Personalized Schedules for Kidney Transplant Patients

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1 Introduction

We begin with an introduction to the data set. According to the inclusion criteria of the study, a total of 239 kidney transplant patients were included in the data set. The transplantation characteristics of these patients is presented in Table 1. The data set also includes periodical measurements of serum creatinine (SCr) and protein creatinine ratio (PCR), which are biomarkers used to check the state of the transplant. The median number of repeated SCr and PCR measurements per patient are 45 and 37, respectively. For SCr 95% of the observations are taken before 6 years, while for PCR they are taken before 5.4 years. The median time between two SCr measurements is 10 days, while the same for PCR is 14 days.

Table 1: Observed transplantation characteristics of the studied population (n = 239).

Quantitative characteristics		
Name	Mean	SD
Receiver age (at baseline)	50.70	13.09
Donor age	49.73	12.66
Donor BMI	25.10	4.43
Receiver BMI	25.43	4.31
Panel reactive antibody percentage (before transplantation)	4.81	14.20
Cold ischemia time (minutes)	887.25	522.95
#Days on dialysis prior to transplantation	1334.91	1283.93
#Anti-hypertensive medicaments (at 3 months after transplantation)	1.58	0.96
#HLA A, B and DR mismatches between donor and recipient	2.81	1.57

Categorical characteristics	
Name	Category (%)
Receiver gender	Female (42.68 %)
Donor gender	Female (56.49 %)
Delayed graft function after transplantation	No (67.78 %)
Previous transplantation	No (84.45 %)
Diabetes mellitus	No (84.52 %)
Known cardiovascular events before transplantation	No (61.92 %)
Deceased donor	No (25.94 %)

In the cohort, 44 out of 239 patients observed graft failure (death-censored). The survival probability one year post transplantation is 97.87%. The graft survival probabilities and 95% CI estimated using Kaplan-Meier estimator are presented in Figure 1.

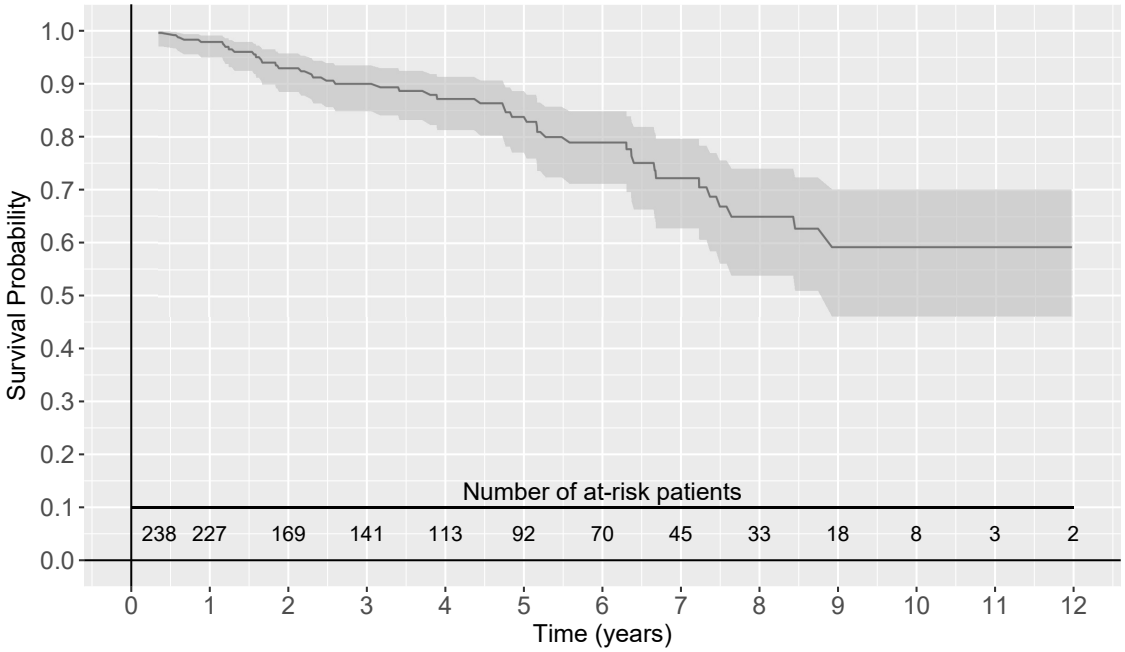

Figure 1: Graft survival probabilities and 95% CI estimated using Kaplan-Meier estimator.

2 Joint Model

Our goal is to check if SCr and PCR both, are useful to predict graft failure. To this end, we model the two longitudinal outcomes and graft failure together using joint models (JMs) for time to event and longitudinal data (Rizopoulos, 2012; Tsiatis and Davidian, 2004). In this model we use log transformed values of both SCr and PCR (Fournier et al., 2016). More specifically, we model the impact of log(SCr) value and log(SCr) velocity, log(PCR) value and log(PCR) velocity, and transplantation characteristics on the hazard of graft failure. In this regard, the JM consists of multivariate longitudinal sub-model to model the evolution of SCr and PCR and a relative risk sub-model to model of the impact of transplantation characteristics and biomarkers on the hazard of graft failure. The longitudinal evolution of the two outcomes over time is modeled flexibly using B-splines, with the boundary knots placed at 0.039 and 6 years (minimum and 0.95 quantile of the time of measurements two outcomes) and internal knots placed at 0.082, 0.219 (30 and 80 days recommended by the clinicians) and one year. In addition, the effect of transplantation characteristics on the longitudinal outcomes is also accounted. The model formulation is presented in section A of supplementary material.

