**A personalized data-driven strategy to monitor the development of renal allograft failure with serum creatinine trajectories**

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**Abstract**

**Background:** There is a lack of evidence on how to monitor renal function after renal transplantation. The aim of this study was to address the association between longitudinal markers of renal function and death-censored graft failure (DCGF) and to create a personalized surveillance strategy to monitor patients after renal transplantation.

**Methods:** We conducted an observational cohort study in patients transplanted at the Amsterdam UMC (N=239) and collected all serum creatinine (SCr) and urinary protein-to-creatinine ratio (PCR) measurements. We created statistical joint models and a personalized surveillance strategy. Upon simulation, we evaluated the number of surveillance intervals, intervention offset (difference between the estimated and observed time when the risk of DCGF exceeded 5%) and graft failure offset (difference between the estimated time the risk of DCGF exceeded 5% and the observed graft failure time) between the personalized and KDIGO-based fixed surveillance approach currently operational in our hospital.

**Results:** The joint model showed an aHR of 1.43 (95% credible interval [CI] 1.27-1.59, p<0.001) for SCr and an aHR of 1.10 (95% CI 0.99-1.22, p=0.08) for log SCr slope. A joint model that included both SCr and PCR trajectories did not reveal a better AUC compared to a model with only SCr trajectories. The personalized strategy resulted in a median (IQR) of 14 (6.0) versus 29 (8.5) intervals and intervention offset, whereas graft failure offset remained the same compared to the fixed protocol.

**Conclusions:** This personalized surveillance approach can reduce the number of outpatient visits, physician time burden and healthcare costs without a loss of predictive accuracy.

**Introduction**

Renal transplantation is the preferred renal replacement therapy for patients with end-stage renal disease. Compared to dialysis, renal transplantation improves patient survival, cardiovascular outcome and quality of life 1–4. Short-term graft survival is excellent 5, but unfortunately long-term graft survival has not benefitted from improvements in treatment regimens to the same extent 5. Due to imbalances in immune status, medication toxicity, infections and all sorts of other environmental perturbations that influence the patients’ well-being, graft function fluctuates. Altogether these perturbations can lead to a renal function decline prior to graft failure that can be either steadily slow, but also rapidly progressive and therefore patients need to be continuously monitored for early detection of deteriorating graft function to allow for advances diagnostics (e.g. transplant biopsy) and/or treatment of the underlying cause of renal failure as early as possible.

Continuous screening results in a significant burden on patients as well as physicians and healthcare costs. The current Kidney Disease: Improving Global Outcome (KDIGO) guideline recommends that serum creatinine is measured at least daily the first 7 days after transplantation, 2-3 times per week for week 2-4, weekly for months 2-3, every 2 weeks for months 4-6, monthly for months 7-12 and every 2-3 months thereafter 6. These interval recommendations are not based on supporting data, but rather on expert consensus, which is acknowledged by the writers of the KDIGO guideline. Figure 1 illustrates this clinical challenge: when does a transplant physician need to schedule the patient’s next hospital visit?

In the current era, a data-driven clinical decision support system (CAD) to monitor the risk of graft failure might be a valuable tool that can assist transplant physicians in personalizing outpatient management and adjust the hospital visits according to the individual patient’s graft failure risk profile. Therefore, we introduce a novel data-driven surveillance approach to predict the risk of graft failure from serum creatinine trajectories. Based on the patient’s risk prediction, we can identify the most optimal time-point to plan the next hospital visit for each patient on an individual basis. By simulation, we compared our personalized surveillance approach with the clinical practice of a fixed visit schedule based on the current KDIGO guideline recommendation. We illustrate that our personalized surveillance strategy can drastically reduce the number of hospital visits in both patients who do and do not develop graft failure without a loss in time for proactive intervention (e.g. biopsy).

**Methods**

*Study population*

We used data from a cohort study in the Amsterdam University Medical Centers, a tertiary referral hospital in Amsterdam, the Netherlands. The electronic patient database was used to collect all relevant data. All information was processed anonymously according to the code of conduct by the Dutch Medical Scientific Society (FDMSS) and the study was performed in accordance with the Declarations of Helsinki and Istanbul 14. The records of 239 end-stage renal disease patients that underwent renal transplantation at our institute from June 1, 1996 to October 31, 2009 were screened. The inclusion criteria for the study were: age at baseline ≥18 years who had >1 serum creatinine (SCr) measurement (in umol/L) during follow-up. Last follow-up date was April 29, 2014. Initial immunosuppressive therapy consisted of steroids combined with a proliferation inhibitor (mostly mycophenolate mofetil or mycophenolic acid) and a calcineurin inhibitor (mostly tacrolimus).

