Accepted Manuscript

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Please cite this article as: Chan EY, Nguyen DT, Kaleekal TS, Goodarzi A, Graviss EA, Gaber AO, for the Houston Methodist Lung Outcomes Group, The Houston Methodist lung transplant risk model – a validated tool for pre-transplant risk assessment, *The Annals of Thoracic Surgery* (2019), doi: https://doi.org/10.1016/j.athoracsur.2019.03.108.

The Houston Methodist lung transplant risk model – a validated tool for pre-transplant risk assessment

Running Head: Houston Methodist Lung Txp Risk Model

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ABSTRACT

BACKGROUND: Lung transplantation is the gold standard for a carefully selected patient population with end-stage lung disease. We sought to create a unique risk stratification model using only preoperative recipient data to predict one-year postoperative mortality during our pre-transplant assessment.

METHODS: Data of lung transplant recipients at Houston Methodist Hospital (HMH) from 1/2009 to 12/2014 were extracted from the United Network for Organ Sharing (UNOS) database. Patients were randomly divided into development and validation cohorts. Cox proportional-hazards models were conducted. Variables associated with 1-year mortality post-transplant were assigned weights based on the beta coefficients, and risk scores were derived. Patients were stratified into low-, medium- and high-risk categories. Our model was validated using the validation dataset and data from other US transplant centers in the UNOS database

RESULTS: We randomized 633 lung recipients from HMH into the development (*n*=317 patients) and validation cohort (*n*=316). One-year survival after transplant was significantly different among risk groups: 95% (low-risk), 84% (medium-risk), and 72% (high-risk) (p<0.001) with a C-statistic of 0.74. Patient survival in the validation cohort was also significantly different among risk groups (85%, 77% and 65%, respectively, p<0.001). Validation of the model with the UNOS dataset included 9,920 patients and found 1-year survival to be 91%, 86% and 82%, respectively (p < 0.001).

CONCLUSIONS: Using only recipient data collected at the time of pre-listing evaluation, our simple scoring system has good discrimination power and can be a practical tool in the assessment and selection of potential lung transplant recipients.

Lung transplantation is the treatment of choice for end-stage lung diseases in carefully selected recipients. While the first human lung transplant was performed in 1963[1], the introduction of cyclosporine in 1983 allowed for improved survival and opened the modern era of organ transplantation. Subsequent advances have included improvements in immunosuppression, organ procurement and preservation techniques, and the introduction of the Lung Allocation Score[2-4]. Post-transplant mortality in lung transplantation remains high[5], with one-, three- and five-year survival rates trailing other solid organ transplants. Oversight of transplant programs involves multiple organizations including the United Network for Organ Sharing (UNOS). Additional oversight by the Centers for Medicare and Medicaid Services (CMS) started in 2007 to ensure that minimum outcome requirements are met[6]. Regulators use data and outcome measures developed by the Scientific Registry of Transplant Recipients (SRTR) risk adjustment model to assess performance of transplant program outcomes in comparison to their expected outcomes. The SRTR model analyzes both recipient and donor factors to assess each patient's risk. Of the 35 variables in this model, 16 are donor-dependent and unknowable at the time of recipient evaluation.

It is widely recognized that meticulous screening and appropriate selection of potential recipients are crucial to favorable outcomes. Unfortunately, little data-driven guidance exists for how to optimize selection, and the International Society for Heart and Lung Transplantation (ISHLT) guidelines rely on institutional experience and expert opinion[7].

We sought to create a data-driven model to assist in the risk stratification of lung transplant candidates using only variables available during the evaluation process prior to listing. Preoperative risk models have been developed for the transplantation of other organs[8,9], and used to correlate comorbidities with outcomes[10-12]. Other models to predict outcomes in lung transplantation exist, but routinely incorporate donor criteria or have not been validated[13-20]. To the best of our knowledge, our risk model is unique in exclusively using preoperative recipient data to predict lung transplant mortality in a validated manner.

