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Differential effects of donor factors on post-transplant survival in lung transplantation

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BACKGROUND: Predicting post-transplant (PT) survival in lung allocation remains an elusive goal. We analyzed the impact of donor factors on PT survival and how these relationships vary among transplant recipients.
METHODS: We studied primary bilateral lung transplant recipients (n = 7,609) from the US Scientific Registry of Transplant Recipients (19 February 2015-1 February 2020). Main and interaction effects were evaluated and adjusted across candidate age, sex, and diagnosis. Models predicting PT survival were compared to the PT Composite Allocation Score model (PT-CAS): (1) Cox regression donor multivariable model (COX), (2) COX + PT-CAS, (3) random forest model (RF), and (4) RF + PT-CAS. Model discrimination and calibration measures were compared.
RESULTS: Interactions between donor and recipient factors emerged by age: lower survival for donation after circulatory death organs for recipients aged 55 to 69 years, donor smoking for recipients aged 30 to 54 and 70+, Hispanic donor for recipients < 30, non-Hispanic Black donor for recipients aged 30+; sex: cytomegalovirus mismatch for males; diagnosis: higher donor recipient weight ratio for diagnosis group C (e.g., cystic fibrosis), donor diabetes for diagnosis group D (e.g., idiopathic pulmonary fibrosis). COX and RF models performed similarly to PT-CAS; however, the combined COX + PT-CAS model had improved discrimination (1-year area under the receiver operator characteristic curve [AUC] PT-CAS 0.609 vs 1-year AUC COX + PT-CAS 0.626) and improved calibration across a broader range of predicted risk.
CONCLUSIONS: The influence of donor factors on recipient PT survival differed by age, sex, and diagnosis. The addition of donor factors to existing models predicting PT survival led to only modest improvement in prediction accuracy. Future efforts may focus on optimizing matching strategies to improve donor utilization.
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Background

Lung allocation continues to evolve in the United States (US) and worldwide. In March 2023, one of the largest system-wide changes in transplant policy occurred in the

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US with the adoption of the continuous distribution framework to minimize the impact of geographic proximity on candidate access to donor lung offers.[1-3] In the US, lung allocation is now determined by the Composite Allocation Score (CAS) which assigns less importance to geographic proximity compared to previous allocation systems.[4] At the same time, there has been heightened governmental focus on the performance of organ procurement organizations by the Centers for Medicare and Medicaid Services.[1] These multilevel systemic changes have led to increased organ offers and competition among geographically diverse candidates for the same organs.[5,6]

The lung transplant community has long been interested in the impact of donor factors on recipient survival, yet these factors are not considered in allocation or in the prediction of recipient post-transplant survival. A fundamental challenge to understanding the role of donor factors in transplant policy is their differential influence on post-transplant outcomes. The literature on donor risk is vast yet most studies have focused on methods to optimize donor selection to improve recipient outcomes, but this methodology may inadvertently contribute to decreased donor utilization.[7] This study differs from prior efforts by aiming to identify if consideration of complex interactions between donors and recipients can improve the predictive accuracy of post-transplant survival models. The secondary goal of this work was to create a framework by which donor factors could be evaluated in an individualized way to determine the degree to which some recipients may be less sensitive to the impacts of donor factors.

In this work, we examined the extent to which donor factors are related to post-transplant survival, and how these relationships vary among clinically diverse recipients by age, sex, and diagnosis.[8-12] Understanding variation in risk created by choices involved at the time of donor selection is more important than ever as candidates now have access to a larger donor pool allowing for more precision in donor selection in the CAS system.

Methods

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. Adult primary bilateral lung transplant recipients from the SRTR from 19 February 2015 to 1 February 2020 were studied. Single lung transplants were excluded to avoid confounding based on candidate characteristics known at the time of listing that could be associated with poorer post-transplant survival (e.g., age, frailty, multimorbidity). The US lung transplant allocation system categorizes pulmonary diseases into 4 main diagnosis groups: group A, obstructive lung disease; group B, pulmonary vascular disease; group C, cystic fibrosis and immunodeficiency disorders; and group D, restrictive lung disease. The study was approved as exempt research by the Cleveland Clinic Institutional Review Board (#21-1162) and abides by the International Society for Heart and Lung Transplantation ethics statement.

We summarized continuous measures using median and interquartile ranges (IQR) and compared recipient mortality groups using Wilcoxon Rank-Sum testing. Categorical factors were summarized using counts and percentages and were compared between recipient mortality groups using chi-square tests. Donor factors were first evaluated for correlation across clinically defined domains (donor health, donor death, donor demographics, donor lung function, and mismatch) and evaluated for correlation using Cohen's D from Wilcoxon Z-scores for comparing a continuous and categorical variable, and the Phi coefficient[13] for comparing 2 categorical variables (Tables S1 and S2).

We first built univariable main effects Cox proportional hazard survival models for each donor risk factor using PROC PHREG in SAS 9.4 software.[14] Next, we assessed interactions between donor risk factors and recipient age, sex, and diagnosis group, respectively, to identify significant interaction effects to be included in a final multivariable model (Table S3). The significance of these interactions was identified if (1) the joint distribution test was significant at $p < 0.05$ or (2) the significance of the hazard ratios between age, sex, and diagnosis groups differed. Hazard ratios and 95% confidence intervals for overall survival were calculated (Appendix).

