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Projecting Long-Term Graft and Patient Survival after Transplantation

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ABSTRACT

Objective: In spite of increases in short-term kidney transplant survival rates and reductions in acute rejection rates, increasing long-term graft survival rates remains a major challenge. The objective here was to project long-term graft- and survival-related outcomes occurring among renal transplant recipients based on short-term outcomes including acute rejection and estimated glomerular filtration rates observed in randomized trials. **Methods:** We developed a two-phase decision model including a trial phase and a Markov state transition phase to project long-term outcomes over the lifetimes of hypothetical renal graft recipients who survived the trial period with a functioning graft. Health states included functioning graft stratified by level of renal function, failed graft, functioning regraft, and death. Transitions between health states were predicted using statistical models that accounted for renal function, acute rejection, and new-onset diabetes after transplant and for donor and recipient predictors of long-term graft and patient survival. Models were estimated using data from 38,015 renal transplant recipients from the United States Renal Data System. The model was populated with data from a 3-year, randomized phase III trial comparing belatacept to cyclosporine. **Results:** The decision model was well calibrated with data from the United States Renal Data System. Long-term extrapolation of Belatacept Evaluation of Nephroprotection and Efficacy as Firstline Immunosuppression Trial was projected to yield a 1.9-year increase in time alive with a functioning graft and a 1.2 life-year increase over a 20-year time horizon. **Conclusions:** This is the first long-term follow-up model of renal transplant patients to be based on renal function, acute rejection, and new-onset diabetes. It is a useful tool for undertaking comparative effectiveness and cost-effectiveness studies of immunosuppressive medications.
Keywords: decision model, end stage renal disease, modeling, renal transplant.

Introduction

Rapid increases in the incidence of end-stage renal disease and aging of the population in industrialized countries are leading to growing numbers of individuals requiring lifelong renal replacement therapy and a greater call on limited health care resources for this condition. In the United States, the incidence of end-stage renal disease doubled between 1998 and 2008, from 183 to 351 per million population [1]. Renal transplantation offers substantial benefits over long-term dialysis [2] and is the treatment of choice for end-stage renal disease [3]. The number of persons with end-stage renal disease being placed on US wait lists for kidney transplantation continues to grow each year, with approximately 99,250 candidates registered as of December 2013 [4].

The success of renal transplantation has arisen in large measure as a result of the efficacy of immunosuppressive medications. Early trials in kidney transplantation from the 1970s demonstrated that azathioprine and prednisone were efficacious for immunosuppression, leading to improvements in the end points of graft and patient survival [5,6]. The introduction of cyclosporine in 1978 led to the use of acute rejection as the primary trial end point [7–14] because graft failure and death became too rare to design realistically sized trials within reasonable periods of observation.

In spite of reductions in acute rejection [15], long-term renal graft and patient survival have not improved, and transplant researchers are shifting focus to other surrogates as end points [16]. For instance, renal functioning at 1 year posttransplant has been shown to be associated with long-term graft and patient survival [17–20] and new-onset diabetes is known to be a major complication after kidney transplant [21].

Most published decision models of immunosuppressive medications in kidney transplant are based primarily on associations between acute rejection and graft and patient survival. Although episodes of acute rejection can have deleterious consequences to the patient, be costly to treat, and increase the risk of graft failure, acute rejection alone is not a reliable predictor of long-term outcomes [22]. The specific objective of this study is to

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develop a decision model that incorporates the observed post-transplant distributions of renal function, acute rejection, and new-onset diabetes at the end of follow-up in randomized trials to estimate the effect of immunosuppressant therapy on graft and patient survival among renal transplant recipients in the United States.

Methods

Model Structure and Outputs

The decision model includes two phases (Fig. 1). Phase 1, the "trial period," incorporates renal functioning (categorical estimated glomerular filtration rates [eGFRs] measured in mL/min/1.73 m^2) and the probabilities of experiencing unintended and undesirable outcomes at the end of follow-up of a randomized trial: new-onset diabetes, acute rejection, graft failure, and death. It is assumed that individuals with an eGFR of less than 15 mL/min/1.73 m^2 are in the graft failure state.

