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The Role of Donor Chronic Alcohol Abuse in the Development of Primary Graft Dysfunction in Lung Transplant Recipients

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Abstract

Primary graft dysfunction (PGD) following lung transplantation is clinically similar to the acute respiratory distress syndrome (ARDS). Since alcohol abuse independently increases the incidence of ARDS in at-risk individuals, we hypothesized that donor alcohol use is correlated with an increased risk of PGD. As a pilot we collected alcohol use histories using a validated instrument, the Alcohol Use Disorder Identification Test (AUDIT) questionnaire, from 74 donors and correlated these with the development of PGD in corresponding recipients. Nineteen percent (14/74) of donors were classified as heavy alcohol users, as defined by AUDIT scores ≥ 8. In the first 4 days post-transplantation, similar percentages of recipients developed Grade 3 PGD on at least one day (heavy alcohol user=29% (4/14) v lighter alcohol user=27%(16/60)); however, recipients receiving a lung from a heavy alcohol user were more likely to have multiple and consecutive days of Grade 3 PGD, especially in the first 48 hours post-transplant. Both median length of stay in the ICU and hospital were somewhat longer in the heavy alcohol user group (9 v 7 days, and 19.5 v 17.5 days, respectively). If these preliminary findings are validated in a multi-center study, they would have important implications not only for our understanding of the pathophysiology of PGD, but also for the development of novel treatments based on the evolving evidence from experimental and clinical studies on how alcohol abuse renders the lung susceptible to acute edematous injury.

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Disclosures

The authors do not have any conflicts of interest.

Keywords

Primary Graft Dysfunction; Lung transplantation; Lung donor; Recipient; AUDIT; Alcohol use

INTRODUCTION

Primary graft dysfunction (PGD) is the leading cause of death in the immediate period following lung transplantation and has an incidence of 15–25%[1]. Unfortunately, there are no effective therapies, and even with supportive care the mortality can be as high as 43%[2;3]. It had previously been assumed that the factors predisposing to PGD pertain to the surgical procedure or to the allograft recipient[4]. However, compelling experimental and clinical evidence suggests that donor-related risks factors are also important in the development of PGD. For example, it is now recognized that donor characteristics such as age, smoking, and mismatches with the donor in sex or race contribute to poor recipient outcomes[4]. We recently demonstrated a potential association between elevated donor levels of Receptor for Advanced Glycation End-products (RAGE) and the development of PGD[5]. In addition, other studies have shown that donor biomarkers such as IL-8[6], VEGF[7], and certain gene expression profiles[8] are associated with an increased risk of developing PGD. Importantly, since there are no proven medical treatments for PGD, identification of additional biomarkers to accurately identify allografts that are at higher risk for developing this serious condition are needed[9].

The features of PGD represent essentially a *form fruste* of the acute respiratory distress syndrome (ARDS), the most severe form of acute lung injury (ALI), which occurs within the unique context of lung transplantation[10]. In the past 15 years a strong independent association between alcohol abuse and ARDS has been identified, and our group at Emory University has been at the forefront of investigating the mechanisms by which alcohol abuse renders the lung susceptible to acute edematous injury. Specifically, alcohol abuse independently and significantly increases the risk of ARDS 2–4-fold in critically ill individuals[11;12]. Although the mechanisms underlying this association are still being investigated, we have clear evidence from experimental models and clinical studies that chronic alcohol ingestion causes oxidative stress and depletes the pool of the antioxidant glutathione within the alveolar space[13;14]. Alcohol-induced oxidative stress causes previously unrecognized alveolar epithelial dysfunction including increased paracellular permeability, decreased liquid clearance, impaired surfactant production, and decreased cell viability[13;15–17].