The parameters of the JM are estimated using the R package **JMbayes** (Rizopoulos, 2016), which uses the Bayesian methodology to estimate the model parameters (section B, supplementary material). The quantitative transplantation characteristics are standardized to avoid convergence issues in parameter estimation. Out of 239 patients, we use the data of only those 238 patients for whom both PCR and SCr data is available. The parameter estimates for the longitudinal sub-model for SCr and PCR are provided in Table 2 and Table 3, respectively. The effect of transplantation characteristics on both outcomes is small and ignorable, and hence not discussed. The evolution of SCr and PCR over time is depicted in Figure 2, and Figure 3, respectively. @Hessel: We have to explain why the creatinine levels dip.

The parameter estimates for the relative risk sub-model are provided in Table 4. We found that the log SCr levels are strongly associated with the hazard of GR. More specifically, given all other variables remain the same, if the creatinine levels become twice, the hazard of graft failure increases three fold. log PCR levels and velocity are not strongly associated with hazard of GR. To further verify if they are required in the model in presence of both log SCr levels and velocity, we fitted two more JMs. In the first JM we modeled the association between log SCr levels and velocity and hazard of graft failure. In the second JM we modeled the association between log PCR levels and velocity and hazard of graft failure. We then calculated time dependent AUC, that is, area under the curve (Rizopoulos, 2016; Rizopoulos, Molenberghs, and Lesaffre, 2017) values for

Table 2: Parameter estimates for the longitudinal model for SCr.

Variable	Mean	Std. Dev	2.5%	97.5%	P
Intercept	5.226	0.080	5.064	5.378	<0.000
Receiver age	-0.063	0.022	-0.107	-0.019	0.010
Donor age	0.083	0.020	0.045	0.119	<0.000
Donor BMI	-0.011	0.021	-0.054	0.028	0.612
Receiver BMI	0.018	0.023	-0.025	0.060	0.420
#HLA mismatches between donor and recipient	0.020	0.022	-0.022	0.065	0.342
Panel reactive antibody percentage	0.048	0.027	-0.008	0.100	0.082
#Anti-hypertensive medicaments	0.040	0.020	0.001	0.080	0.048
Cold ischemia time	0.029	0.035	-0.039	0.102	0.390
#Days on dialysis prior to transplantation	0.015	0.029	-0.042	0.071	0.580
Receiver gender: Male	0.197	0.042	0.111	0.276	<0.000
Previous transplant: Yes	0.016	0.064	-0.115	0.141	0.786
Donor gender: Male	0.053	0.042	-0.027	0.136	0.198
Delayed graft function: Yes	0.118	0.049	0.025	0.216	0.006
Diabetes Mellitus: Yes	-0.103	0.059	-0.217	0.012	0.076
Cardiovascular events before transplantation: Yes	-0.047	0.043	-0.129	0.044	0.272
Deceased donor: Yes	0.163	0.082	0.004	0.313	0.044
Spline: visit time [0.039, 0.082] years	-0.440	0.041	-0.517	-0.358	<0.000
Spline: visit time [0.082, 0.219] years	-0.182	0.053	-0.284	-0.081	<0.000
Spline: visit time [0.219, 1] years	-0.545	0.081	-0.712	-0.395	<0.000
Spline: visit time [1, 6] years	0.007	0.083	-0.155	0.176	0.946
σ	0.190	0.001	0.187	0.192	

Table 3: Parameter estimates for the longitudinal model for PCR.

Variable	Mean	Std. Dev	2.5%	97.5%	P
Intercept	3.731	0.179	3.398	4.083	<0.000
Receiver age	0.030	0.052	-0.066	0.138	0.604
Donor age	0.209	0.047	0.118	0.301	<0.000
Donor BMI	-0.019	0.051	-0.121	0.084	0.716
Receiver BMI	-0.116	0.050	-0.219	-0.021	0.014
#HLA mismatches between donor and recipient	-0.013	0.049	-0.112	0.086	0.776
Panel reactive antibody percentage	0.047	0.061	-0.066	0.166	0.446
#Anti-hypertensive medicaments	0.056	0.047	-0.03	0.147	0.208
Cold ischemia time	0.062	0.082	-0.097	0.211	0.468
#Days on dialysis prior to transplantation	0.006	0.066	-0.120	0.134	0.952
Receiver gender: Male	-0.026	0.094	-0.207	0.166	0.798
Previous transplant: Yes	0.035	0.149	-0.241	0.332	0.816
Donor gender: Male	0.114	0.096	-0.079	0.303	0.228
Delayed graft function: Yes	0.043	0.118	-0.174	0.275	0.740
Diabetes Mellitus: Yes	0.153	0.135	-0.124	0.396	0.256
Cardiovascular events before transplantation: Yes	-0.016	0.106	-0.221	0.199	0.890
Deceased donor: Yes	0.144	0.193	-0.246	0.509	0.462
Spline: visit time [0.039, 0.082] years	-0.821	0.090	-0.989	-0.638	<0.000
Spline: visit time [0.082, 0.219] years	-0.578	0.131	-0.838	-0.304	<0.000
Spline: visit time [0.219, 1] years	-0.898	0.160	-1.218	-0.587	<0.000
Spline: visit time [1, 6] years	0.460	0.234	0.015	0.927	0.036
σ	0.479	0.004	0.472	0.486	

