The Association Between Extravascular Lung Water and Critical Care Outcomes Following Bilateral Lung Transplantation

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Background. Primary graft dysfunction (PGD) is a syndrome of acute respiratory failure that complicates 30% of bilateral lung transplants. Higher grades of PGD correlate with higher severity of respiratory failure and unfavorable outcomes. Immediate PGD determination posttransplant, however, is not always predictive of PGD over subsequent days or intensive care unit outcomes. We aimed to evaluate whether extravascular lung water index (ELWI) measured immediately post bilateral lung transplant was associated with higher severity of PGD at 72 h and duration of mechanical ventilation. Methods. We conducted a prospective, observational study of bilateral lung transplant patients admitted to the intensive care unit. ELWI measurements were performed at admission, 6, 12, 24, 36, 48, 60, and 72 h following transplant or until extubation. We evaluated the association between admission ELWI and 72-h PGD grade and duration of mechanical ventilation. Results. Across 56 patients enrolled, 268 transpulmonary thermodilution measurements were conducted. At admission, median ELWI increased with PGD grade (grade 1: 9 mL/kg [interquartile range (IQR), 8–11 mL/kg], grade 2 [10 mL/kg (IQR, 8–12 mL/kg)], and grade 3 [17 mL/kg (IQR, 14–19 mL/kg); P < 0.001]). Using multivariable Poisson regression analysis adjusting for confounders, admission ELWI elevation was associated with higher severity of PGD at 72 h (incidence rate ratio [IRR], 1.06; 95% confidence interval, 1.01–1.12) and duration of mechanical ventilation (IRR, 1.62; 95% confidence interval, 1.23–2.14). The combination of an ELWI of ≥13 mL/kg and partial pressure of oxygen/fraction of inspired oxygen ≤ 100 within 6 h of admission had high sensitivity (75%) and specificity (100%) for grade 3 PGD at 72 h (area under the curve, 0.95) and performed better than ELWI or partial pressure of oxygen/fraction of inspired oxygen alone. Conclusions. Our exploratory study demonstrates an association between admission ELWI and high grades of PGD at 72 h and longer duration of ventilation. These results provide the impetus to study whether goal-directed ELWI algorithms can improve transplant outcomes.

Primary graft dysfunction (PGD) is a syndrome of acute respiratory failure largely related to ischemia-reperfusion injury that complicates approximately 30% of bilateral lung transplants.1 In its most severe form, PGD is associated with prolonged mechanical ventilation, higher rates of chronic lung allograft dysfunction and increased mortality.2,3 Current PGD grading according to the International Society for Heart and Lung Transplantation occurs at 4 time points following transplantation: grade 1, grade 2, grade 3, and grade 4. Each grade is associated with a certain level of severity and risk, with grade 4 being the most severe. Immediate PGD determination posttransplant however, is not always predictive of PGD over subsequent days or intensive care unit outcomes. This study aimed to evaluate whether extravascular lung water index (ELWI) measured immediately post bilateral lung transplant was associated with higher severity of PGD at 72 hours and duration of mechanical ventilation.

