Clinical Risk Factors for Primary Graft Dysfunction after Lung Transplantation

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***Rationale*: Primary graft dysfunction (PGD) is the main cause of early morbidity and mortality after lung transplantation. Previous studies have yielded conflicting results for PGD risk factors.**

***Objectives*: We sought to identify donor, recipient, and perioperative risk factors for PGD.**

***Methods*: We performed a 10-center prospective cohort study enrolled between March 2002 and December 2010 (the Lung Transplant Outcomes Group). The primary outcome was International Society for Heart and Lung Transplantation grade 3 PGD at 48 or 72 hours post-transplant. The association of potential risk factors with PGD was analyzed using multivariable conditional logistic regression.**

***Measurements and Main Results*: A total of 1,255 patients from 10 centers were enrolled; 211 subjects (16.8%) developed grade 3 PGD. In multivariable models, independent risk factors for PGD were any history of donor smoking (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.2–2.6; $P = 0.002$); $F_{I_{O_2}}$ during allograft reperfusion (OR, 1.1 per 10% increase in $F_{I_{O_2}}$; 95% CI, 1.0–1.2; $P = 0.01$); single lung transplant (OR, 2; 95% CI, 1.2–3.3; $P = 0.008$); use of cardiopulmonary bypass (OR, 3.4; 95% CI, 2.2–5.3; $P < 0.001$); overweight (OR, 1.8; 95% CI, 1.2–2.7; $P = 0.01$) and obese (OR, 2.3; 95% CI, 1.3–3.9; $P = 0.004$) recipient body mass index; preoperative sarcoidosis (OR, 2.5; 95% CI, 1.1–5.6; $P = 0.03$) or pulmonary arterial hypertension (OR, 3.5; 95% CI, 1.6–7.7; $P = 0.002$); and mean pulmonary artery pressure (OR, 1.3 per 10 mm Hg increase; 95% CI, 1.1–1.5; $P < 0.001$). PGD was significantly associated with 90-day (relative risk, 4.8; absolute risk increase, 18%; $P < 0.001$) and 1-year (relative risk, 3; absolute risk increase, 23%; $P < 0.001$) mortality.**

***Conclusions*: We identified grade 3 PGD risk factors, several of which are potentially modifiable and should be prioritized for future research aimed at preventative strategies.**

Clinical trial registered with www.clinicaltrials.gov (NCT 00552357).

Keywords: lung transplantation; clinical risk factors; primary graft dysfunction

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Primary graft dysfunction (PGD) is a form of acute lung injury occurring after lung transplantation and is the major cause of early post–lung transplant morbidity and mortality. Previous studies of PGD clinical risk factors have produced conflicting results, possibly because of small sample sizes, inconsistencies in PGD phenotype, and inability to control for multiple confounding variables.

What This Study Adds to the Field

We performed a multicenter, prospective cohort study of 1,255 lung transplant recipients across 10 US transplant centers. We identified receipt of an organ from a donor with any smoking history, elevated $F_{I_{O_2}}$ during allograft reperfusion, preoperative sarcoidosis or pulmonary arterial hypertension, use of cardiopulmonary bypass, single lung transplant, large-volume blood product transfusion, elevated pulmonary arterial pressures, and overweight or obese recipient body habitus as risk factors for grade 3 PGD. Several of these risk factors are potentially modifiable, and thus may suggest preventative strategies, whereas other risk factors should be prioritized for future mechanistic research efforts.

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* A complete list of members may be found before the beginning of the REFERENCES.

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Primary graft dysfunction (PGD) is a form of acute lung injury (ALI) that occurs within the first few days after allograft reperfusion in lung transplant recipients. The incidence of PGD is 10–30% and is the major cause of mortality within the first post-transplant year (1, 2). PGD leads to increased duration of mechanical ventilation and intensive care unit length of stay, poor functional outcomes, and increased risk of bronchiolitis obliterans syndrome (3, 4). Investigations that specifically evaluate PGD risk factors have the potential to profoundly affect future outcomes in patients undergoing lung transplantation.

Previous studies of PGD risk factors have produced conflicting results. Some explanations for these variances include small sample sizes; inconsistencies in PGD phenotype; inability to control for multiple confounding variables; and frequent use of retrospective, single center, or administrative data sets that lack rigorous PGD definitions (5, 6).

In 2005, the International Society for Heart and Lung Transplantation (ISHLT) standardized the PGD definition to facilitate research on risk factors associated with the development of this syndrome (7). Subsequent studies have demonstrated the construct validity of this definition with clinical outcomes and biologic markers of ALI severity (8, 9). In this study, we aimed to identify donor, recipient, and perioperative risk factors for PGD using the ISHLT definition in a large, multicenter, prospective cohort study design.