*Measures and outcomes*

Included in the database were potential predictors of kidney function and graft failure. Extracted were: donor age, donor gender, donor body mass index (BMI), donor type, number of human leukocyte antigen (HLA) A, B, DR mismatches, cold ischemic time, panel reactive antibodies (PRA) before transplantation, recipient dialysis vintage, recipient blood pressure, recipient age, recipient gender, recipient BMI and recipient cardiovascular diseases. The following data on baseline medication use after transplantation were collected: immunosuppressive regiments (calcineurin inhibitors, prednisone, proliferation inhibitors, induction therapy, mammalian target of rapamycin inhibitors), anti-hypertensives (diuretics, inhibitors of the renin-angiotensin-aldosterone system, beta blockers and calcium channel blockers), statins and the use of antiglycemic medication or insulin. These were extracted only once within the first year after transplantation, whereas SCr was measured repeatedly over time till the patient either had a transplant failure (death or graft failure) or was not followed up anymore. If there were multiple SCr measurements per day, we took the mean of the measurements for analysis. We evaluated death-censored graft survival, defined as graft loss leading to dialysis treatment, as event and right-censored for death with a functioning graft.

*Joint model*

To calculate the association between serum creatinine trajectories and death-censored graft failure, we used a joint model. The joint model consists of a longitudinal sub-model for the SCr trajectories over time and a relative risk sub-model for modeling time to graft failure. It then estimates the parameters of the two sub-models by modeling their joint distribution. Thus, we obtain the impact of longitudinal measurements of SCr (absolute levels and relative velocity) on graft failure. We estimated the parameters in the joint model using Bayesian methodology fitted to the dataset with SCr as a continuous variable that was measured multiple times after transplantation. 8,10,18. A detailed and formal description of the joint model can be found in Appendix A and B.

*Personalized risk prediction strategy*

The following steps illustrate the analytic strategy:

1. Develop personalized risk profile for the patient based on the trajectory of SCr and risk of graft failure (see Fig 2A). We calculated the time u at which the cumulative risk of graft failure is 5%. We intended 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 (see Fig 2B). The next measurement was then scheduled at a follow-up time at which the information gain due to a new measurement was maximum (3.42 years in our illustration).
3. Update the risk profile, using new measurement (see Fig 2C). At the new follow-up visit, we measure creatinine level. If the risk for graft failure <5%, we would repeat step 1-2.

*Validation study with simulated patients*

The personalized schedules for the patients were then compared with the fixed schedule from the KDIGO guideline in the same cohort. We compared 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 observed 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%.

*Sensitivity analyses*

In a sensitivity analyses, we determined whether a 5% risk is enough for proactive treatment. If a lower 6-month risk, such as 2.5% is chosen, then more time for proactive treatment will be available. Thus, we compared the results from the personalized schedules with the fixed schedule for both 2.5% and 5% risk.

*Data analysis*

Continuous variables are presented as mean with standard deviation (SD). Kaplan Meier was used to estimate death-censored graft survival. Results from the JM are presented as regression coefficients with standard deviation and 95% credibility intervals (CIs). Analyses were conducted using R (version 3.4.2) with the GitHub version of the JMbayes package (dated Nov 7, 2017) 10, and survival package (version 2.41). Hyperlinks to all source codes for the joint model fits and the simulation study can be found in Appendix D.

**Results**

*Cohort characteristics*

Most of the 239 kidney transplant patients were recipients of deceased donors (177, 74%, Table 1). Mean recipient age was 51 (SD 13) years, and majority firstly transplanted (85%). In the follow-up period, we included a total of 13189 SCr measurements and the median number of repeated SCr measurements per patient was 45. Ninety-five percent of the observations were taken before 6 years. The median time between two SCr measurements was 10 days. Figure 3 illustrates death-censored graft survival. At one year, 97.9% still had a functioning graft (95% confidence interval 96.1 - 99.7), and this was 83.9% (95% confidence interval 78.2 - 89.6) at 5 years.

*Joint model results*

In the longitudinal sub-model for SCr trajectories, donor age, recipient age, recipient gender, recipient anti-hypertensive medicament use, and delayed graft function were significantly associated (Table 2). In the sub-model for graft failure, the current SCr and slope of SCr were significantly associated (Table 3). Figure 4 illustrates the joint model for a random selected patient. For any given patient at any time point, an increase of the current SCr with 25% and other variables remained the same, the hazard of graft failure increased 1.43 times (adjusted HR 1.43, 95%CI 1.27-1.59, p<0.001). For patients having the same current SCr and other variables remained the same, the hazard for graft failure increased 1.10 times if the slope of the log SCr values increased from -0.21 to 0.23 (1st and 3rd quartiles of the fitted slope of log SCr; adjusted HR 1.10, 95% CI 0.99 to 1.22, p=0.010. Current SCr and slope SCr.