Methods. A prospective, observational study of bilateral lung transplant patients admitted to the intensive care unit was conducted. ELWI measurements were performed at admission, 6, 12, 24, 36, 48, 60, and 72 hours following transplant or until extubation. The association between admission ELWI and 72-hour PGD grade and duration of mechanical ventilation was evaluated. Across 56 patients enrolled, 268 transpulmonary thermodilution measurements were conducted. At admission, median ELWI increased with PGD grade (grade 1: 9 mL/kg [interquartile range (IQR), 8–11 mL/kg], grade 2 [10 mL/kg (IQR, 8–12 mL/kg)], and grade 3 [17 mL/kg (IQR, 14–19 mL/kg); P < 0.001]). Using multivariable Poisson regression analysis adjusting for confounders, admission ELWI elevation was associated with higher severity of PGD at 72 hours (incidence rate ratio [IRR], 1.06; 95% confidence interval, 1.01–1.12) and duration of mechanical ventilation (IRR, 1.62; 95% confidence interval, 1.23–2.14). The combination of an ELWI of ≥13 mL/kg and partial pressure of oxygen/fraction of inspired oxygen ≤ 100 within 6 hours of admission had high sensitivity (75%) and specificity (100%) for grade 3 PGD at 72 hours (area under the curve, 0.95) and performed better than ELWI or partial pressure of oxygen/fraction of inspired oxygen alone. These results provide the impetus to study whether goal-directed ELWI algorithms can improve transplant outcomes.
transplant (0, 24, 48, and 72 h) and categorizes lung injury severity.\(^1\) Early PGD grading has less predictive validity compared with later times (24, 48, or 72 h).\(^2\) We currently lack methods of accurately identifying patients within the first few hours following transplant who are at higher risk of worsening PGD grade over subsequent days.

The freshly transplanted lung is particularly sensitive to excess fluid owing to loss of integrity in the alveolar-capillary membrane. The balance between maintaining adequate cardiac preload with excessive fluid accumulation in the susceptible lung is challenging. Excessive fluid administration in the "leaky capillary" phase of reperfusion injury, however, can result in a transition to higher PGD grades within a few hours. Consequently, an accurate method of measuring intravascular volume, extravascular lung water, and pulmonary permeability index is particularly attractive in the early post transplant period.\(^4,6\) Moreover, earlier assessment of PGD risk could potentially inform intensive care unit (ICU) management.

The measurement of extravascular lung water indexed to predicted body weight (ELWI) through the technique of transpulmonary thermodilution is a method of estimating pulmonary edema that has been previously validated.\(^7-11\) An evolving body of evidence has demonstrated its association with acute respiratory distress syndrome (ARDS) development/prognosis.\(^12-14\) Few studies have evaluated it in the immediate postoperative setting of lung transplant.\(^15\) Our objectives were to evaluate the association between (1) ELWI and PGD grade, (2) early ELWI and severity of PGD at later time points, (3) ELWI and duration of mechanical ventilation, and (4) whether ELWI can increase the prognostic value of PGD classification over arterial oxygen and chest X-ray alone.

**MATERIALS AND METHODS**

We conducted an exploratory prospective, observational study of consecutive bilateral lung transplants patients in the Toronto Lung Transplant Program from October 2015 to May 2018. Patients were approached for consent in pretransplant clinic and enrolled in the study when a donor became available. Patients who had a single lung transplant, immediate need for extracorporeal life support prior to ELWI measurements, an intracardiac shunt, or any contraindications to femoral arterial line were excluded. The study was approved by our institutional Research Ethics Board (University Health Network REB Number 12-0373).

**Extravascular Lung Water Measurements**

We measured ELWI using a Pulse Contour Cardiac Output (PiCCO) hemodynamic monitoring device (Pulsion Medical, Munich, Germany). The PiCCO method uses transpulmonary thermodilution to estimate ELWI and pulmonary vascular permeability index (PVPI). PVPI is the ratio of ELWI and pulmonary blood volume and is an indirect reflection of the alveolar-capillary integrity.\(^14,16-22\) A detailed description of the transpulmonary thermodilution technique is found in Appendix S1 (SDC, http://links.lww.com/TXD/A443).

Dedicated femoral arterial catheters were inserted intraoperatively. Each patient was connected to a PiCCO monitor upon arrival to the ICU. Transpulmonary thermodilution measurements were performed at admission, 6, 12, 24, 36, 48, 60, and 72 h using 15 mL of cold saline (0–4 °C) in triplicate through a central line in the superior vena cava. If the patient was extubated before 72 h, the measurements were stopped. This was decided given a desire to remove the femoral arterial line to help facilitate full engagement in physiotherapy following extubation. ELWI (mL/kg) indexed to predicted body weight and PVPI were collected on all patients. Clinicians were blinded to the measurements by shielding the PiCCO values.

