The impact of extending follow-up for the PTAUC model from 1 year to 5 yearsafter transplant

February 17, 2021

Prepared By
Andrew Wey, PhD; Melissa Skeans, MS; Maryam Valapour, MD, MPP; Katie Audette, MS

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1 Summary

The lung allocation score has two components: waitlist area under the curve (WLAUC) and posttransplant area under the curve (PTAUC). Historically, these values are the expected number of days of patient survival without transplant or posttransplant, respectively, over 1 year. However, 1-year posttransplant patient survival may fail to capture the relatively poor long-term survival of certain subgroups of recipients (eg, older versus younger recipients). Thus, LAS may prioritize short-term over long-term survival benefit. This report investigated the differences between 1-year and 5-year posttransplant models for PTAUC.Multiple 5-year posttransplant models were investigated because covariate effects may differ for short- versus long-term follow-up. Specifically, a piecewise exponential model (PEM) with time-varying effects was investigated in addition to the traditional Cox proportional hazards model. The different modeling frameworks had similar predictive performance, as measured by cross-validated C-statistics. Spearman correlations estimated the similarity between the *ranks* of different PTAUC values for recipients receiving a transplant between January 1, 2018, and December 31, 2018. The Spearman correlation between the 5-year and the corresponding 1-year PTAUC values was 0.89, similar to the correlation of updating the parameterization of the 1-year Cox proportional hazards model (eg, considering a different form for the effect of recipient age). Differences in the PTAUC scale used in continuous allocation (ie, PTAUC scaled to 0-1) were notably larger across certain recipient subgroups. For example, the 5-year PTAUC scale had larger differences between older and younger recipients than the 1-year PTAUC scale. Thus, a transition from a 1-year to a 5-year PTAUC scale would not noticably change the ranking of recipients if PTAUC were theonly factor in allocation. It may impact the ordering within a continuous-allocation framework due to its interaction with other factors in continuous allocation.

Update: The larger differences in the PTAUC scale for 5-year posttransplant outcomes would require relatively larger differences in WLAUC to achieve similar allocation priority, especially for candidates with relatively high WLAUC. To address the potential impact on allocation, a TSAM study was performed for current allocation and two continuous distribution allocation systems with and without 5-year PTAUC scales. The current allocation system had minor differences between the 1- and 5-year PTAUCscales. However, the continuous distribution systems had notable differences: candidates aged 65 and older and diagnosis grouping D had lower transplant rates and a proportion of transplants with a 5-year compared to a 1-year PTAUC scale.

2 Background

On October 23, 2020, the OPTN Lung Committee requested an analysis to better understand the role of long-term patient survival in the model for posttransplant area under the curve (PTAUC). The committee was particularly concerned about the effect of recipient age changing during posttransplant follow-up after 1 year. In response, SRTR proposed the following data request for understanding the potential effect of including long-term patient survival in the model for PTAUC on the rank ordering of candidates.

3 Data request

Examine the effect of including long-term patient survival on the ranking within PTAUC.

1. A model for PTAUC with at least 5 years of posttransplant follow-up that specifically allows for the possibility of nonproportional effects of, for example, recipient age at transplant.
2. The change in the rank ordering of PTAUC calculated with
    - 1 year of posttransplant follow-up;
    - 5 years of posttransplant follow-up from a model with proportional effects, and;
    - 5 years of posttransplant follow-up from a model with nonproportional effects. This will allow the committee to distinguish between the effects of moving to 5 years of posttransplant follow-up versus allowing for the possibility of nonproportional effects.
3. An assessment of the C-statistic across the different models for PTAUC.

4 Methods

4.1 Study population

The cohort included lung transplant recipients aged 12 years or older at transplant from January 1, 2014 to December 31, 2018. For consistency and comparability, the models for 1-year and 5-year outcomes used the same set of transplant recipients. Recipient follow-up was administratively censored on the 1- or 5-year transplant anniversary, depending on the outcome of interest, or July 31, 2020, whichever was earliest. Each model included the covariates in the recently approved lung allocation score (LAS) posttransplant model (see Table 1 for a complete list and descriptive statistics). The covariates in the recently approved LAS allowed a more direct comparison with the PTAUC score under consideration for continuous allocation.

Continuous variables were "trimmed" to the 1st and 99th percentiles to reduce the influence of outliers. Ten iterations of multiple imputation (MI) handled missing data, and Rubin's rules combined estimates across the iterations of MI.

4.2 Modeling frameworks

The Cox proportional hazards (PH) model estimated the previous LAS posttransplant models with 1-year posttransplant patient survival as the outcome. The Cox PH model assumes proportional hazards, which means the effect of, for example, recipient age is the same during the entirety of posttransplant follow-up. In other words, the effect of age during the first month after transplant is the same as the effect during the 12th month after transplant. Violations of the PH assumption could lead to poor predictive performance of the LAS posttransplant model, potentially causing inappropriate prioritization of candidates.

To investigate the effect of a more flexible model, a piecewise exponential model (PEM) with time-varying effects estimated posttransplant patient survival. PEMs are similar to the Cox PH model (ie, usually assume proportional hazards). However, PEMs can more easily include time-varying effects, weakening the PH assumption from "the same effect during the entirety of posttransplant follow-up" to "same effect during *a priori* defined intervals of posttransplant follow-up." PEMs with time-varying effects can improve predictive performance in the presence of substantial non-PHs (see, for example, Wey et al., 2020). Notably, PEMs and the Cox PH model have one important difference: the Cox PH model imposes no structure on the baseline hazard, while PEMs assume the baseline hazard is piecewise constant within *a priori* defined intervals, which could impact the predictive performance of both models.

