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Deceased Donor Kidney Transplantation for Older Transplant Candidates: A New Microsimulation Model for Determining Risks and Benefits

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Background. Under the current US kidney allocation system, older candidates receive a disproportionately small share of deceased donor kidneys despite a reserve of potentially usable kidneys that could shorten their wait times. To consider potential health gains from increasing access to kidneys for these candidates, we developed and calibrated a microsimulation model of the transplantation process and long-term outcomes for older deceased donor kidney transplant candidates. **Methods.** We estimated risk equations for transplant outcomes using the Scientific Registry of Transplant Recipients (SRTR), which contains data on all US transplants (2010–2019). A microsimulation model combined these equations to account for competing events. We calibrated the model to key transplant outcomes and used acceptance sampling, retaining the best-fitting 100 parameter sets. We then examined life expectancy gains from allocating kidneys even of lower quality across patient subgroups defined by age and designated race/ethnicity. **Results.** The best-fitting 100 parameter sets (among 4,000,000 sampled) enabled our model to closely match key transplant outcomes. The model demonstrated clear survival benefits for those who receive a deceased donor kidney, even a lower quality one, compared with remaining on the waitlist where there is a risk of removal. The expected gain in survival from receiving a lower quality donor kidney was consistent gains across age and race/ethnic subgroups. **Limitations.** Limited available data on socioeconomic factors. **Conclusions.** Our microsimulation model accurately replicates a range of key kidney transplant outcomes among older candidates and demonstrates that older candidates may derive substantial benefits from transplantation with lower quality kidneys. This model can be used to evaluate policies that have been proposed to address concerns that the current system disincentivizes deceased donor transplants for older patients.

Highlights

- The microsimulation model was consistent with the data after calibration and accurately simulated the transplantation process for older deceased donor kidney transplant candidates.
- There are clear survival benefits for older transplant candidates who receive deceased donor kidneys, even lower quality ones, compared with remaining on the waitlist.
- This model can be used to evaluate policies aimed at increasing transplantation among older candidates.

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In the United States, persons who are 65 y or older make up a large and growing proportion of patients with end-stage kidney disease (ESKD), from 36% to 48% between 1985 and 2009.[1] There is a clear survival benefit to receiving a kidney transplant. Men and women with ESKD aged 65 to 69 y have a remaining life expectancy of 4.8 and 4.9 y if on dialysis or 11.6 and 12.6 y if transplanted, respectively.[2]

However, choosing whether to transplant an individual involves weighing the initial risk of mortality within the first year of transplantation against the potential for longer-term benefits of survival and improved quality of life. Prior studies suggest that for older patients, it takes longer for the benefits of transplantation to outweigh the initial risks from the procedure.[3] While about 50% of patients with ESKD are 65 y or older, they comprise only 20% of patients who receive transplants.[4] This suggests that there is a large, unmet need for these patients.

Despite the exceptionally long waiting times experienced by many patients, some of whom suffer greatly on dialysis, many potentially usable kidneys are discarded. A recent study found that 62% of the kidneys discarded in the United States would have been transplanted under France's system.[5] Another study found that older candidates preferred accepting a lower-quality kidney instead of waiting longer for a higher-quality kidney.[6] These observations suggest that there is an opportunity to use donor kidneys that would currently be discarded to provide more transplants for older candidates, thereby shortening wait times.

It has been suggested that the waste problem may be due to the pressure to optimize transplant outcomes as program performance on selected outcomes are subject to national comparisons.[7] Although performance metrics are being revised, transplant programs are currently assessed on 3 primary performance metrics: first-year graft and patient survival, transplantation rate, and waitlist mortality rate.[8] These metrics have led to unintended consequences of systematic bias against transplanting sicker patients and using less optimal donor kidneys, exacerbating risk aversion and the underprovision of transplantation of older candidates, incentivizing the selection of healthier candidates and higher-quality organs.[9]

To evaluate policies that influence transplantation rates among the older ESKD population, it is first necessary to develop a model that can accurately simulate the complex processes encompassing competing risks from listing, transplantation, graft loss, and death. We estimated a series of risk equations using complete US kidney transplant data such that when they were combined and calibrated, they accurately predict key pre- and posttransplant outcomes and hence quantify the long-term outcomes of transplanting kidneys of different quality in older ESKD candidates.

Methods

Data

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight of the activities of the OPTN and SRTR contractors.