**Data Collection and Outcomes**

Patient demographic variables, indication for transplant, donor variables, intraoperative support, ICU clinical variables were collected. PGD was graded at times 0, 24, 48, and 72 h (with the partial pressure of oxygen (PaO\(_2\)) fraction of inspired oxygen (FiO\(_2\)) taken at the same time as the ELWI measurements). Our primary outcome was the association between admission ELWI and PGD grade at 72 h. Secondary outcomes included duration of mechanical ventilation and PGD grade at 48 h. Admission ELWI measurements were those obtained 3–6 h after admission to the ICU. This timepoint was chosen to provide time for patient stabilization, recruitment and postoperative associated fluid shifts. PGD was evaluated by 2 independent reviewers who were blinded to the PiCCO measurement values (J.T., L.D.S.) (Appendix S3, SDC, http://links.lww.com/TXD/A443). PGD 0 or 1 were categorized as grade 1 for analytic purposes given the absence of significant short-term outcome differences between grades 0/1.

**Statistical Analysis**

ELWI thresholds have been previously described, with a threshold of ≤7 mL/kg as normal lung water and ≥10 mL/kg correlating with pulmonary edema (SD ± 4).\(^23-25\) Assuming a minimal clinically important difference of 3 mL/kg between high and low grades of PGD, an alpha statistic of 0.05, and a power of 0.80, we would require 56 patients.

We first evaluated the crude distribution of admission ELWI and PVPI across PGD grade using ANOVA. For our primary analysis, multivariable Poisson regression was performed to evaluate the association between admission ELWI and PGD grade at 72 h. All clinically relevant variables were evaluated to be incorporated into the model (patient, donor, ICU, transpulmonary thermodilution; Table S1, SDC, http://links.lww.com/TXD/A443). We first conducted a univariate analysis evaluating these variables and their association with PGD grade at 72 h. Any variables with a P < 0.2 on univariate analysis were incorporated into a multivariable Poisson regression analysis. We forced known prognostic variables for PGD into the model (age, sex, body mass index, transplant indication, donor smoking history, admission preservation time, intraoperative cardiopulmonary support, and receipt of blood products).\(^26\) In a secondary analysis, we evaluated the association between early ELWI and PGD at 72 and 48 h and duration of mechanical ventilation using multivariable Poisson regression analysis adjusting for patient, donor, and ICU variables as described above. All variables were assessed for multicollinearity using tolerance statistics (values <0.4 indicative of multicollinearity), and only 1 member of a correlated set was retained for the final model. Results were summarized using incidence rate ratios (IRRs) and 95% confidence intervals (CIs).
Receiver operating characteristic curves were generated to evaluate sensitivity and specificity, likelihood ratios, and positive/negative predictive values of different early ELWI cut points and their association with (1) grade 3 PGD at 72 h, (2) grade 3 PGD at 48 h, and (3) prolonged mechanical ventilation (mechanical ventilation for >48 h). Furthermore, we evaluated different early EVLW cut points in combination with different thresholds of PaO₂/FiO₂, take at the same time points (>300, 201–300, 101–200, ≤100). Finally, in an exploratory analysis, we evaluated if there was a difference in duration of mechanical ventilation within strata of PGD grade across high/low ELWI relative to the median value for that grade.

Categorical variables were summarized using counts and proportions. Continuous variables were reported using means (SD) or medians (interquartile ranges [IQRs]) where appropriate. Parametric and nonparametric values were compared using the t test or Wilcoxon rank sum where appropriate. ANOVA was used in the setting of >2 comparisons. Proportions were compared using the χ² test. Correlations were evaluated using Spearman correlation rho coefficient, Database management and all statistical analyses were performed using Stata 13.0 (StataCorp LP, College Station, TX). Results were considered statistically significant if P < 0.05.

