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Primary Graft Dysfunction Grade 3 following Pediatric Lung Transplantation is Associated with Chronic Lung Allograft Dysfunction

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Abstract

Background: Severe primary graft dysfunction (PGD) is associated with the development of bronchiolitis obliterans syndrome (BOS), the most common form of chronic lung allograft dysfunction (CLAD), in adults. However, PGD associations with long-term outcomes following pediatric lung transplantation are unknown. We hypothesized that PGD grade 3 (PGD 3) at 48- or 72-hours would be associated with shorter CLAD-free survival following pediatric lung transplantation.

Methods: This was a single center retrospective cohort study of patients ≤ 21 years of age who underwent bilateral lung transplantation between 2005 and 2019 with ≥ 1 year of follow-up. PGD and CLAD were defined by published criteria. We evaluated the association of PGD 3 at 48- or 72-hours with CLAD-free survival by using time-to-event analyses.

Results: Fifty-one patients were included (median age 12.7 years; 51% female). The most common transplant indications were cystic fibrosis (29%) and pulmonary hypertension (20%). Seventeen patients (33%) had PGD 3 at either 48- or 72-hours. In unadjusted analysis, PGD 3 was associated with an increased risk of CLAD or mortality (HR 2.10, 95% CI 1.01–4.37, p=0.047). This association remained when adjusting individually for multiple potential confounders. There was evidence of effect modification by sex (interaction p = 0.055) with the association of PGD 3 and shorter CLAD-free survival driven predominantly by males (HR 4.73, 95% CI 1.44–15.6) rather than females (HR 1.23, 95% CI 0.47–3.20).

Conclusions: PGD 3 at 48- or 72-hours following pediatric lung transplantation was associated with shorter CLAD-free survival. Sex may be a modifier of this association.

Keywords

primary graft dysfunction; chronic lung allograft dysfunction; bronchiolitis obliterans syndrome; pediatric; transplant; rejection

INTRODUCTION

Chronic lung allograft dysfunction (CLAD) was recently defined to help standardize nomenclature surrounding the clinical care and research of lung transplant recipients and is comprised of four phenotypes: bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), mixed, and undefined.[1] BOS is the most common form of CLAD and, in adults, post-transplant recipient risk factors for BOS development include primary graft dysfunction (PGD), acute rejection *(≥ A2)*, lymphocytic bronchitis *(≥B2)*, episodes of acute cellular rejection, humoral rejection, community acquired viral infection, CMV pneumonitis, and bacterial and fungal infections.[2] BOS is also the leading cause of pediatric lung transplantation mortality beyond the first year.[3] Risk factors for BOS isolated to the pediatric population are less studied and include multiple episodes of acute rejection.[4] Pediatric risk factors are likely distinct from adult risk factors given differences in age-dependent primary indications for transplant, developing immune systems in children,

and increased use of bilateral lung transplantation in children compared to adults.[5,6,7] Much less is known about CLAD in pediatrics as an overall entity and risk factors for CLAD may be different compared to adults given different indications of transplant, co-morbidities, surgical strategies, perioperative management, and response to immunosuppression.

The development of BOS in adults has been linked to severe (Grade 3) PGD during the first 72 hours following lung transplantation. PGD occurs in approximately 22% of pediatric lung transplant recipients and between 10–30% of adult lung transplant recipients.[8,9,10] Major risk factors for PGD include both recipient characteristics such as primary diagnosis of pulmonary arterial hypertension, higher pulmonary arterial pressure, and obesity as well as donor characteristics such as smoking, aspiration, and undersized donor relative to recipient.[11] In adults, severe PGD is associated with worse short- and long-term clinical outcomes, including development of BOS and mortality.[2,9,12–16] The mechanisms for the association between PGD and CLAD are not yet fully elucidated, but ischemic reperfusion injury, immune-mediated response, nitric oxide synthesis impairment, and early systemic inflammatory response have been implicated.[12,17–20]

Considering the underlying differences in pediatric and adult lung transplantation, important knowledge gaps remain with respect to pediatric PGD and its association with morbidity and mortality outcomes. Thus, the purposes of this study were to describe the evolution of PGD in the first 72 hours and to determine the association of severe PGD with CLAD-free survival in pediatric patients who received bilateral lung transplantation. We hypothesized that PGD grade 3 (PGD 3) at 48- or 72-hours would be associated with worse CLAD-free survival.

MATERIALS AND METHODS

Study Design and Population

We performed a single center, retrospective cohort study of patients ≤ 21 years of age who underwent bilateral lung transplantation at the Children's Hospital of Philadelphia (CHOP) between January 1, 2005, and December 31, 2019, with at least 1-year of follow-up post-transplant. Subjects were excluded if they underwent combined heart-lung transplant or had a limited post-operative course such that PGD status was unable to be determined at 48- or 72-hours following transplant (Figure 1). Figure S1 is a directed acyclic graph (DAG) that depicts the causal framework of our analysis. This study was approved by the CHOP Institutional Review Board with a waiver for informed consent and was in compliance with the ISHLT Ethics statement.

Primary Exposure Definition

PGD was graded using accepted adult criteria by two investigators (A.S.H. and N.Y.) who were blinded to the outcome as defined by the most recent ISHLT consensus statement.[16] The primary exposure was PGD 3 at 48- or 72-hours following reperfusion of the second lung during the transplant procedure. PGD 3 was defined as the presence of pulmonary edema on chest radiograph and a $Pa_{O2}/F_{IO2} < 200$ (or $Sa_{O2}/F_{IO2} < 235$ if an arterial blood

gas was not available) or if the patient was supported with extracorporeal lung support with the presence of pulmonary edema on chest radiograph.