This report primarily focuses on the potential effect of transitioning from 1-year to 5-year patient survival for the posttransplant LAS model. However, due to anticipated non-PHs and a correspondingly more complicated modeling framework, a series of models were estimated to understand the effect of the different modeling decisions: (1) an updated parameterization for the posttransplant LAS model, (2) using PEMs instead of a Cox PH model (ie, the effect of the different baseline hazard functions), and (3) the integration of time-varying effects. The specific models were:

1. A Cox PH model for 1-year patient survival with the current LAS parameterization. That is, variables used the same form as the recently approved update to the LAS.
2. A Cox PH model for 1-year patient survival with an updated parameterization.
3. A PEM for 1-year patient survival without time-varying effects.
4. A Cox PH model for 5-year patient survival. This model used an updated parameterization.
5. A PEM for 5-year patient survival without time-varying effects.
6. A PEM for 5-year patient survival with time-varying effects

The Cox PH model with the current LAS parameterization used the variables as defined in the recently approved update to the LAS. The PEMs and the Cox PH models with updated parameterizations used linear splines with as many as six evenly spaced knots, allowing for the possibility of nonlinear effects for continuous variables. The least absolute shrinkage and selection operator (LASSO) simultaneously selected predictive covariates and estimated the effects for the PEMs and Cox PH models with updated parameterizations.

C-statistics at 1 and 5 years posttransplant compared the predictive performance of each model. The C-statistics were estimated with 10-fold cross-validation within each MI iteration. The final C-statistic was the average across the 10 iterations of MI.

4.3 Relative priority

For each model, the PTAUC was calculated for recipients who underwent transplant from January 1, 2018 to December 31, 2018. The interpretation of the 1-year PTAUC is “the number of days a patient is predicted to live in the first year posttransplant.” Similarly, the interpretation of the 5-year PTAUC is “the number of days a patient is predicted to live in the first 5 years posttransplant.” The proposed continuous allocation systems rescale PTAUC to values between 0 and 1. Thus, the 1- and 5-year PTAUC was divided by 365 and 1825, respectively, to better understand the change within the context of continuous allocation.

Spearman correlations estimated the similarity between the relative rankings of PTAUC between each model. A Spearman correlation of 1 means the ranks of the two PTAUC scales were identical, while a Spearman correlation of 0 means the ranks of the two PTAUC scales were unrelated. In addition, means and standard deviations described the PTAUC scale for specific recipient subgroups (eg, younger versus older recipients) across the different models. Lastly, the WLAUC was also calculated for the same recipients. The 0.1, 0.3, 0.5, 0.7, and 0.9 quantiles of the WLAUC scale were estimated, allowing a comparison of the changes in the PTAUC scales with potential changes in WLAUC.

4.4 TSAM study

A thoracic simulation allocation modeling (TSAM) study was performed to better understand the effect of transitioning from a 1-year to a 5-year PTAUC model. The TSAM study was a two-factor factorial study. The first factor was the type of PTAUC model: 1-year or 5-year PTAUC. The 1- and 5-year PTAUC models were the updated Cox models with the respective follow-up. The second factor was the ‘base’ allocation system: the current allocation system (ie, concentric circles), LAS 1:1 continuous allocation system, and LAS 2:1 continuous allocation system. The two continuous allocation systems were two of the four allocation systems from the first TSAM data request for continuous distribution.

TSAM included candidates on the waiting list at some point between January 1, 2018, and December 31, 2019. Donors with a transplanted lung or heart between January 1, 2018, and December 31, 2019 were included. TSAM only generated match runs for the organs eventually transplanted during the cohort period, which aligned with the observed offer acceptance data.

Within TSAM, offer acceptance models to predict whether an offered organ will be accepted for transplant. The offer acceptance models are logistic models. The models used offers from match runs for donors recovered between January 1, 2018, and December 31, 2019. The match runs had at least 1 acceptance, and offers after the last acceptance were excluded. The lung offer acceptance model included candidate factors (age, sex, blood type, smoking history, prior malignancy, prior cardiac surgery, hypertension, LAS, diagnosis group), donor factors (age, sex, blood type, BMI, cause of death, smoking history, history of hypertension, height, donor-to-recipient height and weight ratios, public health service increased risk of disease transmission, HBV and HCV status, PO2, DCD status, offer number). Three separate lung offer acceptance models were estimated: (1) a model for offers to pediatric candidates, (2) a model for offers to adult candidates from donors without a previous acceptance, and (2) a model for offers to adult candidates from donors with a previous acceptance. The second model was used when a donor had2 lungs available, and the third model was used when the donor had only 1 lung available.

The LASSO estimated the offer acceptance models. The LASSO ‘shrinks’ covariate effects towards 0, which can improve predicted error, and effects with small or no effect are set to exactly 0, effectively performing model selection. Linear splines estimated the effect of continuous covariates with evenly spaced knots.

5 Results

5.1 Descriptives

The average recipient age was 57 years, and most recipients had a diagnosis grouping of D. The detailed diagnosis categories in the PTAUC model were uncommon. Nonidiopathic pulmonary fibrosis was the most common detailed diagnosis (8.8%), and lymphangioleiomyomatosis was the least common (0.4%). Most variables did not have any missing data, although 4.5% and 9.16% of recipients had missing values for cardiac index and oxygen at rest, respectively.

Table 1: Descriptive statistics for the risk factors included in the PTAUC model. Mean and standard deviations summarized continuous variables, and frequencies and percents summarized categorical variables. The descriptive statistics for the continuous variables were calculated before trimming outlier values to the 1st and 99th percentiles. Descriptions of missingness were not reported for variables without missing values.

