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ORIGINAL ARTICLE

Center volume and primary graft dysfunction in patients undergoing lung transplantation in the United States – a cohort study

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SUMMARY

Lung transplantation primary graft dysfunction (PGD) is common and portends poor outcomes. We examined the association of lung transplant center volume with PGD and the risk of mortality. The United Network for Organ Sharing transplant registry was queried for adult lung transplants from March 2015 to March 2019. Recipients were stratified by the occurrence of grade 3 PGD 72 h post-transplant, defined using modified ISHLT criteria. The adjusted association between volume and PGD as well as post-PGD survival was analyzed. 7322 recipients were included, among whom approximately 21% (n = 1525) experienced grade 3 PGD. After adjustment, increasing annualized lung transplant volume was associated with a decrease in the odds of PGD in a near-linear fashion (OR 0.94 per 10 transplants, 95% CI 0.89–0.99). Furthermore, increasing annualized lung transplant center volume up to approximately 55 transplants per year was associated with improved survival among patients with grade 3 PGD (HR 0.87 per 10 transplants, 95% CI 0.79–0.94). Increasing annual lung transplant center volume is associated with a decreased incidence of grade 3 PGD. Further, increasing volume among low- and medium-volume centers is associated with improved survival of patients who experience PGD.

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Key words
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Introduction

Despite a growing global experience with clinical lung transplantation over the past several decades, recipient survival remains the lowest among the most commonly transplanted organs in the United States [1,2]. While improvements have been made in patient selection and operative techniques, primary graft dysfunction (PGD) continues to be a significant cause of post-transplant morbidity as well as both short- and long-term mortality [3–6]. As a result, multiple studies have been performed to identify clinical risk factors associated with the development of PGD [7–9]. Examination of these risk factors serves to improve our understanding of the pathogenesis of PGD, identify recipient populations at increased risk, and ultimately aid in our ability to prevent PGD as well as treat patients who are afflicted.

While prior analyses have demonstrated a significant association between lung transplant center volume and recipient survival, the link between center volume and PGD remains to be elucidated [10–13]. Examination of

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this association has important implications for improving recipient outcomes and quality of care. We aimed to determine the association between annual lung transplant center volume and the incidence of recipient PGD, as well as the association between volume and mortality following the occurrence of PGD using a large national registry. We hypothesized that increasing lung transplant volume was associated with a decreased incidence of PGD as well as decreased mortality of recipients with PGD.

Materials and methods

Study population

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research (STAR) files containing deidentified donor and recipient transplant data from October 1987 through March 2019 with follow-up information through June 2019. The database includes prospectively collected data for all organ transplants performed in the United States during this period. We queried the UNOS database for all first-time, adult (age ≥18), single or bilateral lung transplant recipients between March 2015 and March 2019 and their associated donors (Fig. 1). The study period was selected based upon the availability of recipient 72-h oxygenation data within the database. Recipients undergoing multi-organ transplantation, and those who died within 72 h of transplantation for causes other than primary graft failure were excluded. Recipients requiring invasive mechanical ventilation with missing 72-h oxygenation (P/F ratio) data were also excluded. Table S1 and Fig. S1 present a comparison of recipient baseline characteristics and survival, respectively, of those excluded from the study with included recipients that were intubated and not on ECMO at 72-h post-transplant.

Data analysis

Unadjusted descriptive analyses of baseline recipient and donor characteristics as well as PGD outcomes were performed, stratified by center volume. High volume was defined as centers performing greater than the 90th percentile of lung transplants annually (>70), averaged over the study period. Baseline demographic and clinical characteristics are presented as median (interquartile range) for continuous variables and percent (count) for categorical variables, unless otherwise specified. Donor/recipient predicted total lung capacity (pTLC) ratios were calculated using previously published regression equations [14,15]. Pulmonary hypertension was defined as mean pulmonary artery pressure ≥25 mmHg.