To model waitlist outcomes and post–deceased donor transplant outcomes, we constructed 2 cohorts using the

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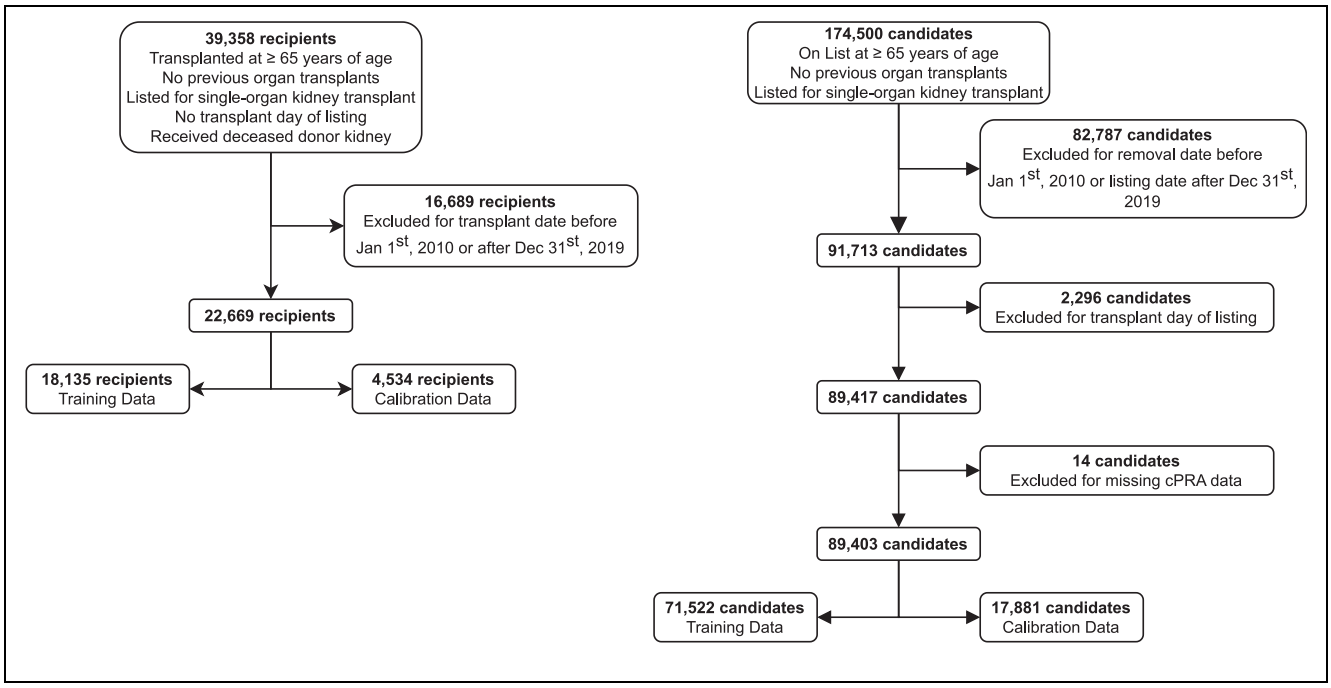

Figure 1 Cohort construction.
Cohort inclusion/exclusion criteria flow chart. A total of 18,135 recipients and 71,522 candidates were used to construct risk prediction equations, and 4,534 recipients and 17,881 candidates were used to calibrate the model.

SRTR data: 1 for waitlist outcomes and 1 for transplant outcomes (Figure 1). The cohort for waitlist outcomes included all kidney transplant candidates who were active on the transplant list at age 65 y or older between January 1, 2010, and December 31, 2019. We excluded those listed for multiorgan transplants or who had received a prior organ transplant. The cohort for transplant outcomes included all deceased donor kidney transplant recipients aged 65 y or older at the time of transplant, with the transplanting having occurred between January 1, 2010, and December 1, 2019. We excluded those listed for multiorgan transplants or who had received a prior organ transplant. This study was approved by the Institutional Review Board of Stanford University (protocol 40876).

Statistical Analysis

We estimated the relevant regression equations for each cohort based on 80% of the available observations with 20% withheld for the purpose of calibrating the microsimulation that combines our estimated equations and accounts for competing risks. We estimated equations to predict waitlist and transplant outcomes. Waitlist outcomes included time to deceased donor kidney transplant, living donor kidney transplant, death on the waitlist, and other removals from the list. Transplant outcomes include 30-d mortality, 30-d graft loss; delayed graft function (DGF), 30-d graft success (defined as no complications within the first 30 d), time to long-term graft loss, time to death with a functioning kidney transplant, and time to death after graft loss. We estimated each equation separately. The equation to predict 30-d outcomes used a multinomial logistic regression, with each outcome being mutually exclusive. Equations for all other outcomes derived from parametric survival analyses. For these equations, we assumed that the hazard function follows a parametric distribution. We examined the graphical representation of Cox-Snell residuals compared with hazards and compared the Akaike information criterion to determine the appropriate distribution.[10] We tested the fit of the following distributions: Weibull, Gompertz, log-normal, and log-logistic. Models using Weibull, log-normal, and log-logistic distributions were parameterized as accelerated-failure time models, while models using the Gompertz distribution were parameterized as proportional-hazards models.