Primary Outcome Definition

The primary outcome was CLAD-free survival for patients who received primary and repeat bilateral lung transplants. CLAD-free survival was defined as the development of CLAD or death from any cause, whichever occurred first. The classification and timing of diagnosis of CLAD were determined by two investigators (W.W. and B.J.) blinded to PGD status utilizing accepted adult criteria based on the 2019 ISHLT consensus statement definition as well as histopathology and radiologic findings suggestive of chronic allograft rejection when spirometry data was not obtainable.[1] The process of classification used in this study is outlined in Figure S2. Due to the limitations in the pediatric population, our approach to the diagnostic criteria of CLAD for this study differed from the current adult ISHLT diagnostic criteria as the most common phenotypes of CLAD, BOS and RAS, primarily rely on pulmonary function testing (PFT) as a diagnostic tool. Obtaining objective pediatric pulmonary function data is often restricted by developmental milestones or the lack of adequate technique, and only spirometry data that met ATS guidelines was included.[21] Please see the Supplementary Material for a more detailed description of CLAD determination for this study.

The general approach for monitoring for the development of CLAD during the study timeframe is outlined in Table S1. Definitions of acute cellular rejection, antibody-mediated rejection, and post-transplant infectious variables as well as a description of pre- and post-transplant clinical management are included in the Supplementary Material.

Statistical Analyses

Statistical analyses were conducted with STATA/IC 16.1 SE (StataCorp, College Station, TX). Data were summarized as median and interquartile range (IQR) or percentages. Continuous data were compared with Wilcoxon rank-sum test, and categorical data by Fisher exact test or Pearson's chi-square.

For survival analyses, time zero was the time of PGD measurement (72 hours following transplant) and CLAD-free survival was the primary outcome. Kaplan-Meier estimates were generated for the probability of CLAD-free survival for both the primary and secondary analyses with the log-rank test used for curve comparison. Cox proportional hazards regression was performed for the association of PGD 3 at 48- or 72-hours with the outcome of CLAD-free survival. Confounders chosen *a priori* were included into the model one variable at a time to not overfit the model given the small number of patients who developed PGD 3. Age and sex were specifically assessed for effect modification. Proportional hazards assumptions were tested with log-log plots of survival, plot of empirical survival versus predicted survival, and with the score test using Schoenfeld residuals. The overall fit of the Cox models was assessed with Cox-Snell residuals. A sensitivity analysis was performed using patients who underwent primary bilateral lung transplantation only. P values < 0.05 were considered significant.

RESULTS

Fifty-five pediatric subjects underwent bilateral lung transplantation at our institution during the study timeframe with 51 included in the primary analysis (Figure 1): 33% (17/51) of patients developed PGD 3 at 48- or 72-hours following transplant. For the entire cohort, the median age at the time of transplant was 12.7 years (IQR 8.0–15.8) with 59% (30/51) of patients ≥ 12 years of age and 10% (5/51) ≥ 18 years and 51% (26/51) were female (Table 1). The most common indications for lung transplant were cystic fibrosis (29%) and pulmonary hypertension (20%) (Table 1). Patients who developed PGD 3 had higher VIS scores, required higher mean airway pressure, and more frequently received iNO but did not have higher rates of acute kidney injury (Table S2).

Fifty-one percent (26/51) of the overall cohort developed CLAD at a median time of 846 days (IQR 462–1746) post-transplant. Seventy-six percent (13/17) of patients with PGD 3 developed CLAD at a median time of 599 days (IQR 515–1349) post-transplant (Table 2). Eighty-five percent (22/26) of patients who developed CLAD were diagnosed by spirometry while the remaining 4 patients were diagnosed with CLAD by imaging. Fifty-eight percent (15/26) patients with CLAD had histopathologic evidence of chronic rejection. There were no differences between patients who developed CLAD and those who did not in regard to evidence of cellular rejection, evidence of antibody-mediated rejection, or post-transplant infectious characteristics (Table 3).

The relative proportion of patients with PGD grade 2 and 3 decreased while that of PGD grade 0 and 1 increased during the first 72 hours, respectively (Figure 2). Thirty-three percent (17/51) of patients had PGD 3 at either 48- or 72-hours following lung transplant.

Kaplan-Meier estimates showed a difference between the probability of CLAD-free survival between those with and without PGD 3 (Figure 3). The median time to development of CLAD or death for the PGD 3 group was 3.3 years (95% CI: 1.3–3.7 years) compared to 5.6 years (lower 95% CI bound of 4.8 years) for those who did not develop PGD 3. When stratified by sex, the difference between the PGD 3 and no PGD 3 groups remained in males only (Figure 4).

In unadjusted Cox proportional hazards analysis, PGD 3 at 48- or 72-hours was associated with an increased risk of CLAD or death (HR 2.10, 95% CI 1.01–4.37, p=0.047). This association remained when adjusting individually for sex, age at the time of transplant, sex mismatch, CMV pneumonitis prior to development of CLAD, CARV detected via PCR within 12 months of transplant, or Pseudomonas or Aspergillus isolated via culture prior to CLAD (Table 4). This association lost statistical significance at the $p < 0.05$ threshold when adjusting for primary diagnosis of CF ($p = 0.064$), primary diagnosis of PH ($p = 0.099$), donor to recipient height ratio (p=0.062), evidence of cellular rejection prior to CLAD (p=0.052 for Grade A, p=0.051 for Grade B), and evidence of antibody-mediated rejection prior to CLAD (p=0.050) (Table 4). There was evidence that sex may be an effect modifier of the association between PGD 3 and CLAD-free survival (p=0.057), with the association of PGD 3 with shorter CLAD-free survival driven predominantly by male subjects (HR 4.73, 95% CI 1.44–15.6), rather than females (HR 1.23, 95% CI 0.47–3.20). Testing confirmed

that the proportional hazards assumption was valid for this data. Schoenfeld residuals for PGD 3 covariate showed p-values > 0.9 for all unadjusted and adjusted models. Overall model fit was tested with Cox-Snell residuals and showed reasonable model fit, especially after inclusion of an interaction term for sex.