Grade 3 PGD was defined using a modification of the definition from the 2016 consensus report of the International Society of Heart and Lung Transplantation's working group on PGD [3]. Grade 2 PGD was defined as a P/F ratio at 72 h post-transplant >200 and ≤300. PGD grade 3 was defined as a P/F ratio at 72 h post-transplant ≤200 or use of ECMO support at 72 h post-transplant. Patients not requiring invasive ventilation or ECMO at 72 h post-transplant were classified as not having grade 3 PGD. Oxygenation, ventilation, and ECMO data for recipients prior to 72 h post-transplant were not available for analysis. Comparisons between volume cohorts were performed using the Wilcoxon rank sum test for continuous variables and the Pearson χ^2 test or Fisher's exact test for categorical variables.

Multivariable logistic regression was used to model the association between annualized lung transplant center volume and the incidence of grade 3 PGD. Model

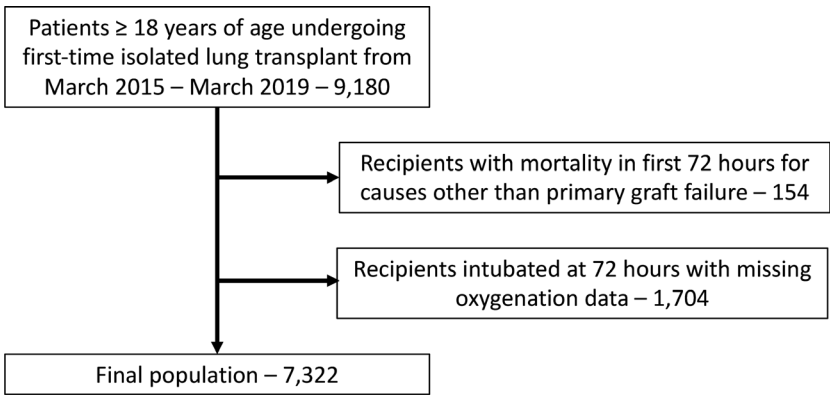

Figure 1 Study inclusion and exclusion criteria.

covariates were selected *a priori* based upon known risk factors of PGD from the literature and availability within the database. A sensitivity analysis was performed to test the unadjusted association between center volume and grade 3 PGD where patients who died in the first 72 h without cause of death listed as PGD (previously excluded, $n = 78$) were classified as having grade 3 PGD. To examine the association between annualized lung transplant center volume and the overall risk of mortality following the development of PGD, a Cox Proportional Hazards model of post-transplant survival was constructed only including the subpopulation of patients that developed PGD. Model covariates were again selected *a priori* based upon clinical experience and data availability. The interaction between annualized center volume and the use of ECMO at 72-h post-transplant was tested. For both multivariable models, linearity of continuous variables with the outcome was assessed using restricted cubic splines (RCS). For ease of interpretation, nonlinear relationships were modeled using piecewise linear splines or with transformation to a categorical variable where appropriate. To account for correlations arising from hospital-level clustering, a random intercept was used for the multivariable logistic regression model and robust variance estimators were used for the multivariable Cox model. Two-sided *P*-values ≤ 0.05 were considered statistically significant unless otherwise indicated. Observations with missing data pertaining to logistic regression covariates were excluded from adjusted analyses but included in unadjusted analyses ($n = 351$, 4.8% of recipients). All statistical analyses were performed using R version 3.5.1 (Vienna, Austria). This analysis was deemed exempt by the Duke University Institutional Review Board.

Results

Patient and center characteristics

In total, 72 lung transplant centers were included in the analysis (Fig. 2) with a median annual lung transplant volume of 23 (IQR 13–41). 7322 lung transplant recipients met study inclusion criteria including 2086 (28.5%) and 5236 (71.5%) that were transplanted at highest volume (≥90th percentile) and remaining centers (<90th percentile), respectively. Median follow-up time was 383 days (IQR 200–748). Recipient baseline demographic and clinical characteristics are presented in Table 1. Recipients at highest volume centers were older, more likely male, White, and diagnosis group D [idiopathic pulmonary fibrosis (IPF)] and were less likely to have a history of diabetes, be diagnosis group A (chronic obstructive pulmonary disease) or C (cystic fibrosis), and be treated with IV antibiotics in the two weeks prior to transplant. Compared with remaining centers, recipients transplanted at high-volume centers had a similar lung allocation score at transplant but spent a shorter amount of time on the waitlist.

