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HEAVY ALCOHOL USE IN LUNG DONORS INCREASES THE RISK FOR PRIMARY GRAFT DYSFUNCTION

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Abstract

Background—Heavy alcohol use is known to increase the risk of acute lung injury and the acute respiratory distress syndrome. This is in part due to increased production of reactive oxygen species. We hypothesized that recipients of lungs from heavy drinkers would be more susceptible to lung injury following transplantation.

Methods—In this retrospective cohort study, donor histories and transplant outcomes were reviewed in 192 consecutive lung transplant recipients. Donors were classified as *No Alcohol Use*, *Moderate Alcohol Use*, or *Heavy Alcohol Use* based on documented donor histories.

Results—Freedom from mechanical ventilation took longer in the lung transplant recipients whose donors had *Heavy Alcohol Use*, compared to those whose donors had *No Alcohol Use* or *Moderate Alcohol Use*, $p=0.01$. At admission to the ICU, the *Heavy Alcohol Use* group had median PaO₂/FiO₂ ratio 219 (IQR: 162–382), compared to 305 (IQR: 232–400) in the *Moderate Alcohol Use* group and 314 (IQR: 249–418) in the *No Alcohol Use* group, $p=0.005$. The odds of developing severe primary graft dysfunction (PGD) in the *Heavy Alcohol Use* group versus the *No Alcohol Use* group were 8.7 times greater (95% CI 1.427–53.404, $p=0.019$) after controlling for factors known to be associated with PGD.

Conclusions—Recipients of donors with a heavy alcohol use history had an over 8 times greater risk of developing severe PGD following lung transplant. The increase in PGD resulted in poorer gas exchange in the recipients of donor lungs from heavy alcohol users, and these recipients subsequently required mechanical ventilation for a longer time following transplant. Further investigation into lung donors with heavy alcohol use histories is necessary to determine those at highest risk for PGD following transplant.

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Keywords

alcohol; lung; lung transplant; primary graft dysfunction

Introduction

Compared to other solid organ recipients, lung transplant recipients have a high morbidity and mortality following transplantation (Lodhi et al., 2011). Although the number of patients undergoing lung transplantation has increased by more than 15 fold in the last 20 years, the overall 5 year survival has only improved by about 10% (Christie et al., 2010). Early mortality following lung transplant is highest from primary graft dysfunction (PGD), affecting 15–55% of recipients (Christie et al., 2005a). PGD is an acute lung injury in the allograft secondary to ischemia of the graft and subsequent reperfusion injury. Ischemia in the graft results in formation of reactive oxygen species (ROS), which upon reperfusion can damage pulmonary alveolar cells, with the end result, in severe cases, being diffuse alveolar damage (Christie et al., 2005a). Mortality rates for severe PGD are up to 30–40% and if the recipient survives, there are additional consequences including protracted recovery and implications for long-term survival with an increased risk of chronic rejection (Christie et al., 2005b).

The effects of heavy alcohol use by donors on lung function after transplantation, and the ultimate impact on recipients' outcomes are unknown. In cardiac and renal transplantation, 20–25% of donors are from known alcohol abusers (Tsao et al., 2008, De La Zerda et al., 2007, Lin et al., 2005). A majority of organ donors arise from high risk situations such as trauma, where 50% of victims of fatal motor vehicle accidents, homicides, hypothermia, and 20% of suicide attempts are legally intoxicated at hospital admission (1989, Miller and Spicer, 2012). There is a scarcity of knowledge regarding alcohol use in donors of lung allografts. It is well known that chronic alcohol abuse has negative consequences for both pulmonary and immune function. Chronic alcohol abuse increases the risk two fold for acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (Moss et al., 1996). Additionally, the alcoholic lung is susceptible to alcohol-mediated oxidant stress and alveolar epithelial dysfunction, leaving the lung vulnerable to edematous injury in response to acute stresses (Moss et al., 1996, Brown et al., 2001). How the alcoholic lung, with its susceptibility to damage by reactive oxygen species, handles the stresses of ischemia reperfusion in lung transplantation is not known.

Considering that the alcoholic lung is more susceptible to ALI than the lung from a non-drinker, the added strain that lung transplantation places on the lung allograft may lead to further risk for lung injury following the surgery. The main objective of this study is to evaluate, for the first time, the relationship between heavy donor alcohol use and clinical outcomes following lung transplantation, particularly in the early post-surgical period and consequence for the development of PGD. We hypothesized that heavy donor alcohol use would increase the risk of PGD.

