing capacity of the lung for carbon monoxide (D_{LCO}) percentage of predicted and room air resting pulse oximetry (Sp_{O_2}) data can be combined in a linear regression formula to screen for PH in patients with IPF.⁴ It was shown that a cutoff of 25 mm Hg for the formula-estimated mean pulmonary artery pressure (MPAP) had sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for PH (defined as mean pulmonary artery pressure [MPAP] from RHC > 25 mm Hg) of 71%, 81%, 71%, and 81%, respectively. By selecting a lower cutoff of 21 mm Hg for the formula-estimated MPAP, we maximized sensitivity (100%) for PH (defined as MPAP from RHC > 25 mm Hg) with the least compromise in specificity (40%).⁴ The performance of the formula was assessed by bootstrap techniques; however, internal validation does not guarantee adequate performance in other populations.^{10,11} Hence, independent external validation is essential before recommendations can be made for adoption in clinical practice.^{12,13} Accordingly, the aim of this study was to validate the PH screening formula in an external population of IPF patients.

MATERIALS AND METHODS

Validation Sample

We reviewed the medical records of all IPF patients from the Inova Fairfax Hospital between July 1997 and February 2007 and from University of California, Los Angeles (UCLA) Medical Center between July 2006 (following the close of the derivation study⁴) and June 2007. Hence, the group of patients in this study is totally separate from that used to develop the formula.⁴ The Inova Fairfax Hospital and UCLA institutional review boards approved the study. All patients met accepted diagnostic criteria for IPF, and the majority (71%) had histopathologic evidence of usual interstitial pneumonia.¹⁴ One hundred thirty-two IPF patients were candidates for inclusion in this study. To be included in the study, participants had to have had RHC and have pulmonary function test (PFT) and Sp_{O_2} data while breathing room air within 3 months of the RHC. All RHCs were performed as part of standard lung transplant evaluation. Patients were excluded for the following reasons: (1) missing data (46 patients), and (2) PFT or Sp_{O_2} not done within 3 months of RHC (26 patients). Sixty patients met the entry criteria and comprised the validation cohort (Inova Fairfax Hospital, 35 patients; UCLA, 25 patients).

Measurements

We defined PH as resting MPAP from RHC > 25 mm Hg.¹⁵ Pulmonary artery occlusion pressure < 15 mm Hg and pulmonary vascular resistance > 3 Wood units were not required to define PH because these measurements do not provide prognostic information above and beyond MPAP in IPF patients.^{1,7} Hence, we selected MPAP > 25 mm Hg from RHC as the outcome to screen for with our method and later confirm with RHC (when the rest of the hemodynamic variables would become available). Standard methodology was used for PFTs and pulse oximetry.^{16,17} After at least 5 min of rest, Sp_{O_2} was measured on room air. The equations of Crapo et al¹⁶ were used to calculate predicted FVC values. The equations of Crapo and Morris¹⁷ were used to calculate predicted D_{LCO} values. To assess the impact of alternate predicted values on the discriminatory capacity of the method, we tested additional equations

for predicted FVC¹⁸ and D_{LCO}.^{19,20} The following equation, derived by our group,⁴ was used to calculate predicted MPAP (in millimeters of mercury):

$$\text{MPAP} = -11.9 + 0.272 \times \text{SpO}_2 + 0.0659 \times (100 - \text{SpO}_2)^2 + 3.06 \times (\text{percentage of predicted FVC / percentage of predicted DLCO}).$$

Statistical Analysis

Our objectives were to test the utility of the MPAP estimation formula by assessing both the accuracy of the MPAP prediction and the reliability of the PH prediction. First, the quality of the MPAP prediction was assessed by examining the percentage of MPAP estimates that fell within 5 and 10 mm Hg of the MPAP measured by directly RHC. This was also examined separately in the UCLA and Inova Fairfax Hospital samples. The Pearson correlation coefficient between the predicted MPAP and RHC-measured MPAP was examined. Second, the discriminatory ability of the PH-prediction method was assessed using the area under the receiver operating characteristic curve (AUC).^{21,22} The AUC was also examined separately in the UCLA and Inova Fairfax Hospital samples, and we tested for a difference in the two AUC figures using the method published by Hanley and McNeil.²¹ All tests were two tailed, and p values < 0.05 were required for statistical significance. All statistical analysis was performed using statistical software (SAS version 9.1; SAS Institute; Cary, NC; and MedCalc for Windows, version 9.2.0.0; MedCalc Software; Mariakerke, Belgium).