Donor characteristics are presented in Table S1. Donors of allografts transplanted at highest volume centers were older, more likely to have a history of cigarette or cocaine use, diabetes, hypertension, cancer, and pulmonary infection. They were also more likely donation after circulatory death (DCD) donors and were associated with slightly longer graft ischemic times. Highest volume centers were less likely to transplant allografts from donors with traumatic brain injury and donors from both cohorts had similar preprocurement oxygenation (PaO_2/FiO_2 ratio).

Primary graft dysfunction

Unadjusted rates of grades 2 (defined as 72-h P/F ratio between 200 and 300) and 3 PGD stratified by center volume are presented in Table 2. There were similar rates of grade 2 PGD in both volume cohorts (~15%). Approximately 21% of lung transplant recipients experienced grade 3 PGD including 17.3% ($n = 360$) and 22.2% ($n = 1165$) from highest volume and remaining centers, respectively. The median 72-h PaO_2/FiO_2 ratio was 277 (IQR 178–386) and 7.9% ($n = 580$) of recipients required ECMO support.

Association between center volume and PGD

Logistic regression was performed to examine the association between various clinical factors, including annualized transplant center volume, and the incidence of PGD. After adjustment for known risk factors of PGD (Table 3), increasing annualized lung transplant volume was associated with a significant decrease in the odds of PGD (OR 0.94 per 10 transplants, 95% CI 0.89–0.99). A plot of the adjusted association between annualized lung transplant center volume, modeled using restricted cubic splines, and the probability of grade 3 PGD is presented in Fig. 3, demonstrating a near-linear relationship. A similar relationship was observed in a sensitivity analysis where patients who died in the first 72 h with cause of death not listed as PGD were classified as having grade 3 PGD (Fig. S2). Donor factors significantly associated with PGD included increasing donor age (OR 1.05 per 5 years, 95% CI 1.02–1.07) and donor

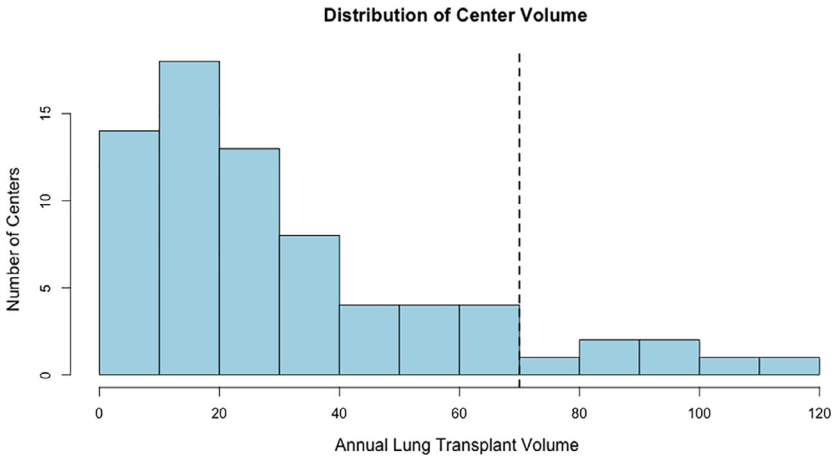

Figure 2 Distribution of annual lung transplant center volume during the study period. Dashed vertical line marks 90th percentile.

cigarette use (OR 1.32, 95% CI 1.04–1.66). Recipient factors significantly associated with PGD included Black race (vs White, OR 1.82, 95% CI 1.50–2.22), increasing BMI (OR 1.09 per unit over 25 kg/m^2, 95% CI 1.06–1.12), diagnosis group B (vs A, OR 4.62, 95% CI 3.46–6.17) and D (vs A, OR 1.90, 95% CI 1.62–2.24), pulmonary hypertension (OR 1.36, 95% CI 1.19–1.55), and ischemic time longer than 5 h (OR 1.49, 95% CI 1.29–1.72). Protective factors against PGD included recipient male sex (OR 0.72, 95% CI 0.63–0.82) and single organ lung transplantation (vs bilateral, OR 0.77, 95% CI 0.65–0.91).