all of the three JMs. The time dependent AUC were calculated periodically at an interval of 6 months. The first AUC was calculated at 6 months since transplantation and the last AUC was calculated at 3 years since transplantation. The resulting AUC values are plotted in Figure 4 and listed in Table 5. It can be seen that the model with both longitudinal outcomes performs the

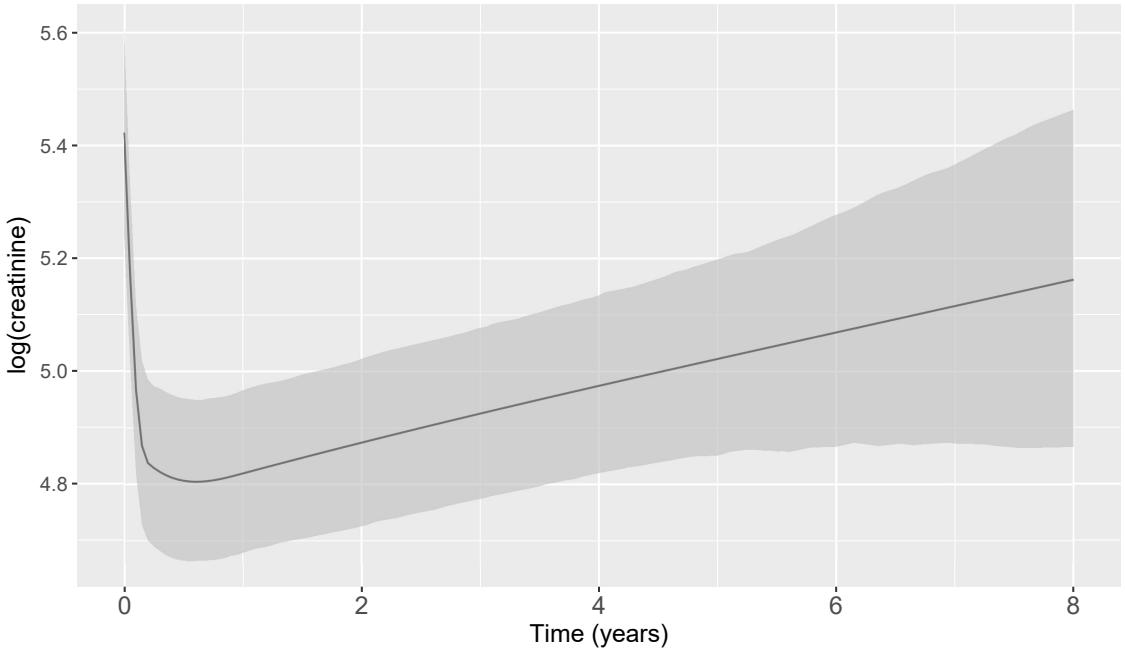

Figure 2: Fitted longitudinal evolution of SCr and 95% credible interval for a patient with the transplantation characteristics described in Table 1.