Materials and Methods

Study Design and Population

The medical records of all patients who underwent lung transplantation between January 1, 2007 and December 31, 2011 at Loyola University Medical Center in Maywood, IL were reviewed. Patients were included in the study cohort if the donor history was available, and excluded from the study if they expired during lung transplant surgery. This investigation was approved by the Loyola University Chicago institutional review board LU204445.

Classification of the Donor Alcohol Status

Donor histories were obtained from donor charts made available to the recipient's transplant center by the United Network of Organ Sharing (UNOS). Information obtained included gender, age, smoking history, cause of death, and hospital admission blood tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT). If available, liver biopsy and liver allocation were recorded. UNOS collects donor demographics and extensive histories by administration of the "Medical History & Behavioral Risk Assessment Questionnaire" to donor families by a UNOS intake coordinator, usually a nurse or social worker. This questionnaire includes an assessment of donor alcohol use. According to the National Institute of Alcohol Abuse and Alcoholism (NIAAA) guidelines, greater than 3 drinks per day for females or 7 drinks per week, and 4 drinks per day for males or 14 drinks per week, are considered heavy alcohol users (Alcoholism, 2005).

Donors were then categorized into 3 groups, "*Heavy Alcohol Use*", "*Moderate Alcohol Use*", and "*No Alcohol Use*", based on donor alcohol history as the primary determinant (Table 1). Additionally, the use of alcohol biomarkers, abnormal AST, ALT, or GGT, or AST:ALT ratio greater than 2, which is strongly suggestive of alcoholic liver disease (Sorbi et al., 1999, Nyblom et al., 2004), and liver biopsy results were utilized as a secondary confirmation into the classification of *Heavy Alcohol Use*. This was done in order to avoid misclassification since the donor history was taken by proxy. If the donor had no history of alcohol use the donor was considered "*No Alcohol Use*". If the donor had occasional drinking by history then the donor was categorized as "*Moderate Alcohol Use*". *Heavy Alcohol Use* donors had a history suggestive of heavy alcohol use according to NIAAA guidelines (Alcoholism, 2005), and additional clinical evidence of alcohol abuse, such as abnormally elevated alcohol biomarkers or abnormal liver biopsy. If there was insufficient or conflicting donor data available to accurately categorize the donor, the patient was excluded from the study.

Clinical Information

Recipient charts were reviewed for transplant information, survival, days requiring mechanical ventilation, partial pressure of arterial oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) at regular intervals following intensive care unit (ICU) admission. Standard lung transplant protocols at our center included Perfadex® as the lung perfusate, and FiO_2 of 100% at time of reperfusion of the lung allograft. Arterial blood gases were checked per protocol including at the time of arrival to ICU (T_0) and every 12 hours following while

intubated and/or requiring fluctuating amounts of oxygen. PGD was defined and graded according to standard International Society of Heart and Lung Transplant (ISHLT) guidelines (Christie et al., 2005a). To be considered severe PGD, the diagnosis was noted by the attending physician in the patient's medical record following lung transplant. This then avoided other possible causes for low PaO₂ in the post-operative period, such as intrathoracic bleeding or pneumonia, from inadvertently being categorized as severe PGD. Standard maintenance immunosuppression regimen during the study period included a calcineurin inhibitor (tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil), and steroids. Patients routinely received induction immunosuppression with either basiliximab or dacluzamib during the study period, with the exception of those patients seronegative for cytomegalovirus receiving an allograft from a cytomegalovirus seropositive donor.

