OPEN

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

Laveena Munshi, MD, MSc,[1,2] Marcelo Cypel, MD,[3,4] Alaa Mohamed, MD,[1] Alyaa Elhazmi, MD,[1] Eddy Fan, MD,[1,2] Damon Scales, MD,[2,5] Jussi Tikkanen, MD,[4,6] Lorenzo Del Sorbo, MD,[1] Niall D. Ferguson, MD,[1,2] Shaf Keshavjee, MD,[3,4] and John Granton, MD[1,4,6]

Background. Primary graft dysfunction (PGD) is a form 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.

(*Transplantation Direct* 2022;8: e1376; doi: 10.1097/TXD.0000000000001376).

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

Received 21 January 2022. Revision received 2 July 2022.

Accepted 6 July 2022.

[1] Interdepartmental Division of Critical Care Medicine, Department of Medicine, Mount Sinai Hospital/University Health Network, University of Toronto, Toronto, ON, Canada.

[2] Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada.

[3] Division of Thoracic Surgery, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada.

[4] Toronto Lung Transplant Program, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada.

[5] Department of Critical Care, Sunnybrook Health Sciences Center, University of Toronto, Toronto, ON, Canada.

[6] Division of Respirology, Department of Medicine, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada.

This study was supported by a grant from the Ontario Thoracic Society.

The authors declare no conflicts of interest.

L.M. was involved in study inception, design, execution, analysis, and article development. M.C. and J.G. were involved in study inception, design, and oversight of article. A.M. and A.E. were involved in data collection. E.F., D.S., J.T., L.D.S., N.D.F., and S.K. were involved in design and article review.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Laveena Munshi, MD, MSc, Interdepartmental Division of Critical Care Medicine, Department of Medicine, Mount Sinai Hospital, 600 University Avenue, 18-206, Toronto, ON M5G 1X5, Canada. (Laveena.munshi@sinaihealth.ca).

Copyright © 2022 The Author(s). Transplantation Direct. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001376

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).[1,2] 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. Lung transplant operative approach, intraoperative support, and postoperative care were conducted in accordance with our transplant program's standard practice (**Appendix S2**, **SDC**, http://links.lww.com/TXD/A443).

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.[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 PaO_2/FiO_2 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 χ^2 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 at $P < 0.05$.

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, defined as the time from lung procurement to reperfusion of the first lung, was 10.3 ± 5 h. Intraoperative cardiopulmonary support was used in 48% of cases (44% extracorporeal life support). The mean Acute Physiology and Chronic Health Evaluation II score was 18 ± 4 and median initial arterial oxygen on 100% FiO_2 was 355 mm Hg (240–445 mm Hg). The median duration of mechanical ventilation was 2 d (1–5 d) with 56% of patients extubated within 48 h of ICU admission.

TABLE 1.

Baseline characteristics

Recipient characteristics	Cohort
Age (mean ± SD)	55 ± 11
Sex	31 (58%) Male
Transplant indication	19 (35%) IPF
	17 (31%) COPD/emphysema
	6 (11%) CF
	4 (7%) Scleroderma
	3 (5%) Hypersensitivity pneumonitis
	2 (4%) Bronchiectasis
	4 (7%) Other
BMI	26 (IQR, 20–29)
Donor characteristics	
Donor type	42 (82%) Neurologic determination of death criteria
Donor age (mean ± SD)	48 ± 19
Donor smoking history	24 (44%) Yes
	30 (54%) No
	1 (2%) Unknown
Donor duration of mechanical ventilation	2 d (IQR, [1–3 d])
Ex vivo lung perfusion	14 (25%)
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
	2 (4%) CPB
OR blood transfusions	26 (47%)
ICU characteristics	
Acute Physiology and Chronic Health Evaluation II score (mean ± SD)	18 ± 4
Admission PaO_2/FiO_2	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; FiO_2, fraction of inspired oxygen; ICU, intensive care unit; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; OR, operating room; PaO_2, partial pressure of oxygen.

Primary Graft Dysfunction

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).

