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Lower tidal volume ventilation post-bilateral lung transplantation is associated with ventilator-free days

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Abstract

Background: There is limited evidence regarding the effect of invasive mechanical ventilation practice post-bilateral lung transplantation. Invasive mechanical ventilation practice may be associated with prolonged ventilation, particularly when referenced to donor anthropometrics.

Methods: This was a single-centre retrospective cohort study that included consecutive adult bilateral lung transplant recipients between 2015 and 2021 who were ventilated for a minimum of 24 h post-surgery. Lower and higher tidal volume subgroups were defined for mean and maximum values indexed to both donor and recipient predicted body weight over the first 72 h. The primary outcome was ventilator-free days in the first 28 days, and this was analysed using the Wilcoxon rank sum test and a competing risks regression. We used a Cox proportional hazards model to examine the relationship of ventilator-free days and tidal volume and 90-day survival.

Results: The cohort included 111 recipients, and the median ventilator-free days for the entire cohort was 25 (21–26). Lower tidal volume indexed to donor predicted body weight after 48 and 72 h was associated with more ventilator-free days (25 (23–26) vs. 24 (17–26), $p = .04$ and 24 (21–25) vs. 20 (14–24), $p = .02$) and increased cumulative incidence of successful extubation (sub-distribution hazard ratio 1.54 (1.07–2.20), $p = .02$ and SHR 1.87 (1.07–3.27), $p = .03$). Ventilator-free days and lower tidal volume were associated with increased 90-day survival.

Conclusions: Lower tidal volume ventilation indexed to donor predicted body weight is associated with more ventilator-free days post-bilateral lung transplantation.

Editorial Comment: Postoperative ventilation with lower tidal volume indexed to the donor's predicted body weight was associated with more ventilator-free days in patients undergoing bilateral lung transplantation. No difference was found between lower versus higher tidal volume ventilation for other patient-important outcomes. The results highlight the need for larger prospective clinical trials.

1 | INTRODUCTION

The acute respiratory distress syndrome (ARDS) literature on invasive mechanical ventilation (IMV) has identified a mortality benefit associated with lower tidal volume and plateau pressure limitation, collectively termed lung protective ventilation (LPV).[1–3] Primary graft dysfunction (PGD) is the most common complication post-lung transplantation and is associated with worse short- and long-term outcomes.[4,5] The clinical syndrome of PGD shares many similarities with ARDS, including a definition based on PaO_2:FiO_2 (P:F) ratio in the presence of bilateral infiltrates on chest radiograph.[6] Given the evidence of benefit from LPV in ARDS, experts in lung transplantation have called for similar strategies to be evaluated in the perioperative IMV of lung transplant recipients.[7,8]

While there is some evidence to suggest that the selection of protective ventilation settings based on donor predicted body weight (dPBW) is associated with reduced risk of PGD grade 3 at 48–72 h post-transplant,[9] other studies have been unable to demonstrate associations of ventilation practice and patient-centred outcomes.[10,11] International survey data suggest that in real-world practice, ventilation settings are more commonly selected based on recipient PBW, and that 32% of patients are extubated in the first 24 h post-transplant.[8]

The aims of this study were to provide a detailed description of ventilation practice and cardiorespiratory physiology in the immediate post-transplant period and to determine, with reference to the essential components of lung protective ventilation, the association of ventilation practice with short- and medium-term patient-centred outcomes. We hypothesised that bilateral lung transplant (BLTx) recipients are subject to ventilation settings that are potentially unsafe and not adequately identified and reported, particularly as tidal volume is more commonly selected with reference to recipient PBW. In selecting a higher risk cohort (patients ventilated for a minimum of 24 h) we also hypothesised that there would be an association of ventilation practice with short- and medium-term patient-centred outcomes, including ventilator-free days.

2 | METHODS

2.1 | Study design and patient selection

This was a retrospective observational cohort study conducted in a state referral centre for cardiopulmonary transplant in Sydney, Australia. Serial adult bilateral lung and heart–lung transplant recipients in the period between January 2015 and December 2021 who had been continuously ventilated for at least 24 h post-transplantation were included. Single lung transplant recipients and patients who were extubated within 24 h post-transplantation were excluded. Patients who received extra-corporeal membrane oxygenation (ECMO) support in the immediate post-operative period were excluded from ventilation parameter analyses as the use of ECMO facilitates independent alterations in ventilator settings. Data were collected from electronic medical record systems, patient files, and the Australian and New Zealand cardiothoracic organ transplant registry (ANZCOTR) donor database. The anonymised data was extracted and stored in the REDCap data management system from which it was exported for statistical analysis. The study is reported as per the STROBE statement (https://www.strobe-statement.org; see Appendix S1).

Baseline data pertaining to recipient, donor, and surgical factors that have previously been described as risk factors for PGD[5] were collected. Detailed organ support and physiological data for the first 72 h were recorded as this is the period during which PGD is defined, where time zero was at intensive care admission. Hourly ventilation data was collected over the first 72 h post-transplant for the following variables: mode, tidal volume (mL), peak pressure (cmH_2O), positive end-expiratory pressure (PEEP; cmH_2O) and respiratory rate (min^{-1}). This data was used to calculate hourly values for dynamic driving pressure (peak pressure − PEEP; cmH_2O), dynamic compliance (tidal volume/(peak pressure − PEEP); mL/cmH_2O) and dynamic mechanical power (0·098 × respiratory rate × tidal volume × (peak inspiratory pressure − (0.5 × dynamic driving pressure)); J/min).[12] Intubation time, interval extubations, and the time of final successful extubation were collected. For patients extubated in the first 72 h, organ support and physiological data were collected until the end of the 72nd hour.

Tidal volumes were subsequently indexed to both recipient (rPBW) and donor PBW (dPBW) and reported and analysed as mean and maximal values for each of the time periods of 0–24, 0–48, and 0–72 h (T24, T48 and T72). Donor and recipient PBW were calculated as follows: male $PBW = 50 + 2.3(height - 60)$ and female $PBW = 45.5 + 2.3(height - 60)$. For the continuous variables of both mean and maximum values for tidal volume for each period (T24, T48 and T72), lower and higher tidal volume sub-groups were defined. For peak pressure, driving pressure, and mechanical power sub-group definition, previously described thresholds were used as these had at least equivalent model fit to quantile sub-groups.[3,13,14] There were insufficient recorded values of plateau pressure and hence the surrogate of peak pressure was used.

