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Elevated donor plasminogen activator inhibitor-1 levels and the risk of primary graft dysfunction

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Abstract

Primary graft dysfunction (PGD) following lung transplantation is associated with elevated recipient plasma levels of plasminogen activator inhibitor-1 (PAI-1) and the receptor for advanced glycation end-products (RAGE). However, the significance of these biomarkers in the donor plasma is uncertain. We hypothesized that elevated donor plasma levels of PAI-1 and RAGE would be associated with recipient PGD. We carried out a prospective unmatched case-control study of double lung transplant recipients between May 2014 and September 2015. We compared donor plasma levels of PAI-1 and RAGE using rank-sum tests and t-tests, in 12 recipients who developed PGD grade 2 or 3 within 72 hours postoperatively with 13 recipients who did not. Recipients who developed PGD had higher donor plasma levels of PAI-1 than recipients who did not (median 2.7 ng/mL vs. 1.4; p=0.03). Recipients with PGD also had numerically higher donor plasma levels of RAGE than recipients without PGD although this difference did not achieve statistical significance (median 1061 pg/mL vs. 679; p=0.12). Systemic inflammatory responses in the donor, as reflected by elevated plasma levels of PAI-1 may contribute to the risk of developing PGD. Rapid biomarker assessment of easily available plasma samples may assist in donor lung selection and risk stratification.

Summary—Donor plasma levels of PAI-1 and RAGE are associated with development of PGD in lung transplant recipients. Further investigation into donor biomarker plasma levels is needed.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author BH on reasonable request.

Author contributions: This project received significant assistance from both medical and surgical departments at UCSF. BH and JK carried out concept/design, data analysis and interpretation, article drafting, critical revision and approval. GD assisted with data collection, sample processing, data analysis and article revision and approval, HZ assisted with statistical analysis, article revision and approval, MM assisted with sample analysis, project design, as well as statistical review and manuscript revision and approval, and JG, MB, and JS assisted with project concept, article revision and approval. All authors read and approved the final manuscript.

Keywords

Primary graft dysfunction; biomarker; donor; lung transplantation; plasminogen activator inhibitor 1

Introduction

Severe primary graft dysfunction (PGD) is the main cause of early morbidity and mortality following lung transplantation, affecting approximately 15–30% of recipients post transplantation.[1] Early prediction of PGD could allow earlier interventions and better recipient outcomes. The ability to identify donor lungs at risk for PGD prior to recipient selection would affect recipient outcomes and is the earliest possible time-point for intervention. Multiple characteristics of the donor, such as cigarette smoke exposure and increased age, increase the risk of PGD.[1,2] Other factors, as measured by biomarker levels, may also contribute to PGD risk. For example, plasminogen activation inhibitor 1 (PAI-1), mediates the imbalance of fibrin deposition and degradation in the lung and has been associated with lung injury.[3] Another, the receptor for advanced glycation end-products (RAGE), is a known marker for alveolar epithelial injury.[4] It is therefore not surprising that elevated plasma levels of PAI-1 and RAGE in the recipient are known to be associated with a higher risk of developing PGD.[5,6] Elevated concentrations of different biomarkers in the donor, such as IL-8, endothelin-1, and RAGE, have also been associated with development of PGD in the recipient.[7–9] However, measurements in these studies were conducted on donor bronchoalveolar lavage (BAL) fluid or tissue biopsies from donor lungs.

A blood-based biomarker is easily accessible, with sample collection and processing requiring less training than BAL and tissue. It is plausible yet remains uncertain if plasma levels of biomarkers in the donor are associated with risk of PGD after transplantation. To address this, we carried out a nested case-control study to test the hypothesis that elevated donor plasma levels of PAI-1 and RAGE would be associated with recipient PGD within 72 hours of lung transplantation.

