Longitudinal estimated glomerular filtration rate (eGFR) modeling in long-term renal function to inform clinical trial design in kidney transplantation

Authored by: Luke Kosinski, Eric Frey, Amanda Klein, Inish O'Doherty, Klaus Romero, Mark Stegall, Ilkka Helanterä, Ahmed Osama Gaber, William E. Fitzsimmons, Varun Aggarwal, Transplant Therapeutics Consortium (TTC)

Abstract

Kidney transplantation is the preferred treatment for individuals with end-stage kidney disease. From a modeling perspective, our understanding of kidney function trajectories after transplantation remains limited. Current modeling of kidney function post-transplantation is focused on linear slopes or percent decline and often excludes the highly variable early timepoints post-transplantation, where kidney function recovers and then stabilizes. Using estimated glomerular filtration rate (eGFR), a well-known biomarker of kidney function, from an aggregated dataset of 4904 kidney transplant patients including both observational studies and clinical trials, we developed a longitudinal model of kidney function trajectories from time of transplant to 6 years post-transplant. Our model is a nonlinear, mixed-effects model built in NONMEM that captured both the recovery phase after kidney transplantation, where the graft recovers function, and the long-term phase of stabilization and slow decline. Model fit was assessed using diagnostic plots and individual fits. Model performance, assessed via visual predictive checks, suggests accurate model predictions of eGFR at the median and lower 95% quantiles of eGFR, ranges which are of critical clinical importance for assessing loss of kidney function. Various clinically relevant covariates were also explored and found to improve the model. For example, transplant recipients of deceased donors recover function more slowly after transplantation and calcineurin inhibitor use promotes faster long-term decay. Our work provides a generalizable, nonlinear model of kidney allograft function that will be useful for estimating eGFR up to 6 years post-transplant in various clinically relevant populations.

Read the publication in full: https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.13579