This ‘alcoholic lung’ phenotype is clinically silent in that the physiological perturbations identified in both experimental models and in otherwise healthy alcoholic individuals are not readily detectable without sophisticated measurements, and do not manifest as significant lung dysfunction until an acute inflammatory stress such as sepsis or aspiration unmasks them. Specifically, alcohol abuse alone does not cause lung injury but rather it significantly lowers the threshold for its development. This previously unrecognized association between alcohol abuse and ARDS/ALI was identified only when prospective studies were done using accurate alcohol use assessments such as the Alcohol Use Disorder Identification Test or

AUDIT[12]. However, this type of prospective investigation has not heretofore been applied in the unique context of lung transplantation and PGD. Therefore, we sought to determine if donor alcohol abuse likewise increased the risk of PGD. As a first step and a means of identifying biological plausibility, we demonstrated that chronic alcohol use by the donor exacerbated airway injury in allograft recipients using an experimental rat model of heterotopic tracheal transplantation[18]. We then initiated a single-center pilot study within our Emory Alcohol and Lung Biology Center, in collaboration with the McKelvey Center for Lung Transplantation at Emory University, to collect preliminary data in support of such an association that could stimulate the design and implementation of a larger multi-center study. Such information would have enormous implications for both the selection of lung allograft donors as well as for the development of novel therapeutic approaches to mitigate the devastating consequences of PGD.

We reasoned that this study was important to the lung transplant community, which includes donors, recipients, and the tens of thousands of healthcare professionals involved in lung transplantation. Unfortunately, despite advances in lung transplantation techniques and identification of appropriate selection criteria, our ability to predict which lung allograft recipients will develop PGD is at present imprecise[19], and our limited understanding of the fundamental mechanisms driving the development of PGD have frustrated our attempts to identify effective therapies beyond supportive care. In light of recent experimental and clinical evidence revealing the strong and independent association between alcohol abuse and acute lung injury, we felt there were compelling reasons to examine whether or not donor alcohol abuse increased the risk of PGD. To address this hypothesis, we initiated a pilot study at Emory University through our Alcohol and Lung Biology Center to study the relationship between donor alcohol use and the development of PGD in lung transplant recipients.

PATIENTS AND METHODS

Donor and Recipient Characteristics

Eligibility—Between February 2007 and January 2009 at Emory Hospital in Atlanta, Georgia, 88 consecutive lung transplant recipients and their lung donors were considered for eligibility. Exclusion criteria included: being re-transplanted (n=4), no consent (n=2), and improper lung preparation (n=3). Two subjects received a lung from the same donor; one was randomly selected for inclusion in the analysis. Therefore, in total there were 78 eligible lung allograft recipients, of whom 74 had their donor's alcohol use quantified using the AUDIT. All analyses are based on these 74 recipients.

Donor Lung Criteria—Lung donors were recruited from brain-dead patients consented for lung donation. Donor lungs used for transplantation at our institution had to meet the following inclusion criteria at the time of organ recovery: a) Compatible ABO blood group, b) PaO_2/FiO_2> 300 mmHg, c) Chest radiograph without focal or significant findings consistent with pneumonia or lung contusion, and d) Adequate bronchoscopic assessment was performed to ensure that no obvious aspiration was present. Explanted lungs were

preserved using Perfadex (Vitrolife, Goteborg, Sweden). The allograft ischemia time was recorded for all lung transplants.

Lung Recipients Criteria—Recipients listed at our institution received transplants according to their clinical priorities. Clinical data were available for all lung transplant recipients. This study was approved by the institutional review board at Emory University.

Immunosuppressive Therapy—All recipients received a standard immunosuppression protocol following transplantation, consisting of induction with IL-2 receptor antagonist and maintenance with a three-drug combination with the calcineurin inhibitor tacrolimus, azathioprine, and steroids as described previously[20].

Transplant Infection Prophylaxis—All recipients received antibiotics up to five days after surgery, and subsequent antibiotic therapy length was determined based on final donor culture and intra-operative bronchial cultures obtained by swab at the time of surgery. All recipients received prophylaxis after transplantation against cytomegalovirus, *Pneumocystis jirovecii* and *Aspergillus spp.* as previously described[21].

