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The Lifetime Health Burden of Delayed Graft Function in Kidney Transplant Recipients in the United States

Devin Incerti, Nicholas Summers, Thanh G. N. Ton, Audra Boscoe, Anil Chandraker, and Warren Stevens

Abstract

Background. Although delayed graft function (DGF) is associated with an increased risk of acute rejection and decreased graft survival, there are no estimates of the long-term or lifetime health burden of DGF. **Objectives.** To estimate the long-term and lifetime health burden of DGF, defined as the need for at least one dialysis session within the first week after transplantation, for a cohort representative of patients who had their first kidney transplant in 2014. **Methods.** Data from the United States Renal Data System (USRDS; 2001–2014) were used to estimate a semi-Markov parametric multi-state model with three disease states. Maximum length of follow-up was 13.7 years, and a microsimulation model was used to extrapolate results over a lifetime. The impact of DGF was assessed by simulating the model for each patient in the cohort with and without DGF. **Results.** At the end of 13.7 years of follow-up, DGF reduces the probability of having a functioning graft from 52% to 32%, increases the probability of being on dialysis from 10% to 19%, and increases the probability of death from 38% to 50% relative to transplant recipients who do not experience DGF. A typical transplant recipient with DGF (median age = 53) is observed to lose 0.87 quality-adjusted life-years (QALYs). Extrapolated over a lifetime, the same 53-year-old DGF patient is projected to lose 3.01 (95% confidence interval: 2.33, 3.70) QALYs relative to a transplant recipient with the same characteristics who does not experience DGF. **Conclusions.** The lifetime health burden of DGF is substantial. Understanding these consequences will help health care providers weigh kidney transplant decisions and inform policies for patients in the context of varying risks of DGF.

Keywords

kidney transplant, delayed graft function, graft failure, semi-Markov multi-state model, microsimulation

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In December 2014, nearly 100,000 patients were on the kidney transplant waitlist in the United States after being diagnosed with end-stage renal disease and treated with dialysis.[1] Kidney transplants are a proven treatment option that have been shown to improve survival[2,3] and quality of life,[3–6] yet only a fraction of patients on the waitlist ever receive this benefit.[7] Given the limited supply of available kidney grafts and the high demand from waitlist patients, clinicians tend to exercise caution when assessing risks and evaluating patients for transplantation.[8,9] One such risk is the complication of delayed graft function (DGF). DGF is a manifestation of acute kidney injury with attributes unique to the transplant process where the transplanted kidney does not initially function posttransplant. The definition of DGF varies across transplant centers, regions, and countries with over 10 definitions having been used in the literature.[10,11] The

Corresponding Author
Devin Incerti, Precision Health Economics, 555 12th St. Suite #1725, Oakland, CA 94607, USA
(Devin.Incerti@PrecisionHealthEconomics.com)

most common definition—both in the academic literature and in epidemiologic registries—is the need for dialysis in the first postoperative week.[12] A recent study comparing the definitions suggested that no one definition is inherently superior and proposed the use of dialysis within the first week after transplant as the most straightforward.[13] A recent review of over 80,000 US deceased donor kidney transplant recipients revealed that, although considerable center-level variation exists, at a national level 27% of transplant recipients developed DGF.[14] This is notable given that patients with transplants complicated by DGF are at a greater risk for graft failure and acute rejection.[15]

To make an informed decision considering the relative benefits of various treatment pathways, it is valuable for patients and care providers to understand both the probability of complications and the lifetime impact of those complications on a patient's well-being. Risk prediction models have been developed to assist with kidney transplant decision making by identifying individual patients at high risk for developing adverse outcomes, such as DGF, prior to actual transplantation.[16,17] However, proper decision making about transplantation requires full knowledge and appreciation of the magnitude of risk being undertaken. Observational, single-center studies examining health outcomes from DGF in the United States are often hindered by small sample sizes and short- or medium-term patient follow-up.[18–20] US-based registry cohort studies, while having much greater sample sizes, also tend to have limited follow-up time.[21,22] As a result, much is known about the short-term (<5 years) effects of DGF on graft survival and acute rejection,[15] but little is known about its long-term consequences such as its impact on mortality.