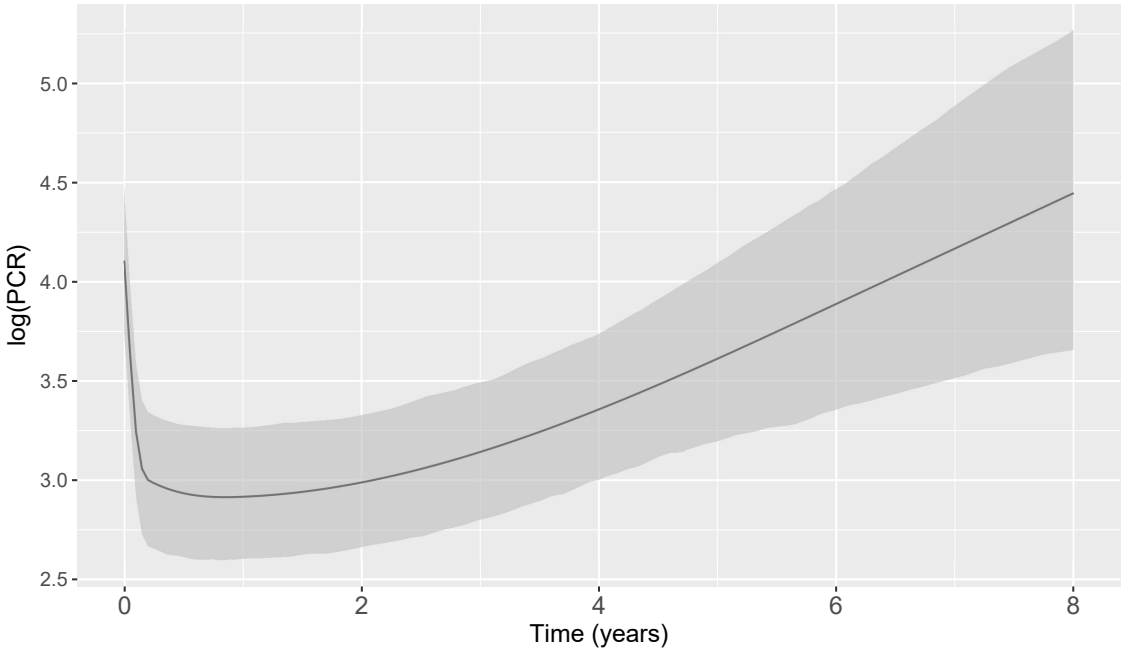

Figure 3: Fitted longitudinal evolution of PCR and 95% credible interval for a patient with the transplantation characteristics described in Table 1.

same as the model with only creatinine, to discriminate between patients who obtain graft failure versus others. Hence modeling PCR may not be necessary.

3 Personalized Schedules for Measurement of SCr

Currently, the schedule for measurement of SCr levels and fixed and common for all patients. SCr levels are measured 20 times in the first year after transplantation and every three months thereafter. Such fixed and frequent schedules are often burdensome for the patients. Patients who

Table 4: Relative risk sub-model estimates for mean and 95% credible interval.

Variable	Mean	Std. Dev	2.5%	97.5%	P
Previous transplant: Yes	0.305	0.339	-0.099	0.986	0.352
#HLA mismatches between donor and recipient	0.048	0.093	-0.114	0.269	0.620
Cold ischemia time	-0.051	0.105	-0.277	0.133	0.644
#Days on dialysis prior to transplantation	-0.013	0.102	-0.251	0.178	0.934
log PCR	0.145	0.125	-0.056	0.431	0.188
Slope(log PCR)	0.021	0.058	-0.076	0.145	0.828
log Creatinine	1.599	0.241	1.067	2.063	<0.000
Slope(log Creatinine)	0.203	0.123	-0.017	0.443	0.082

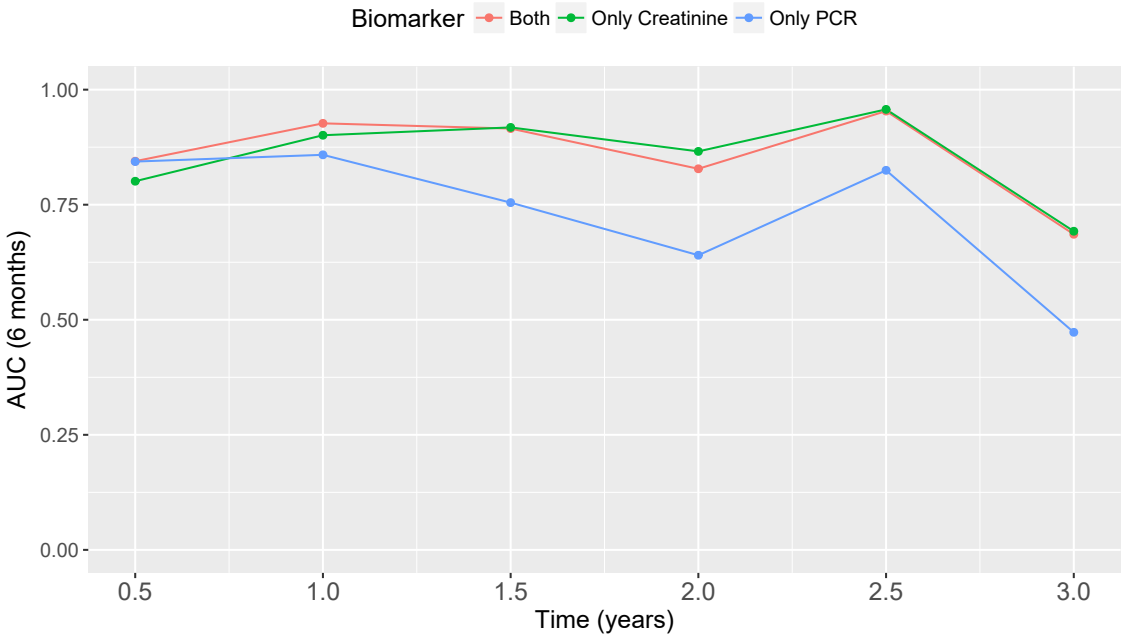

Figure 4: Area under curve characteristics for the JMs fitted to the kidney transplant data set.

Table 5: Area under curve characteristics for the JMs fitted to the kidney transplant data set.

