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Low Potassium Dextran is Superior to University of Wisconsin Solution in High Risk Lung Transplant Recipients

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Abstract

Background—The ideal solution for recovery of donor lungs remains unknown. Low potassium dextran (LPD) solution is most common, but University of Wisconsin (UW) solution is also used. The United Network for Organ Sharing (UNOS) database allows assessment of preservation solutions in a large cohort of lung transplant (LTx) patients.

Methods—We retrospectively reviewed the UNOS dataset for adult primary LTx patients (2005–2008) whose donor lungs were recovered with UW or LPD solution. Patients were stratified by UW vs. LPD, and secondarily grouped by quartiles of the lung allocation score (LAS) to examine high risk recipients. Kaplan-Meier (KM) short term mortality (30d, 90d, 1 yr), and rejection in the 1st yr, were examined for intervals with adequate follow-up. Cox proportional hazard regression using 11 variables examined all cause 1-yr mortality.

Results—Of 4455 patients, 4161 (93.4%) received LPD lungs and 294 (6.6%) received UW lungs. 1105 (24.8%) patients died during the study. There was no mortality difference based on flush solution with all patients examined together. However, patients in the upper two LAS quartiles (Q3:37.8-45.4, Q4:>45.4) receiving LPD lungs had greater 1 yr survival (81.5% vs. 73.5%, $p=0.02$). On multivariable analysis, flush with UW solution resulted in an increased risk of 1 yr mortality (Hz ratio 1.77[1.21–2.58], $p=0.003$) compared to LPD. Preservation solution did not affect rejection rates in the year after LTx. KM modeling demonstrated the impact of flush solution on survival ($p=0.02$).

Conclusions—This study is the largest modern cohort to evaluate the effect of donor lung flush solutions on survival in adult LTx. UW solution increases the risk of 1 yr mortality in high risk LTx recipients.

Keywords

Lung Transplantation; UNOS; organ preservation

Background

Lung transplantation (LTx) has emerged as the standard therapy for patients with end stage lung disease, with improved survival and quality of life.^{1–3} However, early graft dysfunction

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(EGD) remains a common and devastating complication. EGD occurs in 10–25% of LTx and accounts for nearly 30% of deaths within 30 days.^{4–6} Experimental studies and clinical reports implicate ischemia-reperfusion injury in the development of EGD.⁴ Preservation technique is a putative mediator of early graft function, and much clinical and laboratory research has focused on optimal preservation solutions.

Preservation solutions simulate either intracellular or extracellular ion concentrations. Perfadex (Vitrolife, Englewood, CO) is a low potassium dextran (LPD) solution and is the most commonly used extracellular solution in the United States. University of Wisconsin (UW) solution (ViaSpan, DuPont Pharmaceuticals, Wilmington, DE) is an intracellular solution that has been used widely for solid organ preservation. Experimental animal studies have noted a beneficial effect of LPD compared to UW in ischemia-reperfusion injury and reactive oxygen species formation.^{7–9} Previous human studies have compared the intracellular solution LPD with various extracellular solutions, though no comparison between LPD and UW exists. These studies demonstrate LPD lungs have improved early graft function without a survival benefit, but are limited by low sample size.^{10–13}

Implementation of the lung allocation score (LAS) has shifted the demographics of LTx recipients in the United States.^{14, 15} The United Network for Organ Sharing (UNOS) registry provides the opportunity to address this question in the post-LAS era. Therefore, we examined the UNOS dataset to test the hypothesis that high risk patients receiving LPD preserved lungs have a survival advantage over recipients of UW stored lungs.

Methods

Data Source

The UNOS Standard Transplant Analysis and Research (STAR) database represents an open cohort of prospectively collected data involving all United States patients receiving LTx from 1987 until December 2008, with follow-up extending until September 2009. Our institution deemed IRB approval unnecessary as no patient or center identifiers were included in this analysis.

Study Design

This study was a retrospective cohort design, including adult (>17 years) patients undergoing LTx in the post-LAS era (March 2005-present). Exclusion criteria included incomplete preservation solution information, heart-lung transplantation, and patients with prior LTx. The cohort was stratified according to whether donor lungs were preserved in LPD (LDS) or University of Wisconsin (UW) solution.