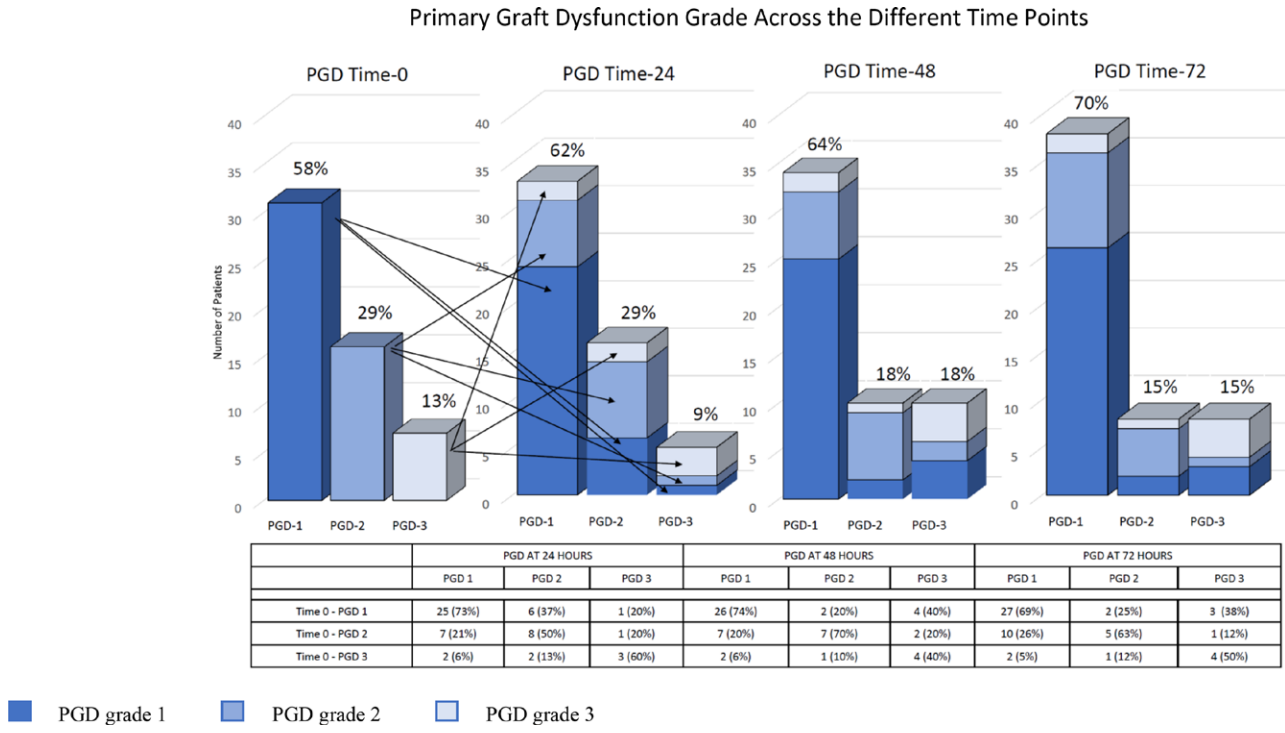
Extravascular Lung Water

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, 1.7–2.5) 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 PaO_2/FiO_2 and ELWI was evaluated across all time points. ELWI had a significant negative correlation with PaO_2/FiO_2, for which the strength of this association was greatest at a $PaO_2/FiO_2 < 200$ (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.



	PGD AT 24 HOURS			PGD AT 48 HOURS			PGD AT 72 HOURS		
	PGD 1	PGD 2	PGD 3	PGD 1	PGD 2	PGD 3	PGD 1	PGD 2	PGD 3
Time 0 - PGD 1	25 (73%)	6 (37%)	1 (20%)	26 (74%)	2 (20%)	4 (40%)	27 (69%)	2 (25%)	3 (38%)
Time 0 - PGD 2	7 (21%)	8 (50%)	1 (20%)	7 (20%)	7 (70%)	2 (20%)	10 (26%)	5 (63%)	1 (12%)
Time 0 - PGD 3	2 (6%)	2 (13%)	3 (60%)	2 (6%)	1 (10%)	4 (40%)	2 (5%)	1 (12%)	4 (50%)

FIGURE 1. PGD distribution over time. Grade 0/1 PGD were categorized as grade 1. All extubated patients were categorized as grade 1 PGD. PGD, primary graft dysfunction.

TABLE 2.