Statistical Analysis

Standard descriptive statistics, including medians and interquartile ranges (IQR) for continuous variables or frequencies and percents for categorical variables, were used to describe clinical and demographic characteristics of the study population. Bivariate comparisons among donor alcohol groups were performed using Pearson's χ^2 for categorical variables and Kruskal-Wallis tests for continuous variables. Due to non-normal outcomes, the more conservative Kruskal-Wallis test was used; however, one-way ANOVA results did not differ appreciably and are not presented. Bonferroni adjusted pairwise comparisons for significant Kruskal-Wallis tests were conducted using Wilcoxon Rank Sum tests. Multivariate logistic regression was then performed to assess the effect of donor alcohol use on risk of PGD while controlling for potential confounding variables known to be independent risk factors for PGD including use of cardiopulmonary bypass, a pulmonary diagnosis of pulmonary hypertension or sarcoidosis, body mass index (BMI), any smoking use in the donor, recipient of single lung transplant, and ischemic time (Diamond et al., 2013). Severe PGD in the multivariate logistic regression model was defined by persistence of PGD grade 3 at 48 or 72 hours according to the ISHLT criteria (Christie et al., 2005a) and noted in the patient chart. Survival estimates and freedom from mechanical ventilation were obtained utilizing Kaplan Meier survival curves and assessed with a log-rank value. Statistical significance was considered relevant with a p -value less than 0.05. Analyses were performed using SAS 9.3 (SAS Institute, Cary NC).

Results

Patient Characteristics

During the defined study period there were 192 lung transplants performed. 16 patients had insufficient donor histories, and 3 recipients suffered from an intraoperative death, and therefore 173 lung transplant donor-recipient pairs were included in the study cohort. The 16 excluded patients were compared to the entire cohort of 173 patients for all variables examined during this investigation. The excluded patients did not differ from the study cohort in any demographic, clinical, or laboratory variable except transplant type. Seventy-five percent of the excluded patients underwent single lung transplantation compared to only 44% of the study cohort ($p=0.02$). Donor demographics, biomarkers of alcohol use at

hospital admission, liver allocation, and causes of death are listed in Table 2. Median donor age was significantly higher in the *Heavy Alcohol Use* group compared to the *No Alcohol Use* group [29 (IQR: 24–43) versus 25 (IQR: 18–37), $p=0.022$]; however, the difference in age between the *Heavy Alcohol Use* and the *Moderate Alcohol Use* groups was not statistically significant ($p=0.22$). There was also a greater percentage of male donors in the *Heavy Alcohol Use* group, with 73% male versus 63% male in *Moderate Alcohol Use* versus 43% in *No Alcohol Use*, $p=0.003$. A greater percentage of current or former cigarette smokers was present in the *Heavy Alcohol Use* group compared to the *No or Moderate Alcohol Use* groups, $p<0.001$. AST and AST:ALT ratios were significantly higher in the *Heavy Alcohol Use* group compared to the *No Alcohol Use* group, with the median ratio being 2.25 (IQR: 1.09–2.96) in those with *Heavy Alcohol Use*, compared to 1.35 (IQR: 1.04–1.94) in the *No Alcohol Use* group, $p=0.012$. No other pairwise comparisons were significant for AST; however, the AST:ALT ratio was also higher in the *Heavy Alcohol Use* group compared to the *Moderate Alcohol Use* group, $p=0.0027$.

Recipient demographics are reported in Table 3, and are categorized based on the donor history of alcohol use described in the methods section. Median BMI was significantly higher in the *Heavy Alcohol Use* group at 27.1 (IQR: 24.5–30.7) compared to the *No Alcohol Use* group 23.7 (IQR: 20.5–27.4), $p=0.003$ and the *Moderate Alcohol Use* group 25.07 (IQR: 21.8–26.9), $p=0.027$. Otherwise, there were no significant differences in any of these variables by donor alcohol use; however, there were generally less male recipients in the *No Alcohol Use* group, 45.7%, compared to the other groups, with 55.1% male recipients in the *Moderate Alcohol Use* and 53.5% in the *Heavy Alcohol Use* group. There were no significant differences in lung allocation score (LAS), ischemic time of the lung allograft between groups, and utilization of cardiopulmonary bypass during the surgery. More single lung transplants were performed in the *Moderate Alcohol Use* group; however, the differences were not significant.

Clinical Outcomes

Freedom from mechanical ventilation occurred sooner in the lung transplant recipients whose donors had *No Alcohol Use* or *Moderate Alcohol Use*, compared to the recipients whose donors had *Heavy Alcohol Use* ($p=0.01$), Figure 1. In the early post-operative period, $\text{PaO}_2/\text{FiO}_2$, or P/F ratio, was significantly worse in the first 24 hours (Figure 2) and continued to be significantly worse at all time points following lung transplantation in those recipients whose donors had *Heavy Alcohol Use* compared to those recipients whose donors had *No Alcohol Use*, Table 4. The P/F ratio was only worse for the *Heavy Alcohol Use* group compared to the *Moderate Alcohol Use* group at 24, 48 and 72 hours post lung transplantation ($p=0.017$, $p=0.003$, $p=0.026$). Table 4 contains the median P/F ratio for each measured time point available following lung transplantation, and the ratios are significantly lower for the *Heavy Alcohol Use* group at each time point out to 72 hours.