When excluding patients with repeat bilateral transplants from the dataset, the Kaplan-Meier estimates and proportional hazard model associations confirmed the conclusions of the primary analysis (Figure S3, Table S3).

DISCUSSION

In this pilot study, PGD 3 at 48- or 72-hours following pediatric lung transplantation was common and associated with worse CLAD-free survival when controlling individually for sex, age at the time of transplant, sex mismatch, CMV pneumonitis prior to development of CLAD, CARV detected via PCR within 12 months of transplant, or Pseudomonas or Aspergillus isolated via culture prior to CLAD. Further, the effect sizes of this association were similar when adjusting for primary diagnosis of CF or PH, donor to recipient height ratio as well as evidence of cellular or antibody-mediated rejection prior to CLAD. This relationship appeared to be much stronger in males compared to females.

To the best of our knowledge, this is the first pediatric study to demonstrate an association between severe PGD with CLAD-free survival. Multiple adult studies have shown an association of severe PGD with the development of BOS, and therefore CLAD, and worse BOS-free survival.[2,9,12–16] Mechanisms responsible for this association are presumably related to the immune response surrounding damage to the lung allograft induced by PGD.[11, 22] In our primary analysis, we focused on several confounders, including recipient demographic as well as post-transplant graft rejection and infectious variables (Supplemental Figure 1). Importantly, the effect sizes in the adjusted analyses for the Cox regression models were between HRs 2–2.3 even though some of the p-values breached the pre-specified significance of $p < 0.05$. One reason for this may be that our study was underpowered. The recipient diagnosis of PH as the indication lung transplantation showed the most change in the statistical significance. Pre-operative PH, RV systolic dysfunction, and LV diastolic dysfunction are all known risk factors for PGD.[21,23,24] Although post-operative RV dysfunction has been shown to improve within 2 months of lung transplantation in pediatric patients with severe PH,[25] it is unclear if this recovery is permanent, particularly in the setting of pulmonary vascular dysfunction that may occur with episodes of post-transplant infections or acute rejection. Whether post-operative PH, RV systolic function, or LV diastolic function are risk factors for the development of CLAD independent of a causal pathway through PGD are research questions that deserve future study.

Adjustment for AMR and ACR also caused the association between severe PGD and CLAD-free survival to become non-significant at the pre-defined threshold. For AMR, our study was likely underpowered given that only 18% (9/51) of patients in the total cohort had evidence of AMR prior to CLAD. In contrast, 75% of patients (38/51) had evidence of Grade A and/or Grade B ACR within 18 months of transplant. This may be driven by Grade

B as over half of patients who developed CLAD had evidence of Grade B ACR compared to less than 30% of those no did not develop CLAD. As AMR and ACR are major and modifiable risk factors for the development of CLAD, further work should focus on if they can be modified by PGD prevention and treatments.

In our study, pediatric male transplant recipients showed a strong association between PGD and CLAD whereas female recipients did not. In contrast to our findings, sex stratified survival analysis in the pediatric population showed higher survival rates in males compared to females.[26] Mangiameli et al suggested that male recipient and gender mismatching after lung transplantation were positive predictive prognostic factors in children and adolescents.[26] Although recent publications found that older recipient age of pediatric lung transplant was associated with increased risk of BOS[27] and inferior outcomes in adolescent lung transplant recipients compared to younger children and adults,[28] there was no suggestion of effect modification by age when stratified by < or ≥ 12 years in this pilot study (Table 3). Further study of the roles and mechanisms of both age and sex of both donors and recipients and their associations with worse outcomes following pediatric lung transplantation is warranted.

As discussed, since obtaining accurate and objective PFT data in pediatrics is often limited by lack of adequate technique or developmental considerations, our approach to the diagnostic criteria of CLAD differed from the current adult ISHLT diagnostic definitions as the most common phenotypes of CLAD, BOS and RAS, primarily rely on spirometry as a diagnostic tool.[1] Our modified pediatric CLAD definition was consistent with another recent pediatric study[29] and included PFT, radiographic, and histologic criteria. Lung clearance index using multiple breath washout maneuvers has also been suggested in pediatrics to detect small airway disease not captured by spirometry.[30] A pediatric-specific CLAD definition that incorporates alternate methods for measuring pulmonary function, standardizing the use of serial imaging and transbronchial biopsies, as well as the potential addition of newer technologies, such as the use of cell-free DNA, would be greatly beneficial to the pediatric lung transplant community. This is particularly important given both the lower volume of pediatric lung transplants worldwide and differences in age-dependent immunologic responses to transplantation. We encourage future reporting and definition transparency in future publications.

In this study, we described the time course and evolution of PGD in the first 72 hours post lung transplantation (Figure 2). Most patients who experienced PGD 3 at 48- or 72-hours post-transplant also had PGD 3 during the first 0–24 hours post-transplant. However, 35% (6/17) of patients with PGD 3 at 48- or 72-hours were categorized as PGD 0 or PGD 1 in the immediate perioperative period. Given the mechanistic plausibility of the association between severe PGD and post-transplant outcomes, investigations in adult populations have focused on efforts to prevent or lessen the risk of severe PGD development, such as perioperative extracorporeal membrane oxygenation (ECMO),[31,32] ex-vivo lung perfusion,[33,34] or treatments with pulmonary vasodilators[35] and statins.[36] Additional studies with multi-center pediatric cohorts should be sought after to confirm our findings, as this may help guide the general understanding and management of complications following PGD in pediatrics and which patients may benefit from more aggressive management or

prevention of modifiable risk factors for PGD. Further investigations of pediatric-specific risk factors for the development of PGD, as well as biomarker patterns in the evolution of severe PGD, may afford clinicians the ability to improve related outcomes.