In this study, we examine long-term outcomes by using a long follow-up (median = 7.1 years, maximum = 13.7 years) of data from the United States Renal Data System (USRDS) and extrapolate results over a lifetime using a microsimulation model. Simulation and other extrapolation techniques have been used to estimate the cost-effectiveness, comparative effectiveness, and lifetime health burdens associated with kidney disease,[7,23–26] but have not been used to study the effects of DGF. For example, Wolfe and colleagues,[23] in a seminal paper, used survival models to calculate differences in life expectancy between patients with and without transplant—also known as life years from transplant—which has been applied to inform kidney allocation policies.

In this study, we use the data in the USRDS to estimate a semi-Markov parametric multi-state model—a generalization of standard survival analysis to multiple disease states.[27–31] The richness of the data source enables us to estimate the model using individual patient data based on thousands of transplant recipients. After estimating the statistical model, we made predictions by developing a microsimulation and simulating outcomes for individual patients. The simulated output was then used to quantify the lifetime health burden of DGF for US kidney transplant recipients, which will help health care providers properly weigh kidney transplant decisions and inform policies for patients in the context of varying risks of DGF.

Methods

Sample and Model Overview

We developed a multi-state model to quantify the disease burden of DGF following kidney transplantation. Figure 1 illustrates a patient's passage through the model where he or she begins with a transplant, at which point the graft is functioning until it either fails and the patient goes onto dialysis or the patient dies. A patient on dialysis can then either have a subsequent transplant (and return to a functioning graft state) or die while on dialysis. Therefore, there are four possible transitions in the model. These possibilities highlight the two transient health states (transplant/functioning graft, dialysis) in our model and the single absorbing state (death).

To help ensure that transition rates were consistent with real-world clinical outcomes, we modeled transitions between states using a semi-Markov model, which allows transition rates to be a flexible function of time spent in a given state. We estimated the burden of DGF in two stages by first estimating transition rates absent DGF and then estimating the effect of DGF on transition rates. This two-stage approach has two primary benefits. First, it allowed us to accurately predict clinical outcomes

Precision Health Economics, Oakland, California (DI, NS, TGNT, WS); Alexion Pharmaceuticals Inc., New Haven, Connecticut (AB); Brigham and Women's Hospital, Boston, Massachusetts (AC). AB was employed by Alexion Pharmaceuticals, Inc. at the time the manuscript was drafted; AC is a consultant for Alexion Pharmaceuticals, Inc. DI and NS are employees of Precision Health Economics; TT and WS were employees of Precision Health Economics at the time the manuscript was drafted. Precision Health Economics provides consulting and research services to a variety of firms in the pharmaceutical, biotechnology, and health insurance industries. The data reported here have been supplied by the United States Renal Data System. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the US government. Financial support for this study was provided entirely by a contract with Alexion Pharmaceuticals, Inc. The funding agreement ensured the authors' independence in designing the study, interpreting the data, writing, and publishing the report.

