Dynamic predictions of long-term kidney graft failure: an information tool promoting patient-centred care.

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Abbreviations: AUC: Area Under ROC Curve; CI: Confidence Interval; HLA: Human Leukocyte Antigen; dynPG: Dynamic prediction of Patient and Graft survival; KTFS: Kidney Transplant Failure Score; SCr: Serum Creatinine; SD: Standard Deviation

Abstract

Background. Informing kidney transplant recipient of their prognosis and disease progression is of primary importance in a patient-centered vision of care. By participating in decisions from the outset, transplant recipients may be more adherent to complex medical regimens due to their enhanced understanding.

Methods. We proposed to include repeated measurements of Serum Creatinine (SCr) in addition to baseline characteristics in order to obtain dynamic predictions of the graft failure risk that could be updated continuously during patient follow-up. Adult recipients from the French DIVAT cohort transplanted for the first or second time from a heart beating or living donor, and alive with a functioning graft at 1-year post-transplantation were included.

Results. The model was composed by 6 baseline parameters in addition to the SCr evolution. We validated the dynamic predictions by evaluating both discrimination and calibration accuracy. The area under ROC curve varied from 0.72 to 0.76 for prediction times at 1 and 6-years post-transplantation respectively, while calibration plots showed correct accuracy. We also provide an online application (https://shiny.idbc.fr/DynPG).

Conclusion. We have created a tool that for the first time in kidney transplantation individually and dynamically predicts graft failure risk, and believe that it could encourage willing patients into participative medicine.

Keywords: Kidney transplantation, Dynamic prediction, Graft failure, Serum Creatinine, Shared decision-making, patient-centered care.

Introduction

Health researchers and policy-makers are increasingly encouraged to promote patient-centered care that is respectful of patient preferences, needs and values. Shared decision making moves the patient-physician relationship away from traditional, paternalistic practices, and aims to increase patient knowledge about their disease and to improve medication adherence (1,2). This paradigm is well developed in chronic disease such in renal insufficiency (3), and particularly in kidney transplantation, where medical staff have become aware that integrating patient preferences in core outcomes of clinical trials should improve relevance to patients and clinical decision-making (4). Among outcomes, it has recently been shown by Howel et al. that in kidney transplantation, patient preferences prioritize the graft survival before any risk of adverse outcomes such infections or cancers (5). Therefore, providing the individual graft survival prediction, according to the willingness of each patient, could be a first step to improving patient health status information and to promoting patient-centered care.

Thanks to publications from national registries or cohorts, most physicians are able to provide graft prognostic information at a population level. However, at an individual level, this information is more difficult to assess because of the multiplicity of factors involved in the risk of graft failure. In this context, we proposed the Kidney Transplant Failure Score (KTFS) to predict at 1-year post-transplantation the probability of graft survival within the seven following years (6). The usefulness of this score is currently under study in a randomized clinical trial to drive the patient follow-up between 1 and 3 years post-transplantation (7). However, its main limitation was the absence of update after 1-year post-transplantation. Moreover, informing willing patients at each outpatient visit of their middle-term prognosis could help to increase their comprehension of a reinforced burden of

treatment and follow-up, and commit them in the decision-making process (1,8). Alternatively, this information can be a good way of avoiding the unnecessary stress many transplant recipients experience, particularly those who may have a daily sense of imminent graft loss.

As outlined by the recent systematic review of predictive models in kidney transplantation proposed by Kaboré et al. (9), the development of a model for dynamic predictions is needed. For instance, Serum Creatinine (SCr) may be useful to compute dynamic predictions and to improve existing time-fixed predictive models. In order to incorporate longitudinal measurements in predictive models, the joint modelling of both marker evolution and time-to-failure has recently been developed (10,11). Few studies have been based on such approaches in kidney transplantation (12–14). Nevertheless, none of these models have been used for dynamic predictions.

In this context, we recently proposed a shared random effect joint model for the SCr evolution and the patient graft failure risk (15). Features included in this model, in addition to SCr values during the follow-up, were: recipient age at transplantation, recipient gender, recipient histories of diabetes and cardiovascular diseases, graft rank, pre-transplantation immunization against class I Human Leukocyte Antigen (HLA), donor age, donor gender, donor living status and data collected during the first year post-transplantation, the occurrence acute rejection episode(s) and SCr levels (µmol/L) at 3 and 6-months post-transplantation.

The objective of the present study was to provide to willing patients the ability for them to determine middle-term risk of graft failure by using a simple calculator. To reach this goal, we simplified the initial joint model and proposed the ‘Dynamic prediction of Patient and

Graft survival' (DynPG) by reducing the number of predictors and then validating the corresponding dynamic prognostic capacities.

