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Plasma Receptor for Advanced Glycation Endproducts Predicts Duration of ICU Stay and Mechanical Ventilation in Patients Following Lung Transplantation

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Abstract

Background—Primary graft dysfunction, formerly termed reperfusion pulmonary edema, is the leading cause of short-term complications after lung transplantation. New evidence shows that alveolar type I epithelial cells play an active role in alveolar fluid transport and are therefore presumed to be critical in the absorption of pulmonary edema. We tested the potential relevance of a novel marker of alveolar type I cell injury, the receptor for advanced glycation end products (RAGE), to short-term outcomes of lung transplantation.

Methods—Prospective, observational cohort study of 20 patients undergoing single lung, bilateral lung, or combined heart-lung transplantation. Plasma biomarkers were measured 4 hours after allograft reperfusion.

Results—Higher plasma RAGE levels were associated with both a longer duration of mechanical ventilation and longer intensive care unit length of stay, in contrast to markers of alveolar type II cell injury, endothelial injury, and acute inflammation. Specifically, for every doubling in plasma RAGE levels, the duration of mechanical ventilation increased on average by 26 hours, adjusting for

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ischemia time (95% CI 7.4-44.7 hours, p=0.01). Likewise, for every doubling of plasma RAGE levels, intensive care unit length of stay increased on average by 1.8 days, again adjusting for ischemia time (95% CI 0.13-3.45; p=0.04). In contrast, the clinical diagnosis of primary graft dysfunction was not predictive of these short-term outcomes.

Conclusions—Higher levels of plasma RAGE measured shortly after reperfusion predicted poor short-term outcomes from lung transplantation. Elevated plasma RAGE levels may have both pathogenetic and prognostic value in patients following lung transplantation.

Keywords

Primary graft dysfunction; reperfusion pulmonary edema; biomarkers; alveolar epithelium; acute lung injury

Introduction

The term primary graft dysfunction (PGD) describes the spectrum of pulmonary ischemia-reperfusion injury occurring immediately after lung transplantation and encompasses the clinical entities formerly termed primary graft failure, reperfusion injury, reperfusion pulmonary edema, early graft dysfunction, and post-transplantation acute lung injury. PGD is the most common early complication after lung transplantation, occurring in 10-25% of recipients,(1) and has been demonstrated to predict duration of mechanical ventilation, hospital length of stay, and mortality in this population.(2-4) A recent international consensus group formed by the International Society of Heart and Lung Transplantation (ISHLT) defined PGD as a syndrome of early allograft dysfunction and lung injury marked by bilateral radiographic infiltrates consistent with pulmonary edema and a PaO_2/FiO_2 ratio of less than 300.(1) The consensus group further categorized PGD based on the degree of hypoxemia (Table 1) and recommended that the timing of the dysfunction be noted as well. This consensus definition encompasses a wide range of severity of disease and provides standardized criteria for this important syndrome in order to improve and facilitate future research.

The clinical, radiographic, and histologic presentations of PGD are very similar to those of acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS). ALI/ARDS is a common, frequently fatal syndrome of noncardiogenic pulmonary edema that develops in the setting of specific clinical conditions like sepsis, severe trauma, and pneumonia. It is defined by the presence of bilateral infiltrates, a PaO_2/FiO_2 of less than 300, and the absence of clinical evidence of left atrial hypertension. Biomarkers of endothelial injury, lung epithelial injury, acute inflammation, and disordered coagulation and fibrinolysis have important pathophysiologic and prognostic value in ALI.(5-10) Recently, a novel biomarker, the receptor for advanced glycation end products (RAGE), was reported to reflect alveolar type I cell injury in humans with ALI.(11) This new marker may be particularly useful given the recent discovery of the important and active role of the alveolar type I cell in alveolar fluid clearance.(12)

In contrast, in the transplantation literature, plasma biomarkers of lung injury have not been as extensively explored in clinical settings. Plasma interleukins (IL) 6 and 8 have been reported to correlate with poor short-term outcomes after transplantation,(13,14) and plasma levels of IL-6, 8 and 10 were higher in patients with more severe allograft injury in one recent small single center study.(15) In addition, plasma levels of plasminogen activator inhibitor-1 (PAI-1) and Protein C, markers of disordered coagulation and fibrinolysis, were recently found in a prospective cohort of lung transplant patients to be associated with PGD.(16) However, plasma biomarkers of lung epithelial injury have not been studied in this setting. Sensitive measures are needed to determine which patients have the most severe tissue injury after allograft

reperfusion and to identify which patients are at highest risk for both short and long-term adverse outcomes. The objective of our study was to determine whether plasma levels of RAGE are elevated in PGD, as they are in ALI/ARDS, and whether they have prognostic value for important clinical outcomes in the setting of lung transplantation.