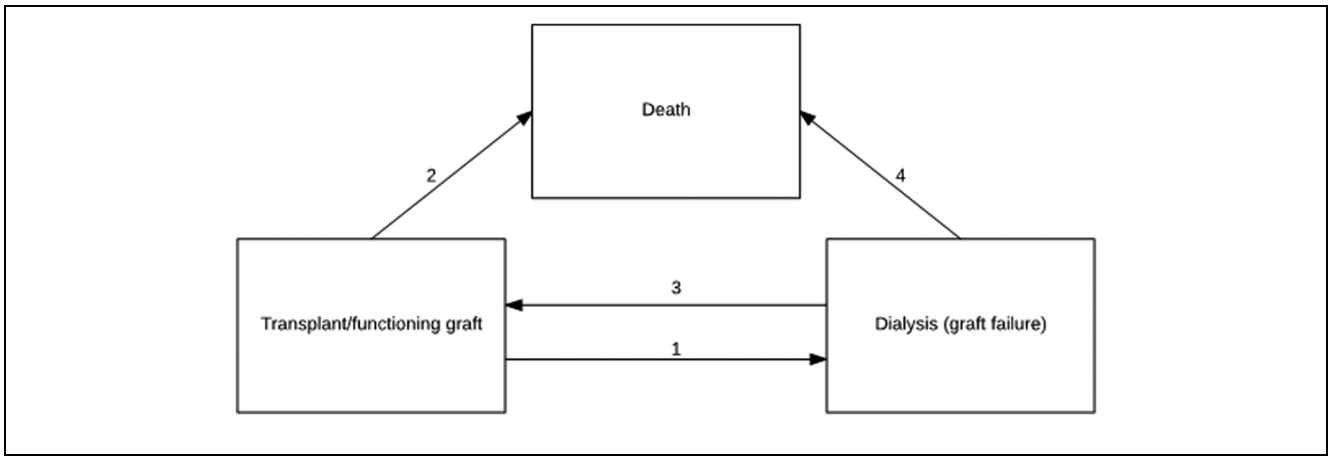

Figure 1 Diagram of a multistate model for kidney transplantation. The boxes represent the 3 disease states and 4 possible transitions (1, transplant/functioning graft to dialysis; 2, transplant/functioning graft to death; 3, dialysis to transplant/functioning graft; 4, dialysis to death). Patients begin the model with a transplant and remain in the functioning graft state until it fails, at which point the patient either goes onto dialysis or the patient dies. A patient on dialysis can then either have a subsequent transplant (and return to a functioning graft state) or die while on dialysis.

Table 1 Number and Percentages of Transitions Between Disease States[a]

Origin State	Patients	Destination State		
		Functioning Graft	Dialysis	Death
No DGF, n (%)				
Functioning graft	131,217 (100%)	92,375 (70%)[b]	21,031 (16%)	17,811 (14%)
Dialysis	21,031 (100%)	2,216 (11%)	11,421 (54%)[b]	7,394 (35%)
DGF, n (%)				
Functioning graft	31,224 (100%)	17,271 (55%)[b]	8,553 (27%)	5,400 (17%)
Dialysis	8,553 (100%)	1,042 (12%)	3,955 (46%)[b]	3,556 (42%)

DGF, delayed graft function.
[a]Patients can be in each state more than once.
[b]Patients who remained in origin state until end of follow-up.

by age and sex without losing observations with missing covariates. Second, we were able to estimate the clinical impact of DGF by using a model designed to minimize confounding rather than a model designed to predict outcomes. Long-run health outcomes were simulated over a lifetime by using the parameters of the multi-state state model as inputs for a microsimulation.

The parameters of the multi-state model were estimated using data from the USRDS for patients who had any kidney transplant during the time period spanning 2001 to 2014, yielding a maximum length of follow-up of 13.7 years. We limited our sample to patients aged 18 and older who had a transplant in 2001 or later, which resulted in a sample of 159,183 unique patients and a total of 162,441 transplants. Additional details of the observations dropped from our analysis are provided in the eMethods section of the Online Supplement.

Transitions Without DGF

Transitions for patients without DGF were modeled as a function of patient age and sex. In addition, variables were included that indicated whether a transplant occurred after 2009 and whether it was a patient's first transplant.

Table 1 shows the number of non-DGF patients at risk for transitioning from each state, as well as the number of actual transitions from origin states to destination

states. Of the 131,217 times that a non-DGF patient had a transplant in our estimation sample, 92,375 had a functioning graft until the end of follow-up; 21,031 had a graft fail; and 17,811 died. Of the 21,031 observations in which a patient was on dialysis after a graft failure, 2,216 had a subsequent transplant; 11,421 remained on dialysis until the end of follow-up; and 7,394 died.