METHODS

Study Design and Subject Selection

The Lung Transplant Outcomes Group (LTOG) is a US National Institutes of Health sponsored, multicenter, prospective cohort study designed to evaluate risk factors for PGD. Details of subgroups in the LTOG cohort have previously been described (10–13). We included patients aged 18–80 years undergoing single or bilateral lung transplantation at 10 US transplant centers between March 2002 and December 2010 (*see* Table E1 in the online supplement). Clinical parameters were collected prospectively. Additional information was verified from the US United Network for Organ Sharing. The institutional review boards at each center approved this study.

Definition of PGD

PGD was graded according to ISHLT criteria, which is based on Pa_{O_2}/FI_{O_2} ratio and the presence of diffuse parenchymal infiltrates in the allograft on chest radiograph. Chest radiographs were interpreted independently by two physicians masked to the clinical variables, with adjudication of conflicts by a third reviewer (PGD grade classification kappa = 0.95) (7). The primary outcome was the presence of grade 3 PGD (Pa_{O_2}/FI_{O_2} ratio < 200) at 48 or 72 hours after transplantation, previously demonstrated to have construct validity for long-term outcomes and concurrent lung injury markers (3, 8). We performed a sensitivity analysis using grade 3 PGD occurring at any point within 72 hours of transplantation as a secondary outcome (3).

Candidate Risk Factor Selection and Definition

Potential risk factors for grade 3 PGD previously identified in the literature or with hypothetical clinical or biologic plausibility were selected for analysis *a priori* (5–7, 14–20). Details of covariate definitions are included in the online supplement.

Statistical Analysis

Candidate risk factors were cross-classified for evidence of collinearity and zero cell counts. Recipient body mass index (BMI) was included as a categorical variable in multivariable modeling because of its observed nonlinearity. Transplant center was evaluated as a fixed effect using conditional logistic regression. A limited number of hypothesis-driven interaction terms were evaluated using multiplicative conditional logistic regression. A parsimonious final model was developed by eliminating factors that were not confounders based on a less than 20% change in odds ratio (OR). Ischemic time was forced into the final multivariable model. A preoperative diagnosis of pulmonary arterial hypertension was evaluated in a multivariable model without mean pulmonary artery pressure (mPAP) and bypass use given the strong collinearity with these variables. A secondary analysis evaluating risks within bilateral lung transplant (BLT) and single lung transplant (SLT) recipient groups individually was also performed. We approached the problem of missing data using multiple imputation. Analyses proceeded by use of 10 imputed datasets, and confidence intervals (CIs) for point estimates of the ORs were determined using the "mim" command in STATA 11.2 software (STATA Corp., College Station, TX). Postestimation marginalized standardized risks for grade 3 PGD were calculated based on the final logistic regression model for selected categorical variables. Individual data elements had varying degrees of missing data, ranging from 0–46% (*see* Table E2). STATA 11.2 was used for all analyses; GraphPad Prism 5 (GraphPad Software, La Jolla, CA) was used for generating graphs.

RESULTS

There were 2,011 lung and heart-lung transplants performed at study centers during the study period. Of these, 1,255 patients were enrolled in the cohort study (Figure 1). There were no significant differences in sex or age, but there was more chronic obstructive pulmonary disease, less cystic fibrosis, and more SLT in the enrolled group (*see* Table E3). A total of 211 subjects (16.8%; 95% CI, 14.7–18.9) met criteria for grade 3 PGD, and 386 subjects (30.8%; 95% CI, 28.2–33.3) met the secondary PGD definition of grade 3 PGD at any time during the first 72 hours after transplantation.

Clinical characteristics are presented in Table 1. Of the 479 subjects receiving a lung from a donor with any previous smoking history, 101 (21%) developed grade 3 PGD, compared with 14% (110 of 776) receiving a lung from a lifelong nonsmoker.

