Lung Transplant Mortality Is Improving in Recipients With a Lung Allocation Score in the Upper Quartile

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Background. **Since the introduction of the Lung Allocation Score (LAS), the mean LAS has risen. Still, it remains uncertain whether mortality has improved in the most severely ill lung transplant recipients over this time period.**

Methods. **Using the United Network for Organ Sharing database, we identified 3,548 adult lung transplant recipients from May 4, 2005, to March 31, 2014, with a match-time LAS in the upper quartile (>75th%ile). We divided this population across three eras: 1 = May 4, 2005, to December 31, 2008 (n = 1,280); 2 = January 1, 2009, to December 31, 2011 (n = 1,266); and 3 = January 1, 2012, to March 31, 2014 (n = 1,002). Cox proportional hazards models were constructed for the primary outcomes of 30-day and 1-year mortality to assess the independent impact of the era of transplantation.**

Results. **The mean LAS at time of transplant for patients in the upper quartile in eras 1, 2, and 3 was 63, 73, and 79, respectively ($p < 0.001$). Later eras of transplantation benefited from a significant improvement in survival at 1 year (log-rank $p = 0.001$) but not at 30 days (log-rank $p = 0.152$). After risk adjustment, lung transplantation in more recent eras was associated with improved mortality at both 30 days (era 3 hazard ratio [HR] = 0.50, 95% confidence interval [CI] 0.32% to 0.78%, $p = 0.002$) and 1 year (era 2 HR = 0.77, 95% CI 0.64% to 0.94%, $p = 0.008$; era 3 HR = 0.54, 95% CI 0.43% to 0.68%, $p < 0.001$).**

Conclusions. **Despite a progressively rising LAS, survival is improving among recipients with the highest LAS at the time of lung transplantation. This calls into question the notion of a maximum LAS beyond which lung transplantation becomes futile, a so-called LAS ceiling.**

(Ann Thorac Surg 2017;103:1607–13)

The United Network for Organ Sharing (UNOS) is responsible for the coordination and allocation of solid organ transplantation in the United States. Before 2005, priority for lung allocation was given to those with the longest time on the transplant wait list, with additional consideration given to those with pulmonary fibrosis [1, 2]. As a result of population trends and scarcity of available donors, the lung transplantation wait list was steadily growing, and mortality for those on the wait list was rising [3–5]. In May 2005, a paradigm shift in lung allocation occurred when the Organ Procurement and Transplantation Network approved a Lung Allocation Score (LAS) [6].

The LAS scoring system was designed to balance the likelihood of wait list and posttransplantation survival at 1 year, after demographic factors and the physiologic derangements associated with end-stage lung disease were taken into account. Ultimately, the LAS was intentioned to provide a more equitable allocation of lungs [6]. Since the implementation of the LAS, substantial declines in the duration of time on the wait list and improved wait list mortality have been observed without a concomitant downtrend in posttransplantation survival [7, 8]. Over the past 10 years, pretransplantation LAS has risen steadily. In fact, the percentage of patients with an LAS greater than 50 has more than doubled since 2006 [9]. Previous studies have demonstrated that a higher LAS is predictive of mortality within the first year of lung transplantation, prompting a discussion of whether there should be a threshold LAS beyond which transplantation should be considered futile—a threshold referred to by previous investigators as an LAS ceiling [8–10]. However, no specific LAS cutoff for transplantation has been established at this time [11].

We hypothesized that survival has improved over time in recipients who are the most critically ill at the time of lung transplantation. The present study seeks to assess evolving trends in posttransplantation survival since the

Accepted for publication Nov 17, 2016.

Presented as a poster at the Thirty-sixth Annual Meeting of The International Society for Heart and Lung Transplantation, Washington, DC, April 27–30, 2016.

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0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2016.11.057

inception of the LAS in patients with an LAS in the upper quartile at the time of transplantation.

Patients and Methods

Patient Selection

We queried the UNOS Scientific Registry of Transplant Recipients (SRTR) database for all adult patients (≥18 years of age) who underwent isolated lung transplantation from May 4, 2005, to March 31, 2014. These patients were stratified into four quartiles based on their LAS at the time of transplantation. Patients without a calculated LAS at the time of transplantation were excluded. Local institutional review board approval was not required because the UNOS SRTR database is deidentified and this study did not meet the definition of human subjects research.