We built a multivariable model comprised of the 3 recipient variables (age, sex, and diagnosis group), significant donor factors, and significant interactions obtained from the models above. Model reduction using backward elimination was undertaken by elimination of donor factors and interactions using a significance criterion of $p < 0.05$. We then built 3 models in addition to the one described above to understand the impact of incorporating donor factors in predicting post-transplant survival and compared these to the post-transplant survival model used in the CAS (PT-CAS).[15] These included (1) a multivariable Cox regression donor factor and interactions model (COX), (2) a multivariable Cox regression donor factor and interactions model with the addition of variables included in the PT-CAS model (COX + PT-CAS), (3) a random forest machine learning model (RF),[16] and (4) an RF model including PT-CAS variables (RF + PT-CAS). The predictive accuracy of these models was evaluated using the area under the receiver operator characteristic curve (AUC), Brier score, and calibration plots. In all survival analyses, recipients who were still alive at the time of the last follow-up were censored from analysis, and the proportional hazards assumption was validated using Schoenfeld residuals. Model comparison was restricted to the subset of transplant recipients who had complete data on CAS post-transplant factors. Ten-fold cross-validation was used to evaluate time-dependent AUC estimates using R version 4.2.3 with time-dependent AUC calculations using the riskRegression package.[17,18]

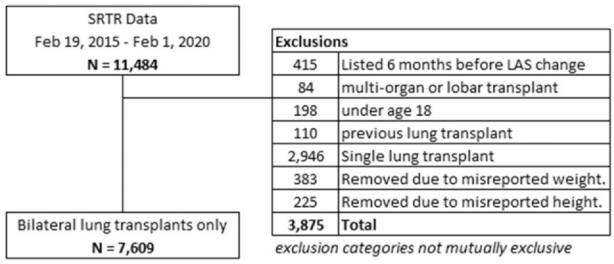

Figure 1 Study Cohort Flow Diagram. LAS, lung allocation score; SRTR, Scientific Registry of Transplant Recipients.

Results

Recipient and donor cohorts

Adult recipients of bilateral lung transplants (n = 7,609) were included (Figure 1). The median recipient age was 59 years (IQR: 49-64 years) and the median duration of follow-up was 21.4 months (IQR: 14.1-34.2). At 1 year, 90.1% of recipients remained alive and 0.4% were censored. At 3 years, 76.6% of recipients remained alive and 20.5% were censored. At 5 years, 68.6% of recipients remained alive and 49.5% were censored. Recipient characteristics were largely similar among residual cohorts (Table 1). The median donor age was 33 years (IQR: 24-46 years), and common causes of death included anoxia (30.7%), cerebrovascular accident (28.9%), and head trauma (40.4%). Other donor characteristics included a median body mass index of 26 (IQR: 22-30), median total ischemic time of 335 minutes (IQR: 281-397), 40% female, 77.5% non-Hispanic White (NHW), 5.1% donation after circulatory death (DCD), 94.1% Epstein-Barr virus (EBV) positive, 62.2% cytomegalovirus (CMV) positive, and 26% were designated as US public health service increased risk donors (Table 2).[19]

Multivariable model accounting for interactions

Univariable and robust interaction modeling to determine inclusion of interactions in the final multivariable model is reported in the Appendix (Tables S4-S7). The multivariable model considering interactions revealed differences among recipient subgroups by age, sex, and diagnosis group. First, for recipients < 30 years, male donors were associated with improved post-transplant survival while Hispanic donors were associated with lower post-transplant survival. For those 31 to 54 and ≥70 years, donor smoking was associated with lower post-transplant survival. Further factors associated with lower post-transplant survival for recipients ≥70 years included non-Hispanic Black (NHB) race, DCD donor, and CMV mismatch. Second, for male recipients, CMV mismatch was associated with lower post-transplant survival. Third, an increasing donor to recipient weight ratio was associated with lower post-transplant survival for groups C and D while donor diabetes was only a risk factor for group D (Table 3). A forest plot displays the hazard ratios from the multivariable model (Figure 2). Notably, for all variables except donor/recipient weight ratio, assessing the donor factor as a main effect only did not achieve statistical significance, highlighting the value of investigating interaction effects across recipient subgroups of age, sex, and diagnosis.

Model comparison

For the model comparisons, 437 recipients were omitted due to missingness of values used in the CAS post-transplant survival model. The most common missing factor was the cardiac index (n = 427). Post-transplant model discrimination and calibration of the new models were compared to the current PT-CAS model. The donor multivariable model without PT-CAS variables had a median AUC of 0.606 at 1 year, similar to the CAS post-transplant model (AUC = 0.609). Discrimination was improved when adding the donor multivariable model to the CAS post-transplant variables (COX + PT-CAS) with an AUC of 0.626 at 1 year. The RF model had a median AUC of 0.604 and 0.614 before and after including the CAS post-transplant variables, respectively. These trends were similar at 3 and 5 years (Figure 3A). Five-year predicted mortality risk estimates for all models were reasonably well-calibrated but the combined Cox regression donor multivariable model and PT-CAS model resulted in improved calibration across a wider range of predicted risk for post-transplant mortality (Figure 3B).

Discussion

Principal findings

We demonstrate that the effects of donor characteristics on lung transplant recipients differ by candidate age, sex, and diagnosis. Despite using multiple modeling strategies to incorporate donor factors, minimal gains occurred in predicting recipient post-transplant survival.

Findings in context

Efforts to characterize donor risk in the lung transplant literature have focused on strategies to clarify donor selection parameters and have employed a mix of single-center,[20,21] national,[22-24] or multinational data.[25] These studies have resulted in distilled donor scoring systems or metrics guiding donor utilization, which while clinically valuable, may lead to oversimplification of risk or contribute to behavioral shifts contributing to lower rates of organ utilization. Our work is grounded in the science of post-transplant risk prediction; and, in-line with the lung transplant literature, we found survival heterogeneity across recipient age,[8,26-28] recipient sex,[29] donor race/ethnicity,[30] donor smoking,[31] and CMV mismatch.[32,33] We additionally uncovered variation in the effects of donor risk factors across recipient age, sex, and diagnosis. Increased risk emerged with mismatches across sex, size, viral serology,

Table 1 Candidate Descriptive Statistics Stratified by Time Alive After Transplant

