Kidney Transplant Personalized Schedules

1 Quick Introduction

In the AMC kidney transplant study, creatinine measurements are scheduled for all patients as per a fixed schedule: 20 times in the first year since transplantation, and 4 times per year after that. Such a fixed and frequent schedule is driven by the need to provide proactive treatment to patients before graft failure occurs. However, the risk of graft failure varies from patient to patient and also changes for each patient over time. Consequently, in case of slowly progressing patients, a fixed and frequent schedule of creatinine measurements leads to many unnecessary financially burdensome (on both healthcare systems and patients) visits to the clinic. In contrast, a fixed but infrequent schedule of creatinine measurements, increases the risk of having less time available for proactive treatment, for faster progressing patients. Here, the time available for proactive treatment is defined as the difference between the true time of graft failure of a patient, and the time at which patient is provided specialized care (proactive treatment) to avoid graft failure.

This article is motivated by the need to better balance the number of creatinine measurements (burden) and the time available for proactive treatment, than in practice currently. We intend to achieve this by personalizing the schedule of creatinine measurements. To this end, we utilize the data of the patients of the AMC study (see Figure 1 for illustration).

The personalized approach that we uses in this paper [Rizopoulos et al., 2015], utilizes the historical creatinine measurements of each patient at each visit, and its relationship with the risk of graft failure, to find the optimal time of the next creatinine measurement, for that patient. This requires first finding the association between the history of creatinine measurements of a patient and the risk of graft failure. To estimate this association, we use the AMC kidney transplant dataset. It consists of longitudinally measured creatinine outcomes for 239 patients over a period of 10 years. Out of the 239 patients, a total of 44 were observed to have graft failure (see Figure 2 for Kaplan-Meier curve).

Standard approaches for individually modeling the creatinine outcome (using a linear mixed model) and its impact on the risk of graft failure (using a cox model), gives biased results. This is due to the fact that patients who observe the graft failure event do not have a complete set of creatine measurements. Their missing creatinine values were more likely to be high and hence the graft-failure process should be accounted in the model for creatinine measurements. Secondly, it is likely that the rate of creatinine measurements is also associated with the risk of graft-failure. In order to estimate the two associations (value and velocity with graft failure), we utilize a joint model for time-to-event and longitudinal data [Rizopoulos, 2012, Tsiatis and Davidian, 2004]. A joint model (JM) consists of a longitudinal sub-model for the longitudinal outcome and a relative risk sub-model for modeling the time of graft failure. It then estimates the parameters of the two sub-models by