PGD grade was assigned for each 24-h period up to 72 h with reference to the International Society of Heart and Lung Transplantation (ISHLT) definition.[6] PGD sub-groups were defined at T72 as PGD grade 3 and PGD grade <3 (grade 0–2).[15] The chest radiograph findings were determined by independent assessment and agreement between a radiology and intensive care specialist. In addition, daily maximum or minimum values for the first 72 h for P:F ratio, pH, arterial carbon dioxide partial pressure, ventilatory ratio (minute ventilation [mL/min] × partial pressure of carbon dioxide [mm Hg])/(predicted bodyweight in kg × 100 [mL/min] × 37.5 [mm Hg]),[16] vasoactive-inotrope score (VIS),[17] lactate, and Sequential Organ Failure Assessment (SOFA) score were recorded. The net fluid balance, including fluid removal on dialysis if used, within the first 72 h post-transplant was calculated. Measures of donor–recipient size match including PBW ratio, predicted total lung capacity ratio (pTLC), donor predicted: recipient actual total lung capacity ratio were calculated. These were analysed as continuous variables and as the following sub-groups: undersized (<0.9), matched (0.9–1.1), oversized (>1.1). Predicted lung volumes and spirometric values were calculated using

the Global Lung Function Initiative calculator (http://gli-calculator.ersnet.org/docs.html).

The primary outcome was ventilator-free days (VFDs) in the first 28 days post-transplant as defined by Yehya et al.[18] Successful extubation was defined as the final extubation in the first 28 post-operative days in 28-day survivors. The secondary outcomes included: PGD grade 3 at 72 h post-transplant, ICU and hospital length of stay, ICU and hospital outcome, baseline lung allograft dysfunction (BLAD)[19] and 90-day mortality.

2.2 | Statistical analysis

Patient characteristics, ventilation, physiological, and outcome variables were reported as means with standard deviation (SD) or medians with interquartile range (IQR) based on normality of distribution.

VFDs were analysed using both the Wilcoxon rank-sum test and as a competing risks regression (CRReg) based on Fine and Gray's proportional sub-hazards model. The competing risks regression models are reported as sub-distribution hazard ratios (SHR) with the 95% confidence intervals (CI) and plots of the cumulative incidence function (CIF) of successful extubation.

Binary logistic regression and Cox proportional hazards regression were performed to analyse the association of ventilator-free days and tidal volume sub-groups with 90-day mortality. The models were adjusted for age, sex, and PGD grade 3 at 72 h. All analyses are reported with a two-sided *p*-value, with $p < .05$ set to denote statistical significance. Statistical analyses were performed using Stata/SE 17.0 software (StataCorp, TX, USA). The study plan was registered on

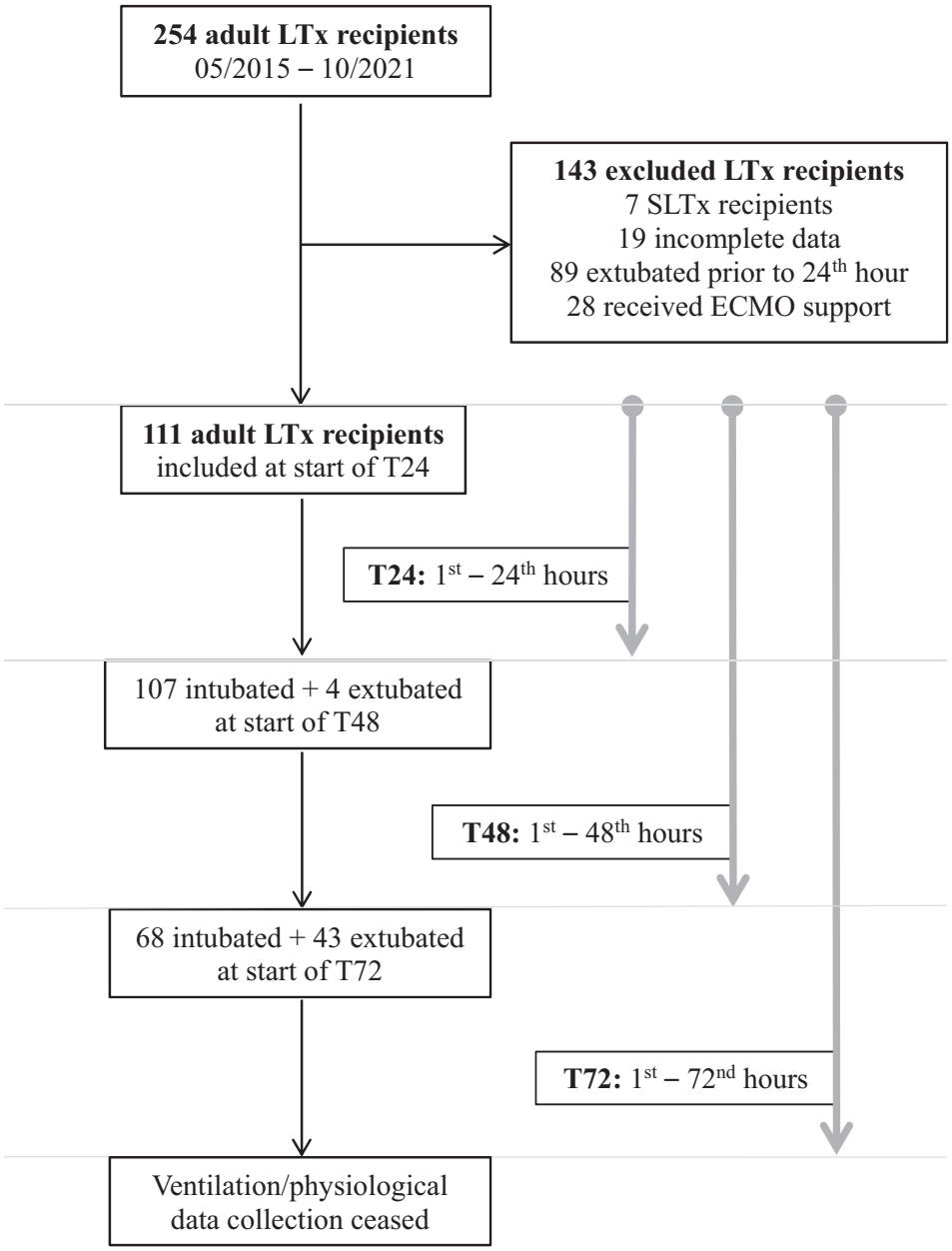

FIGURE 1 Study cohort development and overview of the ventilation and physiological data collection period over the first 72 h post-bilateral lung transplantation. ECMO, extra-corporeal membrane oxygenation; LTx, lung transplant; SLTx, single lung transplant.

the Open Science Framework (10.17605/osf.io/8hgrm) before final data analyses commenced.