RESULTS

One-hundred thirty-seven patients consented to be part of the study, 87 were called for transplant, and 56 were eligible (Figure S1, SDC, http://links.lww.com/TXD/A443). Fifty-five patients were included in the analysis as 1 patient was cannulated for extracorporeal membrane oxygenation (ECMO) immediately following transplant without an opportunity for transpulmonary thermodilution to be performed. Patient characteristics are summarized in Table 1. The mean recipient age was 55 ± 11 y, 58% were male, and idiopathic pulmonary fibrosis was the most common indication for transplant (35%). The majority of donors fulfilled neurologic death determination criteria (82%) and 25% underwent ex vivo lung perfusion. The mean total preservation time, Acute Physiology and Chronic Health Evaluation II score was 18 ± 4 and median initial arterial oxygen on 100% FiO₂ was 355 mm Hg (240–445 mm Hg). The Health Evaluation II score was 18 ± 4 and median initial arterial oxygen on 100% FiO₂ was 355 mm Hg (240–445 mm Hg). The proportion of patients with PGD grades 1, 2, and 3 at time 0 was 58%, 29%, and 13%, respectively. At 72 h, the incidence of grade 1 PGD increased to 70%, and grade 2 and 3 PGD were 15% (Figure 1; Table 2). The incidence of PGD was not consistent over time with only 50% of grade 3 PGD at 72 h classified as grade 3 PGD at time 0 (Figure 1). Across those classified as grade 1 PGD upon admission to the ICU, 22%, 19%, and 16% developed a higher severity of PGD at times 24, 48, and 72 h, respectively (Figure 1).

Primary Graft Dysfunction

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Extravascular Lung Water

We conducted 268 transpulmonary thermodilution measurements and 220 PGD determinations over the course of the study. Median ELWI at admission was 9 mL/kg (IQR, 8–11 mL/kg) for grade 1 PGD, 10 mL/kg (IQR, 8–12 mL/kg) for grade 2 PGD, and 17 mL/kg (IQR, 14–19 mL/kg) for grade 3 PGD (P < 0.001). Median PVPI on admission was 2 (IQR, 1–5) for grade 1 PGD, 2.1 (IQR, 1.6–3.1) for grade 2 PGD, and 4.1 (IQR, 3.2–5.3) for grade 3 PGD (P < 0.001) (Figure 2). The correlation between PaO₂/FiO₂ and ELWI was evaluated across all time points. ELWI had a significant negative correlation with PaO₂/FiO₂, for which the strength of this association was greatest at a PaO₂/FiO₂ < 200 (Spearman rho, 0.68; P < 0.001) (Figure 3).

In a post hoc analysis, we evaluated admission ELWI and PVPI across patients who received ex vivo lung perfusion and patients who received intraoperative cardiac support (Table S2, SDC, http://links.lww.com/TXD/A443).

Correlation Between ELWI and PGD

Age, sex, body mass index, transplant indication, donor smoking history, intraoperative cardiopulmonary support, total preservation time, Acute Physiology and Chronic Health Evaluation II on arrival to ICU, first PGD grade, and admission ELWI were incorporated into the multivariable model.

| TABLE 1. Baseline Characteristics | Cohort |
|-----------------------------------|--------|
| **Recipient characteristics**     |        |
| Age (mean ± SD)                   | 55 ± 11|
| Sex (male, female)                | 31 (58%) Male |
| Transplant indication             |        |
| Donor age (mean ± SD)             | 48 ± 19|
| Donor smoking history             | 24 (44%) Yes|
| Donor duration of mechanical ventilation | 2 d (IQR, 1–3 d) |
| Mean ex vivo lung perfusion time (mean ± SD) | 266 ± 45 min |
| Mean total preservation time      | 10.3 ± 5.3 h |
| **Operative characteristics**     |        |
| Intraoperative support            | 24 (44%) ECLS |
| OR blood transfusions             | 2 (4%) CPB |
| ICU characteristics               |        |
| Acute Physiology and Chronic Health Evaluation II score (mean ± SD) | 18 ± 4 |
| Admission PaO₂/FiO₂               | 355 (IQR, 240–445) |
| Inhaled nitric oxide on arrival to ICU | 10 (42%) |
| Duration of mechanical ventilation | 2 d (IQR, 1–5 d); 44% >48 h |

