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Lung Transplantation Advanced Prediction Tool: Determining Recipient's Outcome for a Certain Donor

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Background. Many risk-prediction models for lung transplantation are centered on recipient characteristics and do not account for impact of donor and transplant-related factors or only examine short-term outcomes (eg, predicted 1-y survival). We sought to develop a comprehensive model guiding recipient-donor matching. **Methods.** We identified double lung transplant recipients (≥12 y old) in the United Network for Organ Sharing Registry (2005–2020) to develop a risk scoring tool. Cohort was divided into derivation and validation sets. A total of 42 recipient, donor, and transplant factors were included in the analysis. Lasso method was used for variable selection. Survival was estimated using Cox-proportional hazard models. An interactive web-based tool was developed for clinical use. **Results.** A derivation cohort (n = 10660) informed the model with 13-recipient, 4-donor, and 2-transplant variables. Adjusted risk scores were computed for every transplant and grouped into 3 clusters. Model-estimated survival probabilities were similar to the observed in the validation cohort (n = 4464) for all clusters. The mortality increases for medium- and high-risk groups was similar in both derivation and validation cohorts (C statistics for 1-, 5-, and 10-y survival were 0.67, 0.64, and 0.72, respectively). The web-based application estimated 1-, 5-, 10-y survival and half-life for low- (92%, 73%, 52%; 10.5 y), medium- (89%, 62%, 38%; 7.3 y), and high-risk clusters (85%, 52%, 26%; 5.2 y). **Conclusions.** Advanced methods incorporating machine/deep learning led to a risk scoring model (including recipient, donor, and transplant factors) and a web-based clinical tool providing short- and long-term survival probabilities for recipient-donor matches. This will enable risk-based matching that could improve utilization of and benefit from a limited donor pool.

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Lung transplantation (LTx) faces a suboptimal organ allocation scheme, with long waiting times and high waiting list mortality for transplant candidates. Although the lung allocation score (LAS) stratifies recipient risk and contributes to lowering waiting time, mortality remains 15% for adult and 22% for pediatric patients awaiting LTx.[1] On the other hand, only 20% of all multiorgan donors are utilized for LTx in the United States, compared with 50% in European countries.[2,3] An important factor contributing to the apparent shortage of organs in the United States is the usage of nonstandardized and often stringent donor selection criteria: Over 15 different characteristics that vary between centers are considered while selecting donors.[4]

The role of each of these characteristics and their combined effect is largely unknown. Other solid organ transplant groups have successfully devised comprehensive donor risk stratification systems based on the combined impact of these characteristics to standardize their matching process.[5] For example, the kidney donor profile index, adapted by the United Network for Organ Sharing (UNOS) in 2014, resulted in increased utilization of organs, and

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increased transplant rates for the most difficult-to-match patients, reaching up to 6-fold in some cases, with better or at least similar early graft survival.[6-9] There is a need for a similar tool to quantify the risk for LTx and allow better and more standardized recipient-donor matching.

There is increasing evidence from the LTx community, and from other solid organ transplantation, that high-risk donors can be matched to certain recipients without compromising outcomes while increasing organ utilization rate. However, this does not hold true for all cohorts of recipients.[10-16] An allocation system based on recipient, donor, and transplant characteristics rather than just recipient characteristics may optimize both clinical outcomes and organ utilization nonetheless. A recently introduced mortality after lung transplantation score does incorporate both donor and recipient factors and improves upon other risk scores but is limited by use of short-term survival.[17]

Our aim is to take initial steps to developing a LTx allocation system that focuses on increasing utilization but also the number of years alive with a transplant for the whole community maximize benefit from a limited donor pool. We took advantage of new statistical methodologies and the incorporation of machine and deep learning into prediction models to develop an objective risk scoring model that includes recipient, donor, and transplant factors. For demonstrating an wider applicability of the proposed risk scoring model, a web-based clinical tool that can predict the median survival time and the 1-, 5-, and 10-y survival probabilites of possible recipient-donor matches was also developed.

MATERIALS AND METHODS

All UNOS patients who received a double LTx between January 2005 and March 2020 and were aged ≥12 y at transplant were eligible for analysis. This age cutoff was used because a similar allocation system and LAS are applicable to candidates ≥12 y. Patients who received retransplantations, those who had other solid organ transplant simultaneously or had missing posttransplant survival status were excluded. Details of how the recipient, donor, and transplant variables were selected, and the methods to assign a risk score are provided in the Supplement (**SDC**, http://links.lww.com/TP/C396).

The categories for the variables were formed using prior published work (age and estimated glomerular filtration rate [eGFR]) and clinical relevant cutoffs (Karnofsky Performance Status and eGFR). Missing data were imputed for records with only a single missing data point, whereas records with multiple missing data points were excluded. Imputation of missing data for recipient and donor variables was conducted separately using the recipient and donor characteristics, respectively, assuming that the data was missing at random, that is, that data missingness can be fully explained by the observed information.[18] The Supplement (**SDC**, http://links.lww.com/TP/C396) contains the illustration of the imputation methods. The survival distributions for the included and not included recipients in the study were examined to ensure that both groups had similar patterns.

Once the adjusted total risk scores were derived, our goal was to group the total score vector into distinct clusters with homogeneous survival risks. Using the expectation-maximization clustering algorithm, total scores were grouped into 3 groups: low, medium, and high risk.[19] The optimum number of clusters was determined using the Silhouette score. For each recipient-donor match, we computed the probability of belonging to each cluster and assigned the recipient-donor match to the cluster with the largest probability.

We calculated model-based short-, medium-, and long-term survival probabilities and their 95% confidence interval (CI) for each risk group in the validation cohort data and compared them with the observed percentages. We also compared the derivation and validation cohorts by examining the Kaplan-Meier (KM) survival curves of each risk group and by computing the hazard ratios between risk groups. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.5.0 (R Core Team, 2018). The glmnet (V2. 0-18), an R package was used to perform the variable selection analyses. Institutional Review Board was obtained, and patient consent was waived.

According to algorithms discussed above, a web-based tool was designed to make predictions on long-term (1, 5, and 10 y) survival probabilities and half-life for any given recipient-donor match. The goal was to provide a tool to make an informed decision for the recipients at the time of transplant.

RESULTS

A total of 19 263 eligible double LTxs were performed in the study period, and 15 124 were included in the analysis. Cohort selection is detailed in Figure 1. Details on missing data and imputation results are presented in the Supplement (**SDC**; http://links.lww.com/TP/C396).

