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Human Leukocyte Antigen Mismatch is Associated with Grade 3 Primary Graft Dysfunction at 72 Hours Following Bilateral Sequential Lung Transplantation: A Single-Center, Retrospective Cohort Study

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ABSTRACT

Background: The role of donor-recipient human leukocyte antigen (HLA) mismatch as a risk factor for developing primary graft dysfunction (PGD) after lung transplantation is not well understood. We describe a novel association between increased donor-recipient HLA mismatch and grade 3 PGD after bilateral lung transplantation.

Methods: We retrospectively evaluated donor and recipient demographic data, co-morbidities, intraoperative interventions and outcomes in 99 consecutive adult patients undergoing primary bilateral lung transplantation. The primary outcome of this study was grade 3 PGD at 72 hours. Secondary outcomes included intensive care and hospital lengths of stay and mortality.

Results: Eighteen patients (18%) met criteria for grade 3 PGD at 72 hours postoperatively. More non-Caucasian recipients (27.8% vs. 7.4%, p=0.026), and more patients with interstitial lung disease (72.2% vs 43.2%, p=0.031) developed grade 3 PGD. The use of inhaled epoprostenol (OR 4.38, 95% CI: 1.02-20.16, p=0.048), increased HLA mismatches (OR 2.85, 95% CI: 1.31-7.45, p=0.017) and the use of each 250mL unit of PRBCs during the intraoperative period (OR 0.77, 95% CI: 0.58-0.97, p=0.048) were independently associated with grade 3 PGD. Patients diagnosed with grade 3 PGD spent significantly longer time in the intensive care unit (22 days [6;74 days] vs. 7 days [2;83 days], p=<0.001) and hospital (30.5 days [10;83 days] vs. 18 days [3;97 days], p=0.012), and survival was significantly worse for those with PGD3 at 72 hours (log-rank p=0.009).

Conclusion: Our data indicate, for the first time, that HLA donor-recipient mismatch is an independent risk factor for developing grade 3 PGD at 72 hours after bilateral lung transplantation.

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Introduction

Lung transplantation remains the definitive therapy for patients with end-stage lung disease and respiratory failure. Despite advances in surgical techniques, patient selection, and postoperative management strategies, mortality rates following lung transplantation remain as high as 15% at one year and 50% at five years after transplant [1,2]. Severe primary graft dysfunction (PGD) after lung transplantation has an incidence ranging from 10-50%, and has been identified as an independently contributing risk factor for postoperative mortality [1-5]. In a recent 10-center study with 1255 patients having undergone lung transplantation, the authors describe an array of perioperative variables independently associated with developing severe postoperative PGD including any history of donor smoking, increased inspiratory oxygen concentration (FIO2) during lung reperfusion, use of cardiopulmonary bypass, high recipient body mass index (BMI), and high mean recipient pulmonary artery pressure [6]. Although immunologic injury is thought to be

another potential contributor to severe PGD and HLA mismatch has been associated with decreased long-term survival after lung transplantation, the exact role of donor-recipient human leukocyte antigen (HLA) mismatch in development of severe PGD is not well-defined [7]. While one recent study suggests an increased incidence of PGD grade 2-3 at 48 hours in patients with early donor specific antibody (DSA) development, a previous study found that PGD was associated with the subsequent development of anti-HLA class II but not anti-HLA class I DSA [8]. While these previous studies examined the relationship between DSA development and PGD, no previously published study has reported the relationship between HLA mismatch and severe PGD [9]. Herein, we describe donor and recipient risk factors, specifically including donor-recipient HLA mismatch, that are associated with developing grade 3 PGD in the first 72 postoperative hours in adults undergoing bilateral lung transplantation at a single-center quaternary care academic medical center.