Association between center volume and mortality after PGD

To examine the association between lung transplant center volume and overall mortality following the occurrence of PGD, a multivariable Cox Proportional Hazards model was constructed including patients categorized as experiencing grade 3 PGD (Table 4). While increasing annualized lung transplant center volume up to 55 transplants per year was associated with improved overall survival in this cohort (HR 0.87 per 10 transplants, 95% CI 0.79–0.94), increased center volume over 55 per year was associated with worsening survival (HR 1.24 per 10 transplants, 95% CI 1.06–1.45). A significant interaction (P = 0.006) between center volume and 72-h ECMO utilization was identified (Fig. 4), demonstrating that patients with grade 3 PGD requiring ECMO support had improved survival at higher volume centers. Other identified factors independently associated with worse survival among patients with grade 3 PGD included CNS tumor as donor cause of death (HR 4.57, 95% CI 1.98–10.55) and increasing recipient age over 60 (HR 1.25 per 5 years, 95% CI 1.08–1.46).

Discussion

In this analysis of a large national US transplant registry, which included a modern cohort of over 1500 patients with grade 3 PGD following lung transplant, we examined the association between annualized lung transplant center volume with the incidence of recipient PGD as well as post-PGD failure to rescue. We demonstrated a significant near-linear relationship between increasing annual center volume and decreasing odds of recipients experiencing PGD. Further, increasing transplant center volume to approximately 50–60 transplants annually was associated with decreased mortality of recipients with PGD.

To our knowledge, this is the first study performed to date analyzing the association between center volume and PGD in lung transplantation. Prior studies have identified multiple donor- and recipient-specific risk factors of PGD; however, most of these analyses were performed using smaller single-center or regional cohorts not suitable for a robust analysis of volume [7,8,16,17]. While the relationship between volume and PGD is evident, the mechanism of this relationship is less clear. Donor and recipient selection do not appear to be significant drivers of this association as higher and lower volume centers have similar distributions of known risk factors for PGD (Table 1) including recipient BMI, pulmonary hypertension, and single organ lung transplantation. Furthermore, several known PGD risk factors are actually more prevalent at highest volume centers (Table 1, Table S1) including donors with

Table 1. Recipient baseline characteristics stratified by transplant center volume below and above the 90th percentile.