Materials and Methods

Study Design

We carried out a hospital-based pilot case-control study of 25 recipients nested in a cohort of 71 consecutive recipients undergoing bilateral lung transplant at the University of California, San Francisco between May 1, 2014 and September 30, 2015. We compared donor plasma levels of PAI-1 and RAGE in 12 recipients who developed PGD grade 2 or 3 by the International Society for Heart and Lung Transplantation (ISHLT) criteria[10] within 72 hours postoperatively to levels in 13 recipients who developed only PGD grade 0 or 1. Recipient PaO_2:FiO_2 ratio was measured concurrently with chest radiograph at intensive care unit (ICU) admission (T0), 24 hours after reperfusion (T24), 48 hours after reperfusion (T48) and 72 hours after reperfusion (T72). All recipients were enrolled as part of their participation in a broader study of improving outcomes in lung transplantation through the development of a clinical database and bio-repository.

Study Population

Any recipient receiving a lung transplant at our institution between May 1, 2014 and September 30, 2015 was screened for inclusion in our study. Exclusion criteria were: enrollment in an ex-vivo lung perfusion (EVLP) trial, being listed for combined heart and lung transplant, undergoing a single lung transplant, undergoing a re-transplantation, having an unexpected malignancy in the recipient, an intraoperative cardiac arrest in the recipient, severe pulmonary artery hypertension with systolic pressure exceeding 100 mmHg in the recipient, and missing plasma samples precluding biomarker measurements. Given that the pilot nature of this study and our small numbers limited our ability to adjust for potential confounders, these exclusion criteria were chosen in an attempt to obtain a small yet relatively similar recipient population. Inclusion criteria for the study were: having undergone a bilateral lung transplant during the study period and having available donor plasma samples. All controls had no evidence of PGD grade 2 or 3 at any time-point within 72 hours postoperatively. All cases had persistent PGD grade 2 or 3 at ≥ 2 time-points within 72 hours postoperatively. In order to account for potential variations in associated biomarker levels given severity of PGD grade, further sensitivity analyses were also conducted by limiting cases to only those recipients who developed PGD grade 3. For these sensitivity analyses, cases with persistent PGD were further narrowed to those recipients who developed PGD grade 3 at any time-point, as opposed to those who developed persistent PGD grade 2 only, as well as those who developed persistent PGD grade 3 at ≥ 2 time-points.

Definition of Primary Graft Dysfunction

As defined by ISHLT criteria, [10] development of PGD was determined by the recipient PaO_2/FiO_2 ratio and chest radiograph review. Time-points for PGD grading were at T0, T24, T48 and T72. PaO_2:FiO_2 ratio was obtained from the electronic medical record. Chest radiographs were reviewed to determine the presence or absence of infiltrates. Any recipient receiving post-operative extracorporeal oxygenation (n=3) was graded as PGD grade 3.

Data Collection and Management

Donor clinical characteristics were extracted from the UNet donor database from the United Network for Organ Sharing. Characteristics included donor age, sex, body mass index (BMI), ethnicity, cause of death, history of tobacco use, history of drug use, days of mechanical ventilation and last measured PaO2:FiO2 ratio before organ recovery, presence of infiltrates on chest radiograph and computed-tomography scan, abnormal bronchoscopy, and cytomegalovirus (CMV) status. Recipient data was collected retrospectively and entered into the same electronic data system. Recipient data consisted of age, sex, BMI, ethnicity, pre-transplant location (home vs. ward or ICU), pre-transplant necessity of extracorporeal membranous oxygenation or tracheostomy/mechanical ventilation, systolic, diastolic and mean pulmonary artery pressures, lung allocation score, CMV status, and use of preoperative immunosuppression. Intra-operative data consisted of total lung ischemia time (averaged between left and right lungs), and the amount and type of intraoperative blood products. Post-operative data consisted of chest radiograph data and PaO2:FiO2 ratio

measured upon recipient arrival to the ICU and daily, days of ventilation, days until ICU discharge, days until hospital discharge and 30-day survival.

Measurement of Plasma Biomarkers

Donor blood was collected immediately before organ recovery, refrigerated, and centrifuged within 12 hours or less. Plasma was then collected and stored at −80°C until immediately before the assay was performed. Plasma levels of biomarkers were measured in duplicate using enzyme-linked immunosorbent assay kits (ELISA) for RAGE (RAGE ELISA; R&D, Minneapolis, MN) and PAI-1 (PAI-1 ELISA; R&D, Minneapolis, MN).