Patients and methods

Study Population

Data were extracted from the French, multicentric, observational and prospective DIVAT cohort (www.divat.fr, CNIL final agreement, decision DR-2025-087 N°914184 the 15 February 2015). All participants gave informed consent. A total of 4121 patients met the following inclusion criteria: adult recipients who received a first or second renal graft transplanted between January 2000 and August 2013 from a living or heart beating deceased donor, alive with a functioning graft at 1-year post-transplantation and maintained under Tacrolimus and Mycofenolate. This whole sample was randomly split: 2/3 of the patients (n=2749) were used as a learning sample to estimate models. The other 1/3 of the patients (n=1372) were grouped with a more recent second group of patients, also extracted from the DIVAT database, transplanted between September 2013 and October 2016 (n=1217). This combined group served as the independent sample for validation (n=2589).

Outcomes

The baseline was the 1-year post-transplantation anniversary in order to focus on the chronic phase of renal transplantation evolution. Since the initial visit will not be exactly at 1-year post-transplantation, we constrained the visit to be in-between 8 and 16 months post-transplantation. The endpoint was the time to graft failure defined as the first event between return-to-dialysis, pre-emptive re-transplantation and death with a functioning graft. We considered the SCr (µmol/L) evolution, as the yearly recorded levels until graft

failure. We chose a window of prediction of 5 years as a relevant time horizon in order to provide middle-term prognosis.

Statistical analyses

The high number of predictors in the joint model we initially proposed (provided in appendix, table S1) (15) was due to the etiologic objective of our previous study, i.e. to describe the factors associated with both the SCr and/or the graft failure risk.

In the present prognostic context, the SCr evolution being on the causal pathway between baseline factors and graft failure risk, we used the learning sample to construct a more parsimonious joint model removing all baseline parameters previously associated with the longitudinal SCr process. Indeed, the baseline factors associated with SCr evolution were therefore indirectly related to graft failure risk. In addition, the donor gender initially associated with graft failure risk was retrieved because of non-significance ($p>0.05$) and no added value in prognostic capacities. Finally, the retained joint model used to define the DynPG was composed of annual post transplantation SCr values and 6 baseline variables: recipient age at transplantation, graft rank, history of cardiovascular disease (except hypertension), occurrence of at least one acute rejection episode during the first year post-transplantation (only treated acute rejections were considered) and pre-transplantation immunization against HLA Class I. The latest was defined as positive if at least one donor specific antibody was identified by Luminex® Single Antigen Bead technology within 6 months pre-transplantation, unless at least one donor specific antibody was not identified but a later assessment by Luminex® screening or other technique (enzyme-linked immunosorbent assay (ELISA) or Complement Dependent Cytotoxicity (CDC)) was positive pre-transplantation.

DynPG was defined as the probability to be free of graft failure within the next 5 years, for each prediction time from 1-year to 6-years post-transplantation, as formally defined in the Web supplementary materials. This maximum prediction time was retained since there were 178 patients still at risk of graft failure at 11-years post-transplantation in the validation sample.

Prognostic performances were reported according to the TRIPOD recommendations (16,17). An R2-type curve was used to evaluate global performances (18). The discriminative capacities were evaluated by the Area Under the ROC Curve (AUC) for dynamic predictions (19). The calibration was described by comparing predicted values within subgroups (defined from quantiles of predictions) to observed graft and patient survivals (computed using the Kaplan-Meier estimator). All analyses were implemented using R (v3.3.0) and the JM (v1.4.7), prodlim (v1.6.1), survival (v2.39.2), timeROC (v0.3) and shiny packages (20–25).

Results

Description

A total of 2749 patients constituted the learning sample data while 2589 patients served as the validation sample data. Table 1 compares these two samples. The patients for validation were more frequently immunized against HLA class I (40.3% versus 32.7%) and II antigens (35.5% versus 29.8%), with more frequent comorbidities (14.1% versus 11.6% for history of diabetes; 37.0% versus 31.3% for history of dyslipidemia; 11.0% versus 8.3% for history of neoplasia), as well as a shorter mean Cold Ischemia Time (16.0 ± 9.5 hours versus 17.8 ± 9.8 hours). These differences may be explained by the inclusion of the 1217 more recently transplanted recipients in the validation study cohort.

During the follow-up, 259 patients in the validation sample returned to dialysis, 6 were pre-emptively re-transplanted and 196 died with a functioning graft. In the learning sample, 275 returned in dialysis, 3 were pre-emptively re-transplanted and 203 died. The median follow-up time was 3.1 years (26). The graft and patient survival probabilities at 8-years post-transplantation were 71.4% (95% Confidence Interval - CI from 68.8% to 74.1%) for the validation sample versus 71.8% (95%CI from 69.3% to 74.5%) for the learning sample (Figure S1, log-rank test p=0.5191).