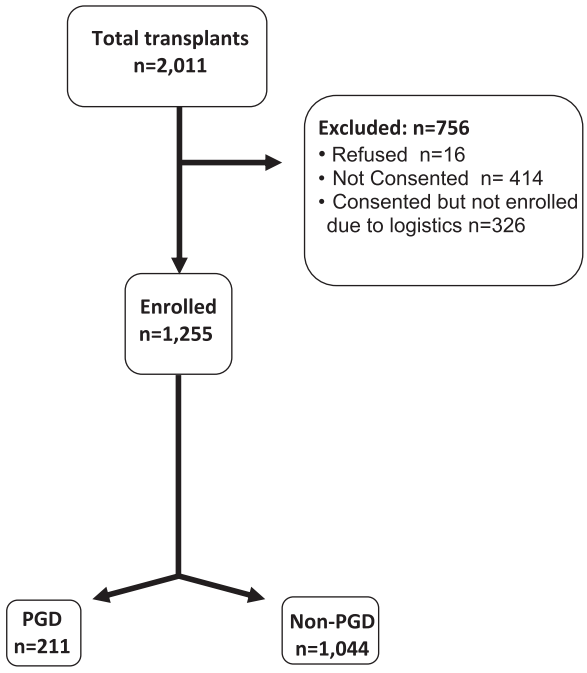

Figure 1. Flow diagram for subject enrollment. Of 2,011 transplants performed at the participating centers, 1,255 were enrolled in the Lung Transplant Outcomes Group cohort. "Not consented" refers to patients who were transplanted before being approached for consent. "Consented but not enrolled due to logistics" includes patients who were unable to give a blood sample as part of the study.

TABLE 1. UNIVARIATE ANALYSIS OF DONOR, RECIPIENT IN PERIOPERATIVE VARIABLES STRATIFIED BY PGD STATUS

Covariate	PGD *(n = 211)*	Non-PGD *(n = 1,046)*	*P* Value
	Donor Variables		
Male sex, n, (%)	116 (55)	646 (62)	0.06
Age, mean	35.2	34.4	0.4
Mode of death, n (%)			0.2
Trauma	79 (37)	437 (42)	
Stroke	91 (43)	393 (38)	
Anoxia	13 (6)	98 (9)	
Other	28 (13)	116 (11)	
Race, n (%)			0.8
White	137 (65)	665 (64)	
African American	45 (21)	216 (21)	
Other	29 (14)	163 (15)	
Any smoking, yes	101 (48)	378 (36)	0.001
Smoking >20 pack-years, yes	42 (20)	156 (15)	0.07
Heavy alcohol use, yes	28 (13)	160 (15)	0.4
Lowest Pa_{O_2} on $F_{I_{O_2}} = 1$	290	307	0.1
	Recipient Variables		
Sex and parity, n (%)			0.04
Male	117 (55)	592 (57)	
Female with no pregnancy	19 (9)	136 (13)	
Female with one pregnancy	7 (3)	59 (6)	
Female with two or more pregnancies	68 (32)	257 (25)	
Age, mean	53.3	53.6	0.8
BMI, mean	26.8	24.7	<0.001
BMI category, n (%)			<0.001
<18.5	16 (8)	103 (10)	
18.5–25	55 (26)	454 (43)	
25–30	90 (43)	349 (33)	
>30	50 (24)	138 (13)	
Pulmonary diagnosis, n (%)			<0.001
Chronic obstructive pulmonary disease	56 (27)	418 (40)	
Idiopathic pulmonary fibrosis	91 (43)	364 (35)	
Cystic fibrosis	16 (8)	162 (16)	
Sarcoidosis	17 (8)	26 (2)	
Pulmonary arterial hypertension	12 (6)	28 (3)	
Other	19 (9)	45 (4)	
mPAP	34.7	28.0	<0.001
mPAP severity category, n (%)			<0.001
<25 mm Hg (normal)	63 (30)	454 (43)	
25–40 mm Hg (mild)	83 (39)	475 (46)	
41–55 mm Hg (moderate)	47 (22)	89 (9)	
>55 mm Hg (severe)	18 (9)	26 (2)	
PRA class 1, n (%)			0.9
No	190 (90)	948 (91)	
<10	11 (5)	48 (5)	
⩾10	10 (5)	48 (5)	
PRA class 2, n (%)			0.9
No	197 (93)	981 (94)	
<20	8 (4)	37 (4)	
⩾20	6 (3)	26 (2)	
Race, n (%)			0.008
White	167 (79)	902 (86)	
African American	32 (15)	84 (8)	
Other	12 (6)	57 (5)	
	Operative Variables		
Ischemic time, min	328	316	0.1
Transplant type, single, n (%)	69 (33)	358 (34)	0.7
Inhaled nitric oxide use, yes, n (%)	80 (38)	393 (38)	0.9
PRBC >1 L, n (%)	71 (34)	210 (20)	<0.001
Reperfusion P_{CO_2}, n (%)			0.7
<30	10 (5)	52 (5)	
30–50	132 (63)	684 (66)	
>50	69 (33)	308 (30)	
Crystalloid, ml	945	891	0.6
Reperfusion $F_{I_{O_2}}$, %	67	57	<0.001

(Continued)

TABLE 1. (CONTINUED)

Covariate	PGD (*n = 211*)	Non-PGD (*n = 1,046*)	*P* Value
Reperfusion F_{IO_2} category, n (%)			<0.001
21–40%	54 (26)	412 (39)	
>40%	157 (74)	632 (61)	
Cardiopulmonary bypass use, yes, n (%)	131 (62)	335 (32)	<0.001

Definition of abbreviations: BMI = body mass index; F_{IO_2} = fraction of inspired oxygen; mPAP = mean pulmonary artery pressure; PGD = primary graft dysfunction; PRA = panel reactive antibodies.