Methods

Subjects

Twenty consecutive patients undergoing single or bilateral lung transplantation or heart-lung transplantation between May and August 2004 at the Cleveland Clinic were enrolled in this prospective, observational study. All organs were preserved in Euro-Collins solution during the period of study. The study was approved by the Institutional Review Board for Research of the Cleveland Clinic Foundation.

ISHLT Primary Graft Dysfunction Severity Score Calculation

ISHLT PGD severity scores were calculated for all subjects using data collected within 6 hours of lung reperfusion, termed time point 0 (T0) in the ISHLT consensus statement on PGD.(1) The PaO_2/FiO_2 ratio was calculated from the first arterial blood gas obtained in the intensive care unit. The first intensive care unit (ICU) chest radiograph after transplantation was interpreted for study purposes by a single pulmonary physician who was blinded to the patient's clinical status; this information was combined with the PaO_2/FiO_2 ratio in order to calculate the PGD score (Table 1). Caveats to the grading scheme were those defined in the 2005 ISHLT Consensus Statement.(1)

Biological Data

Blood samples were collected from the patients 4 hours after cross clamp release in ethylenediaminetetraacetic acid (EDTA) treated tubes and centrifuged for 10 min at 3000 *g*; plasma samples were then aliquoted and stored at −80° C. Using these samples, we measured plasma levels of 5 biomarkers previously demonstrated to have pathophysiologic and prognostic value in the setting of ALI: RAGE, KL-6, IL-6, IL-8, and intercellular adhesion molecule-1 (ICAM-1). Commercially available enzyme-linked immunosorbent assays (ELISA) were used to measure plasma concentrations of RAGE and ICAM-1 (R&D Systems, Minneapolis, MN), and IL-6 and 8 (Endogen, Pierce Biotechnology Inc, Rockford, IL). KL-6 was measured using a sandwich ELISA using anti-KL-6 mouse monoclonal antibodies as solid phase and enzyme-linked antibodies, as previously described.(17) Of note, some subjects also had plasma biomarker levels measured 1 or 2 hours after cross-clamp release; in those cases, the mean value of the biomarker over the first 4 hours was used for analysis. All markers were not measured on all patients due to limited plasma availability.

Data Analysis

Statistical analysis was performed with STATA/SE 9.2 (College Station, TX). Descriptive analyses were performed using mean values for normally distributed variables and median values for non-normally distributed variables. All plasma biomarker levels were abnormally distributed. Correlations between biomarker levels and continuous outcomes were performed using Spearman correlation coefficients. Analyses of other outcomes were performed using Mann-Whitney rank-sum tests, analysis of variance, and Kruskal-Wallis tests. We used linear regression models to determine the utility of plasma biomarkers to predict short-term clinical outcomes while adjusting for lung ischemia time; for these analyses, biomarker levels were log-transformed in order to apply linear methods. Model checking was performed using residual-based diagnostics.

Results

Demographic characteristics of the twenty study subjects are summarized in Table 2. The mean age of the subjects was 48, and the majority of subjects were female. Chronic obstructive pulmonary disease was the most common reason for lung transplantation (n=10, 50%), and 11 of 20 patients (55%) underwent single lung transplantation. The subjects' post-operative clinical characteristics and short and long-term outcomes are described in Table 3. Of note, 11 subjects (55%) had some degree of PGD (PGD Grades 1-3) at Time 0. At one year, 75% of the patients were alive; of those who survived, 3 (20%) had evidence of chronic allograft dysfunction or bronchiolitis obliterans syndrome (BOS) as defined by pulmonary function parameters.(18)