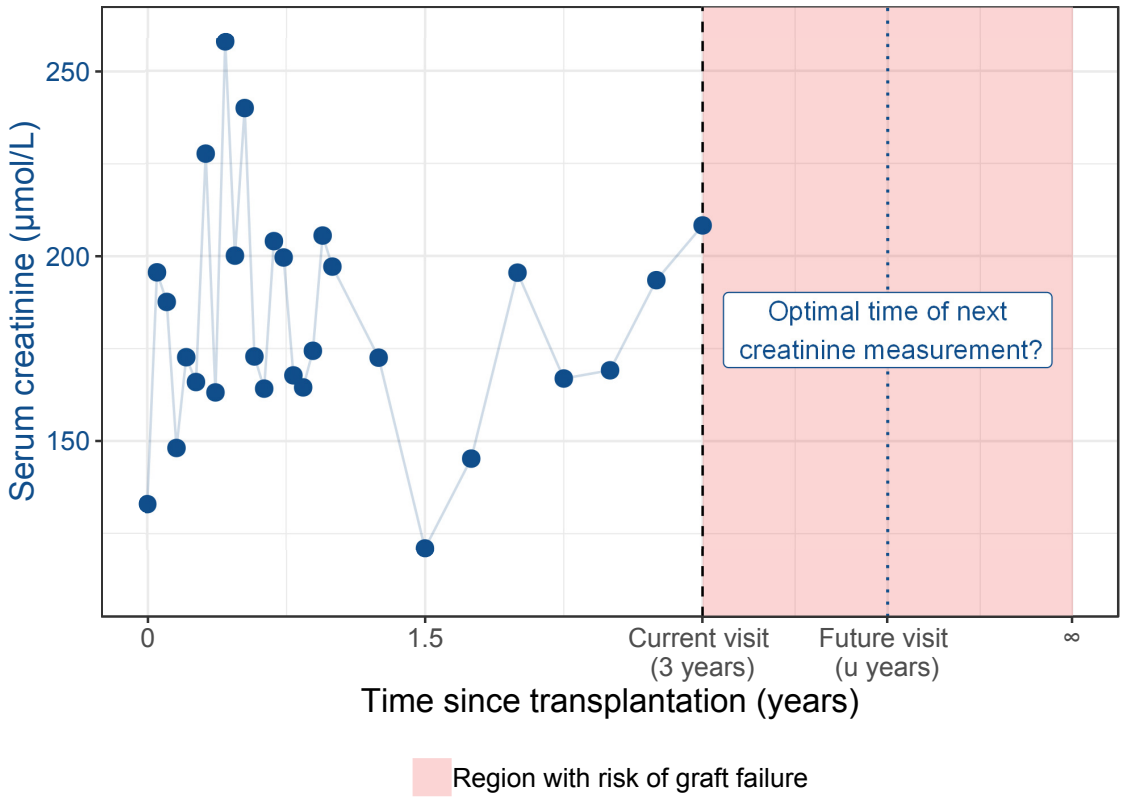

Figure 1: Available data from a patient who had his latest creatinine measurement at 3 years, at which graft failure was not observed. The shaded region shows the time period in which the patient is at the risk of graft failure. We utilize the entire history of creatinine measurements up to the latest follow-up visit to find the optimal time of next creatinine visit.

modelling their joint distribution. Thus, we obtain the impact of each outcome on the other. Figure 3 illustrates the joint model that we propose in this paper. The hazard shown in Panel C of this figure, depends both on the fitted serum creatinine levels and velocity.

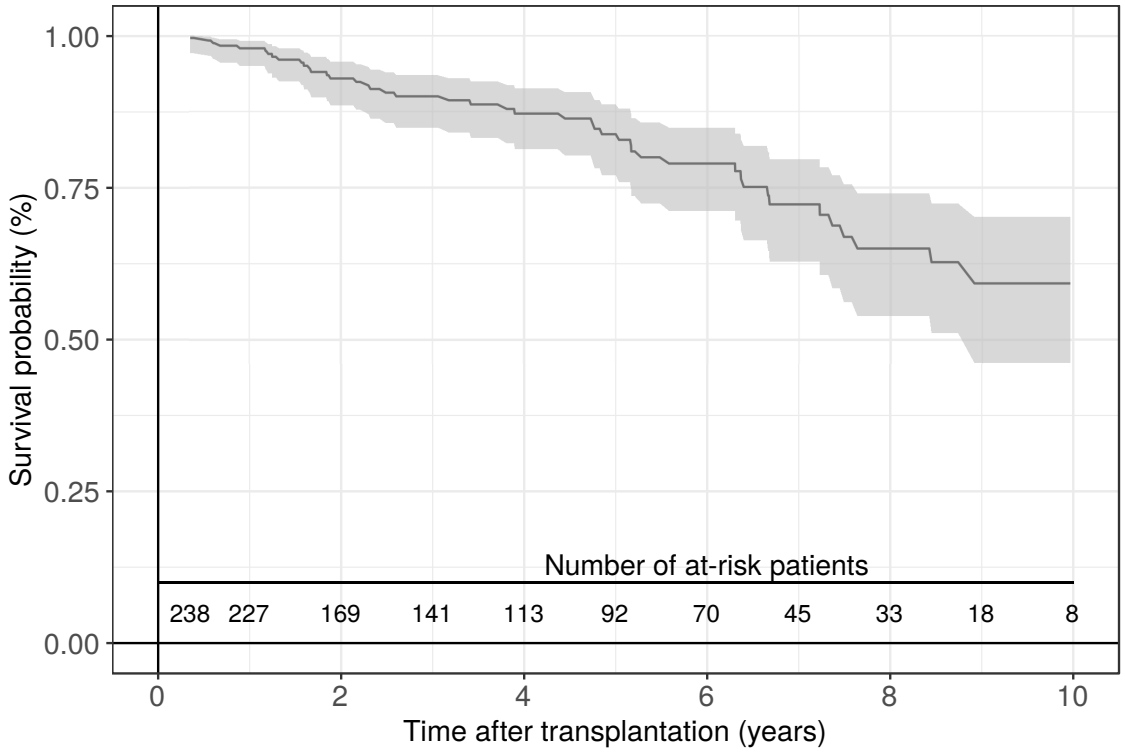

Figure 2: Kaplan-Meier curve showing the survival probability (event: graft failure) at different follow-up times after transplantation.