Percentages may not exactly equal 100% because of rounding.

PGD is defined as grade 3 PGD on Day 2 or 3 after lung transplantation. The distribution of variables presented and the associated *P* values are from a single representative imputed data set.

Nearly 62% (130 of 211) of patients with grade 3 PGD in the cohort received bypass during the transplant procedure, and 28% (130 of 467) of patients receiving bypass developed grade 3 PGD. Donor preoperative oxygenation, as determined by lowest Pa_{O_2} measured as part of an oxygen challenge before lung procurement ($P = 0.1$) or highest oxygen challenge Pa_{O_2} ($P = 0.2$), was not associated with grade 3 PGD ($P = 0.1$).

Conditional multivariable analyses are presented in Table 2. In the fully adjusted multivariable model, independent risk factors for grade 3 PGD included use of cardiopulmonary bypass, SLT, pulmonary hypertension, a preoperative diagnosis of sarcoidosis, higher BMI, large-volume PRBC transfusion, donor smoking history, and increased F_{IO_2} during allograft reperfusion. Of the 1,255 transplant recipients, 479 subjects received an organ from a donor with a history of any prior cigarette use, whereas 198 received an organ from a donor with a history of more than 20 pack-years. Receipt of an organ from a donor with any prior cigarette use was significantly associated with grade 3 PGD (OR, 1.8; 95% CI, 1.2–2.6; $P = 0.002$), whereas receipt of a lung from a donor with a greater than 20 pack-year history had an attenuated association with grade 3 PGD (OR, 1.5; 95% CI, 1.0–2.4; $P = 0.06$). Because of difficulty in accurately collecting F_{IO_2} at reperfusion, the reperfusion F_{IO_2} was missing from 46% of all subjects. In a multivariable complete case analysis of 619 subjects with complete reperfusion F_{IO_2} information, the association between reperfusion F_{IO_2} and grade 3 PGD was significant, with a similar point estimate for the OR as in the fully imputed analysis (OR, 1.1; 95% CI, 1.0–1.3; $P = 0.04$).

Calculated standardized predicted risks of grade 3 PGD for significant individual risk factors are presented in Figure 2. The

TABLE 2. MULTIVARIABLE MODEL USING GRADE 3 PGD AT DAY 2 OR 3 AS THE OUTCOME WITH CENTER AS A GROUPING VARIABLE

Variable	Odds Ratio for PGD	95% Confidence Interval	*P* Value
Transplant type			
Bilateral	Reference	Reference	Reference
Single	2.0	1.2–3.3	0.008
Cardiopulmonary bypass use	3.4	2.2–5.3	<0.001
Recipient sex			
Male	Reference	Reference	Reference
Female without prior pregnancy	0.9	0.4–2.0	0.9
Female with one prior pregnancy	0.6	0.2–1.9	0.4
Female with two or more pregnancies	1.3	0.9–2.1	0.2
Recipient BMI			
18.5–25	Reference	Reference	Reference
<18.5	1.3	0.6–2.8	0.6
25–30	1.8	1.2–2.7	0.01
>30	2.3	1.3–3.9	0.004
Total ischemic time per hour	1.1	1.0–1.2	0.08
Diagnosis			
COPD	Reference	Reference	Reference
IPF	1.2	0.8–1.9	0.3
CF	0.7	0.3–1.4	0.3
Sarcoidosis	2.5	1.1–5.6	0.03
Pulmonary arterial hypertension*	3.5	1.6–7.7	0.002
PRBC transfusion			
None	Reference	Reference	Reference
Up to 1L	1.1	0.7–1.8	0.6
>1L	1.9	1.1–3.2	0.01
mPAP per 10 mm Hg	1.3	1.1–1.5	<0.001
Reperfusion F_{IO_2} per 10% increase	1.1	1.0–1.2	0.01
Reperfusion F_{IO_2} complete case analysis (n = 619)	1.1	1.0–1.3	0.04
Any donor smoking†	1.8	1.2–2.6	0.002
Donor smoking >20 pack-years†	1.5	1.0–2.4	0.06

Definition of abbreviations: BMI = body mass index; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; F_{IO_2} = reperfusion fraction of inspired oxygen; IPF = idiopathic pulmonary fibrosis; mPAP = mean pulmonary artery pressure; PGD = primary graft dysfunction; PRBC = packed red blood cell transfusion volume.

*The odds ratio for pulmonary arterial hypertension was determined using the full model in the absence of mPAP and bypass use given collinearity.