LIMITATIONS

There are several limitations to this study. The retrospective, single center design and the analytic methods only allow for the reporting of associations and do not necessarily signify causality. Despite the relatively high volume of pediatric lung transplants conducted by the study institution, this single-center data may lack generalizability to other institutions with different referral patterns and patient populations. Further, the size of the study population prevented more sophisticated statistical analyses, such as restricted mean survival time and dose-dependent effects of PGD. Lastly, application of the established ISHLT CLAD definition, is limited to pediatric patients who can participate in lung function testing. Therefore, we used a combination of spirometry, histopathology, and radiological findings suggestive of chronic allograft rejection to diagnose CLAD, which is recognized to be clinically relevant in this population but deviates from the standard definitions outlined by adult literature.

CONCLUSIONS

Our study describes the time course of PGD in a cohort of patients who underwent pediatric lung transplantation and further demonstrates the association of PGD 3 at 48- or 72-hours with shorter CLAD-free survival. Sex may be an effect modifier of this association but warrants additional investigation for an improved understanding of this recipient-based clinical factor. Expansion of the study to include multiple, large transplant centers might allow transplant physicians to better understand the implications of PGD on both short- and long-term outcomes for pediatric lung recipients. Additional studies examining donor, recipient, and perioperative risk factors for severe, late PGD in the pediatric population should also be considered, as an improved understanding of this impactful clinical condition can help guide efforts to prevent its development and mitigate downstream deleterious effects. Finally, there is an urgent need for a pediatric-specific CLAD definition that incorporates alternate methods for measuring pulmonary function as well as the standardization of serial imaging and transbronchial biopsies in algorithms for diagnosing CLAD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FINANCIAL DISCLOSURE

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Abbreviations:

BOS	bronchiolitis obliterans syndrome
CARV	community associated respiratory virus
CF	cystic fibrosis
CHOP	Children's Hospital of Philadelphia
CLAD	chronic lung allograft dysfunction
CMV	cytomegalovirus
ECMO	extracorporeal membrane oxygenation
FEV1	forced expiratory volume in 1 second
HR	hazard ratio
ISHLT	International Society for Heart and Lung Transplantation
IQR	Interquartile Range
PCR	polymerase chain reaction
LV	left ventricle
PGD	primary graft dysfunction
PFT	pulmonary function test
PH	pulmonary hypertension
RAS	restrictive allograft syndrome
RV	right ventricle

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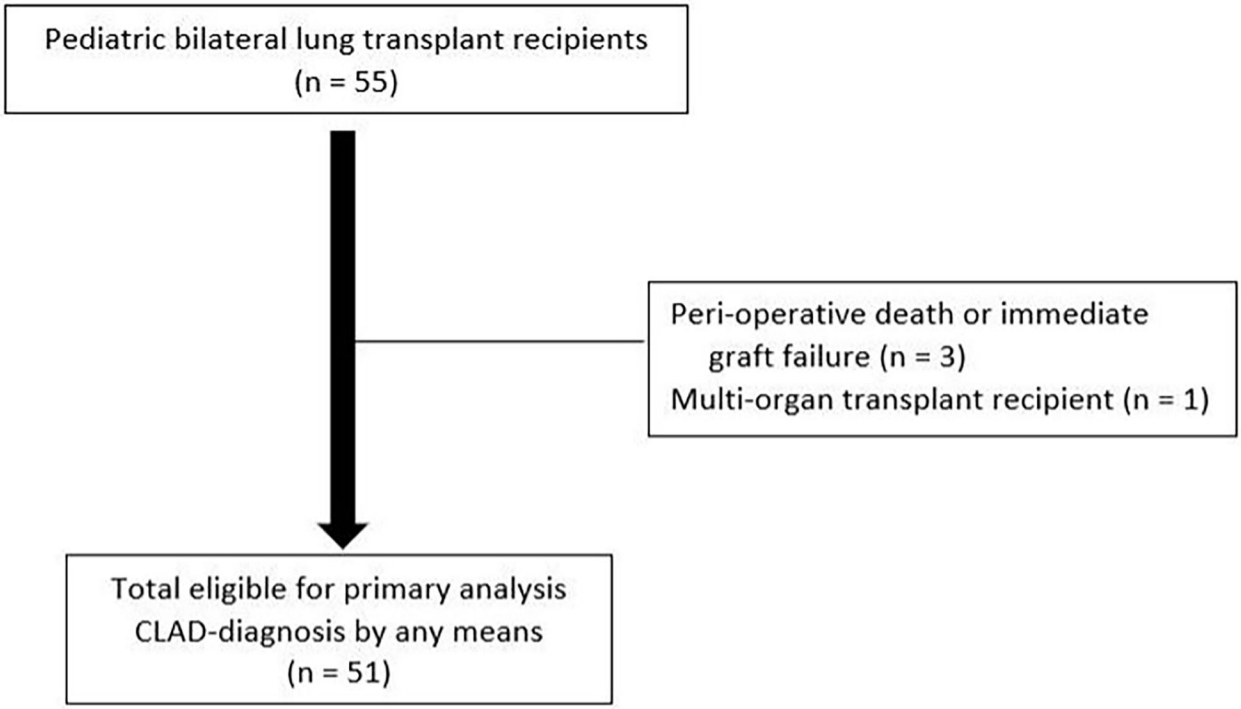