Median (IQR) or mean ± SD.
BMI, body mass index; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IFI, idiopathic pulmonary fibrosis; IQR, interquartile range; OR, operating room; PaO₂, partial pressure of oxygen.
Admission ELWI (IRR, 1.06; 95% CI, 1.01-1.12; P = 0.014) and shorter preservation time (IRR, 0.96; 95% CI, 0.94-0.99; P = 0.007) were associated with the development of more severe PGD at 72h (Table 3). In our secondary analysis, admission ELWI was also associated with the development of more severe PGD at 48h (IRR, 1.06; 95% CI, 1.02-1.10; P = 0.003) (Table S3, SDC, http://links.lww.com/TXD/A443).

**Correlation Between ELWI and Duration of Mechanical Ventilation**

Median duration of mechanical ventilation was consistently longer for higher grades of PGD (Table 2). Recipient, donor, intraoperative, ICU variables, and early ELWI and PVPI variables were evaluated to characterize their association with duration of ventilation. A higher admission ELWI (IRR, 1.62; 95% CI, 1.23-2.14; P = 0.001) and the need for intraoperative support (IRR, 2.12; 95% CI, 1.07-4.19; P = 0.031) was associated with a longer duration of mechanical ventilation. Whereas a longer preservation time (IRR, 0.89; 95% CI, 0.82-0.97; P = 0.010) was associated with a shorter duration of mechanical ventilation (Table 3).

**Early Prediction With ELWI**

The presence of an ELWI measurement >15 mL/kg at any early time point (6 or 12h) had a specificity of 91% and 98%, respectively, for PGD 3 at 72h; however, this threshold demonstrated
low sensitivity (44%; area under the curve [AUC], 0.63–6 h and 44%; AUC, 0.68–12 h) (Table S4, SDC, http://links.lww.com/TXD/A443). The results were similar when evaluating the association with duration of mechanical ventilation and grade 3 PGD at 48 h (Tables S4 and S5, SDC, http://links.lww.com/TXD/A443).

**Combination of ELWI and PaO\(_2\)/FiO\(_2\)**

When ELWI cut points (10–15 mL/kg) within 6 h of admission were evaluated in combination with PaO\(_2\)/FiO\(_2\) thresholds (≤100, 101–200, 201–300, >300) (Table S6, SDC, http://links.lww.com/TXD/A443), an ELWI threshold of ≥13 mL/kg in combination with a PaO\(_2\)/FiO\(_2\) ≤100 had the greatest association with grade 3 PGD at 72 h (specificity, 100%; sensitivity, 75%; AUC, 0.95). These were superior to PaO\(_2\)/FiO\(_2\) thresholds alone.

In an exploratory analysis, we evaluated whether subdividing PGD grades into categories stratified by high/low ELWI determined by their median value at 24 h was associated with a differential duration of mechanical ventilation (Table S7, SDC, http://links.lww.com/TXD/A443). In patients categorized as grade 2 PGD at 24 h, the duration of mechanical ventilation was longer if the ELWI was high (>10 mL/kg; 14 d

**FIGURE 2.** Admission ELWI and PVPI across different PGD grades. ELWI measured in mL/kg and indexed to predicted body weight. ELWI, extravascular lung water index; IQR, interquartile range; PGD, primary graft dysfunction; PVPI, pulmonary vascular permeability index.