PATIENTS AND METHODS

Study population

We queried the UNOS Standard Transplant Analysis and Research (STAR) database for all patients aged 18+ years who underwent lung transplant from January 1, 2009 through December 31, 2014. Patients who were transplanted at Houston Methodist Hospital (HMH) were included. The patients were then randomly assigned by a statistical program into two cohorts at a 1:1 ratio: one for development of the model; one for internal validation. The risk model was developed using data from the development cohort. A final model was created using eight of the preoperative variables. One-year mortality after transplant was used as our primary outcome variable. The performance of the risk model was validated using the validation dataset. The performance of the risk model was then further evaluated and validated using data from all remaining US lung transplant centers.

Statistical analysis

Data were gathered using the 46 variables included in the UNOS STAR database (Appendix 1). We performed univariate analysis on the development cohort. Missing values were treated as missing. Baseline data are reported as median and interquartile range (IQR) for continuous variables, and as frequencies and proportions for categorical variables. Differences in baseline data across groups were compared using the Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

Patient survival was estimated using Kaplan-Meier statistics. Univariate and multivariate Cox proportional-hazards models were used to determine the contribution of potential prognostic variables to the patient outcome. Multivariate Cox proportional-hazards models were fitted using the Bayesian model averaging (BMA) method[21]. In creating the final model from the development cohort, variables requiring donor information were excluded. Risk factors in the final model were assigned weighted points that were proportional to their β regression coefficient values. The risk scores were calculated for each

patient. Patients were divided into 20 subgroups of 5 percentiles of their risk score, and post-transplant mortality at one year were examined in each subgroup. Patients were then consolidated into three risk categories which were statistically significantly distinct in their predictive risk for death at one year: low-risk, medium-risk and high-risk. Median risk for death was calculated for each risk group. Pairwise comparisons of median risk among risk groups were conducted using the Kruskal-Wallis test. The observed and predicted 1-year mortality were depicted using the Stata's *stcoxkm* function. The performance of predictive models and accuracy of the risk score were determined by calculating Harrell's C-statistic and validated in the validation dataset[22]. The performance of our predictive model and the Lung Allocation Score (LAS) were also compared using Stata's "*somersd*" and "*licom*" functions. All analyses were performed on Stata v13.1 (StataCorp, College Station, TX, USA). A *p*-value of <0.05 was considered statistically significant. The study protocol was approved by the institutional review board at the Houston Methodist Research Institute.

RESULTS

From 2009 to 2014, 10,533 patients underwent a lung transplant in the United States. Our institution performed 633 (6.0%). Our patients were randomly assigned to the development (317 patients) and validation (316 patients) cohorts in a 1:1 ratio. The remainder of the UNOS cohort included 9,920 patients (Figure 1). The baseline demographics were not significantly different between development and validation cohorts for virtually all variables (Table 1).

Our primary outcome measure was survival at one year after transplant. We used univariate and multivariate Cox-proportional hazards models to determine the contribution of potential variables to survival. Eight factors were included in the final model: age ≥65 years, diagnosis of restrictive disease (group D), body mass index (BMI) ≥35, diagnosis of diabetes, total serum bilirubin, estimated glomerular filtration rate (GFR) <60, cardiac index, and 6-minute walk distance <400 feet (Table 2). Although mean

pulmonary artery (PA) pressure and mean pulmonary capillary wedge (PCW) pressure were included in the initial multivariate model, they were not significant. The likelihood ratio test comparing the models with and without mean PA and PCW pressure showed no significant difference. Therefore, these two variables were removed from the final model. The variables selected for inclusion in the final model were assigned weighted points proportional to their beta-coefficients (Figure 2). All patients in the development cohort were stratified into low-risk (<7.5 points), medium-risk (7.5 – 18.9 points), and high-risk groups (≥19.0 points), with median risk for death at one year post-transplant calculated for each group.