Variable	Mean/N (SD/Pct.)
Age	57 (14)
Serum creatinine	0.84 (0.31)
Cardiac index	2.9 (0.8)
-Missing	502 (4.5%)
Ventilation status	859 (8%)
Diagnosis group	
A	2921 (26%)
B	434 (4%)
C	1245 (11%)
D	6610 (59%)
N	2 (0%)
Diagnosis: Bronchiectasis (A)	193 (1.7%)
Diagnosis: Lymphangioleiomyomatosis (A)	42 (0.4%)
Diagnosis: Obliterative bronchiolitis (D)	116 (1.0%)
Diagnosis: Pulmonary fibrosis not idiopathic (D)	991 (8.8%)
Diagnosis: Sarcoidosis with PA > 30 mmHg (D)	167 (1.5%)
Diagnosis: Sarcoidosis with PA < 30 mmHg (A)	126 (1.1%)
Oxygen at rest	5.91 (5.84)
-Missing	1027 (9.16%)
Functional status	
No assistance	609 (5%)
Some assistance	9545 (85%)
All assistance	1058 (9%)
Six-minute-walk-distance (feet)	725 (448)

5.2 Estimated time-varying effects

Figure 1 illustrates the U-shaped effect of age over 4 different periods of posttransplant follow-up: younger and older recipients had worse survival (ie, higher hazard ratios) than recipients aged 30 to 50 years (Figure 1). The similar shape of the curve over the 4 different posttransplant timeframes suggests that the PH assumption is not seriously violated, although the slope for older recipients became steeper with longer follow-up, indicating a higher risk of death for recipients older than 60 years during the 3 to 5 years after transplant compared with, for example, the first 90 days after transplant. The Appendix presents similar curves for the effects of oxygen at rest, cardiac index, serum creatinine, and 6-minute walk test over the different periods of follow-up. Notably, the effect of serum creatinine attenuated with longer posttransplant follow-up.

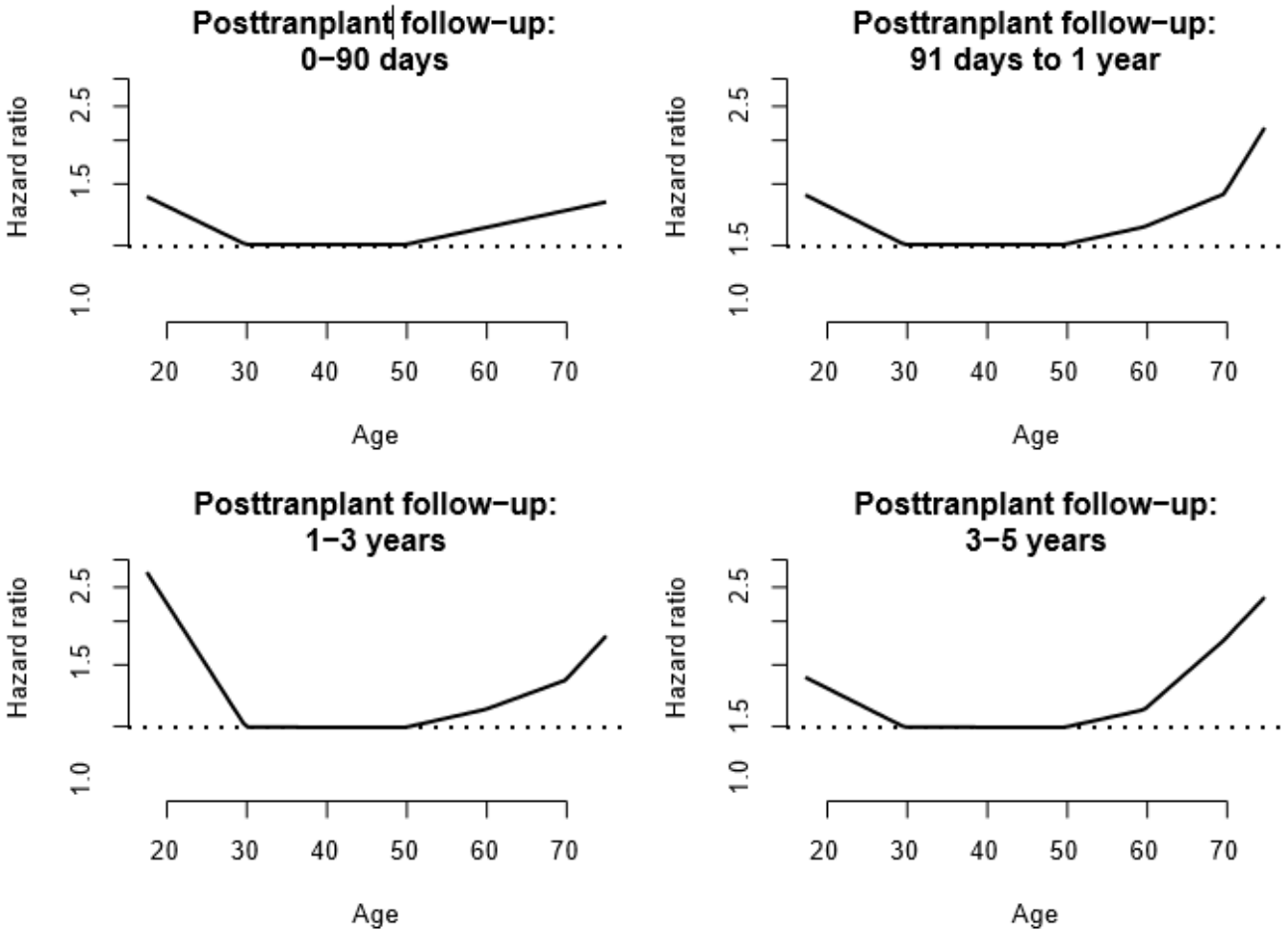

Figure 1: The estimated effect of age across the different periods of posttransplant follow-up.

5.3 C-statistics

None of the predictive models had clearly better or worse performance (Table 2). Instead, the different models had small but consistent differences in predictive performance. The Cox PH model with an updated parameterization had a slightly higher C-statistic at 1 year than the Cox PH model with the current parameterization (60.8% vs 60.2%). The Cox PH model had similar C-statistics as the PEMs without time-varying effects: differences of 0.0% to 0.1% for each comparison. The PEM with time-varying effects had marginally better C-statistics than the Cox PH model (1-year, 0.1%; 5-year 0.2%), and the PEM without time-varying effects (0.2% for 1 and 5 years). Thus, the inclusion of flexible time-varying effects did not notably improve the predictive performance of the posttransplant model underlying the LAS.