Statistical Analysis

Continuous, normally distributed variables were compared between cases and controls using two-tailed t-tests. Continuous non-normally distributed variables are expressed as median values and interquartile range (IQR) and compared using Wilcoxon's rank-sum test. Biomarker levels were not normally distributed and were therefore analyzed using Wilcoxon's rank-sum test. Biomarker levels were also log-transformed to apply t-tests. Because the natural log of zero is an undefined number, any plasma sample with an undetectable level of a biomarker was recorded as ½ of the minimum detectable dose of the assay in order to allow for log-transformation. Categorical variables were compared using Chi-squared or Fisher's exact tests. Correlation between continuous variables was analyzed using Spearman's rank test because of non-linear relationships between continuous predictors and continuous biomarker levels. Because of small sample size, we decided to forgo logistic regression with adjustment. A p-value of <0.05 was considered significant. Power calculations performed using a total cohort of 25 recipients and a significance level of 0.05 demonstrated that we would have power of 0.08 with an effect size of 0.2, 0.22 with an effect size of 0.5, and 0.48 with an effect size of 0.80. Analyses were done using STATA version 14.1 (STATA Corp., College Station, TX) as well as R (v3.3.1).

Ethics approval and consent to participate

This study was approved by the Institutional Review Board, Human Research Protection Program Committee on Human Research (IRB# 15-17276), and informed consent was obtained from all participants. All transplants were performed in concordance with ethical guidelines.

Results

Recipient Selection

Of the 71 recipients who underwent lung transplantation during the study period, 45 met initial inclusion criteria (Figure 1). Thirteen remaining recipients had only grade 0 or 1 PGD and therefore met inclusion criteria to act as controls. Of the remaining 32 recipients, 12 were excluded for having PGD grades 2 or 3 at only 1 time-point. Due to the pilot nature of the study and limited funds, of the remaining 20 recipients, 12 were randomly selected as cases for a total cohort of 25 recipients. Of the 12 cases, 3 never progressed beyond PGD grade 2. Of those 3, 2 had PGD grade 2 at all time-points, and 1 had PGD grade 2 only at 24 hours and was graded PGD grade 0 at the remaining time-points. Of the remaining 9 cases, 2

had PGD grade 3 at all time-points, 4 had PGD grade 3 only at initial grading upon ICU admission, 1 had PGD grade 3 at the 0, 48, and 72 hour time-points, 1 had PGD grade 3 at the 0 and 48 hour time-points, and 1 had PGD grade 3 only at the 72 hour time-point.

Baseline Characteristics of Donors and Recipients

Cases were more likely than controls to have a donor older than age 45 (p=0.039). Cases also had a higher recipient BMI than controls (p=0.001) (Table). In addition, recipient survival to 30 days was 100%.

Donor Biomarker Levels

Donor plasma levels of PAI-1 were higher in cases compared to controls in both the raw (median 2.7 ng/mL (IQR: 2.1, 5.5) vs. 1.4 (IQR: 1.1, 2.9); p=0.03) and log-transformed analysis (ln mean ± SD 1.1 ± 0.2 ng/mL vs. 0.2 ± 1.3; p=0.03). A trend was observed towards higher plasma RAGE levels in donors whose recipients later developed grade 2 or 3 PGD in the raw data (median 1061 pg/mL, (IQR: 475, 1930) vs. 679 (IQR: 400, 747); p=0.11). This association was stronger in the log-transformed analysis (ln mean 7.0 ± 0.3 pg/mL vs. 6.3 ± 0.1; p=0.028) (Figure 2). Sensitivity analyses demonstrated similar trends despite smaller numbers of cases. Donor plasma levels of PAI-1 had a trend towards higher levels in donors whose recipients later developed persistent PGD that included PGD grade 3 at any time-point compared to controls (n=9; ln mean 1.02 ± 0.68 ng/mL vs. 0.56 ± 0.59; p=0.11), as well as in donors whose recipients later developed PGD grade 3 at ≥ 2 time-points (n=4, ln mean 1.09 ± 0.46 ng/mL vs. 0.56 ± 0.59; p=0.13). Donor plasma levels of RAGE were higher in cases vs. controls when cases were defined as persistent PGD that included PGD grade 3 at any time-point (n=9; ln mean 6.91 ± 0.74 ng/mL vs. 6.31 ± 0.45; p=0.03) as well as in donors whose recipients later developed persistent PGD grade 3 at ≥ 2 time-points (n=4; ln mean 6.86 ± 0.46 ng/mL vs. 6.31 ± 0.45; p=0.049). One donor plasma sample had an undetectable level of RAGE and was thus recorded as ½ of the minimum detectable dose of the ELISA.