The study cohort was randomly subdivided into a derivation cohort of 10 660 (70%) cases and a validation cohort of 4464 (30%). Continuous recipient, donor, and transplant data for the derivation and validation cohorts were summarized as median with interquartile range (IQR) and discrete data as percentage with frequency. Nonparametric tests (Mann-Whitney *U* test) were used for testing the difference between 2 medians, and χ^2 test for testing differences between 2 proportions. The comparison between derivation and validation cohorts for each of the recipient, donor, and transplant characteristics is presented in Table 1.

All recipient, donor, and transplant variables with categorical levels reported in Table 1 are included in 3 competing models: Cox-Lasso regression model, Cox regression with backward elimination, and random forest Cox. The optimal lambda (0.011) in Cox-Lasso was within the range of minimum mean crossvalidated error and 1 SE of the minimum and assigned to a value to ensure a balance between model over-fitting and simplicity. We observed less predictive ability with the validation cohort of the other 2 methods, Cox regression with backward elimination and random forest Cox, compared with Cox-Lasso. Specifically, we observed that the 95% CI for the survival probability for the medium- and high-risk groups was overlapping using the other 2 methods. In **Table S1** (**SDC**, http://links.lww.com/TP/C396), we provide the list of variables selected by each of these methods. Overall, the Cox-Lasso provided a more clinically interpretable list of

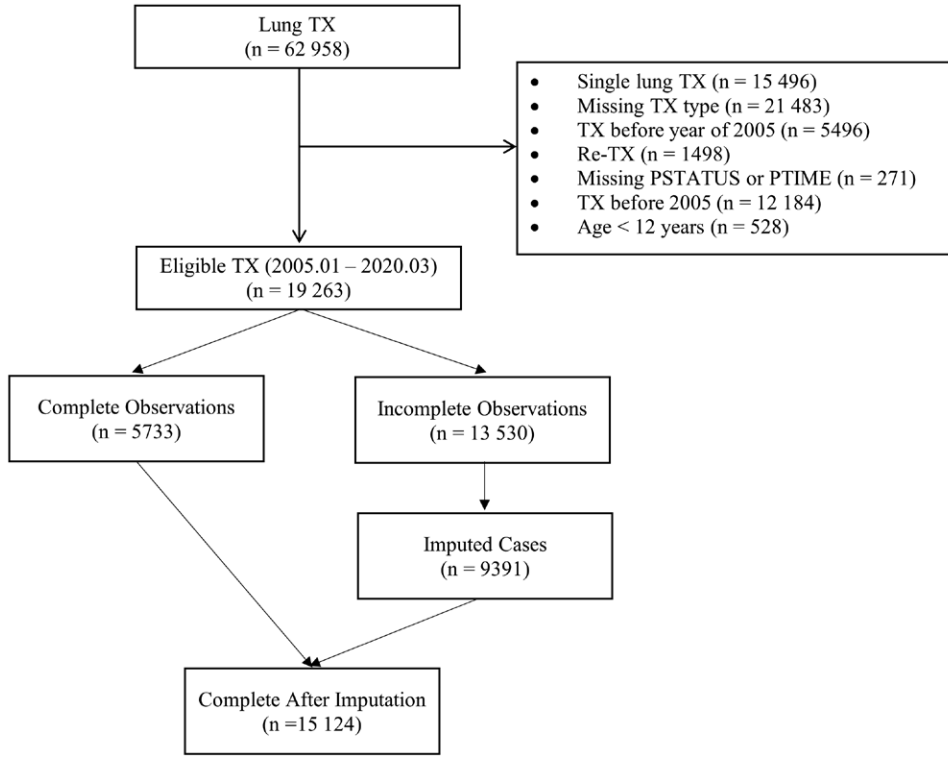

FIGURE 1. Flow diagram on final cohort selection. PSTATUS, patient status; PTIME, patient time, referring to post transplant survival status and time; TX, transplantation.

variables. The variables included in the model were divided into recipient-, donor-, and transplant-specific variables. The recipient variables were age, race, body mass index, initial and end LAS, diagnosis, Karnofsky Performance Status, eGFR, albumin, tobacco, steroid, extracorporeal mechanical oxygenation (ECMO), and ventilator. The donor variables were age, race, tobacco, and diabetes, and the transplant-related variables included cytomegalovirus mismatch and ischemia time (6 h). The regression coefficient estimates of all these variables with 95% CIs are reported in Table 2.

Model Validation

Given the covariate levels of each recipient, the adjusted total risk score was computed for every recipient and Figure 2A shows its density plot. The median of the adjusted total score was 42 (IQR, 31–55). The median survival time with 95% CI for each adjusted total risk score using the Cox regression model is plotted in Figure 2B. We also examined the model's prediction ability by using the adjusted total risk score for short-, medium-, and long-term survival. The C statistics for the mortality of 1, 5, and 10 y were 0.67, 0.64, and 0.72, respectively. These values were acquired from logistic regression models wherein binary indicators were used for 1-, 5-, and 10-y mortality as outcomes and adjusted total risk score as the only covariate.

The adjusted total scores were grouped into 3 clusters by using the expectation-maximization algorithm (Figure 3). The median (IQR) of the adjusted total score was 15 (10–19) in the low-risk cluster, 39 (33–44) in the medium-risk cluster, and 61 (56–68) in the high-risk cluster. The distribution of cases by risk group was very similar for derivation and validation cohorts (Table 3). The observed survival rates by risk group in the validation cohort were within the model estimated 95% CIs, indicating that the model fit was good. The only exception was for 1-y survival in the high-risk group. For each risk group, the KM survival curves from the derivation cohort with 95% CIs (solid line with shaded area in Figure 4) and from the validation cohort (dotted line with shaded area in Figure 4) indicated that good validation criteria were met. The *P* values from the log rank tests for the similarity of 2 KM curves in low-, medium-, and high-risk groups are 0.42, 0.98, and 0.78, respectively. Again, the similarities in hazard ratio estimates between derivation and validation cohorts (Table 3 and Figure 5A and B) provide evidence in support of the Cox-Lasso model.

To make this Lung Transplantation Advanced Prediction Tool (LAPT) readily available for clinicians, a webpage was developed in Hypertext Markup Language with LAPT presented in the form of a simple calculator (link: https://lungscore.research.cchmc.org/96b53228-f7b6-4cb0-bbdf-59bf733d7056). Users can enter recipient, donor, and transplant information to learn the predicted 1-, 5-, 10- y survival, risk classification and associated survival and half-life prediction, an example highlighted in Figures 6 and 7.

DISCUSSION

Presently, the lung allocation system is recipient centric depending mainly on the LAS score, which is derived from recipient characteristics. Matches are made based on LAS and on individual programs' perception of how different donor and transplant characteristics may or may not affect their patient's outcome. However, a complimentary tool developed using machine learning algorithms (MLAs)

TABLE 1.