Table 2: The C-statistics at 1 and 5 years after transplant for the different predictive models. The C-statistic at, for example, 1 year was the proportion of recipients who died within 1 year with a higher predicted risk of dying by 1 year. The 5-year posttransplant models can predict the risk of dying at 1 and 5 years, allowing the calculation of the C-statistic at 1 and 5 years after transplant.

	1-year models			5-year models		
Year	Cox PH (current)	Cox PH (updated)	PEM (no-TV)	Cox PH (updated)	PEM (no-TV)	PEM (yes-TV)
1-year	60.2%	60.8%	60.7%	58.9%	58.8%	59.0%
5-year	–	–	–	59.2%	59.2%	59.4%

5.4 Relative priority

5.4.1 Correlation table

The Spearman correlations of the PTAUC scales had consistent and notable trends across the different models (Table 3). The Cox PH models with updated parameterizations and the PEMs without time-varying effects had nearly perfect Spearman correlations for the 1-year and 5-year models (ie, the correlations rounded 1), suggesting that the transition from a Cox PH model to a PEM without time-varying effects did not meaningfully change the ranking of individual recipients. The 5-year PEM models with and without time-varying effects had a Spearman correlation of 0.97, suggesting that the integration of time-varying effects did not noticably alter recipient rankings. The 5-year Cox PH model and PEM without time-varying effects had a Spearman correlation of 0.89 with the corresponding 1-year models. The 1-year Cox PH models with and without an updated parameterization also had a Spearman correlation of 0.89. Thus, transitioning from 1-year to 5-year posttransplant outcomes had a similar impact on recipient rankings as updating the parameterization of the current posttransplant model.

Table 3: The Spearman correlations between the PTAUC scale of each model for recipients who underwent transplant between January 1, 2018, and December 31, 2018.

	1-year models			5-year models		
Model	Cox PH (current)	Cox PH (updated)	PEM (no-TV)	Cox PH (updated)	PEM (no-TV)	PEM (yes-TV)
1-year: Cox PH (current)	1.00	0.89	0.89	0.80	0.80	0.81
1-year: Cox PH (updated)	–	1.00	1.00	0.89	0.89	0.85
1-year: PEM (no-TV)	–	–	1.00	0.89	0.89	0.84
5-year: Cox PH (updated)	–	–	–	1.00	1.00	0.98
5-year: PEM (no-TV)	–	–	–	–	1.00	0.97
5-year: PEM (yes-TV)	–	–	–	–	–	1.00

5.4.2 PTAUC scale across patient subgroups

The PTAUC scales had clear and consistent trends across the different outcomes and models (Table 4). The transition from 1-year to 5-year posttransplant outcomes magnified differences in PTAUC across some recipient subgroups. For example, when comparing the Cox PH models with updated parameterizations, the average difference between recipients aged 35 to <50 years and recipients 65 years or older was 0.02 for the 1-year model (0.94 vs 0.92) but 0.07 for the 5-year model (0.81 vs 0.74). In contrast, the differences across the lung diagnosis groups were more similar. Diagnosis groups B and C had the largest average differences: 0.04 for the 1-year model (0.90 vs 0.94) and 0.06 for the 5-year model (0.75 vs 0.81). The larger differences in the

5-year PTAUC scale across age-groups could alter the relative ranking of candidates in continuous allocation because older candidates would require, for example, correspondingly larger differences in the WLAUC scale to achieve the same relative ranking.

Recipients younger than 18 years had the only notable difference between the 1-year Cox PH models with and without an updated parameterization. Specifically, these recipients had an average PTAUC scale of 0.96 with the current parameterization and 0.92 with the updated parameterization. The lower PTAUC in the updated parameterization was likely due to the U-shaped relationship between recipient age and posttransplant patient survival (eg, see Figure 1). This effect was not captured in the current parameterization, in which age had a linear effect for recipients aged 45 years and older and no effect for recipients younger than 45 years. The 5-year Cox PH model and the PEM with time-varying effects had no notable differences in the corresponding PTAUC scales.

Table 4: The mean and standard deviation for the PTAUC scales across recipient subgroups. The PTAUC scales were reported for the 1-year Cox model with the current parameterization [1-year: Cox PH (current)], the 1-year Cox model with a new parameterization [1-year: Cox PH (new)], the 5-year Cox model with an updated parameterization [5-year: Cox PH (updated)], and the PEM model with time-varying effects [5-year: PEM (yes-TV)]. Each scale was standardized between 0 and 1, regardless of the original length of follow-up.

Variable	1-year: Cox PH (current)	1-year: Cox PH (updated)	5-year: Cox PH (updated)	5-year: PEM (yes-TV)
Overall	0.93 (0.03)	0.93 (0.03)	0.77 (0.05)	0.77 (0.05)
Recipient age				
12-<18	0.96 (0.01)	0.92 (0.01)	0.71 (0.06)	0.71 (0.05)
18-<35	0.94 (0.03)	0.94 (0.03)	0.78 (0.06)	0.78 (0.05)
35-<50	0.94 (0.03)	0.94 (0.03)	0.81 (0.05)	0.81 (0.04)
50-<65	0.93 (0.02)	0.93 (0.03)	0.79 (0.04)	0.79 (0.04)
65-	0.92 (0.02)	0.92 (0.03)	0.74 (0.05)	0.74 (0.04)
Diagnosis group				
A	0.94 (0.02)	0.94 (0.02)	0.79 (0.05)	0.79 (0.04)
B	0.89 (0.03)	0.90 (0.03)	0.75 (0.05)	0.75 (0.05)
C	0.94 (0.02)	0.94 (0.02)	0.81 (0.05)	0.80 (0.05)
D	0.92 (0.02)	0.92 (0.03)	0.76 (0.05)	0.77 (0.05)