Primary Graft Dysfunction (PGD) treatment—PGD treatment involved administration of diuretics, prolonged mechanical ventilation with adjusted FiO_2 and positive end-expiratory pressure, and inhaled NO as required.

Predictor and Outcomes definitions

Definition of Alcohol Abuse—The Alcohol Use Disorder Identification Test (AUDIT) is a 10 question questionnaire that queries recent alcohol use, alcohol dependence symptoms, and alcohol-related problems, and has a sensitivity >90% to distinguish hazardous and harmful alcohol use whether the information is self-reported or obtained from a surrogate add [22;23]. Respondents with scores ≥ 8 are categorized as heavy alcohol users, and those with scores < 8 are categorized as light alcohol users.

Scoring of Primary Graft Dysfunction (PGD)—PGD was scored from 0 to 3 using chest radiographs and PaO_2/FiO_2 ratios per the guidelines of the International Society for Heart and Lung Transplantation. Scores were assigned at regular and/or specified intervals during the first 96 hours post lung transplantation[24]. Prior to removal of their endotracheal tube, all recipients received a bronchoscopy to assess bronchial anastomosis and bronchoalveolar lavage fluid (BALf) was obtained and submitted for culture. Furthermore, for recipients fitting clinical criteria of PGD, trans-bronchial biopsies were performed to rule out additional potential causes for abnormal radiographs/poor oxygenation.

Covariates Examined

Potential confounding variables were examined that could influence any observed association between donor alcohol abuse and subsequent PGD. These included:

Donor variables—Age, sex, race, smoking history (> 1 pack yr), and cause of death.

Recipient variables—Age, race, sex, and underlying lung disease, length of stay (LOS) in the intensive care unit and overall hospital LOS.

Surgical variables—Transplant procedure, utilization of pulmonary cardiopulmonary bypass, ischemia time, duration of mechanical ventilation.

Length of Stay—Length of stay (LOS) in the intensive care unit and the overall hospital LOS

Statistics

As this was a single center pilot study with a limited number of participants, we recognized that it was unlikely that we would be able to identify a statistically significant difference in the incidence of PGD in allograft from donors with or without alcohol abuse unless that difference was very large. Therefore, the primary goal was to make comparisons that could be used to design a larger multi-center trial if our results suggested that donor alcohol abuse could be associated with a clinically meaningful difference in the incidence of PGD. In this context, we planned from the outset to present the descriptive results of this pilot study. Specifically, we report the number and percentage of subjects in each category. In addition, we calculated the odds ratio of developing PGD when receiving an allograft from a donor with alcohol abuse versus receiving an allograft from a donor without alcohol abuse using logistic regression and employing a generalized linear mixed model methodology to account for multiple measurements per patient over time. Covariate adjusted odds ratios were estimated via a series of two variable models (i.e., alcohol status and one of the potentially confounding covariates). Lung transplant donor and recipient demographic and clinical characteristics other than PGD outcomes were examined for their relationship to donor alcohol abuse status (donor and recipient age: Wilcoxon rank sum test; all categorical variables: Fisher's Exact test; ICU and hospital LOS: Log-Rank test). All tests were two-sided. All analyses were completed using SAS v9 for Windows 7 Enterprise (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

The most common indication for transplant was COPD (50% of all transplants) followed by idiopathic pulmonary fibrosis (IPF) (41%). 65/74 of all transplants (88%) included in the analyses were bilateral lung transplants. The median age of these donors was 30.5 years (range 12–62 years). The most common cause of death among donors was traumatic head injury (47.0%).

Donor and Recipient Demographics by Donor Alcohol Use Category

Fourteen of the recipients (19%) received a lung from a donor with heavy alcohol use (Table 1). The two donor alcohol use groups were similar for age, racial distribution, and smoking history. The heavy alcohol use group had somewhat more deaths due to traumatic injury (64% v 43%; p=0.23), and a higher proportion of males (93% v 47%; p=0.002). Recipients in the two groups were similar for age, racial distribution, indication for transplant,

transplant type, use of cardiopulmonary bypass, racial mismatch (African-American to Caucasian), and ischemia time. Recipients of lungs from heavy drinkers were more likely to be male (93% vs. 50%; p=0.005). A gender mismatch (female to male) was somewhat less likely in the heavy alcohol use group 7% vs. 20%, although this difference was not statistically significant Median length of stay in the ICU and in the hospital was 2 days longer in the heavy alcohol use group.