Discussion

In this study, we found higher donor plasma levels of PAI-1 and a trend towards higher donor plasma levels of RAGE in lung transplant recipients who later developed severe PGD compared to those who did not. These findings provide suggestive early evidence that donor abnormalities in coagulation and fibrinolysis may contribute to the risk of developing PGD in lung transplant recipients.

Our findings are consistent with other work investigating the association of postoperative levels of PAI-1 in the recipient with PGD following lung transplantation. In one prospective cohort study of lung transplant recipients, PAI-1 and Protein C were measured preoperatively in lung transplant recipients and at 6, 24, 48, and 72 hours after allograft reperfusion.[6] Plasma levels of PAI-1 at 6, 24, and 48 hours post-reperfusion were higher in recipients who developed PGD than in those who did not. PAI-1 levels were not different between groups at either the preoperative or 72-hour post-operative time-points. Preoperative protein C levels did not differ between recipients with PGD and those without

PGD, but were lower at each post-operative time point in recipients with PGD. Thus, low protein C and elevated PAI-1 plasma levels in the early postoperative period were associated with PGD. This temporal finding suggests that impaired fibrinolysis and hypercoagulability may be important early in the time-course of PGD. Moreover, this finding gives even further support for the impact of elevated PAI-1 levels in the donor plasma, the earliest possible point of measurement in the time course of PGD.

Our results are consistent with descriptions of the pathophysiology of lung injury. The role of coagulation and fibrinolysis in lung dysfunction has been previously described.[3] The normal lung has a fine balance between fibrin deposition and fibrin degradation, modulated by the conversion of plasminogen to plasmin, a fibrinolytic enzyme. This conversion is mediated by PAI-1 and PAI-2. In the presence of inflammation, multiple cell types including alveolar macrophages, pulmonary vascular endothelial cells, and possibly alveolar epithelial cells, are stimulated to release PAI-1. Several human models of lung injury have shown that elevated levels of PAI-1 inhibit fibrin degradation and result in fibrin accumulation.[3] Increased levels of PAI-1 and impaired fibrinolysis likely play a role in lung injury and PGD, as supported by our results.

Our finding of a trend between elevated donor levels of RAGE and PGD is also consistent with previous research that identifies an association between RAGE and lung injury in non-transplant populations. The binding of advanced glycation end products (AGEs) to their receptor (RAGE) prompts cell signaling and activation.[11] RAGE localizes to the basolateral membrane of type 1 alveolar epithelial cells, where it can sustain and propagate a transient pro-inflammatory reaction that can progress from acute to sustained cellular dysfunction.[11] BAL levels of RAGE are associated with increased ischemic time and impaired alveolar fluid clearance.[12] Furthermore, elevated post-operative plasma levels of RAGE have been found to be associated with recipient development of PGD, duration of mechanical ventilation, and ICU length of stay. [13–15] Similarly, elevated levels of RAGE in donor BAL have also been associated with recipient development of PGD.[7] These findings lend further support to our observed trend and suggest that donor RAGE expression and type 1 alveolar epithelial cell injury plays a role in recipient development of PGD.