PGD Grade

PGD grade was evaluated at multiple time points following admission to the ICU after lung transplantation, based on a scoring system ranging from 0–3 with severe PGD represented by a grade of 3 (Christie et al., 2005a). There was a significant association between the

donor alcohol use group and PGD grade at ICU admission ($p=0.0004$). PGD grades by time post-transplant are displayed in Figure 3. The highest percentage of PGD grade 3 at time of ICU admission was seen in the *Heavy Alcohol Use* group with 33% of the transplant recipients being admitted to the ICU with severe PGD, compared to only 8% in the *Moderate Alcohol Use* group, and 5% in the *No Alcohol Use* group (Figure 3A). By 72 hours after admission to the ICU, 16% of recipients in the *Heavy Alcohol Use* group had persistent severe PGD, compared to only 2.5% in the *No Alcohol Use* group and none in the *Moderate Alcohol Use* group (Figure 3D).

Due to the potential for confounding variables, a multivariate logistic regression model was constructed to assess the risk of developing severe PGD in recipients whose donors had various levels of alcohol use. The regression model controlled for the following variables when determining the odds of severe PGD in each alcohol group: use of cardiopulmonary bypass, a diagnosis of pulmonary hypertension or sarcoidosis, BMI, any donor smoking history, single lung transplant and ischemic time (Table 5). The full model was selected based on the AIC selection criterion and interactions were not significant. Five observations were excluded in the multivariate analysis due to missing values in the explanatory variables, resulting in 168 observations. After controlling for other variables, the odds of developing severe PGD in recipients of donors with *Heavy Alcohol Use* are 8.7 (95% CI: 1.4–53.4) times higher than the odds of recipients whose donors reported *No Alcohol Use*, $p=0.0190$. There was no difference in risk of developing PGD in recipients of donors with *Moderate Alcohol Use* as compared to *No Alcohol Use*, $p=0.5911$.

Survival

Given the increase in PGD seen in those recipients whose donors had *Heavy Alcohol Use*, we were concerned that this would impair long term survival for this particular group of recipients. Therefore, we assessed survival with a Kaplan Meier survival curve comparing the *Heavy Alcohol Use* group to the combined group comprised of the donors with *Moderate Alcohol Use* and *No Alcohol Use*. We found that those recipients whose donors had *Heavy Alcohol Use* trended towards a poorer survival in the years following lung transplantation compared to the combined group of *Moderate Alcohol Use* and *No Alcohol Use* donors, $p=0.07$.

Discussion

This is the first study designed to explore the impact of heavy alcohol use in lung transplant donors. There are three major findings. First, recipients whose donors had a heavy alcohol use history were at an 8.7 times greater odds of developing severe PGD following lung transplant compared to recipients whose donors did not consume alcohol, with 1/3 of all recipients whose donors had a heavy alcohol use history presenting with severe PGD at ICU admission. Second, the increase in acute lung injury following transplant resulted in poorer gas exchange in the recipients of donor lungs from heavy alcohol users, and subsequently these recipients required mechanical ventilation for a longer duration of time. Finally, there was a trend towards poorer survival in the years following lung transplantation in those recipients whose donors had a heavy alcohol use history.