Waitlist outcome equations control for the following patient characteristics: age at listing, sex, designated race/ethnicity, years of dialysis at activation, year of listing, peak calculated panel reactive antibodies (cPRA), blood type, history of diabetes, history of chronic obstructive

pulmonary disease (COPD), history of peripheral vascular disease (PVD), history of angina/coronary artery disease (CAD), and OPTN region. We use cPRA because it is a metric that represents the likelihood of the candidate rejecting a donor kidney, thus making it more difficult to find a match for patients with high cPRA levels. Blood type affects candidates in a similar fashion, such that candidates are not transplanted with deceased donor organs of a different blood type. Therefore, the probability of receiving a deceased donor transplant is limited by the pool of donors with the same blood type. We categorized designated race/ethnicity into 4 groups: non-Hispanic White (White), Black patients of any ethnicity (Black), non-black Hispanic (Hispanic), and other persons of color of any ethnicity not included in the previous categories. We use OPTN regions to account for regional variation in the supply of donor kidneys. The time variable for these outcomes was time from waitlist activation to event.

Transplant outcome equations control for the following patient characteristics: age at transplant, sex, race/ethnicity, years on dialysis before transplant, peak cPRA, blood type, transplant year, history of diabetes, history of COPD, history of PVD, and history of angina/CAD. Transplant outcomes also control for donor-related characteristics including kidney donor profile index (KDPI) and cold ischemia time. KDPI is a composite metric that takes a variety of donor-related characteristics and transforms them into a continuous value between 0 and 100 that is intended to reflect the risk of graft failure. Cold ischemia time is defined as the time during which the blood supply is cut off from the donor until it is restored in the recipient. Cold ischemia times are typically less than 48 h, with the mean time approximately 18.5 h in our data set. This is an important metric because longer cold ischemia times are associated with decreased quality of the donor kidney. In addition to the above variables, the graft loss, death with function, and death after graft loss equations control for whether the recipient experienced DGF. The equation for death with function did not include the transplant year variable. We capped the effect of the transplant year variable to continue only through 2020 so as not to assume linear trends in transplant outcomes beyond our estimated data. For the graft loss and death with function parametric regressions, the time variable was time from transplant. For the death after graft loss parametric regression, the time variable was time from graft loss.

The statistical analysis was conducted using Stata 14 software.[11]

Microsimulation Model Description

The microsimulation model was implemented using the R programming language.[12] It begins with a cohort of candidates who are 65 y or older on the deceased donor waitlist (Figure 2). For each person, there is a monthly probability of 1 of the 4 possible waitlist outcomes occurring: matching with a deceased donor transplant (event of interest), or else either dying on the waitlist, being removed from the waitlist, and receiving a living donor kidney (censoring events). We assume that those who are removed from the waitlist are removed permanently and are no longer eligible for a transplant. We also assumed that those who reach the age of 100 y without an event occurring die on the waitlist.

Candidates who are matched with a deceased donor kidney enter the posttransplant simulation. The model first determines the quality and recency of the deceased donor kidney with which the candidate is matched in terms of KDPI and cold ischemia time, which are important predictors of transplant outcomes. For each donor organ, we use a copula that correlates KDPI and cold ischemia time based on historical data using the R packages "fitdistrplus" and "copula."[13,14]

Each candidate who receives a deceased donor kidney then faces the risk of events for the first 30-d posttransplant outcomes based on the multinomial logistic regression equation. Those who survive the first 30 d are then followed monthly, facing risks of graft loss, death with function, and death after graft loss based on the time-to-event equations. All transplanted patients are assumed to die at age 100 y if they are still alive. We assume that those who experience graft loss are not added back to the waitlist and are thus not eligible to be retransplanted.

Calibration

We performed calibration to ensure that our model simultaneously matched key observed target outcomes and to reflect uncertainty from these empirical targets via our model parameters to our model-predicted outcomes.[15] We derived our targets from observed outcomes of data held out from equation development. The betas for each regression are jointly distributed, so we sought to vary the coefficients of each equation probabilistically while preserving the correlation structure. To do this for parametric survival models, we followed the method of Briggs et al.,[16] which involves a copula-like approach to sample from the multivariate normal distribution of the parameters based on a Cholesky decomposition of the covariance matrix. Our priors assume no correlation