5.4.3 Comparison with WLAUC

The difference in 5-year PTAUC between recipients aged 35-<50 and 65 and older was similar to the difference between, for example, the 50th and 70th quantiles of the WLAUC scale (Table 5). For example, an average recipient aged 35-<50 in the 70th quantile of WLAUC would have "1:1 LAS scores" of 1.02 [ie, $(1-0.92) + 0.94$] and 0.89 (ie, $(1-0.92) + 0.81$) for 1- and5-year PTAUC scales, respectively. In contrast, an average recipient aged 65 or older in the 50th quantile of WLAUC would have "1:1 LAS scores" of 1.07 [ie, $(1-0.85) + 0.92$] and 0.89 [ie, $(1-0.85) + 0.74$] for 1- and 5-year PTAUC scales, respectively. The recipient aged 35-<50 with better expected waitlist survival than the recipient aged 65 or older had notably less priority with a 1-year PTAUC scale but similar priority with a 5-year PTAUC. Thus, a transition from a 1- to a 5-year PTAUC scale could change the ranking of the match run, especially for candidates with relatively high WLAUC.

Table 5: The 10th, 30th, 50th, 70th, and 90th quantiles for the WLAUC and PTAUC scales. The PTAUC scales were reported for the 1-year Cox model with a new parameterization [1-year: Cox PH (new)] and the 5-year Cox model with an updated parameterization [5-year: Cox PH (updated)]. Each scale was standardized between 0 and 1, regardless of the original length of follow-up.

	Quantile				
Scale	10th	30th	50th	70th	90th
WLAUC scale	0.29	0.74	0.85	0.92	0.98
1-year: Cox PH (updated)	0.89	0.92	0.93	0.94	0.95
5-year: Cox PH (updated)	0.70	0.75	0.78	0.80	0.83

5.5 Effect within TSAM runs

5.5.1 Deceased donor transplant rates

The current allocation system did not have notable differences in transplant rates between a 1- and 5-year PTAUC (Table 6). However, the continuous distribution allocation systems (1:1 WLAUC:PTAUC and 2:1 WLAUC:PTAUC) had major differences in transplant rates between a 1- and 5-year PTAUC. Specifically, candidates aged 18-<65 had notably higher transplant rates for 5-year PTAUC than 1-year PTAUC. Conversely, candidates aged 65 and older had notably lower transplant rates for a 5-year PTAUC than a 1-year PTAUC. Similarly, candidates with diagnosis grouping B and C had higher transplant rates for 5-year PTAUC than a 1-year PTAUC. Candidates with diagnosis grouping D had a lower transplant rate for 5-year PTAUC than 1-year PTAUC.

Table 6: Deceased donor transplant rates (transplants per 100 person-years) across different allocation systems with and without a 5-year PTAUC scale [5-year Cox PH (new)]. The different allocation systems were (1) the current allocation system, (2) a 1:1 WLAUC:PTAUC weighting, and (3) a 2:1 WLAUC:PTUAC weighting. The WLAUC and PTAUC scales were standardized between 0 and 1, regardless of the original length of follow-up.

	Current allocation		1:1 WLAUC:PTAUC		2:1 WLAUC:PTAUC	
Variable	1Y PTAUC	5Y PTAUC	1Y PTAUC	5Y PTAUC	1Y PTAUC	5Y PTAUC
Candidate age						
0-<18	112 (106-117)	114 (108-120)	276 (265-287)	273 (267-279)	271 (260-282)	269 (259-279)
18-<35	126 (122-129)	129 (126-131)	155 (152-157)	195 (191-198)	136 (134-138)	168 (165-171)
35-<50	132 (130-134)	139 (136-142)	156 (152-159)	237 (231-242)	140 (138-142)	197 (194-199)
50-<65	151 (150-153)	155 (154-157)	134 (134-135)	144 (143-146)	130 (129-131)	137 (136-137)
65+	295 (292-298)	273 (270-277)	213 (211-215)	149 (148-151)	238 (236-241)	175 (172-177)
Diagnosis grouping						
A	88 (87-90)	88 (87-89)	65 (64-65)	72 (71-73)	53 (52-53)	56 (55-57)
B	122 (116-127)	125 (122-128)	73 (71-75)	113 (111-116)	89 (87-91)	123 (120-126)
C	143 (140-146)	151 (148-155)	213 (208-219)	301 (297-306)	180 (176-183)	247 (244-250)
D	292 (290-294)	289 (287-291)	281 (279-283)	235 (233-237)	311 (309-313)	269 (268-271)

5.5.2 Proportion of transplants

The current allocation system did not have notable differences in recipient characteristics between a 1- and a 5-year PTAUC (Table 7). However, the continuous distribution allocation systems (1:1 WLAUC:PTAUC and 2:1 WLAUC:PTAUC) had major differences in recipient characteristics between a 1- and 5-year PTAUC. Specifically, recipients aged 18-<65 had slightly higher percentages for 5-year PTAUC than 1-year PTAUC. Conversely, recipients aged 65 and older had a notably lower proportion of recipients for a5-year PTAUC than 1-year PTAUC. Recipients with diagnosis grouping D had a notably lower proportion of recipients for a 5-year PTAUC than for a 1-year PTAUC. Diagnosis grouping A, B, and C had relatively small increases in the proportion of recipients.

Table 7: The percent of transplants across candidate characteristics for different allocation systems with and without a 5-year PTAUC scale [5-year Cox PH (new)]. The different allocation systems were (1) the current allocation system, (2) a 1:1 WLAUC:PTAUC weighting, and (3) a 2:1 WLAUC:PTUAC weighting. The WLAUC and PTAUC scales were standardized between 0 and 1, regardless of the original length of follow-up.