Biomarkers	Year 0.5	Year 1	Year 1.5	Year 2	Year 2.5	Year 3
Both SCr and PCR	0.845	0.927	0.915	0.828	0.953	0.686
Only SCr	0.801	0.901	0.918	0.866	0.957	0.692
Only PCR	0.844	0.858	0.755	0.640	0.825	0.473

remain relatively stable after transplantation may not require frequent measurement of SCr in the first year. On the other hand, patients for whom the graft decays faster after the first year, a frequent schedule of SCr may be required to check the state of the graft. In this regard, instead of a common fixed schedule for all patients, we propose using a different schedule for every patient. More specifically, we propose using personalized schedules based on JMs Rizopoulos et al., (2016). This is because, JMs utilize random effects and thus they are inherently patient specific. In this direction, firstly a full specification the joint distribution of SCr levels and time of graft failure is obtained. It is then used to define a patient-specific posterior predictive distribution of time of graft failure, given the observed SCr measurements. The optimal time of the next SCr measurement is the one at which the expected information gained from an extra SCr measurement is maximum. In order to create reasonable predictions, SCr measurements for the first 3 months are taken as per the fixed schedule. This time period corresponds to the time around which we observed an increase in the SCr profile.

Since the SCr measurements are already taken for the kidney transplant patients, in order to demonstrate the efficacy of the personalized schedules we conduct a small simulation. To this end, we first assume a population of kidney transplant patients, whose SCr and hazard of graft failure follow a JM of the form described in Section 2, with parameters equal to the posterior mean of parameters estimated from the joint model fitted to the kidney transplant dataset. From this population we sample 625 patients, which are further split into a training (575 patients) and test (50 patients) part. For the training patients we generate a graft failure time T_i^* as well as a random and non-informative censoring time C_i. For the test patients the graft failure time T_j^* and an intervention time T_j^I is generated. The intervention time is the time at which the 6 month dynamic risk of graft failure of the patient becomes larger than a certain threshold κ. The choice of κ dictates the amount of time at hand between intervention and graft failure. In this simulation we evaluate two κ values, namely 0.05 and 0.025.

Our goal is to compare personalized schedule with the currently used fixed schedule of SCr measurements. To this end, we first fit a joint model of the specification described in Section 2 to the training data set and obtain a MCMC sample from the posterior distribution of the parameters of the JM. Using the fitted JM, we then iteratively schedule SCr measurements for the test patients, until the dynamic risk of graft failure (Rizopoulos, 2011) of the patients becomes larger than the threshold κ. Let N_j^I denote the number of SCr measurements conducted for the j-th test patient. The time difference between the observed intervention time due to the schedule (T_j^S) and the true intervention time, that is, the intervention offset is denoted by $O_j^I = T_j^S - T_j^I$. Lastly, the failure offset $O_j^* = T_j^S - T^* j$ is the time at hand between the observed intervention time and the time of graft failure. Using the test patients, we calculate these measures for both personalized and fixed schedules. It is to be noted that in the ideal scenario, N_j^I will be one, and offset O_j^I will be zero.

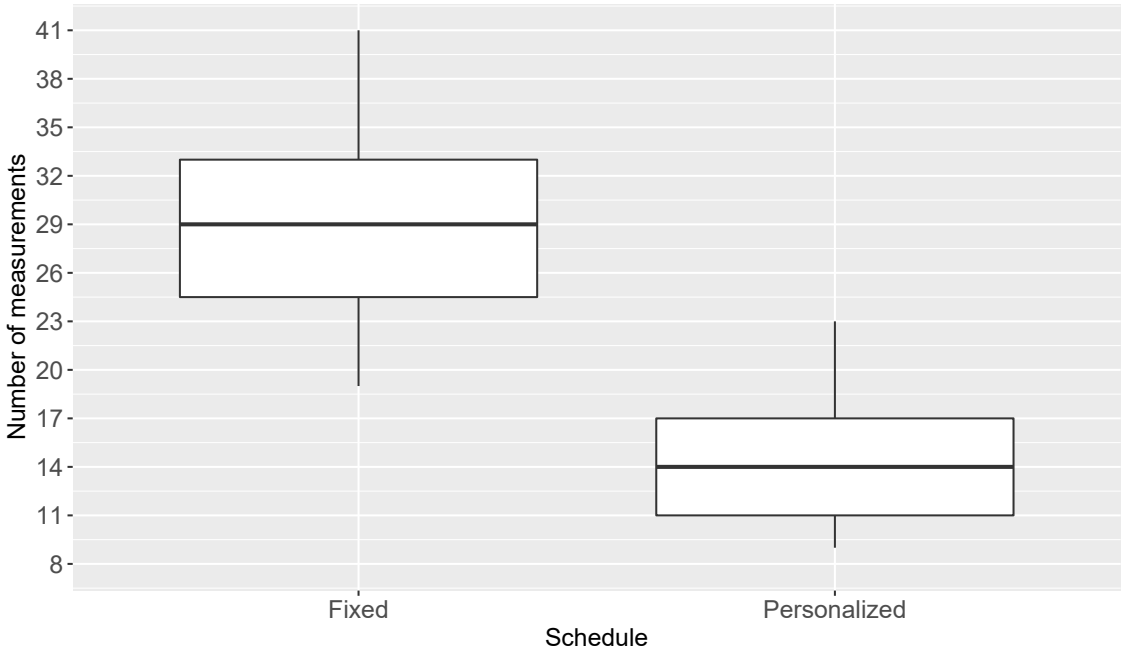

Figure 5: Boxplot of the number of SCr measurements N_j^I for the test patients, for $\kappa = 0.05$.