Recipient factor	Total	Alive at 1 year	Alive at 3 years	Alive at 5 years
	(*n* = 7,609)	(*n* = 6,822)	(*n* = 4,262)	(*n* = 1,451)
Deceased	–	757 (9.9%)	1,784 (23.4%)	2,393 (31.4%)
Recipient age at listing	59.0 [49.0, 64.0]	58.0 [49.0, 64.0]	58.0 [48.0, 64.0]	57.0 [49.0, 63.0]
Recipient age at transplant	59.0 [50.0, 65.0]	59.0 [49.0, 64.0]	58.0 [49.0, 64.0]	57.0 [49.0, 63.0]
BMI	25.8 [22.0, 29.0]	25.7 [22.0, 29.0]	25.6 [21.8, 28.9]	25.4 [21.6, 28.7]
Recipient height (cm)	170.2 [162.6, 177.8]	170.2 [162.6, 177.8]	170.2 [162.6, 177.8]	170.2 [162.6, 177.8]
Recipient weight (kg)	74.8 [61.7, 86.3]	74.4 [61.7, 86.2]	73.9 [61.2, 86.2]	73.9 [61.2, 85.7]
Post-transplant survival (median, months)	21.4 [14.1, 34.2]	25.7 [18.6, 34.8]	31.3 [27.2, 38.4]	41.8 [37.4, 42.5]
Recipient sex				
Female	3,063 (40.3)	2,745 (40.2)	1,719 (40.3)	580 (40.0)
Male	4,546 (59.7)	4,077 (59.8)	2,543 (59.7)	871 (60.0)
Recipient race/ethnicity				
Non-Hispanic White	5,946 (78.1)	5,337 (78.2)	3,348 (78.6)	1,145 (78.9)
Non-Hispanic Black	830 (10.9)	729 (10.7)	454 (10.7)	156 (10.8)
Hispanic	620 (8.1)	569 (8.3)	339 (8.0)	120 (8.3)
Other	213 (2.9)	187 (2.7)	121 (2.8)	30 (2.1)
Diagnosis grouping				
A	1,999 (26.3)	1,824 (26.7)	1,157 (27.1)	386 (26.6)
B	426 (5.6)	366 (5.4)	217 (5.1)	54 (3.7)
C	963 (12.7)	885 (13.0)	589 (13.8)	204 (14.1)
D	4,221 (55.5)	3,747 (54.9)	2,299 (53.9)	807 (55.6)
Insurance				
Private	3,552 (46.7)	3,194 (46.8)	2,056 (48.2)	742 (51.1)
Public—Medicaid	655 (8.6)	600 (8.8)	375 (8.8)	132 (9.1)
Public—Medicare	1,494 (19.6)	1,318 (19.3)	783 (18.4)	242 (16.7)
Government (other)	1,817 (23.9)	1,633 (23.9)	1,011 (23.7)	325 (22.4)
Other	91 (1.2)	77 (1.2)	37 (0.9)	10 (0.7)
Functional status				
Performs activities of daily living with NO assistance	339 (4.5)	309 (4.5)	177 (4.2)	66 (4.5)
Performs activities of daily living with SOME assistance	6,432 (84.5)	5,797 (85.0)	3,658 (85.8)	1,246 (85.9)
Performs activities of daily living with TOTAL assistance	838 (11.0)	716 (10.5)	427 (10.0)	139 (9.6)

Abbreviations: BMI, body mass index.
Statistics are presented as median [P25, P75], *n* (column %).

and immunological profiles. The impact of these mismatches differed among subgroups of recipients possibly due to inherent baseline risk for subgroups (e.g., age).

We used a staged modeling strategy guided by clinical knowledge to first assess the relatedness of domains of donor factors. Next, we evaluated both donor and recipient factors by building univariable models to inform interaction evaluation across recipient subgroups; these results informed the development of multivariable Cox and machine learning models. These models were then compared to the existing PT-CAS model. Notably, despite these focused and iterative efforts to study individualized donor effects on post-transplant survival, our model performed only slightly better compared to the existing model of candidate-only factors known at the time of allocation. This model (COX) consisting of only recipient age, sex, diagnosis, and donor factors correctly categorized the outcome of death (discrimination) in nearly an identical fashion to the existing PT-CAS model. Combining this model with the existing PT-CAS model (COX + PT-CAS) resulted in a slight improvement in discrimination but importantly, demonstrated more accurate agreement in model-predicted risk to observed data (calibration) across a wider range of recipient post-transplant mortality risk.

The similarity in model performance between the donor (COX) and existing PT-CAS model suggests that donor factors may be similarly important to the candidate variables used in US allocation models but may not provide a large additional benefit after candidate characteristics have already been considered. These improvements in the ability to correctly categorize the outcome (discrimination), while small, may still represent a clinically important difference.[34] Despite this challenge, measures of discrimination (e.g., AUC) still provide one of the best measures of a model's predictive ability.[35] The existing PT-CAS model underpredicts mortality for low-risk recipients and overpredicts mortality for high-risk recipients and is only well-calibrated across a very narrow range of risk. Our combined

Table 2 Donor Descriptive Statistics Stratified by Recipient Time Alive After Transplant