Figure 1:
Study flow chart

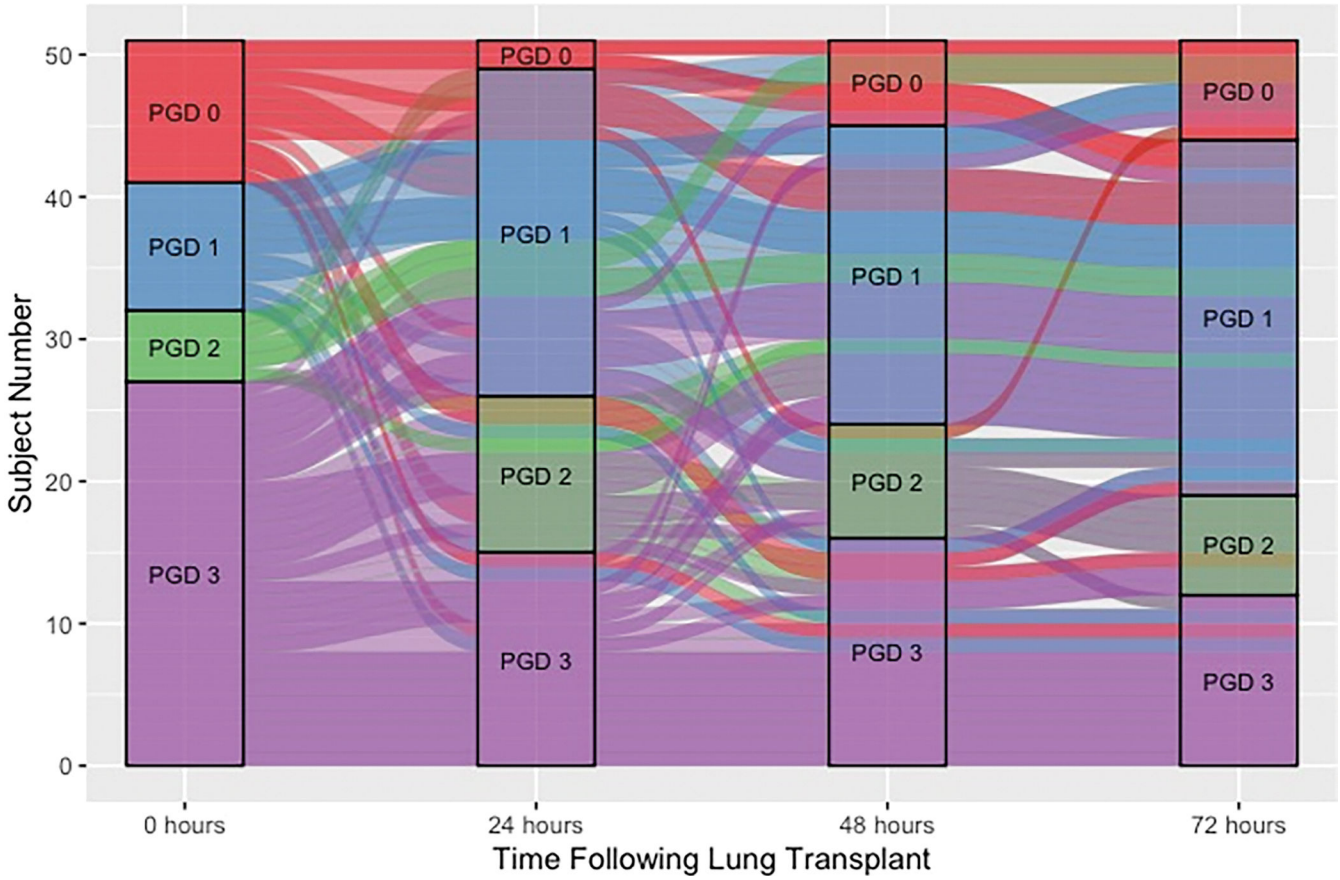

Figure 2:

Alluvial plot showing the distribution of PGD grade for individuals and PGD groups during the first 72 hours following lung transplantation.