Development of PGD

Using the consensus ISHLT definitions, PGD Grades of 0, 1, 2, and 3 at 48 hours (T48) post lung transplantation occurred in 43%, 27%, 14%, and 17% of recipients, respectively. A little over a quarter of recipients in both groups had Grade 3 PGD on at least one day during the first 4 days post-transplant (Table 2). However, PGD was more persistent among recipients of lungs from heavy alcohol users, with 50% of these PGD cases lasting 4 days (compared to 13% in the light alcohol group). Additionally, their PGD was more likely to occur on consecutive days. However, these differences between the two groups are based on a small number of cases with Grade 3 PGD. On each of the first 4 post-transplant days the incidence of PGD 3 was higher in the heavy alcohol use group (Table 3). The greatest difference between the light and heavy groups was apparent on the first two days (light vs. heavy 18% vs. 29% at 6–24 hrs; 13% vs. 29% at 25–48 hrs), with small differences thereafter (15% vs. 21% at 49–72 hrs; 8% vs. 14% at 73–96 hrs). On the first two days there also was a substantial difference in the incidence of Grade 2 PGD 2 (17% vs. 0% on both days).

Odds Ratio of Developing PGD in Allograft from Alcoholic vs. Non-Alcoholic Donors

Using a method that takes into account the multiple days of Grade 3 PGD measurement on each person, we compared the two groups for their odds of developing Grade 3 PGD. Without controlling for any potential confounders, the odds ratio was 1.8 with a 95% confidence that the true value falls in the interval 0.6 and 5.6. Controlling for either the donor factors of age, TBI, and smoking, or for the recipient factors of diagnosis, race mismatch, gender mismatch, CPB, and type of transplant (bilateral or not) had minimal effect on the odds ratio (range 1.7–1.9). On average, the rate of PGD 3 per day was 22% in the heavy alcohol use group compared to 14% in the lighter use group.

DISCUSSION

We found that one-fifth of the lung donors at our center in this study had heavy alcohol intake when classified by validated instruments such as AUDIT. In addition, while the risk of developing Grade 3 PGD at least once in the first days post transplantation appeared similar between the two groups, the number and duration of episodes of PGD 3 also appear greater when the allograft came from a donor with heavy alcohol use. For example, as disclosed in table 2, PGD 3 lasting 4 days was present in 2/4 vs. 2/15 of recipients that experienced any PGD 3. In parallel, we observed somewhat longer ICU and hospital lengths-of-stay if the donor had an AUDIT ≥ 8, and the recipients of allografts from donors with alcohol abuse had more Grade 3 PGD at 48 hours post transplantation. These findings build on prior observations that lung allograft recipients with Grade 3 PGD within the first

48 hours following transplant had significantly decreased long-term survival, as well as longer ICU and hospital stays, when compared with recipients who had Grade 1 or 2 PGD[25].

Taken together, our findings in this pilot study are consistent with the multi-center studies showing that alcohol abuse increases the risk of developing ARDS ~4- fold in critically ill individuals and raise concern that donor alcohol abuse could significantly increase the risk of PGD following lung transplantation. Our preliminary findings in this single-center pilot study are provocative as they suggest that donor alcohol abuse may have an adverse effect on outcome following transplantation that cannot be predicted by our current risk-stratification criteria. Therefore, we believe it is imperative for the lung transplant community to perform a larger multi-center study to either validate or refute an association between donor alcohol abuse and PGD, as either result will be valuable as we work to improve outcomes following lung transplantation.