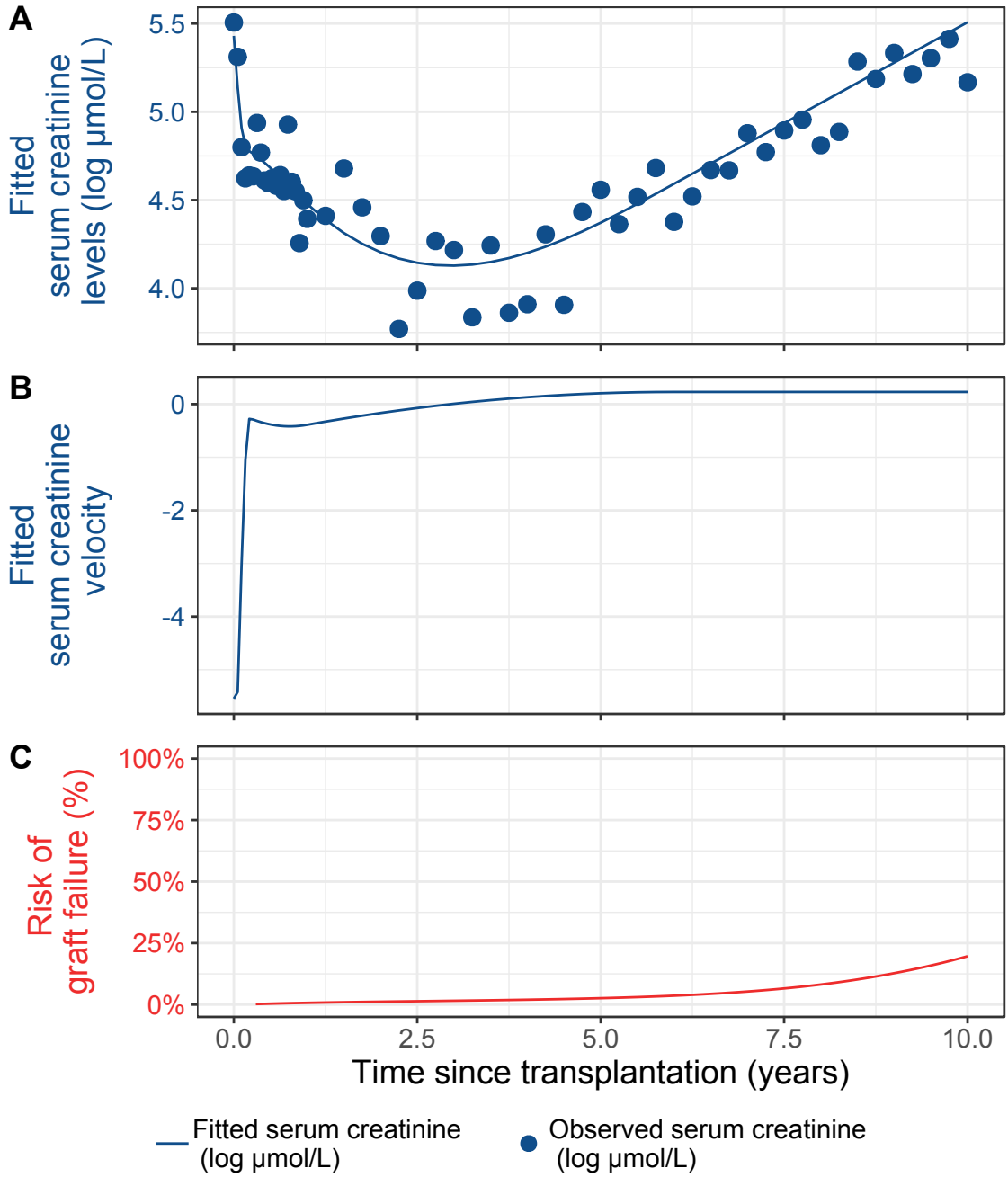

Figure 3: **Illustration of the joint model** fitted to the kidney transplant patient. **Panel A:** shows the observed and fitted log transformed serum creatinine levels. **Panel B:** shows the estimated velocity (velocity cannot be observed directly) over time for serum creatinine levels. **Panel C:** shows the risk of graft failure. It depends on both the fitted serum creatinine levels and velocity.

1.1 Personalized Approach

The joint model is an effective tool to develop risk (of graft-failure) profiles of patients in the future follow-up periods (see Figure 4). We propose that if the risk that the patient will have a graft failure within the next 6 months of the latest follow-up visit, is more than a certain threshold (for example: 5%) then proactive treatment should be provided. If however, the risk of graft-failure in next 6 months is below the threshold, then a new measurement should be planned within a period (it will be more than 6 months indeed) in which the risk does not exceed 5%. For faster progressing patients this period will be small, and for slower progressing patients this period will be larger.

We then estimate the net gain in information on graft failure due to a new creatinine at all possible future follow-up times, within the aforementioned period [Rizopoulos et al., 2015]. We schedule a measurement at a time point at which it is estimated that the net gain in information on graft failure will be the maximum.

In order to aid in medical decision making, we next provide a set of steps illustrating the personalized approach for creatinine measurements:

1. **Develop personalized risk profile**: Illustrated in Figure 4.

   At the current follow-up visit of a new patient, we use the joint model fitted to the AMC dataset to develop a risk (of graft failure) profile of the patient, and find the time u at which the cumulative risk of graft failure is 5%. We intend to schedule personalized measurements only in a time window between the current visit and time u (3.9 years in our illustration).

2. **Find personalized optimal time of the next measurement**: Illustrated in Figure 5.

   We then use the joint model fitted to the AMC dataset to estimate the expected information gain due a new creatinine measurement at all future follow-up times between the current visit and time u (3.9 years in our example). The next measurement is then scheduled at a follow-up time at which the information gain due a new measurement is maximum (3.42 years in our illustration).