Within the development cohort, the low-risk group had a survival of 95%, the medium-risk group had a survival of 84%, and the high-risk group had a survival of 72% (Table 3). The risk for death at one year was significantly different among the three groups using pairwise comparisons with the Kruskall-Wallis test (Figure 3). Risk scores and risk stratification were recalculated for patients in the validation cohort, and the mortality at one year after transplant was again found to be significantly different between the low- and high-risk groups, and between the medium- and high-risk groups (85%, 77%, and 65%) (Figure 4). The calculated risk scores within groups were similar between the development and validation cohorts (Table 4). The performance and accuracy of a model can be evaluated using the Harrell's C-statistic, and we found both the development and validation cohorts to be highly predictive and accurate (0.74 and 0.67, respectively).

We then repeated the analysis with the 9,920 patients comprising the remainder of the UNOS cohort. Stratifying the cohort into low-, medium- and high-risk groups again produced statistically significant differences in survival at 1 year (91%, 86%, and 82%, respectively) (Figure 4). We also compared our risk score with the original risk prediction in the LAS system. In the development cohort, our model, which used the Cox proportion hazard modeling with only eight variables for the final scoring system, had a C-statistic of 0.74 (95% CI 0.66, 0.81), while the LAS (using 17 covariates) at listing and LAS at transplant had a C-statistic of 0.58 (95% CI 0.49, 0.68; p=0.002) and 0.63 (95% CI 0.55, 0.72; p=0.022),

respectively. In the validation cohort, our model had a C-statistic of 0.67 (95% CI 0.59, 0.72), while the LAS at listing and LAS at transplant had a C-statistic of 0.58 (95% CI 0.50, 0.66; p=0.07) and 0.55 (95% CI 0.47, 0.63; p=0.017), respectively (data not shown). The distributions of weight score of individual variables used in the final model were stratified by risk group and are presented in Supplemental Table S1. Recipient and donor characteristics of patients who died within the first year after a lung transplantation are presented in Supplemental Table S2. Although our model was developed to predict the 1-year mortality, the model still has good C-statistic in predicting 2-year and 5-year mortality with a C-statistic of 0.70 for both 2-year and 5-year survival analyses. Meanwhile, the similar C-statistic in predicting 2-year and 5-year mortality of the LAS was 0.62 (p=0.06) and 0.60 (p=0.01), respectively (data not shown).

Risk score calculator mobile application

We have created a free mobile application for our risk score calculator
<https://oaa.app.link/ZDtVwwekWN > which is compatible with both iOS and Android mobile platforms (free registration OpenAsApp is required to access the calculator). The application provides a calculated risk score (in points) and risk group (low, medium, or high) for easily accessible use. The results can be printed to a .pdf file.

COMMENT

In this analysis, we developed and validated a simple prognostic scoring system using eight demographic and clinical characteristics which are routinely available at the time of pre-listing evaluation. This scoring model is straightforward to use and has good discrimination power in both development and validation. With the availability of the simple mobile application, the scoring system can be an easy and practical adjunct for transplant physicians in the evaluation of lung transplant candidates. Using the model to

stratify patients into three distinct risk groups, clinicians will be able to quickly identify patients who have the highest potential risk of post-transplant mortality, allowing these patients to be further assessed, optimized, or rejected for listing. Our study of 10,553 lung transplant patients demonstrates a strong relationship between the Houston Methodist lung transplant risk model and recipient outcomes, with higher-risk groups corresponding to statistically significant increases in one-year mortality. We validated our findings internally by applying the model to a randomized validation cohort, as well as nationally using the UNOS database. Among the variables used in our predictive model, restrictive disease, eGFR<60 and six-minute walk distance <400 feet were more likely responsible for having higher risk score in high-risk patients. These risk factors were found in a significantly higher proportion in high-risk patients, especially those patients who died within one year after transplant.

Appropriate selection of transplant recipients requires thorough and comprehensive evaluation by a multidisciplinary group of specialists. While myriad potential comorbidities exist, we created our model starting with all the variables available in the UNOS STAR dataset and narrowing them down to eight variables that are clinically and statistically significant, as well as routinely evaluated as part of the pre-transplant workup. By calculating their risk scores, patients can be placed in distinct categories according to their risk for one-year mortality after transplant. These low-, medium- and high-risk groups have statistically significantly different survival when tested in the development and the UNOS cohorts. When applied to the validation cohort, we found significant differences in mortality between the low- and high-risk groups, as well as between the medium- and high-risk groups, but not between the low- and medium-risk groups. This reinforces the intended utility of the model to allow effective identification of patients who may be too risky for transplant prior to listing.