	Current allocation		1:1 WLAUC:PTAUC		2:1 WLAUC:PTAUC	
Variable	1Y PTAUC	5Y PTAUC	1Y PTAUC	5Y PTAUC	1Y PTAUC	5Y PTAUC
Recipient age						
0-<18	2 (2-2)	2 (2-2)	3 (3-3)	3 (3-3)	3 (3-3)	3 (3-3)
18-<35	9 (9-9)	9 (9-9)	10 (10-10)	11 (11-11)	10 (10-10)	10 (10-11)
35-<50	14 (13-14)	14 (14-14)	15 (15-15)	17 (17-17)	14 (14-14)	16 (16-16)
50-<65	45 (45-46)	46 (46-46)	45 (44-45)	46 (45-46)	44 (44-44)	45 (45-45)
65+	30 (30-30)	29 (29-29)	28 (28-28)	24 (24-24)	29 (29-29)	26 (26-26)
Diagnosis group						
A	21 (21-21)	21 (21-21)	17 (17-17)	18 (18-18)	14 (14-14)	15 (15-15)
B	7 (6-7)	7 (7-7)	5 (5-5)	6 (6-7)	6 (6-6)	7 (7-7)
C	11 (10-11)	11 (11-11)	12 (12-12)	13 (13-13)	12 (12-12)	13 (13-13)
D	62 (62-62)	61 (61-62)	66 (66-66)	62 (62-63)	68 (68-68)	65 (65-65)

6 Discussion

This report investigated whether long-term patient survival would change the patient rankings in the PTAUC component of LAS. Secondarily, there was an interest in the effect of more complex models because of concern that the traditional Cox proportional hazards model would fail to capture an evolving effect of recipient age over posttransplant follow-up. For both 1-year and 5-year patient survival, more complex models had similar predictive performance to the traditional Cox PH model. Last, the order of patients by PTAUC was similar regardless of the underlying model.

The effect of moving from 1-year to 5-year outcomes was less clear, especially in the context of continuous allocation. Specifically, the increased variability of the 5-year model allows more discrimination among patient outcomes. In the 1-year models, mean PTAUC scales varied little by age, meaning outcomes were quite similar across age-groups. In the 5-year models, PTAUC scales had more variability, meaning outcomes had larger differences across age-groups. The interaction of these larger differences with other factors used in continuous allocation could change patient rankings and, therefore, motivated a TSAM study.

In the TSAM study, there were notable differences across patient age groups and diagnosis groupings between 1- and 5-year PTAUC for the continuous allocation policies but not the current allocation policy. Continuous allocation policies may increase the relative importance of WLAUC and PTAUC compared with the current allocation policy, potentially explaining the differing effects. Regardless, the results clearly demonstrated that a 5-year PTAUC could notably change the relative access to transplant for different groups of patients within a continuous allocation system.

7 Appendix

7.1 Structure of piecewise exponential models (PEMs)

The baseline hazard of the PEMs was *a priori* split into the following posttransplant intervals: 0-3 days, 4-7 days, 8-14 days, 15 days to 1 month, 1-2 months, 2-3 months, 3-4 months, 4-5 months, 5-6 months, 6 months to 1 year, 1-2 years, 2-3 years, 3-4 years, and 4-5 years. The PEM with time-varying effects for 5-year posttransplant patient survival allowed different effects for 0-90 days, 91 days to 1 year, 1-3 years, and 3-5 years after transplant. Notably, the PEM with time-varying effects also included an overall effect, allowing the LASSO to 'select' only the overall effect for risk-factors with PHs.