3. **Update the risk profile, using new measurement**: Illustrated in Figure 7

   At the new follow-up visit of the patient at 3.42 years, we measure creatinine levels. Then using the joint model fitted to the AMC dataset, we estimate the risk of graft failure within the next 6 months. In this illustration the risk is 6.1%. Since this is higher than the risk threshold of 5%, we suggest intervening to provide proactive treatment. If the risk would have been less than 5%, we would repeat, starting from step 1.

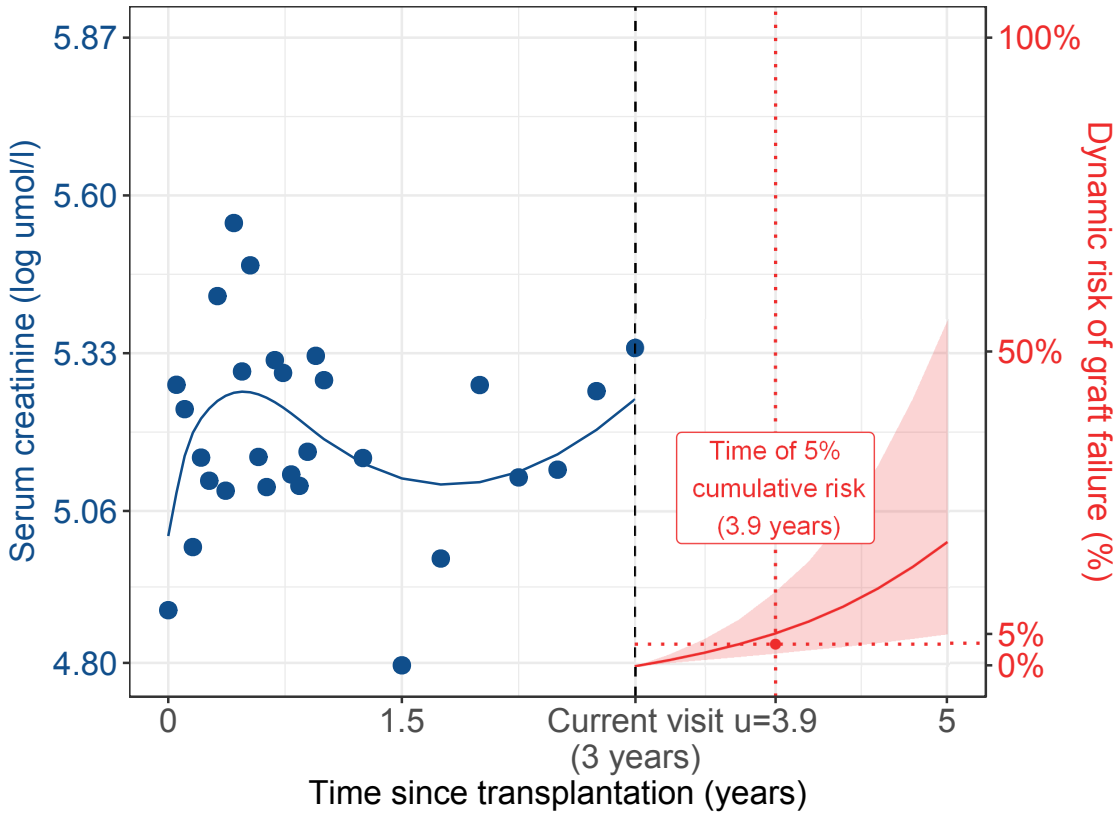

Figure 4: **Step 1: Develop personalized risk profile**. Figure shows, fitted profile of log transformed serum creatinine measurements (in blue), and the estimated cumulative risk (with 95% credible interval) of graft failure for future follow-up periods (in red). The time at which the cumulative risk of graft failure is 5% is time $u = 3.9$ years.