**FIGURE 3.** Correlation between PaO\(_2\)/FiO\(_2\) and ELWI demonstrated a strong negative correlation between ELWI and PaO\(_2\)/FiO\(_2\) at values <200. ELWI, extravascular lung water; FiO\(_2\), fraction of inspired oxygen; LCI, lower confidence interval; PaO\(_2\), partial pressure of oxygen; P/F, PaO\(_2\)/FiO\(_2\); UCI, upper confidence interval.
were associated with later development of higher grade PGD and longer duration of mechanical ventilation independent of recipient, donor and PGD grade on admission. An ELWI value ≥13 mL/kg within the first 6 h of admission in combination with a PaO2/FiO2 ≤100 following transplant had the greatest specificity, sensitivity, and AUC in predicting 3 PGD at 72 h compared with PaO2/FiO2 alone. The 6-h timepoint was chosen to provide sufficient time for the patient’s physiologic state to be stabilized after the operating room (OR), transported to the ICU and transitioned to ICU care. Further work needs to be done to evaluate this relationship, however, our preliminary results may indicate that ELWI provides added precision to the prognostic value of the current International Society for Heart and Lung Transplantation PGD grading.

There exists evidence demonstrating the association between ELWI and ARDS development, severity, and prognosis following high-risk surgeries.17-19 In 1 study, ELWI was collected following surgery in patients at high risk for acute respiratory failure.27 It was demonstrated that an ELWI cutoff of 10 mL/kg on day 1 had an 88% specificity in predicting progression to respiratory failure at a mean of 2.6 d before patients met clinical criteria for ARDS. In lung transplantation, preliminary data have characterized the use of transpulmonary thermodilution in ex vivo lung perfusion in swine and human models,28-30 and for intraoperative hemodynamic monitoring.31 However, we are aware of only 1 study to date that has evaluated its use in 42 patients following bilateral lung transplant and 5 single lung transplants. In this study, Pottecher et al15 measured ELWI postperfusion and postoperatively. They found that an ELWI threshold of 14 mL/kg was associated with the development of grade 3 PGD. Their primary outcome was the presence of grade 3 PGD evaluated at any time point following transplant, which predominantly occurred 6 h following reperfusion. Our study complements these findings; however, we elected to focus on PGD grade at 72 h following transplant given that it has greater prognostic implications than early posttransplant PGD determinations.1-3 This discrepancy in prognostic power for early versus late PGD determinations is likely attributable to evolving hemodynamic and respiratory physiology immediately following chest closure, the impact of transportation to ICU and redistribution of fluid administered intraoperatively. Additionally, we focused solely on bilateral lung transplant and excluded single lung transplant recipients given the limitations of PGD grading in this setting. Finally, our study also evaluated the combination of ELWI and PaO2/FiO2.

Our study suggests that admission ELWI may strengthen early prognostic capabilities in determining which patients progress to severe PGD and prolonged mechanical ventilation. Importantly, in our exploratory analysis, it also suggested that ELWI, in combination with PaO2/FiO2 may have better discriminatory abilities in determining ICU outcomes. Taken together, ELWI, combined with PaO2/FiO2, may have a promising role in prognosticating the course in the ICU, triaging for early extubation versus prolonged mechanical ventilation and identification of at-risk patients who may benefit from future proactive interventions targeted at preventing PGD. Given the greater focus on a conservative fluid strategy—even in the setting of shock—it remains unclear if tailoring fluid management to ELWI could prevent against worsening severity of PGD.

Our study has a number of important limitations. First, despite 268 measurements, the sample size of our study was limited, which may have contributed to the number of statistically significant findings. Further, there was limited variability in ELWI measurements despite 268 measurements, the sample size of our study was limited, which may have contributed to the number of statistically significant findings. Further, there was limited variability in ELWI measurements despite 268 measurements. This may have limited the ability to fully explore the relationship between ELWI and PGD severity grade and duration of mechanical ventilation. Finally, our study was conducted in a single center and may not be generalizable to other clinical settings.