Variable	Volume <90th percentile (n = 5236)	Volume ≥90th percentile (n = 2086)	*P*-value
Male sex	3084 (58.9%)	1306 (62.6%)	0.004
Age [median (IQR)]	60 (51–66)	63 (55–68)	<0.001
BMI [median (IQR)]	25.6 (21.8–28.9)	25.8 (22.3–28.8)	0.065
Ethnicity			
White	4155 (79.4%)	1714 (82.2%)	0.019
Black	495 (9.5%)	175 (8.4%)	
Hispanic	444 (8.5%)	138 (6.6%)	
Other	142 (2.7%)	59 (2.8%)	
Recipient history			
Diabetes	1060 (20.2%)	371 (17.8%)	0.018
Malignancy	419 (8.0%)	213 (10.2%)	0.003
Pulmonary hypertension	2675 (53.7%)	1113 (55.9%)	0.10
Diagnosis group			
A	1522 (29.1%)	542 (26.0%)	<0.001
B	209 (4.0%)	82 (3.9%)	
C	642 (12.3%)	180 (8.6%)	
D	2863 (54.7%)	1282 (61.5%)	
Recipient creatinine [mg/dl, median (IQR)]	0.80 (0.67–0.96)	0.80 (0.69–0.98)	0.013
Recipient bilirubin [mg/dl, median (IQR)]	0.40 (0.30–0.60)	0.40 (0.30–0.60)	<0.001
Pre-transplant status			
Intensive care unit	552 (10.5%)	171 (8.2%)	0.007
Hospitalized (non-ICU)	516 (9.9%)	224 (10.7%)	
Not hospitalized	4168 (79.6%)	1691 (81.1%)	
Medical therapy			
IV antibiotics in two weeks before transplant	567 (10.8%)	138 (6.6%)	<0.001
Ventilator support at transplant	159 (3.0%)	66 (3.2%)	0.83
ECMO support at transplant	208 (4.0%)	77 (3.7%)	0.62
ABO blood type			
A	2114 (40.4%)	837 (40.1%)	0.055
B	538 (10.3%)	259 (12.4%)	
AB	210 (4.0%)	76 (3.6%)	
O	2374 (45.3%)	914 (43.8%)	
Days on waitlist [median (IQR)]	58 (18–165)	37 (11–114)	<0.001
Lung allocation score [LAS, median (IQR)]	39.9 (34.7–50.6)	39.3 (34.7–49.5)	0.056
Single organ lung transplant (SOLT)	1476 (28.2%)	622 (29.8%)	0.17
Donor-recipient pTLC ratio [median (IQR)]	1.0 (0.9–1.2)	1.0 (0.8–1.2)	0.41

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; pTLC, predicted total lung capacity.

Table 2. Unadjusted rates of grade 3 primary graft dysfunction (PGD) stratified by transplant center volume below and above the 90th percentile.

Outcome	Volume <90th percentile (n = 5236)	Volume ≥90th percentile (n = 2086)	*P*-value
Primary graft dysfunction, grade 2*	441 (15.1%)	161 (15.3%)	0.93
Primary graft dysfunction, grade 3†	1165 (22.2%)	360 (17.3%)	<0.001
72-h PaO_2/FiO_2 ratio [median (IQR)]	265 (175–381)	303 (188–400)	<0.001
72-h ECMO requirement	433 (8.3%)	147 (7.0%)	0.015

ECMO, extracorporeal membrane oxygenation.

*72-h P/F ratio 200–300.

†Modified ISHLT definition including intubated recipients requiring ECMO at 72-h post-transplant or with a P/F ratio ≤200.

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Table 3. Multivariable logistic regression model for factors independently associated with grade 3 PGD.

Predictor	Odds ratio	95% Confidence interval		*P*-value
		Lower	Upper	
Annualized lung transplant volume (per 10 transplants)	0.94	0.89	0.99	0.014
Donor age (per 5 years)	1.05	1.02	1.07	<0.001
Donor cigarette use	1.32	1.04	1.66	0.021
Donor heavy alcohol use	1.17	0.98	1.38	0.075
Recipient male sex	0.72	0.63	0.82	<0.001
Recipient ethnicity (reference: white)				
Black	1.82	1.50	2.22	<0.001
Hispanic	1.27	1.01	1.60	0.039
Other	1.99	1.43	2.77	<0.001
Recipient BMI <25 kg/m^2 (per unit)	0.99	0.96	1.03	0.62
Recipient BMI ≥25 kg/m^2 (per unit)	1.09	1.06	1.12	<0.001
Diagnosis group (reference: A)				
B	4.62	3.46	6.17	<0.001
C	0.90	0.67	1.20	0.46
D	1.90	1.62	2.24	<0.001
Pulmonary hypertension	1.36	1.19	1.55	<0.001
Ischemic time >5 h	1.49	1.29	1.72	<0.001
Single organ lung transplant (reference: bilateral)	0.77	0.65	0.91	0.002
Annualized lung transplant volume (per 10 transplants)	0.94	0.89	0.99	0.014
Donor age (per 5 years)	1.05	1.02	1.07	<0.001
Donor cigarette use	1.32	1.04	1.66	0.021
Donor heavy alcohol use	1.17	0.98	1.38	0.075
Recipient male sex	0.72	0.63	0.82	<0.001
Recipient ethnicity (reference: white)				
Black	1.82	1.50	2.22	<0.001
Hispanic	1.27	1.01	1.60	0.039
Other	1.99	1.43	2.77	<0.001
Recipient BMI <25 kg/m^2 (per unit)	0.99	0.96	1.03	0.62
Recipient BMI ≥25 kg/m^2 (per unit)	1.09	1.06	1.12	<0.001
Diagnosis group (reference: A)				
B	4.62	3.46	6.17	<0.001
C	0.90	0.67	1.20	0.46
D	1.90	1.62	2.24	<0.001
Pulmonary hypertension	1.36	1.19	1.55	<0.001
Ischemic time >5 h	1.49	1.29	1.72	<0.001
Single organ lung transplant (reference: bilateral)	0.77	0.65	0.91	0.002