Donor factor	Total (n = 7,609)	Recipient alive at 1 year (n = 6,822)	Recipient alive at 3 years (n = 4,262)	Recipient alive at 5 years (n = 1,451)
Calculated donor age (years)	33.0 [24.0, 46.0]	33.0 [24.0, 46.0]	32.0 [23.0, 46.0]	32.0 [22.0, 45.0]
Donor BMI	26.0 [22.0, 30.0]	26.0 [22.0, 30.0]	26.0 [22.0, 30.0]	26.0 [22.0, 30.0]
Donor height (cm)	172.7 [165.0, 178.0]	172.7 [165.0, 178.0]	172.7 [165.0, 178.0]	172.7 [165.0, 180.0]
Donor/recipient height ratio	1.01 [0.97, 1.05]	1.01 [0.97, 1.05]	1.01 [0.97, 1.05]	1.01 [0.97, 1.05]
Donor weight (kg)	76.0 [65.9, 87.9]	76.2 [66.0, 88.0]	76.0 [66.0, 87.7]	75.7 [65.9, 86.6]
Donor/recipient weight ratio	1.04 [0.86, 1.3]	1.04 [0.86, 1.3]	1.04 [0.86, 1.3]	1.04 [0.86, 1.3]
Total ischemic time	335.0 [281.0, 397.0]	333.0 [279.0, 393.0]	329.0 [275.0, 388.0]	329.0 [268.0, 393.0]
Lung pO_2 on 100%	418.0 [322.0, 484.0]	419.0 [322.0, 485.0]	419.0 [315.0, 486.0]	414.0 [282.0, 482.0]
Serum creatinine	1.00 [0.71, 1.5]	1.00 [0.71, 1.5]	1.00 [0.71, 1.4]	0.99 [0.70, 1.4]
Donor sex				
Female	3,043 (40.0)	2,690 (39.4)	1,653 (38.8)	564 (38.9)
Male	4,566 (60.0)	4,132 (60.6)	2,609 (61.2)	887 (61.1)
Donor race/ethnicity				
Non-Hispanic White	4,741 (62.3)	4,276 (62.7)	2,680 (62.9)	917 (63.2)
Non-Hispanic Black	1,342 (17.6)	1,174 (17.2)	750 (17.6)	254 (17.5)
Hispanic	1,198 (15.7)	1,086 (15.9)	655 (15.4)	225 (15.5)
Other	328 (4.3)	286 (4.2)	177 (4.2)	55 (3.8)
Donor history of diabetes	587 (7.8)	510 (7.5)	311 (7.3)	91 (6.3)
Donor hepatitis B status	204 (2.7)	167 (2.4)	94 (2.2)	29 (2.0)
Donor hepatitis C status	268 (3.5)	246 (3.6)	86 (2.0)	2 (0.14)
Donor history of cancer	122 (1.6)	109 (1.6)	60 (1.4)	16 (1.1)
Donor history of hypertension	1,882 (24.9)	1,664 (24.5)	1,023 (24.1)	342 (23.7)
Donor HIV positive	21 (0.28)	19 (0.28)	11 (0.26)	3 (0.21)
Donor abnormal bronchoscopy	2,157 (29.1)	1,934 (29.0)	1,230 (29.6)	456 (32.3)
Donor abnormal chest X-ray	5,065 (66.7)	4,539 (66.7)	2,780 (65.4)	930 (64.2)
Donor cause of death				
Anoxia	2,282 (30.7)	2,042 (30.7)	1,219 (29.2)	380 (26.7)
Cerebrovascular stroke	2,148 (28.9)	1,911 (28.7)	1,206 (28.9)	410 (28.8)
Head trauma	3,005 (40.4)	2,709 (40.7)	1,748 (41.9)	635 (44.6)
Donor blood type				
A	2,780 (36.5)	2,494 (36.6)	1,563 (36.7)	541 (37.3)
AB	186 (2.4)	167 (2.4)	94 (2.2)	29 (2.0)
B	874 (11.5)	786 (11.5)	487 (11.4)	170 (11.7)
O	3,769 (49.5)	3,375 (49.5)	2,118 (49.7)	711 (49.0)
Donor EBV positive	6,724 (94.1)	6,028 (94.1)	3,777 (94.2)	1,304 (95.0)
Donor CMV positive	4,712 (62.2)	4,243 (62.5)	2,610 (61.5)	882 (61.0)
EBV mismatch	907 (12.9)	810 (12.9)	480 (12.2)	146 (10.8)
CMV mismatch	3,618 (47.8)	3,229 (47.6)	2,028 (47.8)	688 (47.6)
ABO non-identical but compatible match	473 (6.2)	423 (6.2)	264 (6.2)	99 (6.8)
Height mismatch	5,109 (67.1)	4,583 (67.2)	2,851 (66.9)	951 (65.5)
Race mismatch	3,404 (44.7)	3,016 (44.2)	1,856 (43.5)	609 (42.0)
Sex mismatch	2,340 (30.8)	2,097 (30.7)	1,318 (30.9)	446 (30.7)
HLA mismatches (N)				
0	7 (0.10)	6 (0.09)	3 (0.07)	0 (0.00)
1	42 (0.59)	38 (0.59)	27 (0.67)	7 (0.52)
2	216 (3.0)	192 (3.0)	123 (3.1)	44 (3.2)
3	843 (11.8)	772 (12.0)	481 (12.0)	164 (12.1)
4	1,838 (25.7)	1,663 (25.9)	1,051 (26.2)	361 (26.6)
5	2,587 (36.2)	2,300 (35.9)	1,446 (36.1)	480 (35.4)
6	1,621 (22.7)	1,443 (22.5)	880 (21.9)	299 (22.1)
Donor/recipient mismatches (N)				
0	453 (6.0)	422 (6.2)	262 (6.1)	108 (7.4)
1	1,829 (24.0)	1,639 (24.0)	1,048 (24.6)	347 (23.9)
2	2,709 (35.6)	2,415 (35.4)	1,512 (35.5)	525 (36.2)
3	1,950 (25.6)	1,770 (25.9)	1,085 (25.5)	358 (24.7)

(*continued on next page*)

Table 2 (*Continued*)

Donor factor	Total (*n* = 7,609)	Recipient alive at 1 year (*n* = 6,822)	Recipient alive at 3 years (*n* = 4,262)	Recipient alive at 5 years (*n* = 1,451)
4	587 (7.7)	502 (7.4)	306 (7.2)	98 (6.8)
5	80 (1.05)	73 (1.07)	48 (1.1)	14 (0.96)
6	1 (0.01)	1 (0.01)	1 (0.02)	1 (0.07)

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen.