† Two alternate determinations of donor smoking history were included in separate multivariable models.

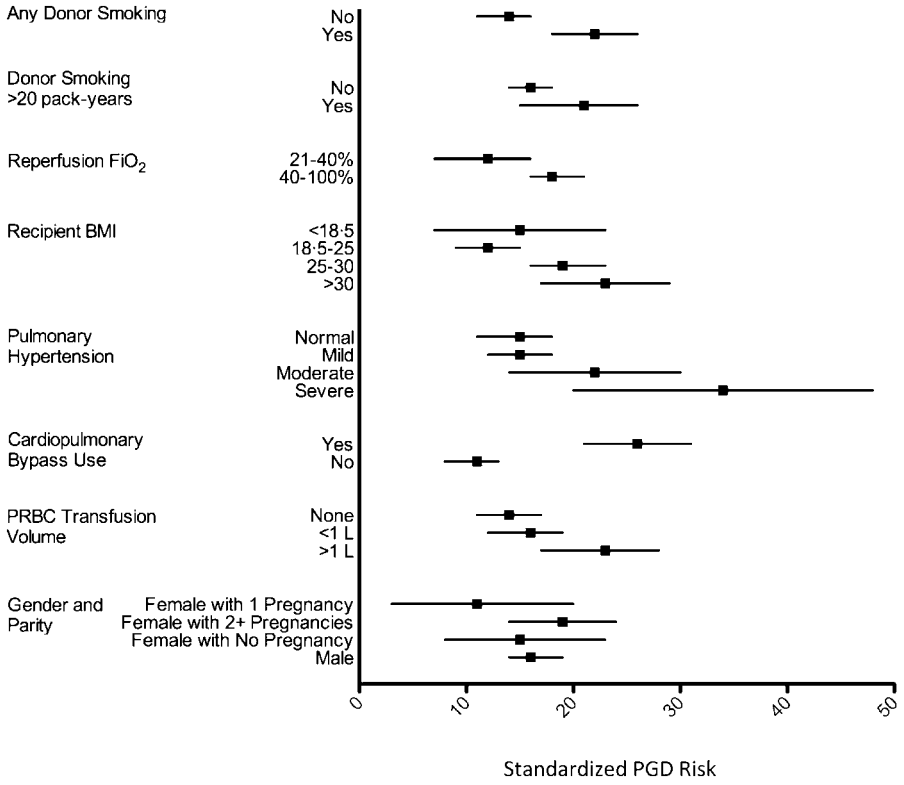

Figure 2. Standardized grade 3 primary graft dysfunction (PGD) risk for donor, recipient, and perioperative variables. Standardized risk of grade 3 PGD represents the postestimation marginalized standardized risks for grade 3 PGD and was calculated based on the final logistic regression model. *Dots* represent the point estimate for adjusted standardized risk from a logistic regression equation containing donor smoking, reperfusion $F_{I_{O_2}}$, total ischemic time, recipient sex and parity, World Health Organization categorized severity of pulmonary hypertension, volume of packed red blood cell (PRBC) transfusion, recipient body mass index (BMI), use of cardiopulmonary bypass, transplant type, center, and preoperative diagnosis, with the *bar* representing 95% confidence intervals. Standardized risks represent the estimated risk of grade 3 PGD if all variables were kept stable except for altering the variable of interest; for example, the estimated grade 3 PGD risk if all of the patients alternatively received or did not receive cardiopulmonary bypass.

predicted risk of grade 3 PGD increased with increasing $F_{I_{O_2}}$ during allograft reperfusion from 12% (95% CI, 7–16%) at $F_{I_{O_2}}$ less than 0.4 to 18% (95% CI, 16–21%) at $F_{I_{O_2}}$ greater than or equal to 0.4, an absolute risk increase (ARI) of 6%. Overweight recipients had an ARI of 7% for grade 3 PGD compared with normal weight, whereas obese recipients had an ARI of 11% for grade 3 PGD. Large-volume blood transfusion was associated with an ARI of 9%, donor smoking was associated with an ARI of 5%, and cardiopulmonary bypass was associated with an ARI of 15%.

As shown in Figure 3, there was significant variation in the incidence of grade 3 PGD across the 10 centers included in the cohort, ranging from 2–27%. There was no significant detected interaction of grade 3 PGD risk factors by center, and evaluation of individual significant risk factors within the four largest centers did not identify substantial variation in risk factor effect estimates across centers. Sensitivity analyses conducted using grade 3 PGD at any time point were consistent with analyses using the primary endpoint (*see* Table E4), although the association with mPAP (OR, 1.1; 95% CI, 1.0–1.3; $P = 0.05$) was attenuated. Additionally, total ischemic time (OR per hour, 1.2; 95% CI, 1.0–1.3; $P = 0.005$) and pretransplant diagnosis of idiopathic pulmonary fibrosis (OR, 1.5; 95% CI, 1.1–2.1; $P = 0.02$) demonstrated significant association with development of grade 3 PGD using this alternate outcome definition.