PGD grade details

PGD and ELWI characteristics	PGD 1	PGD 2	PGD 3
Time 0	32 (58%)	16 (29%)	7 (13%)
Time 24	34 (62%)	16 (29%)	5 (9%)
Time 48	35 (64%)	10 (18%)	10 (18%)
Time 72[a]	39 (70%)	8 (15%)	8 (15%)
PaO_2/FiO_2	396 (332–446)	259 (225–270)	152 (108–186)
Median admission ELWI (IQR) mL/kg	9 (8–11)	10 (8–12)	17 (14–19)
Median admission PVPI (IQR)	2.0 (1.7–2.5)	2.1 (1.6–3.1)	4.1 (3.2–5.3)
Time 0 h PGD categorization			
Duration of mechanical ventilation, d, median (IQR)	2 (1–3)	3 (1–9)	13 (3–33)
Time 24 h PGD categorization			
Duration of mechanical ventilation, median (IQR)	1 (1–2)	8 (3–17)	4 (3–33)
Time 48 h PGD categorization			
Duration of mechanical ventilation, median (IQR)	1 (1–2)	4 (3–6)	19 (11–25)
Time 72 h PGD categorization			
Duration of mechanical ventilation, median (IQR)	1 (1–2)	3 (2.5–4)	14 (9–29)

[a]PGD grade at 6 h not provided as a separate Chest X-Ray was not performed at this time.
ELWI, extravascular lung water indexed to predicted body weight mL/kg; IQR, interquartile range; PGD, primary graft dysfunction; PVPI, pulmonary vascular permeability index.

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 72 h (Table 3). In our secondary analysis, admission ELWI was also associated with the development of more severe PGD at 48 h (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 12 h) had a specificity of 91% and 98%, respectively, for PGD 3 at 72 h; however, this threshold demonstrated

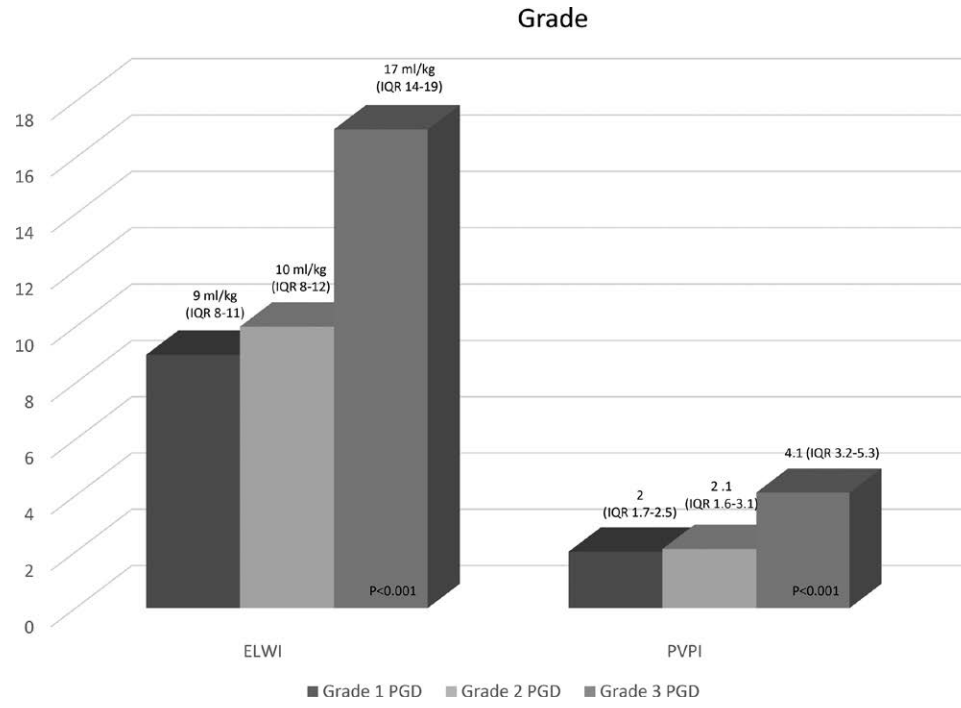


FIGURE 2. Admission ELWI and PVPI across different PGD grades. ELWI measured in mL/kg and indexed to predicted body weight. ELWI, extravascular lung water index; IQR, interquartile range; PGD, primary graft dysfunction; PVPI, pulmonary vascular permeability index.