Our findings are consistent with a growing body of experimental and clinical evidence that excessive alcohol use renders the lung susceptible to injury. The initial link between alcohol abuse and ARDS was identified in a retrospective analysis of a clinical database of 351 subjects admitted to an intensive care unit with an acute illness that placed them at risk for ARDS[11]. This association was later confirmed in a prospective, multi-center study of 220 patients admitted with severe sepsis[12]. In the initial study the relative risk was ~2:1. However, in the latter study in which a validated case definition of an alcohol use disorder was used, the relative risk of ARDS in alcoholic individuals was ~3.7:1. Therefore, it is reasonable to be concerned that there is an increased relative risk of PGD following transplantation of lung allografts from donors with significant alcohol abuse, and that a larger multi-center study would confirm our preliminary findings in this pilot study. In fact, even if we had determined in this pilot study that donor alcohol abuse significantly increased the relative risk of PGD at the $P<0.05$ level, we would still need to confirm this finding in a larger, multicenter study to ensure that the association was indeed generalizable.

To our knowledge, the AUDIT Questionnaire has not been used in other clinical studies of lung donors, particularly to assess whether or not their ante mortem alcohol use was associated with poorer post-transplant outcomes in lung allograft recipients. Although the standardized UNOS questionnaires given to the surrogates of all potential organ donors include questions about alcohol use, those questions do not allow for specific and accurate classification of alcohol use disorders. Our group and others have used the AUDIT Questionnaire in similar studies of critically ill individuals that have identified the increased risk of acute lung injury in patients with alcohol use disorders[12]. Importantly, in many cases we have relied on surrogates to answer the AUDIT questionnaires for their loved ones, and this use of surrogates has been independently validated by other investigators[33]. Therefore, although the use of the AUDIT Questionnaire in the particular context of lung transplantation is unique, its validated use in other clinical studies of critical illness and acute lung injury support its use in this and future clinical studies of primary graft dysfunction and other post-transplant outcomes.

The main limitation of our pilot study was that it was a single center study with a small number of alcoholic donors and a moderately small total number of subjects. Therefore, we

recognized from the outset that it was very likely that our study would be under powered to identify a statistically significant association between donor alcohol abuse and the subsequent development of PGD. In addition, donor alcohol use was assessed by donor surrogates. Although this could potentially lead to greater misclassification of alcoholics than with self-reports, if anything one might expect surrogate questionnaires to under-estimate the true incidence of alcohol abuse by donors. If so, then the true impact of alcohol abuse could be even greater than estimated by our study. Further, because of the small numbers of subjects in this study, we could not simultaneously control for multiple confounding factors related to both donor and recipient characteristics. Lastly, we presented donor alcohol effects only on PGD and length of initial hospital stay; other outcomes such as infections, oxidative stress, re-hospitalizations, and long-term outcomes were not examined.

However, if these preliminary findings are validated in a larger multi-center study, they would have important implications. As there are approximately 2000 lung transplants performed in the United States annually, donor alcohol abuse may be responsible for a substantial number of cases of PGD and its associated morbidity and mortality. Therefore, we believe this pilot study and its findings are provocative, and that the increased risk of PGD in the context of donor alcohol abuse is consistent with extensive experimental and clinical evidence that overwhelmingly implicates alcohol abuse in the development of acute lung injury in other settings.

The role of donor-derived factors in the pathogenesis of PGD was highlighted by a report of significant association of PGD among shared lung, kidney, and heart recipients from the same donor[26]. Despite optimization of donor and recipient selection criteria and advances in surgical techniques, PGD remains essentially refractory to treatment and is the primary cause of mortality in the immediate post-transplant period[1;2;27;28]. As a result, a considerable body of research has focused on identifying donor risk factors that are associated with poor outcomes following transplantation. Elevated donor pre-transplant levels of biomarkers such as RAGE[5], IL-8[6] and VEGF[7] are associated with increased risk or severity of PGD in recipients in the post-transplant period. This current study suggests that donor alcohol abuse is a factor that may have a greater impact on the risk of PGD than any other single factor identified to date. Therefore, if our results are validated in a larger, multi-center study they could have important implications not only for lung donor screening also for the generation of novel therapeutic interventions. Specifically, we could capitalize on the ever-increasing knowledge of the mechanisms by which alcohol abuse renders the lung susceptible to injury to design and test treatments to limit the incidence and/or severity of PGD.