3 | RESULTS

There were 254 lung transplants performed during the study period, with complete data analyses performed in a final 111 patients (108 bilateral lung transplant and 3 heart–lung transplant recipients) (Figure 1).

3.1 | Patient characteristics

The patient characteristics for the entire cohort are provided in Table 1. The median recipient age was 59 years (48–62 years) and 42.3% of recipients were female. Transplantation was performed using cardiopulmonary bypass in 90.1% of cases and 27.9% of allografts were retrieved following donation after circulatory determination of death (DCDD).

3.2 | Ventilator-free days

The median number of VFDs for the entire cohort was 25 (21–26). At day 28, 101 (90.9%) patients had been successfully extubated, 7 patients remained intubated, and 3 (2.7%) patients had died (see Tables S1 and S2).

3.2.1 | Wilcoxon-rank sum

Comparison of all ventilation sub-groups using the Wilcoxon rank sum test is detailed in Figure 3, Tables 3 and S4. There were no differences in VFDs between the lower and higher tidal volume sub-groups indexed to both donor and recipient PBW at T24. At T48, there were fewer VFDs in both the higher mean and maximum tidal volume sub-groups when indexed to donor PBW. For the tidal volume sub-groups indexed to recipient PBW at T48, there was no difference in VFDs between the mean tidal volume sub-groups and fewer VFDs in the higher maximum tidal volume sub-group. At T72, there were fewer VFDs in the higher mean tidal volume sub-groups when indexed to donor PBW and no difference between the maximum tidal volume sub-groups. For the tidal volume sub-groups indexed to recipient PBW at T72, there was no difference in VFDs between the mean and maximum tidal volume sub-groups.

3.2.2 | Competing risk regression

The CRReg models determined the cumulative incidence of successful extubation in the context of the competing risk of death in the first 28 days. The SHRs, 95% CIs, and *p*-values for CRReg models are included in Tables 3 and S4, the CIF plots for the mean and maximum tidal volume sub-groups are shown in Figures 2 and S1 respectively, and the SHRs with 95% CIs for all other ventilation parameters are shown in Figure 4.

At T24, there were no differences in the cumulative incidence of successful extubation between all the tidal volume sub-groups when indexed to both donor and recipient PBW. For tidal volume indexed to donor PBW at both T48 and T72, there was a lower cumulative incidence of successful extubation in the higher mean and maximum tidal volume sub-groups in both the unadjusted and adjusted models. For tidal volume indexed to recipient PBW, there were no differences in the cumulative incidence of successful extubation for mean or maximum tidal volume sub-groups in the adjusted models at both T48 and T72.

TABLE 1 Patient characteristics.

Baseline characteristics	$n = 111$
Recipient factors	
Recipient age; years (IQR)	59 (48–62)
Recipient sex; female %	42.3
BMI; kg/m^2 (SD)	24.3 (±4.4)
Primary diagnosis; %	
COPD	45.1
ILD	28.8
CF	3.6
Other	22.5
Donor factors	
Donor age; years (IQR)	51 (32–61)
Sex match; matched %	67.6
Donor smoking; yes %	49.6
Donor P:F ratio; mmHg (IQR)	417 (366–467)
Size match	
Donor/recipient PBW ratio (SD)	1.02 (±0.16)
Donor/recipient pTLC ratio (SD)	1.00 (±0.19)
Donor pTLC/recipient aTLC ratio (IQR)	1.03 (0.87–1.46)
pTLC ratio sub-groups, %	
<0.9	32.4
0.9–1.1	34.2
>1.1	33.3
Surgical factors	
Organ retrieval; DBD %	72.1
Redo-surgery; redo %	6.3
Maximum ischaemic time; min (IQR)	317 (265–383)
CPB use; yes %	90.1
pRBC transfusion; units (IQR)	2 (0–4)

Abbreviations: aTLC, actual total lung capacity; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; DBD, donation after brain death; ILD, interstitial lung disease; P:F ratio, arterial oxygen partial pressure:fraction of inspired oxygen ratio; PBW, predicted body weight; pRBC, packed red blood cells; pTLC, predicted total lung capacity.

TABLE 2 Ventilation parameters and organ function measures for the entire cohort and for secondary outcome sub-groups.