Data are not available for all subjects. Missing values: Total ischemic time (longest by right/left) = 24; pO_2 at 100 % FiO_2 = 12; serum creatinine = 6; donor history of diabetes (yes/no) = 46; donor hepatitis B status = 3; donor hepatitis C status = 1; donor history of cancer (yes/no) = 52; donor history of hypertension (1 = yes, 0 =no) = 48; donor HIV status (positive/negative) = 96; donor abnormal bronchoscopy (yes/no) = 192; donor abnormal chest X-ray (yes/no) = 15; donor cause of death (3 levels) = 174; EBV serology status = 460; donor CMV status (positive/negative) = 34; EBV mismatch = 583; CMV mismatch = 41; number of HLA mismatches - current match at transplant = 455. Statistics are presented as median [P25, P75], *n* (column %). Italics denote significance at the level of 0.05.

COX + PT-CAS model-predicted risk more accurately across a wider range, which could lead to more accurate prioritization of candidates for transplant. Here, an improvement in AUC of 0.02 means that the COX + PT-CAS will predict the correct order of observations by survival time in an additional 2 out of 100 patients compared to its current performance. In this cohort, the COX + PT-CAS model may have resulted in correcting the ranking of 152 more patients demonstrating that even small improvements in model performance have implications for allocation as the post-transplant model informs 25% of an individual's access to transplant in the US. It is important to highlight that risk prediction in the lung transplant population is inherently difficult given the relative homogeneity of candidates and donors stemming from stringent selection procedures.[36] Another challenge in studying individual factors is the risk for a Table 2 fallacy where multiple adjusted effect estimates are presented from a single model which can lead to inaccurate interpretations of the effect estimates for confounders.[37] For this reason, we performed individual interaction testing to identify variables and relationships to guide further study of differential risk across age, sex, and diagnosis groups and focused on the comparison of model discrimination and calibration.

Donor and candidate matching in practice

In the US, implementation of the CAS has increased donor organ offers to waitlist candidates, which opens opportunities for deeper consideration of match quality in organ offer acceptance decisions. Candidate and donor factors are often considered in silos, but a deep understanding of how these factors interact has remained elusive. The main goal of this work was to determine how donor factors differentially influenced recipient survival and to study if their inclusion could improve the ability to predict survival after lung transplantation. The secondary goal of this work was to lay the framework for how the field can begin to individualize predictions for candidates. While donor risk is often assessed broadly across a population, it has been shown that donor risk does not impact recipients equally,[22] a finding demonstrated by this study. For example, we found differential effects across donor race and race mismatching emerged as a risk factor in univariate analysis. Specifically, Hispanic donors were found to impart increased risk for recipients aged < 30 years. However, NHB donors (ref NHW) imparted risk for recipients aged ≥30 while NHB donors (ref Hispanic) imparted risk for recipients aged ≥55. Multiple hypotheses could explain these findings, including differences in recipient age cohorts by disease or sex or differences in unmeasured donor factors being captured by the variable of race. However, these differential findings require further study into the influence of socioeconomic position, geography, and biological embodiment of social adversity on the donor life course.[30,38,39] It is difficult to disentangle the effects of donor socioeconomic position, race/ethnicity, and overall health status on recipient outcomes. These findings should not be interpreted to further narrow donor selection but serve as a call for more research into this area of study.

Applications in donor utilization

Notably, our work supports existing efforts to consider donor risk (e.g., scoring systems) in the donor selection process[20,24] but encourages their use to inform and optimize both individual- and population-level allocation outcomes. Considering both risk stemming from donor factors and expected post-transplant outcomes, as is already in practice in US kidney allocation,[40,41] may allow for expansion of the donor supply and offer population-level survival gains by identifying improved matching algorithms for individual candidates. If pooled risk is only considered in a population of homogeneous candidates, optimization of post-transplant risk predictions will remain an elusive goal, but accounting for interactions of donor and recipient factors offers an opportunity for future efforts focused on individualized risk prediction.

While the most obvious utility of identifying the optimal donor and recipient match is to maximize individual-level

Table 3 Adjusted Hazard Ratios for Overall Survival From Multivariable Model Evaluating Candidate and Donor Interaction Effects