Comparison of recipient, donor, and transplant characteristics by derivation and validation cohorts using the recipient, donor, and transplant characteristics available in UNOS national data set

Characteristic table of validation and derivation cohorts			
Characteristics type/measures	**Validation**	**Derivation**	***P*[a]**
Recipient characteristics			
Age median, y	57 [46–63]	57 [45–63]	0.5284
Age groups			0.0509
12–29	10.7% (478)	11.4% (1215)	
30–49	19.6% (876)	19.8% (2112)	
50–59	30.1% (1343)	27.7% (2953)	
60–64	20.0% (893)	20.7% (2209)	
≥65	19.6% (874)	20.4% (2171)	
Sex			0.1377
Female	41.4% (1847)	42.7% (4550)	
Male	58.6% (2617)	57.3% (6110)	
Race/ethnicity			0.9404
White	79.7% (3557)	79.5% (8470)	
Black	10.3% (462)	10.4% (1106)	
Hispanic	7.3% (327)	7.6% (810)	
Other	2.6% (118)	2.6% (274)	
Body mass index, kg/m^2	25.3 [21.2–28.7]	25.0 [21.1–28.6]	0.0624
Diagnosis			0.3287
Obstructive lung disease	28.2% (1259)	28.5% (3034)	
Pulmonary vascular disease	4.9% (217)	5.1% (544)	
Cystic fibrosis	16.3% (729)	17.3% (1842)	
Restrictive lung disease	50.6% (2259)	49.2% (5240)	
Initial LAS	37.3 [33.6–44.8]	37.1 [33.6–44.5]	0.8107
End LAS	41.6 [35.3–55.2]	41.1 [35.3–55.5]	0.8387
Functional status (KPS)			0.6286
<30	15.2% (678)	14.9% (1592)	
30–59	42.4% (1893)	43.3% (4611)	
≥60	42.4% (1893)	41.8% (4457)	
eGFR, mL/min/1.73 m^2	101 [81–126]	101 [80–126]	0.6204
Albumin, g/dL	3.90 [3.50–4.30]	3.90 [3.50–4.30]	0.2174
Tobacco use			0.3375
No	45.2% (2016)	46.0% (4905)	
Yes	54.8% (2448)	54.0% (5755)	
Recent infection			0.5090
No	86.0% (3840)	85.6% (9126)	
Yes	14.0% (624)	14.4% (1534)	
Steroid use			0.3542
No	55.3% (2468)	56.1% (5981)	
Yes	44.7% (1996)	43.9% (4679)	
ECMO pretransplant			0.4078
No	94.6% (4222)	94.9% (10 117)	
Yes	5.4% (242)	5.1% (543)	
Ventilation pretransplant			0.4287
No	93.6% (4179)	93.3% (9942)	
Yes	6.4% (285)	6.7% (718)	
CMV			0.5739
Negative	45.9% (2047)	45.4% (4835)	
Positive	54.1% (2417)	54.6% (5825)	
Donor characteristics			
Age median, y	32 [22–46]	32 [22–46]	0.6643
Age groups			0.6811
<50	80.7% (3604)	81.0% (8637)	
≥50	19.3% (860)	19.0% (2023)	
Sex			0.4475
Female	40.1% (1789)	40.7% (4343)	
Male	59.9% (2675)	59.3% (6317)	
Race/ethnicity			0.0266
Other	82.5% (3685)	81.0% (8636)	
Black	17.5% (779)	19.0% (2024)	

Continued next page

TABLE 1. (Continued)

Characteristic table of validation and derivation cohorts

Characteristics type/measures	Validation	Derivation	P[a]
Body mass index, kg/m^2	25.2 [22.3–29.0]	25.3 [22.4–29.0]	0.7808
Tobacco use			0.7566
No	92.0% (4106)	92.1% (9821)	
Yes	8.0% (358)	7.9% (839)	
Hypertension			0.5446
No	76.8% (3430)	76.4% (8142)	
Yes	23.2% (1034)	23.6% (2518)	
Diabetes			0.2819
No	93.1% (4155)	92.6% (9869)	
Yes	6.9% (309)	7.4% (791)	
Bronchoscopy abnormal			0.5901
No	73.0% (3257)	73.4% (7823)	
Yes	27.0% (1207)	26.6% (2837)	
Chest X-ray abnormal			0.2028
No	41.1% (1834)	42.2% (4499)	
Yes	58.9% (2630)	57.8% (6161)	
HIV			0.7476
No	82.4% (3680)	82.7% (8811)	
Yes	17.6% (784)	17.3% (1849)	
Recent infection			0.6463
No	31.1% (1388)	31.5% (3355)	
Yes	68.9% (3076)	68.5% (7305)	
Pa_{O_2}/FiO2 ratio			0.4060
<200	1.4% (64)	1.4% (150)	
200–299	6.7% (301)	6.7% (713)	
300–399	25.6% (1143)	26.9% (2872)	
≥400	66.2% (2956)	65.0% (6925)	
PEEP			0.3321
≤5	81.1% (3620)	81.8% (8716)	
>5	18.9% (844)	18.2% (1944)	
Adjusted tidal volume			0.7469
≤8	26.9% (1199)	27.0% (2875)	
8–12	65.5% (2922)	65.7% (7004)	
>12	7.7% (343)	7.3% (781)	
Arterial blood pH	7.42 [7.38–7.46]	7.42 [7.38–7.46]	0.0476
Arterial blood $-HCO_3$	23.8 [21.5–26.2]	23.7 [21.2–26.3]	0.2028
Deceased donor cause of death			0.9791
Other	67.8% (3025)	67.8% (7226)	
Cerebrovascular/stroke	32.2% (1439)	32.2% (3434)	
Circumstance of death			0.6812
Other	82.7% (3690)	82.4% (8782)	
MVA	17.3% (774)	17.6% (1878)	
Mechanism of death			0.5583
Other	67.3% (3006)	66.8% (7126)	
Intracranial hemorrhage/stroke	32.7% (1458)	33.2% (3534)	
CMV			0.6287
Negative	37.6% (1679)	37.2% (3965)	
Positive	62.4% (2785)	62.8% (6695)	
Transplantation characteristics			
Ischemic time median, h	5.48 [4.55, 6.52]	5.48 [4.53, 6.52]	0.7511
Ischemic time groups			0.9940
<6 h	63.3% (2824)	63.3% (6743)	
≥6 h	36.7% (1640)	36.7% (3917)	

[a]Continuous data were compared using Wilcoxon rank-sum test and were reported as median [interquartile range]. Categorical variables were compared using χ^2 analysis and are reported as % (n).
CMV, cytomegalovirus; ECMO, extracorporeal mechanical oxygenation; eGFR, estimated glomerular filtration rate; KPS, Karnofsky Performance Status; LAS, lung allocation score; MVA, motor vehicle accident; PEEP, positive end-expiratory pressure; UNOS, United Network for Organ Sharing.

that matches recipient and donor, based on their respective risk factors, and includes transplant-related factors to optimize the best pairing is not far-reaching. In fact, the use of machine learning compared with other methods, is more effective and efficient at detecting hidden patterns in large data sets.[20] MLAs are being used in other solid organ transplants. A new allocation system for kidney transplant was proposed, with different combination of variables

TABLE 2.