Pre-transplant risk factors and their effect on outcomes have been extensively described. While other papers have explored similar ideas in solid organ transplantation[23-26], our Houston Methodist Hospital Lung Transplant Risk Model is unique in its ability to create a risk stratification tool to predict post-transplant outcomes for lung transplant recipients based entirely on pre-transplant recipient data. By not

depending on donor factors, our model provides additional data that can be used to evaluate pre-transplant patients during the Medical Review Board (MRB) discussion. The standard-of-care for risk assessment has been set by the SRTR using a model that depends heavily on donor factors. Our model has a C-statistic of 0.74, which compares favorably with the SRTR model (C-statistic of 0.6326[27]).

Current guidelines for evaluation of potential lung transplant recipients rely on expert opinion and anecdotal evidence, leaving individual centers to employ divergent and subjective methods for determining selection criteria. The original LAS derived rational and data-driven risks for pre-transplant risk assessment of both pre-transplant mortality and post-transplant mortality. However, since its initial derivation, the indices have not been validated in the current era of newer therapies, current immunosuppression, and surgical approaches[28]. Additionally, the head-to-head comparison of the LAS and our predictive model suggested that our model has better discrimination power. It was our goal in designing the Houston Methodist Lung Transplant Risk Model that we would create a data-driven tool that could produce objective data for use in evaluating these complex patients. We now employ the model as one of many components in our lung transplantation selection and listing process. Although the model serves as a useful adjunctive tool during our MRB discussions, the model is not the final determinant of listing. Additional validation and calibration, with the addition of more variables, would be needed to apply the model to predicting mortality during listing.

Our study had several limitations, some of which were inherent to studies that rely on retrospective data. First, the data used in this study were extracted from the UNOS database, where only certain pre-transplant risk factors are available. By starting with all available variables and data, we have chosen the covariates which best predicted one-year survival post-transplant. The Bayesian Model Averaging (BMA) method, a well validated tool for model-building, was used to avoid the pitfalls of stepwise regression. Although restrictive disease, BMI ≥ 35, diabetes, and cardiac index were not significant in our final model, these variables also included in the scoring system as these variables were identified by previous studies as potential risk factors for worse outcomes after lung transplantation[19,29-31] Second,

although we performed 633 lung transplants at Houston Methodist over this six-year period, our development cohort of 317 patients is relatively small for modeling purposes. Third, the modeling, by design, excludes donor selection criteria which can have profound impact on outcome. While we may be able to achieve greater statistical significance with the inclusion of donor data, our goal was to develop and create a robust model that can help transplant physicians in the selection of patients for listing, prior to the availability of the donor data. Our model, however, has a good predictive performance and retains statistical significance when validated against a national cohort. Fourth, center-specific factors may skew the weight of individual variables in a model based on our center's outcomes. While this model was created based only on our center's patients, the validation of the model against the UNOS cohort of nearly 10,000 patients argues for its generalizability. Additionally, as with most retrospective database analyses, missing values and classification errors may affect the quality of the data upon which our model is based. Finally, although the risk groups were statistically significantly different in their risk of one-year mortality in the development and UNOS cohorts, there was not a statistically significant difference between the low- and medium-risk groups in the validation cohort. This finding may suggest that our model may be most useful in distinguishing high-risk patients from low- and medium- risk patients.

One potential future application of this model is in the optimization of patients considered to be high-risk at the time of initial evaluation. While some risk factors are non-modifiable (age, restrictive disease), other risk factors could be considered modifiable (BMI, six-minute walk distance, cardiac index) and may be improved preoperatively to mitigate a recipient's risk factors prior to listing. Programs of pulmonary rehab, cardiology evaluation and intervention, and nutritional counseling can be employed to improve the risk score and potentially allow patients to proceed more safely to transplant. Prospective analyses will help in evaluating the application of this tool.