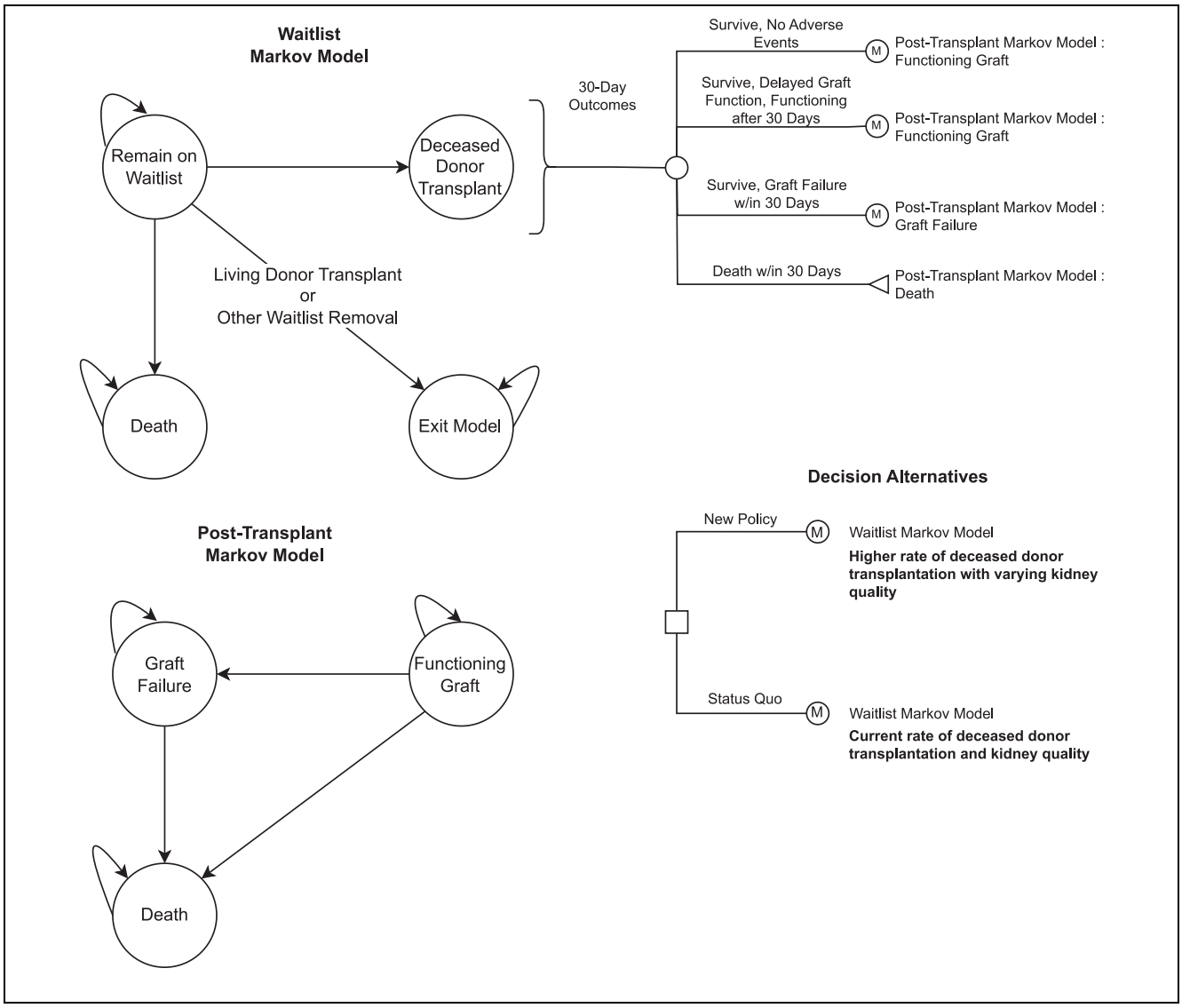

Figure 2 Model diagram.
Model diagram in which individuals start in the waitlist Markov model. If they receive a deceased-donor transplant, they have 1 of the 30-d outcomes before entering the posttransplant Markov model.

across the coefficients from different equations. We simulated 100,000 individuals with the microsimulation model for each parameter set. Using the simulations from each parameter set, we then calculated the goodness of fit based on a sum of squared errors for each outcome divided by the number of targets for each outcome, then summing across all outcomes, so that each outcome was given equal weight. This procedure was repeated 4,000,000 times, resulting in 4,000,000 parameter sets. We then used acceptance sampling with the goal of generating good coverage of the width of our targets by retaining the top 100 best-fitting parameter sets. Finally, these parameter sets are weighted by the sum of the absolute mean differences from the targets divided by the number of targets for each outcome, to give weight to the relative goodness of fit within the top parameter sets. We conducted all further analyses with these 100 best-fitting sets, with their expectations and percentiles weighted by their relative goodness of fit.

To further ensure that we matched the data as precisely as possible, in addition to comparing modeled outcomes to our prespecified targets, we assessed modeled outcomes on the timing of events for consistency with the empirical data. We compared Kaplan-Meier survival curves of the observed, held-out data to the simulated

survival curves generated by each of the 100 accepted parameter sets. We repeated this exercise for key subgroups including by race/ethnicity and by diabetes status.