Because of concern that grade 3 PGD after an SLT may be misclassified secondary to the impact of the native lung on $Pa_{O_2}/F_{I_{O_2}}$ ratio, SLT and BLT were evaluated using separate analyses (*see* Table E5). Donor smoking history was significantly associated with grade 3 PGD in SLT recipients (OR, 2.0; 95% CI, 1.1–3.7; $P = 0.03$) and BLT recipients (OR, 1.7; 95% CI, 1.0–2.7; $P = 0.03$). Cardiopulmonary bypass use was also a significant risk factor among single (OR, 5.0; 95% CI, 2.2–11.6; $P < 0.001$) and bilateral (OR, 3.7; 95% CI, 2.1–6.3; $P < 0.001$) recipients. Increasing mPAP was only significantly associated with grade 3 PGD among BLT recipients (OR per 10 mm Hg increase, 1.3; 95% CI, 1.1–1.6; $P = 0.001$), although only four SLT recipients had a mPAP greater than 60 mm Hg.

The impact of grade 3 PGD on unadjusted 90-day and 1-year mortality is presented in Table 3. The primary definition of grade 3 PGD at 48 or 72 hours after transplant was associated with a relative risk (RR) of 4.8 (95% CI, 3.3–7.0; $P < 0.001$) for death within 90 days of transplant compared with those without grade 3 PGD and an ARI of 18% (95% CI, 12–24). Grade 3 PGD was associated with a significantly increased 1-year mortality (RR, 3.0; 95% CI, 2.3–3.9; $P < 0.001$) compared with those without grade 3 PGD, and an ARI of 23% (95% CI, 15–30). Although the magnitude of the association between grade 3 PGD and mortality was attenuated when the alternate definition of any grade 3 PGD within 72 hours was used in the

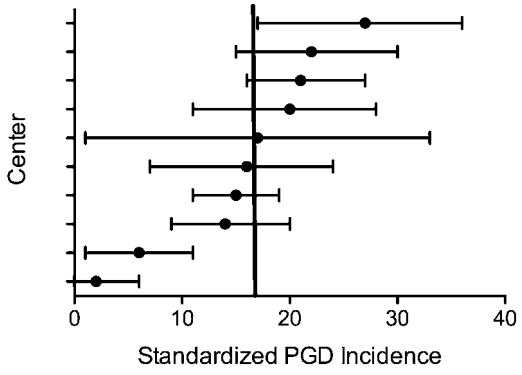

Figure 3. Standardized incidence of grade 3 primary graft dysfunction (PGD) across the 10 centers. Standardized risk of grade 3 PGD represents the postestimation marginalized standardized risks for grade 3 PGD and was calculated based on the final logistic regression model. *Dots* are the point estimates and *error bars* represent the 95% confidence intervals.

TABLE 3. UNADJUSTED ASSOCIATION OF GRADE 3 PGD AT 48 OR 72 HOURS WITH 90-DAY AND 1-YEAR MORTALITY

Outcome	Risk in Those with PGD	Risk in Those without PGD	Risk Ratio (95% CI)	Risk Difference (95% CI)	*P* Value
90-d mortality	23%	5%	4.8 (3.3–7.0)	18% (12–24)	<0.001
1-yr mortality	34%	11%	3.0 (2.3–3.9)	22% (15–30)	<0.001

Definition of abbreviations: CI = confidence interval; PGD = primary graft dysfunction.

sensitivity analyses, the association remained significant at 90 days (RR, 3.5; 95% CI, 2.3–5.1; $P < 0.001$) and 1 year (RR, 2.5; 95% CI, 1.9–3.3; $P < 0.001$) (*see* Table E6).

DISCUSSION

In the first prospective, multicenter cohort study of donor, recipient, and perioperative risk factors for grade 3 PGD after lung transplantation, we have identified receipt of an organ from a donor with any smoking history, elevated F_{IO_2} during reperfusion, preoperative sarcoidosis, independent of pulmonary pressures or pulmonary arterial hypertension, use of cardiopulmonary bypass, SLT, large-volume blood product transfusion, elevated pulmonary arterial pressures, and overweight or obese recipient body habitus as risk factors for grade 3 PGD. Several of these risk factors are potentially modifiable (e.g., F_{IO_2} at reperfusion, obesity) and thus may suggest preventative strategies, whereas other risk factors should be prioritized for mechanistic research efforts (e.g., donor smoking status and bypass use). The results of this study may lead to prospective studies evaluating alterations in perioperative recipient management, donor-recipient matching, and potentially recipient selection.