Our study does have some limitations. Given its intent as a pilot study, we made the decision a priori to include only 25 recipients in the study. However, our small sample size limited our power to detect differences, although we were able to overcome this to some extent by log-transforming our data and using the t-test. One consequence of our small numbers was our decision to define cases as recipient PGD grades 2 or 3 as opposed to grade 3 alone, as has been done in other work.[7] In addition, we limited our cases to double lung transplant recipients, and to only those recipients with PGD at > 1 time-point in an attempt to select the most severe cases. While our selection of 12 cases from the 20 that met these criteria was random, we are unable to completely exclude the possibility that bias was introduced during this process. Therefore, we believe our results should be interpreted in the context of a pilot and exploratory study. Further work with larger numbers would be necessary to confirm our results. While we could not control for known donor and recipient risk factors, the differences we did identify were consistent with what has been previously published. In our study, cases were more likely to have a donor >45 years of age. This is consistent with prior

work associating donor age of <21 and >45 years with recipient development of PGD.[2] Recipient weight and obesity are established risk factors for development of PGD, [1] as well as for increased mortality.[16] Consistent with this research, we also found that cases had a higher BMI than controls. The demographics of the recipients in our study therefore support the possible association between an overweight recipient and the development of PGD. Whether specific combinations of donor characteristics contribute to disorders of coagulation in the donor, as seen by elevated levels of PAI-1, and thereby pre-disposing overweight recipients to PGD, is unclear. However, further investigation into these potential associations or pathways could be helpful in determining the pathophysiology of donor age or recipient BMI and an association with PGD.

Although our study has limitations, it features notable strengths, specifically, our focus on donor plasma. While numerous studies have shown that elevated concentrations of different biomarkers in the donor are associated with development of PGD in the recipient, [7–9,17–21] these studies focused on donor BAL fluid or donor lung tissue. Thus far, the only study that focused on donor blood examined the association between enthothelin-1 levels in donor serum and development of PGD in recipients, but did not find a relationship.[9] Indeed, further investigation through measurements of PAI-1 levels in donor BAL as well as blood could provide an interesting confirmation of our results as well as examine the correlation and differences between the two compartments. Both BAL and lung tissue are challenging and expensive to sample, requiring sufficient time and specialized training for both collection and processing. Donor blood represents a compartment that can be easily sampled at bedside with minimal training. Unlike both BAL and tissue, the simple nature of blood collection could allow donor sampling to occur at a vast variety of time-points prior to organ procurement. This could allow early donor lung stratification.

The ability to identify donor lungs at risk for PGD before recipient selection, the earliest time point for intervention and risk stratification, has the potential to significantly affect recipient outcomes. This pilot study has demonstrated the potential importance of the biomarker environment in the donor with short-term outcomes in the recipient. Future research is needed in order to take full advantage of this potential. Risk prediction models constructed using commonly available clinical variables of the recipient have already been developed.[22] In cohorts where prediction using clinical variables alone has failed, other variables such as extra-vascular lung water and protein biomarkers have been more successful.[15] Other studies have shown that combining biologic and clinical characteristics is more predictive than either biomarkers or clinical characteristics alone.[23] However, rapid sample assessment is necessary to realize the full potential of biologic markers. Recent work has demonstrated the possibilities of rapid biomarker analysis using fractal circuits, glass microchips, and gold microelectrodes, resulting in sample-to-answer times of 20–30 minutes. [24,25] Rapid biomarker assessment of both the donor and the recipient could allow for precise donor risk stratification and recipient matching, resulting in superior outcomes. Furthermore, better risk prediction could also identify subjects at risk for PGD for enrollment in future clinical intervention trials.

Conclusions

Elevated donor plasma levels of PAI-1 and a trend towards elevated levels of RAGE found in this nested case-control study provide evidence for a contribution from the donor to the risk of PGD development in recipients of lung transplantation. This finding is consistent with prior work on the importance of inflammation and coagulation factors in the pathogenesis of lung injury. Further work uniting donor biologic and clinical markers into a simple risk assessment tool, in combination with evolving methods of rapid biomarker assessment, could provide a framework for improved donor risk stratification resulting in better recipient outcomes.