Using the 100 best-fitting parameter sets, we then estimated life expectancy for those who receive a deceased donor transplant compared with those who do not receive one. We assumed post–waitlist removal survival times based on the 2020 United States Renal Data System Annual Data Report, which contains survival times by treatment modality and age group through 2018.[2] We will also examine life expectancy for those who receive a transplant in 4 categories of KDPI values: 0 to 20, 21 to 34, 35 to 85, and 86 to 100. These cut points are used for allocation decisions in the following ways: 1) KDPI values of 0 to 20 are first offered to patients with the highest 20% estimated posttransplant survival times, 2) KPDI values of 21 to 34 and 35 to 85 each have their own allocation rules, and 3) KDPI values of 86 to 100 are offered only to candidates willing to accept them.

The data reported here have been supplied by the Hennepin Healthcare Research Institute as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US government. This project was supported by grant T32HS026128 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Results

Model Calibration

From our 4 million parameter sets, we identified the top 100 best-fitting sets. We then compared the simulated outcomes to targets for key model outcomes (weighted mean and 95% credible intervals (CrIs). Figure 3 shows good concordance between the model-predicted and observed outcomes for the top 100 parameter sets. The model shows less uncertainty in the calibrated parameter sets with respect to the pretransplant outcomes as compared with the posttransplant outcomes, since the uncertainty with respect to the posttransplant outcome includes any deviation from the observed pretransplant population and its outcomes. When we instantiated the observed population of individuals who received a transplant, the uncertainty with respect to the posttransplant outcomes was substantially smaller.

A crucial component of accurately predicting posttransplant outcomes is simulating a patient mix of deceased-donor recipients similar to the observed characteristics. Supplementary Table S1 compares the transplant recipient characteristics between the simulated and observed cohorts. The model accurately replicates the patient mix in terms of their observed recipient characteristics.

The model also replicates the timing of key outcomes, as appears in the observed held-out data. Figure 4 shows survival curves resulting from each of the top 100 parameter sets (in gray) compared with the observed survival curve (in red). The line weight for each of the parameter sets represents the relative goodness of fit within the top 100. Corresponding modeled outcomes for key subgroups including by designated race/ethnicity and diabetes status also demonstrated good concordance with the observed data (Supplementary Figures S2 and S3).

Simulated Benefits of Transplantation

Using the best-fitting parameter sets from model calibration, we calculated the estimated weighted mean survival time. Our simulations show that for transplant candidates 65 y and older, the mean survival time for those who do not receive a transplant is 5.9 (95% CrI: 5.7–6.1) y. These values differ by sex, where, on average, male candidates who do not receive transplants are expected to live for 5.7 (95% CrI: 5.5–5.9) y, while female candidates who do not receive a transplant live for 6.1 (95% CrI: 5.9–6.3) y. For those candidates who accept the lowest quality kidneys as measured by a KDPI value of 85 or greater, the expected survival is 8.4 (95% CrI: 6.8–9.9) y (Figure 5). This shows that transplanting with even a lower quality kidney can substantially extend life expectancy. The benefits of receiving a deceased-donor kidney are consistent across designated race/ethnicity and age at listing groups. The average life expectancy for those who receive high KDPI (86+) kidneys in each designated race/ethnicity group is 8.2 (95% CrI: 6.7–9.7) y, 8.4 (95% CrI: 6.5–9.9) y, 8.7 (95% CrI: 7.2–10.2) y, and 9.3 (95% CrI: 7.7–10.5) y for White, Black, Hispanic, and other people of color, respectively (Supplementary Table S8). Transplant-related extension of life expectancy holds true even for those who were added to the waitlist at 75 y of age or older, where the mean survival time for those who receive a high KDPI kidney is 7.2 (95% CrI: 5.6–8.8) y compared with 5.3 (95% CrI: 5.0–5.5) y if they do not receive a transplant.