Methods

In this single center, retrospective cohort study evaluating all primary bilateral lung transplantation in adults between January 1, 2016 and December 31, 2018, donor and recipient demographic data, donor and recipient co-morbidities, intraoperative interventions including incision type, type of intraoperative mechanical support, laboratory results, intraoperative mechanical ventilation strategy, fluid and blood product administration, and outcomes were collected from several hospital registries as well as our electronic medical record (Epic Systems Corporation, Verona, Wisconsin) and United Network for Organ Sharing (UNOS). Our study was approved by the University of Minnesota institutional review board (#1006M83333), which waived the need for consent from individual patients. Patients who had opted out of being included in research studies were excluded.

Donor lungs were preserved with either cold static storage or warm ex vivo lung perfusion (OCS™ Trans Medics Inc, Andover, MA). Intraoperative management for each case including the use of double lumen or single lumen endotracheal tube, volume resuscitation, blood product administration and mechanical ventilatory strategy was at the discretion of the surgical and anesthesia team. All bilateral lung transplantations were carried out using either CPB or VA ECMO through either a clamshell incision or sternotomy, depending on recipient anatomy.

The primary outcome of this study was grade 3 PGD at 72 hours postoperatively based on the 2005 International Society for Heart and Lung Transplantation (ISHLT) PGD working group definition [10,11]. To meet this definition, we calculated a partial pressure of arterial oxygen divided by the fraction of inspired oxygen (P/F ratio) 72 hours postoperatively, and at the same time reviewed the chest radiograph for diffuse parenchymal infiltrates. Secondary outcomes included hospital and ICU lengths of stay and mortality.

Variables of interest were compared between those with and without grade 3 PGD at 72 hours. Categorical variables are displayed as n (%) and compared with Chi-square or Fisher tests. Continuous variables are displayed as median [range] and compared using a Wilcoxon non-parametric test. A logistic regression model was performed for the outcome of grade 3 PGD at 72 hours. All analysis was performed in R ver. 3.6.1.

Results

A total of 105 patients underwent primary bilateral lung transplantation between January 1, 2016 and December 31, 2018. Of these, six patients declined participation in our research database. Of the 99 remaining patients, eighteen patients (18%) met criteria for the primary outcome of grade 3 PGD at 72 hours postoperatively. On univariate analysis, there was no difference in donor or recipient age or gender, or recipient body mass index (BMI) between patients who developed grade 3 PGD at 72 hours and those that did not (Table 1). There was no difference in mean recipient pulmonary artery pressure, donor smoking history or donor alcohol use. There was no difference in the use of either CPB or VA ECMO, graft ischemic time, or the use of the Transmedics Lung OCS System (OCS™ TransMedics Inc, Andover, MA).

Significantly more non-Caucasian recipients (27.8% vs. 7.4%, p=0.026), and proportionately more patients with interstitial lung disease (72.2% vs 43.2%, p=0.031) developed grade 3 PGD at 72 hours, postoperatively. Patients with a higher degree of HLA mismatch were more likely to develop grade 3 PGD at 72 hours postoperatively (5.0 [4.0;6.0] vs. 4.0 [1.0-6.0], p=0.024). Patients who developed grade 3 PGD at 72 hours postoperatively were also more likely to have had inhaled epoprostenol initiated intraoperatively (55.6% vs 21.0%, p=0.007), and to have received intraoperative allogeneic packed red blood cells (PRBC) (475mL [0;3,300] vs 0mL [0;8,700], p=0.032), fresh frozen plasma (FFP)) (611mL [0;2,947] vs 292mL [0;5,880], p=0.048), platelets (528mL [0;2,072] vs 204mL [0;2,554], p=0.037) or cryoprecipitate (158mL [0;836] vs 0mL [0;620], p=0.017).