	All patients	PGD T72 ($n = 111$)			ICU outcome ($n = 111$)			Hospital outcome ($n = 111$)			BLAD ($n = 93$)		
Ventilation and organ function	**$n = 111$**	**PGD <3 ($n = 79$)**	**PGD 3 ($n = 32$)**	***p*-value**	**Alive ($n = 105$)**	**Dead ($n = 6$)**	***p*-value**	**Alive ($n = 101$)**	**Dead ($n = 10$)**	***p*-value**	**No BLAD ($n = 39$)**	**BLAD + ($n = 54$)**	***p*-value**
Ventilation parameters													
Tidal volume; mL/kg (IQR)													
Mean Vt/rPBW	7.5 (6.7–8.4)	7.5 (6.7–8.6)	7.5 (6.8–8.1)	.68	7.5 (6.7–8.4)	7.9 (7.3–8.3)	.53	7.4 (6.7–8.2)	8.3 (7.8–10.3)	**.02**	7.4 (6.8–8.1)	7.4 (6.7–8.5)	.95
Mean Vt/dPBW	7.4 (6.5–8.6)	7.3 (6.5–8.5)	7.8 (6.8–8.9)	0.21	7.3 (6.5–8.4)	9.0 (7.5–10.3)	.07	7.3 (6.5–8.2)	10.1 (7.9–10.3)	**.001**	6.9 (6.4–7.8)	7.6 (6.7–8.5)	**.03**
Maximum Vt/rPBW	11.3 (9.9–13.2)	11.2 (9.9–13.4)	11.8 (10.1–13.0)	0.64	11.3 (9.9–13.3)	11.9 (11.5–12.5)	.33	11.2 (9.9–13.1)	13.2 (11.6–16.4)	**.01**	11.5 (10.3–12.8)	11.1 (9.1–13.1)	.35
Maximum Vt/dPBW	11.4 (9.5–14.3)	11.1 (9.5–13.5)	12.5 (9.4–14.6)	0.22	11.3 (9.1–14.0)	14.4 (11.1–16.2)	.08	11.1 (9.0–13.4)	14.9 (13.7–17)	**.002**	11.0 (8.8–12.9)	10.8 (9.5–14.0)	.66
Peak pressure; cmH_2O (SD)													
Mean Ppeak	22.5 (±3.8)	21.9 (±4.1)	22.5 (±2.9)	.43	23.1 (±3.8)	23.5 (±1.9)	.68	22.5 (±2.9)	22.5 (±2.9)	.63	21.2 (±4.1)	22.8 (±3.6)	**.04**
Maximum Ppeak	28.6 (±4.2)	28.2 (±4.3)	29.6 (±3.6)	.09	28.5 (±4.2)	29.7 (±2.6)	.56	28.5 (±4.2)	29.7 (±3.3)	.38	27.8 (±4.7)	29 (±3.9)	.19
Positive end-expiratory pressure; cmH_2O (IQR)													
Mean PEEP	7.9 (6.3–9.2)	7.8 (6.3–9.1)	8.1 (6.3–9.2)	.78	7.9 (6.3–9.2)	7.6 (6.4–9.8)	.86	7.9 (6.2–9.2)	7.7 (7.1–8.5)	.76	7.6 (6.1–8.7)	8.0 (6.2–9.4)	.32
Maximum PEEP	10 (8–10)	10 (8–10)	10 (9–12)	.17	10 (8–10)	11 (8–12)	.36	10 (8–10)	10 (8–12)	.53	10 (8–10)	10 (8–10)	.32
Dynamic driving pressure; cmH_2O (IQR)													
Mean ΔP	15.3 (±3.1)	15.2 (±3.5)	15.6 (±2.3)	.51	15.3 (±3.3)	15.5 (±1.6)	.85	15.3 (±3.2)	15.7 (±2.8)	.71	14.3 (±3.5)	16.0 (±2.9)	**.01**
Maximum ΔP	20.4 (±3.8)	19.9 (±3.6)	21.6 (±4.0)	**.04**	20.4 (±3.8)	20.7 (±2.8)	.87	20.4 (±3.8)	20.9 (±3.4)	.79	19.9 (±3.8)	20.7 (±3.9)	.32
Dynamic mechanical power; J/min (IQR)													
Mean MP	11.7 (9.4–14.3)	11.3 (9.3–14.1)	13.2 (10.3–15.1)	.1	11.7 (9.4–14.2)	14.2 (11.1–16.6)	.18	11.4 (9.4–14.1)	13.9 (11.8–15.0)	.06	11.2 (9.4–13.4)	11.7 (9.1–14.5)	.25
Maximum MP	16.6 (13.4–21.4)	15.9 (13.2–21.2)	18.8 (14.1–22.0)	.15	16.4 (13.4–21.3)	20.5 (15.1–28.8)	.23	16.0 (13.4–21.2)	20.5 (15.5–28.8)	**.04**	15.5 (13.1–19.8)	16.7 (13.2–21.2)	.42
Dynamic compliance; ml/cmH_2O (IQR)													
Mean Cdyn	32.0 (24.5–42.4)	32.1 (24.5–45.3)	31.6 (24.8–39.0)	.71	32.1 (24.5–42.4)	1.5 (29.9–39.1)	.85	32.1 (24.2–42.4)	31.5 (29.2–39.1)	.64	33.2 (28.2–47.3)	29.7 (21.3–38.5)	**.02**
Minimum Cdyn	20.0 (16.4–25.1)	20.4 (16.4–26.0)	18.9 (16.4–21.7)	.25	17.5 (13.9–22.6)	17.6 (13.1–21.0)	.78	17.3 (13.3–22.5)	20.1 (14.8–23.3)	.48	20.3 (17.5–26.6)	19.0 (15.2–23.6)	.46
Organ function and support parameters													
Maximum SOFA score (SD)	9.9 (±2.4)	9.7 (±2.3)	10.6 (±2.3)	.06	9.9 (±2.4)	10.0 (±2.1)	.95	9.9 (±2.4)	10.2 (±2.2)	.71	9.5 (±2.3)	10.2 (±2.4)	.13
Minimum P:F ratio; kPa (IQR)	22.1 (17.1–32.0)	26.9 (±9.7)	17.3 (±4.7)	**<.001**	22.4 (17.6–32.0)	17.9 (13.2–25.2)	.42	22.4 (17.6–32.9)	19.1 (13.2–25.2)	.21	22.1 (18.3–33.7)	22.9 (16.7–32.0)	.57
Maximum CO_2; kPa (IQR)	6.4 (5.7–7.2)	6.3 (5.6–7.2)	6.5 (5.8–7.3)	.33	6.4 (5.7–7.2)	6.5 (5.7–7.1)	.82	6.4 (5.8–7.3)	5.8 (5.4–7.1)	.11	6.4 (5.9–7.3)	6.4 (5.6–7.4)	.68

(Continues)

TABLE 2 (Continued)

Ventilation and organ function	All patients $n = 111$	PGD T72 ($n = 111$)			ICU outcome ($n = 111$)			Hospital outcome ($n = 111$)			BLAD ($n = 93$)		
		PGD <3 ($n = 79$)	PGD 3 ($n = 32$)	*p*-value	Alive ($n = 105$)	Dead ($n = 6$)	*p*-value	Alive ($n = 101$)	Dead ($n = 10$)	*p*-value	No BLAD ($n = 39$)	BLAD + ($n = 54$)	*p*-value
Maximum ventilatory ratio (IQR)	2.05 (1.81–2.44)	1.98 (1.77–2.34)	2.24 (1.90–2.70)	**.046**	2.00 (1.81–2.36)	2.72 (2.64–2.90)	**.04**	2.03 (1.81–2.36)	2.64 (1.92–2.82)	.11	1.99 (1.82–2.35)	2.05 (1.73–2.36)	.9
Maximum VIS (IQR)	22.9 (13.7–34.3)	21.3 (11.7–30.9)	24.8 (19.0–36.5)	.15	22.7 (13.0–34.3)	24.7 (22.4–29.0)	.61	22.7 (13.0–35.0)	23.9 (21.0–29.0)	.84	21.0 (13.0–29.3)	25.9 (15.3–40.1)	.3
Net fluid balance at 72 h; mL (IQR)	1753 (60–3370)	1832 (±2414)	1960 (±2549)	.81	1811 (±2450)	3064 (±2152)	.21	1699 (±2398)	3743 (±2246)	**.02**	1477 (±1868)	2128 (±2807)	.2
Renal replacement therapy; yes, %	16.2	11.4	28.1	**.03**	16.2	16.7	.98	15.8	20	.66	9.8	22	.18
Minimum pH (IQR)	7.30 (7.26–7.35)	7.30 (±0.07)	7.29 (±0.09)	.42	7.30 (±0.07)	7.33 (±0.05)	.36	7.30 (±0.07)	7.31 (±0.06)	.39	7.29 (±0.06)	7.30 (±0.08)	.6
Maximum lactate; mmol/L (IQR)	3.0 (2.1–4.4)	2.8 (2.1–4.0)	3.3 (2.5–4.5)	.08	2.9 (2.1–4.1)	4.6 (3.2–5.8)	.13	2.9 (2.1–4.0)	4.2 (2.8–5.3)	.08	2.6 (2.2–3.4)	3.1 (2.0–4.5)	.42

