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Clinical Risk Factors and Prognostic Model for Primary Graft Dysfunction after Lung Transplantation in Patients with Pulmonary Hypertension

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Abstract

Rationale: Pulmonary hypertension from pulmonary arterial hypertension or parenchymal lung disease is associated with an increased risk for primary graft dysfunction after lung transplantation.

Objective: We evaluated the clinical determinants of severe primary graft dysfunction in pulmonary hypertension and developed and validated a prognostic model.

Methods: We conducted a retrospective cohort study of patients in the multicenter Lung Transplant Outcomes Group with pulmonary hypertension at transplant listing. Severe primary graft dysfunction was defined as $Pa_{O_2}/FI_{O_2} \leq 200$ with allograft infiltrates at 48 or 72 hours after transplantation. Donor, recipient, and operative characteristics were evaluated in a multivariable explanatory model. A prognostic model derived using donor and recipient characteristics was then validated in a separate cohort.

Results: In the explanatory model of 826 patients with pulmonary hypertension, donor tobacco smoke exposure, higher recipient body mass index, female sex, listing mean pulmonary artery pressure, right atrial pressure and creatinine at transplant, cardiopulmonary bypass use, transfusion volume, and reperfusion fraction of inspired oxygen were associated with primary graft dysfunction. Donor obesity was associated with a lower risk for primary graft dysfunction. Using a 20% threshold for elevated risk, the prognostic model had good negative predictive value in both derivation and validation cohorts (89.1% [95% confidence interval, 85.3–92.8] and 83.3% [95% confidence interval, 78.5–88.2], respectively), but low positive predictive value.

Conclusions: Several recipient, donor, and operative characteristics were associated with severe primary graft dysfunction in patients with pulmonary hypertension, including several risk factors not identified in the overall transplant population. A prognostic model with donor and recipient clinical risk factors alone had low positive predictive value, but high negative predictive value, to rule out high risk for primary graft dysfunction.

Keywords: primary graft dysfunction; lung transplantation; pulmonary hypertension

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Lung transplantation is a therapeutic option for patients with pulmonary hypertension (PH) from parenchymal lung disease or pulmonary arterial hypertension (PAH) refractory to medical therapy. Unfortunately, severe pretransplant PH and PAH are associated with a two- to threefold increased risk for primary graft dysfunction (PGD), a form of acute lung injury that occurs within 72 hours of transplantation (1–3). The most severe form of PGD, grade 3 PGD, is associated with a longer duration of mechanical ventilation, increased intensive care unit length of stay, and higher 30-day mortality (1, 4, 5). Grade 3 PGD also increases the risk for bronchiolitis obliterans syndrome (5, 6).

Despite the link between PH and PGD, little is known about the clinical risk factors associated with the development of PGD within this specific patient population. Better understanding of these clinical risk factors may affect perioperative management and provide therapeutic targets in the future. We aimed to identify donor, recipient, and operative characteristics associated with the development of PGD among patients with PH and to develop a prognostic model for clinical use.

Some of the results of this study were presented in abstract and poster form at the 2015 International Society for Heart and Lung Transplantation conference, April 15–18, Nice, France (7) and American Thoracic Society International Conference, May 15–20, Denver, Colorado (8).

Methods

Population

We included subjects enrolled in the ongoing, multicenter prospective Lung Transplant Outcomes Group cohort who underwent lung transplantation between March 1, 2002, and October 31, 2012 (2, 4, 9). The study sample consisted of transplanted subjects with a mean pulmonary artery pressure (mPAP) $\geq$25 mm Hg, measured by right heart catheterization at the time of listing for lung transplantation. A small number of subjects (11%) did not have preoperative right heart catheterization, and therefore perioperative hemodynamic measurements were substituted. The institutional review boards at each site approved our study, and written informed consent was obtained from each subject.

Outcome Definition

PGD grade was assessed prospectively, using the International Society for Heart and Lung Transplantation criteria, defined by the Pa_{O_2}/FI_{O_2} ratio and the presence of infiltrates within the allograft or allografts (1). Two physicians blinded to the clinical information independently interpreted each center's chest radiographs with adjudication of conflicts by a third physician (kappa for consensus on subject-level grade 3 PGD classification = 0.95). The primary outcome was grade 3 PGD at 48 or 72 hours after reperfusion (herein referred to as PGD), which has been validated and used in previous observational studies (2, 4, 9).

Candidate Prognostic Factors

Potential risk factors for PGD were selected *a priori* on the basis of previous studies or biological plausibility (2, 3, 6, 9–12). Body mass index (BMI) was calculated from measured height and weight and was assessed for inclusion as a linear variable and as a categorical variable. Race/ethnicity was grouped into three categories: Caucasian, African American, or other (including Hispanic and Asian Pacific Islander). Mechanism of donor death was categorized into head trauma, anoxia, stroke, and other, including blunt trauma and suicide. Pretransplant recipient diagnosis was categorized into five groups: chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis, PAH, and other, including sarcoidosis and bronchiolitis obliterans syndrome.