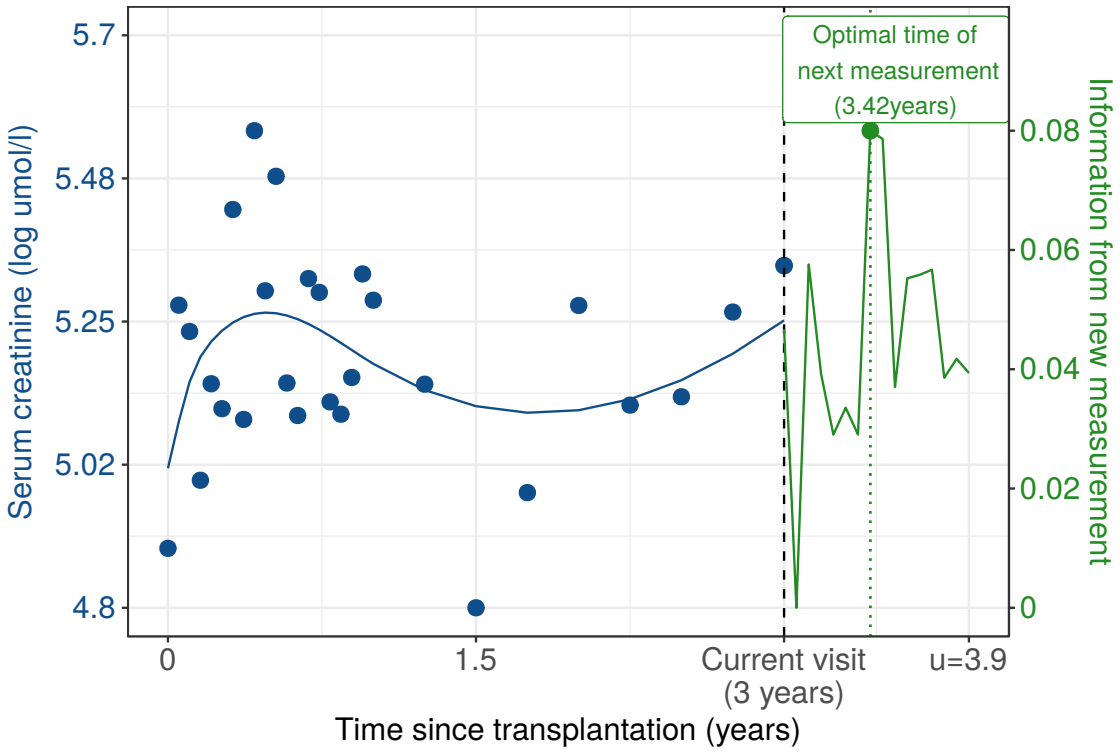

Figure 5: **Step 2: Find personalized optimal time of the next measurement**: Figure shows fitted profile of log transformed serum creatinine measurements (in blue), and the estimated information gain due a new measurement at different follow visits, up to a maximum time $u = 3.9$ years. The optimal for the next measurement is the time at which we expect to the gain the most information, which is 3.42 years in this example.

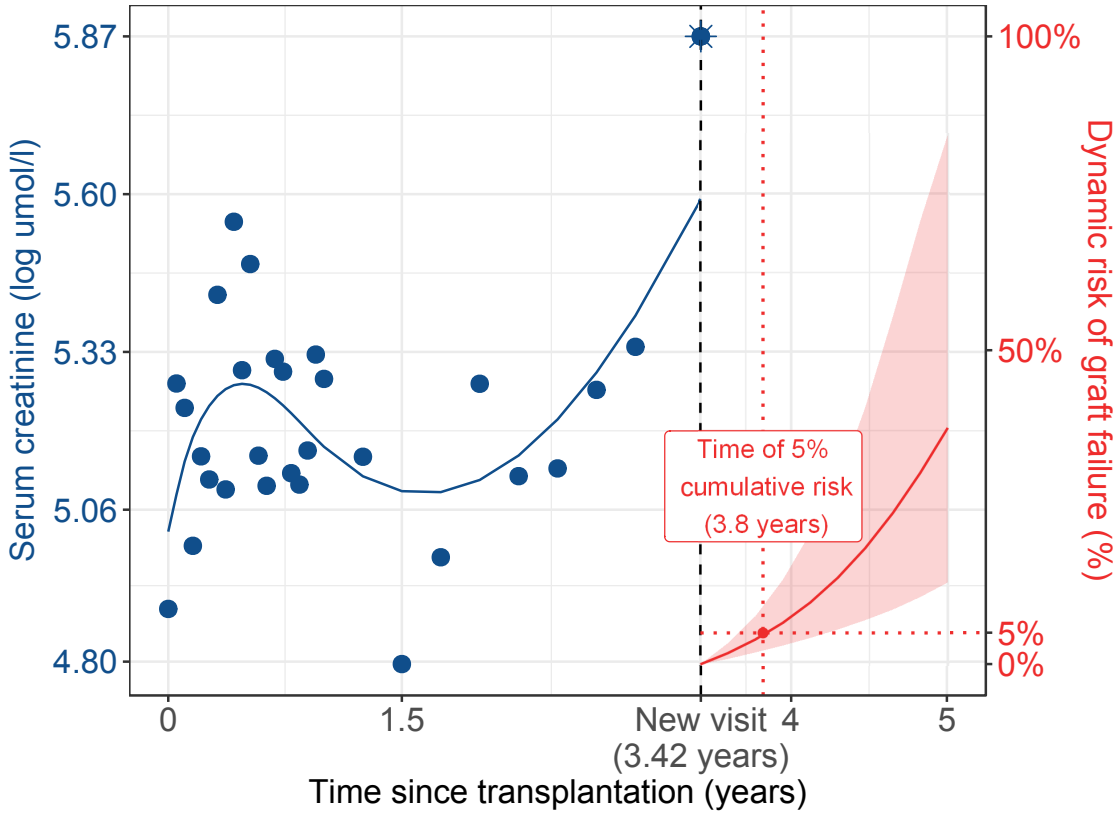

Figure 6: **Step 3: Update the risk profile, using new measurement**: Figure shows fitted profile of log transformed serum creatinine measurements (in blue) up to the new visit of 3.42 years, and the updated cumulative risk (with 95% credible interval) of graft failure for future follow-up periods (in red). The time at which the cumulative risk of graft failure is 5% is time 3.8 years. Since it is within 6 months of the latest visit, we suggest providing proactive treatment at the latest visit.