BMI, body mass index; PGD, primary graft dysfunction.

smoking history, increased graft ischemic times, and recipient IPF. Therefore, protection against PGD at higher volume centers is likely being driven by known risk factors for PGD not captured in the UNOS dataset such as cardiopulmonary bypass use, blood product transfusion, oxygenation during allograft reperfusion, or other unknown perioperative factors. In addition, the timing of ECMO deployment as well as different modalities of ECMO utilized may have also influenced the association between center volume and the risk of PGD.

A significant volume–outcomes relationship persisted even after the occurrence of PGD, which is a novel finding. Multiple prior studies, however, have examined the impact of volume on recipient survival and have largely noted a significant association between increasing annual lung transplant center volume and recipient survival, despite a generally higher risk case mix at higher volume centers [10,11,18,19]. While the exact mechanism of this volume–outcomes relationship is controversial, the existing evidence suggests that higher volume lung transplant centers may be better equipped to rescue patients that experience complications [10,20]. Our finding that increasing volume among low- and medium-volume centers correlates with improved post-

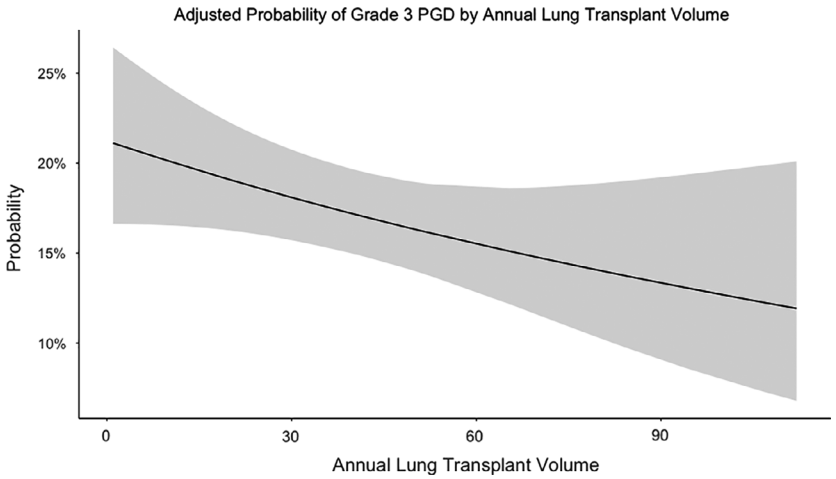

Figure 3 Adjusted logistic regression model for grade 3 PGD using restricted cubic splines (RCS). Shaded area represents 95% confidence interval.

Table 4. Multivariable Cox Proportional Hazards model for factors independently associated with survival among patients who experience grade 3 primary graft dysfunction (PGD).