Statistical Analysis

Continuous variables were summarized with mean and standard deviation or median and interquartile range, where appropriate. Categorical variables were summarized by frequency and percentages. Differences in candidate prognostic variables between those with and without PGD were assessed with unpaired *t*, Mann-Whitney, or chi-squared tests. As with many prognostic studies based on clinical risk factors generated through regular clinical care, some subjects had missing values for one or more variables. Through the method of chained equations, we created 20 imputed datasets using multinomial, ordinal, and linear regression models for missing data (13–15). After the imputation process, out-of-range values were truncated to fall within the appropriate clinical range.

We evaluated all clinically meaningful donor, recipient, and operative candidate predictors based on our examination of their distribution and by preliminary assessments of their association with PGD. Donor, recipient, and operative risk factors with a *P* value $\leq$0.20 on bivariate logistic regression were considered for inclusion into the multivariable explanatory model for PGD. We defined *a priori* the potential interaction between donor and recipient BMI. Collinearity was assessed using Pearson and Spearman correlation coefficients for continuous measures and by cross-classification for categorical factors. To generate a parsimonious multivariable model, covariates that were not confounders based on a less than 20% change in odds ratio (OR) were eliminated by purposeful backward selection. Because subsequent models were nested, the global fit of each model was assessed using the likelihood ratio test. To account for relatedness among subjects at each center, a second explanatory model was created using conditional logistic regression stratified by transplant center. Confidence intervals for point estimates considered the additional variance arising from the imputation of missing values. We used marginal standardization to estimate average risk for PGD from the final explanatory logistic regression model for selected categorical variables and for the continuous variable mPAP.

For the testing and validation of a prognostic model (better suited for clinical use at the bedside), participants were randomly assigned to the derivation or validation cohort in a 1:1 ratio. Model generation in the derivation cohort proceeded using donor and recipient risk factors and the same methods as outlined earlier. The estimates of the predictors identified in the derivation cohort were used to calculate the predicted risk for PGD in the validation cohort. Performance characteristics of the model were assessed. We also evaluated the discriminative ability of the model by using the c-statistic. Overall point estimate and confidence intervals for the performance characteristics were generated using Rubin's method (16). Reporting of the prognostic model follows the items listed in transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

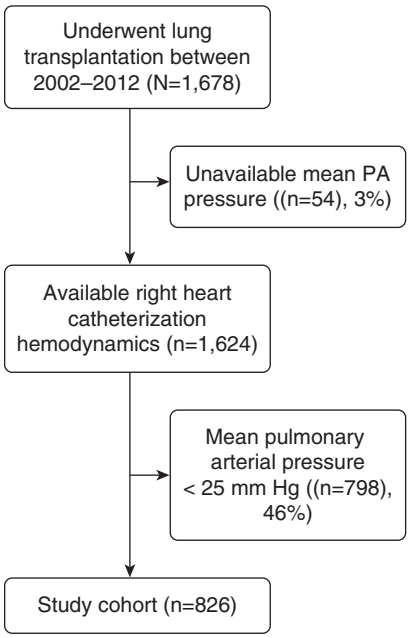

Figure 1. Study cohort. PA = pulmonary artery.

(TRIPOD) (*see* Table E3 in the online supplement) (17).

A P value <0.05 was used to indicate statistical significance. Statistical analyses were performed using STATA software version 12.0 through 14.1 (StataCorp LP, College Station, TX).

Results

Subjects

During the study period, 1,678 subjects underwent lung transplantation in the Lung Transplant Outcomes Group (Figure 1). Of those, 1,624 (97%) had available hemodynamic data. Compared with those in our overall cohort, the 3% with missing hemodynamics were younger (40.4 ± 15.0 vs. 54.5 ± 12.7), were more likely to undergo transplantation for cystic fibrosis (42.6% vs. 12.6%), and had a higher incidence of PGD (31.5% vs. 16.1%). A total of 826 subjects fulfilled criteria for pulmonary hypertension with mPAP ⩾25 mm Hg on right heart catheterization and made up the study sample. The degree of PH was less severe in subjects transplanted for cystic fibrosis, COPD, or ILD compared with subjects with sarcoidosis or PAH (Figure 2).