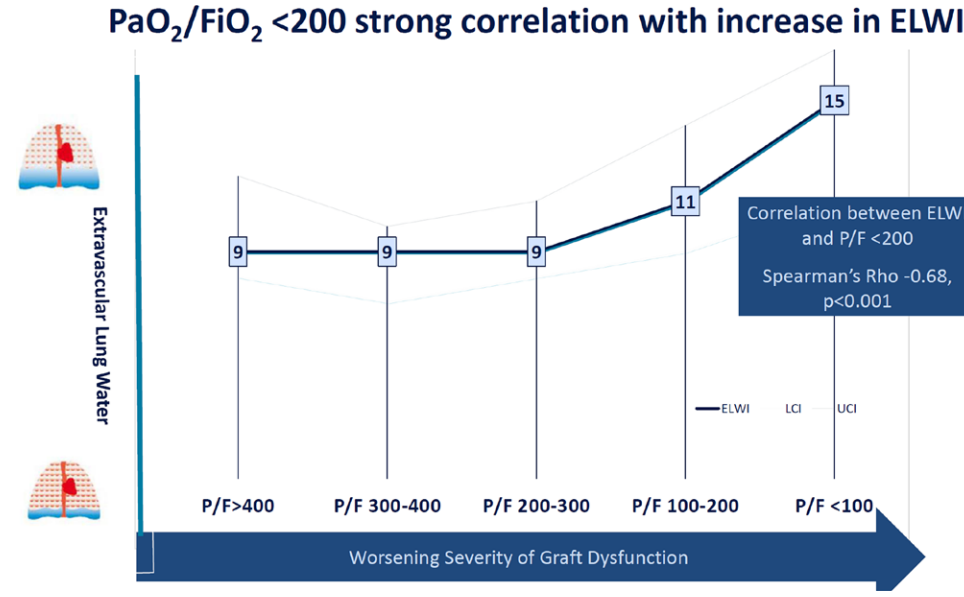


FIGURE 3. Correlation between PaO_2/FiO_2 and ELWI demonstrated a strong negative correlation between ELWI and PaO_2/FiO_2 at values <200. ELWI, extravascular lung water; FiO_2, fraction of inspired oxygen; LCI, lower confidence interval; PaO_2, partial pressure of oxygen; P/F, PaO_2/FiO_2; UCI, upper confidence interval.

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

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
PGD 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 (0.28-2.85)	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 (081-4.71)	0.138
Preservation time (h)	0.80 (0.72-0.89)	<0.001
Duration of Mechanical Ventilation of donor	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
PGD 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.

[IQR, 2–23 d]) compared with low ELWI (≤10 mL/kg; 4 d [IQR, 3–11 d]). Similarly, in patients with grade 3 PGD at 24 h, the duration of mechanical ventilation was higher if the ELWI was high (>12 mL/kg; 30 d [IQR, 4–55 d]) compared with low ELWI (≤12 mL/kg; 3 d [IQR, 3–33 d]). Interestingly, across patients with grade 2 PGD, the length of mechanical ventilation was higher (14 d [IQR, 2–23 d) for those with high ELWI compared with those with grade 3 PGD with low ELWI (3 d [IQR, 3–33 d]).

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) 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 PaO_2/FiO_2 ≤100 following transplant had the greatest specificity, sensitivity, and AUC in predicting 3 PGD at 72 h compared with PaO_2/FiO_2 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 al[15] measured ELWI postreperfusion 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 PaO_2/FiO_2.