Variables Examined and Outcome Measures

Pertinent variables examined within the dataset included: demographic factors (age, gender, race, and education level); markers of pulmonary status (oxygen requirement, six minute walking distance, forced expiratory volume at 1 second (FEV1), forced vital capacity (FVC), FEV1 to FVC ratio, mechanical ventilation prior to LTx, and ICU care prior to transplant); co-morbidities (LAS score, diabetes mellitus, body mass index (BMI), preoperative creatinine levels and hypertension); and transplant variables (ischemic time, HLA mismatch, panel reactive antibody (PRA) level, year of transplant, and wait list times). We further examined donor variables including donor age, race, gender, cigarette use, and BMI.

The primary endpoint was the incidence of 1-year mortality. Secondary outcomes examined were short term mortality (30-day and 90-day), as well as rejection requiring treatment within the first year following LTx.

Statistical Analysis

We compared baseline characteristics among the LPD and UW groups by the student's t-test (continuous variables) and the chi-square test (categorical variables). 30-day, 90-day, and 1-year survival were estimated using the Kaplan-Meier method, as these time intervals have adequate follow-up in the post-LAS era. To compare survival estimates according to preservation solution, the Mantel-Cox log-rank test was used. The entire cohort was analyzed according to the Kaplan-Meier method. Separate Kaplan-Meier analysis was performed in the upper two quartiles of LAS to assess the impact of preservation solution in high risk patients.

A multivariable Cox proportional hazards regression model estimated risk of death with censoring for death, loss to follow-up, and administrative reasons. To construct the multivariable model, independent covariates with potential for confounding were first tested in a univariate fashion. In addition to variables associated with mortality on exploratory analysis ($p < 0.1$), those with biological plausibility and previously recognized risk factors were incorporated in a forwards and backwards stepwise fashion into the multivariable model. The likelihood ratio test and Akaike's information criterion in a nested model approach were used to identify which covariates increased the explanatory power of the model. As the multivariable model was developed with case-wise deletion, all covariates with greater than 15% missing data were not included. The final model incorporated the following covariates: storage solution, recipient age ≥ 65 , creatinine level, ICU prior to transplant, hospitalization prior to transplant, final LAS calculation, organ ischemic time, donor cigarette use, donor age, and donor CMV status.

For all analyses, a p-value of less than 0.05 (two-tailed) was considered significant. Means are displayed with standard deviations. Hazard ratios are presented with 95% confidence intervals (CI). Statistical testing was performed using STATA software (version 9.2 SE, StataCorp LP, College Station, TX).

Results

Cohort Statistics

From 2005 to 2008, 5,712 patients receiving LTx were included in the UNOS database. Patients with previous transplants ($n = 272$), absent storage solution information ($n = 334$), and children ($n = 175$) were excluded. Thus the final study population was 4,459. The mean age of the cohort was 53 ± 13 years with 41.7% females ($n = 1,860$).

Recipient race distribution was: 84.6% Caucasian ($n = 3,774$), 8.6% African American ($n = 385$), 4.8% Hispanic ($n = 213$), and 2.0% Other ($n = 87$). The donor race distribution was: 62.8% Caucasian ($n = 2,802$), 18.0% African American ($n = 802$), 15.4% Hispanic ($n = 688$), and 3.8% Other ($n = 167$). During the study period 1,106 patients died, and 697 patients did not survive one year. One year incidence of death was 18.5 deaths/100 person-years. The mean follow-up was 19 ± 12 months. Throughout the 4 year study period, the number of adult LTx's remained constant, with 1,400 in 2005 and 1,467 in 2008.

Baseline Characteristics

Baseline characteristics were evenly distributed in the LPD versus UW groups, with few exceptions. Patients receiving LPD preserved lungs tended to be elderly, have diabetes, and

have donor cigarette use; whereas patients receiving UW preserved lungs had higher BMI, longer waitlist times, poorer pulmonary function testing, and greater HLA mismatch. Though statistically significant, the absolute differences in these categories were small and unlikely to be of clinical relevance. Ischemic time was similar in both groups. There were no differences based on LAS in the two groups, nor was there any difference in the rate of pre-LTx mechanical ventilation, ICU care, or hospitalization between the two groups. Idiopathic pulmonary fibrosis was the most common indication for LTx in both groups (Table 1).