We measured plasma levels of 5 biomarkers previously demonstrated to have pathophysiologic and prognostic value in acute lung injury: RAGE, KL-6, IL-6, IL-8, and ICAM-1. As explained above, RAGE was recently demonstrated to reflect alveolar type I epithelial cell injury in rats with ALI and was recently shown to be elevated in human subjects with ALI.(11) No data have yet been published on the association between RAGE and outcomes in human subjects with ALI, although it correlated well with the severity of lung injury in a rat model.(11) KL-6 is a marker of alveolar type II epithelial cell injury that is elevated in many fibrotic lung diseases and in ALI/ARDS; in two separate studies, levels were higher in nonsurvivors of ALI than in survivors.(17,19) Interleukins 6 and 8 are inflammatory cytokines associated with both morbidity and mortality in ALI.(8) Intercellular adhesion molecule-1 (ICAM-1) is a marker of endothelial injury as well as neutrophil-endothelial interaction demonstrated to have prognostic value in pediatric lung injury.(6) Median values and interquartile ranges for the biomarkers of interest, stratified by the presence of any PGD (Grade 0 vs. Grades 1-3), are listed in Table 4. There were no significant differences in levels of any of these biomarkers between subjects with PGD grades 1-3 and those with PGD grade 0.

The correlations between each of the biomarkers and short-term outcomes of transplantation are shown in Table 5. Plasma RAGE at 4 hours was significantly correlated with both duration of mechanical ventilation (r=0.54, p=0.04) and ICU length of stay (r=0.67, p=0.009). In contrast, none of the other markers, including KL-6, which reflects alveolar epithelial type II cell injury, were significantly correlated with these outcomes. Similarly, donor age, donor gender, and etiology of recipient lung disease were not associated with these outcomes. There was no association between plasma RAGE levels and the presence of bronchiolitis obliterans syndrome (BOS) at one year or between plasma RAGE levels and mortality at 30 days or one year. Of note, RAGE levels did not differ significantly in patients undergoing single versus double lung transplants, though there was a trend towards higher levels in double lung recipients (median in single lung patients 5,769 pg/ml vs. 21,198 pg/ml in double lung patients, p=0.11 by Mann-Whitney rank-sum).

To account for differing amounts of ischemia time that may have impacted plasma RAGE levels and may also have been related to patient outcomes,(20) we then used linear regression models to analyze the predictive value of plasma RAGE for each outcome while adjusting for allograft ischemia time as a covariate. (Figures 1 and 2 show the regression data *unadjusted* for ischemia time). Using these models, we found that the duration of mechanical ventilation increased on average by 26 hours for every doubling in plasma RAGE levels, adjusting for ischemia time (Table 6; 95% CI 7.4-44.7 hours, p=0.01). Likewise, for every doubling of plasma RAGE levels, ICU length of stay increased on average by 1.8 days, again adjusting for ischemia time (Table 6; 95% CI 0.13-3.45; p=0.04). Adding an adjustment for type of transplant (single vs. double lung) did not significantly affect the results of either regression, though the model fit for ICU days was less optimal with this additional covariate. Results did not differ

significantly when the outcomes were log-transformed to account for possible non-normal distribution (Table 6).

In comparison to plasma RAGE, the PGD score at time 0 was less strongly associated with short-term outcomes in this patient sample. Specifically, PGD score (0-3) was not predictive of duration of mechanical ventilation or of ICU length of stay. PGD score was predictive of the presence of BOS at one year (p=0.03). When PGD score was dichotomized as any PGD (Grade of 1-3) or no PGD (Grade of 0), patients with any PGD had a longer ICU length of stay than those without PGD (median 5.5 days vs. 3 days, p=0.048). Ischemia time was not predictive of duration of mechanical ventilation, ICU length of stay, or BOS at 1 year. Neither PGD score nor ischemia time predicted vital status at 30 days or at one year.

Discussion

The most important result from this study was that plasma RAGE levels 4 hours after lung allograft reperfusion predicted the duration of mechanical ventilation and ICU length of stay, even after adjusting for allograft ischemia time. In contrast, markers of alveolar type II cell injury, endothelial injury, and acute inflammation were not predictive of these outcomes. Further, in this small sample, plasma RAGE had better prognostic value for these short-term outcomes than the clinical diagnosis of PGD.