A total of 157 subjects with PH (19.0%) fulfilled criteria for PGD (Table 1). Lower donor BMI and donor smoking exposure were associated with the development of PGD. Recipient BMI, mPAP, and pulmonary vascular resistance were higher in those with PGD. The majority of our cohort underwent bilateral lung transplantation without a significant difference in transplant type based on PGD status (111 [71.2%] with PGD vs. 482 [72.2%] without PGD; $P = 0.52$). A higher proportion of subjects with PGD received cardiopulmonary bypass (CPB) during the transplant procedure (106 [68.9%] vs. 263 [39.8%]; $P < 0.001$). The PGD group received a greater volume of packed red blood cell (pRBC) transfusion ($P = 0.005$).

Explanatory Model

Using multivariable logistic regression in the 826 recipients with PH, donor tobacco smoke exposure, recipient female sex, higher recipient BMI, listing mPAP, right atrial pressure (RAP), and creatinine at time of transplant were associated with PGD (Table 2). Perioperative CPB use, pRBC transfusion volume, and reperfusion FI_{O_2} also increased PGD risk (Table 2). Donor obesity was associated with a lower risk for PGD (OR, 0.52; 95% confidence interval [CI], 0.28–0.95; $P = 0.03$). Standardized predicted risks of PGD are displayed in Figures 3 and 4. There is a positive correlation between mPAP and the standardized risk for PGD (Figure 3).

Because pretransplant diagnosis was collinear with mPAP ($r = 0.44$; $P < 0.001$) and CPB (Chi-square $P < 0.001$), it could not be included in the main model with these other variables. Therefore, we created another model and substituted pretransplant diagnosis for mPAP and

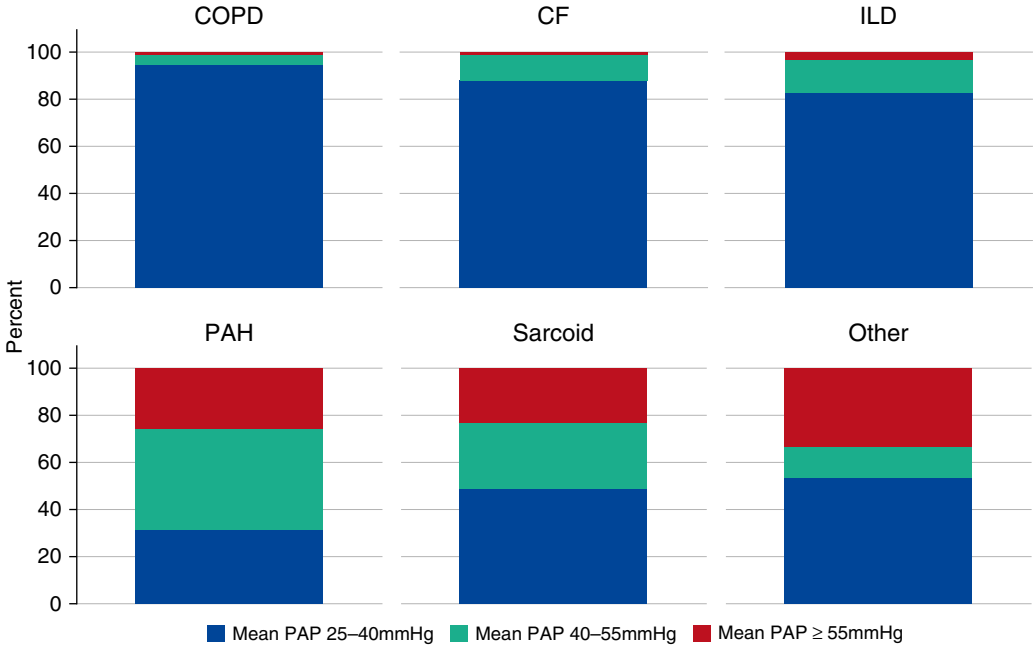

Figure 2. Percentage of patients with mild, moderate, and severe pulmonary hypertension, stratified by diagnosis. CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; PAP = pulmonary artery pressure.