Survival

When the entire cohort was analyzed without stratification, overall survival at 1 year was 82.5%. After stratification by preservation solution, in the entire cohort there was no difference in 30-day, 90-day, or 1-year KM survival. However, when examining 1-year KM survival in high risk patients (LAS Q 3–4), there was a benefit conferred by LPD stored lungs (81.2% vs 73.3%, $p=0.02$) (Table 2). There was no difference in 30-day or 90-day survival in high risk LAS patients when stratified by storage solution. The 1-year incidence rate for death in LPD (18.3 deaths/ 100-person years) stored lungs versus UW (21.2 deaths/ 100-person years) stored lungs did not differ significantly. Survival curves are presented in Figure 1–2.

Multivariable Analysis

Following risk adjustment with Cox multivariable analysis, storage with LPD increased the hazard of 1-year mortality in high risk patients (Table 3). LTx recipients of UW stored lungs had a 75% increase in the risk of adjusted 1-year mortality compared to patients receiving LPD stored lungs (HR1.75, CI[1.20–2.56], $p=0.004$). Additional predictors of mortality on multivariable analysis included: age>65 years, recipient creatinine level, pre-LTx hospitalization, and pre-LTx ICU care. A diagnosis of cystic fibrosis was found to be protective.

Rejection

For all LAS quartiles, the UW group had a higher risk of having a rejection episode in the year after transplant on univariate analysis (41.3% versus 30.6%, $p<0.01$). In the risk-adjusted multivariable logistic regression model this difference persisted (OR1.84, CI[1.17–2.88], $p=0.007$). Although a greater proportion of patients in the UW stored lung group had HLA-mismatch, this variable was also accounted for in the regression model, and found to be independently associated with risk of rejection (OR1.29, CI[1.03–1.62], $p=0.03$). Other significant risk factors for rejection were donor age and ischemic time.

Discussion

This analysis used prospectively collected UNOS data in the post-LAS era to evaluate the impact of preservation solution on survival in United States LTx patients. During the study period, the majority of patients in the US received lungs stored with LPD solution, with a smaller proportion of patients receiving UW preserved lungs. Patients were stratified based on LPD versus UW preservation solution, and 1-year survival was examined. Because high risk patients according to LAS calculations are known to have worse 1-year survival, we performed a sub-analysis in this cohort of patients to assess any impact on survival.¹⁶ After risk-adjustment, UW preservation solution imparts a 75% increase in the risk of 1-year mortality in the upper two quartiles of LAS patients. In high risk patients receiving UW solution, the absolute difference in 1-year survival was 7.9%.

Short-term mortality and having a treated rejection episode within one year were examined as secondary outcome measures. 30-day and 90-day survival analysis revealed no significant

differences in high risk patients or in the cohort as a whole. Rejection was more frequent in patients receiving UW versus LPD stored lungs, occurring in 41.3% and 30.6% of patients, respectively. On univariate analysis, HLA-mismatch was more common in patients receiving UW stored lungs. This finding is prominent as HLA-mismatch is known to affect the odds of rejection.¹⁷ However, after risk-adjustment with multivariable logistic regression, recipients of UW stored lung had an 84% increase in the odds of a rejection episode requiring treatment. HLA-mismatch also independently increased the odds of rejection by 29%.

Multivariable Analysis

A multivariable Cox hazard regression model was used to assess the impact of potential confounding variables on 1-year survival. When high risk patients were included in the model, age>65, recipient creatinine, hospitalization before LTx, and intensive care unit before LTx were all significant predictors of 1-year mortality. Older age and pre-LTx hospitalization are known risk factors for worse 1-year survival.¹⁸ With the exception of age>65, which was more common in the LPD group, the remainder of these variables was evenly distributed between the two study groups. A LTx diagnosis of cystic fibrosis (CF) improved 1-year survival with a 42% reduction in the hazard of death. There was an equal proportion of CF patients in the UW and LPD groups.

