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RESEARCH ARTICLE

The role of mechanical ventilation in primary graft dysfunction in the postoperative lung transplant recipient: A single center study and literature review

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Abstract

Background: Primary graft dysfunction (PGD) is still a major complication in patients undergoing lung transplantation (LTx). Much is unknown about the effect of post-operative mechanical ventilation on outcomes, with debate on the best approach to ventilation.

Aim/Purpose: The goal of this study was to generate hypotheses on the association between postoperative mechanical ventilation settings and allograft size matching in PGD development.

Method: This is a retrospective study of LTx patients between September 2011 and September 2018 (n = 116). PGD was assessed according to the International Society of Heart and Lung Transplantation (ISHLT) criteria. Data were collected from medical records, including chest x-ray assessments, blood gas analysis, mechanical ventilator parameters and spirometry.

Results: Positive end-expiratory pressures (PEEP) of 5 cm H_2O were correlated with lower rates of grade 3 PGD. Graft size was important as tidal volumes calculated according to the recipient yielded greater rates of PGD when low volumes were used, a correlation that was lost when donor metrics were used.

Conclusion: Our results highlight a need for greater investigation of the role donor characteristics play in determining post-operative ventilation of a lung transplant recipient. The mechanical ventilation settings on postoperative LTx recipients may have an implication for the development of acute graft dysfunction. Severe PGD was associated with the use of a PEEP higher than 5 and lower tidal volumes and oversized lungs were associated with lower long-term mortality. Lack of association between ventilatory settings and survival may point to the importance of other variables than ventilation in the development of PGD.

KEYWORDS
lung transplant recipients, postoperative mechanical ventilation, primary graft dysfunction, protective lung ventilation

Editorial Comment

Risk factors for complications after lung transplantation may include choices for intra and post-operative ventilatory management, when considering allograft size matching. This retrospective analysis of experience from one center explored associations between recipient and allograft size, PEEP, and tidal volume levels with risk for post-operative graft dysfunction.

1 | INTRODUCTION

Sixty years of lung transplantation (LTx) have led to the advancement of surgical and perioperative techniques, and yet the procedure remains hindered by a high risk of mortality and morbidity. The complications of LTx can be traced back both to primary graft dysfunction (PGD) and chronic lung allograft dysfunction (CLAD).[1] The consideration of these complications is important in the light of a mere 59% survival rate 5 years following transplantation.[2]

PGD is acute graft dysfunction in the 72 h following LTx and is graded by the severity of the decrease in the PaO_2/FiO_2 ratio concomitant with the appearance of infiltrate on chest imaging.[3] Grade 3 or severe PGD has an impact on early mortality and is associated with CLAD.[4-7] CLAD, marked by a persistent decrease in FEV_1, arises in 35% of LTx patients after 5 years and contributes to the overall 27% survival rate 10 years after transplant.[8] Interventions that reduce the rate of PGD could thus have consequences for both the short-term and long-term outcomes of LTx patients. All-cause mortality within the first 30 days following the transplantation can be influenced by the incidence of PGD, as a study on over 5,000 patients across an international registry found that those with PGD had a 42.1% 30-day mortality rate relative to the 6.1% in those without.[5]

While a singular etiology of PGD is yet unproven, there are a number of known factors correlated with PGD, including increasing donor age and smoking history.[9] Given the potential role of ischemia-reperfusion injury as well as the risk of ventilatory induced lung injury (VILI), settings for mechanical ventilation must be carefully considered.[1,10,11] The optimization of size matching may also be a factor in reducing rates of PGD as stress and over-distension of alveoli lead to VILI.[12]

PGD has been shown to be clinically and histologically analogous to acute respiratory distress syndrome (ARDS)[13,14] and so discussion has grown regarding the application of established ARDS protective ventilation strategies to prevent PGD. Protective ventilation refers to the use of a low tidal volume of 6 ml/kg.[15,16]

A mismatch in lung sizes between the donor and the recipient could lead to undersized allografts receiving relatively higher tidal volumes when calculated according to the donor's predicted body weight (donor PBW).[17] As larger tidal volumes are associated with an increased risk of development of ARDS[18] and due to the parallels between ARDS and PGD, tidal volumes when calculated according to the recipient rather than the donor could impact the development of PGD.

An international survey conducted by Beer et al[19] demonstrated that the majority of practitioners consider only the recipient's PBW when setting either volume or pressure-assisted ventilation. 58% of respondents did not even have donor information. The codification of guidelines for mechanical ventilation could lead to a decrease in the rates of allograft dysfunction. This study aims to determine the role of considering both donor and recipient characteristics when determining ventilation settings and the relationships of these factors to PGD.

2 | METHODS

2.1 | Patients

This retrospective study includes all LTx recipients at the Department of Cardiothoracic Surgery, Anaesthesia and Intensive Care Unit at Lund University Hospital in Lund, Sweden, between September 2011 and September 2018 ($n = 116$). The study was approved by the local ethical committee (Dnr 2016/638). Recipients and donors were approved for transplantation by our standard clinical routine, in line with latest guidelines.[20] Graft matching was based on donor height, ±10% pTLC mismatch, HLA-, antibody-, and ABO blood group matching. Recipient and donor characteristics are shown in Table 1. The type of intraoperative machine perfusion and the ischemic times for the lungs, as defined by the time between the clamp placement on the donor and reperfusion in the recipient were reported in Table 2.

PGD was defined and classified as grade 0, 1, 2, or 3 according to the ISHLT definition[3] as outlined in Table 3. The definition is reached upon evaluation of chest X-ray, blood gases (partial pressure of oxygen in arterial blood, PaO_2) and oxygen concentration in inhaled air (FiO_2). PGD was evaluated every 24 h during the first 72 h postoperatively. Chest X-rays were assessed by a clinical radiologist for evaluation of the presence of infiltrates and/or pulmonary edema. Patients treated with postoperative ECMO were classified as grade 3 PGD.

