Who is the high-risk recipient? Predicting mortality after lung transplantation using pretransplant risk factors

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Objectives: The purpose of this study was to create a preoperative risk stratification score (RSS) based on pretransplant recipient characteristics that could be used to predict mortality following lung transplantation.

Methods: United Network for Organ Sharing provided deidentified patient-level data. The study population included 8780 adult recipients (age > 12 years) having lung transplantation from January 1, 1999, to December 31, 2006. Multivariate logistic regression (backward, $P > .10$) was performed. Using the odds ratio for each identified variable, an RSS was devised. The RSS included only pretransplant recipient variables and excluded donor variables.

Results: The strongest negative predictors of 1-year survival included extracorporeal membrane oxygenation, decreased estimated glomerular filtration rate, total bilirubin >2.0 mg/dL, recipient age, hospitalization at time of transplant, O_2 dependence, cardiac index <2, steroid dependence, donor:recipient weight ratio <0.7, all non–cystic fibrosis/chronic obstructive pulmonary disease etiologies, and female donor–to–male recipient. Threshold analysis identified 4 discrete groups: low risk, moderate, elevated risk, and high risk. The 1-year actuarial survival was 80.4% for the entire group, compared with 56.8% in the high-risk group (RSS > 7.2, n = 490; 6%).

Conclusion: Pretransplant recipient variables significantly influence both early and late survival following lung transplantation. Some patients face a higher than average risk of mortality during their first year posttransplant, which challenges the goals of equitable organ allocation. RSS may improve organ allocation strategies by avoiding the potential negative impact of performing transplantation in extremely high-risk candidates.

Supplemental material is available online.

Lung transplantation offers substantial benefits to patients with end-stage lung disease.[1-3] Unfortunately, as organs available for transplant remain critically scarce, achieving maximal benefit from transplantation is predicated on improved recipient selection.[4] To this end, the risks and benefits associated with performing transplantation in various groups of lung transplant candidates must be better understood.

The purpose of this study is to risk stratify lung transplant candidates based on pretransplant recipient characteristics. Specifically, this analysis used objective methods to identify pretransplant recipient characteristics associated with posttransplant survival at 1 year. Based on these factors, a risk stratification score (RSS) was developed to predict 1-year mortality following lung transplantation in adolescents and adult recipients.

METHODS

Data Collection

Use of these data is consistent with the regulations of our university's Institutional Review Board and the United Network for Organ Sharing (UNOS)'s Data Use Agreement. The Standard Transplant Analysis and Research Dataset were provided by UNOS (data source #033108-3).

Study Population

All recipients aged 12 years and older having lung transplantation between January 1, 1999, and December 31, 2006, were included in the study population. Patients were excluded if they had other simultaneous organ transplantation (n = 17). Follow-up data were provided through February 8, 2008. Patients were followed from the date of transplant until death, retransplantation, or date of last known follow-up, which was the last day of follow-up data provided by UNOS.

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Abbreviations and Acronyms

ALT = alternate list transplant
BMI = body mass index
ECMO = extracorporeal membrane oxygenation
LAS = lung allocation score
OR = odds ratio
ROC = receiver operating characteristic
RSS = risk stratification score
SSLR = stratum-specific likelihood ratio
UNOS = United Network for Organ Sharing

Outcome Measures

The primary outcome measure was 1-year mortality. In survival analysis, the outcome of interest was death (n = 3420, 39%). Patients lost to follow-up (n = 102, 1%), those who had retransplantations (n = 210, 2%), and those alive at last known follow-up (n = 5014, 57%) were censored at the date of last known follow-up.

Data Analysis

All data were analyzed using a statistical software package, Stata 9 (Stata Corp, College Station, Tex). Continuous variables are reported as means ± standard deviation and compared using the Student *t* test. To compare categorical variables, the chi-square test was used. Kaplan-Meier analysis with log-rank test was used for time to event analysis. All reported *P* values are 2-sided.

Logistic regression was used to develop a model to predict 1-year mortality to assess the simultaneous effect of multiple variables on survival following lung transplant. Variables included in the model are summarized in Table 1. All variables significant in univariate analysis were included in the regression, and backward selection ($P < .10$) was used to construct the models. The odds ratio (OR) and 95% confidence interval are reported for each factor. Using the OR calculated in regression analysis, weights were assigned for each risk factor. Model discrimination between survivors and nonsurvivors was assessed by calculating the area under the receiver operating characteristic (ROC) curve.

Patients' risk strata were calculated using threshold analysis with ROC curves and stratum-specific likelihood ratios (SSLR). ROC curves were generated by plotting sensitivity on the ordinate and 1 − specificity on the abscissa with RSS as a continuous variable and 1-year mortality as a binary outcome.[5] SSLRs and 95% confidence intervals were generated using threshold values at regular intervals as previously described.[6,7] Threshold values were determined by combining adjacent volume strata with other statistically indistinct strata based on the presence of SSLRs with overlapping 95% confidence intervals. Threshold values occurred when 2 statistically distinct strata could be formed. This process was repeated until no additional threshold values were found.

RESULTS

Study Population

Analysis included 8780 lung transplant recipients with 22,452.1 person-years at risk and 2.56 ± 2.12 mean follow-up years. Due to missing data, 1007 (11%) were excluded from logistic regression.

Risk Factors

The logistic regression model of postoperative mortality is shown in Table 1. The model had good ability to discriminate between survivors and nonsurvivors with an area under the receiver operator characteristic curve of 0.67 (0.64–0.69).

Risk Groups

Threshold analysis identified 4 discrete groups (Table 2): low risk, moderate, elevated risk, and high risk. Patients with scores > 7.2 were in the high-risk group (n = 490; 6%). No single high-risk characteristic was sufficient to place recipients in the high-risk group, and nearly 93% of recipients in the high-risk group contained 5 to 7 risk factors. This pattern of stacked risk factors persisted in the elevated-risk group, with 69% of this group having 5 to 7 high-risk characteristics. In contrast, the majority of recipients in the low-risk (99.8%) and moderate-risk (77.4%) groups had between 0 and 4 risk factors. The high-risk group had a 1-year actuarial survival of 57% and a median survival of 1.97 years. Survival functions and statistics can be found in Figure 1 and Table 2.

DISCUSSION

The importance of patient selection in lung transplantation is supported both by clinical observation as well as objective data.[4,8] This analysis provides further evidence that it is possible to risk stratify lung transplant candidates based on pretransplant characteristics.

High-Risk Recipient Characteristics

No single risk factor was sufficient to place a recipient in the highest risk category. However, the strongest negative predictor of 1-year mortality was extracorporeal membrane oxygenation (ECMO) dependence, with only 44% alive at 1 year. ECMO and hospitalized at transplant, which all ECMO patients were, was sufficient to place recipients in the highest category; therefore, all ECMO-dependent candidates (n = 34) were in the high-risk group. While it is possible that in the future ECMO will be offered to less morbid patients given newer cannula configurations and the potential for ''walking'' ECMO, during the study period recipients on ECMO had, on average, 5.7 risk factors.

Other strong predictors included retransplantation, poor renal function, poor liver function, and advanced-age recipients. The majority of recipients in the high-risk group had between 5 and 7 risk factors. This supports the concepts that stacking risk factors presages poor outcome.

How Do High-Risk Patients Fare?

When comparing the high-risk group with the other groups, the risk of death in the first year posttransplant was 2- to 3-fold higher. Furthermore, long-term survival was significantly diminished, with median survival of the high-risk group approximately one-third of the low-risk and moderate-risk groups. For the high-risk group, transplantation has limited clinical effectiveness. This finding

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