This prospective study is the first to specifically examine these biomarkers of lung epithelial and endothelial injury, which are well-validated in patients with ALI/ARDS, in the setting of lung transplantation. Levels of RAGE in lung transplant patients in this study were in fact similar to levels in patients with ALI that we recently published and higher than those in normal controls in that previous study as well.(11) In addition, this study is the first to compare the predictive ability of biomarkers of lung injury to those of clinical predictors like PGD and to demonstrate that RAGE has prognostic value for short-term patient outcomes in this setting.

Why might RAGE be a better predictor of short-term outcomes in this study than a clinical scoring system like PGD? The current classification system for PGD was developed primarily to standardize diagnostic criteria so as to improve the uniformity and generalizability of future research. As such, it encompasses a wide range of organ dysfunction and may be an overly broad instrument for predicting specific clinical outcomes. Similarly, the consensus definition developed for acute lung injury,(21) which has been extremely useful for the purposes of clinical research, has not proven to be a good predictive instrument.(22) By more directly quantifying lung epithelial cell injury, plasma RAGE may provide a more sensitive measure of actual allograft tissue damage that can predict short-term outcomes with greater precision. Alternatively, it may be that our small sample size limited our ability to detect the prognostic value of the PGD scoring system, which has been well-demonstrated in other studies.(3)

The finding that plasma RAGE (a marker of alveolar type I cell injury) was of greater prognostic value than plasma KL-6 (a marker of alveolar type II cell injury) is intriguing and has at least four potential explanations. Alveolar type I cells constitute 95% of the alveolar epithelium, so it may be that their greater quantity translates to a more sensitive marker of injury. Alternatively, it may be that injury to the type I cell is more deleterious to the function of the lung epithelium, particularly in light of the new data confirming the critical role of the type I cell in alveolar fluid transport and the resolution of alveolar edema.(12) A third possibility is that our small sample size prevented us from detecting a relationship between KL-6 and short-term outcomes.

A fourth possibility is that plasma RAGE levels in this study may reflect conditions other than alveolar epithelial cell injury. While RAGE has been recently implicated as a marker of alveolar type I epithelial cell injury(11) and is most abundant in the lung,(23) it is not specific for

alveolar type I cells; RAGE has also been demonstrated in vascular endothelium,(24) nervous tissues,(25) and other cell types in the lung(26) and is involved in systemic inflammatory responses such as sepsis.(27) Thus, it is possible that the prognostic value of RAGE in this sample reflects its role in systemic inflammation rather than its role as a marker of alveolar type I cell injury. This possibility, however, should not diminish the potential value of RAGE as a biomarker with prognostic value in the post-transplant setting. Other biomarkers reflective of potentially systemic phenomena such as PAI-1 have been demonstrated to have prognostic value in both the ALI(9) and post-transplant(16) settings.

Our study has some limitations. First, it is a small, single-center study; as such, it lacks the power needed to study longer-term outcomes such as mortality and to adjust for all potential confounders. Thus, it is possible that biomarkers may have particular prognostic value in certain subsets of patients—for instance, that results may differ in single vs. bilateral lung transplantation—or that the etiology of the recipient's lung disease may impact the results. Likewise, as in all small studies, results may be significantly impacted by outlier values; however, we used non-parametric analyses for the biomarker data throughout to mitigate this concern. The small sample size also makes the study underpowered to generate conclusions about negative associations; therefore, the negative correlations in this study should be interpreted with caution. Second, we only studied plasma data from the first 4 hours after reperfusion; repeating the analysis of these markers at later time points may be more informative or generate different results, although early blood sampling will certainly be of more practical value for prognostic purposes. Third, we collected information on PGD only at T0, within 6 hours of allograft reperfusion; PGD scores at 24, 48, and 72 hours may be more useful. Finally, we are unable to differentiate between RAGE generated in the allograft donor and that generated in the allograft recipient. A larger study may be able to study a broader range of both donor and recipient clinical characteristics to examine whether particular characteristics of either are highly associated with plasma RAGE levels.