2.2 | Postoperative management and mechanical ventilation

Patients were admitted to the intensive care unit (ICU) designated specifically for cardiothoracic surgical patients wherein each patient received tailored care by a cardiothoracic anaesthesiologist for their postoperative care. All patients in this study were ventilated using a Servo-I Ventilator (Getinge AB, Gothenburg, Sweden) under the pressure-regulated volume-controlled (PRVC) mode. Due to the unique challenges that each transplant recipient faces, guidelines are in place with a goal of ventilating at 5–6 ml/kg calculated according to

TABLE 1 Recipient and donor characteristics ($n = 116$)

Variable				
Recipient demographics				
Sex; Female			57 (49.1%)	
Age at LTx, years			53.7 (60.7–42.4)	
Height, cm			170.7 ± 9.3	
Weight, kg			66.8 ± 17.3	
BMI, kg/m^2			22.8 ± 5.0	
Pediatric LTx, age <18 years			2 (1.7%)	
Diagnosis				
COPD/Emphysema/A1ATD			40 (34.5%)	
Cystic Fibrosis			22 (19.0%)	
IPF/PF specified			24 (20.7%)	
Other (PPH, Sarcoidosis)			30 (25.9%)	
Single LTx			9 (7.8%)	
Lung Retransplantation			7 (6.0%)	
ECMO use			11 (9.5%)	
Preoperative			4 (3.4%)	
Postoperative			11 (9.5%)	
Ventilator Characteristics	T0	T24	T48	T72
FiO_2	0.47 ±.13	0.36 ±.10	0.32 ±.07	0.33 ±.11
Tidal volume (ml)	448 ± 83	465 ± 101	451 ± 104	455 ± 130
Donor demographics				
Sex; Female			67 (57.8%)	
Age, years			54.0 (63.0–40.0)	
Age <18 years			6 (5.2%)	
Height, cm			170.5 ± 8.9	
Weight, kg			74.2 ± 15.1	
BMI, kg/m^2			25.4 ± 4.0	
Days on MV			$\tilde{x}$ = 1.65 (3–1)	
LOS in ICU			$\tilde{x}$ = 7 (17.75–5)	
Reintubated			36 (31.0%)	
Return to ICU			24 (20.7%)	

Note: Numbers are expressed as the mean $\bar{x} \pm$ SD (when parametric), median $\tilde{x}$ (interquartile range) or numerical values (%).

Abbreviations: A1ATD, α-1-antitrypsin deficiency; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; IPF, Idiopathic Pulmonary Fibrosis; LTx, Lung transplantation; PF, Pulmonary fibrosis; PPH, primary pulmonary hypertension; T0, time of admission to the ICU; T24, 24 h after admission; T48, 48 h after admission; T72, 72 h after admission.

the recipient with a PEEP of 5 and plateau pressure less than 30 cm H_2O but ventilatory measures are adjusted according to regular blood gas measurements and clinical evaluation by the attending anaesthesiologist. The patient is kept at a head elevation of 30° to unload the right heart chamber for the prevention of right heart failure. The attending physician used the recipient characteristics to determine appropriate ventilatory settings at the time of admission to the ICU. Ventilatory settings and measures in this study were collected and a positive end-expiratory pressure (PEEP) and a driving pressure were analyzed. The guideline aim was to maintain a PEEP of 5, and the study data categorized patients as either PEEP of 5 or a PEEP greater than 5. However, there were 6 patients who were ventilated at times with pressures less than 5 due to clinical concerns, such as right heart failure and concern over air leakage, but were still included in the analysis. Lung protective ventilation was in this study defined as low tidal volume (≤6 ml/kg),[21] and was calculated on the basis of the donor and the recipient. Patients were then determined to be protectively ventilated relative to the tidal volume for the recipient or the donor.

2.3 | Graft mismatch

A predicted total lung capacity (pTLC) was calculated based on sex, age, and height as described by Eberlein et al.[22]:

pTLC for male = 0.08 × [Height in cm] +0.003 × [age in years] −7.333

TABLE 2 Intraoperative characteristics ($n = 116$)

Variable	
Intraoperative machine perfusion	
ECMO	28 (24.1%)
Average time, minutes	371 ± 135
ECC	67 (57.8%)
Average time, minutes	223 ± 67
Off-pump	20 (17.2%)
Ischemic time	
Right Lung, minutes	236 ± 103
Left Lung, minutes	281 ± 103

Note: Numbers are expressed as the mean $\bar{x}$ ± SD (when parametric), median $\tilde{x}$ (interquartile range) or numerical values (%). ECMO = extracorporeal membrane oxygenation, ECC = extracorporeal circulation. Off-pump refers to patients in whom extracorporeal circulation was not used. Ischemic time was defined as the time from clamp on the donor to the time of reperfusion in the recipient.

TABLE 3 Grading of primary graft dysfunction according to the definition from the International Society of Heart and Lung transplantation (2016)

Grade	Pulmonary Edema on chest X-ray	PaO_2/FiO_2 ratio
0	No	Any
1	Yes	>300
2	Yes	200–300
3	Yes	<200

pTLC for female = 0.059 · x [Height in cm] −4.537

A pTLC ratio was calculated as donor pTLC / recipient pTLC. Grafts were said to be matched if the ratio was between 0.95–1.05. Grafts with a ratio <0.95 were labeled undersized while those >1.05 were oversized.

2.4 | Data collection

Data were extracted from medical record systems; Intellispace critical care and anaesthesia (ICCA, Koninklijke Philips electronics N.V. Amsterdam, the Netherlands) and Melior (Siemens AB, Healthcare service, Solna, Sweden). Mechanical ventilator settings, blood gas samples and chest x-ray results were analyzed at five different time points: preoperatively, on arrival in the ICU, the following morning at 6am, and the two consecutive mornings after. Last day for follow-up was July 23, 2020.

2.5 | Statistical analysis

Categorical variables were presented as numbers (%) and continuous variables were presented as the mean ± SD for parametric data or median (interquartile range) for non-parametric data. Incidence of PGD was analyzed using the independent sample *t*-test for continuous parametric variables, chi^2 and Fisher's exact test (when expected frequency <5) for categorical variables. For non-parametric continuous variables, the Mann–Whitney u-test and Kruskal–Wallis H test were applied. Within PGD groups, statistically significant differences were analyzed using a z-test ran with Bonferroni correction. Survival analysis was determined in a time-related manner with the Kaplan–Meier method and differences between groups were analyzed using the Log-rank test. Statistical significance was defined as $p < .05$. All statistical calculations were performed using SPSS Statistics 26 (IBM Corp., Armonk, NY, US).

3 | RESULTS

3.1 | Patient demographics

Table 1 shows patient characteristics. 49.1% of recipients were female and had a median age of 53.7 years (IQR 60.7-42.4). 92.2% of patients received a double lung transplant and stayed in the ICU for a median of 7 days (IQR 17.75-5). The median number of days on mechanical ventilation was 1.65 (IQR 3-1). Thirty-six patients (31.0%) were reintubated while 24 (20.7%) returned to the ICU during their hospital stay.