Table 1. Patient characteristics by PGD status*

	PGD (*N* = 157)	No PGD (*N* = 669)	*P* Value
Donor variables			
Age, yr	34.6 (14.1) (n = 149)	34.9 (13.7) (n = 643)	0.78
Sex, female n (%)	60 (38.5) (n = 156)	232 (34.8) (n = 665)	0.39
Race, n (%)	n = 155	n = 668	0.73
Caucasian	102 (65.8)	426 (64.4)	
African American	29 (18.7)	142 (21.5)	
Other	24 (15.5)	94 (14.2)	
BMI category, kg/m^2, n (%)	n = 149	n = 643	0.02
<18.5	7 (4.7)	15 (2.3)	
18.5-24.9	80 (53.7)	284 (44.2)	
25-29.9	44 (29.5)	213 (33.1)	
⩾30	18 (12.1)	131 (20.4)	
Mechanism of death, n (%)	n = 156	n = 661	0.74
Head trauma	58 (37.2)	243 (36.8)	
Anoxia	13 (8.3)	75 (11.4)	
Stroke	62 (39.7)	252 (38.1)	
Other	23 (14.7)	91 (13.8)	
Tobacco smoke exposure, n (%)	64 (45.5) (n = 141)	188 (30.4) (n = 618)	0.001
Recipient variables			
Age, yr	52.6 (12.7)	53.5 (12.9)	0.45
Sex, female n (%)	74 (47.1)	266 (39.8)	0.09
Race, n (%)		n = 668	0.11
Caucasian	118 (75.2)	550 (82.3)	
African American	28 (17.8)	80 (12.0)	
Other	11 (7.0)	38 (5.7)	
BMI category, kg/m^2, n (%)	n = 156	n = 658	0.18
<18.5	9 (5.8)	57 (8.7)	
18.5-24.9	52 (33.3)	248 (37.7)	
25-29.9	55 (35.3)	229 (34.8)	
⩾30	40 (25.6)	124 (18.8)	
Pulmonary diagnosis, n (%)			<0.001
COPD	42 (26.8)	266 (39.8)	
Interstitial lung disease	61 (38.9)	215 (32.1)	
Cystic fibrosis	9 (5.7)	91 (13.6)	
PAH	18 (11.5)	36 (5.4)	
Other†	27 (17.2)	61 (9.1)	
Creatinine, mg/dl	0.9 [0.7–1.1]	0.9 [0.7–1.0]	0.10
Hemodynamics			
Right atrial pressure, mm Hg	14 [10–19]	12 [8–16]	0.002
Mean PA pressure, mm Hg	34 [29–43]	30 [27–35]	<0.001
PCWP, mm Hg	12 [9–16] (n = 142)	13 [10–16] (n = 597)	0.20
Cardiac output, L/min	5.1 [4.2–5.9] (n = 127)	5.2 [4.4–6.1] (n = 548)	0.22
Cardiac index, L/min/m^2	2.8 [2.4–3.2] (n = 126)	2.6 [2.2–3.1] (n = 540)	0.06
PVR, Wood units	3.9 [2.6–6.2] (n = 124)	3.3 [2.5–4.6] (n = 539)	0.005
Operative variables			
Transplant type, n (%)			0.52
Single	39 (25.0)	171 (25.6)	
Bilateral	111 (71.2)	482 (72.2)	
Heart/lung	6 (3.9)	15 (2.3)	
Ischemic time, min	321 [270–388]	320 [261–389]	0.65
CPB use, n (%)	106 (68.9)	263 (39.8)	<0.001
pRBC volume >1L, n (%)	55 (35.0)	156 (23.3)	0.005
Reperfusion FI_{O_2}, %	88 [44–98] (n = 92)	50 [25–96] (n = 424)	<0.001
Reperfusion FI_{O_2} category, n (%)	n = 92	n = 424	<0.001
21–40%	21 (22.8)	183 (43.2)	
>40%	71 (77.2)	241 (56.8)	

Definition of abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PGD = primary graft dysfunction; PVR = pulmonary vascular resistance; pRBC = packed red blood cell.

*Continuous variables are presented as mean (standard deviation), median [interquartile range], or n (%)

†Other diagnoses includes sarcoidosis, bronchiolitis obliterans syndrome, and other diagnoses.

CPB. In this model, when compared with COPD, the diagnosis of ILD (OR, 2.03; 95% CI, 1.25–3.40; $P = 0.004$), PAH (OR, 3.14; 95% CI, 1.53–6.43; $P = 0.002$), and sarcoidosis, bronchiolitis obliterans syndrome, and other diagnosis (OR, 2.93; 95% CI, 1.57–5.47; $P = 0.001$) had an increased risk of PGD.

In the conditional logistic regression model conditioned on transplant center, donor tobacco smoke exposure, higher recipient BMI, RAP, and creatinine were significantly associated with PGD. Although the point estimates for female sex, mPAP, pRBC transfusion volume, and reperfusion FI_{O_2} were similar to the explanatory model not conditioned on transplant center (Table E1), the *P* values for these variables increased in the conditional model grouped by center, likely because of the smaller sample size (one center dropped out of the analysis because there were no PGD cases).