Note: $p < 0.05$ (in bold).

Abbreviations: BLAD, baseline allograft dysfunction; PGD, primary graft dysfunction; SOFA, sequential organ failure assessment; VIS, vasoactive-inotrope score.

3.3 | 90-day mortality

Multivariate binary logistic regression and Cox proportional hazards regression were performed for 90-day mortality with the models adjusted for age, sex, and PGD grade 3 at 72 h post-transplant (Table 4). In the Cox model, increased VFDs were associated with a reduced rate of death at 90 days post-transplant (HR 0.92 (0.86–0.99), $p = .02$). We also included mean tidal volume/dPBW (mL/kg) at T24, T48, and T72 as continuous variables in a model adjusted for the same covariates (Table 4). At all time points, mean tidal volume/dPBW was associated with an increased rate of 90-day mortality.

3.4 | Ventilation, organ function and secondary outcomes

The ventilation parameters and secondary outcomes are reported in detail in Tables 2 and S3 and Figures S3–S5.

4 | DISCUSSION

This retrospective study demonstrated that in the first 72 h after surgery, a proportion of BLTx recipients were exposed to tidal volumes (indexed to dPBW), peak pressures, driving pressures, and mechanical power that exceeded the lung protective limits recommended in the management of ARDS. Our data suggest that a higher intensity of mechanical ventilation in the immediate post-operative period is associated with a reduced cumulative incidence of successful extubation and fewer VFDs in the first 28 days. Fewer VFDs were in turn associated with an increased rate of mortality in the first 90 days post-transplant.

Experts have acknowledged the need for a randomised controlled trial of mechanical ventilation post-LTx.[7,9] In contrast to patients emergently intubated for acute respiratory failure, early extubation is the expectation with the majority of LTx recipients.[8] This requires the transition to assisted or synchronised modes of ventilation during which the tidal volume is dependent on the patient-ventilator interaction and hence it may be more difficult to ensure the delivery of protective tidal volumes. Our data provide a detailed description of the ventilation parameters during this important phase for allograft recovery and support the hypothesis that, similar to ARDS patients, LTx recipients are exposed to mechanical load that may be under-recognised and potentially associated with harm.[20] Of note, we also observed the highest pressures and volumes in patients with the lowest P:F ratios who are at increased risk of ventilator-induced lung injury and prolonged ventilation.[21] These observations have implications for the design of a ventilation trial. The seminal trials of lung protective ventilation in ARDS each maintained strict tidal volume targets in the intervention arm.[1,22,23] Prioritising the adherence to specific protective tidal volume targets in the first 72 h post-lung transplant may require the increased use of sedative, analgesic, and paralytic drugs to obtund the patient's respiratory drive. This would represent a

TABLE 3 Mean and maximum tidal volume indexed to donor and recipient PBW sub-group comparison for tidal volume values, ventilator-free days, and competing risk regressions for successful extubation.

	Tidal volume/donor PBW			Tidal volume/recipient PBW		
Tidal volume sub-groups	**Lower Vt**	**Higher Vt**	***p*-value**	**Lower Vt**	**Higher Vt**	***p*-value**
T24 ($n = 111$)						
Mean tidal volume						
Vt/PBW; ml/kg (IQR)	6.5 (6.0–6.9)	8.2 (7.5–9.7)		6.8 (6.2–7.1)	8.0 (7.7–9.0)	
Ventilator-free days (IQR)	25 (23–26)	25 (19–26)	.55	25 (22–26)	24 (19–26)	.94
Competing risk regression for extubation (lower vs. higher tidal volume; SHR (95% CI))	1.02 (0.69–1.48)		.94	0.84 (0.57–1.24)		.38
Maximum tidal volume						
Vt/PBW; ml/kg (IQR)	8.1 (7.6–8.7)	11.9 (10.4–14.7)		8.6 (7.7–9.1)	11.3 (10.4–13.1)	
Ventilator-free days (IQR)	25 (22–26)	24 (19–26)	.23	25 (22–26)	24 (19–26)	.33
Competing risk regression for extubation (lower vs. higher tidal volume; SHR (95% CI))	1.13 (0.81–1.59)		.48	1.26 (0.89–1.79)		.2
T48 ($n = 107$)						
Mean tidal volume						
Vt/PBW; ml/kg (IQR)	6.5 (6.0–7.0)	8.5 (7.8–10.0)		6.7 (6.4–7.2)	8.5 (7.9–9.1)	
Ventilator-free days (IQR)	25 (23–26)	24 (17–26)	**.04**	25 (22–26)	24 (19–26)	.58
Competing risk regression for extubation (lower vs. higher tidal volume; SHR (95% CI))	1.54 (1.07–2.20)		**.02**	0.99 (0.68–1.44)		.96
Maximum tidal volume						
Vt/PBW; ml/kg (IQR)	8.9 (8.1–9.8)	13.5 (12.0–15.9)		9.1 (8.5–10.1)	12.8 (12.1–15.2)	
Ventilator-free days (IQR)	25 (23–26)	24 (17–26)	**.01**	25 (22–26)	24 (18–25)	**.02**
Competing risk regression for extubation (lower vs. higher tidal volume; SHR (95% CI))	1.76 (1.21–2.55)		**.003**	1.12 (0.70–1.79)		.65
T72 ($n = 68$)						
Mean tidal volume						
Vt/PBW; ml/kg (IQR)	6.5 (6.1–7.0)	8.6 (7.8–10.1)		6.8 (6.3–7.3)	8.4 (8.0–9.3)	
Ventilator-free days (IQR)	24 (21–25)	20 (14–24)	**.02**	23 (21–25)	21 (14–24)	.22
Competing risk regression for extubation (lower vs. higher tidal volume; SHR (95% CI))	1.87 (1.07–3.27)		**.03**	0.98 (0.57–1.70)		.95
Maximum tidal volume						
Vt/PBW; ml/kg (IQR)	9.5 (8.3–10.3)	14.3 (12.7–16.4)		9.9 (8.7–10.7)	13.1 (12.1–15.6)	
Ventilator-free days (IQR)	23 (21–24)	20.5 (12.5–24)	.21	22 (20–24)	23 (13–25)	.96
Competing risk regression for extubation (lower vs. higher tidal volume; SHR (95% CI))	1.66 (0.96–2.89)		.07	1.07 (0.68–1.67)		.77

Note: $p < 0.05$ (in bold).