Table 1: Univariate Risk Factors for Development of PGD (n (%) or Median [range])

	No PGD (*n* = 81)	PGD (*n* = 18)	p value
Recipient Gender			0.463
Female	42 (51.9%)	7 (38.9%)	
Male	39 (48.1%)	11 (61.1%)	
Donor Gender			0.34
Female	28 (34.6%)	9 (50%)	
Male	53 (65.4%)	9 (50%)	
Recipient Age (*yrs*)	58.1 (24.1-69.3)	56.7 (24.3-69.3)	0.737
Donor Age (*yrs*)	32.7 (14.3-68.1)	34.6 (16.2-57.9)	0.792
Incision Type			0.979
Clamshell	23 (29.6%)	6 (33.3%)	
Median Sternotomy	57 (70.4%)	12 (66.7%)	
Recipient Race			0.026
Caucasian	75 (92.6%)	13 (72.2%)	
Non-Caucasian	6 (7.4%)	5 (27.8%)	
Donor Race			0.291
Caucasian	66 (81.5%)	17 (94.4%)	
Non-Caucasian	15 (18.5%)	1 (5.56%)	
Etiology of Respiratory Failure			0.031
Cystic Fibrosis	16 (19.8%)	3 (16.7%)	
COPD	28 (34.5%)	1 (5.56%)	
ILD / IPF	35 (43.2%)	13 (72.2%)	
Other	2 (2.4%)	1 (5.56%)	
Mechanical Support			0.297
CPB	69 (85.2%)	13 (72.2%)	
VA ECMO	12 (14.8%)	5 (27.8%)	
Recipient BMI	24.8 (17.2-31.6)	26.1 (17.9-30.9)	0.253
Donor Smoking History			>0.999
Yes	11 (13.6%)	2 (11.1%)	
No	70 (86.4%)	16 (88.9%)	
Donor Heavy Alcohol Use			0.347
Yes	20 (24.7%)	2 (11.1%)	
No	61 (75.3%)	16 (88.9%)	
Post-perfusion $PaCO_2$ (*mmHg*)	43 (31-64)	41 (32-63)	0.204
Mean PAP (*mmHg*)	26 (11-80)	28.5 (16-44)	0.7
Inhaled Pulmonary Vasodilator			0.007
Yes	17 (21%)	10 (55.6%)	
No	64 (79%)	8 (44.4%)	
Graft Ischemic Time (*min*)	343 (204-851)	364 (191-843)	0.577
Use of Transmedics OCS™			>0.999
Yes	8 (9.88%)	2 (11.1%)	
No	73 (90.1%)	16 (88.9%)	
HLA Matches (number, out of 6)	4 (1-6)	5 (4-6)	0.024
Intraoperative IVF (*ml*)	2031 (400-4700)	1800 (507-3800)	0.576
Intraoperative colloid (*ml*)	0 (0-3000)	125 (0-1700)	0.096
Intraoperative RBC (*ml*)	0 (0-8700)	475 (0-3300)	0.032
Intraoperative FFP (*ml*)	292 (0-5880)	611 (0-2947)	0.048
Intraoperative platelets (*ml*)	204 (0-2554)	528 (0-2072)	0.037

Intraoperative cryoprecipitate (*ml*)	0 (0-620)	158 (0-836)	0.017
RBC volume >1L			0.041
Yes	12 (14.8%)	7 (38.9%)	
No	69 (85.2%)	11 (61.1%)	
Initial postoperative FiO2	80 (40-100)	95 (50-100)	0.104

Abbreviations: PGD, primary graft dysfunction, ILD, interstitial lung disease, IPF, Interstitial pulmonary fibrosis, VA ECMO, venous arterial extracorporeal membrane oxygenation, CPB, cardiopulmonary bypass, BMI, Body mass index, PAP, pulmonary artery pressure, OCS, organ care system, HLA, human leukocyte antigen

The use of inhaled epoprostenol (OR 4.38, 95% CI: 1.02-20.16, p=0.048), increased HLA mismatches (OR 2.85, 95% CI: 1.31-7.45, p=0.017) and the use of each 250mL unit of PRBCs during the intraoperative period (OR 0.77, 95% CI: 0.58-0.97, p=0.048) were independently associated with grade 3 PGD at 72 hours postoperatively (Table 2 and Figure 2). Patients diagnosed with grade 3 PGD at 72 hours spent significantly longer time in the intensive care unit (22 days [6;74 days] vs. 7 days [2;83 days], p=<0.001) and hospital (30.5 days [10;83 days] vs. 18 days [3;97 days], p=0.012) (Table 3). Post-transplant survival was significantly worse for those with grade 3 PGD at 72 hours (log-rank p=0.009, Figure 1).