RESULTS

Comparisons of Patients in the Validation and Excluded Cohorts

Patients in the validation sample (n = 60) were younger and had more advanced pulmonary disease than those excluded from the study (n = 72) but were similar to the rest of the cohort with respect to gender, race, and SpO₂ (Table 1). This is consistent with the fact that RHC is offered primarily to patients with advanced disease undergoing lung transplant evaluation.

Accuracy of Predicted MPAP

There was a strong correlation in the expected direction between the predicted MPAP and the RHC-measured MPAP ($r = 0.72$, $p < 0.0001$; Fig 1). For the entire cohort, MPAP prediction was accurate (within 10 mm Hg of RHC measurement) in 93% (95% confidence interval [CI], 84 to 97%) of the patients. Moreover, 72% (95% CI, 60 to 82%) of the predicted MPAPs were within 5 mm Hg of RHC-measured MPAP. The accuracy of the estimated MPAP in the validation sets from Inova Fairfax Hospital and UCLA were similar.

Performance Characteristics of the PH Predictor

The performance of the PH-prediction formula was excellent and very similar to that in the original report (Table 2).⁴ The NPV of the PH predictor is high: 83% of patients with a predicted MPAP ≤ 25 mm Hg did not have PH (defined as MPAP from RHC > 25 mm Hg), while 96% of patients with predicted MPAP ≤ 21 mm Hg did not have PH (defined as MPAP from RHC > 25 mm Hg). Varying the cutoff point of the predicted MPAP changed the sensitivity, specificity, PPV, and NPV of the prediction formula. At one extreme, for a formula-predicted MPAP ≤ 19 mm Hg, the NPV was 100% and the PPV was 39% (for PH defined as MPAP from RHC > 25 mm Hg); at the other extreme, for a formula-predicted MPAP ≤ 35 mm Hg, NPV was 73% and the PPV was 100% (for PH defined as MPAP from RHC > 25 mm Hg). The NPV remained uniformly high (≥ 73%) for various scenarios.

Discrimination is a measurement of the ability to distinguish between patients who do and do not have the outcome of interest, in this case PH.²³ The discriminatory ability of the PH-prediction method was assessed using the AUC (Fig 2). A value of 1.0 indicates that the model perfectly discriminates between patients with different outcomes, while a value of 0.5 indicates that the model contains no predictive information.²³ The discriminatory ability of the PH-prediction method was excellent reflected by an AUC of 0.85 (95% CI, 0.73 to 0.93), which was similar to the AUC in the derivation cohort (0.83).⁴ Furthermore, the discriminatory properties of the PH predictor in the validation sets from Inova Fairfax Hospital and UCLA patients were similar (AUC = 0.82 and AUC = 0.80, respectively; $p = 0.4$). The AUCs were virtually identical when alternate prediction equations were used to calculate predicted FVC and D_{LCO} values (data not shown).

DISCUSSION

We validated a recently developed clinical prediction formula for MPAP in advanced IPF patients. This instrument could serve as a screening method for PH in these patients. The prediction method uses a parsimonious set of readily available physiologic variables (SpO_2 , percentage of predicted FVC, and percentage of predicted D_{LCO}) to identify individuals with a low likelihood of PH, thereby reducing the need for RHC. A screening test will of necessity have an increased ability to avoid missing a true case (sensitivity) at the expense of an increase in the number of individuals without the disease who will erroneously be picked up by the screening program (specificity).²⁴ Thus, altering the criterion of positivity will influence both the sensitivity and specificity of the test. Using a cutoff of 21 mm Hg from the formula (as proposed in the derivation study),⁴ there was high sensitivity and high NPV (95% and 96%, respectively) for PH (defined as MPAP from RHC > 25 mm Hg). Hence, if the formula generates a value ≤ 21 mm Hg, only 5% of IPF patients with PH (defined as MPAP from RHC > 25 mm Hg) will be “missed.” The lower the cutoff of the formula-predicted MPAP, the less the likelihood that the patient will have PH. For instance, if the formula generates a value ≤ 19 mm Hg, no IPF patient with PH (defined as MPAP from RHC > 25 mm Hg) will be missed. Importantly, the high NPV of the method is not because of low prevalence of PH in our study sample. In fact, PH was present in 32% of the sample, a figure comparable to that reported by others.^{1,4,6,7,25}