Simplified joint model of longitudinal SCr measurements and time to graft failure

As summarized in Table 2, we assessed a simpler version of the joint model which was estimated on the learning sample and required 6 fewer covariates than the initially proposed model (15). Recipient age at transplantation, history of cardiovascular disease, 3-months SCr, occurrence of acute rejection episode(s) in the first year post-transplantation, pre transplantation anti-class I immunization and graft rank were significantly associated with graft failure risk ($p<0.05$). For any time 1 year after transplantation, graft failure depended on both the current value and the current slope of the SCr. If a patient had a 25% higher SCr, graft failure risk was twice as high (HR=1.96, 95%CI from 1.79 to 2.15). Moreover, for a given SCr value, where a patient had a steeper increase in SCr, graft failure risk was significantly worse (HR=1.84, 95%CI from 1.11 to 3.04).

Prognostic capacities of the DynPG

Due to missing data for variables needed to compute the predictions, 66 patients were excluded from the analysis. The included (n=2523) and excluded (n=66) patients were relatively comparable (Table S2). As illustrated in Figure 1, the data did not show major

concerns regarding the calibration, even though one can notice better performance in making predictions at early times. The overall prognostic capacities (discrimination and calibration) for predicting patient and graft survival at each transplantation anniversary up to 5 years later, seemed relatively similar for making predictions over the years (Figure 2A). R^2 values ranged from 14% (95%CI from 7% to 21%) to 15% (95%CI from -2% to 33%) at 1 and 6-years post-transplantation respectively. At 6-years post-transplantation, regarding the acceptable calibration, the patient and graft survival would be on average 15% lower for patients who actually had a graft failure compared to those who did not. The corresponding discriminative capacities increased with the post-transplantation time (Figure 2B). The AUC values ranged from 0.72 (95%CI from 0.67 to 0.78) to 0.76 (95%CI from 0.68 to 0.85) at 1 and 6-years post-transplantation. This means that, at 6-years post transplantation, we estimated a 76% probability that the 5-year predicted survival of a subject who actually died or returned to dialysis within the 5-years is lower than that of a subject that did not. Note that accuracy plots revealed similar performance of discrimination and calibration than the joint model previously proposed by Fournier et al. (Figure S2) as well as the model without any variable selection in the survival sub-model (Table S3 , Figure S3).

Examples of dynamic predictions

In order to illustrate how the DynPG could be used in practice, we choose two illustrative clinical cases from the validation sample. We computed their DynPG at each time they came to the hospital thanks to the online web application we developed (available at https://shiny.idbc.fr/DynPG). The SCr measurements and evolution are plotted on the left sides of the plot and the corresponding prediction of the graft and patient survival was plotted on the right side. We also represented the mean crude survival probabilities as a

benchmark, i.e. the graft and patient survival probabilities of patients alive with a functioning graft at the prediction time estimated from the Kaplan-Meier estimator on the learning sample. In order to obtain results interpretable by the large majority of patients, this application also offers visual aids with smileys and short sentences.

Case A: A 51 year old female transplanted with a first graft in 2005, immunized against HLA class I Ag before transplantation, with neither history of cardiovascular diseases nor acute rejection episode during the first year post-transplantation and with a 3-month SCr value at 88 µmol/L. Finally, this woman returned to dialysis in 2014.

At 3-years post-transplantation, this patient had an 87% chance of being alive with a functioning graft 5 years later, i.e. 8-years after her transplantation (95%CI from 46% to 97%, figure 3). At that prediction time, 3-years post-transplantation, her estimated survival curve was above the whole population at-risk at the same time. One year later (4-years post-transplantation), one can observe a significant increase in the SCr, resulting in a significant decrease in the predicted graft and patient survival. Despite subsequent stabilisation of the SCr (5 and 6-years post-transplantation), her prognosis did not improve. At 6-years post-transplantation, the patient has a (predicted) 98% probability of losing her graft or dying before 11-years post-transplantation. Obviously, and without needing the DynPG, most physicians and patients would be worried about the degradation of the graft function observed at 4-years post-transplantation. This would more than likely have resulted in further exploration or modification of the patient follow-up or treatments. Nevertheless, it would also probably be difficult for a physician to precisely estimate the risk of graft failure and to answer to patient interrogation about her chance to keep their graft alive in the near future. The DynPG is designed to perform such a prediction, and could also be pedagogically

beneficial in supporting the medical decision to the patient. From a patient-centered care view, this tool could also be useful for willing patients to slowly and carefully prepare them psychologically and emotionally to their middle-term outcomes and allows them be a participant in their transplantation health status.

Case B: A 60 year old female recipient of a second transplantation in 2007, without history of cardiovascular disease, immunized against HLA class I Ag before the transplantation, with at least one acute rejection episode during the first year of transplantation and with 3-months SCr value at 100 µmol/L. In 2017, this recipient was still alive with a functioning graft.