Donor cigarette use emerged as a significant risk factor for grade 3 PGD, consonant with prior findings of mortality (21). The United Network for Organ Sharing defined donor smoking history of more than 20 pack-years fails to include active smokers with less than 20 pack-years of tobacco exposure and was not statistically significantly associated with grade 3 PGD, possibly because of the small number of high pack-year donors identified in the cohort. Defining donor smoking as any tobacco use includes low total pack-year, active smokers, who may in fact represent a higher-risk donor pool. Our findings are consistent with previous smaller studies suggesting increased risk of grade 3 PGD, higher alveolar-arterial oxygen gradients, and longer intensive care unit length of stay in recipients of lungs from previous smokers (20, 22). The mechanisms of this association are unclear, but cigarette exposure may result in increased oxidative injury and nicotine exacerbates reperfusion injury in experimental models (23). Because smoking status has recently been shown to increase the risk of ALI in trauma patients, it is plausible that tobacco smoke exposure in the donor lung might exacerbate lung injury that occurs at the time of allograft reperfusion (24). However, given the limited pool of available lung donors, it is not currently feasible to exclude patients who were previous smokers as potential lung donors. A recent *Lancet* study demonstrated that, although recipient survival was worse after receipt of a lung from a smoking donor compared with a nonsmoking donor, overall survival was significantly better than if the recipient continued on the wait list (21). However, given that current methods of determining donor smoking history from interview of surrogates may be prone to measurement bias, we believe that more accurate quantification of smoking exposure in donors and research into mechanisms of donor smoking on increasing grade 3 PGD risk are important priorities for future investigation (24, 25).

Increased F_{IO_2} during allograft reperfusion was strongly associated with development of grade 3 PGD, independent of transplant type, bypass use, and pretransplant diagnosis. Cold ischemia of the allograft followed by reperfusion results in a significant oxidative burst (26), which may overwhelm cellular antioxidant pathways and lead to cellular necrosis and apoptosis, production of proinflammatory cytokines, and worsening edema and gas exchange in animal models (27). Although we attempted to determine the F_{IO_2} for each subject before allograft reperfusion, we appreciate that F_{IO_2} is a dynamic variable, which may have been confounded by patient needs during the surgical procedure. Despite the prospective nature of the study and the inclusion of reperfusion F_{IO_2} on the case report forms, we were only able to obtain accurate information on this variable for 54% of the study subjects. However, variability in F_{IO_2} used at reperfusion by center suggests that there is variation in practice-related preference, and not simply a direct result of response to intraoperative changes in physiology. Two centers with the lowest PGD incidence also had the lowest mean reperfusion F_{IO_2}. Although high reperfusion F_{IO_2} secondary to poor functioning of the allograft at the time of reperfusion is not a modifiable PGD risk factor, intraoperative practice patterns and preferences may be modifiable. Future investigations evaluating interventions aimed at decreasing reperfusion F_{IO_2}, while also evaluating immediate allograft function at reperfusion, are warranted.

Tidal volume per kilogram of ideal body weight at reperfusion was not associated with the development of PGD. We were unable to assess the relationship between postoperative ventilator strategies and PGD. Although high tidal volume ventilation has been shown to be a risk factor for ALI, many subjects developed PGD before a time when postoperative ventilatory management would be predicted to affect the risk of ALI (28–30). Ventilator management decisions are made concurrently with the development of PGD, making it difficult to determine whether ventilation strategy is a risk factor for PGD or a response to altered oxygenation. A large percentage of patients are extubated early after transplant resulting in missing data on ventilator management in the postoperative period.

Our study confirms elevated BMI as a potential risk factor for grade 3 PGD as previously reported in a subset of this cohort study (12, 17). In addition to obesity, overweight recipient BMI is also significantly associated with grade 3 PGD risk. Future efforts aimed at understanding the mechanistic link of adiposity and grade 3 PGD are warranted. Although we were also able to establish an association between the use of cardiopulmonary bypass and subsequent development of grade 3 PGD, it was not possible to accurately differentiate planned use of cardiopulmonary bypass from emergent initiation intraoperatively because of deterioration in patient hemodynamics or oxygenation. Differentiating emergent initiation of bypass from planned bypass should be an area of future investigation because it may lead to important alterations in practice patterns. Additionally, although all centers used controlled reperfusion at the cessation of bypass, the exact technique for reperfusion likely varies by center, and we were unable to fully capture these practice variations. Likewise, the relationship of large-volume blood transfusion with grade 3 PGD is difficult to separate from confounding because of unmeasured procedural

characteristics leading to transfusion requirements. Nonetheless, because blood product transfusion in-and-of-itself is associated with ALI in at-risk groups this finding may warrant further research into mechanisms of increased grade 3 PGD risk (31).