### DISCUSSION

Our study showed an association between admission ELWI and PGD grade. Importantly, we noted that elevated admission ELWI measurements (within 3–6 h of admission) generally predicted higher grade PGD and longer duration of mechanical ventilation. This association was independent of recipient, donor, and PGD grade on admission. Our results support the use of admission ELWI as a prognostic marker for PGD, as it was associated with later development of higher grade PGD and prolonged mechanical ventilation.

### TABLE 3.

**Multivariable analyses**

**Factors associated with PGD severity grade at 72 h**

| Recipient variable | IRR (95% CI) | P |
|--------------------|--------------|---|
| Age                | 0.99 (0.99-1.01) | 0.962 |
| Sex (female)       | 0.83 (0.63-1.09) | 0.184 |
| BMI                | 1.02 (0.99-1.05) | 0.106 |

**Indication (reference to IPF)**

| COPD/emphysema | 0.95 (0.69-1.29) | 0.726 |
| CF              | 0.78 (0.52-1.16) | 0.223 |
| Other           | 1.02 (0.75-1.39) | 0.882 |

**Donor smoking history**

| 1.14 (0.91-1.41) | 0.244 |

**Intraoperative blood products**

| 0.93 (0.73-1.17) | 0.517 |

**Preservation time (h)**

| 0.96 (0.94-0.99) | 0.007 |

**Intraoperative support (cardiopulmonary bypass or ECMO)**

| 1.06 (0.79-1.42) | 0.688 |

**APACHE II score**

| 1.02 (0.98-1.05) | 0.335 |

**PDG on admissions (reference grade 1)**

| 2 | 1.25 (0.98-1.61) | 0.076 |
| 3 | 1.27 (0.81-1.99) | 0.301 |
| ELWI at 6 h (mL/kg) | 1.06 (1.01-1.12) | 0.014 |

**Factors associated with duration of mechanical ventilation**

| Recipient variable | IRR (95% CI) | P |
|--------------------|--------------|---|
| Age                | 1.06 (1.01-1.11) | 0.026 |
| BMI                | 1.03 (0.96-1.04) | 0.432 |

**Indication (reference to IPF)**

| COPD/emphysema | 0.90 (0.29-2.85) | 0.853 |
| CF              | 0.58 (0.12-2.74) | 0.489 |
| Other           | 0.49 (0.20-1.20) | 0.121 |

**Donor smoking history**

| 1.94 (0.81-4.71) | 0.138 |

**Preservation time (h)**

| 0.80 (0.72-0.89) | <0.001 |

**Duration of Mechanical Ventilation of donza**

| 1.15 (0.98-1.36) | 0.083 |

**Intraoperative support (cardiopulmonary bypass or ECLS)**

| 2.12 (1.07-4.19) | 0.031 |

**APACHE II score**

| 1.01 (0.92-1.02) | 0.902 |

**PDG on admissions (reference grade 1)**

| 2 | 1.71 (0.84-3.49) | 0.141 |
| 3 | 0.36 (0.04-2.97) | 0.343 |
| ELWI at 6 h (mL/kg) | 1.62 (1.23-2.14) | 0.001 |

No patients with pulmonary hypertension underwent ELWI measurements.

**APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CF, cystic fibrosis; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ELWI, extravascular lung water index; IPF, idiopathic pulmonary fibrosis; IRR, incident rate ratio; other, hypersensitivity pneumonitis, bronchiectasis, bronchiolitis obliterans, scleroderma; PGD, primary graft dysfunction.**
conclusion

ELWI is a promising method to potentially quantify pulmonary edema and prognosticate PGD development. Our exploratory study demonstrates an association between early ELWI and high grades of PGD at 72 h and longer duration of mechanical ventilation. More data is needed to evaluate the reproducibility and generalizability of our findings and whether an ELWI-directed algorithm can improve outcomes by informing early adoption of protective strategies in high-risk patients or preemptive treatment for PGD.

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