Previous Work

Previously published studies comparing LPD against UW solution involve experimental animal models only. Oka et al. published the first comparison of LPD versus UW storage solution using a rabbit lung transplantation model.¹⁹ All donor organs were reperfused after hypothermic storage for 30 hrs. LPD stored lungs demonstrated improved oxygenation and less pulmonary edema compared with standard UW solution. This study revealed short-term information, however, as reperfusion continued for a total duration of 10 minutes. A third group of rabbits receiving modified low potassium UW solution was examined also. Results in this group were comparable to the LPD group, supporting other reports that implicate high potassium content in endothelial dysfunction and generation of reactive oxygen species.^{9, 20}

Hausen et al. compared graft performance in a rat lung transplantation model in which donor organs were cold stored with either LPD, UW, or Euro-Collins solution. In the extended (16 hrs) ischemia model, rat lungs stored with LPD solution exhibited improved pulmonary compliance compared with UW solution.⁸ This finding is consistent with the worse pulmonary edema that was seen in the earlier report by Oka et al. Another experimental study by Chien et al. also found improved oxygenation for donor lungs stored in LPD compared with UW in a rat lung transplantation model.⁷ However, in contrast to earlier rat models, this study demonstrated improved pulmonary edema in UW stored lungs. The conclusion is that more impermeant contents improve cellular swelling, although the authors emphasize that less pulmonary edema did not translate into improved pulmonary function, as UW lungs demonstrated worse gas exchange and pulmonary hemodynamics.

In human studies, several single institution reports compared LPD solutions with other intracellular type solutions (Euro-Collins). LPD stored lungs demonstrated improvement in post-LTx oxygenation,^{13, 21, 22} pulmonary compliance,²³ or EGD.^{11, 24} In contrast, a study by Aziz et al. did not detect any statistically significant clinical benefit, though there was a trend toward fewer deaths due to primary organ failure in the LPD group.²⁵ This study was hampered by low sample size as only 69 patients were included.

Ganesh et al. conducted the only multi-institutional cohort study in 681 LTx recipients to examine survival differences between LPD and Euro-Collins storage solutions.¹⁰ There was no significant survival benefit with either preservation method, though there was a trend toward improved 3-year survival in LPD stored lungs. This study lacked the breakdown of ischemic time by preservation solution; however this issue was subsequently addressed in a response to the editor. Furthermore, in the setting of bilateral lung transplantation, graft ischemic time was reported as time to reperfusion of the first lung which is not consistent with other studies examining survival after LTx.

This study adds to the existent literature by examining data in the post-LAS era using a large multi-institutional modern cohort of LTx recipients. This series provides an overview of the modern practice of preservation technique for donor lungs in the United States. Furthermore, no previous study has directly compared the two most commonly used preservation solutions in the United States—LPD and UW. These results reinforce the importance of preservation technique, and are consistent with many of the findings in experimental animal models.

Limitations

Because of the retrospective cohort approach, it is not possible to certify that all possible confounders have been considered. A strength of the UNOS dataset is the large number of variables available for analysis, however there is a possibility of potential important variables being absent from this analysis. Furthermore, large multi-institutional databases rely on accurate coding. It is difficult to verify that coding errors are not present. However, the assumption is that any coding errors present in the database will occur randomly and thus do not render any bias. If this assumption is false, there is the possibility of residual bias in our conclusions. There were relatively few patients who received UW stored lungs compared with LPD solution, but this finding reflects the current practice of storage technique in the United States. Our methodology attempted to control for this imbalance. As the information included in the UNOS database only involves clinical information, this study does not purport to establish the mechanisms by which storage solution affects survival. That topic has been the focus of many in vivo animal model studies.

Conclusions

This study represents the largest cohort of LTx recipients in the post-LAS era in which the effect of preservation solution on survival has been examined. High risk patients receiving UW stored lungs have decreased 1-year survival when compared to patients receiving LPD stored lungs. In all patients, the risk of rejection is higher in patients receiving UW lungs. LTx centers and organ procurement organizations should give strong consideration to preserving lungs with LPD solution, especially in high risk recipients. As a limited donor pool remains a significant barrier to increasing the number of LTx performed annually, improved preservation technique may further expand the application of this therapy.