Table 2: Independent Risk Factors for Development of PGD

	Adjusted Odds Ratio	95% CI	p value
Independent Risk Factors	4.38	1.02-20.16	0.048
Inhaled Pulmonary Vasodilator	2.85	1.31-7.45	0.017
RBCs per 250cc	0.77	0.58-0.97	0.048

Abbreviations: PGD, primary graft dysfunction, HLA, human leukocyte antigen, RBCs, red blood cells

Table 3: Secondary Clinical Outcomes (Median [range])

	No PGD (n = 81)	PGD (n = 18)	p value
Clinical Outcomes			
ICU LOS (days)	7 [6;74]	22 [2;83]	<0.001
HLOS (days)	18 [3;97]	31 [10;82]	0.012

Abbreviations: PGD, primary graft dysfunction, ICU LOS, intensive care length of stay, HLOS, hospital length of stay

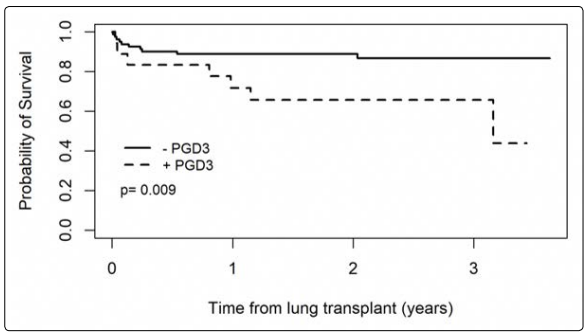

Figure 1: Morality associated with and without developing grade 3 primary graft dysfunction at 72 hours

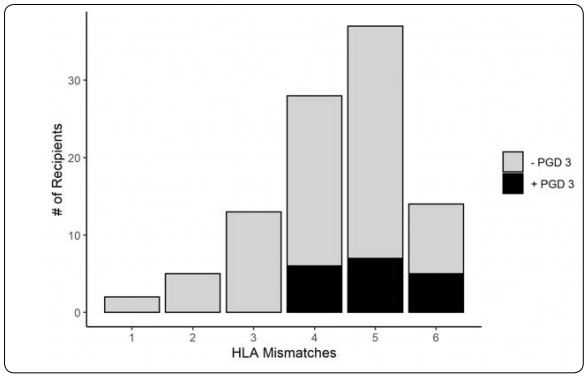

Figure 2: The incidence of grade 3 primary graft dysfunction stratified by HLA mismatch

Discussion

In this single-center retrospective analysis, we found an 18% incidence of grade 3 PGD at 72 hours postoperatively after bilateral sequential lung transplantation in adults. On univariate analysis, non-Caucasian recipient, primary diagnosis of interstitial lung disease, the use of intraoperative epoprostenol, the need for transfusion with RBCs, FFP, platelets and cryoprecipitate, and donor-recipient HLA mismatch were associated with an increased probability of grade 3 PGD at 72 hours postoperatively. On multivariate analysis, grade 3 PGD at 72 hours was independently associated with the use of inhaled, degree of HLA mismatch and the use of PRBC in excess of one liter during the intraoperative period. Our data also suggest a correlation between developing grade 3 PGD at 72 hours postoperatively and increased intensive care unit and hospital lengths of stay, and increase in long-term mortality.