Prognostic Model

Because the risk factors in the conditional logistic regression model conditioned on transplant center were similar to the overall explanatory model, and because we were interested in a generalizable rather than a localized (transplant-center-specific) model, we elected to randomly generate a derivation and validation cohort for the prognostic model (instead of grouping by center). A predicted probability cut-off of 20% was used, as it optimized the sensitivity and specificity of the model and because it approximated the overall PGD incidence. Selecting a threshold that approximates the incidence of the outcome increases the net benefit of a prognostic model (18). Table E2 shows the donor, recipient, and operative characteristics of the derivation and validation cohorts. The derivation and validation cohorts were similar, other than there being somewhat more obese patients in the validation cohort. In the derivation cohort, donor tobacco smoke exposure, female sex, recipient obesity, and higher mPAP were independently associated with PGD (Table 3). Donor obesity had a borderline protective effect on PGD (OR, 0.42; 95% CI, 0.17–1.03; $P = 0.058$). In the derivation cohort, the model had a sensitivity to predict PGD of 57.1% (95% CI, 44.1–70.2%), specificity of 74.5% (95% CI, 69.8–79.3%), positive predictive value of 31.9% (95% CI, 23.6–40.3%), and negative

Table 2. Multivariate explanatory model for PGD

Variable	OR	95% CI	*P* value
Donor tobacco smoke exposure	2.07	1.37–3.13	0.001
Donor body mass index, kg/m^2			
<18.5	2.22	0.84–5.87	0.11
18.5–24.9	Ref	Ref	–
25–29.9	0.74	0.48–1.16	0.19
⩾30	0.52	0.28–0.95	0.03
Recipient female sex	1.52	1.02–2.28	0.04
Recipient body mass index, per 1 kg/m^2 increase	1.05	1.01–1.09	0.02
Right atrial pressure, per 1 mm Hg increase	1.03	1.01–1.06	0.01
Mean PA pressure, per 10 mm Hg increase	1.17	1.00–1.37	0.05
Creatinine, per 1 mg/dL increase	1.57	1.21–2.20	0.009
Cardiopulmonary bypass use	2.52	1.63–3.89	<0.001
Packed red blood cell volume			
None	Ref	Ref	—
<1 L	1.25	0.77–2.04	0.36
⩾1 L	1.69	1.00–2.86	0.05
Reperfusion F_{IO_2}, per 10 mm Hg increase	1.14	1.05–1.24	0.001

Definition of abbreviations: CI = confidence interval; OR = odds ratio; PA = pulmonary artery; PGD = primary graft dysfunction; Ref = reference.

predictive value (NPV) of 89.1% (95% CI, 85.3–92.8%) (Table 4). In the validation cohort, the model had a sensitivity of 46.5% (95% CI, 33.8–59.2%), specificity of 69.3% (95% CI, 64.0–74.6%), positive predictive value of 28.2% (95% CI, 19.9–36.5%), and NPV of 83.3% (95% CI, 78.5–88.2%) (Table 4). Receiver operating characteristic curves (ROC) for both the derivation and validation cohorts are displayed in Figure 5. The closed red circle on the validation ROC curve corresponds to the sensitivity and false-positive rate (calculated as one minus the specificity) for the threshold for PGD of 20% that was used to generate the prognostic model.

Discussion

In a large, prospective cohort study, we have identified several donor, recipient, and operative characteristics associated with the development of grade 3 PGD in subjects with PH, a population known to be at higher risk of PGD (9, 11). This is one of the first studies, to our knowledge, that specifically evaluated the risk factors for grade 3 PGD in this high-risk population. Although some risk factors, including mPAP, diagnosis of PAH, recipient BMI, donor smoking, pRBC, reperfusion F_{IO_2}, and CPB use, were similar to those for PGD in the overall lung transplant population, it is unclear whether the mechanism by which these factors modulate the risk of PGD is similar in those with and without PH. Furthermore, we have detected several risk factors for PGD not previously identified, including RAP and creatinine.

Higher pretransplant RAP and creatinine at the time of transplant were significantly associated with PGD and may reflect decompensated left ventricular (LV) and/or right ventricular (RV) systolic or diastolic function with poor tissue perfusion. The fact that they were not collinear ($r = 0.04$) and were both significantly associated with PGD in a multivariable model suggests each might reflect a different component of decompensated heart failure, including hypervolemia and impaired cardiac output.

Both transplant diagnosis and mPAP were significantly associated with PGD; it is difficult to conclude whether it is the underlying lung disease diagnosis itself or the level of PA pressure elevation that is causal, as these variables were collinear. Pathologic changes in the pulmonary vasculature vary on the basis of the underlying lung disease, and therefore may explain the variability of PGD based on diagnosis (19–22). For instance, in COPD, vasculature remodelling appears to be mediated by tobacco smoke exposure and hypoxic vasoconstriction and results in the development of neointimal lesions with proliferating smooth muscle-like cells in pulmonary arteries (20–22). These lesions differ from the plexiform lesions in PAH characterized by phenotypically altered and proliferating endothelial-like cells. The mechanism by which ILD leads to PH is unknown and may even vary by ILD type, but may involve oxidant–antioxidant imbalance, the endothelin system, or autoimmunity (19). The effect of these differences in mechanisms and pathologic changes on subsequent PGD after transplant is unknown, but may involve different local effects on pulmonary vasculature compliance and resistance and RV and LV function. Alternatively, mPAP elevation itself, regardless of