Abbreviations: SHR, sub-distribution hazards ratio (SHR>1 denotes increased cumulative incidence of successful extubation); Vt, tidal volume.

change in standard practice and the risk: benefit ratio may only be favourable in the sub-phenotype of patients who are ventilated for a longer duration and have a higher baseline risk of VILI.[15] The early identification of this sub-group may require risk stratification by standardised severity assessment[24–26] to allow timely inclusion into a trial comparing standard care to protocolised ventilation based on donor anthropometrics.

Increased risk of PGD is an outcome of estimable clinical significance given its association with early mortality and chronic lung allograft dysfunction (CLAD).[9,27] PGD exhibits a complex pathobiology, and it is feasible that non-protective ventilation may contribute to increased lung injury severity quantified by the P:F ratio at 72 h post-BLTx. However, PGD grade censors patients at 72 h, and for those that remain intubated, there may be other deleterious consequences of non-protective ventilation that are obscured, such as refractory hypoxaemia, barotrauma, persistent air leaks, patient-ventilator asynchrony and multi-organ dysfunction syndrome.[28–30] For this reason, we selected VFDs as our primary outcome, which is a non-specific but potentially more sensitive representation of the complex sequelae of non-protective ventilation in the post-operative period. Fewer VFDs is a significant outcome for patients and a transplantation service. Prolonged ventilation increases the risk of VILI,

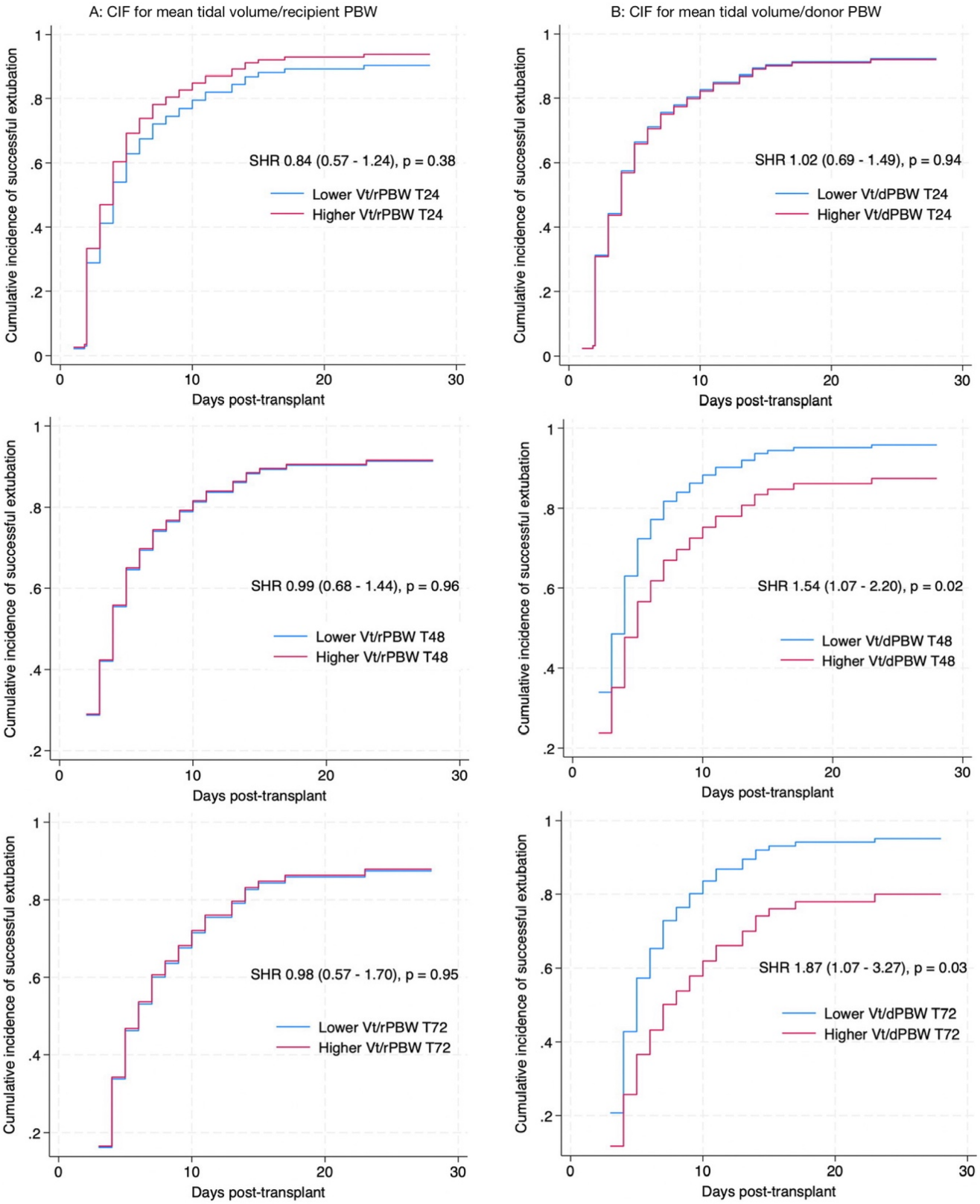

FIGURE 2 Cumulative incidence function plots and sub-distribution hazard ratios with 95% confidence intervals and p-values for mean tidal volume sub-groups (lower Vs. higher tidal volume) indexed to recipient PBW (left column) and donor PBW (right column) at T24, T48 and T72. dPBW, donor predicted body weight; rPBW, recipient predicted body weight; SHR, sub-distribution hazard ratio (SHR >1 denotes increased cumulative incidence of successful extubation); Vt, tidal volume. Model adjusted for recipient age, recipient sex, body mass index, maximum SOFA score, maximum vasoactive-inotrope score, and PGD grade 3 at 72 h.