Donor factor effect	Kaplan-Meier median survival (IQR)		COX PH HR (95% CI)	*p*-value
Donor/recipient weight ratio (HR per ↑ 25%)	Below 1	At/above 1	0.91 (0.86, 0.96)	*< 0.0001*
Donor/recipient weight ratio: group A	6.05 (5.61, .)	6.11 (5.8, 6.29)	0.99 (0.93, 1.05)	0.75
Donor/recipient weight ratio: group B	5.11 (4.43, .)	6.01 (4.64, .)	1.01 (0.89, 1.14)	0.94
Donor/recipient weight ratio: group C	7.15 (., .)	. (6.39, .)	1.12 (1.03, 1.22)	*0.009*
Donor/recipient weight ratio: group D	6.09 (5.96, 6.53)	6.43 (5.76, 7.03)	0.91 (0.86, 0.96)	*< 0.0001*
History of diabetes	No diabetes	Yes diabetes	0.96 (0.77, 1.18)	0.68
History of diabetes: group A	6.14 (5.87, 6.29)	5.24 (4.97, .)	0.94 (0.7, 1.28)	0.72
History of diabetes: group B	6.01 (4.62, .)	6.25 (3.06, .)	0.83 (0.46, 1.51)	0.54
History of diabetes: group C	7.15 (6.48, .)	. (6.26, .)	0.88 (0.53, 1.44)	0.61
History of diabetes: group D	6.35 (6.04, 6.6)	5.06 (4.33, 6.43)	1.21 (1.01, 1.45)	*0.04*
CMV mismatch	No Mismatch	Mismatch	1.1 (0.98, 1.23)	0.10
CMV mismatch: recipient age < 30 years	7.15 (5.35, .)	6.26 (5.58, .)	0.95 (0.7, 1.29)	0.75
CMV mismatch: recipient age 31-54 years	7.03 (6.68, .)	7.17 (6.42, .)	1.09 (0.93, 1.28)	0.28
CMV mismatch: recipient age 55-69 years	6.38 (6.05, .)	5.93 (5.58, 6.11)	1.11 (1, 1.23)	*0.05*
CMV mismatch: recipient age ≥70 years	4.78 (4.13, 5.73)	4.01 (3.24, 4.5)	1.28 (0.97, 1.69)	*0.09*
CMV mismatch: female recipient	6.48 (6.02, .)	6.29 (6.01, 6.91)	1.02 (0.88, 1.19)	0.76
CMV mismatch: male recipient	6.5 (6.3, .)	6.03 (5.68, 6.24)	1.18 (1.04, 1.35)	*0.01*
DCD vs DBD donor	DBD	DCD	0.95 (0.68, 1.31)	0.73
DCD vs DBD: recipient age < 30 years	6.26 (5.58, .)	*Not estimable*	0.52 (0.19, 1.42)	0.20
DCD vs DBD: recipient age 31-54 years	7.03 (6.68, .)	6.48 (6.48, .)	0.86 (0.56, 1.34)	0.51
DCD vs DBD: recipient age 55-69 years	6.14 (6, 6.35)	5.68 (4.18, 6.29)	1.3 (1.06, 1.6)	*0.01*
DCD vs DBD: recipient age ≥70 years	4.42 (4.09, 5.15)	3.82 (0.72, .)	1.36 (0.72, 2.59)	0.35
Smoking history (yes vs no)	No smoking	Yes smoking	1.24 (0.97, 1.58)	*0.08*
Smoking history: recipient age < 30 years	6.39 (5.58, .)	. (4.21, .)	0.9 (0.42, 1.93)	0.79
Smoking history: recipient age 31-54 years	7.03 (6.72, .)	5.75 (3.68, 5.9)	1.61 (1.23, 2.1)	*< 0.0001*
Smoking history: recipient age 55-69 years	6.05 (5.99, 6.29)	6.14 (4.93, .)	0.95 (0.79, 1.14)	0.56
Smoking history: recipient age ≥70 years	4.56 (4.09, 5.17)	2.86 (0.59, 3.96)	1.73 (1.04, 2.88)	*0.03*
Male donor (vs female)	Female	Male	1.12 (0.99, 1.28)	*0.07*
Male donor: recipient age < 30 years	5.35 (4.21, .)	6.39 (6.14, .)	0.64 (0.47, 0.88)	*0.01*
Male donor: recipient age 31-54 years	7.03 (7.03, .)	7.11 (6.48, .)	1.05 (0.89, 1.24)	0.58
Male donor: recipient age 55-69 years	6.02 (5.68, 6.33)	6.14 (6.01, 6.43)	0.95 (0.85, 1.07)	0.39
Male donor: recipient age ≥70 years	4.5 (3.69, 5.17)	4.28 (4.01, 5.42)	0.98 (0.73, 1.31)	0.88
Race and ethnicity: Hispanic vs NHW	Hispanic	NHW	0.98 (0.73, 1.33)	0.91
Hispanic vs NHW: recipient age < 30 years	4.12 (3.29, 6.39)	*Not estimable*	1.8 (1.21, 2.66)	*0.003*
Hispanic vs NHW: recipient age 31-54 years	6.6 (6.16, .)	7.03 (6.68, .)	1.21 (0.96, 1.51)	0.10
Hispanic vs NHW: recipient age 55-69 years	6.53 (5.99, .)	6.14 (5.96, 6.33)	0.95 (0.82, 1.1)	0.50
Hispanic vs NHW: recipient age ≥70 years	. (3.35, .)	5.12 (4.13, 6.01)	1 (0.65, 1.52)	0.99
Race and ethnicity: NHB vs Hispanic	NHB	Hispanic	1.14 (0.95, 1.37)	0.16
NHB vs Hispanic: recipient age < 30 years	6.14 (4.94, .)	4.12 (3.29, 6.39)	0.74 (0.46, 1.18)	0.20
NHB vs Hispanic: recipient age 31-54 years	. (5.75, .)	6.6 (6.16, .)	1.04 (0.8, 1.35)	0.77
NHB vs Hispanic: recipient age 55-69 years	5.49 (4.99, 6.25)	6.53 (5.99, .)	1.33 (1.12, 1.59)	*0.001*
NHB vs Hispanic: recipient age ≥70 years	3.98 (2.71, 4.5)	. (3.35, .)	1.66 (1.04, 2.63)	0.03
Race and ethnicity: NHB vs NHW	NHB	NHW	1.12 (0.84, 1.5)	0.44
NHB vs NHW: recipient age < 30 years	6.14 (4.94, .)	*Not estimable*	1.33 (0.89, 1.98)	0.16
NHB vs NHW: recipient age 31-54 years	. (5.75, .)	7.03 (6.68, .)	1.25 (1.02, 1.54)	*0.03*
NHB vs NHW: recipient age 55-69 years	5.49 (4.99, 6.25)	6.14 (5.96, 6.33)	1.27 (1.11, 1.45)	*< 0.0001*
NHB vs NHW: recipient age ≥70 years	3.98 (2.71, 4.5)	5.12 (4.13, 6.01)	1.65 (1.19, 2.29)	*0.003*

Abbreviations: 95% CI, 95% confidence interval; CMV, cytomegalovirus; DBD, donation after brain death; DCD, donation after circulatory death; EBV, Epstein-Barr virus; HR, hazard ratios; IQR, interquartile ranges; NHB, non-Hispanic Black; NHW, non-Hispanic white; PH, proportional hazards.