Using a cutoff of 21 mm Hg from the formula, however, the specificity and PPV of the method for PH are low: only 51% of patients with a formula-predicted MPAP > 21 mm Hg will have PH (defined as MPAP from RHC > 25 mm Hg). However, it is generally accepted in clinical medicine that a screening test meant to be used on all comers needs to have high sensitivity and NPV, and is typically followed by a more specific confirmatory test with high PPV (*eg*, following a positive antinuclear antibody test result for systemic lupus erythematosus with the anti-DNA antibody test).²⁴ If the new PH predictor is used as a screening test, then confirmatory testing (RHC) will be required in patients with a formula-predicted MPAP > 21 mm Hg in order to confirm and quantify the presence of PH and determine other important hemodynamic variables (pulmonary artery occlusion pressure, cardiac output, pulmonary vascular resistance). However, given that confirmatory RHC offers risk and there are no proven therapies for PH in IPF, clinicians may prefer to miss some PH cases rather than offer more RHC; hence, a higher cutoff (*eg*, formula-predicted MPAP > 25 mm Hg) could be selected.

We expect that this instrument will be used in clinical practice to identify IPF patients who need not undergo invasive assessment for PH. Clinicians can be confident that patients with low values of formula-predicted MPAP are unlikely to have PH by RHC. Furthermore, since outside of lung transplant evaluation, RHCs are not routinely performed in IPF patients, our method could be utilized as an exclusion criterion (formula-predicted MPAP ≤ 21 mm Hg) in clinical trials evaluating pulmonary vasodilator therapies in IPF patients with PH. The use of

our method would not only avoid unnecessary procedural risks to potential research subjects but would enable substantial cost savings. Based on the prevalence of PH in IPF (approximately 30%),^{1,4,6,7,25} three research candidates would need to undergo RHC in order to identify one candidate with PH suitable for inclusion in such trials.

Other methods to predict prevalent PH in IPF are not as reliable. We have shown that echocardiography-estimated right ventricular systolic pressure predicted PH poorly in IPF patients (76% sensitivity, 38% specificity, 56% PPV, and 60% NPV).⁴ In a previous study,⁸ echocardiography predicted PH in patients with various ILD with 85% sensitivity, 17% specificity, 60% PPV, and 44% NPV. Elevated serum level of brain natriuretic peptide is associated with moderate-to-severe PH (MPAP $\geq$ 35 mm Hg) with PPV of 73% and NPV of 92%.²⁵ However, the sensitivity of brain natriuretic peptide to detect mild-to-moderate PH (MPAP of 26 to 34 mm Hg) is unknown, and this method has not been validated. The need for supplemental oxygen together with a $D_{LCO} < 40\%$ also identified the presence of PH in IPF patients.¹ In that study,¹ PH was present in 31.6% of patients; however, the predicted prevalence of PH was 15.2%, suggesting that a prediction based on D_{LCO} alone and the need for supplemental oxygen (yes/no) would not identify 50% of the PH cases. By employing the extent of desaturation rather than the need for oxygen and the FVC/ D_{LCO} ratio in place of D_{LCO} , the prediction method described here increases both sensitivity and NPV.

There are some limitations of this study. All patients in the validation sample underwent evaluation for lung transplantation, reflecting the presence of younger patients with more advanced IPF. Therefore, our results may not apply to the general population of IPF patients (spectrum bias). Unfortunately, RHC measurements are not routinely available from less advanced IPF patients because there are no indications to catheterize these patients. However, several studies^{1-5,25,26} have shown that PH is more prevalent in patients with severe IPF; hence, this population is the one for whom identification of PH is more critical. Younger patients may have more occult collagen vascular disease with autoimmune vasculopathy rather than the hypoxic vasoconstriction or destruction of vessels that may play a larger role in older IPF patients. However, given that the mean age difference between our study and excluded cohorts was relatively small, we do not believe that age differences biased our findings. Since the RHC in this study were not recorded with exercise, we could not assess for exercise-induced PH. However, the implications and clinical importance of exercise-induced PH are unknown. The cross-sectional nature of the study should also be noted. A low formula-predicted MPAP during a single evaluation does not rule out the possibility of PH developing in the future. However, the formula-predicted MPAP can be followed on a serial basis because it is computed using clinical variables that are routinely measured.