We used R's *flexsurv* package[32] to estimate hazards for each of the four transitions using parametric proportional hazard models (exponential, Weibull, and Gompertz). Plots of cumulative hazards for the four transitions are shown in eFigure 1. For each transition, graphical methods were used to choose the best fitting distribution. In particular, we first inspected the cumulative hazard plots to examine the fit of the transition-specific hazard functions. However, since the probability of being in a state is derived by combining the hazard functions of relevant transitions involving that state,[33] we ultimately determined the fit of the model by assessing the probability of being in each of the three disease states, as discussed in the Model Validation section below. The Gompertz distribution was used for the transitions from transplant/functioning graft to dialysis, transplant/functioning graft to death, and dialysis to transplant/functioning graft. The Weibull distribution was used for the transition from dialysis to death. Parameter estimates for the parametric models are provided in eTable 1.

Effect of DGF on Transitions

Table 1 suggests that DGF patients are more likely to transition from a functioning graft to dialysis than non-DGF patients. For instance, 27% of DGF patients transitioned from a functioning graft to dialysis compared to only 16% of patients without DGF. Patients with DGF (17%) were also slightly more like to transition from functioning graft to death than non-DGF patients (14%).

To account for the potential of confounding variables driving these results, we estimated the association between DGF and transition rates controlling for patient and donor characteristics. While the objective of the model for non-DGF patients described in the previous section was to predict absolute transition probabilities stratified by age and sex, the objective here was to estimate the effect of DGF relative to not having DGF on transition probabilities. We therefore attempted to control for all variables correlated with both DGF and transition rates in the USRDS in an effort to minimize confounding. Summary statistics for covariates are reported in eTable 2, and hazard ratios from the model are reported in eTable 3.

To simulate patients with DGF, we applied the DGF hazard ratio to the transition rates for patients without DGF for each transition. More precisely, we multiplied the DGF hazard ratio by the hazard function for each non-DGF transition.

Microsimulation

We used the parameters estimated from the parametric multi-state model to develop a continuous-time stochastic lifetime microsimulation. The model simulates hypothetical patients one at a time from their first transplant until death. To examine the incremental impact of DGF, the model was simulated in a hypothetical situation where, during the initial transplant, each patient had DGF and hypothetical situation where no patient had DGF.

The time spent in each disease state was a function of the transition hazards estimated in the statistical analysis, which depended on the unique characteristics of each individual; specifically, we randomly sampled times to all possible disease states that a patient could transition to and set the next state equal to the disease state with the shortest sampled time. Transition rates for non-DGF patients depended on the covariates in the statistical model for non-DGF patients reported in eTable 1—age, age-squared, gender, whether the transplant occurred after 2009, and whether the transplant was the patient's first transplant—and transition rates for DGF patients were equal to those for non-DGF patients but adjusted by the hazard ratios reported in eTable 3. The covariates age and age-squared were updated at the time of each transition. Likewise, whether a patient had DGF was randomly sampled at the time of each new transplant as a function of whether the patient had DGF during the initial transplant. The probabilities of DGF in re-transplants were 0.29 and 0.16 for patients with and without DGF, respectively, which were estimated based on observed frequencies in the USRDS data.

In order to estimate expected outcomes for current transplant recipients, we simulated a representative cohort of 10,000 patients using the characteristics of patients in the USRDS who had their first transplant in 2014. We also ran the model separately by 5-year age groups by simulating 10,000 patients in each age band. Probabilistic sensitivity analysis was used to quantify uncertainty in model outcomes, where the regression coefficients for each transition were sampled 1,000 times from multivariate normal probability distributions to