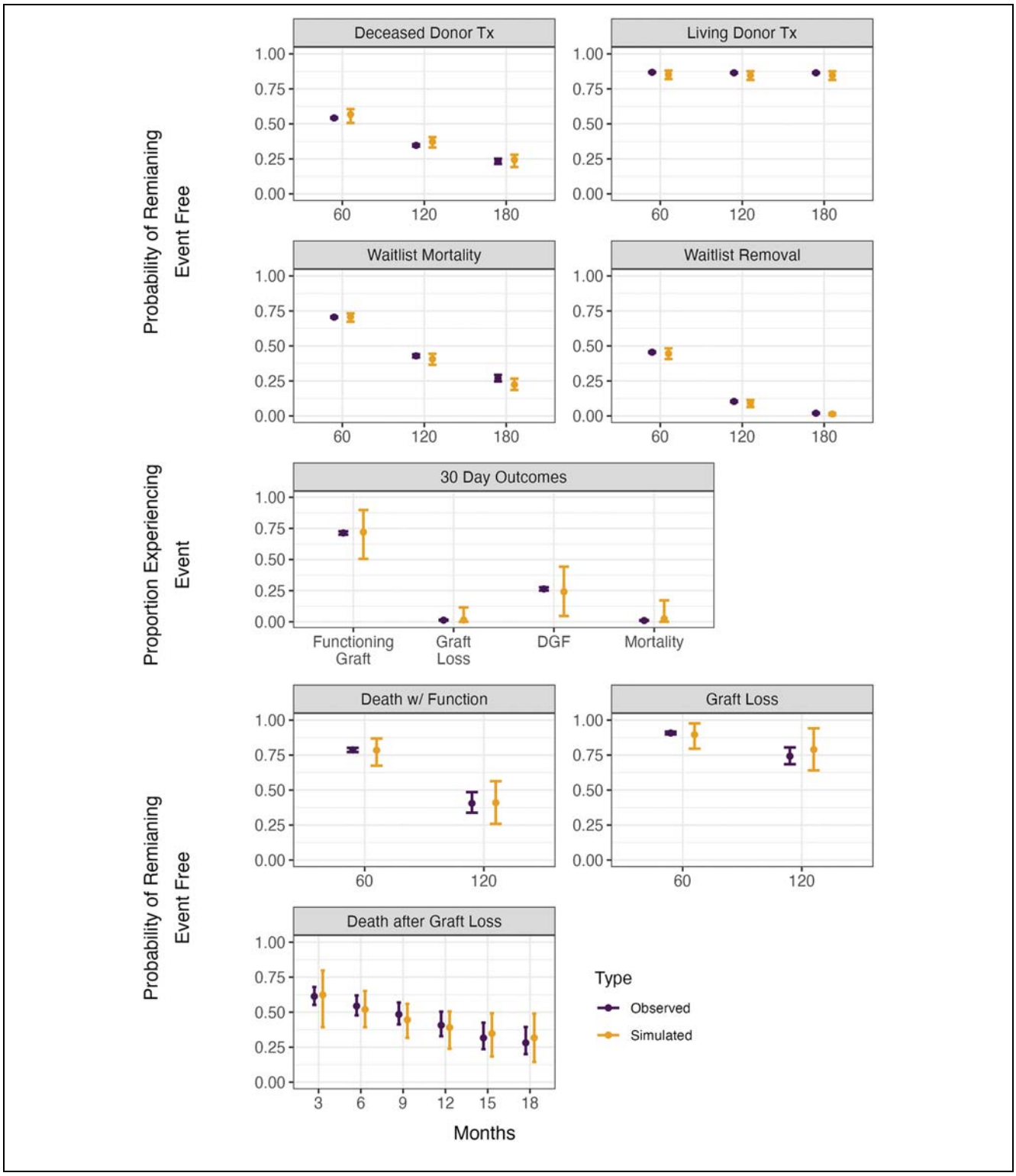

Figure 3 Simulated outcomes compared with observed targets.
Results of calibration comparing observed to simulated targets, showing strong fit to our targets.