3.2 | PGD

Within the first 72 h of their stay in the ICU, 18 patients did not develop any PGD, while 50 developed PGD grade 1 or 2 and 47 developed grade 3 PGD. Those who developed PGD were more likely to have a higher BMI ($p = .003$) and an older donor age was correlated with the development of PGD ($p = .011$), but other general recipient and donor demographics demonstrated no difference. There were no significant differences in the frequency of PGD among different diagnoses nor were there differences between the length of stay in the ICU, rates of reintubation, return to the ICU or days spent on ventilation.

When considering PEEP, there was a significant difference between the 21.3% of grade 3 PGD patients who received PEEP of 5 cm H_2O and the 53.2% who were PGD grade 1 or 2 with this PEEP ($p = .006$). There was a smaller proportion of grade 3 PGD on PEEP of 5 than the 38.9% of grade 0.

In patients whom driving pressure was kept at less than 20 cm H_2O, there was a lower rate in those who developed PGD 3 (48.9%) relative to those with PGD grades 1 or 2 (66.0%) or no PGD (61.1%). While not statistically significant, the data shows a trend of the more severe dysfunction grade being composed more predominantly of patients with higher driving pressure values.

Tidal volumes were calculated either according to the recipient's demographics or according to the donor's, as shown in Tables 4 and 5. When calculated with respect to the recipient, it was found that relative to the group without PGD or to the group with grades 1 or 2, those with grade 3 PGD were made of a significantly greater proportion of individuals receiving a tidal volume ≤6 ml/kg ($p = .037$). When

TABLE 4 Development of primary graft dysfunction at any time during the first 72 h after lung transplantation $n = 115$

Variable	No PGD $n = 18$	PGD Grade 1 or 2 $n = 50$	PGD Grade 3 $n = 47$	p-value
Recipient demography				
Female gender	8 (44.4%)	24 (48.0%)	24 (51.1%)	.885
Age at LTx, years	49.1 (25.0–61.3)	55.5 (45.5–62.0)	52.7 (37.4–60.0)	.167[†]
BMI, kg/m^2	19.8 ± 4.6	22.4 ± 4.6	24.4 ± 4.9	.003
Donor demography				
Female gender	8 (44.4%)	28 (56.0%)	30 (63.8%)	.355
Age, years	42.5 (23.0–56.2)	52.5 (40.8–65.3)	57.0 (46.0–69.0)	.011
Diagnosis				
COPD/Emphysema/A1ATD	6 (33.3%)	22 (44.0%)	12 (25.5%)	.160
Cystic fibrosis	6 (33.3%)	8 (16.0%)	7 (14.9%)	.195
IPF/PF specified	1 (5.6%)	11 (22.0%)	12 (25.5%)	.201
Other	5 (27.8%)	9 (18.0%)	16 (34.1%)	.195
	n = 18	***n = 47***	*n = 47*	
Ventilatory Pressures				
PEEP of 5 cm H_2o until T72	7 (38.9%)	25 (53.2%)[*]	10 (21.3%)[*]	.006
Driving Pressure <20 until T72	11 (61.1%)	31 (66.0%)	23 (48.9%)	.210
			n = 46	
Tidal Volume ≤6 ml/kg				
With respect to recipient until T72	3 (16.7%)	9 (19.1%)	19 (41.3%)	.037
With respect to donor until T72	8 (44.4%)	21 (44.7%)	20 (43.5%)	.977
Tidal Volume >6 ml/kg				
With respect to recipient until T72	15 (83.3%)	38 (80.9%)	28 (59.7%)	.037
With respect to donor until T72	10 (55.5%)	26 (55.3%)	26 (56.5%)	.977
	N = 18	*N* = 50	*n* = 47	
pTLC ratio 5%				
Undersized	6 (33.3%)	18 (36.0%)	14 (29.8%)	.809
Perfect match	9 (50.0%)	14 (28%)	19 (40.4%)	.193
Oversized	3 (16.7%)	18 (36.0%)	14 (29.8%)	.308
	N = 18	*N* = 49	*n* = 45	
Days on MV	2.1± 2.2	4.0 ± 8.2	8.3 ± 14.9	.066
LOS in ICU	11.9 ± 11.8	15.2 ± 19.0	18.6 ± 22.4	.440
Re-intubated	2 (11.1%)	18 (36.7%)	16 (35.6%)	.113
Return to ICU	4 (22.2%)	7 (14.3%)	13 (28.9%)	.225

Note: Numbers are expressed as the median (interquartile range), mean ± SD (when parametrical) or numerical values (%). Level of significance is defined as $p < .05$.

Abbreviations: A1ATD, alfa-1-antitrypsin deficiency; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit; IPF, Idiopathic Pulmonary Fibrosis; LOS, Length of stay; Lx, Lung transplantation; MV, Mechanical Ventilation; PGD, Primary graft dysfunction; PF, Pulmonary fibrosis; PEEP, positive end expiratory pressure; pTLC, predicted total lung capacity; T72, 72 h post operatively.

*=between group difference $p < .05$ using a z-test ran with Bonferroni correction.

calculated according to the donor, there were no significant differences between any of the groups. The average tidal volume at the time of admission to the ICU was 448 ± 83 ml, and was 465 ± 101 ml after 24 h, 451 ± 104 ml at 48 h, and 455 ± 130 ml at 72 h.

The pTLC ratio compares the donor lung capacity to that of the recipient. Among those whose graft was considered "matched," 21.4% had no PGD while 33.3% experienced either grade 1 or 2 and 45.2% experienced grade 3 PGD (Figure 1A). In the undersized category, only 15.8% did not have PGD while 47.4% had grade 1 or 2 and 36.8% had grade 3 (Figure 1A). Lastly only 8.6% with oversized grafts had no PGD and 36.0% had grade 1 or 2 and 29.8% had grade 3 (Figure 1A).

TABLE 5 Values of ventilation parameters and ischemic times $n = 115$

Variable	No PGD $n = 18$	PGD Grade 1 or 2 $n = 50$	PGD Grade 3 $n = 47$
Ventilatory parameters			
Tidal volume ml per kg of recipient	7.97 ± 1.63	7.19 ± 1.86	6.73 ± 2.08
Tidal volume ml per kg of donor	6.32 ± 1.78	6.45 ± 1.37	5.76 ± 1.87
PEEP	5.68 ± 1.09	5.21 ± 0.92	6.00 ± 1.57
Driving pressure	9.93 ± 5.92	16.37 ± 37.64	13.08 ± 5.66
Ischemic time of left lung (min)	222.1 ± 67.22	282.4 ± 95.39	299.7 ± 113.6
Ischemic time of right lung (min)	238.2 ± 107.1	243.1 ± 96.06	232.0 ± 105.7

Note: Numbers are expressed as the mean ± SD.