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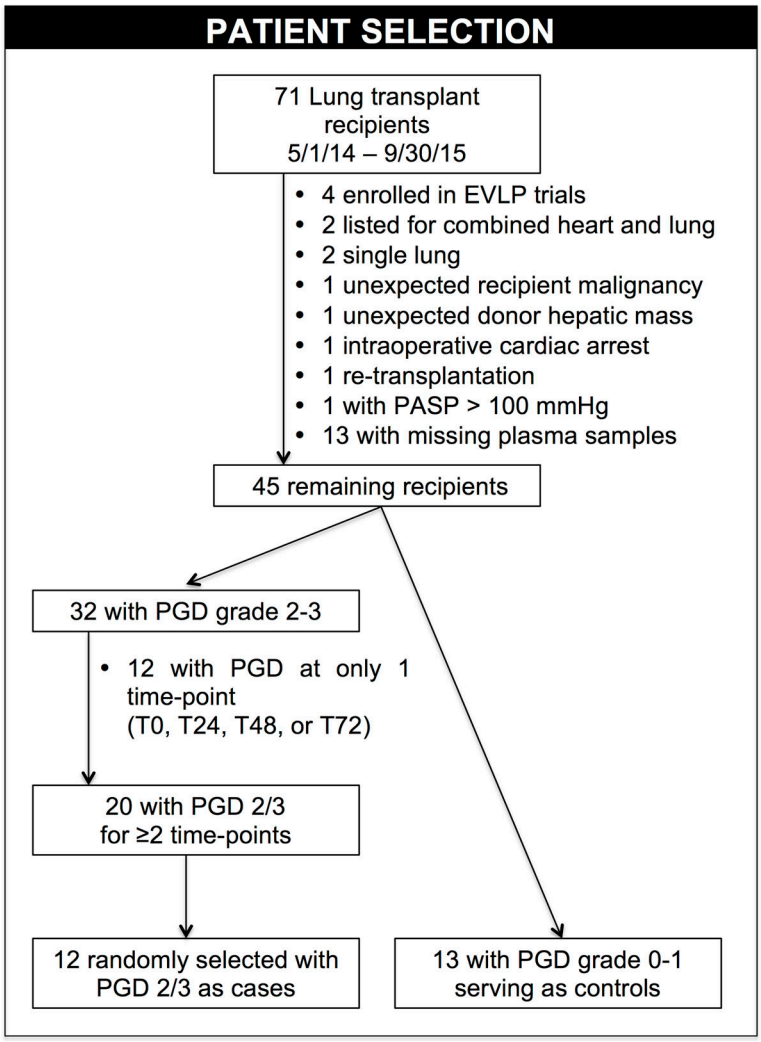

Figure 1.

