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Impact of lung allocation score on survival in cystic fibrosis lung transplant recipients

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KEYWORDS:
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BACKGROUND: The lung allocation score (LAS) has changed organ allocation for lung transplantation in the United States. Previous investigations of transplant recipients reported an association between high LAS and an increased risk of death after lung transplantation. We hypothesize that a high LAS predicts survival in lung transplant recipients with cystic fibrosis (CF) in the United Network for Organ Sharing Scientific Registry of Transplant Recipients database.

METHODS: A cohort study was conducted of 1,437 U.S. adult lung transplant recipients with CF from May 1, 2005, through December 31, 2012. The cohort was divided into a high-risk group and a low-risk group based on LAS. Survival data were examined using Kaplan-Meier estimates and Cox proportional hazard models to compare survival. The primary outcome was adjusted survival at 1 year after lung transplantation.

RESULTS: The high-risk group of 318 patients with a median LAS of 69.6 (interquartile range 56.3–87.2) was compared with a low-risk group of 1,119 patients with a median LAS of 38.8 (interquartile range 36.3–42.3). Patients in the high-risk group had a 41% increased relative risk of cumulative mortality at 1 year after transplantation compared with the low-risk group (16.1% vs 12.0%). After adjustment for known predictors of mortality, the risk of death at 1 year after transplantation remained elevated (hazard ratio = 1.41; 95% confidence interval = 1.00–2.01). The high-risk group had worse survival at 90 days and 2 years after lung transplantation.

CONCLUSIONS: High LAS are associated with worse survival in lung transplant recipients with CF.
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Lung transplantation is a widely accepted therapeutic option for patients with cystic fibrosis (CF) and advanced pulmonary disease.[1] Appropriately chosen lung transplant candidates can benefit from prolonged survival and improved health-related quality of life.[2,3] However, donor lung availability is limited, and long-term post-transplant outcomes are sub-optimal with a median 5-year survival of 54%.[4]

In May 2005, the United Network for Organ Sharing (UNOS) implemented the lung allocation score (LAS) to prioritize patients awaiting lung transplantation in the United States. The LAS uses validated demographic and clinical data (Table 1) to prioritize candidates by "net-transplant benefit"

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Table 1 Lung Allocation Score Components

Waiting list urgency parameters
Age
Body mass index
Diagnosis
Functional status
FVC (% predicted)
Pulmonary artery systolic pressure
O_2 requirement at rest
Diabetes mellitus
6-minute walk distance <150 feet
Continuous mechanical ventilation
Pco_2
Post-transplant survival variables
Age
Functional status
FVC (% predicted)
Continuous mechanical ventilation
Diagnosis
Pulmonary capillary wedge pressure

FVC, forced vital capacity; Pco_2, Partial pressure of carbon dioxide.

based on waitlist urgency and predicted post-transplant survival.[4] Waitlist urgency is defined as predicted 1-year survival without lung transplantation, and post-transplant survival is defined as predicted 1-year survival with lung transplantation.[5] Scores range from 0 to 100 with a higher score reflecting individuals with most urgent need and greatest chance of success after transplantation. Use of the LAS has been associated with shorter waitlist times and improved survival.[5–9]

The UNOS Scientific Registry of Transplant Recipients (SRTR) database has been used to examine post-transplant survival in lung transplant recipients with a high LAS. In a previous publication, our group investigated all lung transplant recipients 3 years after institution of the LAS and found an 8% absolute increase (75% vs 83%) in 1-year post-transplant mortality for patients in the highest LAS quintile (LAS >46) compared with patients in the lower 4 quintiles (LAS ≤ 46).[7] Studies investigating the impact of the LAS on survival in patients with chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and pulmonary hypertension reported a 5% to 15% survival difference in high-risk LAS groups compared with the low-risk groups.[9–12] However, these studies did not adjust their findings for other identified survival predictors, including donor cytomegalovirus (CMV) status, donor lung ischemic time, and patient insurance status.[13–16]

A rigorous investigation of the strength of association between LAS and survival is particularly important in patients with CF, who represent a unique sub-set of the transplant population. The relative youth of these patients compared with other lung transplant recipients, variable adherence to medications, and pre-transplant history of chronic infection may differentially impact the LAS-survival relationship. Thus, we hypothesize that high LAS scores may be associated with worse survival in lung transplant recipients with CF.

Methods

The present study used de-identified data from the UNOS SRTR database of the thoracic organ transplant registry.[4]

Study design

Adult (≥ 18 years old) patients with CF undergoing first-time lung transplantation in the United States were entered into the study between May 1, 2005, the date of LAS implementation, and December 31, 2012. Patients undergoing combined heart-lung transplantation or repeat lung transplantation were not included.

Our analysis examined the following independent variables: age, sex, body mass index, creatinine, diabetic status, forced expiratory volume at 1 second (FEV_1), forced vital capacity (FVC), pre-transplant hemodynamic measures, 6-minute walk test, supplemental oxygen use, serum partial pressure of carbon dioxide (Pco_2), pre-transplant mechanical ventilation, educational attainment (high school diploma or less v any degree of post-secondary education), insurance status (private v non-private), center volume, donor CMV status, graft ischemic time, waitlist time, and LAS. Donor CMV status was characterized as high risk if positive and low risk if negative, based on previously reported data.[13,17]

Our primary end-point was 1-year post-transplant survival. Secondary end-points included 90-day, 2-year, and 5-year post-transplant survival. Furthermore, we examined survival for lung transplant recipients who survived to 1 year, known as conditional 1-year survival. Study subjects were censored if they were lost to follow-up or the study period ended.

Statistical analysis

Descriptive analysis was performed with calculation of mean, SD, and median for continuous variables and proportion for categorical variables. Bivariate analyses were conducted using Student's *t*-tests, or Wilcoxon's rank sum test for continuous variables and chi-square or Fisher's exact tests for categorical variables. The top quintile of the cohort by LAS corresponded to a LAS near 50; for clarity, this cutoff was chosen to describe a high-risk cohort (LAS ≥ 50) and a low-risk comparison group (LAS <50) as modeled in previous studies.[5,18] We also examined LAS as a continuous variable and as a variable rescaled in increments of 10 to provide clarity of hazard estimates. Survival was modeled using the Kaplan-Meier product limit estimator with statistical differences between survival curves assessed using the Mantel-Cox log-rank test.[19] Cox proportional hazard regression models were used to account for possible differences in survival patterns that may be due to imbalances in severity of illness between the 2 groups.[20] Covariates in multivariable analyses were chosen based on biologic significance and clinical relevance. To address bias from missing data (assumed missing at random), the multivariate imputation by chained equations method of multiple imputation in Stata (5 datasets were imputed and analyzed; StataCorp LC, College Station, TX) was performed. Conditional survival at 1 year was examined in a similar fashion.

Statistical significance was defined as a 2-tailed $\alpha < 0.05$. There was $>80\%$ power to detect a relative risk difference of 1.3 between groups, assuming a sample size of 1,000 patients and overall mortality rate of 15%. All statistical analyses were performed using Stata software (version 11.0). Patients in the UNOS database give informed consent permitting their de-identified records to be used for research purposes. The study was reviewed and approved by the institutional review board at Johns Hopkins School of Medicine.