Nearly 25% of the recipients in the cohort had received lungs from donors with heavy alcohol use histories. The incidence of donor alcohol abuse in lung transplantation has not been explored previously, but this rate is consistent with other solid organ transplants, where 23% of cardiac donors and 21% of renal donors were alcohol dependent (Lin et al., 2005, Tsao et al., 2008, De La Zerda et al., 2007). The ideal lung donor is younger than age 55 and has a limited smoking history (Van Raemdonck et al., 2009). Currently, the alcohol history of the donor is not considered relevant when selecting potential lung donors. At least 3 in 10 adults in the United States drink at levels that increase their risk for physical, mental and social problems (Grant BF, 2003). People aged 18–24 years have a higher prevalence (28.2%) of alcohol use and binge drinkers in this age group consume in higher amounts (9.3 drinks/occasion) (Centers for Disease and Prevention, 2012). In addition to an increased risk of liver disease, these heavy drinkers have a greater risk of hypertension, gastrointestinal bleeding, depression, hemorrhagic stroke, cancer, sepsis, pneumonia, and acute lung injury (Rehm et al., 2003, Moss et al., 1996, Jong et al., 1995). Heavy drinkers have an increased chance of engaging in high risk behaviors including road traffic accidents, violence, and self-injuries including suicide attempts, which ultimately place a young person at risk of trauma and subsequent brain death (Poulose and Srinivasan, 2009, Miller and Spicer, 2012, 1989). These are the risk factors that are present in many of our lung donors.

A history of alcohol abuse is an independent risk factor for the development of ALI and ARDS (Moss et al., 1996). The underlying mechanisms responsible for the increased susceptibility to ALI in the alcoholic lung are multifactorial and include decreased mucociliary clearance, pulmonary epithelial dysfunction, susceptibility to oxidative stress, and impaired innate immunity in the alveolar space (Kershaw and Guidot, 2008). Chronic alcohol abuse has been shown to impair surfactant production and increase oxidant-mediated apoptosis in alveolar epithelial cells, resulting in impaired alveolar epithelial barrier function and decreased alveolar liquid clearance (Guidot and Brown, 2000, Brown et al., 2001, Guidot et al., 2000). The alcoholic lung is susceptible to induced oxidative stress by an increase in ROS generation and depletion of antioxidants, such as glutathione, in the alveolar epithelial lining fluid (Moss et al., 2000). Upon procurement of donor lungs for transplantation, during the period of cold ischemia, there is formation of ROS which damage pulmonary epithelium upon reperfusion. The damaged epithelium then upregulates inflammatory cascades, contributing to worsening of the acute lung injury following lung transplant, otherwise defined as PGD (de Perrot et al., 2003). Therefore, in theory when the alcoholic lung undergoes the additional stresses of ischemia and reperfusion during lung transplantation, the likely explanation for the increased development of early graft injury which we observed in this investigation, may be due to an increased generation of ROS and depletion of antioxidants in the alcoholic lung. Animal models have also demonstrated an increase in graft dysfunction following organ transplantation. In a rat cardiac transplant model, acute alcohol abuse increased the susceptibility of donor hearts to ischemia/reperfusion injury (Li et al., 2012). In a rat tracheal transplant model, alcohol abuse was shown to increase the expression of transforming growth factor-beta (TGF- β) and interleukin 13 (IL-13), possibly leading to an increase in fibrosis (Mitchell et al., 2009). Further investigation into possible alcohol related mechanisms, and its impact during the ischemia reperfusion period in lung transplantation is needed.

UNOS collects information on donor alcohol use utilizing a questionnaire administered to the donor family by the UNOS on-site coordinator prior to procurement. After answering questions about the donor's alcohol history, the UNOS on-site coordinator categorizes the donor, either yes or no, as having "Heavy alcohol use, 2+ drinks/daily". This designation has been used in previous investigations of PGD, as part of multivariable logistic regression analysis (Diamond et al., 2013). The alcohol characterization by UNOS of heavy alcohol use could be considered less thorough than NIAAA's definition of alcohol abuse. For example, according to NIAAA, greater than 3 drinks per day in females and greater than 4 drinks per day in males is considered heavy alcohol use. Contrast this with the UNOS definition of 2+ drinks daily, which may lead to a number of donors being categorized as heavy drinkers whose history or alcohol biomarkers do not support this diagnosis. Additionally, NIAAA also defines more than 7 drinks in a female per week, and more than 14 drinks in a male per week as "heavy alcohol use". In the UNOS categorizations, some donors may be categorized as non-heavy drinkers (i.e. female with 1–2 drinks per day). The grouping is not standardized, and is dependent on how the intake coordinator subjectively decides to categorize a particular donor. This may be one reason why alcohol abuse in previous statistical models may not have shown an increased risk for PGD in lung transplantation (Diamond et al., 2013). In the investigation presented here, our categorization of the donor drinking history, in particular, our categorization of *Heavy Alcohol Use* utilizing both the NIAAA definition of *Heavy Alcohol Use* plus the additional use of clinical evidence of alcohol use in the form of abnormal liver biopsy or elevated alcohol biomarkers, led to a more stringent assessment of heavy alcohol use in the donors compared to the current categorization used by UNOS. Utilizing the AST:ALT ratio, liver biopsy results, or perhaps including biomarkers of alcohol use such as urine ethyl glucuronide (Staufer et al., 2011) or carbohydrate deficient transferrin (Conigrave et al., 2002), in coordination with a validated method to collect the donor history could provide a more accurate assessment of a donor's actual alcohol use. Relying on proxy histories from a donor's family member alone may not be accurate, particularly if these histories are not collected utilizing a standardized, validated method. Administration of the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C) (Bradley et al., 1998), which is a quick 3 question validated screening test for heavy drinking, to donor families would enhance donor alcohol history, which is extremely important in assessing alcohol use given the results of this investigation.

