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, O₂ 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 im-

proved 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 post-transplant 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 $\pm$ 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 $1 - \text{specificity}$ 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 discrim-

inate 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

TABLE 1. Risk factor score model variables

	Points	OR	95% CI	P value
Risk score variables				
ECMO	6.9	6.937	2.391–20.127	.000
Recipient eGFR (mL/min) < 33	2.3	2.269	1.431–3.598	.000
Recipient age (y) ≥ 70	2.3	2.261	1.163–4.395	.016
Total bilirubin > 2.0 mg/dL	2.2	2.172	1.653–2.852	.000
O ₂ requiring ≥ 5 L	2.1	2.071	1.583–2.709	.000
Etiology retransplantation	2.1	2.055	1.413–2.989	.000
Etiology sarcoidosis	1.9	1.905	1.357–2.674	.000
Etiology A1A deficiency	1.9	1.864	1.421–2.444	.000
Hospitalized at the time of transplant	1.8	1.837	1.483–2.277	.000
O ₂ requiring 1–4 L	1.7	1.685	1.353–2.099	.000
Etiology pulmonary hypertension	1.7	1.677	1.166–2.412	.005
Recipient age (y): 55–70	1.4	1.373	1.194–1.579	.000
Cardiac index < 2	1.4	1.363	1.074–1.731	.011
Etiology pulmonary fibrosis	1.3	1.326	1.120–1.569	.001
Requiring steroids	1.3	1.325	1.155–1.521	.000
Donor:recipient weight ratio < 0.7	1.3	1.292	1.024–1.630	.031
Etiology: other	1.3	1.266	0.967–1.657	.086
Female donor to male recipient	1.2	1.213	1.001–1.470	.049
Other variables				
BMI < 18.5 (underweight)		1.188	0.952–1.482	.128
BMI 25–29.99 (overweight)		1.092	0.928–1.286	.290
BMI 30–34.99 (obese)		1.065	0.849–1.337	.585
Center volume		0.998	0.998–0.999	<.001
Clinical evidence of infection		0.965	0.831–1.120	.637
Diabetes (recipient) ≥ 6 y		1.682	0.732–3.868	.221
Diabetes (recipient) 0–5 y		1.312	0.800–2.151	.282
Diabetes complicated by CVA		1.743	0.273–11.144	.557
Diabetes complicated by PVD		0.725	0.148–3.559	.692
Diabetes complicated by renal failure (eGFR < 40 mL/min)		0.718	0.205–2.515	.604
Dialysis dependent		0.819	0.242–2.773	.748
Donor age		1.001	0.995–1.008	.643
Donor drug use in the last 6 mo		0.872	0.642–1.184	.379
Donor eGFR (mL/min)		0.999	0.992–1.007	.850
Donor history of cancer		0.673	0.373–1.215	.189
Donor insulin dependence		1.073	0.588–1.955	.819
Etiology cystic fibrosis		1.035	0.729–1.471	.847
Female donor to female recipient		1.004	0.842–1.198	.964
FEV ₁ :FVC ratio		0.866	0.638–1.175	.355
Hepatitis C+ donor		4.890	1.805–13.251	.002
Hepatitis C+ recipient		1.119	0.681–1.840	.658
HLM mismatch ≤ 3		1.080	0.884–1.320	.452
Hypertension ≥ 6 y		1.031	0.645–1.650	.898
Hypertension 0–5 y		1.174	0.936–1.474	.166
Infection within 2 wk of transplant		1.112	0.863–1.434	.412
Inotropic support at the time of transplant		1.236	0.908–1.682	.178
Intubated at the time of transplant		1.135	0.744–1.732	.558