In contrast to case A, one can observe no increase in the SCr level according to time post-transplantation, as illustrated by Figure 4. At 5-years post-transplantation, the 10-years patient and graft survival was estimated at 89% (95%CI from 68% to 97%). While the baseline prognosis was worse for case B compared to case A, the consideration of the SCr evolution illustrates the importance of updating the initial prediction. This example emphasizes the usefulness of the proposed dynamic model compared to the existing fixed-time models (6,27–29). Providing these predictions and its pedagogical interpretation could be important for reassuring this patient about her middle-term prognosis.

Discussion

While medical decisions are usually made by physicians on behalf of patients, shared decision making is increasingly considered as an essential part of quality healthcare delivery (1). The P4-medicine descriptor, i.e. the predictive, preventive, personalized and participatory medicine, is nowadays a largely developed concept in the literature, but is not often applied in clinical practice (30). More generally, informing kidney transplant recipients

of their prognosis may increase adherence to treatment plans, as patients recognize their active role in the decision-making process (1,8). The multiplicity of the risk factors in kidney transplantation requires synthetic tools to estimate the graft failure risk. In this study, for the first time to our knowledge, we propose and validate a simple model to dynamically predict patient and graft survival. We also propose an online application (https://shiny.idbc.fr/DynPG), that is similar to the one proposed for patients suffering from chronic heart failure (31).

This web application provides meaningful predictions for both the clinician and the patient. For instance, for the case A patient, one can predict at 5-years post-transplantation the poor graft and patient survival prognosis at 10-years post-transplantation. This result can be used to better understand the decision of a change in follow-up or treatment and to prepare the patient psychologically and emotionally for accepting dialysis as the next step of her disease treatment. In contrast for the case B patient, the DynPG could be useful in reducing anxiety and stress and to improving the patient's well-being.

In addition, such a predictive tool can possibly help to better organize healthcare visits by adapting their schedule or type for each patient according to the predicted graft and patient survival (32–34). For instance, it would be possible to reduce the follow-up of the case B patient after her second anniversary of transplantation. A more efficient allocation of resources can bring economic benefits and may also improve the patient's quality of life (no travel requirements, less stress associated with medical examinations, etc.).

Some important limitations have to be considered. Firstly, the DynPG is based on SCr (µmol/L) as the only longitudinal marker for dynamic predictions. We choose SCr instead of estimated glomerular filtration rate because a number of studies have shown that the two markers have equivalent prognostic capacities but the SCr is easier to obtain (no calculation

required and the physician can use the laboratory result directly) (35,36). Obviously, additional longitudinal markers such as proteinuria, post-transplantation anti-HLA immunisation, occurrence of cytomegalovirus infection or pyelonephritis, could probably improve the prognostic capacities of the DynPG, but we are cognisant that the inclusion of multiple longitudinal markers in joint models is currently a subject of research among the Biostatistic community (37). Secondly, our variable selection may be debated. From the joint model previously proposed by Fournier et al., we removed variables in the longitudinal sub-model using an expert background knowledge. Even if alternative strategies may be relevant (38–40), our proposed parsimonious joint model appeared robust in terms of predictive performances when comparing it to the initially-published Fournier model and the joint model without variable selection in the survival sub-model. Thirdly, the prediction of graft failure can be seen as a limitation because a non-negligible part of death with a functioning graft was associated with a cause other than the transplantation. Despite this, note that the alternative solution consisting of right-censoring death would have also been open to criticism. Fourthly, the 95%CI of the dynamic predictions may be considered as relatively large particularly for later prediction times, possibly due to a decreased number of at-risk patients. Importantly, let recall that our results may be valid on cohorts respecting similar inclusion criteria and with comparable patients characteristics to our study, otherwise interpretation of predictions can be misleading. Finally, we arbitrarily choose a horizon window of 5-years to make predictions at mid-term. Different horizon windows could also be of interest. For instance, it may be possible to consider earlier re-entry to waiting lists for pre-emptive re-transplantation if the individual predicted risk is really high in a shorter horizon window of 1-year.