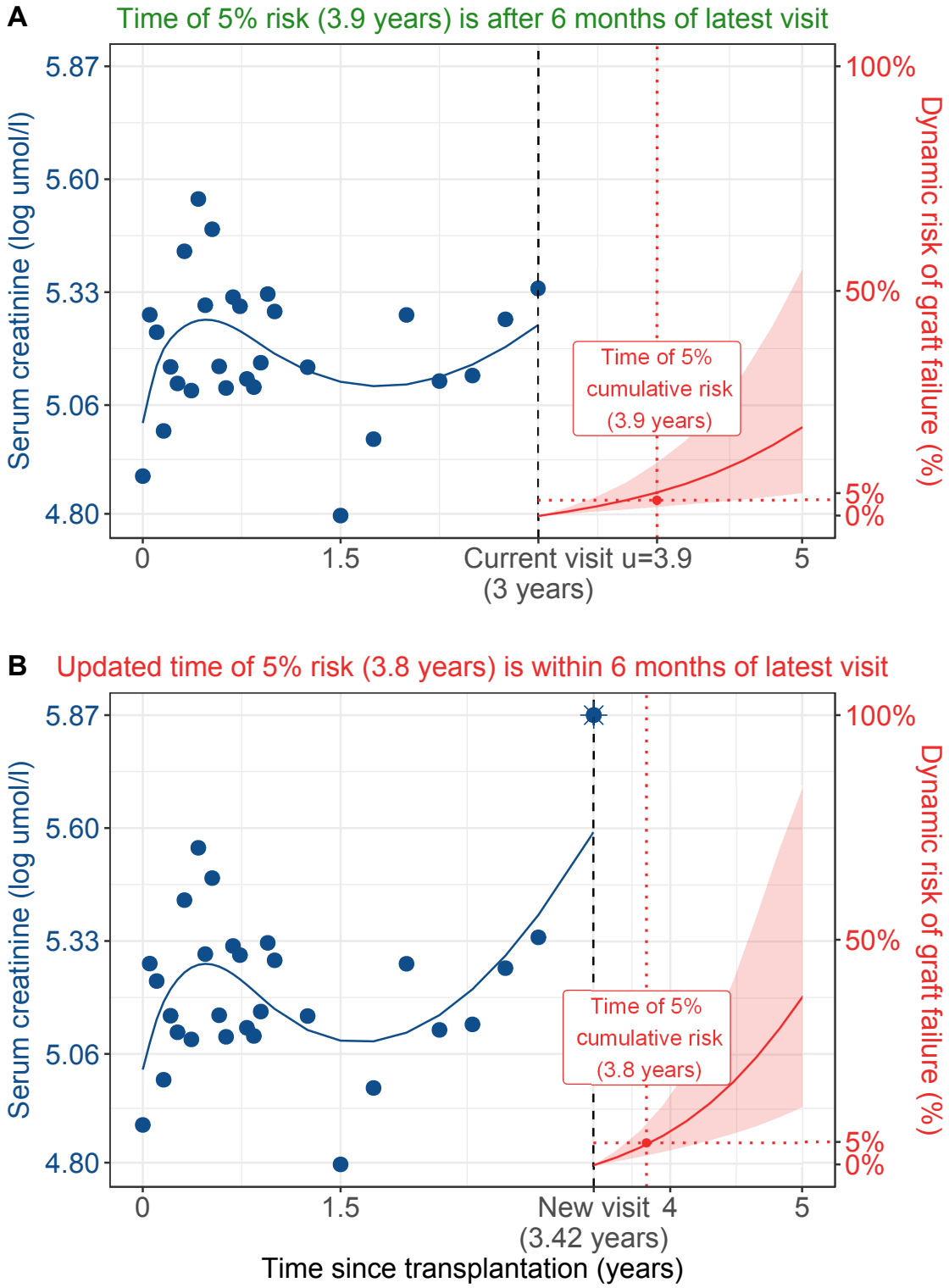

Figure 7: **Step 1 and 3**: Graph showing change in dynamic risk before and after a new measurement is taken. In sub-graph B the time of 5% risk is within 6 months of latest visit. Hence patient may be given proactive treatment.

2 Simulation Study

Although the personalized screening approach is motivated by the AMC study, it is not possible to evaluate it on the AMC dataset. This is due to the fact that the AMC patients have already had their creatinine levels measured as per the AMC protocol. Thus in order to apply the personalized scheduling approach and compare it with the fixed schedule, we conduct a simulation study. For a realistic comparison, we simulate data from the joint model that we fitted to the AMC dataset. The simulated population has the same follow-up period of 10 years as the AMC study. In addition the recovered relations between creatinine measurements, and the risk of graft failure, are retained in the simulated population. The graft failure rate (event rate) is also similar in our simulation study (see Figure 2).