Abbreviations: PEEP, positive end expiratory pressure; PGD, Primary graft dysfunction.

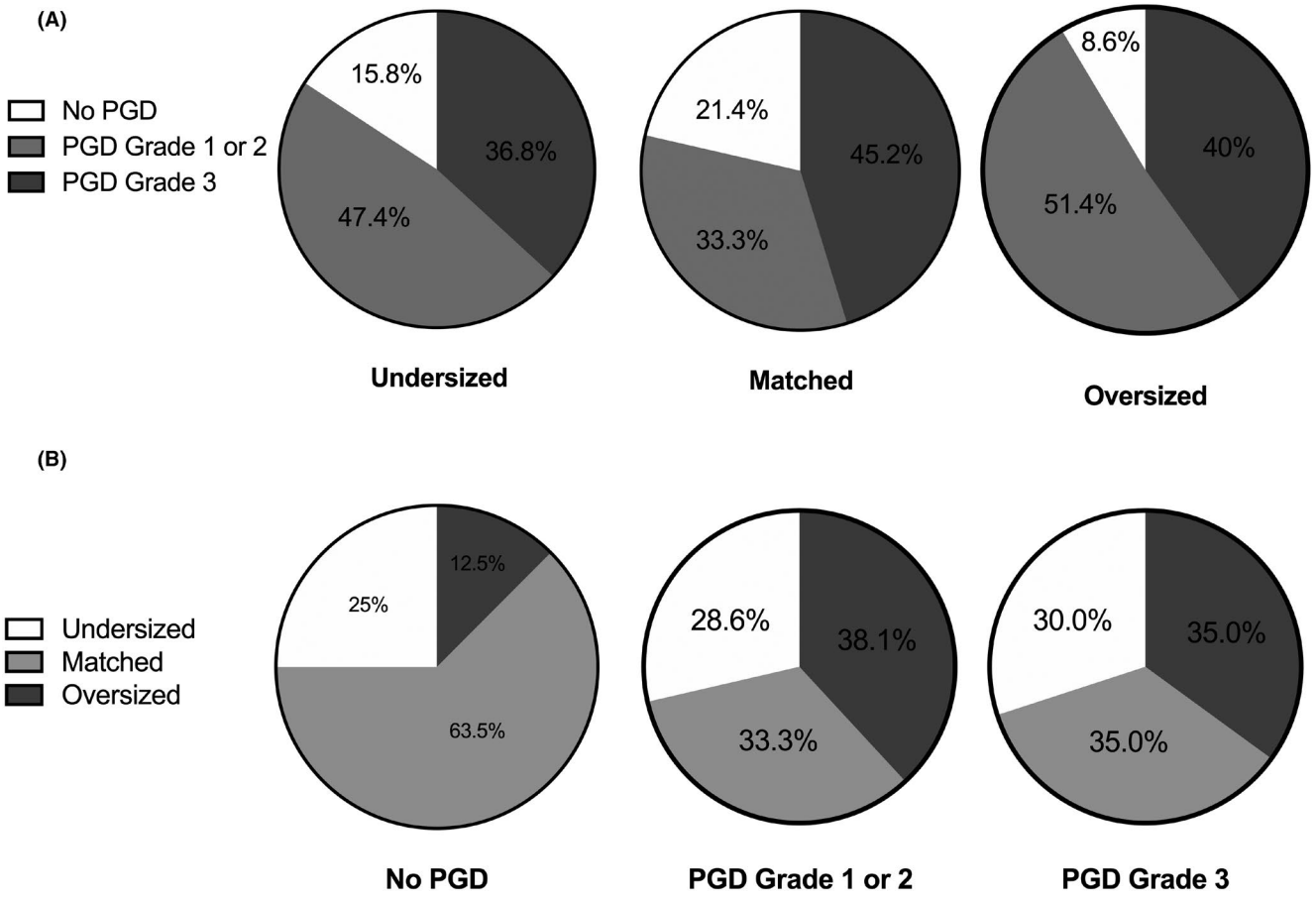

FIGURE 1 PGD Incidence Correlated to Size Matching of the Graft. Grafts were defined as undersized when the predicted total lung capacity (pTLC) ratio of donor to recipient was less than 0.95. Matched grafts were considered to be those in the ratio range of 0.95–1.05 while values above 1.05 were allocated as oversized. Both undersized and oversized grafts (A) had a trend of slightly PGD grade 1 or 2 and grade 3 relative to matched grafts. The relationship between size matching and graft dysfunction was then also considered specifically among those patients who received a tidal volume less than 6 ml/kg when calculated according to the donor (B). * $p < .05$, ** $p < .01$. PGD, primary graft dysfunction

3.3 | Survival

Sixty-three of the patients (54.3%) were alive at the last date of follow-up, compared to 53 (45.7%) who had passed.

When examining PEEP values, driving pressures and tidal volumes, these parameters were not statistically significantly different in survivors versus non. There were also no significant differences in the survival rates between the three groups of PGD. However, there

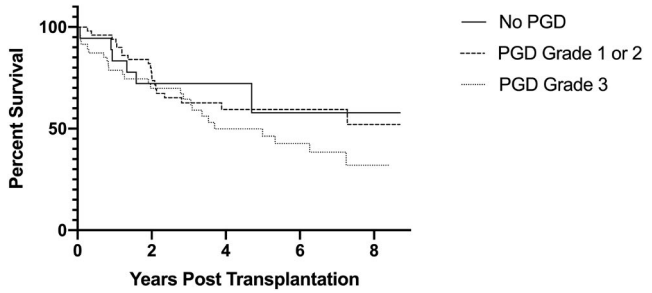

FIGURE 2 Kaplan-Meier plot. Survival in lung transplant recipients was stratified according to primary grade dysfunction (PGD) classifications and was tracked through a follow up time of July 17, 2020. No PGD, $n = 18$; PGD grade 1 or 2, $n = 50$; PGD grade 3, $n = 47$

was a tendency for lower survival in PGD grade 3 compared to the other groups (Figure 2). The size of the graft, however, was a significant factor in survival. Of those patients who were deceased, 47.2% were considered to have a strict match (the pTLC ratio was between 0.95 and 1.05) while 20.8% had oversized grafts, meaning a graft with a ratio greater than 1.05 (Table 6). In the patients that lived, only 27.0% of them had matched grafts while 39.7% had oversized grafts. In patients with matched pTLC ratios, the number deceased was significantly higher than those who survived ($p = .024$) and in patients with oversized ratios, the number of deceased was significantly lower than those who survived ($p = .028$).