Finally, predictive tools of this type where the patient is actively involved raise significant ethical and practical questions for a smart and safe use in a patient-centered point of view, such as how to transmit prediction information to the patient and which information has to be given. In our online application, we proposed an interpretation inspired from Hollnagel's proposal (41). For instance, for the patient Case A presenting at 3 years post-transplantation an 87% chance of being alive with a functioning graft 5 years later, the message delivered to the patient could be: *"Among a group of 100 patients with comparable characteristics and having the same creatinine evolution, research indicates that 87 patients will be alive with a functioning graft 5 years later while 13 will have a graft failure. Among them, we don't know if it is a return to dialysis, a pre-emptive retransplantation or a death with a functioning graft. We also do not know to which group you will belong to."* Henderson and Keiding also recognized that punctual prediction should be communicated with caution since it neglected the variability surrounding the prediction (42). In that sense it may be relevant to provide interval of predictions. Accordingly, we believe that the first step would be to trial the DynPG with nephrologists as a tool for informing and preparing their willing patients of their future graft survival probability and clinical management strategy. In parallel, we are working on patient perception and feelings when confronted with their predicted risk of graft failure in order to avoid patient abandonment due to their predicted result or cognitive or psychological misinterpretation of their outcome. One may envisage the use of our online application in an educational motivation. For instance, presenting to one patient different hypothetical scenarios about their serum creatinine evolution may illustrate the modification of the incurred graft failure risk and thus incite the patient to be more compliant. We have also planned to evaluate the possible impact of the DynPG by focusing on the well-being of patients by measuring their anxiety, stress and adherence levels.

In conclusion, we have proposed and validated the DynPG as a dynamic predictive tool based on only 6 factors in addition to the SCr values during the follow-up of the patient. These dynamic predictions could provide useful information for both patient and physician, and assist in promoting a synergistic decision making process.

Conflict of Interest Statement

The authors declare no conflict of interest for this study.

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Authors' Contributions

Marie-Cécile Fournier: Conceptualization, Methodology, Formal analysis, Writing - original draft, review and editing. Yohann Foucher: Conceptualization, Methodology, Writing - review and editing. Paul Blanche : Formal analysis, Writing - review and editing. Christophe Legendre, Sophie Girerd, Marc Ladrière, Emmanuel Morelon, Fanny Buron, Lionel Rostaing, Nassim Kamar, Georges Mourad, Valérie Garrigue, Grégoire Couvrat-Desvergnes: Data acquisition, Writing - review and editing. Magali Giral : Conceptualization, Clinical mentorship, Writing - review and editing. Etienne Dantan: Project administration, Conceptualization, Methodology, Writing - original draft, review and editing.

References

1. Gordon EJ, Butt Z, Jensen SE et al. Opportunities for shared decision making in kidney transplantation. American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2013; 13: 1149–1158.

2. Jamieson NJ, Hanson CS, Josephson MA et al. Motivations, Challenges, and Attitudes to Self-management in Kidney Transplant Recipients: A Systematic Review of Qualitative Studies. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2016; 67: 461–478.

3. O'Hare AM. Patient-Centered Care in Renal Medicine: Five Strategies to Meet the Challenge. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2018; 71: 732–736.

4. Sautenet B, Tong A, Chapman JR et al. Range and consistency of outcomes reported in randomized trials conducted in kidney transplant recipients: a systematic review. Transplantation 2018;

5. Howell M, Wong G, Rose J, Tong A, Craig JC, Howard K. Patient Preferences for Outcomes After Kidney Transplantation: A Best-Worst Scaling Survey. Transplantation 2017; 101: 2765–2773.

6. Foucher Y, Daguin P, Akl A et al. A clinical scoring system highly predictive of long-term kidney graft survival. Kidney International 2010; 78: 1288–1294.

7. Braun WE, Schold JD. Transplantation: strength in numbers-predicting long-term transplant outcomes. Nature Reviews. Nephrology 2011; 7: 135–136.

8. Vandecasteele SJ, Kurella Tamura M. A patient-centered vision of care for ESRD: dialysis as a bridging treatment or as a final destination? Journal of the American Society of Nephrology: JASN 2014; 25: 1647–1651.

9. Kaboré R, Haller MC, Harambat J, Heinze G, Leffondré K. Risk prediction models for graft failure in kidney transplantation: a systematic review. Nephrology Dialysis Transplantation 2017; 32: ii68–ii76.

10. Rizopoulos D. Joint Models for Longitudinal and Time-to-Event Data: With Applications in R. CRC Press, 2012.

11. Brankovic M, Kardys I, Hoorn EJ, Baart S, Boersma E, Rizopoulos D. Personalized dynamic risk assessment in nephrology is a next step in prognostic research. Kidney International 2018; 94: 214–217.

12. Moranne O, Maillard N, Fafin C, Thibaudin L, Alamartine E, Mariat C. Rate of renal graft function decline after one year is a strong predictor of all-cause mortality. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2013; 13: 695–706.

13. Garre FG, Zwinderman AH, Geskus RB, Sijpkens YWJ. A joint latent class changepoint model to improve the prediction of time to graft failure. Journal of the Royal Statistical Society: Series A (Statistics in Society) 2008; 171: 299–308.

14. Rizopoulos D, Ghosh P. A Bayesian semiparametric multivariate joint model for multiple longitudinal outcomes and a time-to-event. Statistics in Medicine 2011; 30: 1366–1380.