Creation of Eras

The time period of this analysis was divided into three discrete eras to enable the assessment of changes in survival over time. Era 1 was defined as May 4, 2005, to December 31, 2008. Era 2 was defined as January 1, 2009, to December 31, 2011. Era 3 was defined as January 1, 2012, to March 31, 2014. the time periods associated with each era were chosen so as to allocate a similar number of patients to each and to capture temporal trends in the LAS profiles.

Outcomes

The primary outcomes of this study were perioperative survival, defined in this study as survival beyond 30 days, and short-term survival, which we defined as survival beyond 1 year after transplantation.

Statistical Analysis

The baseline recipient and donor characteristics were compared across three eras. Recipient-specific variables included age, gender, race, body mass index (BMI), cause of lung disease, Karnofsky performance status (KPS), history of diabetes, estimated glomerular filtration rate (GFR), ventilator status, smoking history, extracorporeal membrane oxygenation (ECMO) needs at time of transplantation, preoperative intensive care unit (ICU) admission, history of malignancy, previous transplantation, long-term steroid use, total serum bilirubin, days on the wait list, and 6-minute walking distance. Donor-related variables included age, gender, race, history of diabetes, history of hypertension, smoking history, and BMI. Transplantation-specific characteristics included ischemia time longer than 6 hours, single lung transplantation, and gender matching. Variables with data missing for more than 10% of patients were excluded from future statistical models. No imputing was performed for missing data.

The unadjusted impact of the era of transplantation on both 30-day and 1-year survival was first assessed as a time-to-event analysis by the method of Kaplan and Meier. Univariable Cox proportional hazards modeling was then used to determine the influence of each of the recipient-, donor-, and transplantation-specific variables on postoperative mortality. Covariates associated with increased mortality ($p < 0.2$) were entered manually forwards into a multivariable Cox proportional hazards model. Akaike Information Criteria and Likelihood Ratio testing allowed for construction of the most parsimonious model for each of our outcomes. Finally, the impact of each of the eras of transplantation was tested in the multivariable models.

Continuous variables (mean and standard deviation) were compared with one-way analysis of variance (ANOVA). Categoric variables (number and percentage) were compared with Pearson χ^2 analysis. All p values were two-sided, and significance was defined by a p value <0.05. Stata 12.1 (StataCorp, College Station, TX) was used for all statistical analysis.

Results

Demographic-Specific, Recipient-Specific, and Donor-Specific Factors

A total of 14,170 adult patients underwent isolated lung transplantation from May 4, 2005 (inception of LAS), to March 31, 2014. Patients with an LAS in the upper quartile (n = 3,548) at the time of transplantation were then isolated for remaining analyses (era 1, n = 1,280; era 2, n = 1,266; era 3, n = 1,002). The mean LAS at the time of transplantation for those with an LAS in the upper quartile increased across the three eras: 63 ± 15 in era 1 (range, 45.8 to 95.1), 73 ± 15 in era 2 (range, 51.6 to 95.7), and 79 ± 13 in era 3 (range, 57.3 to 97.1) ($p < .001$) (Fig 1). LAS at the time of initial listing also changed significantly across eras (era 1, 48 ± 20; era 2, 54 ± 23; era 3, 58 ± 23, $p < .001$). Similarly, the average change in LAS from initial listing to time of transplantation was significantly different across eras (era 1, 16 ± 21; era 2, 19 ± 23; era 3, 21 ± 23, $p = 0.011$).

A review of recipient, donor, and transplant characteristics revealed significant differences in BMI and

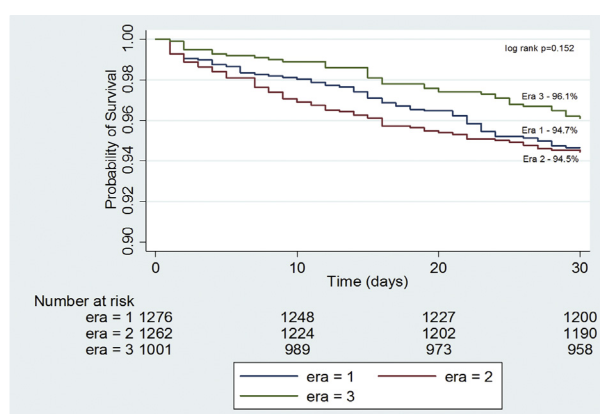

Fig 1. Kaplan-Meier survival analysis for lung transplant recipients 30 days after transplantation. The differences in probability of survival in more recent eras did not reach statistical significance (log rank p = 0.152).