7.2 Time-varying effect of O2

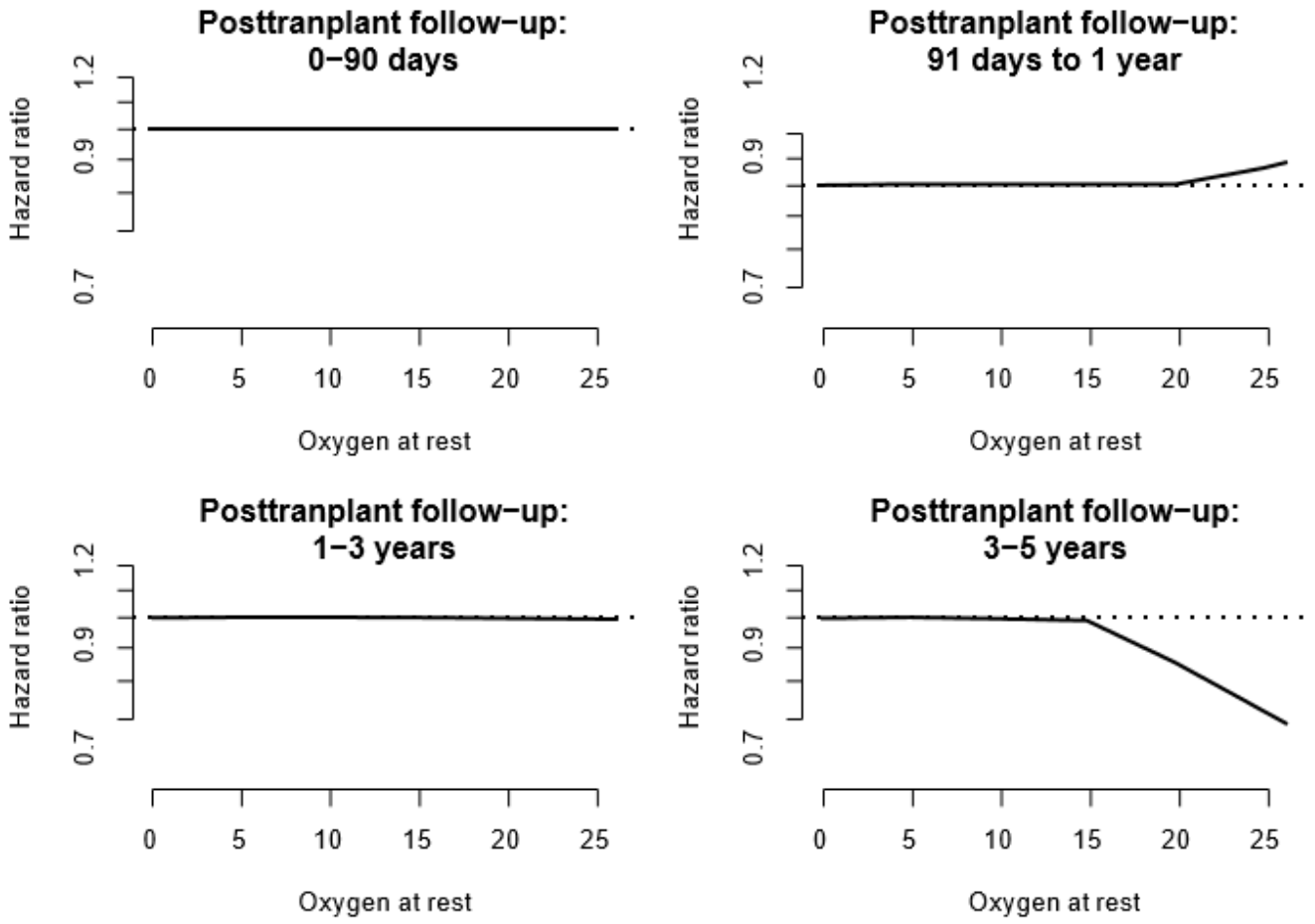

Figure 2: Estimated effect of O2 across the different periods of posttransplant follow-up.

7.3 Time-varying effect of cardiac index

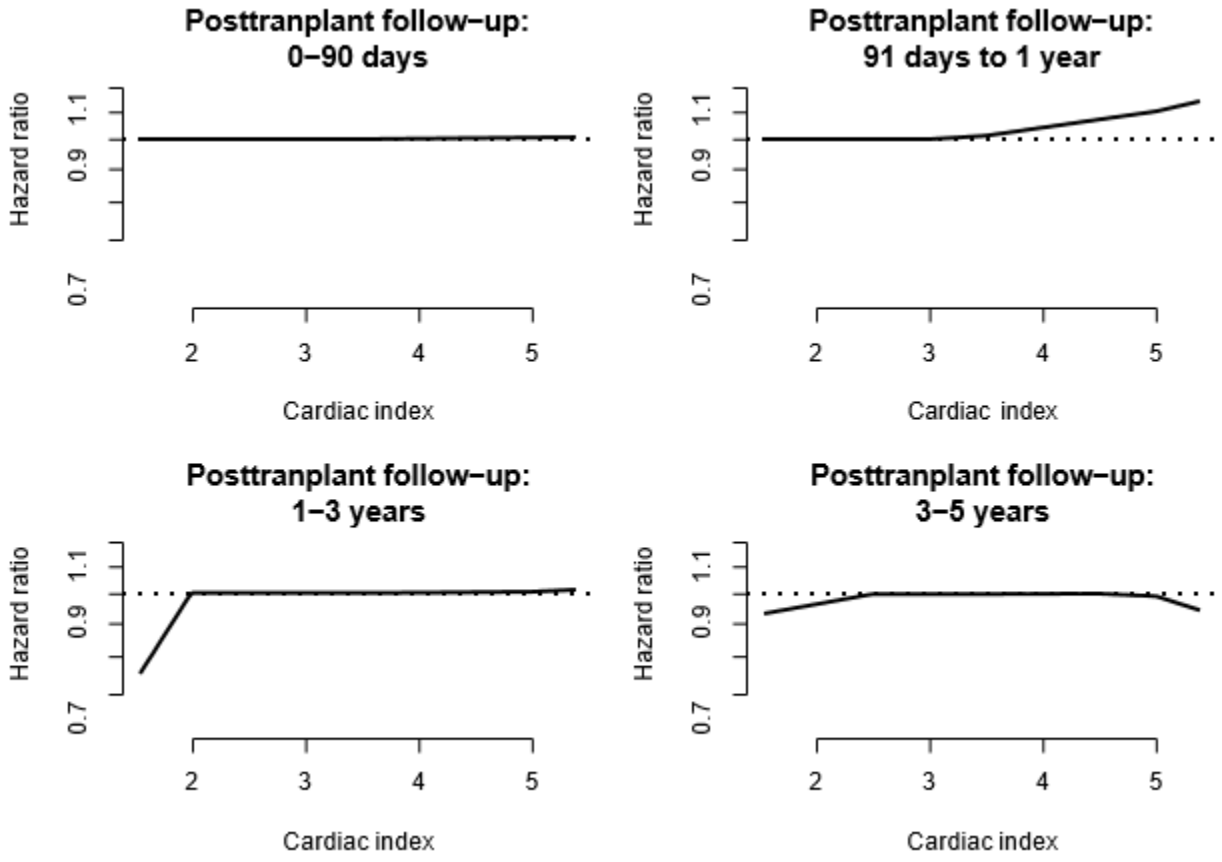

Figure 3: Estimated effect of cardiac index across the different periods of posttransplant follow-up.