In summary, plasma RAGE, a marker of alveolar type I cell injury, was associated with longer duration of mechanical ventilation and ICU length of stay in patients undergoing lung transplantation, even after adjusting for allograft ischemia time. Furthermore, in this small sample, plasma RAGE measured within 4 hours of allograft reperfusion had better prognostic value for these short-term outcomes than did the clinical diagnosis of PGD. Further studies are needed to replicate these results in larger and broader populations, to examine the role of biomarkers in predicting important longer-term outcomes like BOS and mortality, and to determine whether RAGE has additive value when combined with established clinical predictors of outcomes.(28)

Acknowledgments

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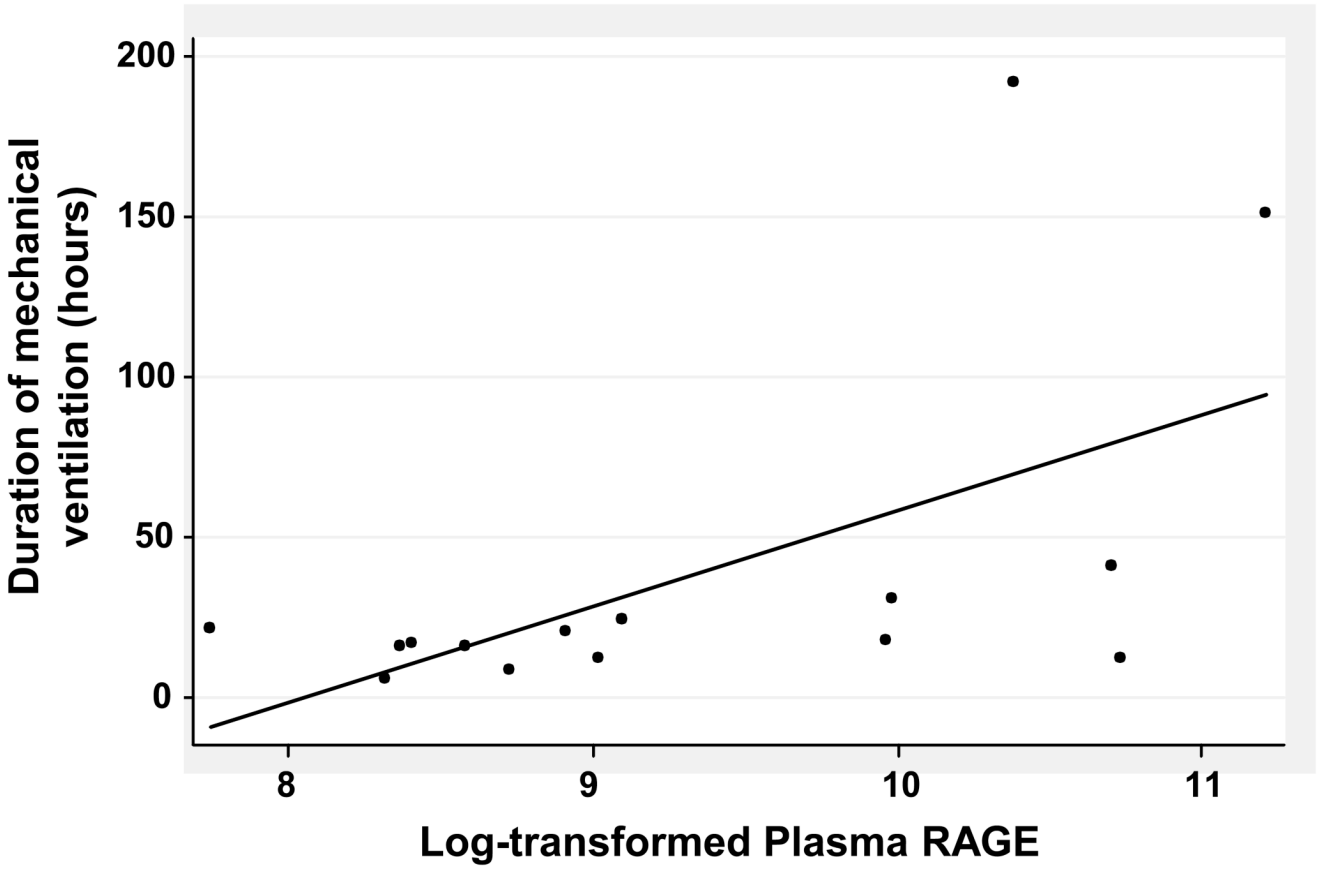

Figure 1.
Correlation of natural log-transformed plasma RAGE levels with duration of mechanical ventilation, measured in hours. For every one-log increase in plasma RAGE, the duration of mechanical ventilation increased by 30.1 hours (p=0.023); put differently, for every doubling in plasma RAGE, the duration of mechanical ventilation increased by 20.8 hours.