*Validation study with simulated patients*

Figure 5 compares the performance of the 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 ten year follow-up (54% of all patients), and the patients who are right censored at ten years (46% of all patients). In sensitivity analyses, a more conservative threshold of 2.5% risk of graft failure risk in 6 months resulted in more time for proactive treatment while the number of scheduled visits remained the same (see Figure…. Or in Appendix?).

**Discussion**

The joint model enabled us to study the dynamic trajectory of SCr and PCR and to specify their association with the risk of graft failure and optimize the screening visits. We demonstrate that SCr has better discriminative ability for risk of graft failure than PCR. Static baseline clinical data were associated with evolution of SCr, and if included in the model for death-censored graft failure, donor and transplant characteristics were not associated with graft outcome anymore. Nephrologists routinely supervise both the current SCr and PCR level and their increase. Indeed, our results suggest not only the current value of SCr is important but also how rapid the rate of increase to this SCr value is. We compared an empirical personalized surveillance schedule based on the fitted JM with the one-size-fits-all fixed schedule that is currently used in our hospital, consisting of 20 SCr measurements in the first year after transplantation and hereafter every 3 months, which is already less stringent than the surveillance schedule as proposed by the KDIGO guidelines 6. With the JM, that is inherently patient specific, we show that a personalized surveillance approach may result in obtaining less SCr measurements while the information to predict the risk of irreversible graft failure remains the same. Therefore, the framework of joint models allows one to tailor surveillance to the needs of individual patients and adapt during follow-up. Patients who have a stable allograft function after transplantation may not require frequent outpatient visits with measurement of SCr. On the other hand, patients for whom graft function deteriorates faster after the first year, a frequent schedule of SCr may be required to determine the best moment for, if possible, intervention (e.g. by timely planning of a transplant biopsy).

Multiple studies have modelled progressively worsening kidney function in a fixed time-window using linear trajectories to evaluate the risk of graft failure 19–22. This approach less frequently also included nonlinearity of progression 23,24. Only five studies included nonlinear renal function trajectories in a joint model with renal outcome: four in renal transplantation 17,25–27, with an average follow-up ranging from 6.8 months to around 6 years after transplantation, and one in native chronic kidney disease 18. In line with our findings, these studies all showed that both the current SCr value as well as the SCr slope associated with irreversible renal allograft outcome. Of these studies, only the study by Rizopoulos et al. investigated the added value of proteinuria (as a binary measure) in renal transplantation 17. They showed in multivariate joint modeling that eGFR, proteinuria (as a binary measure) and hematocrit trajectories associated with graft outcome. Extending on this, we showed in the current study that the joint model that only included SCr trajectories had similar time-dependent discriminative power as the joint model that included both SCr and PCR trajectories. Although we postulate that PCR does not add discriminative value in the joint model that included SCr trajectories, we acknowledge that this might be the case in patients with a recurrence of primary proteinuric renal disease after transplantation (e.g. primary focal and segmental glomerulosclerosis).

The current study is the first in nephrology to use joint model estimates to tailor the SCr surveillance schedule to the individual renal transplant recipient. Our statistical simulation study resulted in a nearly 50% reduction in the number of necessary visits. This 50% reduction in screening moments can be directly translated to a reduction in patient management costs, physician time and it will also aid to a higher quality of life for transplant recipients due to a decrease in scheduled hospital visits. When we extrapolate our results to show the national and global potential of this personalized surveillance approach, assuming a fixed surveillance approach that is similar to our hospital, an estimated €500 per screening and the prevalence and incidence of number of transplanted patients in the Netherlands 28, the personalized surveillance could reduce annual costs by more than €14.500.000 in The Netherlands. Considering the WHO 2015 worldwide kidney transplantation activity, based on the Global Observatory on Donation and Transplantation (GODT) data, produced by the WHO-ONT collaboration 29, the personalized surveillance could reduce costs by more than €630.000.000 annually worldwide. We have to acknowledge that the fixed surveillance protocol is a guideline. In daily practice, treating physicians personalize the screening intensity according to prior knowledge on the individual patient (expert opinion-based personalized surveillance).