This study is important for three reasons. First, it establishes the empirical validity of a new, easy-to-use, clinical screening method for PH in advanced IPF patients.¹¹ Second, this study shows that the formula can be applied in advanced IPF populations from different geographic areas/medical centers, that is, the method is transportable.^{11,12,23} Third, a cutoff of formula-predicted of 21 mm Hg has high sensitivity and NPV for PH (defined as MPAP from RHC $>$ 25 mm Hg), so as to justify withholding RHC from patients predicted least likely to have PH (formula-predicted MPAP $\leq$ 21 mm Hg). This would prevent unnecessary risk, discomfort, and cost to this group of patients.

In conclusion, the recently developed PH screening method in IPF is valid and transportable with a high NPV and good discriminatory ability in patients with IPF. The use of this screening method will prevent unnecessary RHC.

Abbreviations

AUC, area under the receiver operating characteristic curve
 CI, confidence interval
 DL_{CO}, diffusing capacity of the lung for carbon monoxide
 IPF, idiopathic pulmonary fibrosis
 MPAP, Mean pulmonary artery pressure
 NPV, negative predictive value
 PFT, pulmonary function test
 PH, Pulmonary hypertension
 PPV, positive predictive value
 RHC, right-heart catheterization
 Sp_{O2}, resting room air pulse oximetry
 UCLA, University of California, Los Angeles

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REFERENCES

1. Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006;129:746–752. [PubMed: 16537877]
2. Nadrous HF, Pellikka PA, Krowka MJ, et al. The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis. *Chest* 2005;128:2393–2399. [PubMed: 16236900]
3. Weitzenblum E, Ehrhart M, Rasaholinjanahary J, et al. Pulmonary hemodynamics in idiopathic pulmonary fibrosis and other interstitial pulmonary diseases. *Respiration* 1983;44:118–127. [PubMed: 6836187]
4. Zisman DA, Ross DJ, Belperio JA, et al. Prediction of pulmonary hypertension in idiopathic pulmonary fibrosis. *Respir Med* 2007;101:2153–2159. [PubMed: 17604151]
5. Hamada K, Nagai S, Tanaka S, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. *Chest* 2007;131:650–656. [PubMed: 17317730]
6. Patel NM, Lederer DJ, Borczuk AC, et al. Pulmonary hypertension in idiopathic pulmonary fibrosis. *Chest* 2007;132:998–1006. [PubMed: 17873194]
7. Nathan SD, Noble PW, Tudor RM. Idiopathic pulmonary fibrosis and pulmonary hypertension: connecting the dots. *Am J Respir Crit Care Med* 2007;175:875–880. [PubMed: 17255562]
8. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003;167:735–740. [PubMed: 12480614]
9. Zisman DA, Karlamangla AS, Ross DJ, et al. High-resolution chest computed tomography findings do not predict the presence of pulmonary hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2007;132:773–779. [PubMed: 17573485]
10. Bleeker SE, Moll HA, Steyerberg EW, et al. External validation is necessary in prediction research: a clinical example. *J Clin Epidemiol* 2003;56:826–832. [PubMed: 14505766]