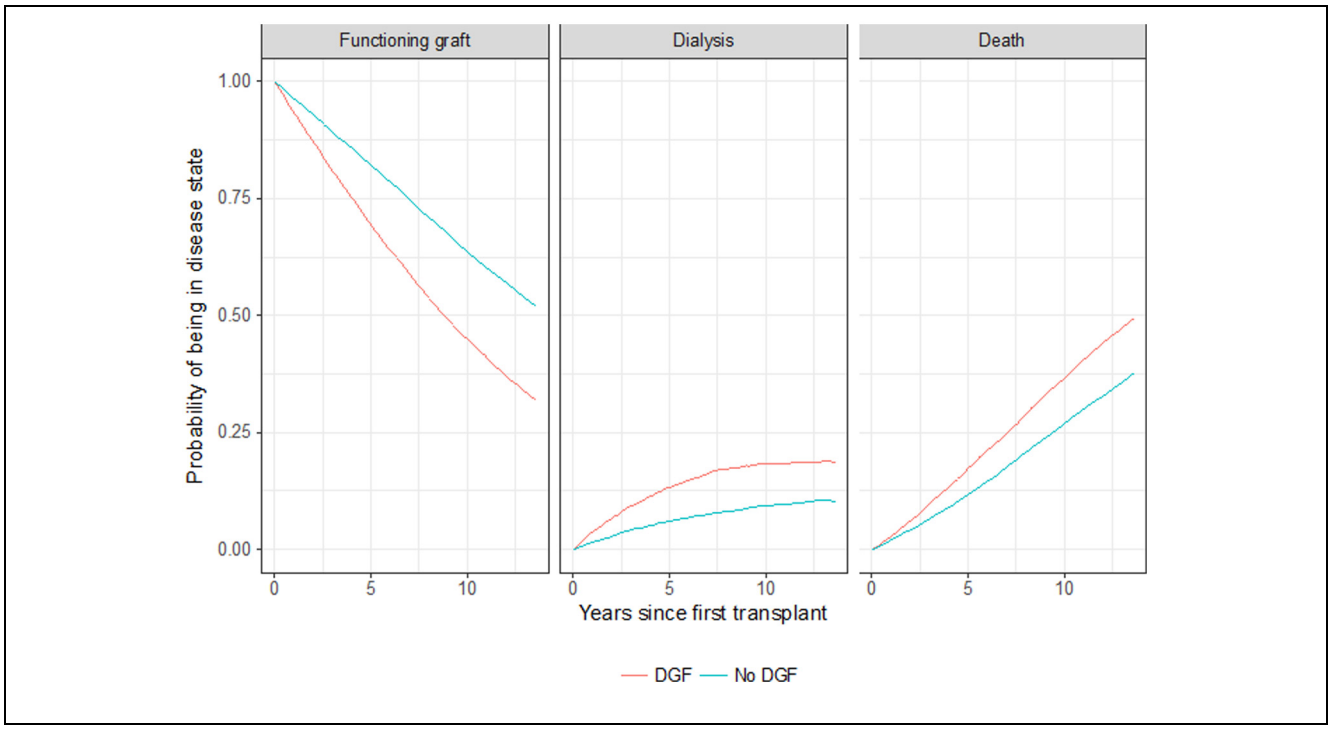

Figure 2 Estimated probability of being in disease state following transplantation by DGF status using microsimulation.

generate probability distributions for expected quality-adjusted life-years (QALYs). The number of simulated patients and samples in the probabilistic sensitivity analysis were large enough that expected outcomes and Bayesian credible intervals were stable.

The simulation was used to estimate 1) the probability of being in each disease state (functioning graft, on dialysis, or death) posttransplant and 2) QALYs posttransplant. Results were compared for patients who experienced DGF versus those who did not experience DGF. To estimate QALYs, we weighted each year lived with a functioning graft and dialysis by 0.84 and 0.68, respectively, based on QALY weights from the literature.[25,34] Additional details of the algorithm and calculation of disease state probabilities are provided in eMethods in the Online Supplement. The model was programmed using C++ and integrated with R using the *Rcpp* package so that it could be run quickly.[35]