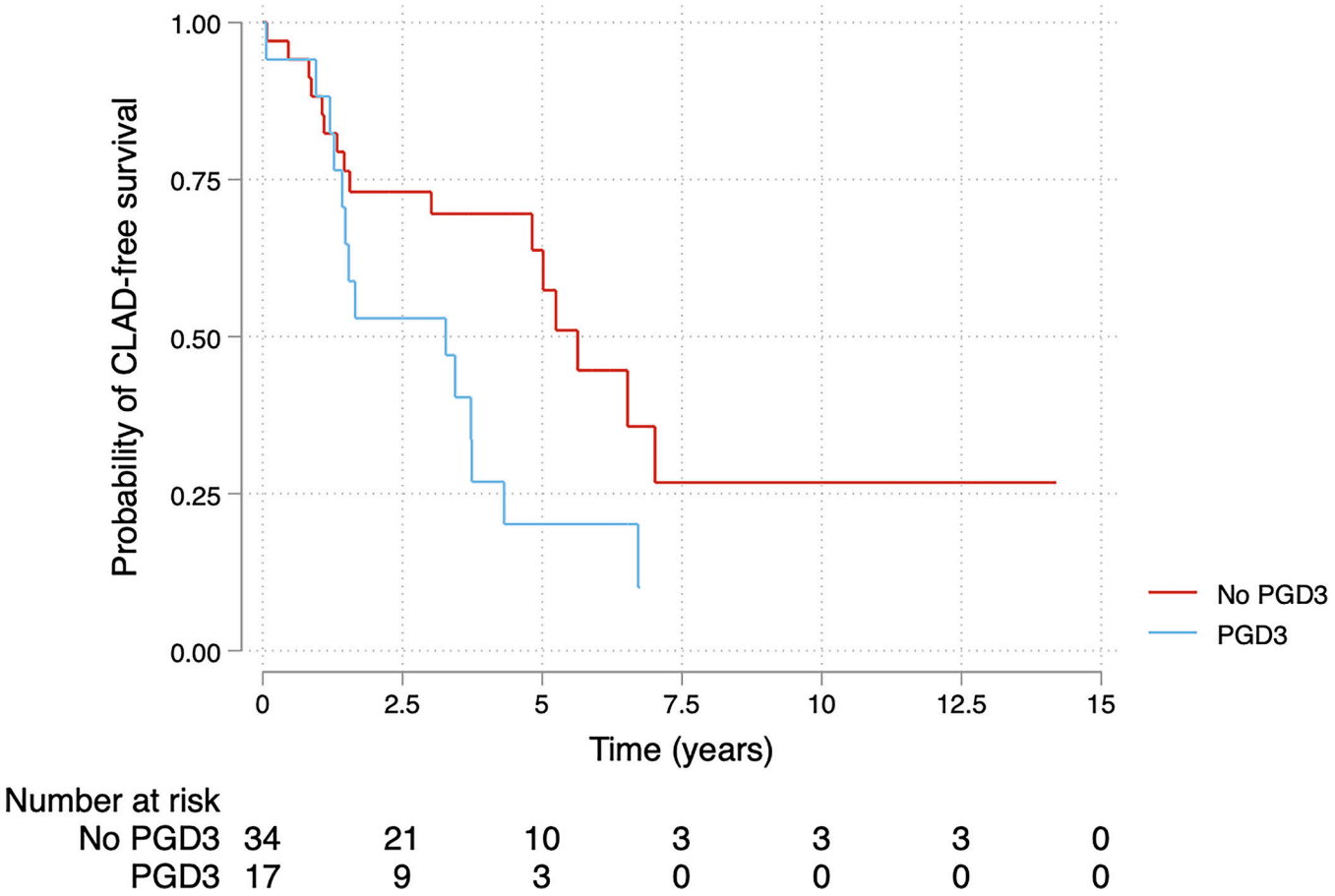

Figure 3:

Kaplan-Meier estimates for the probability of CLAD-free survival in patients who had PGD 3 at 48- or 72-hours post-lung transplant (PGD 3) and those who did not (No PGD 3). Log-rank test p=0.042.