A boxplot of the observed values of the number of SCr measurements N_j^I, intervention offset O_j^I and failure offset O_j^* are presented in Figure 5, Figure 6 and Figure 7, respectively. The mean number of SCr measurements for personalized schedule is 14.46 whereas it is 27.60 for fixed schedule. In addition the standard deviation for number of SCr measurements is 9.17 for fixed schedule and 4.03 for personalized schedule. That is, personalized schedule not only schedule less N_j^I on average but the variation in N_j^I from patient to patient is also less. The mean absolute intervention offset for personalized schedules is 0.445 whereas for fixed schedules it is 0.448. The personalized schedule also has less standard deviation for absolute O_j^I, with it being 0.285 for personalized schedule and being 0.338 for fixed schedule. There is indeed a risk that either of the schedule can exceed the true graft failure time. In this regard, 12% of the times the graft failure is

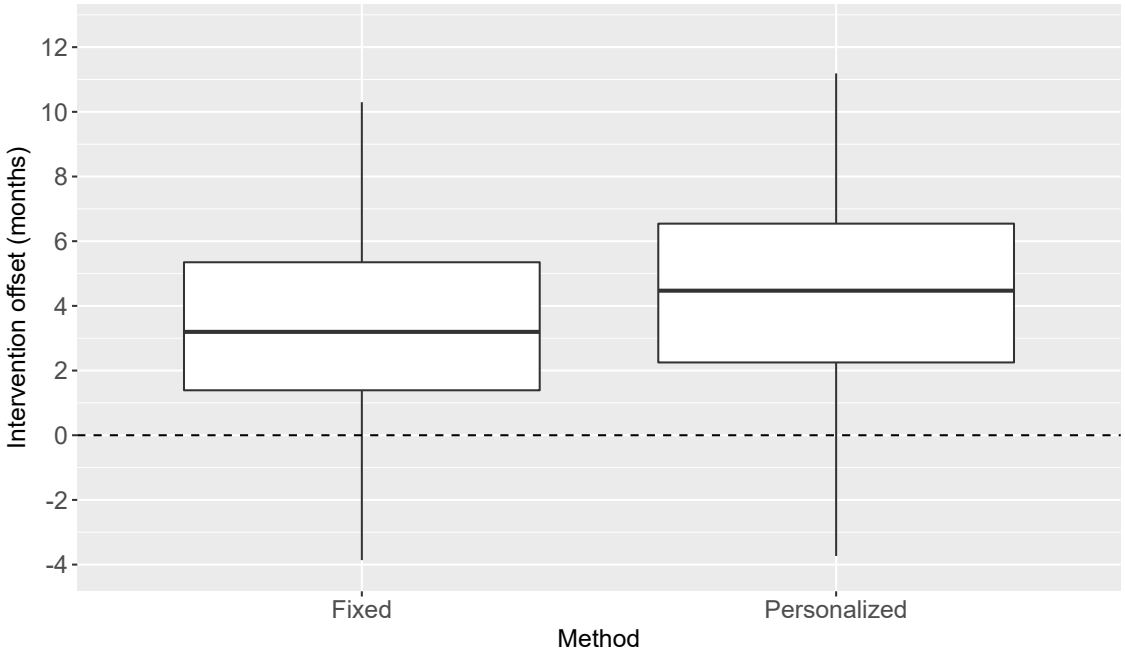

Figure 6: Boxplot of the intervention offset O_j^I for the test patients, for $\kappa = 0.05$. The zero offset mark is displayed with the dashed line.