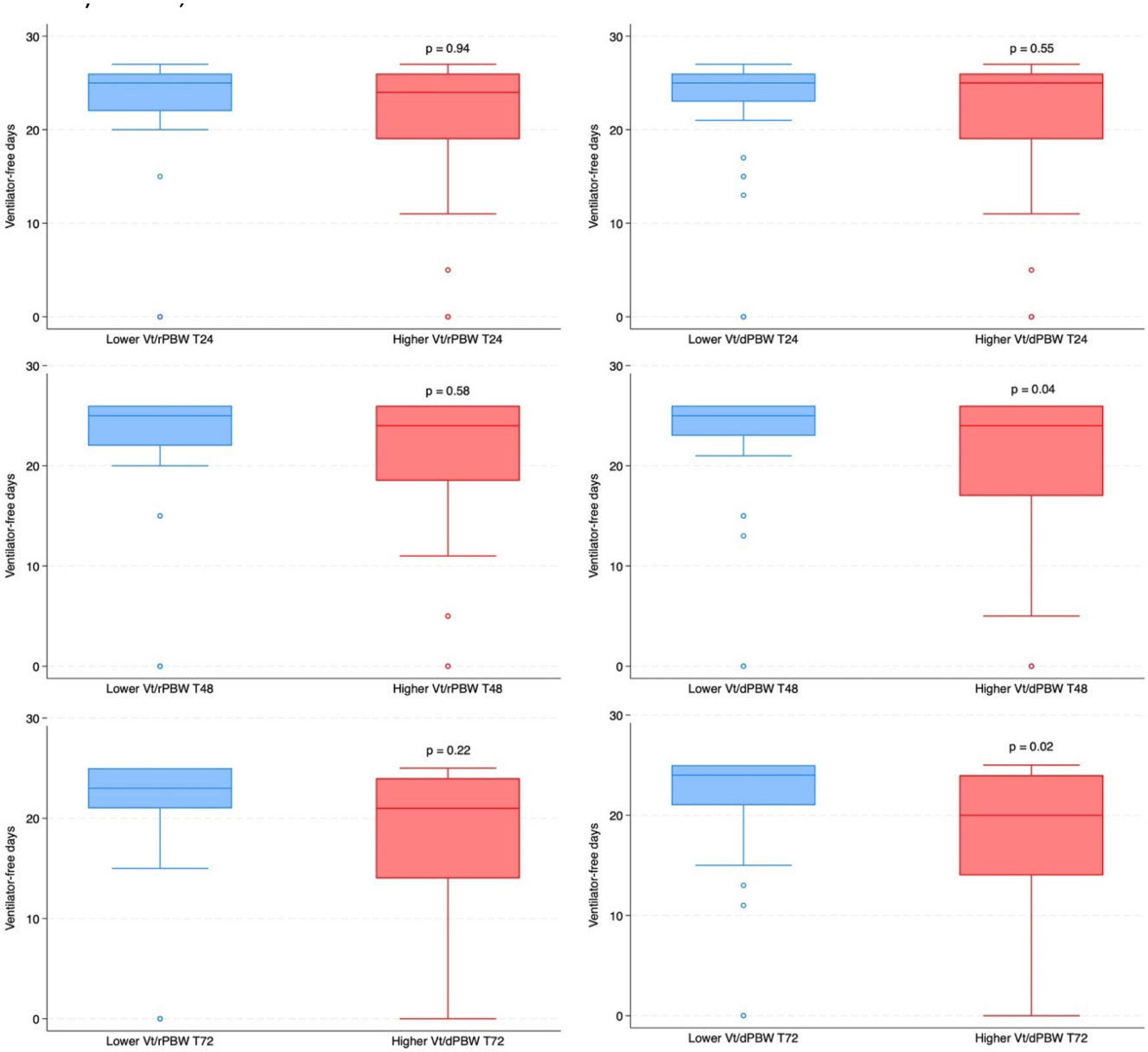

FIGURE 3 Ventilator-free days box plots and p-values for mean tidal volume sub-groups (lower vs. higher tidal volume) indexed to recipient PBW (left column) and donor PBW (right column) at T24, T48 and T72. dPBW, donor predicted body weight; rPBW, recipient predicted body weight; Vt, tidal volume.

ventilator-associated pneumonia and neuromuscular complications, in addition to increasing resource utilisation. We have tried to address the limitations of this outcome by adhering to a recommended standard definition and analysis method.[18]

In our analysis, for sub-groups with an SHR >1, the inference is that the co-variable is associated with an increased cumulative incidence of successful extubation. The magnitude of the effect of the variable on the SHR does not correlate quantitatively with the magnitude of the effect on the cumulative incidence function.[31] For this reason, we have provided the SHRs with the significance level and the CIF curves for the most relevant co-variables and models. Yehya et al. noted that if the competing risk regression model is dominated by extubation, as opposed to mortality, then the rank sum test approach may provide more statistical power. Nonetheless, within our specific cohort of patients there was a consistent association of lower tidal volume ventilation indexed to dPBW and a higher cumulative incidence of successful extubation and more VFDs in the first 28 days post-transplant.

The tidal volume sub-groups were defined retrospectively and thus the correlation of lower tidal volume and probability of successful extubation does not infer a causal relationship. In the simplest terms, patients who were ventilated with higher tidal volumes after 48- and 72-h post-transplant had a lower cumulative incidence of successful extubation over the first 28 days. During this period, patients