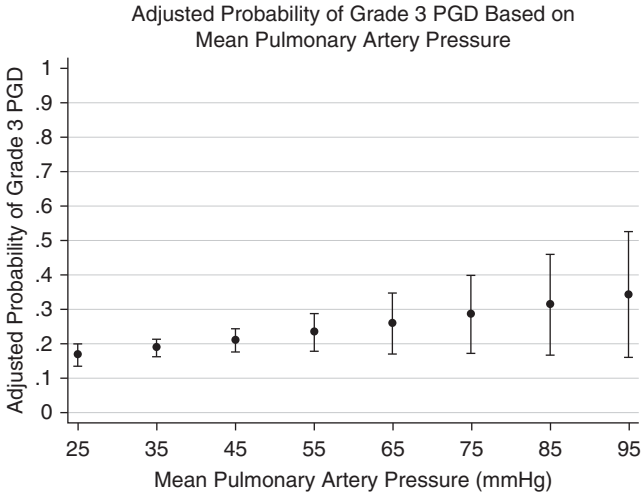

Figure 3. Adjusted probability of grade 3 primary graft dysfunction (PGD) based on mean pulmonary artery pressure. Adjusted for donor tobacco smoke exposure, donor body mass index, recipient female sex, recipient body mass index, right atrial pressure, mean pulmonary artery pressure, creatinine, cardiopulmonary bypass use, packed red blood cell transfusion volume, and reperfusion fraction of inspired oxygen.

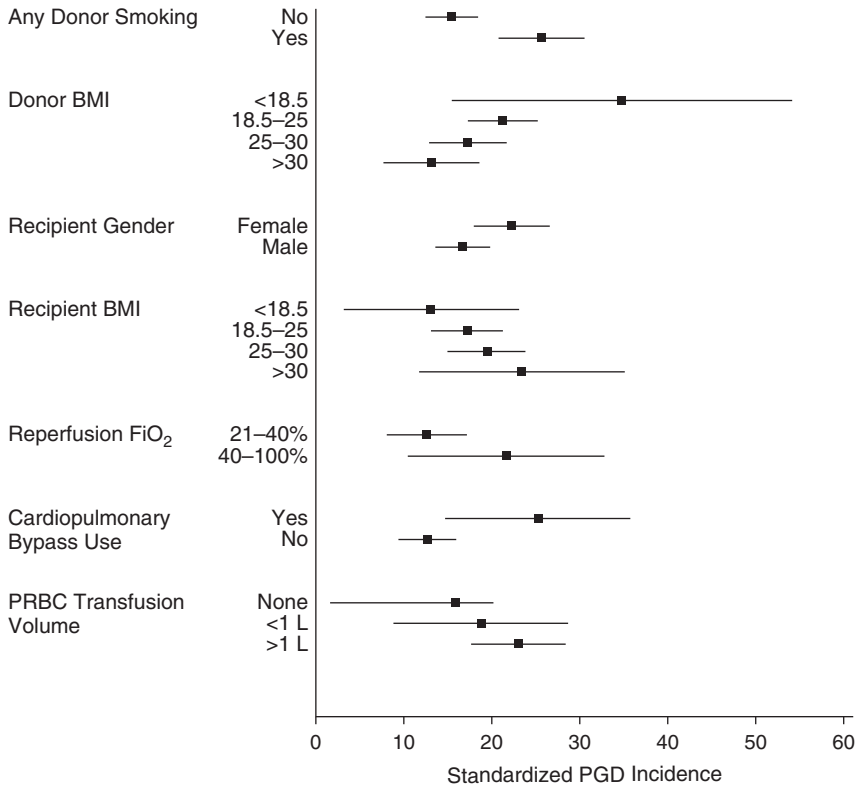

Figure 4. Adjusted probability of grade 3 primary graft dysfunction for donor, recipient, and perioperative covariates. BMI = body mass index; PGD = primary graft dysfunction; PRBC = packed red blood cell. Adjusted for donor tobacco smoke exposure, donor body mass index, recipient female sex, recipient body mass index, right atrial pressure, mean pulmonary artery pressure, creatinine, cardiopulmonary bypass use, packed red blood cell transfusion volume, reperfusion fraction of inspired oxygen.

underlying etiology, may increase the risk for PGD. This is supported by the exposure–response relationship we observed between mPAP and the standardized risk for PGD (Figure 3).