Estimation of regression coefficients with 95% CIs from the Cox-Lasso regression using derivation cohort

Lung TX				
Cox-Lasso				
			95% CI	
Variable names	Labels	Coefficients	Lower	Upper
Recipient variables				
Age, y	12–30	0		
	30–50	−0.2817	−0.3537	−0.2275
	50–60	−0.1037	−0.1764	−0.0773
	60–65	0		
	≥65	0.1811	0.1798	0.3008
Race	White	0		
	Black	0.0150	0.0093	0.1913
	Hispanic	0		
	Other	0		
BMI, kg/m^2	<18.5	0		
	18.5–30	−0.0874	−0.2185	−0.0526
	≥30	0		
Diagnosis groups	Obstructive pulmonary disease	0		
	Pulmonary vascular disease	0.0108	0.0178	0.2821
	Cystic fibrosis	−0.0254	−0.1921	−0.0044
	Restrictive pulmonary disease	0		
LAS	<50	0		
	50–75	0.0348	−0.0074	0.1781
	≥75	0		
End LAS	<50	0		
	50–75	0		
	≥75	0.0179	−0.0487	0.1341
KPS	<30	0		
	30–60	0		
	≥60	−0.0654	−0.2152	−0.0408
eGFR, mL/min	≤50	0		
	<50	0.1726	0.1092	0.4406
Albumin, g/dL	<3.4	0		
	≥3.4	−0.0350	−0.1921	−0.0143
Tobacco use	Yes	0.0305	0.0197	0.1552
Steroid	Yes	0.0105	0.0029	0.1036
ECMO pretransplant	Yes	0.0148	−0.0358	0.2377
Ventilator pretransplant	Yes	0.0660	−0.0311	0.2106
Donor variables				
Age, y	<50	0		
	≥50	0.0778	0.0261	0.1837
Race	Other	0		
	Black	0.0378	0.0229	0.1746
Tobacco use	Yes	0.0289	0.0166	0.2057
	No	0		
Diabetes	Yes	0.0053	0.0018	0.1958
	No	0		
TX variables				
CMV mismatch	Yes	0.0316	0.0270	0.1356
	No	0		
Ischemia time	<6	0		
	≥6	0.0506	0.0303	0.1444

BMI, body mass index; CI, confidence interval; CMV, cytomegalovirus; ECMO, extracorporeal mechanical oxygenation; eGFR, estimated glomerular filtration rate; KPS, Karnofsky Performance Status; LAS, lung allocation score; TX, transplantation.

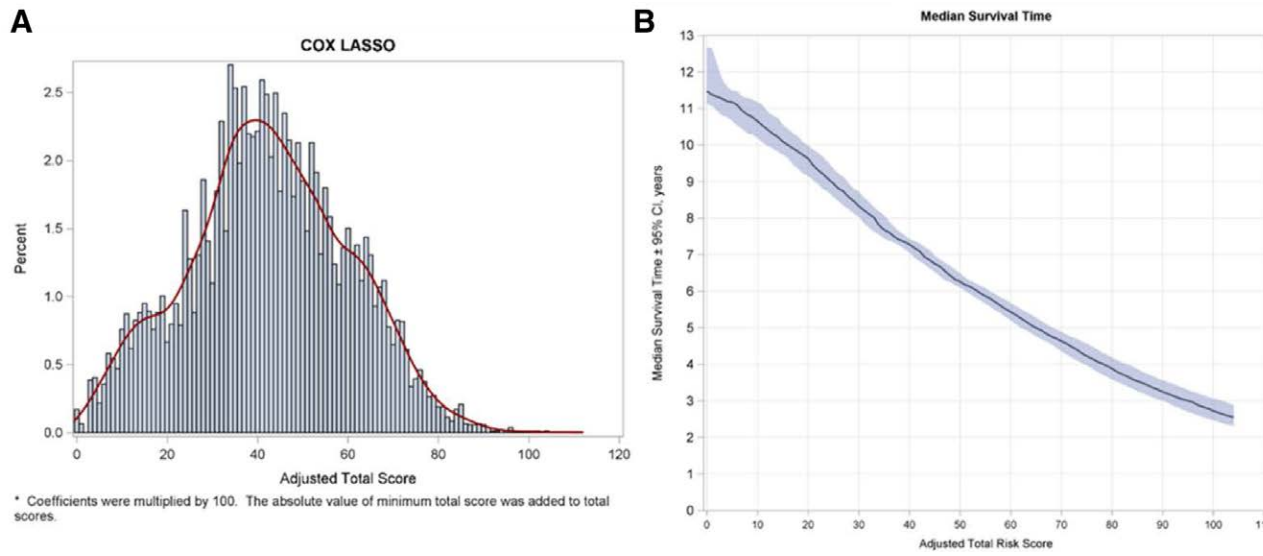

FIGURE 2. Adjusted total scores from Cox-Lasso model using the derivation cohort. A, Distribution of adjusted total score. B, Median survival time with 95% confidence interval (CI) for each adjusted total risk score using the Cox regression model.

used for 2 separate age groupings based on coefficients from an ensemble of statistical methods, including the Lasso models.[21] MLAs were also used in the liver transplantation field in an Australian study predicting early graft rejection.[22] Another study reported that the compilation of liver recipient and donor factors provided better 3-mo prediction of graft survival compared with using isolated donor and recipient factors for matching.[23]

In the LTx field, MLAs are still not widely utilized, and LAS continues to be the main factor used to determine transplant urgency. Nevertheless, majority of patients listed for LTx fall under a narrow range of LAS values, with only 17% having a score greater than 50 in 2018.[24] Therefore, using LAS alone does not account for the heterogeneity of recipients. Furthermore, donor factors should be accounted for, and some clinicians have proposed matching based on donor and recipient factors, employing beyond the usual donor factors of ABO and height compatibility. Evidence supporting matching on age has been reported that corroborate our finding of age as a major influence on both donor and recipient scores.[25,26] Subsequently, Hall et al concluded that although donor-to-recipient age matching was not an independent risk factor, it should still be included when considering the totality of