TABLE 1. Continued

	Points	OR	95% CI	P value
Ischemic time (h)		1.045	1.002–1.090	.042
Male donor to female recipient		1.018	0.831–1.246	.867
Prostaglandin at the time of transplant		0.924	0.296–2.886	.892
Recipient age (y) 18–39		1.453	0.961–2.197	.077
Recipient age (y) 40–55		1.398	0.900–2.171	.136
Recipient eGFR (mL/min) 33–53		1.224	0.912–1.643	.179
Six-min walk < 150 ft		1.056	0.842–1.324	.639
Transplant year		0.880	0.932–0.000	.906
Treated for resistant infection		1.067	0.653–1.745	.794

BMI, Body mass index; CI, confidence interval; CVA, cerebral vascular accident; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; PVD, peripheral vascular disease.

raises concerns regarding the appropriateness of allocating organs to such high-risk patients.

Lung Allocation Score

In May 2005, the Organ Procurement and Transplantation Network implemented the lung allocation score (LAS). With subsequent increases in the number of transplants, decreases in wait time, and reductions in deaths on the waiting list,⁹ LAS has been a significant advance from the previous allocation system, which was based strictly on waiting list time. However, LAS is more heavily weighted toward the risk of mortality on the waiting list than risk of posttransplant mortality⁶—not surprisingly, LAS is inversely related to short-term survival (Appendix 1). Therefore, given the findings that LAS is also associated with higher rates of primary graft dysfunction and longer intensive care unit lengths of stay,⁹ there remains concern that an increasing number of critically ill candidates with an unacceptably high risk of poor outcome will be transplanted.¹⁰ In fact, over the duration of this study, the percentage of recipients falling within the low-risk category decreased from 42.4% in 1999 to 32.7% in 2006; concurrently the percentage of recipients categorized as high risk by the RSS increased from 4.9% in 1999 to 8.6% in 2006 (Appendix 2).

Implications for Recipient Selection and Organ Allocation

In an effort to limit allocation of scarce organs to candidates with a high likelihood of poor posttransplant outcome, it may be prudent to incorporate a safeguard in the current allocation system. Such a system could utilize an RSS, such as presented here, to estimate a candidate's posttransplant risk. Candidates with a risk exceeding a predetermined threshold would have their LASs significantly reduced or be inactivated.

A second possibility is to implement an alternate list transplant (ALT) strategy, a strategy used by a number of heart

TABLE 2. Risk group strata thresholds and outcomes

	Low risk	Moderate risk	Elevated risk	High risk	Total
n	3055	3411	800	490	7756
%	39.4	44.0	10.3	6.3	
Score	<3.50	3.50–5.80	5.90–7.20	>7.20	5.0
SSLR	0.61	1.03	1.55	3.20	
LL SSLR	0.56	0.96	1.34	2.70	
UL SSLR	0.67	1.09	1.80	3.79	
Actuarial 1-y survival (%)	87.1	80.4	73.1	56.8	80.4
Median survival (y)	5.45	4.41	3.80	1.97	4.70
Number of risk factors (%)					
0–4	99.8	77.4	30.9	5.2	77.6
5–7	0.2	22.6	69.1	92.5	22.3
≥ 8	0.0	0.0	0.0	2.4	0.1

SSLR, Stratum-specific likelihood ratio; LL, lower limit; UL, upper limit.

transplant centers. Under ALT, high-risk recipients are only eligible for organs if the organ is not suitable for any potential standard recipient.¹¹ As donor organs utilized by ALT recipients would often otherwise be discarded, this strategy may expand the use of potential donor organs. Conversely, these lower-quality donor organs would likely be associated with further diminished outcomes. Considering the significant potential benefits and risks, outcomes, including survival, quality of life, and cost-effectiveness, recipients would have to be closely monitored to determine the viability of such a strategy.

A third possibility would be to refer high-risk candidates to high-volume centers. Multivariate regression demonstrated that increased center volume is associated with superior survival at 1 year. In this analysis, high-risk candidates had a 50.0% 1-year survival at centers that transplant fewer than 10 recipients per year compared with 66.7% 1-year survival at centers transplanting more than 20 recipients annually.