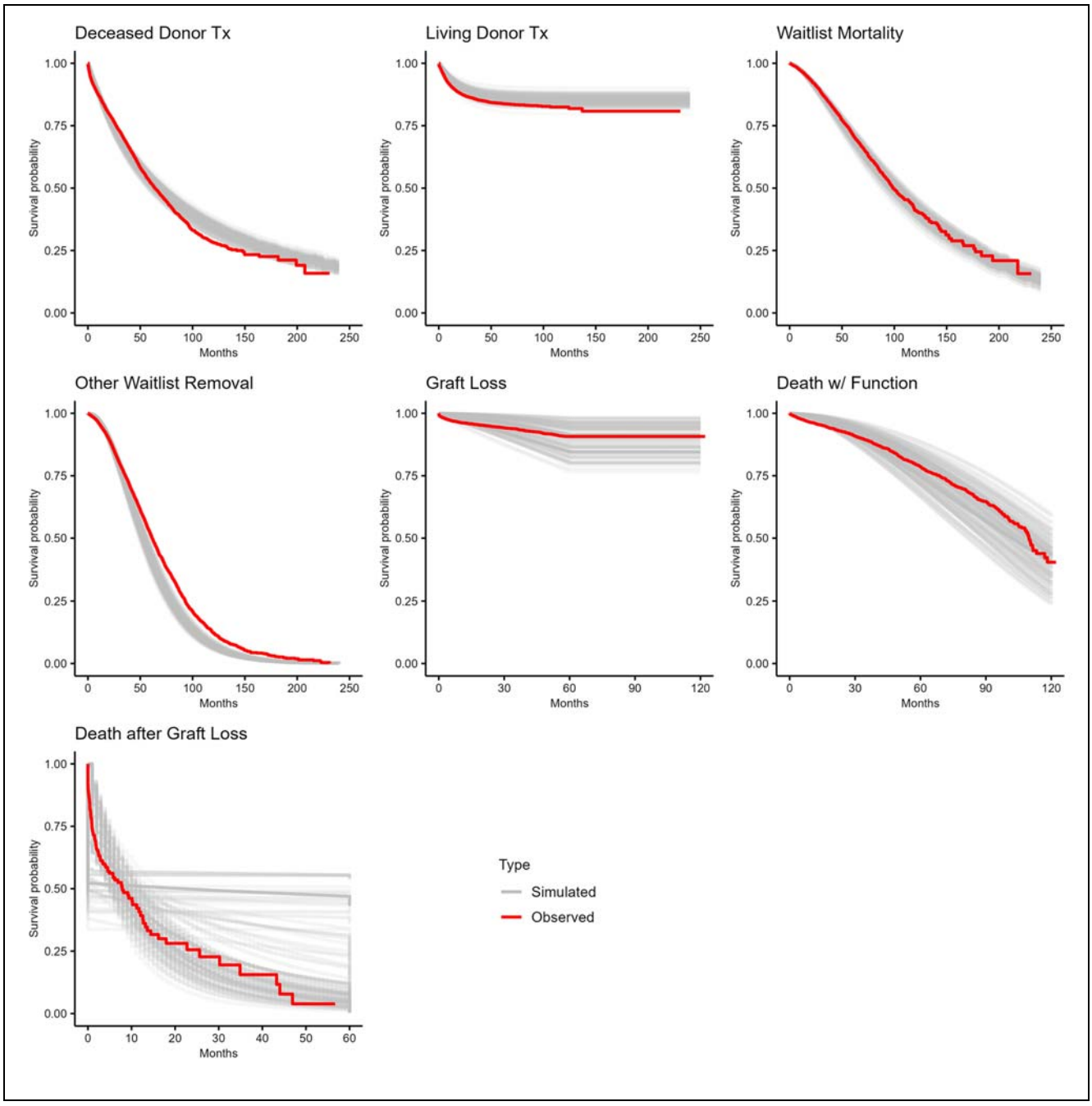

Figure 4 Kaplan-Meier curves: simulated versus observed outcomes.
Kaplan-Meier curves comparing simulated to observed survival. The gray curves each represent 1 of the simulated best-fitting parameter sets, while the red curve represents the observed data.

Discussion

To evaluate the effects of policy options relating to allocation of kidneys, it is necessary to develop a model that can simulate the entire transplantation process for the older ESKD population. Our microsimulation model accurately replicates a range of key kidney transplant outcomes among older candidates and demonstrates that they may derive substantial benefits even from suboptimal kidneys that are currently infrequently transplanted. We developed and calibrated the series of risk equations