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 PaO_2/FiO_2 may have better discriminatory abilities in determining ICU outcomes. Taken together, ELWI, combined with PaO_2/FiO_2, 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 relatively small and derived from a single institution; therefore, our findings are primarily meant to be hypothesis-generating. However, reassuringly, our results are consistent with what is known in the literature-to-date on this topic. Additionally, our study demonstrated the potential benefit of combining ELWI with PaO_2/FiO_2. The low incidence of grade 3 PGD in our program may have limited the power of our study. Note that this cannot be explained by our exclusion of patients on ECMO (all classified as grade 3 PGD), as <3.5% of transplants require postoperative ECMO in our program for any indication. Second, ELWI measurements were indexed to predicted body weight derived from the recipient; however, it remains unclear whether the results would be modified if indexed to donor. Given that the lungs are size-matched, we did not anticipate this would contribute in a large amount to inaccuracies. Third, given time pressures in the OR, we felt it was a more pragmatic approach to obtain admission ELWI measurements in the ICU. Admission measurements were taken between 3 and 6 h of ICU admission as opposed to immediate postadmission to ICU. This was pragmatically driven given the time needed to stabilize the patient, titrate sedation, adjust vasopressors after fluid shifts in the OR and adjust ventilator settings following OR transport. This timepoint was felt to represent early graft function, yet not be impacted in any major way by ICU-associated fluid management. Fourth, we limited our analysis to bilateral lung transplant given the greater validity of the PGD classification across bilateral transplant compared with single lung transplant. Given this, our study is not generalizable to single lung transplant. Furthermore, ELWI measurements are not reliable in the setting of ECMO or in the presence of intracardiac/intrapulmonary shunts and therefore these populations were excluded. Fifth, we elected to combine grade 0/1 PGD given the absence of clinical difference in critical care outcomes between the 2 grades. Finally, although not the primary focus of our analysis, longer preservation time was associated with lower grade of PGD at 72 h and shorter duration of mechanical ventilation. The patients with longer preservation times were more likely to have received ex vivo lung perfusion in our study, which has been shown to be associated with equivalent or less PGD at 72 h in previous studies by our group.[32,33] Median preservation time of lungs that received ex vivo lung perfusion was 19 h (IQR, 17–20 h) compared with 7 h (IQR, 6–9 h) for lungs that did not.

Our study supports the need for further evaluation of the potential utility of ELWI to predict the trajectory of patients after bilateral lung transplantation. Future studies are needed to evaluate whether incorporating ELWI into future definitions of PGD can assist in prognosticating outcomes. Although we demonstrated an association between early ELWI and outcomes, it remains unclear if these are simply a marker of severity of illness or whether therapeutic intervention (eg, diuresis/fluid restriction) can modify outcomes. We need to further evaluate whether a fluid, positive end-expiratory pressure, and/or sedation tailored algorithms incorporating ELWI can minimize progression to higher grades of PGD at later time points. Early measurements may also act as a triaging mechanism to identify patients who may undergo early extubation. Abnormally elevated ELWI values could also guide early initiation of protective therapies.

CONCLUSIONS

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.

REFERENCES

1. Snell GI, Yusen RD, Weill D, et al. Report of the ISHLT working group on primary lung graft dysfunction, part 1: definition and grading – a 2016 consensus group statement of the International Society for Heart and Lung Transplant. *J Heart Lung Transplant*. 2017;36:1097–1105.
2. Diamond JM, Arcasoy S, Kennedy CC, et al. Report of the ISHLT working group on primary lung graft dysfunction, part 2: epidemiology, risk factors and outcomes – a 2016 consensus group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017;36:1104–1114.
3. Lee JC, Christie JD, Keshavjee S. Primary graft dysfunction: definition, risk factors, short- and long-term outcomes. *Semin Respir Crit Care Med*. 2010;31:161–171.
4. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564–2575.
5. Neamu RF, Martin GS. Fluid management in acute respiratory distress syndrome. *Curr Opin Crit Care*. 2013;19:24–30.
6. Besen BA, Taniguchi LU. Negative fluid balance in sepsis: when and how? *Shock*. 2017;47:35–40.
7. Lange NR, Schuster DP. The measurement of lung water. *Crit Care*. 1999;3:R19–R24.
8. Michard F. Bedside assessment of extravascular lung water by dilution methods: temptations and pitfalls. *Crit Care Med*. 2007;35:1186–1192.
9. Sakka SG, Rühl CC, Pfeiffer UJ, et al. Assessment of cardiac preload and extravascular lung water by single transpulmonary thermodilution. *Intensive Care Med*. 2000;26:180–187.
10. Chung FT, Lin HC, Kuo CH, et al. Extravascular lung water correlates multiorgan dysfunction syndrome and mortality in sepsis. *PLoS One*. 2010;5:e15265.
11. Zhang F, Li C, Zhang JN, et al. Comparison of quantitative computed tomography analysis and single-indicator thermodilution to measure pulmonary edema in patients with acute respiratory distress syndrome. *Biomed Eng Online*. 2014:13:1–13.
12. Monnet X, Anguel N, Osman D, et al. Assessing pulmonary permeability by transpulmonary thermodilution allows differentiation of hydrostatic pulmonary edema from ALI/ARDS. *Intensive Care Med*. 2007;33:448–453.
13. Sakka SG, Klein M, Reinhart K, et al. Prognostic value of extravascular lung water in critically ill patients. *Chest*. 2002;122:2080–2086.
14. Berkowitz DM, Danai PA, Eaton S, et al. Accurate characterization of extravascular lung water in acute respiratory distress syndrome. *Crit Care Med*. 2008;36:1803–1809.
15. Pottecher J, Roche AC, Dégot T, et al; Groupe de Transplantation Pulmonaire des Hôpitaux Universitaires de Strasbourg. Increased extravascular lung water and plasma biomarkers of acute lung injury precede oxygenation impairment in primary graft dysfunction after lung transplantation. *Transplantation*. 2017;101:112–121.
16. Sakka SG, Reuter DA, Perel A. The transpulmonary thermodilution technique. *J Clin Monit Comput*. 2012;26:347–353.
17. LeTourneau JL, Pinney J, Phillips CR. Extravascular lung water predicts progression to acute lung injury in patients with increased risk. *Crit Care Med*. 2012;40:847–854.
18. Kushimoto S, Endo T, Yamanouchi S, et al; PiCCO Pulmonary Edema Study Group. Relationship between extravascular lung water and severity categories of acute respiratory distress syndrome by the Berlin definition. *Crit Care*. 2013;17:R132.
19. Perel A. Extravascular lung water and the pulmonary vascular permeability index may improve the definition of ARDS. *Crit Care*. 2013;17:108.