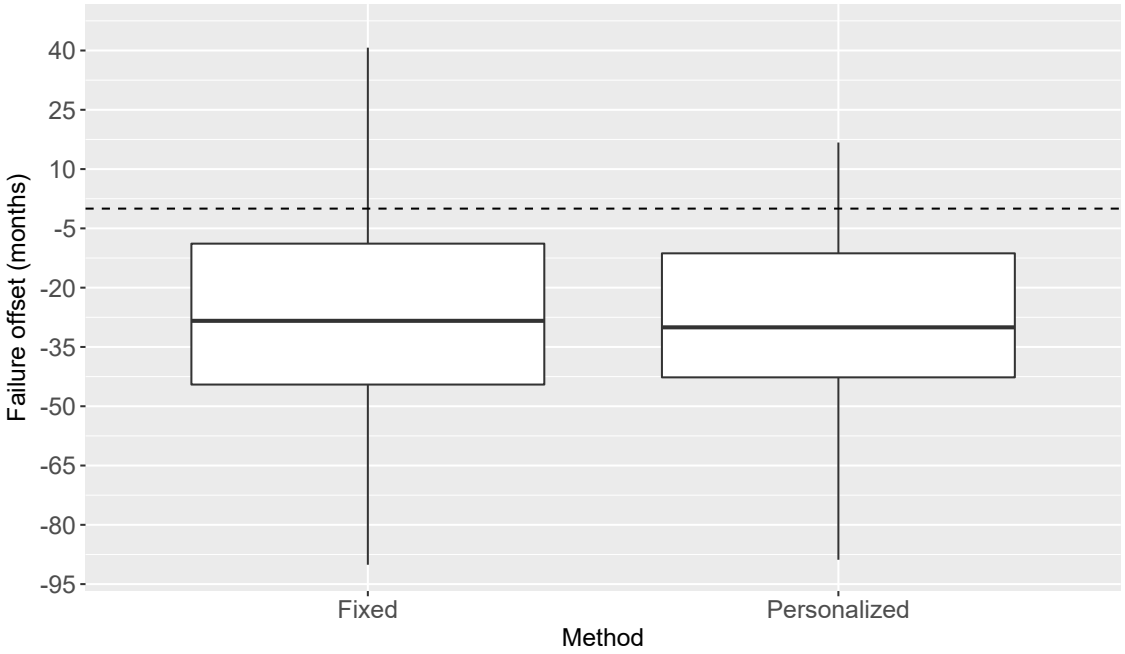

Figure 7: Boxplot of the failure offset O_j^* for the test patients, for $\kappa = 0.05$. The zero offset mark is displayed with the dashed line.

not detected for the test patients when fixed schedule is used. This rate is 14% when personalized schedule is used. Furthermore, the mean absolute failure offset is 2.71 for personalized schedule and 2.76 for fixed schedule. The standard deviation for absolute O_j^* is 1.97 for personalized schedule and 2.21 for fixed schedule.

In order to reduce the risk of overshooting the true graft failure time we propose that a smaller κ of 0.025 is used. The boxplot for the failure offset for this scenario is displayed in Figure 10. In this scenario only for 6% of the patients the graft failure time is exceeded. Boxplot for number of SCr measurements N_j^I and intervention offset O_j^I are displayed in Figure 8 and Figure 9, respectively.

However in this scenario, although the personalized schedule conducts less SCr measurements, it also exceeds the true intervention time more often than the fixed schedule.

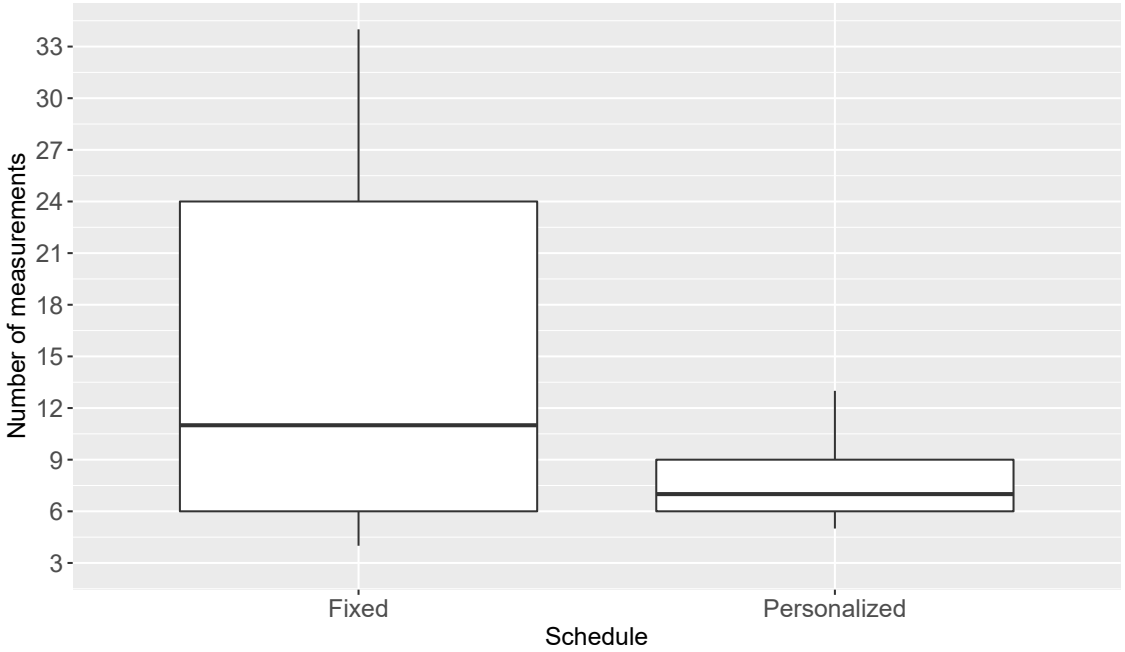

Figure 8: Boxplot of the number of SCr measurements N_j^I for the test patients, for $\kappa = 0.025$.