Predictor	Hazard ratio	95% Confidence interval		*P*-value
		Lower	Upper	
Annualized lung transplant volume <55 (per 10 transplants)	0.87	0.79	0.94	<0.001
Annualized lung transplant volume ≥55 (per 10 transplants)	1.24	1.06	1.45	0.008
Donor age (per 5 years)	1.04	0.99	1.09	0.13
Donor cigarette use	0.98	0.66	1.46	0.92
Donor cause of death (ref: anoxia)				
Cerebrovascular/stroke	0.99	0.74	1.34	0.96
Head trauma	0.87	0.62	1.22	0.43
CNS tumor	4.57	1.98	10.55	<0.001
Other	1.56	0.68	3.60	0.30
DCD donor	0.97	0.56	1.67	0.91
Recipient male sex	0.95	0.77	1.18	0.67
Recipient age <60 (per 5 years)	1.05	0.97	1.12	0.22
Recipient age ≥60 (per 5 years)	1.25	1.08	1.46	0.003
Recipient ethnicity (reference: white)				
Black	1.08	0.79	1.47	0.63
Hispanic	0.73	0.46	1.15	0.17
Other	1.37	0.78	2.40	0.27
Recipient BMI (per unit)	1.01	0.99	1.04	0.35
Recipient diabetes	1.09	0.90	1.31	0.37
Recipient pulmonary hypertension	0.89	0.71	1.12	0.32
Recipient diagnosis group (reference: A)				
B	1.00	0.64	1.58	0.99
C	1.32	0.67	2.63	0.42
D	1.07	0.82	1.40	0.62
Lung allocation score (per unit)	0.99	0.98	1.00	0.03
ECMO prior to transplant	1.16	0.68	1.96	0.59
Single organ lung transplant (ref: BOLT)	0.87	0.64	1.17	0.34
Donor-recipient pTLC ratio (per unit)	1.05	0.93	1.18	0.41
Ischemic time >5 h	1.14	0.91	1.43	0.25

BMI, body mass index; BOLT, bilateral orthotopic lung transplant; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygenation; pTLC, predicted total lung capacity.

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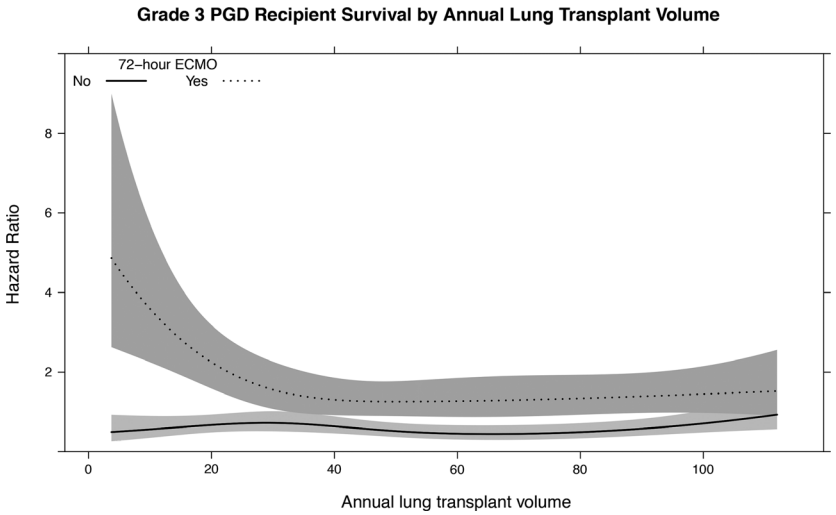

Figure 4 Multivariable Cox Proportional Hazards model for grade 3 PGD recipient survival using restricted cubic splines (RCS) demonstrating interaction between volume and 72-h ECMO usage. Shaded areas represent 95% confidence interval.

PGD rescue also supports this paradigm. However, the worsening survival observed at the highest volume centers suggests a more complex interaction between center volume and post-PGD rescue.