PGD remains the leading cause of early death after lung transplantation in adults with a 15-20% incidence rate at 48- or 72-hours post-transplant [5, 6, 12]. Shortly after the International Society for Heart and Lung Transplantation (ISHLT) working group published the classification system that we currently use to define PGD after lung transplantation, Whitson et al. reported a 17% grade 3 PGD incidence rate at 48 hours postoperatively in 402 consecutive adult patients who had undergone lung transplantation between 1992 and 2004 [4,10,11]. In this study, grade 3 PGD at 48 hours was associated with decreased overall BOS-free survival in this study. In a more recent prospective cohort analysis of 1255 adults undergoing lung transplantations across 10 centers in the United States, the investigators cite a 16.8% incidence of grade 3 PGD at 48 to 72 hours after transplantation, while Samano et al. reported a 15.4 % incidence of grade 3 PGD after 72 hours post-transplantation [6,13]. Despite our relatively small sample size, we corroborate that a 15-20% incidence of grade 3 PGD after 72 hours after lung transplantation has gone unchanged in the last decade.

From the time the ISHLT working group published their original definition in 2005, investigators have compiled a lengthy list of donor and recipient risk factors for PGD. Donor risk factors including smoking history, alcohol use, and lung trauma (contusions, fat emboli or pulmonary thromboembolic events) are associated with increased risk of PGD [4,6,12,14-17]. Recipient risk factors include obesity, and disease processes associated with either primary or secondary pulmonary hypertension [6,12,18-20]. Investigators have also identified a number of perioperative risk factors including the use of cardiopulmonary bypass, large-volume intraoperative transfusion, and an inspired oxygen fraction of greater than 0.4 during lung reperfusion [6,21-23]. Data supporting the association between donor and recipient demographics including age, gender and ethnicity have been conflicting, as has prolonged ischemic time [6, 12, 18, 24-26]. In our cohort, we found similar risk factors associated with grade 3 PGD at 72 hours postoperatively including recipient race, primary diagnosis of interstitial lung disease, and the use of blood products including high volumes of RBCs. Blood product transfusion is a known risk factor for acute lung injury, and in the setting of lung transplantation, should be considered a modifiable risk factor. As such, we often consider factor and fibrinogen concentrates in lieu of allogeneic blood products when addressing non-surgical coagulopathy in our lung transplantation patients [27]. Although we did not find a difference in preoperative mean pulmonary artery pressures, as Whitson et al. described, we found that the use of inhaled epoprostenol was significantly higher in patients who developed grade 3 PGD at 72 hours [4]. Due to the retrospective nature of our study, it is unclear whether inhaled epoprostenol was initiated in order to address poor oxygenation or elevated pulmonary artery pressures. In our institution, inhaled epoprostenol is used for both purposes, and as such, inhaled epoprostenol could be a marker for pulmonary hypertension or an indicator of poor oxygenation after reperfusion.

Finally, we know that matching donor and recipient for HLA antigens significantly decreases the risk of organ rejection [28]. To avoid prolonged ischemic times, HLA typing of the donor is completed prior to removing the organs, a practical challenge for lung transplantation, and a reason HLA matching is rarely done for lung transplantation patients. Even if this were feasible, the extensive polymorphism of the HLA system would make an exact match (zero HLA mismatched donor-recipient) an extremely rare event [29]. The median number of HLA mismatches in lung transplantations on a scale of 0-6 has been shown to be 4 [30]. A number of studies have shown HLA mismatch (>3) to be a strong predictor of long-term graft survival and mortality [7, 31-33]. To the best of our knowledge, we are the first to describe HLA donor-recipient mismatch as an independent risk factor for developing grade 3 PGD at 72 hours postoperatively, even in our relatively small cohort. As of now, HLA classification is a non-modifiable risk factor. In light of our findings however, and due to the significant morbidity and mortality associated with PGD after lung transplantation, we would urge other centers to examine the association between HLA classification and the incidence of PGD in their lung transplantation population. As UNOS progresses toward an allocation system of continuous distribution, HLA mismatch might be incorporated as a risk factor [34].

The limitations of this single-center study include all biases associated with a retrospective design. Additionally, our sample size is small relative to similar studies. Our analysis however is based on data from very detailed and well-maintained institutional lung transplantation and UNOS databases.

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