Estimates calculated from a Cox PH multivariable regression model for overall survival including all terms reported here as well as recipient age, recipient group, and recipient gender (not reported). *p*-values reported from the Cox PH multivariable regression. Median survival reported from Kaplan-Meier analysis; survival estimates reported as a period (".") indicate survival is not estimable (i.e., undefined) due to greater than 50 % survival at the last observed time point. The following covariates were eliminated during variable reduction: recipient gender interaction with gender mismatch and donor cancer; recipient group interaction with donor cancer, hepatitis B, cause of death, EBV mismatch, CMV mismatch, donor gender, race and ethnicity, and smoking history; recipient age group interactions with cause of death, history of diabetes, EBV mismatch, hepatitis B, and hypertension.

HR and 95% CI based on comparison of median (IQR) Kaplan-Meier survival estimates.

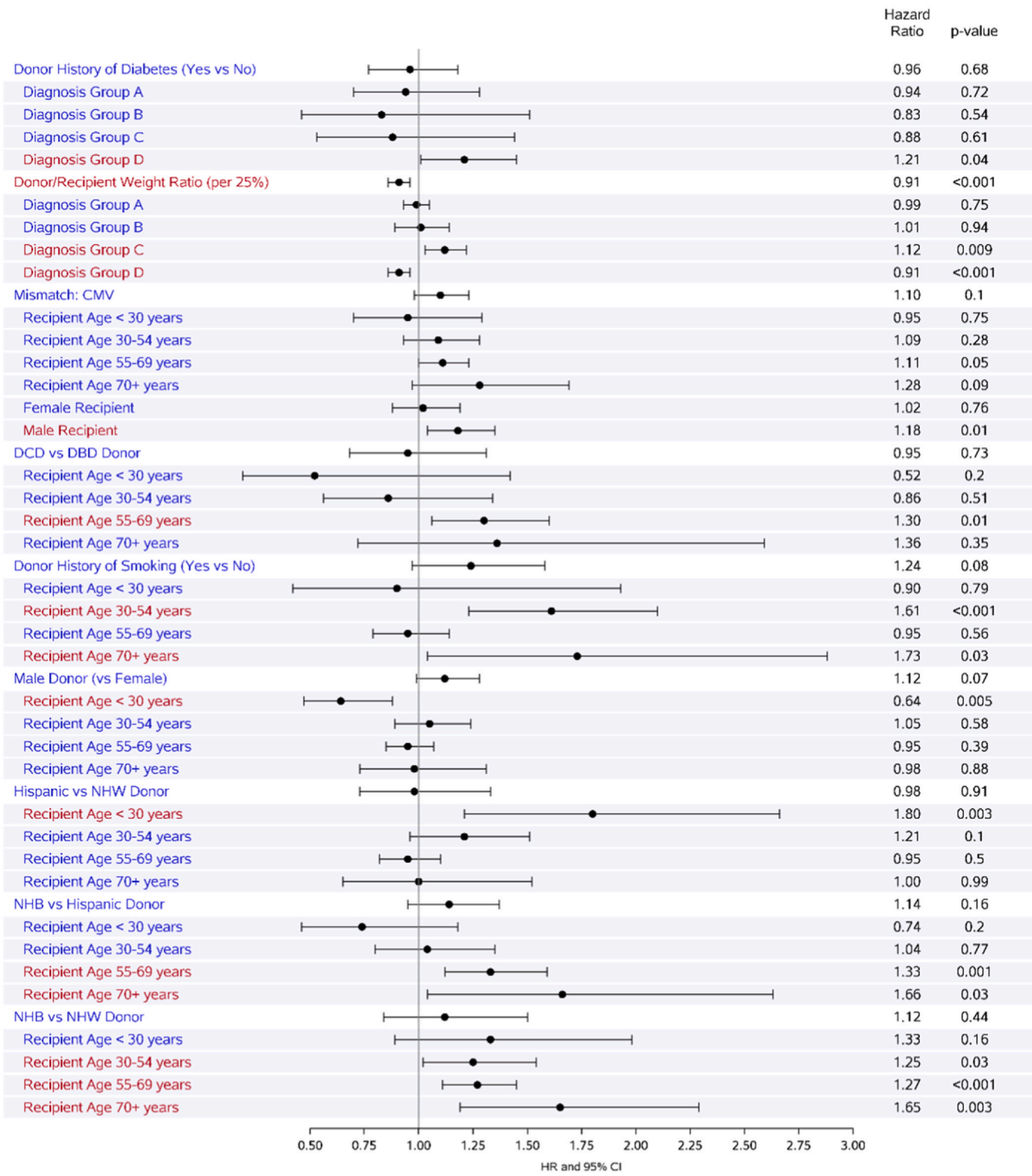

Figure 2 Forest plot of adjusted hazard ratios from the multivariable model. Interaction effects are from the final multivariable model which also included adjustments for candidate age, candidate sex, candidate diagnosis group, donor age, donor/candidate EBV mismatch, donor/candidate height mismatch (> 4 cm difference), and total ischemic time. A hazard ratio > 1 indicates an increased probability of post-transplant death. Interaction effects that are associated with differences in survival are highlighted in red. Interaction effects are noted with shading. 95% CI, 95% confidence interval; CMV, cytomegalovirus; DBD, donation after brain death; DCD, donation after circulatory death; EBV, Epstein-Barr virus; HR, hazard ratios; NHB, non-Hispanic Black; NHW, non-Hispanic white.

survival, it is equally imperative to consider the implications of this work for donor utilization. Donor selection is governed by the concern that donor criteria outside of a relatively narrow range may impart a survival disadvantage to an individual recipient. While this concern is valid, in 2022, 193 people on the waiting list died or became too sick for a transplant while only 18% of donor lungs were utilized in the US.[29] Even small improvements in our tolerance of