Acknowledgments

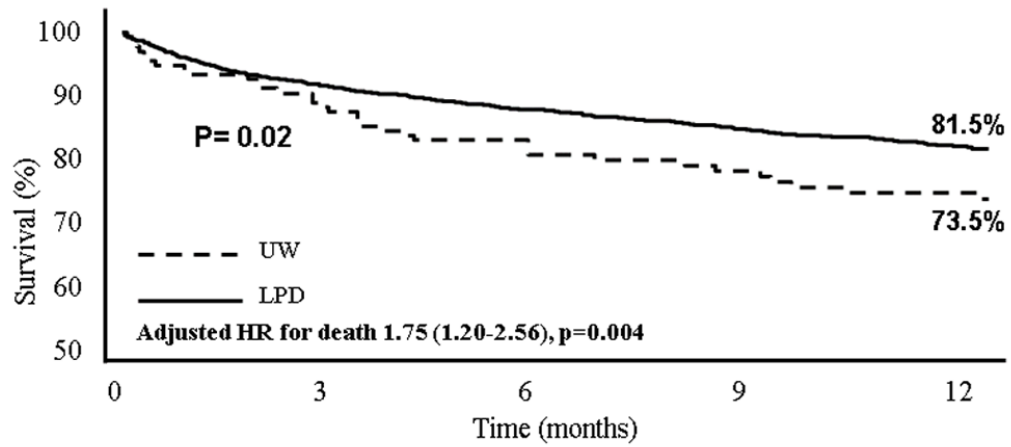
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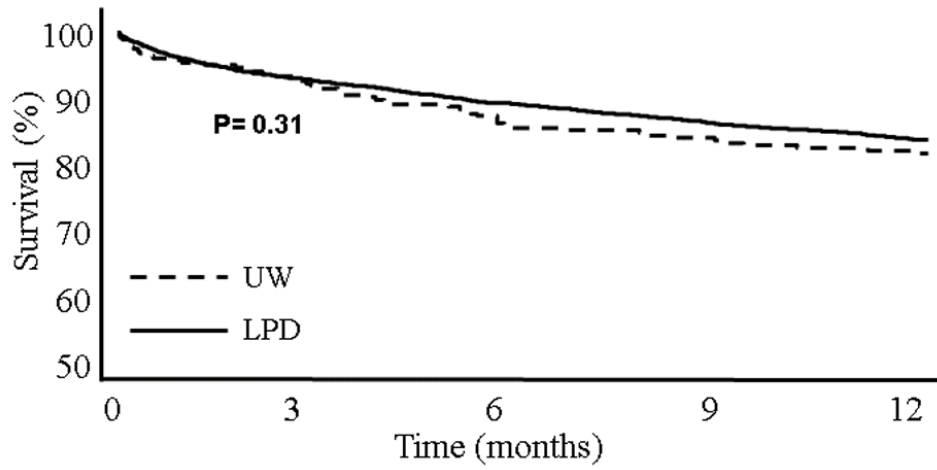
Kaplan-Meier Estimates of 1-Year Mortality 2005-2008
 High Risk Patients Stratified by Flush Solution



	<i>Number at Risk</i>		<i>Median Follow-up 12.6 months</i>		
LPD	2088	1889	1698	1455	1187
UW	140	120	103	91	79

Figure. 1.

Kaplan-Meier Estimates of 1-Year Mortality 2005-2008
Overall Cohort Stratified by Flush Solution



	<i>Number at Risk</i>			<i>Median Follow-up 12.6 months</i>	
LPD	4165	3828	3499	3097	2595
UW	294	264	235	219	200

Figure. 2.