Phase 2, the "extrapolation period," incorporates a Markov model to reflect 20-year follow-up of hypothetical individuals surviving the trial period with a functioning graft. Markov models are used widely in the health economic modeling of disease and represent a reasonable compromise between simplicity on the one hand, which aids transparency and understanding of the model, and flexibility on the other, which allows key aspects of the disease course and treatment pathways to be captured [23]. Starting with the distribution of functioning graft health states, subjects experience declining eGFR over time [24–26], progressing in 1-year cycles. At the end of each cycle, subjects can 1) remain in the same state, 2) experience graft failure and return to hemodialysis, or 3) move to the absorbing death state. Patients are categorized at the end of the trial period into one of four categories of renal functioning defined by the US National Kidney Foundation [27]: eGFR greater than or equal to 60, eGFR greater than or equal to 45 and less than 60, eGFR greater than or equal to 30 and less than 45, and eGFR greater than or equal to 15 and less than 30. While in the functioning graft health states, eGFR is assumed to decline linearly until graft failure occurs at an eGFR of less than 15 mL/min/1.73m^2. Following graft failure, individuals remain in the hemodialysis state until death or regraft. A regraft health state is included because the third most common cause for being placed on a wait list in the United States is a previously failed transplant [28]. Following a regraft, individuals reenter into an undifferentiated functioning graft state and the time to graft failure or death is based on an exponential distribution.

The Markov model is run separately for each functioning graft health state, and the outcome measures are weighted by the observational eGFR distribution from the trial period and summed to obtain results. This allows flexibility because the model can be used to project results from other studies by incorporating information on relevant parameters from those studies. The number of life-years spent in each graft functioning health state is calculated once a subject enters the graft failure state by allocating life-years assuming that eGFR declines linearly over time starting at the entry health state and transitioning through subsequent health states stopping at an eGFR of 15. The time spent in each functioning graft health state is weighted by a utility to obtain quality-adjusted life-years.

Outcomes output by model include cumulative proportions alive with a functioning graft, time alive with a functioning graft,

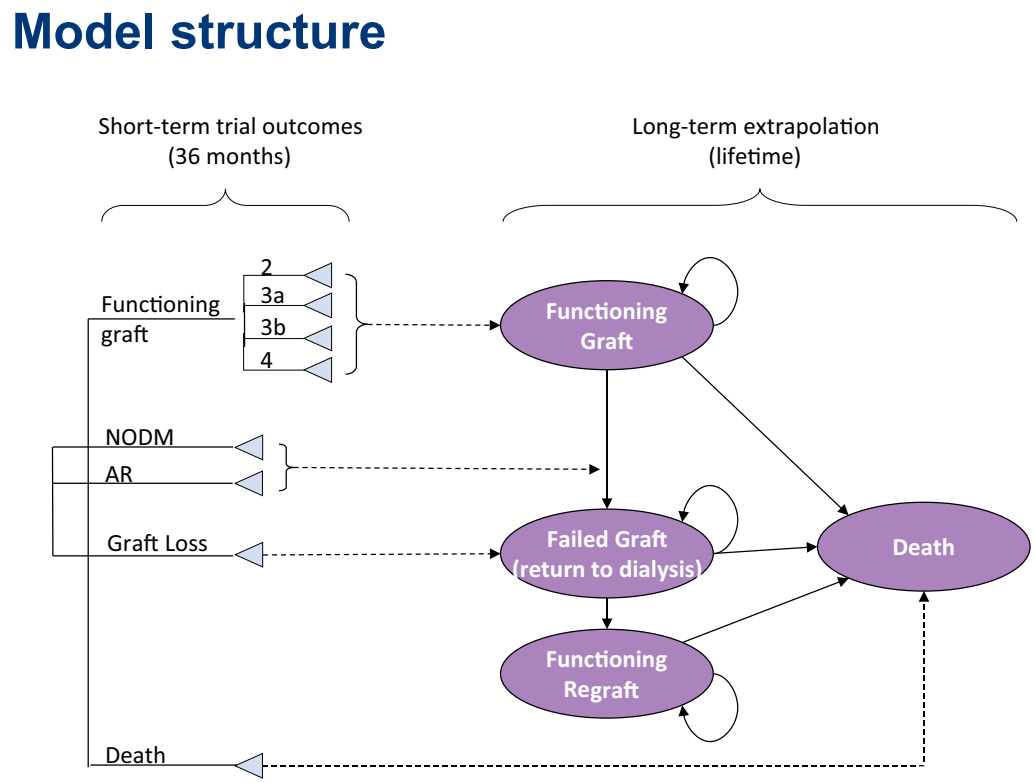

Fig. 1 – Schematic of the decision model for extrapolating long-term outcomes after renal transplantation. AR, acute rejection; eGFR, estimated glomerular filtration rate; NODM, new-onset diabetes mellitus. Functiong graft categories refer to categories of renal functioning defined by the US National Kidney Foundation [27]: 2 = eGFR greater than or equal to 60; 3a = eGFR greater than or equal to 45 and less than 60; 3b = eGFR greater than or equal to 30 and less than 45; and 4 = eGFR greater than or equal to 15 and less than 30.