The number of patients in our simulation study are 239 which is the same as the size of the AMC study. We generate a true graft failure time for each of the patients. A total of 109 out of 239 patients are censored at the 10 year follow-up period mark (matches the event rate shown in Figure 2), and the rest have graft failure times within the 10 year follow-up period. For all patients we generate creatinine measurements as per the schedule of AMC study. We then fit a joint model of the same specification as for the AMC study to the 239 simulated patients.

Our aim is next to apply personalized schedules for these patients and compare it with the fixed schedule. The comparison is based on two factors: the number of measurements each approach schedules, and the time available for proactive treatment in each approach. The time available for proactive treatment is defined as the difference between the time of the true graft failure and the time of intervention (for proactive treatment). For any given patient, the time of intervention is the follow-up time at which the risk that the patient will obtain graft failure within the next 6 months is more than 5%. This patient and follow-up visit specific risk is estimated from the observed creatinine measurements. Whether a 5% risk is enough for proactive treatment is indeed debatable. If a lower risk such as 2.5% is chosen, then more time for proactive treatment will be available for each patient. In this paper, we compare results for both 2.5% and 5% risk.

3 Results

Figure 8 and Figure 9 compares the performance of fixed and personalized schedule of creatinine measurements, for a 5% risk threshold to provide proactive treatment. The comparison is done separately for the patients who observe graft failure in 10 year follow-up (54% of all patients), and the patients who are right censored at 10 years (46% of all patients). The boxplots are based on results obtained from all 239 simulated patients.