Table 1

Baseline demographics stratified by flush solution

4,459 Patients	Perfadex N=4,165	UW N=294	P-Value*
<u>Recipient Demographics and Comorbidities</u>			
Age	53.5 (±12.8)	52.5 (±12.3) [†]	0.2
Age≥65	1696/4165 (40.7%)	98/294 (33.3%)	0.01
Male	2434/4165 (58.4%)	165/294 (56.1%)	0.4
Gender-matched	2898/4165 (69.6%)	214/294 (72.3%)	0.2
Caucasian	3522/4165 (85.6%)	252/294 (85.7%)	0.6
African-American	359/4165 (8.6%)	26/294 (8.8%)	0.9
Hispanic	202/4165 (4.8%)	11/294 (3.7%)	0.4
Other	82/4165 (2.0%)	5/294 (1.7%)	0.7
Diabetes	707/4127 (17.1%)	33/294 (11.2%)	0.009
Hypertension	538/2255 (23.9%)	41/192 (21.4%)	0.4
Creatinine	0.88 (±0.54)	0.86 (±0.31)	0.4
Body Mass Index (BMI)	24.9 (±66.0)	26.7 (±13.8)	<0.001
Days on wait list	249 (±432)	330 (±465) [†]	<0.001
End LAS calculation	42.82 (±14.09)	42.38 (±13.77)	0.6
Quartile 1	1029/4165 (24.7%)	84/294 (28.6%)	0.1
Quartile 2	1048/4165 (25.2%)	70/294 (23.8%)	0.6
Quartile 3	1043/4165 (25.0%)	71/294 (24.1%)	0.7
Quartile 4	1045/4165 (25.1%)	69/294 (23.5%)	0.5
<u>Recipient Hemodynamics and Pulmonary Function</u>			
Pre-LTx Mean PAP (mmHg)	27.3 (±10.7)	26.4 (±9.8)	0.2
Pre-LTx PVR (dyn·s/cm ⁵)	3.4 (±2.7)	2.9 (±2.0)	<0.001
Pre-LTx ventilation	185/4165 (4.4%)	9/294 (3.1%)	0.2
Pre-LTx ICU care	296/4165 (7.1%)	19/294 (6.5%)	0.7
Pre-LTx hospitalization	596/4165 (14.3%)	34/294 (11.6%)	0.2
O ₂ requirement - mean (±sd)	3.6 (±3.0)	3.5 (±2.9)	0.5
Six minute walking distance < 150 ft	222/4165 (5.3%)	25/294 (8.5%)	0.02
FEV1 %predicted – mean (±sd)	37.8 (±21.2)	34.8 (±20.1)	0.02
FVC %predicted – mean (±sd)	49.0 (±17.6)	46.6 (±16.2)	0.02
FEV/FVC – mean (±sd)	0.58 (±0.26)	0.57 (±0.26)	0.6
<u>Recipient Insurance and Education</u>			
Private Insurance/self pay	2648/4165 (63.6%)	182/294 (61.9%)	0.6
Medicare	1071/4165 (25.7%)	72/294 (24.5%)	0.6
Medicaid	310/4165 (7.4%)	23/294 (7.8%)	0.8
Other Insurance	135/4165 (3.2%)	17/294 (5.85%)	0.02
College or Graduate	1920/3538 (54.2%)	137/264 (51.9%)	0.5
Pre-college	1618/3538 (45.7%)	127/264 (48.1%)	0.5
<u>Primary Diagnosis</u>			

4,459 Patients	Perfadex N=4,165	UW N=294	P-Value*
COPD	1266/4165 (30.4%)	90/294 (30.6%)	0.9
CF	532/4165 (12.8%)	37/294 (12.6%)	0.9
IPF	1365/4165 (32.8%)	91/294 (31.0%)	0.5
Other	1002/4165 (24.1%)	76/294 (25.9%)	0.5
Donor Variables			
Donor diabetes	220/4156 (5.3%)	15/293 (5.1%)	0.9
Donor age	33.6 (\pm 14.4)	31.4 (\pm 14.2)	0.8
Cigarette use	650/4137 (15.7%)	29/293 (9.9%)	0.008
HLA-mismatch	2057/3498 (58.0%)	109/194 (56%)	0.5
CMV mismatch	1093/4165 (26.2%)	79/294 (26.9%)	0.8
Ischemic time (hours)	5.0 (\pm 1.6)	5.0 (\pm 1.9)	0.8