20. Martin GS, Eaton S, Mealer M, et al. Extravascular lung water in patients with severe sepsis: a prospective cohort study. *Crit Care*. 2005;9:R74–R82.
21. Isakow W, Schuster DP. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol Lung Cell Mol Physiol*. 2006;291:L1118–L1131.
22. Cottis R, Magee N, Higgins DJ. Haemodynamic monitoring with pulse-induced contour cardiac output (PiCCO) in critical care. *Intensive Crit Care Nurs*. 2003;19:301–307.
23. Tagami T, Kushimoto S, Yamamoto Y, et al. Validation of extravascular lung water measurement by single transpulmonary thermodilution: human autopsy study. *Crit Care*. 2010;14:R162.
24. Tagami T, Sawabe M, Kushimoto S, et al. Quantitative diagnosis of diffuse alveolar damage using extravascular lung water. *Crit Care Med*. 2013;41:2144–2150.
25. Jozwiak M, Teboul JL, Monnet X. Extravascular lung water in critical care: recent advances and clinical applications. *Ann Intensive Care*. 2015;5:38.
26. Gandevia SC, Gorman RB, McKenzie DK, et al. Effects of increased ventilatory drive on motor unit firing rates in human inspiratory muscles. *Am J Respir Crit Care Med*. 1999;160:1598–1603.
27. Kor DJ, Warner DO, Carter RE, et al. Extravascular lung water and pulmonary vascular permeability index as markers predictive of post-operative acute respiratory distress syndrome: a prospective cohort investigation. *Crit Care Med*. 2015;43:665–673.
28. Hillinger S, Hoerstrup SP, Zollinger A, et al. A new model for the assessment of lung allograft ischemia/reperfusion injury. *J Invest Surg*. 2000;13:59–65.
29. Kofidis T, Strüber M, Warnecke G, et al. Antegrade versus retrograde perfusion of the donor lung: impact on the early reperfusion phase. *Transpl Int*. 2003;16:801–805.
30. Trebbia G, Sage E, Le Guen M, et al; Foch Lung Transplant Group. Assessment of lung edema during ex-vivo lung perfusion by single transpulmonary thermodilution: a preliminary study in humans. *J Heart Lung Transplant*. 2019;38:83–91.
31. Della Rocca G, Costa GM, Coccia C, et al. Preload index: pulmonary artery occlusion pressure versus intrathoracic blood volume monitoring during lung transplantation. *Anesth Analg*. 2002;95:835–843, table of contents.
32. Cypel M, Yeung J, Mingyao L, et al. Normothermic ex-vivo lung perfusion in clinical lung transplantation. *NEJM*. 2011;364:1431–1440.
33. Yeung JC, Krueger T, Yasufuku K, et al. Outcomes after transplantation of lungs preserved for more than 12 h: a retrospective study. *Lancet Respir Med*. 2017;5:119–124.