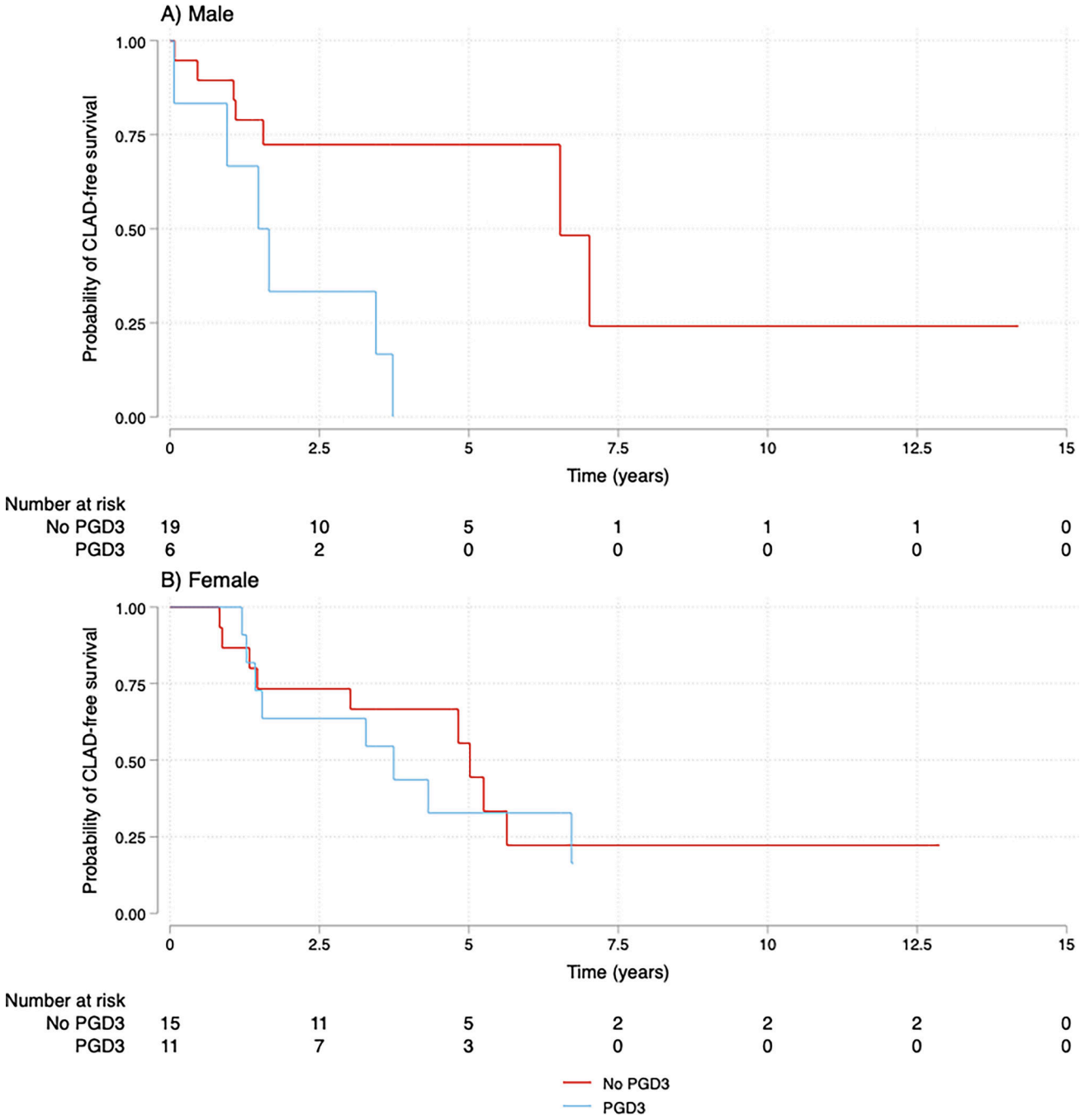

Figure 4:

Kaplan-Meier estimates for probability of CLAD-free survival for those who had PGD 3 at 48- or 72-hours post-lung transplant (PGD 3) and those who did not (No PGD 3) stratified by sex. Panel A depicts males from the cohort (log-rank test p=0.0049). Panel B depicts females from the cohort (log-rank test p=0.6688).

Table 1.

Baseline patient characteristics at the time of lung transplant for the total cohort with comparison between patients who developed primary graft dysfunction grade 3 (PGD 3) at 48- or 72-hours following transplant and those who did not (No PGD 3).

Baseline Patient Characteristics	Total N=51	No PGD 3* N=34	PGD 3* N=17	p-value*
Median Age (IQR) – years	12.7 (8.0–15.8)	13.1 (10.9–15.8)	12.4 (5.3–14.1)	0.63
Age stratified – no. (%)				0.07
< 2 years	7 (14%)	4 (12%)	3 (18%)	
2–11 years	14 (27%)	9 (26%)	5 (29%)	
12–17 years	25 (49%)	20 (59%)	5 (29%)	
18–21 years	5 (10%)	1 (3%)	4 (24%)	
Sex – no. (%)				0.24
Male	25 (49%)	19 (59%)	6 (35%)	
Female	26 (51%)	15 (44%)	11 (65%)	
Race – no. (%)				0.81
Asian	1 (2%)	0 (0%)	1 (6%)	
Black	5 (10%)	4 (12%)	2 (6%)	
White	27 (53%)	18 (53%)	12 (53%)	
More than one race	3 (6%)	2 (6%)	1 (6%)	
Unknown or not reported	15 (29%)	10 (29%)	5 (29%)	
Ethnicity – no. (%)				1.00
Hispanic	18 (35%)	12 (35%)	6 (35%)	
Non-Hispanic	33 (65%)	22 (65%)	11 (65%)	
Median Height (IQR) – cm	133 (102–154)	142 (125–155)	123 (65–140)	0.045
Median Weight (IQR) – kg	31.6 (19.1–41.4)	34.2 (23.0–41.4)	29.1 (16.6–41.4)	0.33
BMI (IQR) – kg/m^2	17.5 (15.1–19.8)	17.3 (15.1–19.7)	18.0 (15.3–23.6)	0.45
Reason for Transplant – no. (%)				0.005
Cystic Fibrosis	15 (29%)	13 (38%)	2 (12%)	
Alveolar Capillary Dysplasia	2 (4%)	2 (6%)	0 (0%)	
Interstitial Lung Disease	1 (2%)	0 (0%)	1 (6%)	
Bronchiolitis obliterans	6 (12%)	5 (15%)	1 (6%)	
Pulmonary hypertension	10 (20%)	2 (6%)	8 (47%)	
Lung GVHD	2 (4%)	2 (6%)	0 (0%)	
Other	15 (29%)	10 (29%)	5 (29%)	
Procedure – no. (%)				0.29
Bilateral	47 (92%)	30 (88%)	17 (100%)	
Repeat bilateral	4 (8%)	4 (12%)	0 (0%)	
Donor-Recipient Sex Match – no (%)				1.00
None	29 (57%)	19 (56%)	10 (59%)	
Female Donor / Male Recipient	8 (16%)	6 (18%)	2 (12%)	
Male Donor / Female Recipient	14 (27%)	9 (26%)	5 (29%)	
Median D/R Height Ratio (IQR)	1.08 (0.98–1.12)	1.08 (1.03–1.10)	1.05 (0.96–1.12)	0.30

Baseline Patient Characteristics	Total N=51	No PGD 3* N=34	PGD 3* N=17	p-value*
Functional Status – no. (%)				
Independent	8 (16%)	8 (24%)	0 (0%)	0.040
Some Dependence	17 (33%)	10 (29%)	7 (41%)	0.53
Total Dependence	17 (33%)	11 (32%)	6 (35%)	1.00
Assisted Ventilation – no. (%)				0.054
Nocturnal	16 (52%)	15 (60%)	1 (8%)	
Continuous	15 (48%)	10 (40%)	5 (83%)	
Supplemental Oxygen – no. (%)	42 (91%)	30 (91%)	12 (92%)	1.00
Diabetes – no. (%)	13 (28%)	11 (33%)	2 (15%)	0.29
‡6 Minute Walk Test (IQR) – feet	500 (0–1007)	400 (0–990)	594 (0–1230)	0.75
Median CPB Time (IQR) - min	195 (159–248)	185 (158–247)	221 (194–248)	0.11
Median Ischemic Time (IQR) - min				
Right Lung	296 (253–344)	304 (259–345)	280 (245–334)	0.40
Left Lung	279 (253–297)	278 (255–292)	286 (232–316)	0.74

*Continuous data were compared with Wilcoxon rank-sum test and categorical data were compared with Fisher's exact test or Pearson's chi-square, where appropriate

‡N=46.