A limitation of this study is the retrospective nature of this investigation. In particular, the alcohol histories of the donors are from family members and not the donor directly. Despite this, the addition of alcohol biomarkers to the donor history in those considered *Heavy Alcohol Use*, most likely increased the accuracy of the history and categorization of this heavy drinker group. Donors with heavy alcohol use had an AST:ALT ratio consistently higher than 2, which is strongly indicative of alcohol abuse (Nyblom et al., 2004, Sorbi et al., 1999). Investigating in a prospective manner, which we have initiated at our institution, will allow for a more accurate identification of heavy donor alcohol use, by measuring the presence of alcohol utilizing biomarkers, such as urine ethyl glucuronide, which can detect the presence of alcohol metabolites for up to 4–5 days after the last drink (Staufer et al., 2011). An additional limitation is that the alcohol histories of the recipients are not recorded. Recipients of lung transplantation are advised to abstain from alcohol prior to lung

transplantation. At our transplant center, like other lung transplant centers, any recipient with a recent alcohol abuse history is either not listed for transplant if actively drinking, or required to attend a formal alcohol abstinence program followed by random monitoring for alcohol biomarkers in the urine, with a recorded abstinence period of greater than 6 months to 2 years. Erim et al. evaluated 113 patients awaiting lung transplantation and diagnosed dependence on alcohol in 3/113 (2.6%) (Erim et al., 2009). Evon and coworkers found that 29% of recipients admitted to drinking alcohol while on the wait list for lung transplant, although self-reported numbers of drinks per week ranged from 2–5, which is well below the NIAAA definition of alcohol abuse (Evon et al., 2005, Alcoholism, 2005). Therefore, recipient alcohol intake is likely not impacting the results following lung transplant reported here. Finally, there is a possibility that other substances, such as smoking, could be affecting the development of PGD in this group. The *Heavy Alcohol Use* group, not surprisingly had a higher percentage of ever smokers. Current transplant guidelines recommend accepting lungs from donors with smoking histories less than 20 pack years (Van Raemdonck et al., 2009), therefore, these donors were either not heavy smokers, or had quit smoking previously. Donor smoking use was controlled for in our regression model, and did not impact the significance of PGD development in heavy drinkers. Despite this, the combined effect of smoking and drinking in potential organ donors should be investigated thoroughly in future studies. Illicit drug use has not been associated with PGD, although it has not been investigated, and would be of interest in future investigations.

Our findings could have implications for recipients of lung transplantation, and may perhaps limit the donor organ pool. We do not advocate that alcoholic donors be deemed unacceptable for lung donation. In fact, our results in Figure 3 indicate that the majority of these donor organs actually fared well, with only a PGD grade of 0 or 1. Instead, we noted an increased risk in some of these organs for the development of severe PGD. Moving forward, additional investigations into deciphering which alcoholic lungs are at highest risk for developing PGD would be most useful for improving outcomes in our recipients. The alcohol use history in donors should be collected in a standardized way between Organ Procurement Organizations within UNOS, utilizing validated methods such as the AUDIT-C to collect donor information.