When analyzing the survival rates, it was determined that the effect of graft size on survival was most apparent in COPD/emphysema/A1ATD patients in whom there was a significantly increased number of surviving oversized grafts relative to matched grafts that died ($p = .019$). Of those with COPD who survived, 61.1% had oversized grafts while in the deceased patients, 54.5% had matched grafts (Figure 3).

4 | DISCUSSION

A relationship between mechanical ventilation of lung recipients and the development of severe PGD may exist, but the current associations discussed here are hypothesis generating. In this study, in all the individuals who did develop grade 3 dysfunction, 78.7% of those were patients who had been ventilated with a PEEP higher than 5 cm H_2O (Figure 4A, Table 4). Given the association between a PEEP of 5 and lower PGD in this study, it might be favorable to apply a pressure that allows for patency of the alveoli and lung protection while taking into account the loss of bronchial circulation of a new transplant. Furthermore, while not statistically significant, the same pattern was observed regarding driving pressure. There should be further investigation as to the causation of how and why higher proportions of patients with grade 3 PGD correlated with higher pressure settings.

TABLE 6 Analysis of survival after transplantation $n = 116$

Variable	Deceased	Alive	*p*-value
	n = 53	*n = 63*	
Recipient demography			
Female gender	21 (39.6%)	36 (53.7%)	.060
Age at LTx, years	55.3 (42.7–62.4)	53.4 (42.4–59.8)	.365
BMI, kg/m^2	23.2 ± 4.8	22.5 ± 5.1	.449
Donor demography			
Female gender	30 (56.4%)	37 (55.8%)	.817
Age, years	56.0 (41.0–62.0)	53.0 (37.0–63.5)	.769
Diagnosis			
COPD/Emphysema/A1ATD	22 (41.5%)	18 (28.6%)	.144
Cystic fibrosis	5 (9.4%)	17 (27.0%)	.016
IPF/PF specified	11 (20.8%)	13 (20.6%)	.987
Other	15 (28.3%)	15 (23.8%)	.582
Ventilatory pressures†			
PEEP of 5 cm H_2o until T72	19 (35.1%)	23 (38.7%)	.961
Driving pressure <20 until T72	29 (59.5%)	36 (57.3%)	.914
Tidal volume ≤6 ml/kg†			
With respect to recipient until T72	15 (32.4%)	16 (25.3%)	.708
With respect to donor until T72	19 (43.2%)	30 (44.0%)	.205
Tidal volume >6 ml/kg†			
With respect to recipient until T72	36 (67.9%)	45 (71.4%)	.708
With respect to donor until T72	32 (60.4%)	31 (49.2%)	.205
pTLC ratio 5%			
Undersized	17 (32.0%)	21 (33.3%)	.886
Perfect match	25 (47.2%)	17 (27.0%)	.024
Oversized	11 (20.8%)	25 (39.7%)	.028
Days on MV	7.1 ± 14.1	4.2 ± 8.2	.020
LOS in ICU	18.8 ± 22.4	13.9 ± 16.8	.035
Re-intubated†	21 (39.6%)	15 (23.8%)	.061
Return to ICU†	15 (28.3%)	9 (28.3%)	.060

Note: Numbers are expressed as the median (interquartile range), mean ± SD (when parametric) or numerical values (% of deceased or alive). Level of significance is defined as $p < .05$.

Abbreviations: A1ATD, alfa-1-antitrypsin deficiency; BOS, bronchiolitis obliterans syndrome; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease; ICU, Intensive care unit; IPF, Idiopathic Pulmonary Fibrosis; LOS, Length of stay; LTx, Lung transplantation; MV, Mechanical Ventilation; PF, Pulmonary fibrosis; PEEP, positive end expiratory pressure; pTLC, predicted total lung capacity.

†= deceased $n = 37$, alive $n = 75$.

The rationale for such investigation lies in the evidence that ischemia-reperfusion injury can lead to pulmonary edema and diffuse alveolar damage and may have a central role in the development of PGD.[1] Additionally, greater capillary stress in the face of size mismatch is hypothesized to be a potential mechanism to explain the incidence of PGD 3 in single LTx.[3] Stress and over-distending alveoli may also lead to ventilator-induced lung injury,[10,11] which could occur with high levels of PEEP and peak inspiratory pressures.

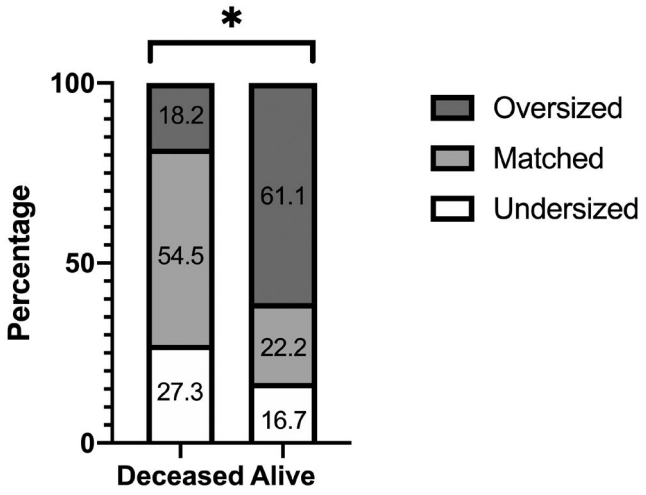

FIGURE 3 Survival is Related to Size Matching in COPD/Emphysema/A1ATD Patients. Patients were assessed for their status through July 2020 and classified according to their graft pTLC ratio. Oversized was defined as a graft with a ratio greater than 1.05. The relationship between the size of the graft and survival was then considered with regard to the diagnosis of the recipient, with COPD/emphysema/A1ATD emerging as having a significant relationship. * $p < .05$, ** $p < .01$. COPD, chronic obstructive pulmonary disease; A1ATD, alpha-1 antitrypsin deficiency