Model Validation

We conducted a number of analyses to check our assumptions. First, we examined the sensitivity of our results to the parametric distributions used in the model. We began by comparing results from our parametric approach to a less model driven semiparametric approach. In particular, we compared the accuracy of our parametric microsimulation during available follow-up time (13.7 years) to a microsimulation using the Cox multi-state model. Second, we checked the external validity of our estimates by comparing our results to estimates from official reports and published studies cited in the Results section. We focused specifically on median graft survival and life expectancy following transplantation. Third, we considered the potential impact of re-transplantation given the shortage of data for patients receiving multiple transplants.[24]

Results

Disease State Probabilities

Figure 2 plots the probability that a patient occupies a given disease state at any given time after their first transplant. Patients with DGF are less likely to have a functioning graft at all times following transplantation, spend considerably more time on dialysis, and have higher mortality rates than patients without DGF. At the end of follow-up (13.7 years), DGF patients have a 32% chance of having a functioning graft, a 19% chance of being on dialysis, and a 50% chance of being deceased.

Table 2 Quality-Adjusted Life Years by DGF Status and Time Since First Transplant From the Microsimulation[a]

Age Group	Quality-Adjusted Life Years		
	No DGF	DGF	QALYs Lost
Follow-up (13.7 years)			
20–24	10.59 (10.37, 10.82)	9.92 (9.52, 10.32)	0.67 (0.37, 0.97)
25–29	10.58 (10.39, 10.78)	9.92 (9.58, 10.26)	0.67 (0.38, 0.95)
30–34	10.52 (10.35, 10.70)	9.86 (9.54, 10.17)	0.67 (0.41, 0.92)
35–39	10.42 (10.27, 10.57)	9.73 (9.45, 10.02)	0.69 (0.45, 0.93)
40–44	10.24 (10.09, 10.40)	9.51 (9.25, 9.77)	0.74 (0.51, 0.96)
45–49	10.01 (9.86, 10.15)	9.21 (8.95, 9.47)	0.80 (0.57, 1.02)
50–54	9.70 (9.56, 9.84)	8.83 (8.58, 9.07)	0.87 (0.66, 1.08)
55–59	9.29 (9.14, 9.45)	8.32 (8.08, 8.56)	0.97 (0.76, 1.17)
60–64	8.79 (8.64, 8.95)	7.72 (7.49, 7.95)	1.07 (0.87, 1.28)
65–69	8.23 (8.07, 8.39)	7.06 (6.83, 7.30)	1.17 (0.97, 1.37)
70–74	7.56 (7.38, 7.73)	6.30 (6.08, 6.55)	1.25 (1.05, 1.45)
75–79	6.83 (6.64, 7.01)	5.53 (5.29, 5.77)	1.30 (1.10, 1.48)
All	9.28 (9.14, 9.44)	8.34 (8.10, 8.58)	0.95(0.73, 1.15)
Lifetime			
20–24	31.01 (28.85, 33.10)	30.30 (27.74, 32.77)	0.71 (−0.88, 2.35)
25–29	28.22 (26.36, 30.07)	26.82 (24.60, 29.16)	1.40 (−0.01, 2.93)
30–34	25.59 (24.06, 27.14)	23.52 (21.65, 25.48)	2.07 (0.77, 3.41)
35–39	23.15 (21.82, 24.50)	20.56 (18.92, 22.21)	2.58 (1.44, 3.74)
40–44	20.75 (19.66, 21.85)	17.83 (16.53, 19.16)	2.91 (1.89, 3.90)
45–49	18.53 (17.62, 19.45)	15.50 (14.48, 16.59)	3.03 (2.16, 3.82)
50–54	16.44 (15.67, 17.20)	13.43 (12.57, 14.31)	3.01 (2.33, 3.70)
55–59	14.39 (13.79, 15.03)	11.50 (10.83, 12.18)	2.89 (2.31, 3.45)
60–64	12.47 (11.93, 12.98)	9.79 (9.27, 10.36)	2.68 (2.23, 3.14)
65–69	10.81 (10.37, 11.24)	8.37 (7.93, 8.83)	2.44 (2.08, 2.81)
70–74	9.21 (8.85, 9.58)	7.03 (6.65, 7.43)	2.17 (1.85, 2.47)
75–79	7.79 (7.48, 8.12)	5.90 (5.58, 6.22)	1.89 (1.64, 2.15)
All	16.25 (15.46, 17.03)	13.65(12.77, 14.54)	2.60 (1.94, 3.27)