Because of the retrospective nature of this investigation, it is prudent to pursue an investigation in a more thorough, prospective manner to carefully assess risk factors in the alcoholic donor, which may predispose to the development of PGD following lung transplant. In the age of ex-vivo lung perfusion (Cypel et al., 2011), perhaps examination of alcoholic lungs during a period of conditioning may help decipher lungs that are more susceptible to damage by oxidative stress from lungs which are more resilient. This is crucial, not only for the recipient dealing with the increased morbidity and mortality associated with severe PGD, but also in terms of the increased cost to the health care system overall, with more ICU days and increased cost of the transplant. Without any complications and without severe PGD, lung transplant costs approximately \$550,000–800,000 (Bentley TS, 2011). When a recipient develops severe PGD, costs soar into the millions of dollars. This cost does not account for the possibility of future complications, including an increased

risk of developing chronic rejection, which patients with PGD are certainly at risk (Christie et al., 2005b).

In conclusion, we assert that recipients of lungs from donors with heavy alcohol use histories are at an increased risk of developing PGD in the hours following lung transplantation. Additionally, further investigation in a prospective manner, assessing the mechanisms which account for this increased risk of PGD following transplant may shed light on how to minimize the risk for PGD following lung transplantation of alcoholic lungs.

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Figure 1. Freedom from mechanical ventilation following lung transplant

Kaplan-Meier curve demonstrating the first 30 days following lung transplant and need for mechanical ventilation. We compared the recipients whose donors had *Heavy Alcohol Use* to those that had *No* or *Moderate Alcohol Use*. The rate of freedom from mechanical ventilation was higher in those recipients whose donors had *No* or *Moderate Alcohol Use*, $p=0.01$.

Figure 2. Mean $\text{PaO}_2/\text{FiO}_2$ ratios in the post-lung transplant period

In the immediate postoperative period, mean $\text{PaO}_2/\text{FiO}_2$ was significantly worse following lung transplantation in those recipients whose donors had *Heavy Alcohol Use* compared to those recipients whose donors had *No Alcohol Use*, * $p < 0.002$.

Figure 3. PGD Grade Post-Lung Transplant

Percentage of recipients in each donor alcohol group (*No Alcohol Use*, *Moderate Alcohol Use*, and *Heavy Alcohol Use*) with PGD grade 0–3 at time **A.** admission to ICU following lung transplant **B.** 24 hours following lung transplant **C.** 48 hours following transplant, and **D.** 72 hours following lung transplant. The *Heavy Alcohol Use* group had the highest percentage of recipients with severe PGD at every time point.

Table 1

Classification of Donor Alcohol History

Classification*	Current history of drinking alcohol?	Drink >3 per day or 7 per week (females) or drink >4 per day or 14 per week (males) by history?	Liver Biopsy Abnormal	AST:ALT ratio >2 or abnormal alcohol biomarkers
<i>No Alcohol Use</i>	No	No	-	-
<i>Moderate Alcohol Use</i>	Yes	No	-	-
<i>Heavy Alcohol Use</i> [‡]	Yes	Yes	Yes/No	Yes/No

* Patients who did not fit the above classification scheme were excluded (N=16)

[‡]To be classified as *Heavy Alcohol User*, history had to be positive plus either an abnormal liver biopsy or abnormal alcohol biomarkers, AST:ALT ratio >2

Table 2

Clinical Characteristics of Donors

	No Alcohol Use N=81	Moderate Alcohol Use N=49	Heavy Alcohol Use N=43	p-value
Donor age, median (IQR)	25 (18–37)	25 (21–33)	29 (24–43)	0.029*
Donor gender, male %	43%	63%	73%	0.004
Donor smoking hx, yes %	11% (9)	31% (15)	47% (20)	<0.001
GGT, median (IQR)	24.5 (14–40)	19 (13–38)	28.5 (18–52)	NS*
ALT, median (IQR)	26 (19–46)	33 (23–49)	36 (20–65)	NS*
AST, median (IQR)	36 (25–58)	42 (29–62)	53 (31–127)	0.01*
AST:ALT, median (IQR)	1.35 (1.04–1.94)	1.28 (0.92–1.90)	2.25 (1.09–2.96)	0.003*
Liver Allocated, %	97.2%	93.0%	86.1%	0.09
Cause of Death, % (No.)				NA
Gun Shot Wound	18.7% (15)	34.7% (17)	35.7% (15)	
CVA	50% (40)	26.5% (13)	26.2% (11)	
Trauma	16.3% (13)	24.5% (12)	23.8% (10)	
Overdose	2.5% (2)	12.2% (6)	9.5% (4)	
Other	12.5% (10)	2.0% (1)	4.8% (2)	