Conclusion

We have developed the Houston Methodist Lung Transplant Risk Model, a validated tool for preoperative risk stratification based entirely on recipient factors that are readily available at the time of initial evaluation for listing. Scores that differentiate recipients into low-, medium- and high-risk groups are strongly predictive of significant differences in survival at one year after lung transplant, with consistent results when applied to a nation-wide cohort reported to the UNOS database. Our model has excellent predictive performance, and may be most useful in identifying high-risk recipients who may face increased chances of morbidity and mortality after transplant. The model includes modifiable factors that could potentially assist the transplant team in optimizing patients for listing. We hope that our model will offer a simple, practical, and widely applicable tool for lung transplant teams to use in their screening of potential recipients.

Figure Legends

Figure 1: Flow Diagram of the Study

Figure 2: Risk score formula

Figure 3: Kaplan–Meier survival curves stratified by risk group in the development cohort

Figure 4: Kaplan–Meier survival curves stratified by risk group in the validation cohort

Figure 5: Kaplan–Meier survival curves stratified by risk group in US centers other than Houston Methodist Hospital

Supplemental Table 1: Distribution of weight score of individual variables used in the final model

Supplemental Table 2: Recipient and donor characteristics of patients who died within the first year after lung transplantation

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Table 1. Baseline characteristics

	Total		Development		Validation		p-value*
	n	%	n	%	n	%	
RECIPIENT	**633**	**100.0%**	**317**	**50.1%**	**316**	**49.9%**	
Age (years), median (IQR)	61	(52, 67)	61	(53, 67)	61	(51, 67)	0.637
Female Gender	373	58.9%	189	59.6%	184	58.2%	0.722
Restrictive disease	409	64.6%	197	62.2%	212	37.1%	0.193
LAS (continuous)	38.3	(34.3, 47.1)	37.9	(33.7, 45.5)	38.6	(24.8, 48.7)	**0.044**
Transplant type:							0.845
Double	361	57.0%	182	57.4%	179	56.7%	
BMI	26	(22.1, 29.8)	26	(21.9, 29.6)	26	(22.4, 30.0)	0.813
Re-transplant	55	8.7%	28	8.8%	27	8.5%	0.897
Smoking	372	59.0%	191	60.3%	181	57.6%	0.505
Diabetes	160	25.9%	62	20.4%	98	31.3%	**0.002**
Chronic steroid	376	59.7%	188	59.7%	188	59.7%	1.000
Creatinine, median (IQR)	0.8	(0.7, 1.0)	0.8	(0.7, 1.0)	0.8	(.7, 1.0)	0.056
Total bilirubin, median (IQR)	0.50	(0.3, 0.6)	0.50	(0.3, 0.6)	0.50	(0.3, 0.6)	0.985
O2 required at TX	4	(3, 6)	4	(3, 6)	4	(3, 6)	0.305
FEV1 at TX (%)	38	(25, 57)	36	(24, 55)	41	(26, 59)	0.181
Mean PA pressure at listing (mmHg), median (IQR)	24	(19, 32)	24	(19, 30)	24	(20, 33)	0.490
Cardiac index at listing, median (IQR)	3.0	(2.6, 3.5)	3.0	(2.6, 3.5)	3.0	(2.6, 3.5)	0.974
6mn walk distance (feet), median (IQR)	723	(379, 1025)	700	(350, 1002)	741	(400, 1050)	0.373
eGFR (mL/min/1.73m2)	93.7	(76.5, 104.9)	92.9	(72.8, 104.8)	94.3	(79.4, 105.5)	0.166
DONOR							
Donor age <50	592	93.5%	296	93.4%	296	93.7%	0.880
Donor BMI <30	499	79.1%	247	77.9%	252	80.3%	0.471
Donor smoking	92	14.7%	44	14.1%	48	15.2%	0.700
Donor diabetes	63	10.0%	39	12.3%	24	7.6%	**0.048**

*Comparison across groups (development vs. validation) using Chi-square or Fisher's

exact tests for categorical variables and
Kruskal Wallis test for
continuous test as appropriate