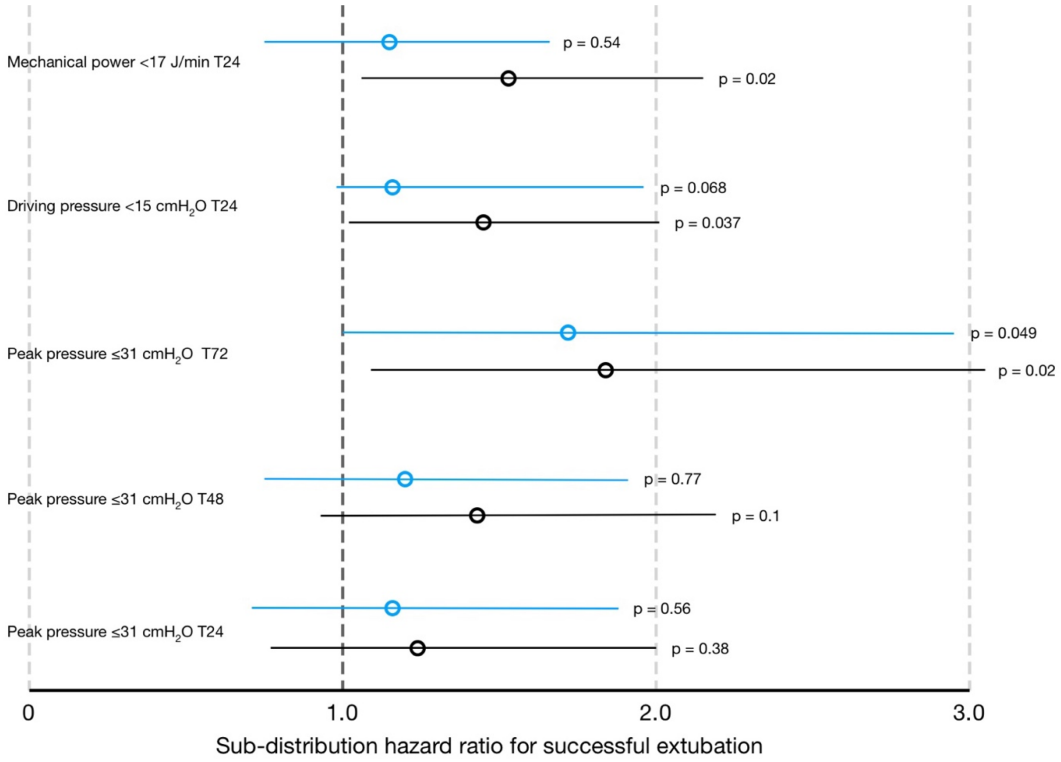

FIGURE 4 Competing risk regression sub-distribution hazard ratios with 95% confidence intervals for successful extubation for ventilation parameter sub-groups. Unadjusted models = black lines; adjusted models = blue lines. Model adjusted for recipient age, recipient sex, body mass index, maximum SOFA score, maximum vasoactive-inotrope score, and PGD grade 3 at 72 h.

are commonly managed with assisted or synchronised modes of ventilation whereby the interaction of the patient's respiratory drive and the ventilator settings determines the delivered tidal volume. Our data suggest therefore that patients who are less likely to be extubated are more likely to breathe at higher tidal volumes. We adjusted our model for covariates that may contribute to prolonged ventilation in the post-operative phase, such as maximum SOFA score as an index of overall organ dysfunction. However, tidal volume may represent a proxy of unmeasured confounders that are independently predictive of fewer VFDs. In this case, it is plausible that tidal volume in assisted ventilation modes is acting as a composite surrogate of other factors that increase minute ventilation such as delirium, pain score, altered chest wall mechanics or concomitant processes driving high oxygen consumption/carbon dioxide production or metabolic acidaemia. This highlights the difficulty in making inferences about the association between tidal volume and patient outcomes with retrospective data. However, the reduced significance in the rPBW sub-groups suggests that the magnitude of tidal volume alone was not sufficient to identify the association with VFDs. This may represent the importance of strain as a determinant of VILI.[32–35] Strain is the ratio of tidal volume/end-expiratory lung volume (EELV), where the EELV in healthy lung is predominantly determined by patient dimensions. Indexing tidal volume to donor anthropometrics is likely a more accurate method to size the allograft and hence to represent the strain associated with any given magnitude of tidal volume. We cannot draw a causal inference between higher tidal volume/dPBW and fewer VFDs, though we can infer that these patients are exposed to higher lung stress and strain and therefore risk of VILI. The emergence of an association after 24 h may represent the accumulation of risk as the area under the curve, and hence dose, of higher tidal volume ventilation increases.

The strengths of this study are the inclusion of a high-risk cohort with a minimum duration of exposure to mechanical ventilation coupled with the incorporation of mean and maximum values to comprehensively model the magnitude of the exposure. The major limitations of this study are predicated on the single-centre retrospective design. The data cannot define causal relationships and may not be representative of practice at other institutions. We have introduced a bias by including patients based on ventilation duration, and the low rate of 90-day mortality means that the relevant regression models may not be adjusted for additional co-variates that may be confounders. Additionally, the lack of previously published data in this patient group meant an effect size estimate was not feasible. This study was designed to be exploratory, and as such we have reported an extensive data set and statistical analyses that increase the probability of identifying significance due to chance alone.

To conclude, this single-centre retrospective study demonstrated that in patients intubated for a minimum of 24 h following bilateral lung transplantation, ventilation with lower tidal volume indexed to donor predicted body weight was associated with an increased

TABLE 4 Multivariate binary logistic regression and Cox proportional hazards regression of 90-day mortality for ventilator-free days and mean tidal volume/donor PBW at T24, T48, and T72.

Ventilation parameter	Multivariate logistic regression				Cox proportional hazards regression; RR (95% CI)			
	Alive ($n = 101$)	Dead ($n = 10$)	OR (95% CI)	*p*-value	Unadjusted	*p*-value	Adjusted	*p*-value
Ventilator-free days	25 (22–26)	0 (0–22)	0.87 (0.81–0.94)	**<.001**	0.91 (0.85–0.97)	**.004**	0.92 (0.86–0.99)	**.02**
Mean tidal volume/dPBW								
T24	7.2 (6.5–7.9)	8.7 (6.9–9.7)	1.48 (1.01–2.18)	**.046**	1.36 (1.01–1.83)	.04	1.37 (1.02–1.83)	.04
T48	7.3 (6.5–8.3)	9.6 (7.5–10.7)	1.81 (1.18–2.79)	**.007**	1.58 (1.15–2.17)	**.005**	1.65 (1.18–2.31)	**.004**
T72	7.3 (6.5–8.2)	10.1 (7.5–10.3)	1.79 (1.15–2.80)	**.01**	1.56 (1.14–2.14)	**.006**	1.64 (1.15–2.33)	**.006**

Note: Models adjusted for age, sex and PGD grade 3 at 72 h. $p < 0.05$ (in bold).
Abbreviations: CI, confidence interval; dPBW, donor predicted body weight; OR, odds ratio; RR, relative risk.

cumulative incidence of successful extubation and more ventilator-free days in the first 28 days post-procedure. This association was not identified when tidal volume was indexed to recipient PBW.

AUTHOR CONTRIBUTIONS

All authors contributed to study design, data analysis, and manuscript development.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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

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