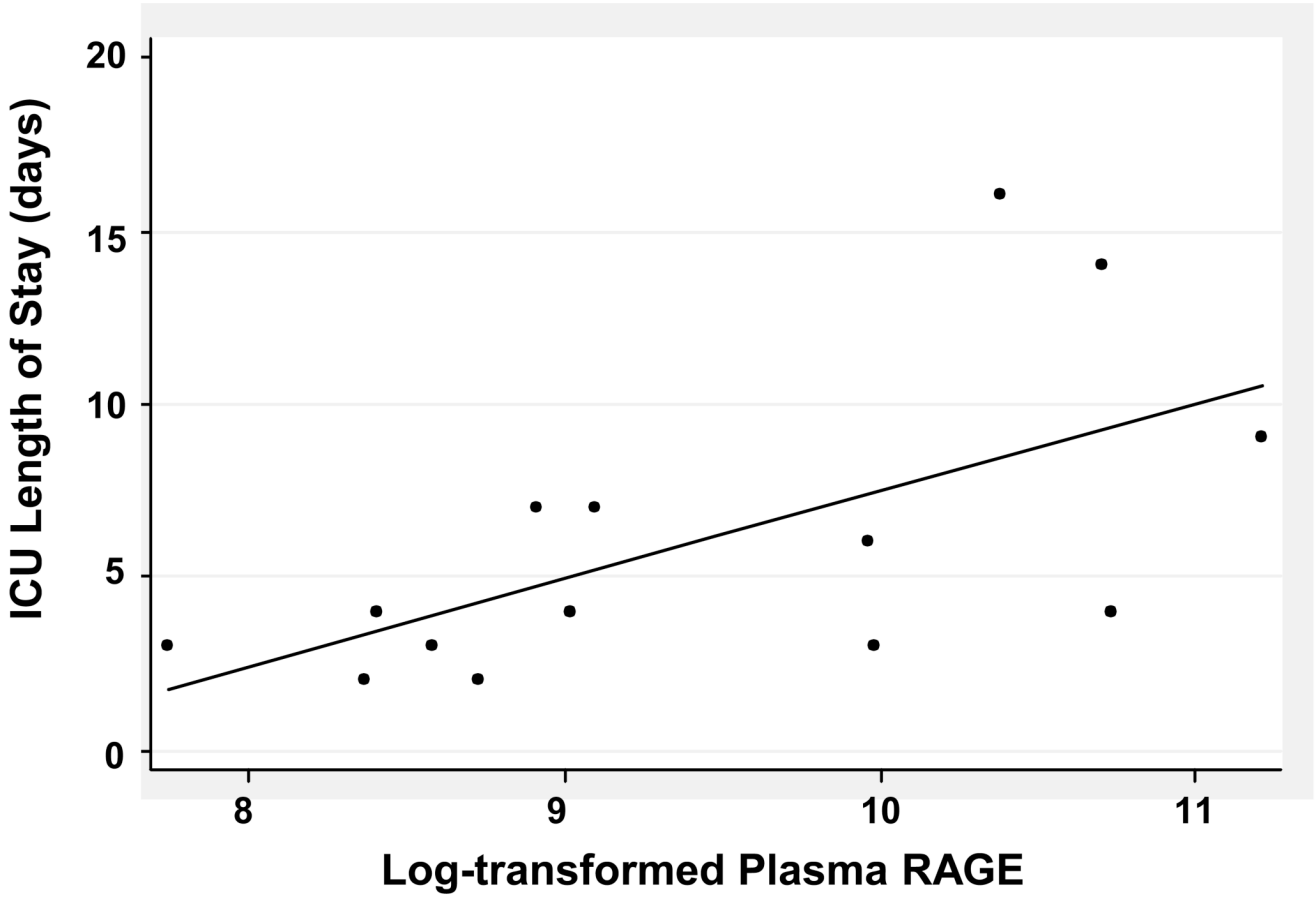

Figure 2.
Correlation of natural log-transformed plasma RAGE levels with duration of intensive care unit (ICU) stay, measured in days. For every one-log increase in plasma RAGE, the length of ICU stay increased by 2.5 days (p=0.018); put differently, for every doubling in plasma RAGE, the length of ICU stay increased by 1.76 days. Of note, ICU length of stay was missing in one patient.