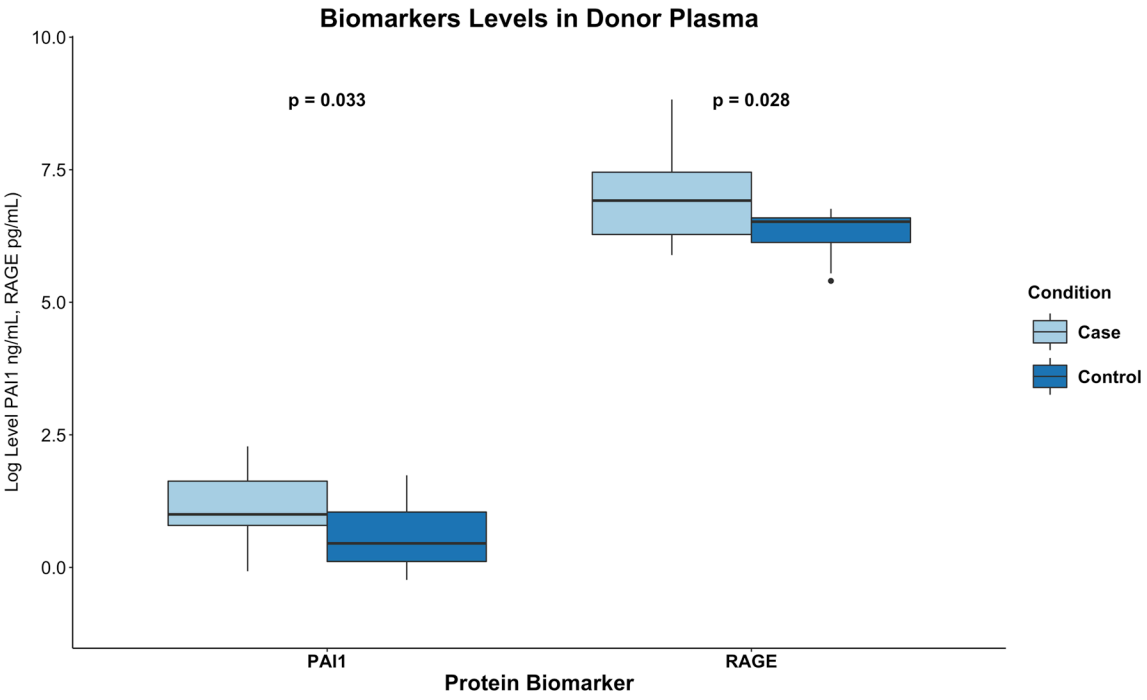

Figure 2.

Table

Donor and Recipient Characteristics

	Cases (n=12)	Controls (n=13)	p
Donor Characteristics			
Age in years, mean ± SD	35 ± 3	29 ± 9	0.179
Age >45 years old, n(%)	4 (33)	0 (0)	0.039
Male gender, n(%)	5 (42)	8 (62)	0.320
BMI, mean ± SD	25 ± 6	26 ± 5	0.634
Race, n(%)			0.815
Caucasian	8 (67)	8 (62)	
African American	2 (17)	1 (8)	
Asian	1 (8)	1 (8)	
Other	1 (8)	3 (23)	
Tobacco usage ever, n(%)	4 (33)	5 (38)	0.560
Drug use ever, n(%)	6 (50)	6 (46)	0.848
Infiltrates on CXR or CT, n(%)	9 (75)	10 (77)	1.000
Trauma as Cause of Death, n(%)	5 (42)	5 (38)	1.000
Abnormal bronchoscopy, n(%)	6 (50)	1 (11)	0.159
Positive CMV status, n(%)	8 (67)	8 (67)	1.000
PaO_2:FiO_2 ratio, mean ± SD	461 ± 57	466 ± 58	0.842
Average total ischemia minutes, median (IQR)	315 (229, 365)	292 (227, 354)	0.603
Days on the ventilator, median (IQR)	5 (3, 6)	5 (2, 6)	0.406
Recipient Characteristics			
Age in years, mean ± SD	56 ± 10	51 ± 9	0.179
Male gender, n(%)	6 (50)	9 (69)	0.327
BMI, mean ± SD	28 ± 4	23 ± 4	0.001
Race, n(%)			0.779
Caucasian	9 (75)	10 (77)	
African American	1 (8)	1 (8)	
Asian	0 (0)	1 (8)	
Other	2 (15)	1 (8)	
CMV positive, n(%)	9 (75)	4 (31)	0.034
CMV mismatch, n(%)	3 (25)	9 (75)	0.226
Pre-transplant location, n(%)			
ICU	5 (42)	3 (23)	0.411
Home	6 (50)	9 (69)	0.327
Ward	1 (8)	1 (8)	1.000
Preoperative ECMO, n(%)	1 (8)	0 (0)	0.480
Preoperative tracheostomy, n(%)	2 (17)	2 (15)	1.000
PAP systolic, mean ± SD	47.8 ± 19.8	44.0 ± 11.74	0.567
PAP mean, mean ± SD	27.6 ± 7.43	27.8 ± 9.56	0.960
Lung allocation score, median (IQR)	71 (48, 90)	52 (44, 75)	0.231

Recipient and donor characteristics of the two groups, presented as mean ± standard deviation or n(%) as appropriate.

SD standard deviation, *BMI* body mass index, *CXR* chest x-ray, *CT* computed tomography, *CMV* cytomegalovirus infection, *ICU* intensive care unit, *ECMO* extra-corporeal membranous oxygenation, *PAP* pulmonary artery pressure, *IQR* inter-quartile range.