Table 2. Cox proportional hazards model and weighted point assignment in the development cohort

Variable	β coefficient	HR	p	95% CI		Weighted Points
Age ≥65	**0.74**	**2.10**	**0.022**	**1.11**	**3.95**	7.4
Restrictive disease	0.42	1.52	0.302	0.69	3.36	4.2
BMI ≥35	0.47	1.60	0.441	0.48	5.28	4.7
Diabetes	0.39	1.47	0.275	0.74	2.95	3.9
Total serum bilirubin	**0.78**	**2.18**	**<0.001**	**1.54**	**3.10**	7.8
Estimated GFR<60	**1.18**	**3.26**	**0.001**	**1.58**	**6.69**	11.8
Cardiac index	-0.01	0.99	0.982	0.64	1.55	-0.1
Six minute walk <400 ft	**1.03**	**2.81**	**0.002**	**1.44**	**5.46**	10.3

Note: Weighted points of a risk factor are calculated using a linear transformation of the corresponding β coefficient [multiplied the β coefficient by a constant (10)].

Table 3. Survival at 1 year post-transplant, by risk group

Risk group	Development (N=317)		Validation (N=316)	
	n (%)	Survival	n (%)	Survival
Low-risk group (<7.5 points)	65 (20.5)	95%	58 (18.4)	85%
Medium-risk group (7.5-18.9 points)	138 (43.5)	84%	154 (48.7)	77%
High-risk group (≥19.0 points)	114 (36.0)	72%	104 (32.9)	65%

Table 4. Median risk score by risk group

Risk group	Development cohort (N=317)		Validation cohort (N=316)		p-value*
	n (%)	Median risk score (95% CI)	n (%)	Median risk score (95% CI)	
Low-risk group (<7.5 points)	65 (20.5)	4.0 (4.0, 6.0)	58 (18.4)	4.0 (3.1, 5.0)	0.595
Medium-risk group (7.5-18.9 points)	138 (43.5)	12.0 (11.0, 13.0)	154 (48.7)	13.0 (12.0, 14.0)	0.420
High-risk group (≥19.0 points)	114 (36.0)	23.5 (22.0, 26.0)	104 (32.9)	25.0 (23.0, 27.0)	0.330

*Comparison across groups (development vs. validation) using Kruskal Wallis test

```
            ┌─────────────────────────────────────┐
            │  10,533 lung transplants from 2009-2014  │
            └─────────────────────────────────────┘
                    │                    │
                    ▼                    ▼
    ┌──────────────────────────┐   ┌──────────────────────────────┐
    │ 633 performed at Houston Methodist │   │ 9,920 performed at all other centers │
    └──────────────────────────┘   └──────────────────────────────┘
            │
            ▼
  ┌──────────────────────┐   ┌──────────────────────┐
  │ 317 in development cohort │   │ 316 in validation cohort │
  └──────────────────────┘   └──────────────────────┘
```
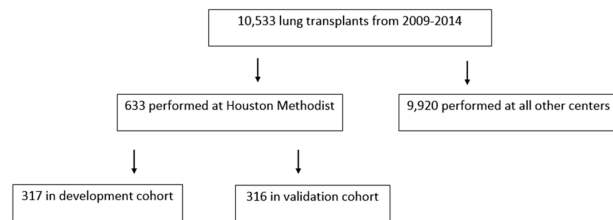
```
      7.4 x    (Age ≥65*)              *Yes=1, No=0
+     4.2 x    (Restrictive disease*)
+     4.7 x    (BMI ≥35*)
+     3.9 x    (Diabetes*)
+     7.8 x    (Total serum bilirubin)
+     11.8 x   (eGFR<60*)
-     0.1 x    (Cardiac index)
+     10.3 x   (6 min walk<400ft*)
-------------------------------------------------------------
=     Risk Score
```

Low risk	< 7.5 points
Medium risk	7.5 – 18.9 points
High risk	≥19.0 points

Log-rank test:
Low-risk group vs. medium-risk group: p=0.24
Low-risk group vs. high-risk group: p=0.01
Medium-risk group vs. high-risk group: p=0.048