15. Fournier M-C, Foucher Y, Blanche P, Buron F, Giral M, Dantan E. A joint model for longitudinal and time-to-event data to better assess the specific role of donor and recipient factors on long-term kidney transplantation outcomes. European Journal of Epidemiology 2016; : 1–11.

16. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement. Annals of Internal Medicine 2015; 162: 55.

17. Moons KGM, Altman DG, Reitsma JB et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration. Annals of Internal Medicine 2015; 162: W1.

18. Fournier M-C, Dantan E, Blanche P. An R2-curve for evaluating the accuracy of dynamic predictions. Statistics in Medicine : n/a-n/a.

19. Blanche P, Proust-Lima C, Loubère L, Berr C, Dartigues J-F, Jacqmin-Gadda H. Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. Biometrics 2015; 71: 102–113.

20. R Development Core Team . R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: 2010.Available from: http://www.R-project.org/

21. Rizopoulos D. JM: An R Package for the Joint Modelling of Longitudinal and Time-to-Event Data. Journal of Statistical Software 2010; 35: 1–33.

22. Gerds TA. prodlim: Product-Limit Estimation for Censored Event History Analysis [Internet]. 2017 [cited 2018 Mar 7] .Available from: https://CRAN.R-project.org/package=prodlim

23. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model [Internet]. Springer-Verlag, New York: 2000 [cited 2018 Mar 7] .Available from: //www.springer.com/us/book/9780387987842

24. Blanche P, Dartigues J-F, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. Statistics in Medicine 2013; 32: 5381–5397.

25. Chang W, Cheng J, Allaire JJ et al. shiny: Web Application Framework for R [Internet]. 2017 [cited 2018 Mar 12] .Available from: https://CRAN.R-project.org/package=shiny

26. Shuster JJ. Median follow-up in clinical trials. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology 1991; 9: 191–192.

27. Lorent M, Giral M, Pascual M et al. Mortality Prediction after the First Year of Kidney Transplantation: An Observational Study on Two European Cohorts. PloS One 2016; 11: e0155278.

28. Kasiske BL, Israni AK, Snyder JJ, Skeans MA, Peng Y, Weinhandl ED. A simple tool to predict outcomes after kidney transplant. American journal of kidney diseases: the official journal of the National Kidney Foundation 2010; 56: 947–960.

29. Moore J, He X, Shabir S et al. Development and evaluation of a composite risk score to predict kidney transplant failure. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2011; 57: 744–751.

30. Flores M, Glusman G, Brogaard K, Price ND, Hood L. P4 medicine: how systems medicine will transform the healthcare sector and society. Personalized Medicine 2013; 10: 565–576.

31. Brankovic M, Akkerhuis KM, van Boven N et al. Patient-specific evolution of renal function in chronic heart failure patients dynamically predicts clinical outcome in the Bio-SHiFT study. Kidney International 2018; 93: 952–960.

32. Jörres A, John S, Lewington A et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: part 2: renal replacement therapy. Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association 2013; 28: 2940–2945.

33. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009; 9 Suppl 3: S1-155.

34. Foucher Y, Meurette A, Daguin P et al. A personalized follow-up of kidney transplant recipients using video conferencing based on a 1-year scoring system predictive of long term graft failure (TELEGRAFT study): protocol for a randomized controlled trial. BMC nephrology 2015; 16: 6.

35. Shaffi K, Uhlig K, Perrone RD et al. Performance of creatinine-based GFR estimating equations in solid-organ transplant recipients. American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation 2014; 63: 1007–1018.

36. Luis-Lima S, Marrero-Miranda D, González-Rinne A et al. Estimated Glomerular Filtration Rate in Renal Transplantation: The Nephrologist in the Mist. Transplantation 2015;

37. Hickey GL, Philipson P, Jorgensen A, Kolamunnage-Dona R. joineRML: a joint model and software package for time-to-event and multivariate longitudinal outcomes. BMC medical research methodology 2018; 18: 50.

38. Heinze G, Dunkler D. Five myths about variable selection. Transplant International: Official Journal of the European Society for Organ Transplantation 2017; 30: 6–10.

39. Tibshirani R. Regression Shrinkage and Selection via the Lasso. Journal of the Royal Statistical Society. Series B (Methodological) 1996; 58: 267–288.

40. Royston P, Sauerbrei W. Multivariable Model - Building: A Pragmatic Approach to Regression Anaylsis based on Fractional Polynomials for Modelling Continuous Variables. John Wiley & Sons, 2008.

41. Hollnagel H. Explaining risk factors to patients during a general practice consultation. Conveying group-based epidemiological knowledge to individual patients. Scandinavian Journal of Primary Health Care 1999; 17: 3–5.

42. Henderson R, Keiding N. Individual survival time prediction using statistical models. Journal of Medical Ethics 2005; 31: 703–706.