In our multivariable analysis, elevated mPAP remained a significant risk factor, independent of diagnosis and use of cardiopulmonary bypass. Potential mechanisms for the elevated grade 3 PGD risk seen with secondary pulmonary hypertension include endothelial shear stress, or circulating humoral factors associated with pulmonary hypertension (17). Future research into these underlying mechanisms may lead to improved preventative strategies.

PGD incidence varied across the 10 centers included in this study (Figure 3). The risk factors identified were also significantly associated within the four largest centers. Some of the differences in PGD incidence across center are explained by risk factor distribution within centers. There was no standardization of recipient criteria, surgical techniques, or perioperative management across the centers in this observational cohort. Intraoperative use of cardiopulmonary bypass ranged from 9–71% and reperfusion $F_{I_{O_2}}$ ranged from 25–90% across centers. Some centers use cardiopulmonary bypass for all BLT procedures. We believe that further evaluation of individual practice paradigms at different transplant centers should be an area of future evaluation.

Several characteristics previously reported as risk factors for grade 3 PGD were not identified as significant risk factors in our study. None of the previously identified donor variables, including sex, race, age, or mode of death were significantly associated with grade 3 PGD (14, 18, 20). Although we did not specifically evaluate a "marginal donor status" definition, our findings may indicate that standard donor variables do not increase grade 3 PGD risk, and that more sophisticated methods to evaluate subclinical lung injury in donors are warranted. Although donor Pa_{O_2} was not identified as a risk factor for PGD, low donor Pa_{O_2} often eliminates a potential organ from use for transplant, thus limiting the range of Pa_{O_2} available for analysis. Differences in our results compared with prior publications may be caused by the more severe phenotype of PGD used as the primary outcome and the prospective collection of covariates in our study.

Although PGD presents as a spectrum of disease severity, we chose a more severe phenotype based on prior research (8). This PGD definition was very strongly associated with increased risk of 90-day and 1-year mortality after transplant, demonstrating the significant impact that grade 3 PGD has on clinical outcomes in the first year after lung transplantation, and providing further validity for the ISHLT definition. Furthermore, sensitivity analyses using an alternate, less severe, PGD definition yielded similar results.

There are several limitations to this study. There is the potential that unmeasured confounding or bias secondary to missing data limited our results. In particular, we were unable to assess the effects of induction therapy because the practice was completely uniform within centers during the study time period. Likewise, although we used multiple imputation to account for missing data, some of the covariates had large percentages of missing data, especially reperfusion $F_{I_{O_2}}$, which may have led to inflated variances caused by uncertainties of imputation. There is the potential for selection bias because not all transplant recipients from each site were enrolled in the cohort (*see* Table E1). However, most sites enrolled most of their patients, and although there were some differences in baseline variables between enrolled and nonenrolled patients, no identified risk factor was more prevalent in the nonenrolled population (*see* Table E3). Additionally, although we imposed strict criteria for PGD, there remains the potential for misclassification bias. We attempted to minimize this possibility, however, by independently reading radiographs and using a standard definition (32, 33). Although the ISHLT PGD criteria were first published online June 4, 2005, patients were enrolled prospectively in LTOG starting in 2002. One hundred twenty-one patients were enrolled before the publication of the PGD guidelines; PGD grades based on the ISHLT guidelines were retrospectively assigned to these patients. Exclusion of these subjects did not change the results. Given the long enrollment period for this study, there is potential for bias based on changes in clinical practice over time. Although patients were first enrolled in 2002 at a single site, 1,158 of the 1,255 patients (92%) were enrolled from June 2005 through December 2010, narrowing the enrollment period for most of the cohort. When evaluating these patients alone, there were no differences in the risk factors identified or their ORs. Additionally, the most recent ISHLT report includes 2004–2010 as a single era when presenting survival analyses (34). There were no differences in the results when transplant year was included as a potential confounder of the relationship between our identified risk factors and grade 3 PGD.

In summary, we identified risk factors for the development of grade 3 PGD after lung transplantation, and demonstrated the high attributable mortality of grade 3 PGD in the modern era of lung transplantation. These findings provide new knowledge to suggest mechanistic studies, including further evaluation of the relationship between donor smoking and PGD, and serve as the basis for evaluating interventions targeting potentially modifiable risk factors, such as body habitus and reperfusion $F_{I_{O_2}}$. Our findings can be used to develop predictive models for PGD that may allow for risk factor modification, more objective donor-recipient matching algorithms, and lead to a more detailed understanding of the incremental risk associated with these factors.

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