11. Wasson JH, Sox HC, Neff RK, et al. Clinical prediction rules: application and methodological standards. *N Engl J Med* 1985;313:793–799. [PubMed: 3897864]
12. Stolwijk AM, Straatman H, Zielhuis GA, et al. External validation of prognostic models for ongoing pregnancy after *in-vitro* fertilization. *Hum Reprod* 1998;13:3542–3549. [PubMed: 9886547]
13. Stolwijk AM, Zielhuis GA, Hamilton CJ, et al. Prognostic models for the probability of achieving an ongoing pregnancy after *in-vitro* fertilization and the importance of testing their predictive value. *Hum Reprod* 1996;11:2298–2303. [PubMed: 8943544]
14. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment; international consensus statement. *Am J Respir Crit Care Med* 2000;161:646–664. [PubMed: 10673212]
15. Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. *Ann Intern Med* 1987;107:216–223. [PubMed: 3605900]
16. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–664. [PubMed: 7271065]
17. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981;123:185–189. [PubMed: 7235357]
18. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187. [PubMed: 9872837]
19. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. *Am J Respir Crit Care Med* 1996;153:656–664. [PubMed: 8564114]
20. Miller A, Thornton JC, Warshaw R, et al. Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state. *Am Rev Respir Dis* 1983;127:270–277. [PubMed: 6830050]
21. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–843. [PubMed: 6878708]
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36. [PubMed: 7063747]
23. Justice AC, Covinsky KE, Berlin JA. Assessing the generalizability of prognostic information. *Ann Intern Med* 1999;130:515–524. [PubMed: 10075620]
24. Dawson, B.; Trapp, RG. Basic and clinical biostatistics. Vol. 3rd ed. New York, NY: McGraw-Hill; 2001. p. 274
25. Leuchte HH, Neurohr C, Baumgartner R, et al. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med* 2004;170:360–365. [PubMed: 15087298]
26. Nathan SD, Ahmad S, Shlobin OA, et al. Pulmonary hypertension and pulmonary function testing in idiopathic pulmonary fibrosis. *Chest* 2007;131:657–663. [PubMed: 17356077]

FIGURE 1.
Relationship between predicted MPAP and RHC-measured MPAP ($r = 0.72$, $p < 0.0001$).

FIGURE 2. Receiver operating characteristic analysis of predicted MPAP vs RHC-measured MPAP in 60 patients with IPF. AUC = 0.85 (95% CI, 0.73 to 0.93).

Table 1

Descriptive Statistics for Major Characteristics*

Characteristics	Validation Sample (n = 60)	Excluded (n = 72)	p Value [†]
Age, yr	62.6 (8.0)	65.8 (10.6)	0.03
Male gender	73.0	62.8	0.16
Race	0.12		
Non-Hispanic white	75.0	79.0	
Hispanic white	6.0	13.2	
Other [‡]	19.0	7.8	
FVC, L	2.2 (0.7)	2.5 (0.8)	0.03
FVC, % predicted	54.8 (19.9)	64.3 (15.8)	< 0.01
DLCO, mL/mm Hg/min	9.0 (3.6)	11.1 (4.8)	< 0.01
DLCO, % predicted	34.03 (12.8)	46.8 (20.2)	< 0.01
Spo ₂ , %	92.7 (4.7)	93.7 (4.6)	0.23
MPAP, mm Hg	23.5 (7.8)	24.2 (9.5) [§]	0.72

* Data are presented as mean (SD) or %. Age and gender were available in 66 of 72 patients. Race was available in 66 of 72 patients. FVC absolute and percentage of predicted values were available in 68 of 72 patients. DLCO absolute and percentage of predicted values were available in 62 of 72 patients. Spo₂ values were available in 64 of 72 patients. MPAP values were available in 26 of 72 patients.

[†] We compared the variables of interest using standard tests for comparing means (Student *t* test), medians (Wilcoxon rank-sum test), and proportions (χ^2 test or Fisher exact test if cell sizes were small).

[‡] Includes Asian and non-Hispanic black.

[§] These 26 patients had RHC data but were excluded because their PFTs or measurement of Spo₂ were not done within 3 months of RHC.

Table 2

Performance Characteristics of the Method in Establishing or Excluding a Diagnosis of PH Defined as MPAP From RHC > 25 mm Hg

Criterion	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %
Formula-predicted MPAP > 19 mm Hg	100 (66–100)	25 (13–41)	39 (13–41)	100 (66–100)
Formula-predicted MPAP > 21 mm Hg				
Validation	95 (74–99)	58 (41–73)	51 (35–70)	96 (78–100)
Derivation, % [†]	100	40	50	100
Formula-predicted MPAP > 25 mm Hg				
Validation	63 (38–84)	85 (70–94)	67 (36–86)	83 (63–89)
Derivation, % [†]	71	81	71	81
Formula-predicted MPAP > 35 mm Hg	21 (6–46)	100 (91–100)	100 (22–99)	73 (60–82)

* PH was considered to be present when MPAP by RHC was > 25 mm Hg.

[†] For comparison purposes, the performance of the predictor in the original derivation cohort is also listed.⁴