Size matching is recognized as an important parameter of consideration during lung transplantation. As noted by the ISHLT, while the graft size is a crucial factor in organ donation acceptance, the topic is a yet under-investigated subject.[23] In this study, oversized grafts were found to be advantageous to survival, particularly in patients with a diagnosis of COPD, emphysema, or alpha-1 antitrypsin deficiency. Predicted total lung capacity ratios were used to compare the donor size to the recipient and strict criteria were employed to consider any graft that was above 5% larger than the recipient to be oversized. In a study of donor-to-recipient weight ratio, Delom *et al*. found that a higher ratio was associated with improved survival following bilateral transplantation, accounting for this by pointing to the likely size mismatch between donor and recipient.[24] Furthermore, Shaffer *et al*. found that among transplants in COPD patients, oversized grafts measured by pTLC ratio ≥1 were associated with survival.[25] Eberlein et al. also found that oversized grafts corresponded with lower rates of BOS and higher expiratory airflow capacity after measuring size matching using pTLC ratios.[26]

Another critical ventilatory parameter to consider is tidal volume given existing debate on the use of either recipient or donor characteristics. Currently, many institutions measure relative to the recipient, but the data presented here makes an argument that donor demographics should be used instead. When looking

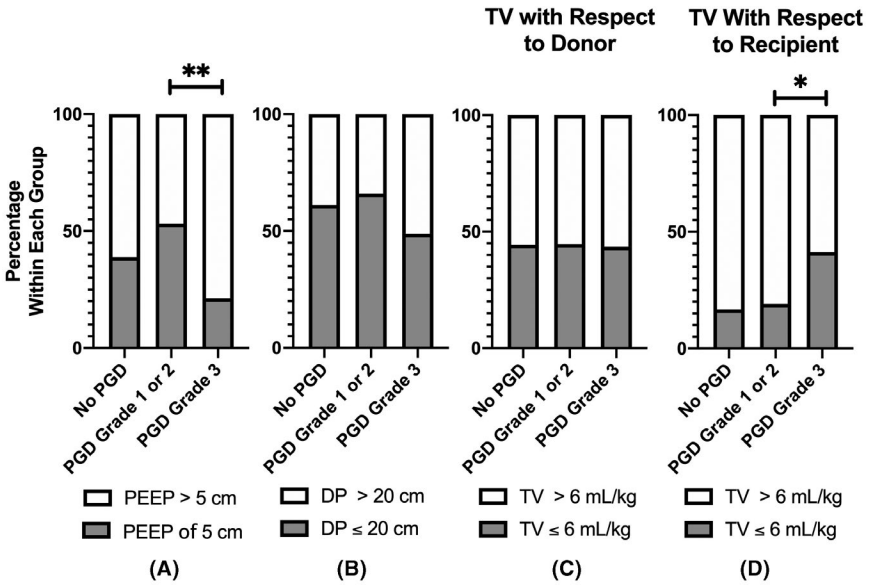

FIGURE 4 Correlation of Protective Volumes and PGD Rates. Patient samples ($n = 115$) were categorized by the ventilation pressures they received and then by the grade of primary graft dysfunction (PGD), being labelled as either having no PGD, PGD grade 1 or 2 or PGD grade 3. Incidence of PGD was determined within the first 72 h following transplantation. The patients with peak expiratory end pressures (PEEP) of 5 cm H_2o were also those who (A) had significantly less grade 3 dysfunction compared to grade 1 or 2. (B) demonstrates the correlations between driving pressure and PGD grades. Tidal volume was calculated according to either donor (C) or recipient (D). PGD grade 3 compared to grade 1 or 2 was found to be correlated with the tidal volume (TV) calculated according to the recipient (D)

at the low tidal volume measured according to the recipient, which is considered protective in ARDS patients, there were increasing proportions of individuals as PGD grades increased. 16.7% of PGD 0 patients had received low tidal volumes (calculated according to the recipient) compared to the 19.1% of grade 1 or 2 and a larger 41.3% of grade 3 (Table 4). The difference could suggest that when trying to employ protective settings, the dimensions of the recipient could not be conducive to providing adequate ventilation to the newly grafted lungs and if mismatched, could increase the risk of developing a more severe acute graft dysfunction. When the tidal volume was calculated according to the donor, however, all differences between the groups were lost (Figure 4C,D, Table 4).

This observation of the effect of tidal volume as measured according to the donor or the recipient could be down to the size of the grafted lung within the recipient and how well they match. Grade 3 PGD patients consisted of either oversized or undersized lungs which made up a combined percentage of 59.6% mismatched lungs compared to the 40.4% that were matched (Figure 1B). In those individuals who are oversized, the larger donor lungs have been placed into a smaller recipient. Thus, it could be hypothesized that by calculating tidal volume according to a recipient, these larger lungs are not getting the adequate ventilation they need. Conversely, by putting smaller donor lungs into a larger recipient and then ventilating according to that larger recipient, damage is induced by overfilling the grafted lungs. In both these cases, by using recipient compared to donor information, damage ensues, leading to acute dysfunction. Decreased tidal volume relative to kilograms of body weight in ARDS patients has translated to decreased mortality and increased number of days without ventilator use, validating the implementation of lung protective ventilation.[15]

Survival in thus study, however, was not found to be affected by low volumes of PEEP, driving pressure, and tidal volumes (Table 6). One limitation of this study is the consideration that as transplantations took place between September 2011 to September 2018, this is a short timeframe to fully understand how mechanical ventilation affects survival. An investigation over a longer patient follow up period will need to be conducted.

Other limitations of this study include emphasis on the hypothesis-generating nature of the associations. The retrospective analysis of a relationship between ventilatory mode and PGD does not allow for conclusions about causal relationships to be drawn. The associations between how ventilation relates to the severity of PGD could be due to the consequence of having more patients with advanced lung dysfunction in the PGD grade 3 group which necessitated ventilation with higher pressures. The choice to ventilate with lower volumes could also have been a measure taken on the part of the anesthesiologist to prevent further damage to already declining lungs. Furthermore, analysis of survival in this study did not reveal an impact on the degree of PGD on mortality, though there was a tendency of lower survival in the PGD grade 3 group. Further study should include a larger number of patients to bolster the power of the study.

The importance of further research on mechanical ventilation settings becomes apparent when considering the current body of literature that exists around our understanding of how to postoperatively ventilate patients. Much of the work that has been done and the recommendations that have been made are based on studies done on ARDS.