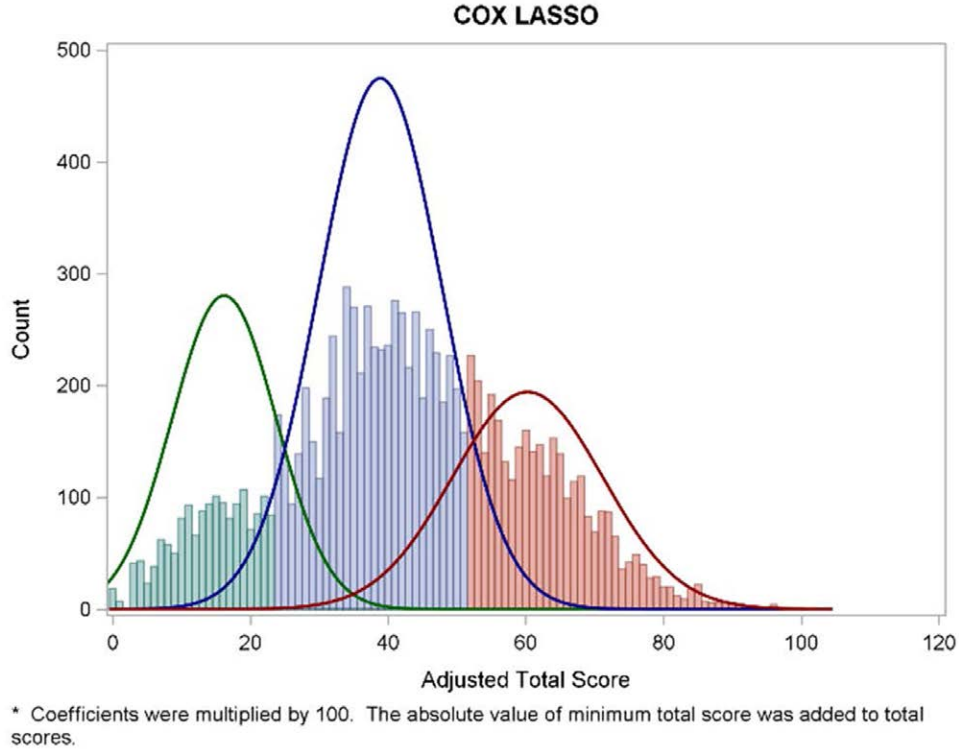

FIGURE 3. The grouping of adjusted total scores in 3 clusters from expectation-maximization (EM) clustering algorithm.

TABLE 3.

Validation results for checking the adequacy of Cox-Lasso model derived from the derivation cohort when applied to validation cohort

Optimal model results	Low risk	Medium risk	High risk
No. of recipients			
Derivation, n (%)	1581 (14.8%)	5799 (54.4%)	3280 (30.8%)
Validation, n (%)	664 (14.9%)	2465 (55.2%)	1335 (29.9%)
Total, n (%)	2245 (14.8%)	8264 (54.6%)	4615 (30.5%)
Mortality rates (validation cohort)			
1 y			
Model estimated	91.4% (90.0%–92.7%)	87.9% (86.8%–89.0%)	83.7% (82.1%–85.3%)
Observed	91.4%	89.0%	81.6%
5 y			
Model estimated	71.3% (67.8%–75.0%)	61.6% (59.5%–63.8%)	51.3% (48.3%–54.5%)
Observed	70.6%	61.3%	52.6%
10 y			
Model estimated	51.9% (46.9%–57.3%)	39.1% (36.0%–42.4%)	27.4% (24.0%–31.4%)
Observed	54.7%	38.3%	27.6%
Hazard ratio: (95% CI); *P*			
Derivation	Reference	1.55 (1.39-1.72); $P < 0.0001$	2.12 (1.90-2.37); $P < 0.0001$
		Ref	1.37 (1.28-1.47); $P < 0.0001$
Validation	Reference	1.43 (1.22-1.68); $P < 0.0001$	1.97 (1.67-2.33); $P < 0.0001$
		Ref	1.38 (1.24-1.53); $P < 0.0001$

CI, confidence interval.

donor and recipient characteristics.[27] This suggests that organs should not be refused based on advanced donor age alone. These studies support our purpose of looking at the interplay of all factors for every patient.