DGF, delayed graft function; QALY, quality-adjusted life year; USRDS, United States Renal Data System.
[a]Point estimate is mean value from probabilistic sensitivity analysis; 2.5% and 97.5% quantiles are in parentheses. Estimates are based on a simulation of all patients in the USRDS who had their first transplant in 2014. The age group "All" consisted of all patients 18 years or older. Median age at first transplant was 53 years.

Meanwhile, their non-DGF counterparts are more likely to have a functioning graft (52%), less likely to be on dialysis (10%), and less likely to be deceased (38%).

QALYs Lost

Table 2 reports QALYs at the end of follow-up and over a lifetime by age group for DGF and non-DGF patients. Over 13.7 years, the burden of DGF is largest for older patients, who are sicker on average. For example, a patient between ages 70 and 74 is predicted to lose 1.25 QALYs while a patient between ages 30 and 34 is only predicted to lose 0.67 QALYs. The average patient lost 0.95 QALYs, and a patient having their first transplant at 53 years of age (the median age) lost 0.87 QALYs.

The burden of DGF is larger over a lifetime but the relationship between age and lost QALYs is less clear. On the one hand, younger patients have more potential years to live, but on the other hand, the effect of DGF is largest in the sickest patients. The burden of DGF is largest in patients between ages 45 and 49, who lose, on average, 3.03 QALYs. QALYs lost become increasingly smaller the further the departure from ages 45 to 49, yet all ages between 30 and 74 lose at least 2 QALYs over a lifetime. On average, 2.60 QALYs are lost due to DGF and a patient having their first transplant at the median age of 53 lost 3.01 QALYs.

Model Validation

eFigure 2 provides a comparison of our parametric simulation to a simulation using the Cox model using available follow-up data. In both simulations, the estimated probabilities of being in each of the three disease states are similar, although there are some differences in the

probability of a functioning graft after year 7. Overall, the predictions suggest that our parametric distributions fit the data well.

Our predictions of graft survival and remaining life expectancy are also consistent with estimates from other studies. For example, our simulation predicts that after 14 years, ~50% of non-DGF patients had a functioning graft, while other studies have found that median graft survival is around 10 to 15 years.[36–38] In addition, as shown in eTable 4, our estimates of life expectancy by age group are similar to those reported by the USRDS.[7]

As shown in eTable 5, rates of re-transplantation within the model were low, which suggests that re-transplantation had a minor impact on the results. DGF patients had, on average, 1.028 transplants, while non-DGF patients had 1.031 transplants. The maximum number of transplants was 3 for both DGF and non-DGF patients.

Discussion

Clinicians continue to view DGF as a potential challenge for kidney transplant recipients, but there remains debate about the extent to which DGF affects graft and patient survival, as the effects are not well understood. With the disparity between the number of donors and those wait-listed for organs, kidney transplantation is proceeding with more marginal kidneys and as a result the risk of DGF is likely to become more significant in coming years.[39] Although knowledge of both the mechanism and risk factors associated with DGF has improved, the development of new interventions that translate this knowledge into improved management of DGF has been scarce. Based on current trends, the use of kidneys from expanded criteria or cardiac death donors is likely to rise, increasing the likelihood of DGF in transplant recipients.