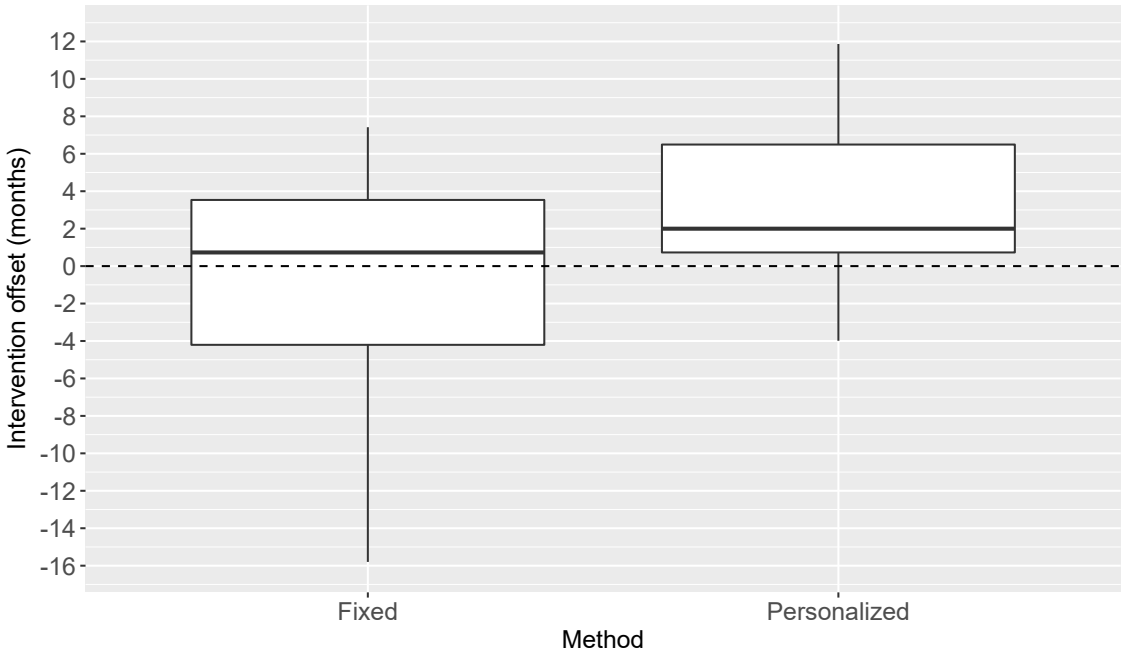

Figure 9: Boxplot of the intervention offset O_j^I for the test patients, for $\kappa = 0.025$. The zero offset mark is displayed with the dashed line.

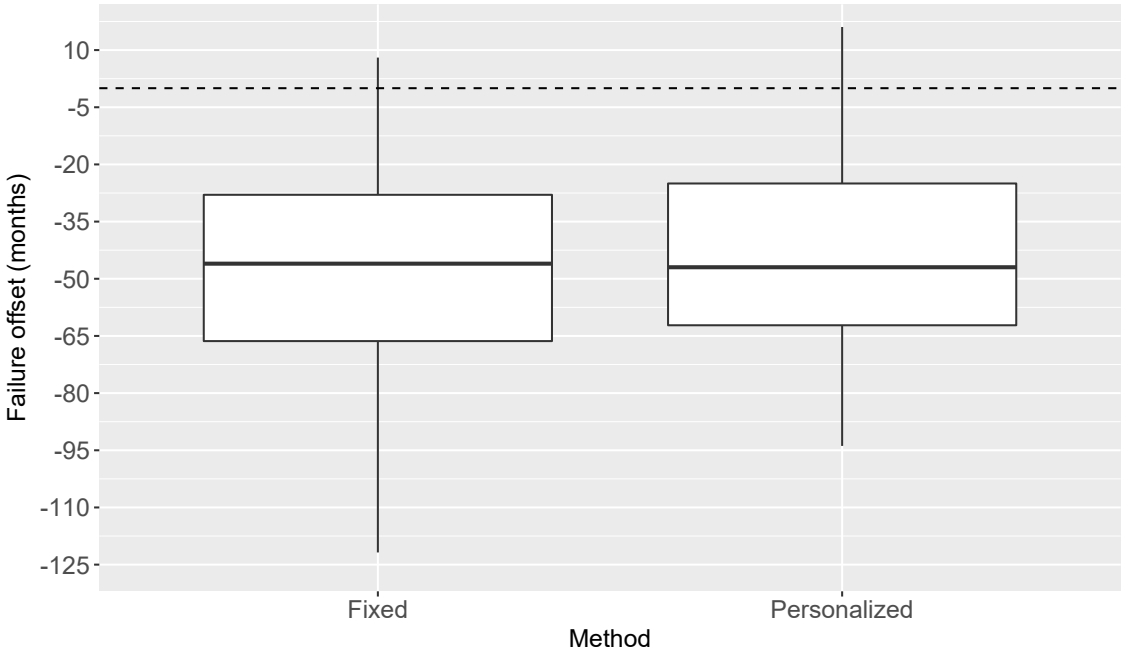

Figure 10: Boxplot of the failure offset O_j^* for the test patients, for $\kappa = 0.025$. The zero offset mark is displayed with the dashed line.

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