In 2000, a landmark study headed up by the ARDS Network used a randomized controlled trial of 861 patients to demonstrate that in the event of pre-existing ARDS, a lower tidal volume was associated with lower mortality rates and a lower number of days without ventilator use.[15] The use of mean tidal volumes in the range of 6 ml/kg of predicted body weight (PBW) has subsequently become more common clinical practice in the scope of ARDS treatment, despite some studies with smaller patient groups that have failed to observe a benefit of small tidal volumes.[27] In a 2010 investigation into mitigating the risk of developing acute lung injury, Determann *et al*. explored the use of a low tidal volume of 6 ml/kg of PBW in critically ill patients and found that cytokine levels and the incidence of ALI/ARDS were reduced as compared to conventional tidal volumes.[28]

Following the logic that low tidal volume may therefore prove beneficial in a lung transplant setting, Mascia *et al*. in 2010 used low tidal volumes in donor patients in an attempt to increase the number of available organs.[29] The number of patients who met donor eligibility criteria had increased in the protective group without any change to six-month survival rates.

Positive end expiratory pressures have also been studied to reduce VILI. As VILI is thought to be a consequence of alveolar stretch secondary to high lung volumes as well as shear stress in opening and closing alveoli,[12] PEEP could be used to circumvent collapse of small airways. PEEP has thus been used in patients with ARDS. A study by the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network found no difference in clinical outcomes between the use of low (8 cm H_2O) PEEP and high (13 cm H_2O) PEEP.[30] In a meta-analysis of trials using higher and lower PEEP in response to ALI and ARDS, different PEEP levels were not associated with hospital survival.

While these studies on ARDS provide valuable insight on beginning to create guidelines for lung transplant patients, these two patient populations are not equivalent. Transplant recipients experience significant medical challenges that require careful consideration, such as the risk for ischemia-reperfusion injury, dynamic hyperinflation in emphysematous single transplant patients, and concerns regarding the bronchial anastomoses across all patients.[21,31] While studies on ARDS patients can serve as a starting point to begin considering ventilation strategies, there must be independent research on the transplant patient population specifically. The studies that have been conducted on transplant patients are outlined in Table 7.

The ventilation guidelines have been explored to some extent for donor patients. Mascia *et al*. compared a PEEP of 3–5 cm H_2O to a protective group setting of 8–10 cm H_2O in donors.[29] As noted, there were more available donor lungs in this protective group but no differences in recipient survival. In an intraoperative study of

TABLE 7 Summary of articles involving the use of transplant-specific patients

Authors	Article type	Patient population	Recommendations/Contributions to the literature	Recommended tidal volume?
Currey et al. 2009[44]	Prospective single center cohort	Lung transplant recipients	Implementation of a respiratory guideline that advises changing values of PEEP and tidal volume based on categories of PaO_2/FiO_2 ratios alongside a hemodynamic guideline was associated with a tendancy for reduced PGD severity following transplantation.	Dynamic based on patient PaO_2/FiO_2
Mascia et al. 2010[29]	Randomized Controlled Trial	Potential Lung Donors	Tidal volumes of 6–8 ml/kg of predicted body weight, PEEP of 8–10 cm H20 led to increased number of patients meeting lung donor eligibility without changing six month survival rates in recipients.	6–8 ml/kg of predicted body weight
Diamond et al. 2013[45]	Prospective multicenter cohort	Lung transplant recipients	In an identification of risk factors associated with PGD across 1,255 recipients, elevated FiO_2 during reperfusion was among the recognized factors. Tidal volume per kg of ideal body weight at reperfusion was not associated and postoperative ventilatory strategies were unable to be assessed.	No
Eberlein et al. 2012[46]	Retrospective Single center cohort	Lung transplant recipients	Undersized grafts as determined by a pTLC ratio $\leq$ 1.0 were associated with higher incidents of PGD, tracheostomy, and greater resource utilization.	No
Eberlein et al. 2013[47]	Retrospective Single center cohort	Lung transplant recipients	Using the same pTLC ratio organizational scheme, concluded that oversized grafts were associated with improved survival in bilateral LTx in idiopathic pulmonary arterial hypertension patients	
Dezube et al. 2013[17]	Retrospective single center cohort	Lung transplant recipients	Undersized and oversized grafts as measured by ratio of predicted total lung capacity (pTLC) of donor to pTLC of recipient were compared. Tidal volumes were higher in undersized grafts when tidal volume was calculated by donor-predicted body weight.	Use donor based calculations
Thakuria et al. 2016[48]	Retrospective single center review	Lung transplant recipients	Patients were grouped according to low (<6 ml/kg), medium (6–8 ml/kg) or high (>8 ml/kg) tidal volumes. There was no difference in short-term and midterm outcomes across these groupings. Patients were also categorized by low (<25 cm H_2o) or high (>25 cm H_2o) inflation pressures and it was found that the low group had shorter ICU stays, higher FEV1's and higher 6 month survival rate.	<6 ml/kg
Verbeek et al. 2017[32]	Randomized Controlled Trial	Intraoperative recipient	Control group of volume-controlled ventilation with 5 cm H_2o PEEP and 6 ml/kg tidal volume was compared to an alveolar recruitment group with pressure controlled ventilation at 16 cm H_2o and 10 cm H_2o PEEP throughout the duration of surgery. There was no sustained benefit to the "open lung ventilation" strategy.	No
Benazzo et al. 2021[49]	Prospective multicenter cohort	Lung transplant recipients	Ventilatory parameters of donors were prospectively measured at standard 6 ml/kg tidal volume and were correlated to the study end point of recipient time on ventilator to reach the conclusion that donor ventilation may assess graft quality.	No

(Continues)