Finally, regardless of how risk stratification is used to improve organ allocation, the RSS may have additional benefits. With increasing quality oversight and variable reimbursement schemes based on performance, introduction of a risk stratification schema may improve quality measures and reimbursement by better accounting for case mix at centers that might otherwise be penalized on these measures for providing care to greater number high-risk transplants.

Future Studies

Additional studies are needed to validate the model presented in this analysis. Furthermore, future studies should consider quality of life and cost implications of transplanting various groups of lung transplant candidates. Finally, future studies should include subanalyses that consider combinations of recipient and donor factors.

FIGURE 1. Legend. Survival function by risk strata. LR, Low-risk; IR, intermediate-risk; ER, elevated-risk; HR, high-risk.

Limitations

These data have several limitations. First, patient registries often suffer from variability in data entry. However, fields contained within this database were generally well populated with a 95% to 99% data entry rate for the majority of variables. Though the UNOS reporting system provided definitions for variables in data guidelines, definitions may vary by center. Second, although the data analysis supports associations between variables and outcomes, causal relationships cannot be determined. Many of the risk factors may simply be markers for poor clinical status before transplantation rather than direct causal factors in poor survival. Third, for the purpose of simplifying the scoring mechanism, continuous variables, such as recipient age, estimated glomerular filtration rate, and body mass index (BMI) were converted to discrete categories. An attempt was made to divide variables by logical or clinical relevant means. For example, recipients were grouped into discrete BMI categories based on the Expert Panel on the Identification, Evaluation, and Treatment Overweight and Obesity in Adults' BMI classification scheme. This strategy, however, decreases the power of the model. Furthermore, it suggests that recipients with similar BMIs (e.g., 34.9 and 35.1 kg/m²) may fall into different risk categories even though it is unlikely that they face significantly different risks based on BMI alone. If applied on a broader scale, a more sophisticated score, using equations that allow for continuous variables, could be assigned. Finally, the RSS remains to be validated, and further studies are required to confirm its accuracy in predicting early posttransplant outcomes. In this analysis, the study population includes patients transplanted from 1999 to 2006. As demonstrated in the multivariate regression analysis, year of transplant had a significant impact on survival. Therefore, to ensure that this score is relevant to the current population of recipients, this model should be validated using the most up-to-date data

(eg, 2007 lung transplant recipients). Furthermore, RSS, like LAS, would likely need to be revised due to temporal changes in the composition of the recipients and new therapeutic adjuncts used in their care.

CONCLUSION

Pretransplant recipient variables significantly influence early and late survival following lung transplantation, suggesting that some patients face a higher than average risk of mortality during the first year posttransplant, as well as severely diminished longer-term survival, that challenges the goals of equitable organs allocation. RSS may improve organs allocation strategies by avoiding the potential poor outcomes associated with transplanting extremely high-risk candidates.

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APPENDIX 1. Short-term survival by LAS

LAS	90-d survival, n (%)*	1-y survival, n (%)*
<40	28 (82.1)	24 (88.9)
40–49	1520 (85.9)	1258 (92.6)
50–59	474 (84.6)	379 (89.2)
60–69	125 (80.8)	93 (88.6)
70–79	65 (78.5)	47 (82.5)
>80	122 (69.7)	86 (78.2)

LAS, Lung allocation score. **P* < .001.

APPENDIX 2. Percentage of recipients by risk group and transplant year

Year	n	Low risk*	Moderate risk	Elevated risk	High risk*
1999	736	42.4	43.6	9.1	4.9
2000	788	43.9	43.8	7.6	4.7
2001	860	44.0	42.0	9.2	4.9
2002	870	38.7	44.8	10.8	5.6
2003	948	40.5	45.3	9.1	5.2
2004	1033	41.0	43.2	10.0	5.9
2005	1267	36.7	44.8	10.0	8.5
2006	1254	32.7	44.0	14.7	8.6

**P* < .001.