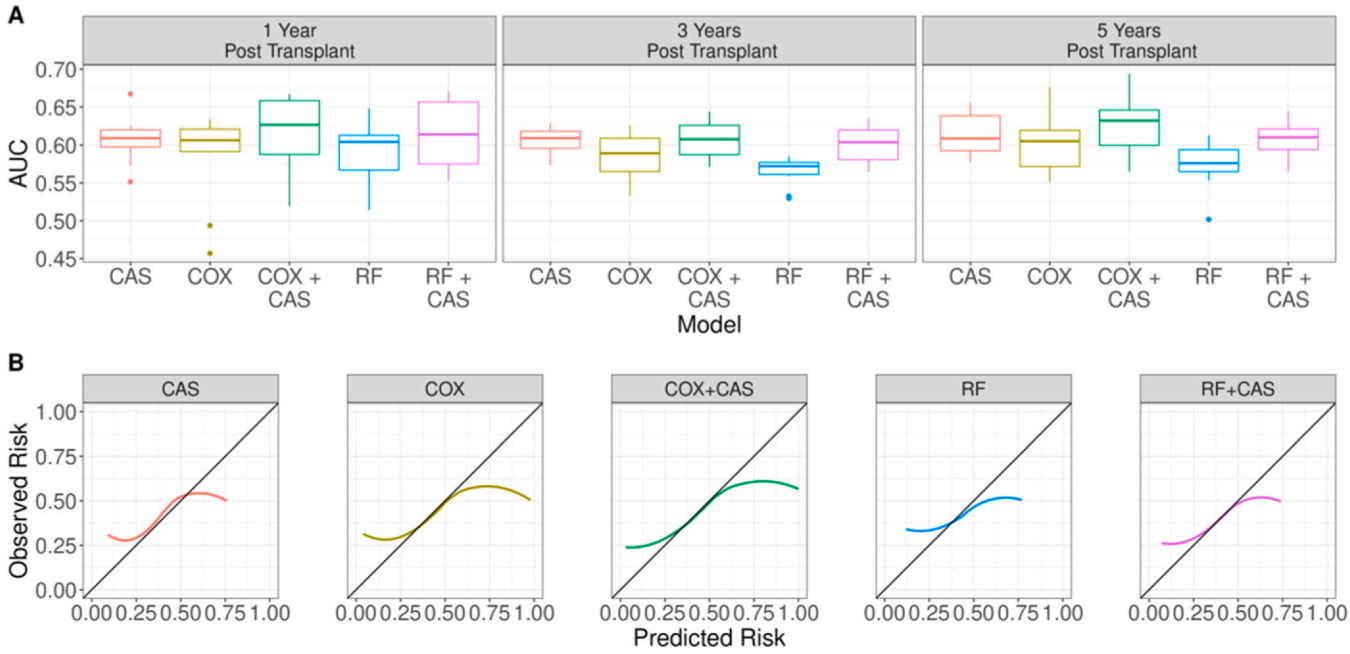

Figure 3 Model comparison by measures of model discrimination and calibration. (A) Boxplots (median, interquartile range (IQR), min/max, and outliers) of the 10-fold cross-validation time-dependent area under the receiver operator characteristic curve (AUC) of the CAS, multivariable model (COX), the multivariable model including the post-transplant CAS outcome model factors (COX + CAS), a random forest equivalent of these 2 models (RF) and RF including the post-transplant CAS outcome model (RF + CAS) at 1, 3, and 5 years post-transplant. (B) Calibration plots of observed risk (y axis) by model-predicted risk (x axis) of the 10-fold cross-validation of these models at 5 years post-transplant. The calibration estimates were plotted with locally estimated smoothing across the 10-fold. CAS, composite allocation score.

donor risk could result in hundreds of lives saved each year. This work represents an important first step toward developing a personalized medicine framework in organ acceptance practices where some candidates may require a donor with more specific characteristics to achieve a survival advantage while another candidate may be able to accept from a broader pool of donors and still achieve a survival advantage.

Limitations

This study is limited to inference about the interaction effects involving donor factors and 3 specific recipient factors: age, sex, and diagnosis group. There may be other recipient factors across which these donor effects vary. Additionally, inference is limited to the preoperative candidate and donor factors and levels provided by the SRTR. These findings may be biased toward the null due to the lack of comprehensive data about the health status of candidates and the homogeneity of the candidate and donor population due to stringent selection processes. This work will be strengthened by the addition of a validation cohort, which would allow a more rigorous comparison between models to avoid overfitting and would allow for more robust testing of differences in prediction among models. Notably, the proportion of extended criteria donor lungs utilized for transplant is lower in the US, and further study in databases such as the Eurotransplant or UK transplant offers an opportunity to consider a wider range of donors (older age, more DCD). This may further demonstrate that more of these donated lungs can be safely used to improve utilization rates. Finally, only recipients of bilateral lung transplants were considered due to the desire to minimize selection bias intrinsic in the selection of procedure type (single or bilateral) and its impact on size-matching parameters and post-transplant survival.

Conclusion

We identified several donor factors that impacted recipient post-transplant survival across age, sex, and diagnosis. Incorporating these effects led to minimal predictive improvements in post-transplant survival.

These findings suggest opportunities for improving matching strategies to optimize donor utilization. Given that donor effects only marginally contributed to variation in survival among transplant recipients, the low donor utilization rates in the US may not be justified. Expansion of donor selection criteria may minimally impact population-level post-transplant survival but offers the opportunity to provide more life-saving lung transplants for those in need.

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Author contributions

J.D., C.L., E.D., P.G., J.R., and M.V. participated in conceptualization, methodology, formal analysis, and investigation. J.D., P.G., and E.D. participated in data curation, visualization, software, formal analysis, and validation. All authors contributed to data interpretation, manuscript revisions, and review of the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100122.

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