Table 1

ISHLT Recommendations for Grading of Primary Graft Dysfunction Severity(1)

Grade	PaO_2/FiO_2	Radiographic infiltrates consistent with pulmonary edema
0	>300	Absent
1	>300	Present
2	200-300	Present
3	<200	Present

Table 2

Demographic Characteristics of Patients (n=20)

Characteristic	Value
Age, years, mean ± SD	48 ± 11
Male gender, n (%)	6 (30)
Etiology of lung disease	
Chronic obstructive pulmonary disease, n (%)	10 (50)
Interstitial lung disease, n (%)	5 (25)
Cystic fibrosis, n (%)	4 (20)
Type of transplant	
Single lung transplant, n (%)	11 (55)
Double lung transplant, n (%)	8 (40)
Heart-lung transplant, n (%)	1 (5)

Table 3

Post-operative Clinical Features and Outcomes

Characteristic	Value
ECMO post-transplant, n (%)	2 (10)
APACHE II score 24 h after transplant, mean ± SD	8.3 ± 4.1
Ischemia time, minutes, mean ± SD*	249 ± 50
PGD score 0, n (%)	9 (45)
PGD score 1, n (%)	2 (10)
PGD score 2, n (%)	2 (10)
PGD score 3, n (%)	7 (35)
Duration of mechanical ventilation, hours, median (IQR)	18 (12-31)
ICU length of stay, days, median (IQR)	4 (3-7)
Alive at 30 days post-transplant, n (%)	19 (95%)
Alive at 1 year post-transplant, n (%)	15 (75%)
Prevalence of bronchiolitis obliterans syndrome at 1 yr†	3 (20% of survivors)

*Data missing for two patients. For double lung transplants, ischemia time taken as longer of two ischemia times.

†Bronchiolitis obliterans syndrome (BOS) defined by 2002 ISHLT criteria.(18) One patient each with BOS stages 1, 2 and 3.

Table 4

Plasma Biomarker Levels at 4 hours Post-Transplant

Biomarker	N	Value in Patients with PGD (Grades 1-3)	Value in Patients with no PGD (Grade 0)	p-value
RAGE (pg/ml)	15	8634 (6398-38517)	6185 (4126-21667)	0.35
KL-6 (U/ml)	15	360 (209-708)	392 (157-574)	0.77
IL-6 (pg/ml)	13	184 (140-234)	306 (220-343)	0.24
IL-8 (pg/ml)	20	53 (38-114)	48 (24-128)	0.73
ICAM-1 (ng/ml)	12	501 (303-540)	267 (212-382)	0.46

Values reported as median (IQR). Markers not measured on all patients due to limited plasma availability.

Table 5

Correlation of Plasma Biomarkers at 4 hours with Short-Term Outcomes

Biomarker	Duration of Mechanical Ventilation (hrs)		ICU Length of Stay (days)	
	Spearman correlation coefficient	P-value	Spearman correlation coefficient	P-value
RAGE	0.54	0.04	0.67	0.009
KL-6	-0.12	NS	-0.26	NS
IL-6	0.37	NS	0.24	NS
IL-8	0.27	NS	0.39	NS
ICAM-1	-0.05	NS	-0.01	NS

Table 6

Relationship Between Plasma RAGE and Short-Term ICU Outcomes—Results of Linear Regressions

Outcome Variable	Coefficient (Change in Outcome per One-Log Change in Plasma RAGE)	p-value
Duration of mechanical ventilation (hours)	37.6 (10.7-64.5)	0.011
ICU Length of Stay (days)	2.6 (0.18-4.97)	0.037
Log-transformed duration of mechanical ventilation (hours)	0.67 (0.21-1.13)	0.008
Log-transformed ICU Length of Stay	0.39 (0.06-0.72)	0.025

Predictor variable for all regressions is natural log-transformed plasma RAGE. All regressions adjusted for ischemia time.