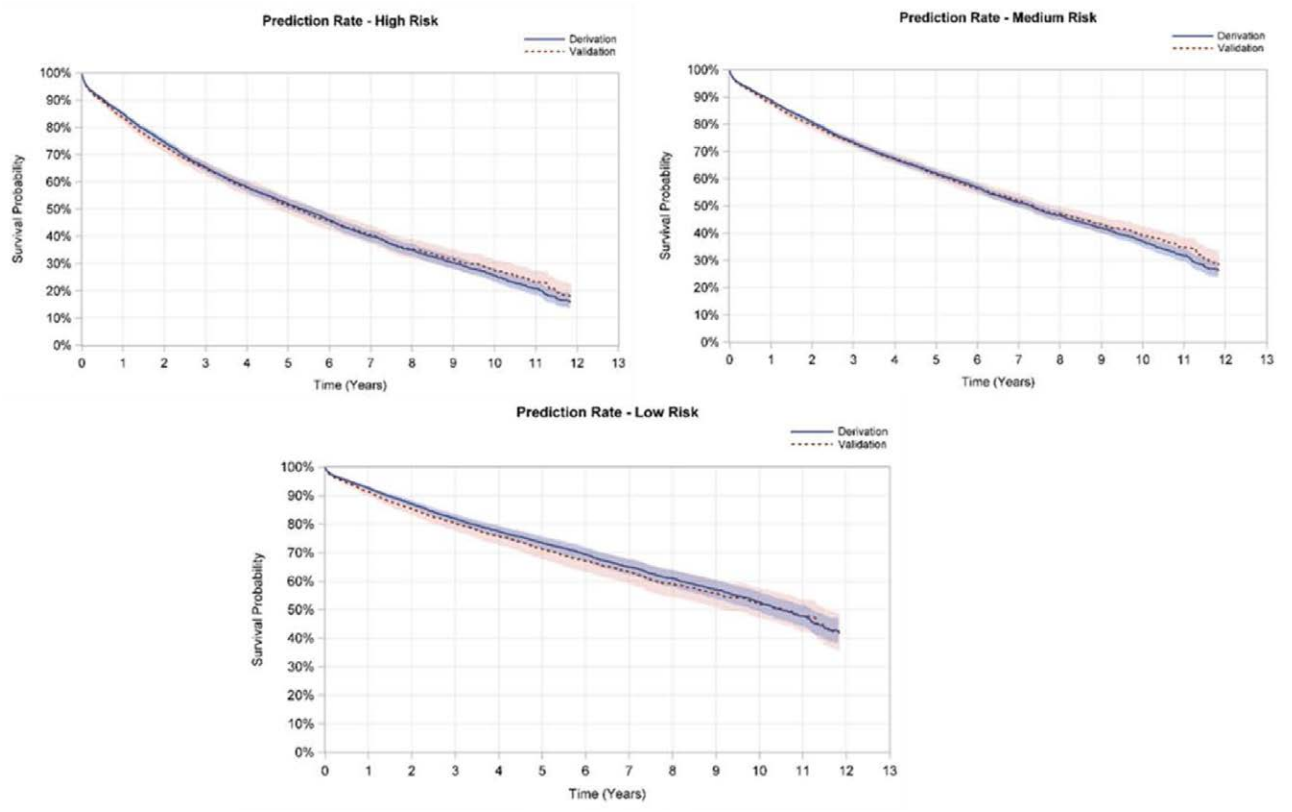

FIGURE 4. Kaplan-Meier (KM) curves from derivation cohort (solid line with 95% confidence intervals [CIs] in shaded area) and from validation cohort (dotted line) for high-, medium-, and low-risk groups.

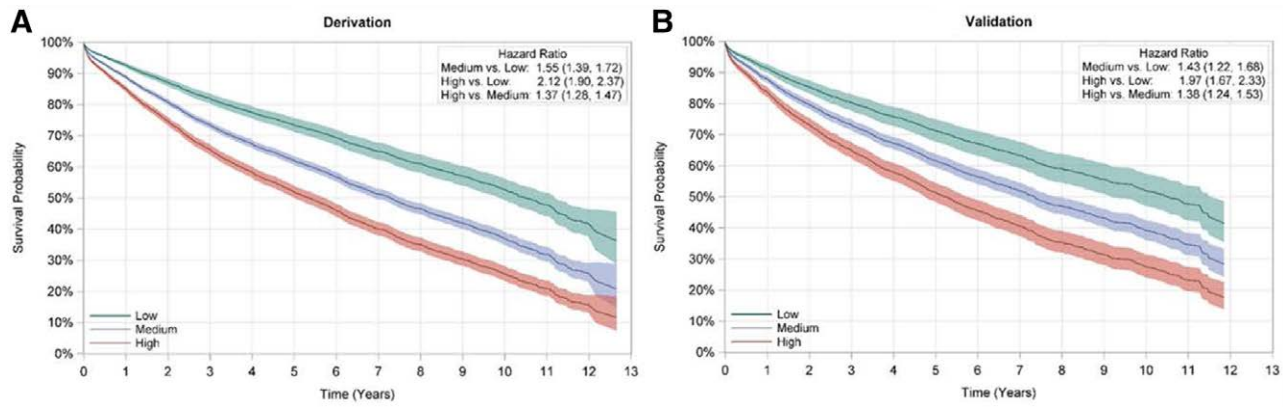

FIGURE 5. Survival probability comparisons among risk groups. A, Hazard ratio estimates with pairwise risk group comparisons for derivation cohort, and the survival probability with 95% confidence intervals (CIs) for each risk group. B, Hazard ratio estimates with pairwise risk group comparisons for validation cohorts and the survival probability with 95% CIs for each risk group.

Other risk factors have also been considered like cytomegalovirus mismatch and ECMO use. Previous studies have suggested that donor and recipient cytomegalovirus mismatch increases the risk of mortality in LTx patients.[28,29] Similar results were reported in our model in which cytomegalovirus mismatch was found to be a significant risk factor. Similar pattern was also seen when considering ECMO use. In fact, prolonged waitlist times have prompted more ECMO use as a bridge to LTx, and ECMO was found to be a significant risk factor that affects posttransplantation survival. Therefore, including ECMO use into the risk score prediction is essential