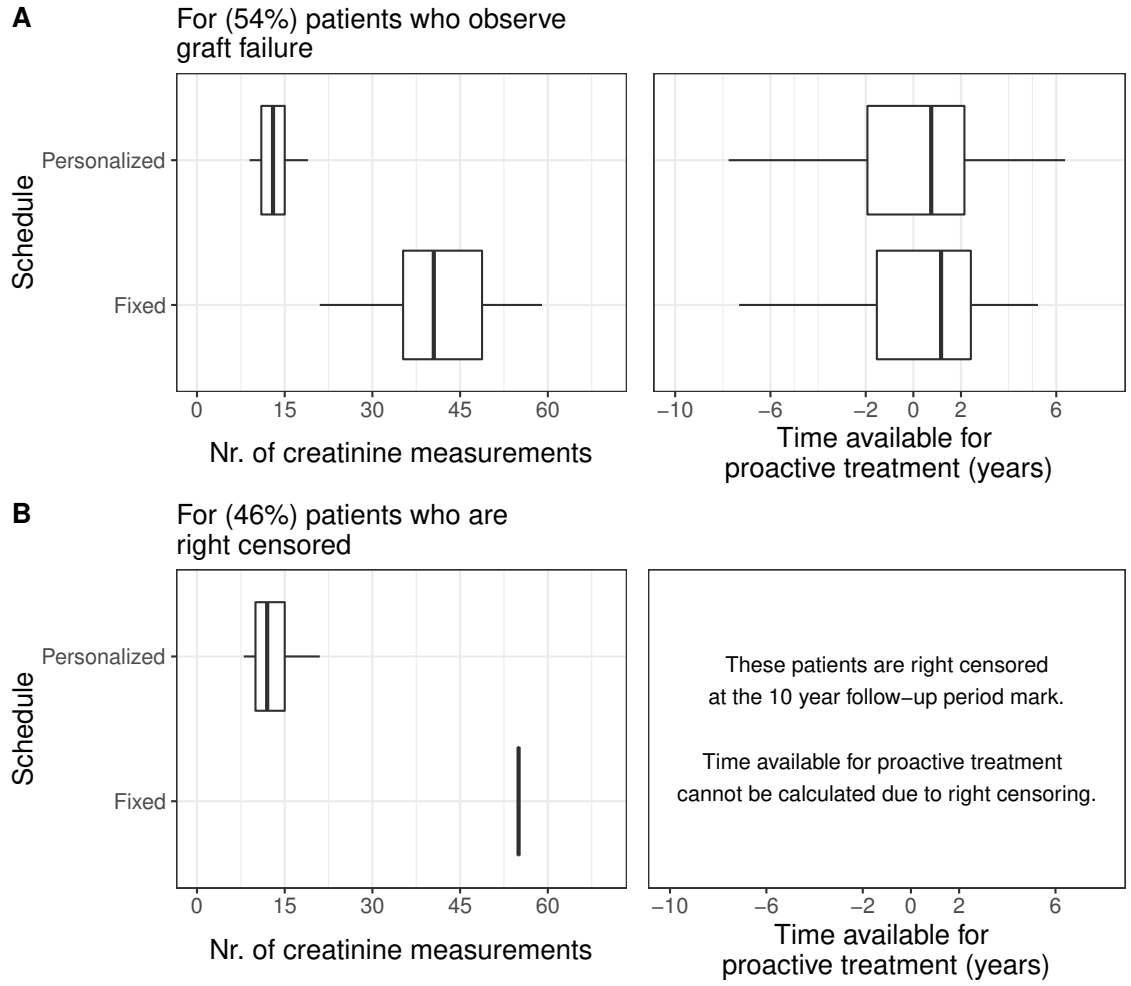

Figure 8: Boxplot showing variation in number of creatinine measurements, and the time available for proactive treatment, in years (time of graft failure - time of intervention) for personalized and fixed schedules. Time of intervention is the follow-up time at which the risk that the graft failure will happen within next 6 months is more than 5%. Creatinine measurements are schedule until the time of intervention. **Panel A:** results for simulated patients who had a graft failure within the 10 year follow-up period. **Panel B:** results for simulated patients who were right censored at the 10 year follow-up period mark.

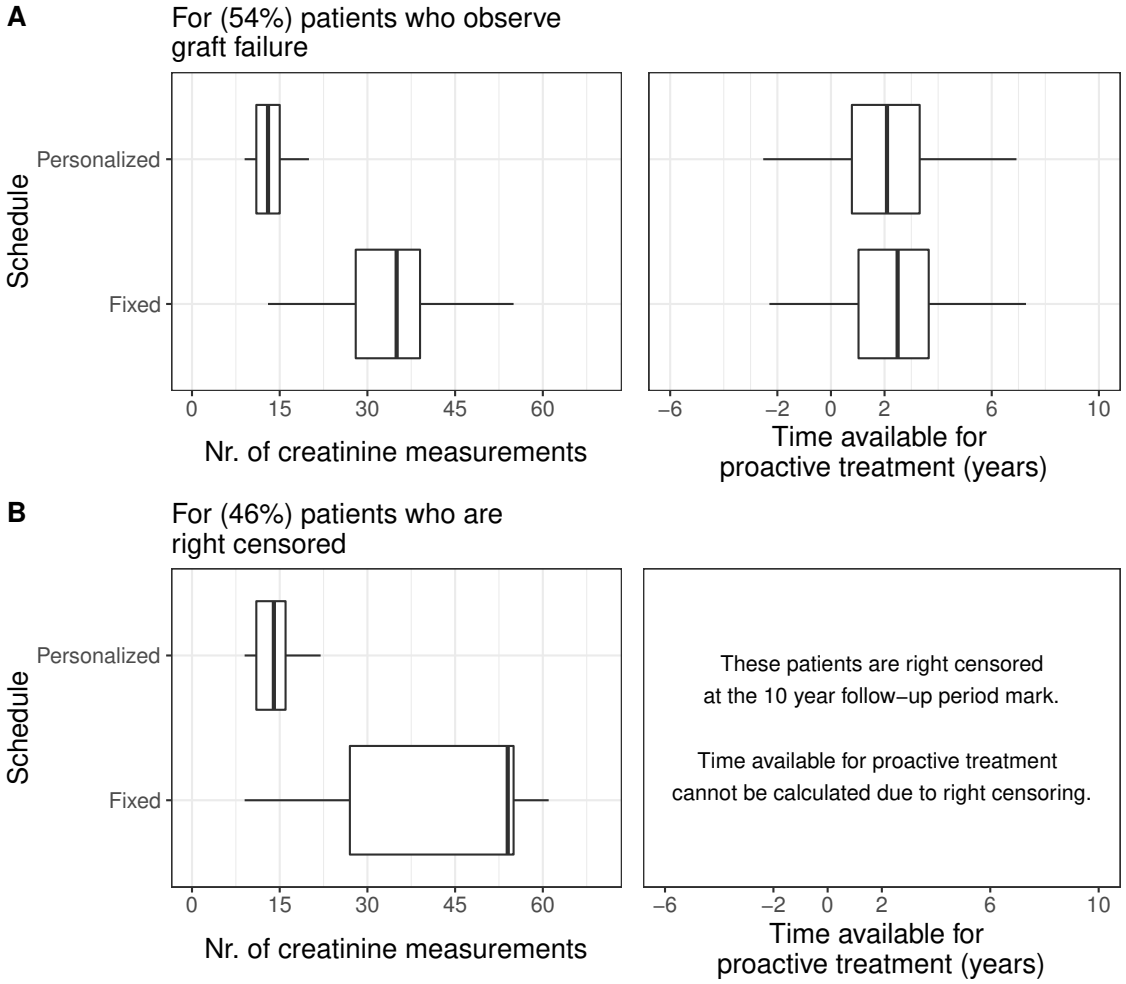

Figure 9: Boxplot showing variation in number of creatinine measurements, and the time available for proactive treatment, in years (time of graft failure - time of intervention) for personalized and fixed schedules. Time of intervention is the follow-up time at which the risk that the graft failure will happen within next 6 months is more than 2.5%. Creatinine measurements are schedule until the time of intervention. **Panel A:** results for simulated patients who had a graft failure within the 10 year follow-up period. **Panel B:** results for simulated patients who were right censored at the 10 year follow-up period mark.

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