Tables and Figures

Table 1: Description of recipients, donors and transplantation characteristics according to the learning sample (n=2749) or the validation sample (n=2589).

	Learning sample (n=2749)		Validation sample (n=2589)		p-value
	NA	estimations	NA	estimations	
Quantitative characteristics : mean ± SD					
Recipient age at transplantation (years)	0	49.71 ± 13.59	0	50.63 ± 14.25	0.0158
Recipient BMI (kg/m²)	10	23.99 ± 4.24	7	24.65 ± 4.43	<0.0001
Donor age (years)	1	50.74 ± 15.52	4	52.12 ± 15.95	0.0013
Last donor SCr (µmol/L)	25	89.91 ± 52.77	21	88.24 ± 53.46	0.2557
Cold ischemia time (hours)	10	17.76 ± 9.79	7	15.96 ± 9.51	<0.0001
Time spent on dialysis (years)	36	2.98 ± 3.08	23	2.93 ± 3.19	0.5649
3-months SCr (µmol/L)	38	138.30 ± 53.38	36	138.77 ± 55.10	0.7528
6-months SCr (µmol/L)	75	136.64 ± 53.18	73	135.43 ± 48.91	0.3930
3-months proteinuria (g/day)	669	0.34 ± 0.87	1151	0.33 ± 0.70	0.7079
6-months proteinuria (g/day)	759	0.30 ± 0.52	1273	0.32 ± 0.76	0.5526
12-months proteinuria (g/day)	706	0.36 ± 0.78	1224	0.33 ± 0.54	0.2501
Categorical characteristics : N (%)					
Recipient men	0	1674 (60.89)	0	1596 (61.65)	0.5737
Second transplantation	0	474 (17.24)	0	442 (17.07)	0.8689
Dialysis technique	4		0		0.4841
Pre-emptive transplantation		342 (12.46)		346 (13.36)	
Hemodialysis		2191 (79.82)		2032 (78.49)	
Peritoneal dialysis		212 (7.72)		211 (8.15)	
Relapsing initial disease	0	799 (29.07)	0	687 (26.54)	0.0393
History of diabetes	0	319 (11.60)	0	365 (14.10)	0.0064
History of hypertension	0	2272 (82.65)	0	2120 (81.88)	0.4654
History of cardiovascular disease	0	933 (33.94)	0	911 (35.19)	0.3380
History of dyslipidemia	0	860 (31.28)	0	957 (36.96)	<0.0001
History of neoplasia	0	228 (8.29)	0	284 (10.97)	0.0009
More than 5 HLA A-B-DR incompatibilities	7	350 (12.76)	3	399 (15.43)	0.0052
Daily anti-HLA immunization of class I	66	876 (32.65)	30	1032 (40.33)	<0.0001
Daily anti-HLA immunization of class II	87	792 (29.75)	45	904 (35.53)	<0.0001
Donor men	8	1545 (56.37)	3	1468 (56.77)	0.7680
Donor vital status	6		7		0.0026
Living donor		418 (15.21)		481 (18.63)	
Cerebrovascular donor death		1309 (47.74)		1151 (44.58)	
Non cerebrovascular donor death		1016 (37.05)		950 (36.79)	
Delayed graft function	15	714 (26.12)	9	714 (27.67)	0.2001
Acute rejection episode(s) during the first year	0	591 (21.50)	0	499 (19.27)	0.0439
Transplanted before 2008	0	2091 (39.17)	0	1369 (49.80)	<0.0001

Abbreviations: BMI Body Mass Index; HLA Human Leucocyte Antigen; NA: Not Available (missing data); SCr Serum Creatinine; SD Standard Deviation

Table 2: Simplified multivariate joint model for longitudinal evolution of logarithmic transformation of serum creatinine (SCr) and risk of graft failure (return to dialysis or death with a functioning graft) in kidney transplant patients (n=2584 patients, 165 patients excluded due to missing data).

	Survival process		
	HR	95%CI	p-value
Current SCr (µmol/L), for an increase of 25%	1.96	[1.79; 2.15]	<0.0001
Current SCr increase (µmol/L), for a growth of 25% in 1 year	1.84	[1.11; 3.04]	0.0176
Recipient age at transplantation (years, standardized)	1.49	[1.33; 1.66]	<0.0001
History of cardiovascular diseases: yes versus no	1.41	[1.16; 1.71]	0.0007
3-months SCr (µmol/L, standardized)	0.83	[0.74; 0.93]	0.0011
Acute rejection episode(s) during the first year: yes versus no	1.46	[1.16; 1.82]	0.0011
Anti-class I immunization: positive versus negative	1.54	[1.22; 1.94]	0.0002
Rank of graft: second versus first	1.31	[1.01; 1.71]	0.0433