Elevated mPAP may increase the risk for PGD through its effect on RV and LV morphology and function. Preserved RV function, as measured by speckle-tracking echocardiography, was associated with the development of PGD, possibly because of increased shear stress on pulmonary vasculature in the transplanted allograft (23). RV pressure and volume overload is associated with LV atrophy and impaired relaxation (24, 25). We have previously shown that impaired LV relaxation is associated with the development of PGD (26). Lastly, although the mechanism by which PH and underlying lung disease increase the risk for PGD may involve local effects on pulmonary arterial compliance and RV and LV morphology, they may also do so by provoking systemic effects including circulation of pro-inflammatory cytokines and activation of innate immunity. Interleukin 6 is associated with mortality in PAH and with PGD (27, 28). Circulating pentraxin 3 is integral in angiogenesis and innate immunity and is elevated in both PAH and PGD (29–31). Further studies are necessary to understand the mechanism or mechanisms by which PH increases the risk for PGD.

Higher recipient BMI was associated with PGD risk similar to previous studies (2, 12). In our study, BMI expressed as a continuous variable was associated with PGD, whereas BMI categorized according to World Health Organization cutpoints was not. This difference might reflect that very high (or low) BMI values are driving the association, and this truncation of the extreme measures dampens the association. Alternatively, BMI categories according to World Health Organization cutpoints for BMI categories may not accurately reflect obesity as it relates to PGD risk. We have previously shown that BMI $\geqslant$30 kg/m^2 was a poor predictor of total body fat-defined obesity (32). Alternate approaches to modeling BMI, especially with large numbers of patients across the range of BMI values, might lead to improved understanding of the relationship between recipient BMI and PGD. In addition, alternative measures of adiposity, including computed tomography scan, dual-energy X-ray absorptiometry, and biomarkers, may improve PGD risk assessment (12, 32). Although recipient obesity was associated with an increased risk for PGD in our study, donor obesity was associated with a decreased risk for PGD. The association of donor obesity and recipient PGD was not modified by recipient BMI (test for interaction, $P = 0.46$). Previous studies have documented a lower risk for other forms of acute lung injury, including acute respiratory

Table 3. Multivariable prognostic model for PGD in derivation cohort

Variable	OR	95% CI	*P* value
Donor tobacco smoke exposure	2.19	1.23–3.91	0.008
Donor body mass index, kg/m^2			
<18.5	1.30	0.25–6.79	0.75
18.5–24.9	Ref	Ref	—
25–29.9	0.53	0.28–1.03	0.06
⩾30	0.42	0.17–1.03	0.06
Recipient female sex	1.92	1.09–3.39	0.02
Recipient body mass index, kg/m^2			
<18.5	1.72	0.55–6.01	0.33
18.5–24.9	Ref	Ref	—
25–29.9	1.66	0.74–2.92	0.27
⩾30	2.52	0.96–5.10	0.06
Mean PA pressure, per 10 mm Hg increase	1.48	1.19–1.83	<0.001

Definition of abbreviations: CI = confidence interval; OR = odds ratio; PA = pulmonary artery; PGD = primary graft dysfunction; Ref = reference.

Table 4. Prognostic model performance characteristics

	Derivation *(N = 413)*	Validation *(N = 413)*
Receiver operator characteristic	72.4%	61.3%
Sensitivity	57.1% (44.1–70.2%)	46.5% (33.8–59.2%)
Specificity	74.5% (69.8–79.3%)	69.3% (64.0–74.6%)
Positive predictive value	31.9% (23.6–40.3%)	28.2% (19.9–36.5%)
Negative predictive value	89.1% (85.3–92.8%)	83.3% (78.5–88.2%)
Prevalence of PGD in the sample	17.4%	20.6%

Definition of abbreviation: PGD = primary graft dysfunction.

distress syndrome, among obese patients (33). One theory suggests obesity induces low-grade inflammation that triggers anti-inflammatory, antioxidant, and other mechanisms that protect the lung against subsequent insults (33–35). Donor obesity might activate anti-inflammatory mechanisms that blunt the subsequent injuries induced by ischemia-reperfusion injury at the time of transplant. Further studies are necessary to better understand this relationship.

Donor tobacco smoke exposure was associated with a twofold increase in the odds of developing PGD. Previous studies have shown that donor smoking also increases the risk for PGD and mortality in the overall transplant population (2, 6). The exact mechanism by which tobacco exposure increases the risk for PGD in the overall population remains unknown; however, it may include increased oxidative stress and epithelial injury (36, 37). Both PH and donor smoking exposure have been associated with increased lipid peroxidation products, suggesting the potential for overlapping mechanisms involving oxidative stress (37, 38). Despite the link between donor tobacco exposure and increased PGD and mortality in the overall lung transplant population, the increased risk associated with accepting a lung from such donor is less than the risk of death while remaining on the transplant list, given the limited donor pool (39). It is unknown whether the same conclusion is true for those with PH.