Table 2

Effect of flush solution on unadjusted Kaplan-Meier estimates of survival (with 95% confidence intervals) in LTx recipients

Survival Time	Perfadex	UW	P-Value
<i>Overall cohort</i>	(N=4,459)	(N=294)	
30 day	95.8% (95.2–96.4)	95.2% (92.0–97.1)	0.6
90 day	92.5% (91.7–93.2)	91.7% (87.9–94.4)	0.7
6 month	89.0% (88.0–89.9)	85.3% (80.7–88.9)	0.07
1-Year	83.3% (82.1–84.5)	81.2% (76.1–85.4)	0.3
<i>LAS Q1 – Q2</i>	(N=2,077)	(N=154)	
30 day	96.3% (95.4–97.1)	97.4% (93.1–99.0)	0.6
90 day	93.9% (92.8–94.9)	96.0% (91.4–98.2)	0.3
6 month	90.6% (89.2–91.8)	90.0% (84.0–93.8)	0.8
1-Year	85.4% (83.8–86.9)	88.4% (82.0–92.6)	0.4
<i>LAS Q3 – Q4</i>	(N=2,088)	(N=140)	
30 day	92.8% (87.0–96.1)	95.3% (94.3–96.2)	0.2
90 day	91.1% (89.8–92.3)	87.0% (80.2–91.6)	0.1
6 month	87.4% (85.9–88.8)	80.2% (72.5–86.0)	0.02
1-Year	81.2% (79.4–83.0)	73.3% (64.8–80.1)	0.02

Table 3

Univariate and multivariable Cox regression analysis for 1-year mortality after LTx in High Risk LAS patients

Variables of interest	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P-value*	HR (95% CI)	P-value†
Additional Variables				
University of Wisconsin	1.52 (1.07–2.16)	0.03	1.75 (1.20–2.56)	0.004
Age	1.02 (1.01–1.03)	<0.001		
Age > 65	1.46 (1.20–1.78)	<0.001	1.43 (1.10–1.89)	0.007
BMI	1.01 (0.99–1.01)	0.4		
Recipient creatinine	1.13 (1.07–1.20)	0.004	1.10 (1.04–1.18)	0.002
Recipient diabetes	0.88 (0.69–1.15)	0.36		
Recipient HTN	1.36 (0.99–0.84)	0.06		
<u>Recipient diagnosis</u>				
COPD	1.06 (0.71–1.58)	0.8		
CF	0.63 (0.47–0.87)	0.003	0.58 (0.41–0.82)	0.002
IPF	1.05 (0.86–1.28)	0.62		
Other	0.97 (0.91–1.04)	0.4		
<u>Acuity</u>				
LAS‡	1.01 (1.00–1.02)	<0.001	0.99 (0.99–1.01)	0.3
O ₂ requirement	1.07 (1.03–1.11)	<0.001		
Six minute walking distance < 150 ft	1.11 (0.92–1.34)	0.3		
FEV1 % predicted	1.01 (1.00–1.01)	0.001		
FVC % predicted	1.01 (1.00–1.01)	0.05		
FEV/FVC – mean (±sd)	1.69 (1.39–2.05)	<0.001		
Ventilator prior to LTx	2.12 (1.56–2.86)	<0.001		
ICU prior to LTx	3.14 (2.49–3.96)	<0.001	2.26 (1.52–3.38)	<0.001
Hospitalized prior to LTx	2.39 (1.94–2.94)	<0.001	2.42 (1.83–3.04)	0.01
<u>Donor and Immunology</u>				
HLA mismatch (0 or 1 antigens matched)	1.02 (0.82–1.28)	0.8		
Age of donor (yrs)	1.01 (1.00–1.01)	0.04	1.00 (0.99–1.01)	0.3
Donor BMI	0.98 (0.96–1.01)	0.3		
Donor cigarette use	1.25 (0.96–1.64)	0.1	1.21 (0.90–1.62)	0.2
Donor diabetes	1.29 (0.84–1.97)	0.25		
BLT	0.84 (0.68–1.04)	0.1		
Ischemic time > 6 hrs	0.95 (0.75–1.21)	0.7	1.05 (0.98–1.12)	0.1