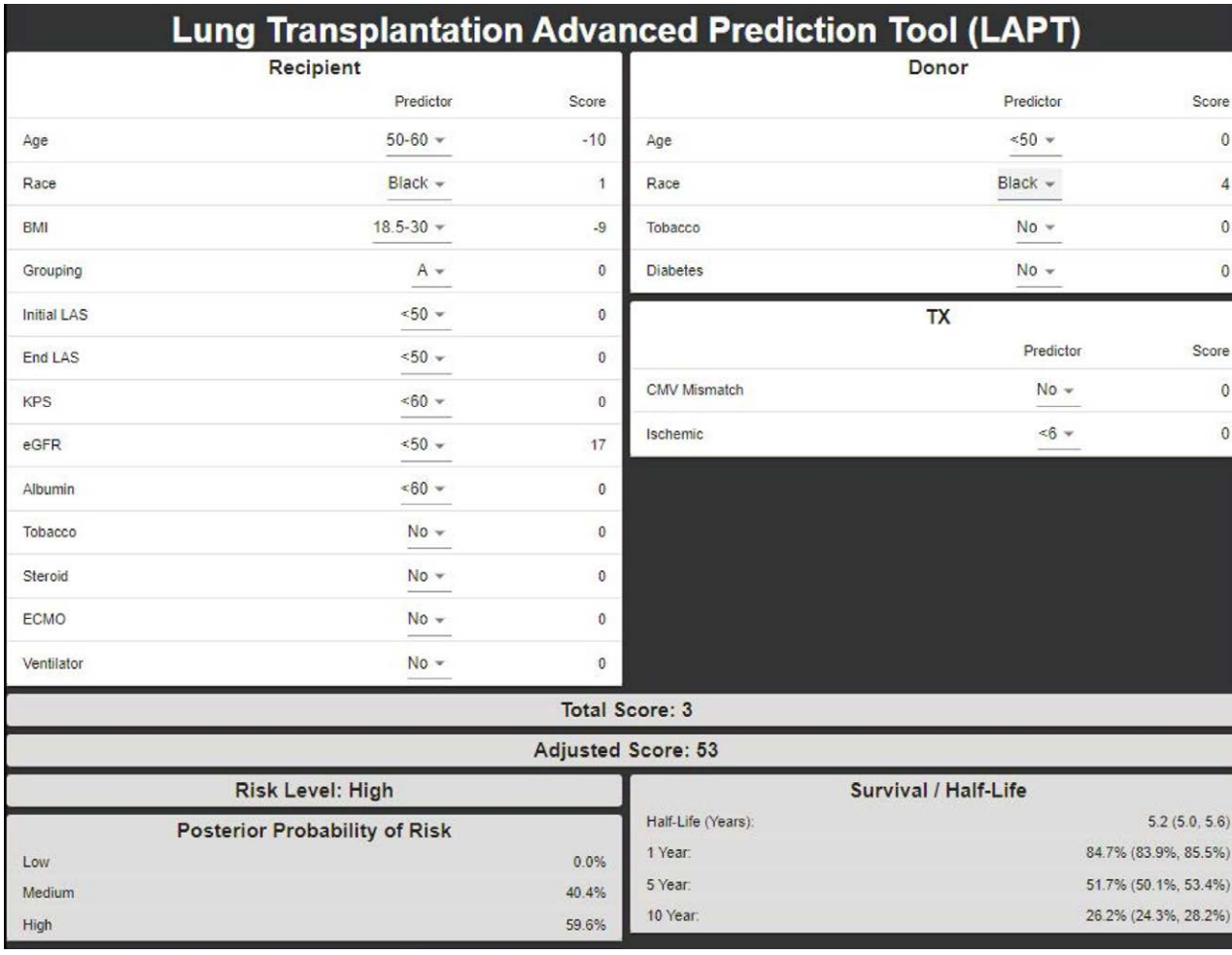

FIGURE 6. Web application example (screenshot) Example 1: A 55-y-old Black female patient diagnosed with obstructive lung disease (COPD) with low estimated glomerular filtration rate (eGFR; <50 mL/min) receiving lungs from a Black donor aged <50 y, nonsmoker, and does not have diabetes. Transplant had a good ischemia time (<6 h). The patient has a 59.6% chance of falling in the high-risk level group with an expected half-life of 5.2 y. BMI, body mass index; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; KPS, Karnofsky Performance Status; LAS, lung allocation score; TX, transplantation.

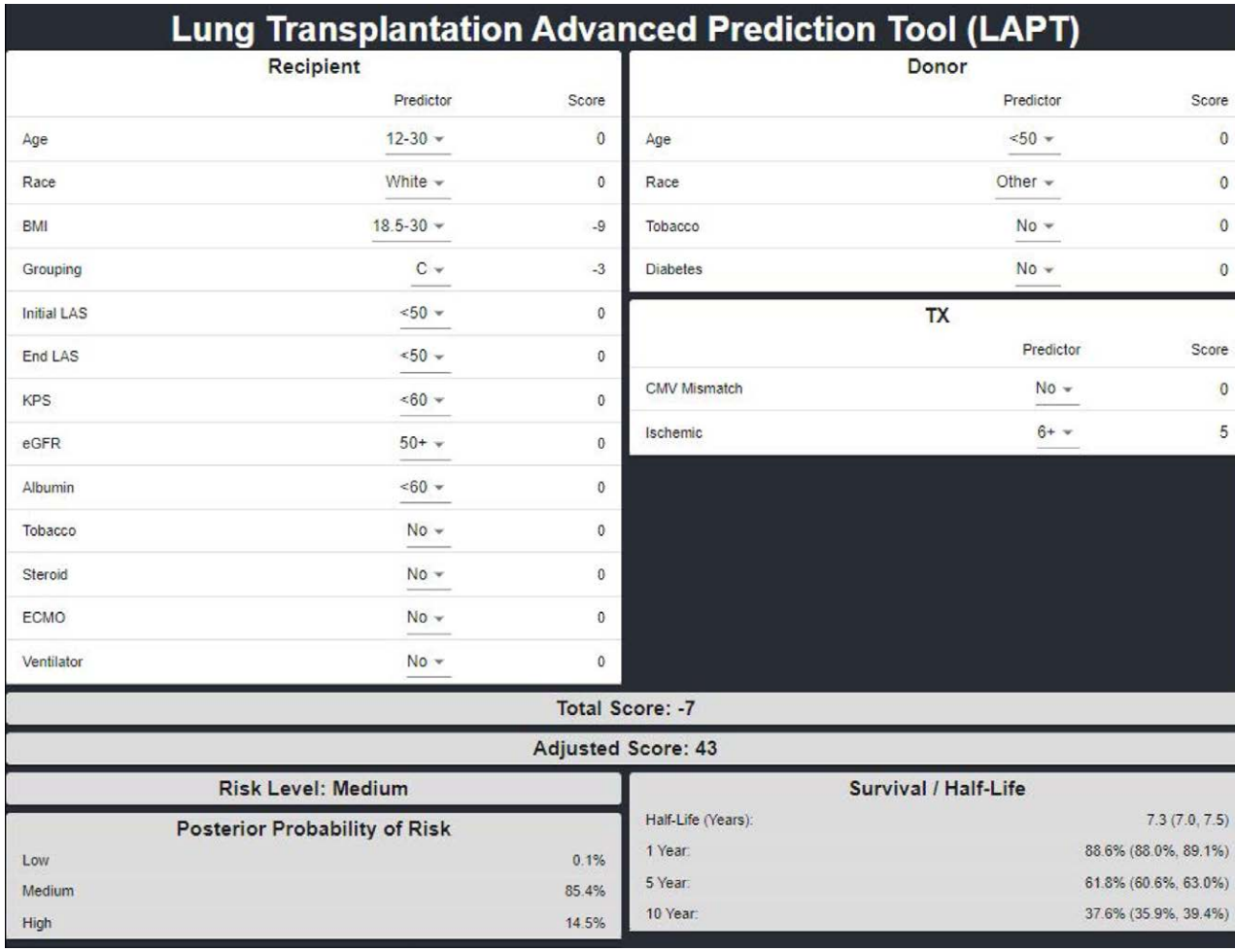

FIGURE 7. Example 2: Thirteen-year-old White male diagnosed with cystic fibrosis, with good organ function (kidney, liver, not on ventilator or extracorporeal mechanical oxygenation [ECMO] support) receiving lungs from a donor who is <50 y, nonsmoker, and no diabetes. Transplant was characterized with prolonged ischemia time (>6 h). Patient has 85.4% chance of being in the medium-risk level with an expected half-life of 7.3 y. BMI, body mass index; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; KPS, Karnofsky Performance Status; LAS, lung allocation score; TX, transplantation.

in this new era of LTx. We do acknowledge that we were unable to discern between veno-venous (VV) and veno-arterial ECMO use, which may affect posttransplant survival differently and that recent use of ECMO, especially VV-ECMO, to improve transplant candidacy rather than an emergent life-saving therapy, is not factored into the model. However, the advantage of the current statistical strategies is that the different use of ECMO may be accounted for indirectly by analyzing so many variables of the donor/transplant/recipient continuum. Patients placed on VV-ECMO to improve candidacy will be quite different than those placed on emergently or for extracorporeal cardiopulmonary resuscitation.