Several operative variables were associated with PGD among those with PH, including CPB use, larger pRBC transfusion volume, and higher reperfusion F_{IO_2}. Although these risk factors overlap with those in the overall transplant population (2, 6), these risk factors may warrant distinct consideration in those with PH. Larger pRBC transfusion volumes may be especially problematic in those with RV or LV dysfunction resulting from PH. Higher F_{IO_2} requirements among those with PH undergoing sequential bilateral lung transplantation may confound reperfusion F_{IO_2}. Hyperoxia may also increase LV filling pressures (40) and exacerbate LV diastolic dysfunction among those with PH. Future studies evaluating these perioperative risk factors in PH may translate into changes in perioperative management.

The ability to detect those at high risk for PGD would better inform patients of their posttransplant mortality, identify subjects for inclusion into research studies, and assist in allocating already scarce organs. Important considerations for developing a prognostic model have been recently discussed (41). Assessment of our prognostic model's performance (Table 4) in both the derivation and validation cohorts yielded moderate sensitivity and specificity with high NPV. Although the NPV of our model is high, the prevalence of PGD at most centers is only 20–30%, which may limit the clinical utility of the model. However, it may help identify a cohort with lower PGD risk for future clinical trial design. The relatively low positive predictive value of our model highlights the difficulty of identifying high-risk recipients and suggests clinical risk factors alone are inadequate to identify high-risk subjects with PH. Further evaluation is warranted to determine whether inclusion of biomarkers into the model would improve clinical utility.

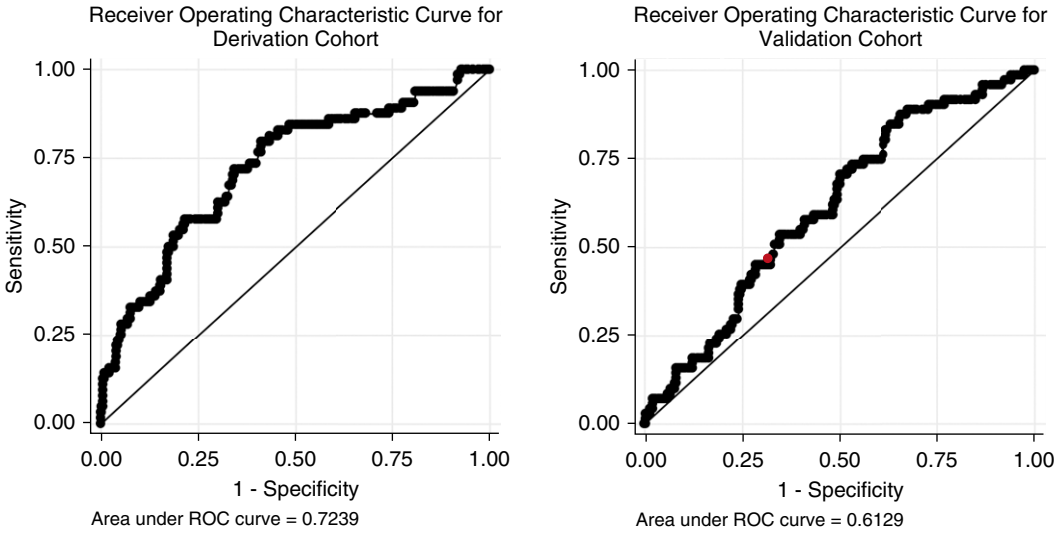

Figure 5. Receiver operating characteristic (ROC) curves for grade 3 primary graft dysfunction. The *red closed circle* on the validation ROC curve reflects the sensitivity and false-positive rate (calculated as one minus the specificity) for the threshold for primary graft dysfunction of 0.20 that was used for prognostic model generation.

Our study has several limitations. Although we have previously published data on risk factors for PGD using the Lung Transplant Outcomes Group database (2), this study focuses on risk factors in patients with PH at especially high risk for PGD. Given the observational nature of our study, we were unable to fully exclude other disease processes with similar radiographic appearances as PGD including diffuse pneumonia or significant pulmonary contusion. However, this definition has been used in other large center trials and has previously demonstrated good construct validity (1, 2, 4, 6). Despite extensive and standardized variable collection, unmeasured confounding is possible. Specifically, detailed information regarding perioperative management, including fluid management, use of pulmonary vasodilators, and emergent versus planned CPB use, were unavailable and represent potential confounders. Preoperative echocardiographic data were not available, but should be incorporated into future trials evaluating the mechanistic link among PH, RV and LV dysfunction, and PGD. There remains a potential for selection bias, as a small number of subjects (54 of 1,678) were excluded because of missing hemodynamics, although this only represents 3% of the overall cohort.

In conclusion, we identified several risk factors associated with the development of grade 3 PGD among those with PH that should be the focus of future mechanistic studies. We demonstrated that a prognostic model for grade 3 PGD in those with PH based on clinical risk factors alone had high NPV, which identifies low-risk transplant recipients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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