The worsening survival associated with very high-volume centers is likely the result of unaccounted for heterogeneity among patients experiencing PGD grade 3 at higher and lower volume centers. After stratifying PGD recipients by ECMO support in the interaction term analysis, it became clear that the sickest of PGD grade 3 patients, those that required ECMO support, had improved outcomes at higher volume centers. While impossible to definitively assess in a retrospective analysis of registry data, it is conceivable that higher volume centers are more comfortable with ECMO deployment and may choose to deploy ECMO earlier in a patient's postoperative course when it is most likely to positively impact outcomes [21]. In addition, while the UNOS registry does not contain the granularity necessary to differentiate between veno-venous (VV) and veno-arterial (VA) ECMO, there may be differences in the utilization of different ECMO modalities at different volume centers. There are likely other additional unknown confounders driving the increased mortality observed among PGD patients at the highest volume transplant centers.

There are several limitations of this study worth mentioning. First, as a retrospective review of a large national transplant registry, we are limited by the quality, accuracy, and availability of predictor variables within the dataset. Importantly, approximately 19% of recipients could not be assigned a PGD category because of missing recipient 72-h oxygenation data and were therefore excluded, introducing a possibility of bias. In a comparison of baseline characteristics and survival between excluded and included recipients (Table S1 and Fig. S1), excluded recipients were generally transplanted at higher volume centers and had improved survival. Therefore, potential bias was minimal as inclusion of these recipients in the study would likely have strengthened the association between transplant volume and decreased rates of PGD. In addition, several known predictors of PGD such as cardiopulmonary bypass use, blood product transfusion, and oxygenation during allograft reperfusion are not coded in the UNOS database and therefore could not be adjusted for in our multivariable analyses. Second, our post-transplant survival analysis was limited by a relatively short follow-up time given the recent time period of the study. Future studies with longer term follow-up are unlikely to result in significantly different findings, however, given the disproportionate impact of PGD in the perioperative period. Third, we included both single and bilateral lung transplantation in this analysis, which may have introduced the possibility of bias given known differences in the manifestation of PGD between the two [22]. The similar incidence of single organ lung transplantation between both volume cohorts likely limited its impact on outcomes, however, which was further mitigated by the inclusion of single versus bilateral lung transplantation in our multivariable models. Lastly, between-center differences likely exist regarding both thresholds for implementing ECMO support in post-transplant patients as well as the modality of ECMO used (VA or VV), which may influence the relationship observed between volume and outcomes. A more detailed analysis of clinical decision-making factors

cannot be robustly analyzed in a large retrospective registry study.

Conclusions

Increasing annual lung transplant center volume is associated with a decreased incidence of grade 3 PGD among adults undergoing first-time lung transplantation since 2015. In addition, increasing volume among low- and medium-volume centers is associated with improved rescue of patients who experience PGD, and in particular those that require ECMO support. These findings have important implications for ongoing global efforts to further elucidate risk factors and management strategies for primary graft dysfunction following lung transplantation. Further, these findings support future studies examining the nature of the relationship between peri-transplant ECMO utilization and the development of PGD, as well as outcomes of patients who experience PGD.

Authorship

OKJ and VR: designed the study, performed the analysis, and wrote the manuscript. BSB, JK, and MGH: contributed to the design of the study and writing as well as reviewing of the manuscript.

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Conflicts of interest

The authors have no relevant conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Recipient baseline characteristics of those patients excluded from the study due to missing 72-h oxygenation data (n = 1704) with included patients that were intubated but not on ECMO at 72-h post-transplant.

Table S2. Donor and allograft characteristics stratified by transplant center volume below and above the 90th percentile.

Figure S1. Kaplan-Meier comparison of recipient survival of those patients excluded from the study due to missing 72-h oxygenation data (n = 1704) with included patients that were intubated but not on ECMO at 72-h post-transplant.

Figure S2. Sensitivity analysis of unadjusted logistic regression model for grade 3 PGD using restricted cubic splines (RCS) where patients who died in the first 72 h for causes other than PGD were classified as having grade 3 PGD.

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