There is considerable experimental evidence that a link between alcohol abuse and PGD is biologically plausible. For example, in an experimental rat model of transplantation, we determined that tracheal allografts from alcohol-fed donor rats were developed more airway obliteration following heterotopic transplantation than tracheal allografts from control-fed rats[18]. These experimental findings argue that alcohol use, independently of factors such as smoking or other illicit drug use renders the airway susceptible to damage following transplantation. This experimental model in the context of airway transplantation builds on extensive earlier studies from our group on the effects of alcohol on lung epithelial function.

For example, we determined that alveolar epithelial type II cells that were isolated from alcohol-fed rats had decreased surfactant production and were more susceptible to oxidant-mediated injury[13]. We also determined that alcohol ingestion alters alveolar epithelial barrier function *in vivo*, as reflected by increased protein leak across the alveolar barrier and decreased alveolar liquid clearance[16]. A common mechanism appears to be that alcohol ingestion dramatically decreases alveolar epithelial levels of glutathione, a critical antioxidant within the alveolar space, and increases both endotoxin-mediated acute edematous injury in isolated lungs that were perfused *ex vivo*[13;29] and sepsis-mediated acute lung injury *in vivo*[17]. Importantly, young and otherwise healthy subjects who meet criteria for alcohol abuse also have profoundly decreased levels of glutathione in their alveolar space[14]. However, although chronic glutathione replacement in the alcohol diet in experimental animal models prevents glutathione depletion and thereby maintains alveolar epithelial function[13;16;17;29;30], it is unlikely that glutathione replacement alone could rescue the alcoholic lung in the context of acute lung injury. For one reason, we determined that N-acetylcysteine, the only approved glutathione precursor available for human use, does not maintain the critical mitochondrial glutathione pool during alcohol feeding and does not preserve surfactant production[30]. This is consistent with previous clinical trials in which N-acetylcysteine therapy was minimally efficacious in patients with established ARDS, although those trials were not directed toward patients with a history of alcohol abuse[31;32]. In addition, the glutathione depletion within the airway is just one marker of the chronic oxidative damage that prolonged alcohol abuse inflicts on the airway, and this damage cannot be immediately reversed simply by the acute administration of glutathione supplements. Taken together, our experimental and clinical studies have identified that alcohol abuse causes previously unrecognized oxidative stress and epithelial dysfunction within the lung, but that clinically significant therapeutic interventions will require a more comprehensive strategy than simple glutathione replacement.

CONCLUSIONS

Our data suggest that donor alcohol abuse may increase the risk of PGD following lung transplantation. Although this is at present a preliminary finding from a relatively small single-center study, it is consistent with the clearly established link between alcohol abuse and ARDS and is supported by a large body of experimental evidence over the past two decades showing that alcohol renders the lung susceptible to acute edematous injury. The results from this pilot study therefore provide a compelling argument to design and conduct a multi-center study to determine whether or not there is a true association between donor alcohol abuse and PGD, and the magnitude of such an association if it exists. Based on the experimental and clinical evidence linking alcohol abuse to ARDS and ALI, there is in fact every reason to believe that PGD, which is essentially ALI/ARDS in the context of lung transplantation, is associated with donor alcohol abuse. The confirmation (or refutation) of such an association is critical to the lung transplant community and would have important implications for the evaluation and risk-stratification of donor-recipient pairs. Perhaps even more importantly, it would provide novel insights into the mechanisms that predispose a lung allograft recipient to develop PGD and therefore could lead to the design and testing of novel therapies to decrease the impact of this dreaded complication.