There seems to be a consensus on the short-term clinical consequences of DGF: a need for several posttransplantation dialysis sessions leading to increased morbidity and an increased length of hospitalization. The long-term consequences of DGF, however, have been heretofore uncertain. One perspective is that the risk of DGF is related to increased cold ischemia time and is associated with a higher incidence of acute rejection, as well as an increased risk of long-term graft failure as a consequence of acute kidney injury.[36,39] The second view is based on recent studies that strongly suggest cold ischemia time-induced DGF may not have deleterious long-term consequences.[40,41] These results are in line with the common observation that patients receiving a kidney transplanted from a donor after cardiac death show a high incidence of DGF, while their long-term results are not significantly different from those of patients receiving a standard criteria donor kidney, who show a much lower incidence of DGF.[42]

One of the reasons for these seemingly inconsistent results may lie in the fact that these studies lacked the ability to follow patients over their remaining lifetime. Differences in patients at 5, 10, or even 15 years may not be easily extrapolated to lifetime outcomes using straightforward linear models. Nonetheless, it is important to take a lifetime perspective in order to account for delayed health outcomes such as deaths or graft failures.[43–45] Indeed, our study showed that differences between DGF and non-DGF populations in both graft survival and life expectancy were considerably larger over a lifetime than during 13.7 years of follow-up.

The model used in this article has some important strengths. First, since we had patient-level data, we were able to estimate a number of different parametric models and ultimately select a model based on fit. Second, we used a semi-Markov model rather than a Markov model (as is typically used in kidney transplantation modeling)[25,26] to simulate long-term outcomes. The advantage of the semi-Markov approach is that it allows future outcomes to depend on both patient history and time in a given health state. Third, we developed a bespoke microsimulation algorithm, which allowed us to develop a more flexible model. For instance, we were able to update the age covariates as patients aged during the simulation and to allow the probability of DGF in subsequent transplants to depend on whether a patient had previously had DGF. Moreover, since our simulation ran quickly, we were able to perform subgroup analyses while still simulating a sufficient number of patients (10,000) and parameter sets (1,000) to generate stable point estimates and credible intervals.

It is important we highlight the limitations inherent in the model as well. First, the impact of DGF on patient and graft survival is based on observational data from the USRDS rather than experimental data from a controlled trial, even though the generalizability, scale, and national representativeness of this real-world data may act as a counterweight to this limitation. In addition, because of the data source used, we were only able to adjust for patient and donor characteristics that were available in the USRDS. There are inevitably much more detailed clinical data available at the patient level, which may improve the accuracy of the model. Third, we did not account for the number of patients on the waiting list when modeling time from transplant failure to a subsequent transplant, which in reality is likely to be a key

driver. However, the ratio of waiting list to transplant recipients has barely moved over the period of the data and if anything the gap has risen. Finally, we do not differentiate between hemodialysis and peritoneal dialysis. While some of these factors may marginally affect the primary outcomes of the model, our belief is that they do so in both directions, and likely to a small degree.

Conclusions

With a growing gap between demand and supply of kidneys leading to more marginal kidneys used for transplantation, the significance of DGF has the potential to rise. As such, a more complete understanding of the full consequences of this complication will be an important factor to both those deciding who receives transplants and when transplants take place, as well as those investing in technologies that would improve outcomes in patients at greater risk or directly suffering from DGF. The lack of consensus in the transplantation field around whether there are significant long-term health consequences to DGF is a barrier to physicians and patients, and the transplantation processes. We consequently developed a microsimulation model and simulated lifetime outcomes for kidney transplant recipients. Our results suggest that DGF significantly reduces life expectancy and increases time on dialysis and, therefore, causes significant reductions in QALYs. Furthermore, the model can be easily adapted to study other resource allocation problems in kidney transplantation where long-term outcomes are of interest.

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Supplemental Material

The online supplementary appendix for this article is available on the *Medical Decision Making Policy & Practice* website at http://journals.sagepub.com/home/mpp.

ORCID iD

Devin Incerti https://orcid.org/0000-0002-4479-8750
Nicholas Summers https://orcid.org/0000-0003-0529-0994

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