The next step is to increase sample size and include more risk factors for graft survival, which might improve the personalized surveillance approach even further. As we included well-known risk factors for graft failure, other biomarkers of interest such as graft histology or longitudinal genomic data could theoretically be introduced to increase accuracy for the underlying disease process that leads to irreversible graft failure. Our findings have to be externally validated in other observational cohorts. Non-inferiority randomized controlled trials in multiple centers with different fixed surveillance protocols should show clinical utility in a back-to-back comparison with expert opinion-based personalized surveillance.

**Author Contributions**

HPS, JK, AT and DR designed the study. SF, JJTHR, FJB and JK collected and processed data. HPS, AT and JK performed statistical analyses. EWS and DR supervised statistical analyses. HPS, AT and JK wrote the article. All authors reviewed and approved the final version of the manuscript.

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| **Table 1.** Characteristics of the transplant cohort (n=239) | |
| **Donor** | **Mean (SD) / N (%)** |
| Age (years) | 49.7 (12.7) |
| Body mass index (kg/m2) | 25.1 (4.4) |
| Donor type |  |
| - Living unrelated | 38 (15.9%) |
| - Living related | 24 (10.0%) |
| - Deceased brain death (DBD) | 98 (41.0%) |
| - Deceased cardiac death (DCD) | 79 (33.1%) |
| **Transplantation** |  |
| Cold ischemia time (hours) | 14.8 (8.7) |
| Pretransplant Panel Reactive Antibodies (PRA) |  |
| - 0% | 181 (75.7%) |
| - >1% | 58 (24.3%) |
| Human Leukocyte Antigen (HLA) -A, -B and -DR mismatches |  |
| - 0 mismatches | 28 (11.7%) |
| - 1 to 3 mismatches | 138 (57.7%) |
| - 4 to 6 mismatches | 73 (30.6%) |
| Delayed graft function (DGF) | 76 (31.8%) |
| **Recipient** |  |
| Age (years) | 50.7 (13.1) |
| Gender (Female) | 102 (42.7%) |
| Body mass index (kg/m2) | 25.4 (4.3) |
| Previous transplantation | 37 (15.5%) |
| Dialysis vintage (years) | 3.7 (3.5) |
| Diabetes Mellitus (DM) at time of transplantation | 38 (15.9%) |
| Cardiovascular events before transplantation | 91 (38.1%) |
| Number of anti-hypertensives |  |
| - 0 | 33 (13.8%) |
| - 1 | 79 (33.1%) |
| - 2 | 85 (35.6%) |
| ≥ 3 | 42 (17.7%) |
| SD, standard deviation. | |

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| --- | --- | --- | --- | --- | --- |
| **Table 2.** Area under curve characteristics for the joint models fitted to the kidney transplant data set | | | | | |
| **Biomarkers** | **Year 0.5** | **Year 1** | **Year 1.5** | **Year 2** | **Year 2.5** |
| Both SCr and PCR | 0.845 | 0.927 | 0.915 | 0.828 | 0.953 |
| Only SCr | 0.801 | 0.901 | 0.918 | 0.866 | 0.957 |
| Only PCR | 0.844 | 0.858 | 0.755 | 0.640 | 0.825 |
| SCr, serum creatinine; PCR, urinary protein-creatinine ratio. | | | | | |

**Figures**

**Figure 1: Death-censored graft failure and 95% confidence intervals.**

The curve and confidence bands were calculated with a Kaplan-Meier analysis.

**Figure 2: Fitted longitudinal evolution of serum creatinine and urinary protein-creatinine ratio measurements.**

Fitted longitudinal evolution of SCr **(A)** and PCR **(B)** with 95% confidence intervals corresponding to a female recipient aged 51 years, BMI 25, first transplantation, no diabetes, no history of any cardiovascular events, of a living female donor aged 50 years, with 3 mismatches on HLA A, B and DR, with 15 hours of cold ischemia time, 5% panel reactive antibodies, and a 4 year history of dialysis.

**Figure 3: Dynamic predictions based on a joint model in an example patient.**

Dynamic prediction of death-censored graft survival probabilities of one an example patient, **(A)** using log SCr values up to 5 years and **(B)** using all available log SCr values.

**Figure 4: Simulation results comparing a fixed versus a personalized surveillance approach based on serum creatinine measurements.**

Box plots of the number of scheduled SCr measurements **(A)**, intervention offset **(B)**, and the graft failure offset **(C)**. Fixed schedules were compared with personalized schedules, depended on the dynamic predictions of the joint model. The threshold was set at 5% risk of graft failure per 6 months. The zero-offset mark (for B and C) is displayed with the dashed line.

**Supplemental Material Table of Content**

Appendix A: Joint model framework

Appendix B: Joint model for the kidney transplant dataset

Appendix C: Personalized schedules for measurements of SCr

Appendix D: Source code