Abbreviations: PGD 3 = primary graft dysfunction grade 3 at 48- or 72-hours post-transplant; IQR = interquartile range; no. = number; cm = centimeters; kg = kilograms; GVHD = graft versus host disease; CPB = cardiopulmonary bypass; min = minutes

Table 2.

Patient outcomes for the total cohort with comparison between patients who developed primary graft dysfunction grade 3 (PGD 3) at 48- or 72-hours following transplant and those who did not (No PGD 3).

Patient Outcomes	Total N=51	No PGD 3* N=34	PGD 3* N=17	p-value*
Median Hospital LOS (IQR) - days	27 (19–49)	25 (19–41)	37 (23–66)	0.091
Median Ventilator Days (IQR)	1 (1–9)	1 (1–4)	7 (2–8)	0.035
Death – no. (%)	14 (27%)	8 (24%)	6 (35%)	0.51
Median Days to Death (IQR)	870 (386–1074)	709 (385–1107)	902 (395–922)	0.80
30-day mortality	2 (4%)	1 (3%)	1 (6%)	1.00
90-day mortality	2 (4%)	1 (3%)	1 (6%)	1.00
1-year mortality	2 (4%)	1 (3%)	1 (3%)	1.00
3-year mortality	11 (22%)	6 (18%)	5 (29%)	0.47
5-year mortality	14 (27%)	8 (24%)	6 (35%)	0.51
Development of CLAD – no. (%)	26 (51%)	13 (38%)	13 (76%)	0.017
CLAD Severity (based on PFT)				0.40
Grade 1	18 (35%)	9 (26%)	9 (53%)	
Grade 2	2 (4%)	1 (3%)	1 (6%)	
Grade 3	2 (4%)	2 (6%)	0 (6%)	
Median Time to CLAD (IQR) - days	846 (462–1746)	1092 (397–1900)	599 (515–1349)	0.86

*Continuous data were compared with Wilcoxon rank-sum test and categorical data were compared with Fisher's exact test or Pearson chi-square, where appropriate.

Abbreviations: PGD 3 = primary graft dysfunction grade 3 at any time between 48- or 72-hours post-transplant; IQR = interquartile range; no. = number; CLAD = chronic lung allograft dysfunction; PFT = pulmonary function test

Table 3:

Graft rejection and infectious characteristics and comparison of patients who developed CLAD and those who did not.

Characteristic	Total N=51	No CLAD N=25	CLAD N=26	p-value*
Evidence of cellular rejection < 18 months	38 (75%)	19 (76%)	19 (73%)	1.0
Grade A	30 (59%)	16 (64%)	14 (54%)	0.572
Grade B	21 (41%)	7 (28%)	14 (54%)	0.089
Evidence of antibody-mediated rejection	9 (18%)	3 (12%)	6 (23%)	0.465
CMV pneumonitis prior to CLAD	6 (12%)	4 (16%)	2 (8%)	0.419
CARV detected with PCR < 12 months	38 (75%)	17 (74%)	21 (81%)	0.349
Pseudomonas isolated via culture prior to CLAD	24 (47%)	10 (40%)	14 (54%)	0.404
Aspergillus isolated via culture prior to CLAD	15 (29%)	7 (28%)	8 (31%)	1.0

*Continuous data were compared with Wilcoxon rank-sum test and categorical data were compared with Fisher's exact test

Abbreviations: CLAD = chronic lung allograft rejection; CMV = cytomegalovirus; CARV = community acquired respiratory virus; PCR = polymerase chain reaction

Table 4.

Cox Proportional Hazards regression for the association of the exposure of PGD 3 at 48- or 72-hours with the outcome of CLAD-free survival.

	Hazard Ratio (95% CI)	p-value
Unadjusted	2.10 (1.01–4.37)	0.047
Adjusted for:		
Recipient sex	2.27 (1.04–4.95)	0.040
CF diagnosis	2.02 (0.96–4.25)	0.064
PH diagnosis	1.99 (0.88–4.52)	0.099
Recipient age at time of transplant	2.09 (1.01–4.35)	0.048
Donor-to-recipient height ratio	2.03 (0.97–4.26)	0.062
Donor-to-recipient sex mismatch	2.19 (1.05–4.58)	0.037
Evidence of cellular rejection < 18 months		
Grade A	2.13 (0.99–4.56)	0.052
Grade B	2.14 (1.00–4.58)	0.051
Evidence of Ab-mediated rejection prior to CLAD	2.08 (1.00–4.37)	0.050
CMV pneumonitis prior to CLAD	2.19 (1.02–4.70)	0.044
CARV detected with PCR < 12 months	2.26 (1.06–4.84)	0.035
Pseudomonas isolated via culture prior to CLAD	2.11 (1.01–4.39)	0.046
Aspergillus isolated via culture prior to CLAD	2.09 (1.01–4.34)	0.048
Stratified analyses		
Recipient sex		0.057 *
Male	4.73 (1.44–15.6)	
Female	1.23 (0.47–3.20)	
Recipient age group		0.387 *
< 12 years	3.18 (0.88–11.5)	
≥ 12 years	1.51 (0.60–3.79)	

* p-value for interaction term

Abbreviations: PGD = primary graft dysfunction; CLAD = chronic lung allograft dysfunction; CF = cystic fibrosis; PH = pulmonary hypertension; Ab = antibody; CMV = cytomegalovirus; CARV = community associated respiratory virus; PCR = polymerase chain reaction