Abbreviations: GGT: gamma-glutamyl transferase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CVA: cerebrovascular accident, IQR: interquartile range

Values expressed as median (IQR) or percentage (frequency) unless otherwise specified

P-values are from Pearson's χ^2 or *Kruskal Wallis test

Table 3**Clinical Characteristics of Recipients**

Donor Alcohol Use	No Alcohol Use N=81	Moderate Alcohol Use N=49	Heavy Alcohol Use N=43	p-value
Percentage of Cohort	46.8%	28.3%	24.9%	
Recipient age, median (IQR)	57 (46–62)	59 (51–64)	55 (45–63)	NS*
Recipient gender, male%	45.7%	55.1%	53.5%	NS
Recipient BMI, median (IQR)	23.7 (20.5–27.4)	25.0 (21.8–26.9)	27.1 (24.5–30.7)	0.001*
Transplant Type, % (No.)				
Single	42% (34)	47% (23)	42% (18)	NS
Bilateral	58% (47)	53% (26)	58% (25)	NS
Diagnosis, %				NA
COPD	28.4% (23)	40.8% (20)	27.9% (12)	
IPF	33.3% (27)	26.5% (13)	27.9% (12)	
Cystic Fibrosis	21% (17)	6.1% (3)	11.6% (5)	
Sarcoidosis	3.7% (3)	6.1% (3)	4.7% (2)	
Pulmonary HTN	0% (0)	2.0% (1)	2.3% (1)	
BOS	1.2% (1)	12.2% (6)	7.0% (3)	
Other	12.3% (10)	8.2% (4)	18.6% (8)	
LAS, median (IQR)	41.1 (35.0–53.0)	39.6 (34.5–47.8)	41.1 (34.3–52.2)	NS*
Ischemic Time, median (IQR)	271.5 (220–322)	277 (224–319.5)	273.8 (204–345)	NS*
Cardiopulmonary Bypass Use	31% (25)	29% (14)	33% (14)	NS

Abbreviations: BMI: body mass index, COPD: chronic obstructive pulmonary disease, IPF: idiopathic pulmonary fibrosis, BOS: bronchiolitis obliterans syndrome, LAS: lung allocation score, IQR: interquartile range

Values expressed as median (IQR) or percentage (frequency) unless otherwise labeled

Table 4PaO₂/FiO₂ post-lung transplantation

Hours	No Alcohol Use	Moderate Alcohol Use	Heavy Alcohol Use	p-value
0	314 (249–418)	305.0 (232–400)	219 (162–382)	0.007
<i>N</i>	81	49	43	
12	352.5 (267.5–405)	316.3 (235–390)	230 (179.7–342.3)	0.003
<i>N</i>	77	46	40	
24	350 (277.5–458)	355 (248.5–457.5)	253.4 (175–347.5)	0.002
<i>N</i>	63	42	38	
48	356.3 (207.5–430.0)	349.2 (220–445)	267.5 (158–320)	0.002
<i>N</i>	38	30	27	
72	325.8 (196.7–450.8)	322.1 (255–430)	235.6 (164–290.9)	0.02
<i>N</i>	28	18	19	

Abbreviations: PaO₂/FiO₂: partial pressure of arterial oxygen/fraction of inspired oxygen, IQR: interquartile range

Values expressed as median (IQR)

N=total number of recipients with P/F ratios available for comparison

P-values are from Kruskal-Wallis Test

Table 5

Multivariate Logistic Regression Analysis

Parameter	Odds Ratio	Confidence Interval	p-value
ETOH			0.01
<i>Heavy Alcohol Use</i>	8.7	1.4–53.4	0.02
<i>Moderate Alcohol Use</i>	0.5	0.04–6.1	0.59
BMI	1.1	0.9–1.2	0.36
CPB	34.0	3.6–320.6	0.002
Single Lung Transplant	1.5	0.2–11.1	0.72
Pulmonary Diagnosis of Pulmonary	3.6	0.4–31.9	0.25
Hypertension or Sarcoidosis			
Donor Smoking History	0.8	0.1–4.5	0.78
Ischemic Time	1.0	0.99–1.0	0.43

Note: Reference level for ETOH = No Alcohol Use