Findings from previously reported risk prediction models also support the claim of needing to include donor, recipient, and transplant factors into the lung allocation decision-making. The mortality after lung transplantation score showed good predictive strength (C statistic = 0.65) and incorporated both recipient and donor characteristics but only predicted 1-y posttransplant mortality.[17] Another example is the Minnesota-donor-lung quality index, which included 17 recipient- and donor-related risk factors and had a high ability to predict donor utilization (area under the curve = 0.76). However, variable selection in that study was restricted to those 17 risk factors subjectively chosen based on a survey score provided by surgeons, in contrast to the statistical methods employed for variable selection in our study.[30] Another model is by Oto and colleagues that showed poor correlation coefficient for 1-y mortality (r = 0.23) even though it correlated with early posttransplant outcomes and was externally validated. In addition, the model used a small sample (n = 87) from a single center and employed only 5 donor variables.[31] All 3 models predicted early posttransplant outcomes and did not account for long-term outcomes. Our results indicated modest area under the curves for 1-, 5-, and 10-y mortality for the adjusted total risk score even though the LAPT was developed to account for long-term survival outcome.

Although not proven, this study and others suggest an alternative hypothetical scenario. Potentially reallocating low-risk donors to low-risk candidates or to whatever candidate cohort that would have the largest positive affect (increasing the number of transplants and the number of y alive with a transplant) for the whole community must be studied. The present system focuses on getting to transplant primarily, which clinically is not the goal for the whole community. The goal should be to ensure the best transplant matches that will result in the largest positive

affect. Having a very ill patient, which we can objectively predict will have a poor result to transplant, use an ideal donor organ is not necessarily a good outcome if a less ideal donor organ could have been used with no significant predicted effect on their survival. This is especially true if that ideal donor organ could now be used for a recipient in whom the predicted survival would significantly increase in comparison to their survival had they received the less ideal donor organ. Supporting evidence for this approach can be found in liver transplantation wherein it was demonstrated that for a given recipient with several potential donors, predicted graft outcomes did not change with recipient characteristics, yet varied based on donor variables.[32] Similarly, Buescher et al[33] proposes a benefit-based allocation to achieve excellent long-term outcomes and increase total life-years saved per year from liver transplantation. The model in this study helps organize the risk factors and determine those with the highest impact on posttransplant outcomes, therefore, predicting survival in a more advanced way to what has been previously described, using an easy-to-use comprehensive risk scoring tool by means of a validated methodology.[17,25,34-36]

In this study, MLAs were used to impute variables with missing data. The variable selection was done using Cox-Lasso model, which was compared with the random forest Cox approach and Cox regression models with backward elimination and was found to have a better prediction. We speculate that the reason is that the Cox-Lasso method applies shrinkage to the variables that have minimal impact on the model, whereas the random forest Cox machine learning method does not. LASSO regression methods are also known to be tolerant methods for dealing with multicollinearity. This is a novel first step in the LTx field, further MLAs will be used and compared in future iterations of this model.

Using the LAPT, clinicians can predict median survival of patients for any risk score (Figure 2B) as well as belonging to 1 of the 3 different risk groups. The risk group was extensively validated using out-of-sample validation data (Table 3 and Figure 4), allowing further to calculate predicted median survival and 1-, 5-, and 10-y survival chance within same risk group. The advantage of using the risk groups in the validation process is that it allowed enough subjects in each risk group. Validating individual risk scores may not be feasible since for some scores there may not be enough validation samples. The categorization of patients is often useful for the prediction tool to be practical. A tool that provides personalized risk prediction for each patient donor organ match is ideal but presently, enough data do not exist to create it. To approach this ideal tool, median survival time with 95% CI was predicted for each individual score (Figure 2B). It is worth noting, however, that patients can differ greatly, and this gradation cannot be caught with the limited variables available, therefore we consider this study as an important first step toward a more precise and advanced prediction tool.

Strengths and Limitations

This study analyzed donor organs that were accepted. Further work is needed to determine if this system has a role in assessing lungs that were declined. The UNOS data set captures many key transplant-related variables, however, it is still limited in collecting some center-level donor information (especially specific bronchoscopy findings) and, therefore, precludes a granular analysis of such data. Also, the tool cannot be externally validated using internationally available registries because it was derived from variables available in UNOS that might not be collected in other countries (eg, LAS). Validating a US-based score in another registry is not uncommon and was done for the kidney donor profile index score for example in a European cohort.[37] Therefore, a more comprehensive score is needed to be available for clinicians worldwide. In addition, even though the tool can predict the risk score of patients, there are patients who fall into the outlier values in the intermediate risk group, which could potentially have a similar outcome to either the low- or the high-risk groups.

To our knowledge, this is the first attempt at matching donor-to-recipient and predicting posttransplant long-term outcomes in LTx using state-of-the-art statistical and machine learning methods. We studied a nationally representative sample of LTx recipients in the contemporary era. The relatively large sample size allowed for examination of characteristics that are not widely available and thus have been rarely, if ever, used in the analysis of the UNOS database. Imputation of variables was very conservative in this study and was only employed to 1 datapoint per record. Therefore, there was less interference in the data and stronger predictability. Also, this study aimed to find a model that would better predict overall rather than short-term survival alone. This deviates from the current system that predominantly aims at increasing the transplants number. Prediction models should not focus solely on decreasing the number of recipients on the waitlist but optimizing their posttransplant outcomes as well. A system that focuses on increasing the number of years alive with a transplant for the whole community would maximize benefit from a limited donor pool. This may mean at times that the most ill patients getting transplanted first is not done. This is also consistent with the growing literature on the use of mechanical assistance to make patients better transplant candidates (eg, good end-organ function, not mechanically ventilated, paralyzed, etc) and the perils of limping into transplant.

In conclusion, LAPT is a scoring system that incorporates donor-, recipient-, and transplant-related factors and could enable matching that goes beyond the stratification of donor versus recipient characteristics. The tool is practical, easy to interpret, and can be widely used by clinicians, in addition to LAS, for the predictability of short- and long-term survival outcomes. Although this current scoring system is a significant step forward, a more precise model that provides best coupling for each individual recipient and donor organ in real-time rather than in cohorts is a continued focus of our efforts. We hope this tool is an initial step in contributing to a lung allocation system that can maximize utilization of organs and posttransplant outcomes for the overall community.

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