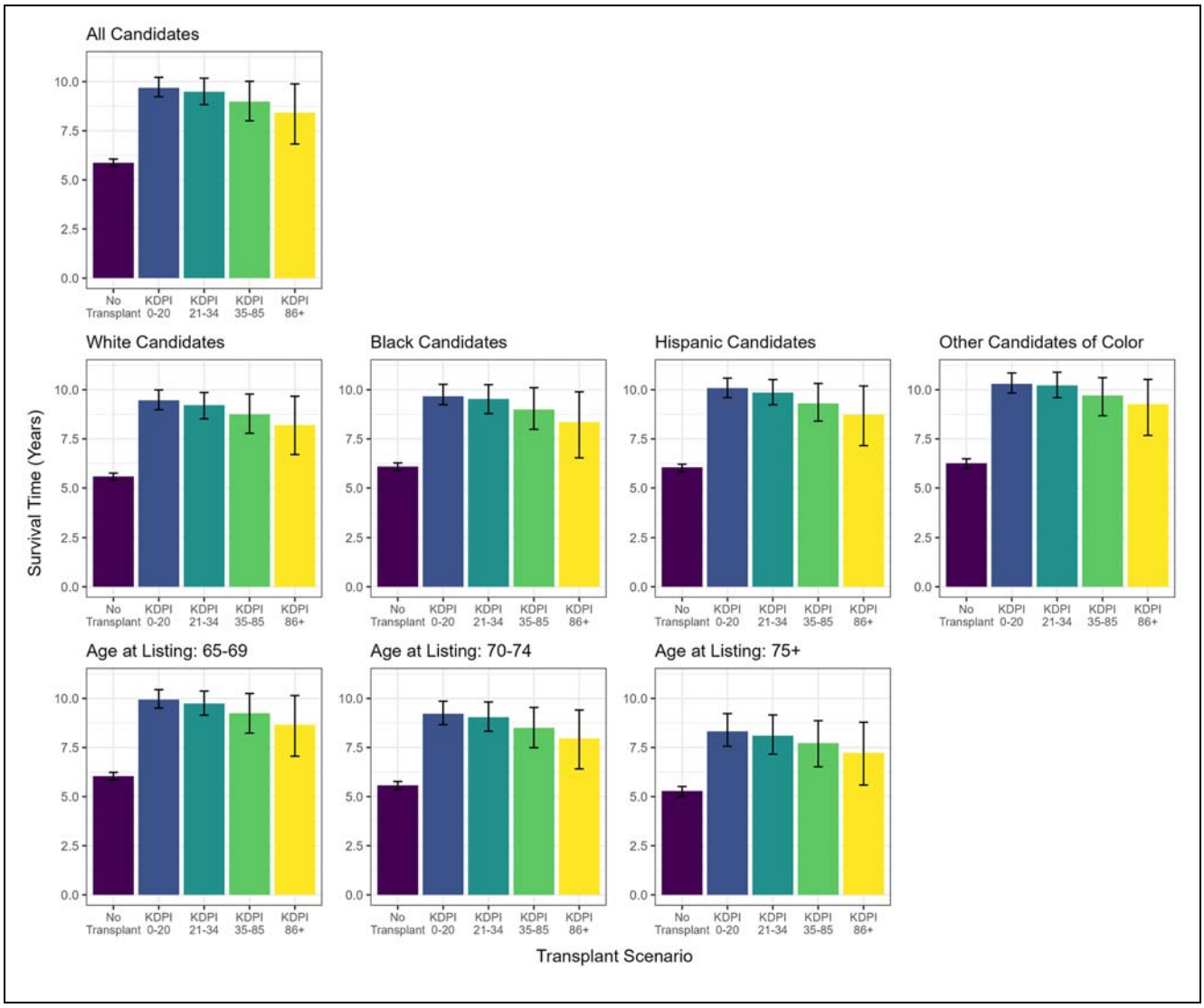

Figure 5 Expected survival by subgroup.
Life expectancy by subgroup. The top row is for all candidates, the middle row is by race/ethnicity, and the bottom row is by age at listing. We see consistent benefits of transplantation across all subgroups.

that encompass competing risks from listing, transplantation, graft loss, and death, using older patient-specific characteristics. We have demonstrated how risk equations that have been developed independently can be combined to accurately predict the outcomes of interest. We have also demonstrated the capability of the model to project life expectancy. The current system likely undertransplants patients 65 y of age and older, as we have shown that they could potentially gain several years of life expectancy even if they are transplanted with lower-quality kidneys that are often discarded.

Compared with France, the United States transplants donor kidneys that are on average higher quality at the cost of discarding many more recovered kidneys. From 2004 to 2014, the mean KDPI of transplanted kidneys in the United States was 45, compared with 60 in France. Unfortunately, the United States also discarded 17.9% of recovered kidneys, while France discarded only 9.1%.[4] Some potential policies to consider that make better use of recovered donor kidneys are a conditional listing policy and an exemption policy. A conditional listing policy would list older candidates only if they are willing

to accept a high KDPI kidney, and an exemption policy would prospectively exempt some older candidates from transplant center performance metrics, incentivizing centers to transplant more older candidates.

It is important to note that the model is not meant to be used as an individual-level risk prediction tool. Rather, its prediction accuracy with respect to the patient population and patient subgroups are most relevant for evaluating the comparative effectiveness of policies.

We were unable to perform external validation due to the comprehensive nature of the SRTR data set and the lack of studies with an older population in non-US settings. However, fitting SRTR data well overall and with respect to subgroups is strong evidence of validity.

One limitation of the model is the limited ability to incorporate socioeconomic variables into the risk equations. While the SRTR data set captures data on all solid-organ transplants in the United States, it does not collect many socioeconomic variables. We tested additional variables that were ultimately omitted because they did not improve the predictions. Ultimately, the designated race and ethnicity variables likely reflect information on how outcomes vary due to socioeconomic differences that correlate with race and ethnicity as well as systemic issues including access to, and systematic biases in, health care. We also would note that in our categorization of race and ethnicity, other persons of color represent a diverse array of groups who might have very different biology and life experience. The model was developed and calibrated for an older kidney transplant population in the United States and would require additional work and validation to apply to transplant systems in other countries. As with all observational and modeling studies, we deal with the issue of residual confounding. By using administrative data, we lack the granularity that would improve our predictions. For example, we are unable to determine how well controlled a patient's diabetes is, which would greatly affect their probability of waitlist and posttransplant outcomes. However, on average, we predict transplant outcomes accurately for the patients with and without diabetes.

Overall, the model we have constructed and calibrated closely mimics the transplantation process, from listing for transplantation through post–deceased donor transplantation outcomes. Alternative allocation policies have been proposed to address concerns that the current system disincentivizes deceased donor transplants for older and sicker patients. It is crucial to provide prospective evidence of policies that will achieve crucial health gains in an underserved, sick population. As the kidney transplant community considers changes to performance metrics, our microsimulation model can serve as a crucial input to shaping the future landscape of kidney transplantation policy.

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Supplemental Material

Supplementary material for this article is available on the *Medical Decision Making* Web site at http://journals.sagepub.com/home/mdm.

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