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Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
AUDIT	Alcohol Use Disorder Identification Test
IPF	Idiopathic pulmonary fibrosis
LTx	Lung transplantation
PGD	Primary graft dysfunction
UNOS	United Network for Organ Sharing

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Table 1

Lung transplant recipient and donor characteristics by donor alcohol status; Emory Transplant Center, February 2007 – January 2009.

	Donor AUDIT score		p-value[2]
	<8 81% (n=60)	≥8 19%(n=14)	
Overall n=74[1]			
Donor characteristics			
Donor Age, median (range) yrs	31 (12–62)	26 (19–54)	0.73
Male Donor	47% (28)	93% (13)	0.0020
Donor Race			0.84
White	50% (30)	57% (8)	
Black	33% (20)	36% (5)	
Other	17% (10)	7% (1)	
Donor smoked ≥1pack-yr	48% (29)	57% (8)	0.77
Donor Traumatic Brain Injury	43% (26)	64% (9)	0.23
Recipient Characteristics			
Recipient Age, median (range) yrs	60 (16–67)	60 (44–69)	0.59
Male Recipient	50% (30)	93% (13)	0.0052
Recipient Race			0.73
White	77% (46)	71% (10)	
Black	22% (13)	29% (4)	
Other	2% (1)	0% (0)	
Recipient Pathology			1.0
COPD	50% (30)	50% (7)	
IPF/ILD	40% (24)	43% (6)	
Other	10% (6)	7% (1)	
Bilateral transplant	88% (53)	86% (12)	.68
Recipient on CP Bypass	27% (16)	21% (3)	1.0
Race Mismatched (Black to White)	28% (17)	29% (4)	1.0
Gender Mismatched (female to male)	20% (12)	7% (1)	0.44
Ischemia time, median (range) minutes[3]			
Left lung	270 (110–403)	256 (120–420)	0.56

	Donor AUDIT score		p-value[2]
	<8 81% (n=60)	≥8 19%(n=14)	
Right lung	274 (110–440)	260 (75–430)	0.57
LOS in ICU, median(range) days	7 (2–68)	9 (3–50)	0.46
LOS in hospital, median(range) days	17.5 (6–150)	19.5 (7–66)	0.75

[1] In 4 out of 77 subjects the AUDIT score is missing; all analyses are based on the subset with AUDIT scores.

[2] donor and recipient age: Wilcoxon rank sum test; all categorical variables: Fisher's Exact test; ICU and hospital LOS: Log-Rank test.

[3] The ischemic time is missing on 13 out of 74 subjects (11 with AUDIT <8, 2 with AUDIT ≥ 8).

Table 2

Grade 3 PGD by donor alcohol status; Emory Transplant Center, February 2007 – January 2009.

PGD	Donor AUDIT score	
	<8 % (n/N)	≥8 % (n/N)
Had grade 3 PGD on at least one of the first 4 post-transplant days	27% (16/60)	29% (4/14)
Among those who had grade 3 PGD		
Length of grade 3PGD, in days		
1	27% (4/15)	0 % (0/4)
2	47% (7/15)	25% (1/4)
3	13% (2/15)	25%(1/4)
4	13% (2/15)	50% (2/4)
Had grade 3 PGD on consecutive days	60% (9/15)	100% (4/4)

[1] One patient in the light alcohol use group (AUDIT<=8) was recorded with grade 3 PGD on one day but had missing PGD information for another day and therefore cannot be categorized for this variable.

Table 3

The relationship between lung transplant recipient PGD score and donor alcohol status, by time period after transplant; Emory University Hospital Lung Transplant Service, February 2007 – January 2009.

		PGD score			
Time period	**n**	**0**	**1**	**2**	**3**
AUDIT score					
6–24 hrs					
<8	60	57%	8%	17%	18%
≥8	14	50%	21%	0%	29%
25–48 hrs					
<8	60	57%	13%	17%	13%
≥8	14	50%	21%	0%	29%
49–72 hrs					
8	60	45%	25%	15%	15%
≥8	14	36%	36%	7%	21%
73–96 hrs					
<8	59	37%	32%	22%	8%
≥8	14	36%	29%	21%	14%