TABLE 7 Continued

Authors	Article type	Patient population	*Review of ARDS/ ALI Lit?*	*Review of transplant recipient ventilation lit?*	Recommendations
Lucangelo et al, 2012[21]	Review	Donor and recipient postoperative care	Yes	No	Advised to use pressure-controlled ventilation modality with low tidal volumes (≤ 6 ml/kg), "moderate PEEP levels", inspiratory pressure less than 20 cm H_2o above PEEP, and permissive hypercapnia. Specific recommendations for reperfusion injury and dynamic hyperinflation.
Verbeek and Myles, 2013.[50]	Review	Intraoperative recipient	Yes	Yes: Lucangelo, 2012 (review)	Concludes that low tidal volumes have become standard practice and that in regards to other parameters, more research is needed.
Bansal et al. 2014[51]	Review	Potential Lung Donors	Yes	Review is specific to lung donors.	Recommends the use of lung protective ventilatory strategies with "adequate" PEEP levels.
Diamond and Ahya, 2014.[52]	Editorial	Lung Transplant Recipients	Yes	Dezube, 2013; Beer, 2014 (survey), Lucangelo, 2012 (review); Verbeek, 2013 (review), Diamond, 2013	Summarizes the question of using donor and recipient characteristics and comments on the literature of dangers of high FiO_2 and potential benefits of high PEEP.
Barnes et al. 2015[53]	Review	Lung transplant recipients	Yes	Cites murine models as well as Currey, 2010;, Eberlein, 2013; Eberlein, 2012, Diamond and Ahya 2014 (editorial); and articles on ECMO	Summarizes considerations for bilateral and single lung transplant as well as bronchial anastomoses including references to murine models. Recommends lung protective ventilation defined as tidal volume ≤ 6 ml/kg and PEEP with ventilation based on donor characteristics.
Geube et al 2019[54]	Review	Lung transplant recipient	Yes	Risk factors for PGD 3 development	Provides a ventilation guideline based on low tidal volume and "optimized" PEEP.

TABLE 8 Summary of articles involving the use of surgical, non-transplanted patients

Authors	Article Type	Patient Population	Recommendations/Contributions to the literature				
			Pressure Controlled Ventilation (PCV) vs Volume Controlled Ventilation (VCV)				
Tugrul et al. 1997[34]	Randomized Controlled Trial	Patients undergoing thoracotomy	PCV compared to VCV was superior in the case of respiratory disease.				
Unzueta et al. 2007[35]	Randomized Controlled Trial	Patients undergoing thoracotomy	PCV provided no benefit in terms of oxygenation compared to VCV during one lung ventilation (OLV).				
Roze et al. 2010[36]	Prospective Observational study	Patients undergoing thoracotomy	PCV vs VCV does not have a clinically significant impact on oxygenation in OLV.				
			"Protective" tidal volumes and PEEP				
			Control or High TV	*Control Group PEEP*	*Protective TV*	*Protective PEEP*	*Finding*
Wrigge et al. 2004[37]	Randomized controlled trial	Patients undergoing thoracotomy or laparotomy	12 or 15 ml/kg body weight	0 cm H_2o	6 ml/kg body weight	10 cm H_2o	No effect on arterial oxygenation or inflammatory reactions
Choi et al. 2006[38]	Randomized Controlled Trial	Patients undergoing at least 5 h of surgery with no prior lung disease	12 ml/kg	0 cm H_2o	6 ml/kg	10 cm H_2o	Higher TV and no PEEP led to bronchoalveolar cogulation.
Unzueta et al. 2012[39]	Randomized controlled trial	Patients undergoing thoracotomy	6 ml/kg	8 cm H_2o	6 ml/kg	Alveolar recruitment maneuver consisting of 10 consecutive breaths at a plateau pressure of 40 and 20 cm H_2o PEEP	OLV, Found alveolar recruitment led to reduced alveolar dead space, improved oxygenation and efficiency of ventilation.
Rozé et al. 2012[40]	Prospective randomized cross-over trial	Patients undergoing thoracotomy	8 ml/kg	5 cm H_2o	5 ml/kg	high PEEP	OLV, high TV and low PEEP had increased oxygenation relative to low TV and high PEEP
Futier et al. 2013[33]	Randomized controlled trial	Intraoperative patients undergoing major abdominal surgery	10–12 ml/kg	no PEEP or recruitment maneuvers	6–8 ml/kg	6–8 cm H_2o with alveolar recruitment maneuver	The protective group was found to have fewer pulmonary complications and required less postoperative ventilatory assistance.
Maslow et al. 2013[41]	Randomized Controlled Trial	Patients undergoing thoracotomy and pulmonary resection	10 ml/kg	0 cm H_2o	5 ml/kg	5 cm H_2o	OLV, High TV and 0 PEEP had less dead space ventilation and postoperative atelectasis
Gu et al. 2014[42]	Meta-analysis	Patients undergoing surgery			5–8 ml/kg		Lower tidal volumes had a lower risk of lung injury and pulmonary infection
Qutub et al. 2014[43]	Randomized controlled trial	Patients undergoing thoracoscopic surgery	6 to 8 ml/kg		4 ml/kg		OLV, lower TV was associated with less lung water content

mechanical ventilation during transplantation by Verbeek *et al*. in 2017, patients undergoing bilateral lung transplantation, a control group with a PEEP of 5 had no changes in primary outcomes compared to a PEEP of 10 cm H_2O.[32]

As there are few studies on transplant recipients specifically, other studies of protective ventilation in surgical procedures, such as abdominal surgery and thoracotomies, are important to consider, as summarized in Table 8. The IMPROVE study demonstrated that intraoperative lung-protective ventilation during abdominal surgery was correlated with lower rates of lung injury when patients were at intermediate to high risk of pulmonary complications.[33] Using both low tidal volumes and PEEP, the protective ventilation group was found to have a lower incidence of intubation for ARDS as well as a shorter length of hospital stay.

There are no set standards in ventilation for lung transplant patients. The majority of recommendations for transplantation have been based on the findings from studies that analyzed patients with ARDS and/or acute lung injury. There are a limited number of studies that have been conducted on surgical patients and a similarly limited number on transplantation patients specifically. These studies and their findings have been outlined in Tables 7 and 8. As PGD and chronic dysfunction continue to hamper the survival of LTx patients, there cannot be enough emphasis on how important continued research on mechanical ventilation is.

5 | CONCLUSION

This study addresses the potential part mechanical ventilation and donor characteristics may play in the development of primary graft dysfunction in lung transplant patients. Despite the lower tidal volumes (lung protective ventilation), there was a high incidence of severe PGD. Thus, other variables may play an important role in the development of PGD. Both mechanical ventilation and other variables, such as lung ischemic time and the use of extracorporeal circulation should be further investigated to determine the primary inciting factors of PGD. Donor characteristics, for example, had a bearing on outcome compared to the recipient demographics in this study. By incorporating information gained on the role of donor characteristics and the importance of mechanical ventilations, the postoperative goal of lowering rates of primary graft dysfunction could be attained.

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CONFLICT OF INTEREST

To the best of our knowledge, there are no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTION

MM, RI, SH, AN, and SL participated in the design of the study. SL wrote the application for the ethical approval. SQ, AN, and SH collected the data. AN, MM, RI, SH, and SL analyzed the data. AN, SQ, and SL drafted the manuscript. All authors read and approved the final manuscript.

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