7.4 Time-varying effect of serum creatinine

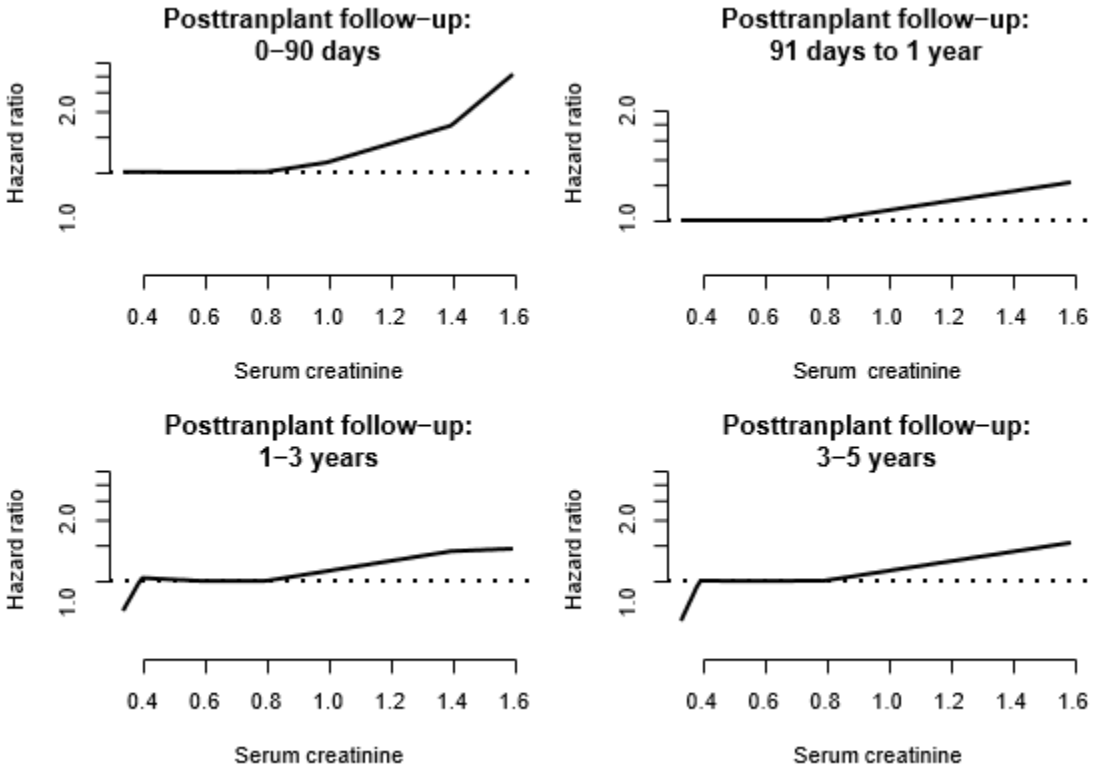

Figure 4: Estimated effect of serum creatinine across the different periods of posttransplant follow-up.

7.5 Time-varying effect of 6-minute walk

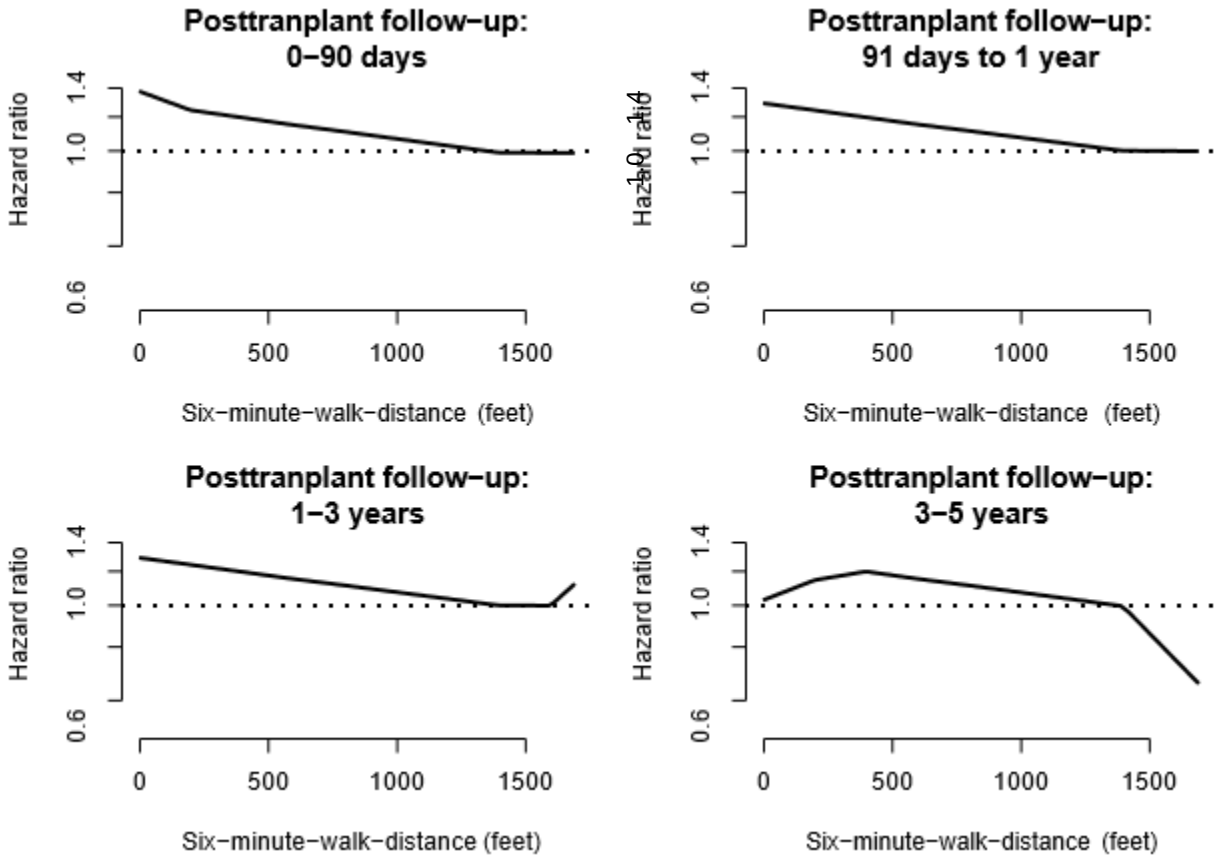

Figure 5: Estimated effect of the 6-minute walk distance across the different periods of posttransplant follow-up.