Referential value for log(SCr) at 1-year post-transplantation was 4.860, 95%CI : [4.846; 4.873]. Referential value for the slope of log(SCr) was 0.024 95%CI : [0.021; 0.028]. This model is adjusted on a period effect with a threshold at 2008 (before 2008 versus after): HR=0.74 [0.58 ; 0.95]

Parameters of the Weibull baseline risk function were: intercept : -20.72 ± 0.97; log(shape): 0.33 ± 0.05; $alpha_1$ = 3.0179 ± 0.2049 95%CI[2.62 ; 3.42] and $alpha_2$ = 3.0567 ± 1.2871 95%CI[0.53 ; 5.58]

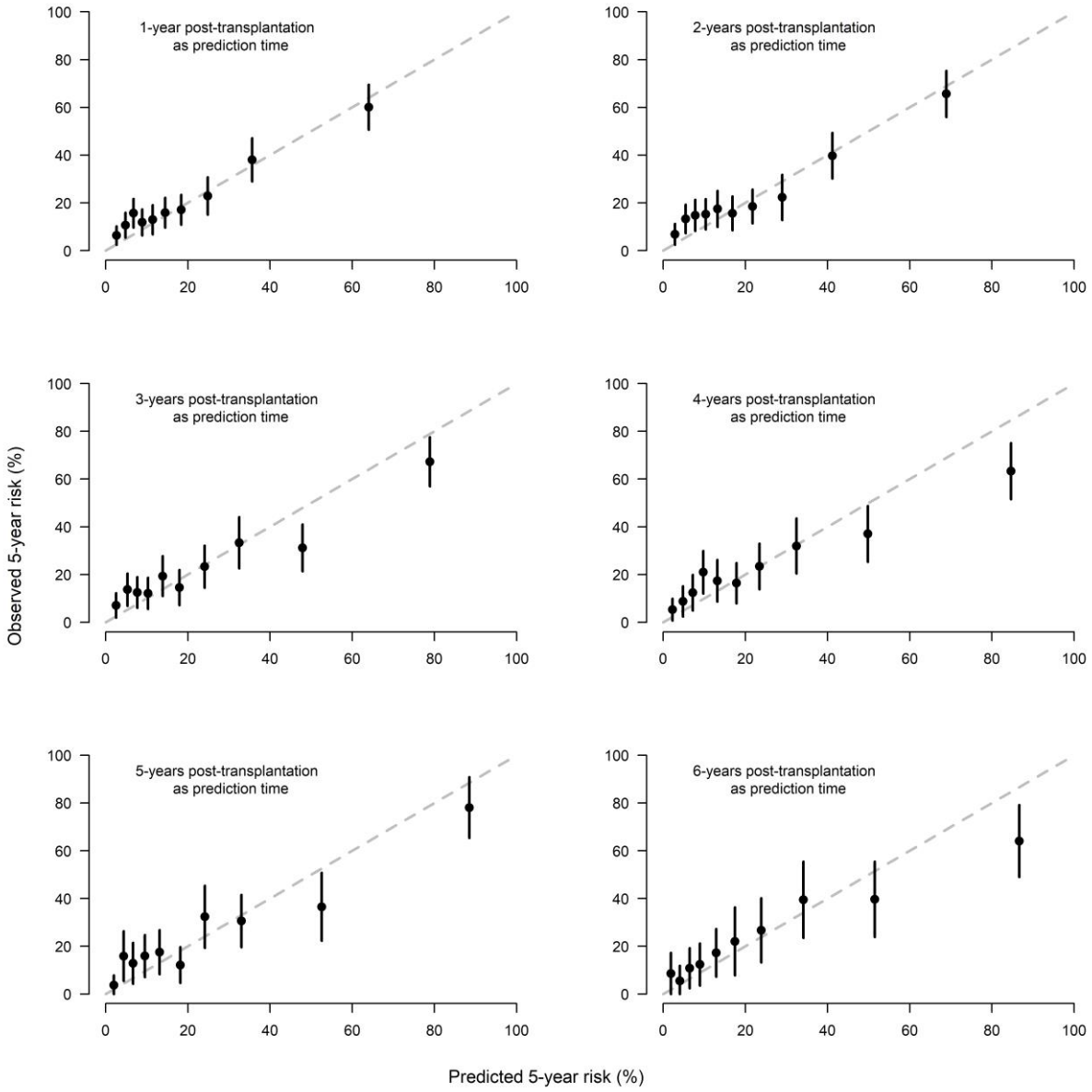

Figure 1: Calibration plot of dynamic predictions on the validation sample (n=2523, 66 observations deleted due to missing data concerning covariates) for prediction times from 1 to 6-years post-transplantation. Mean predicted risks and observed risks (Kaplan-Meier) are displayed for each subgroup, defined from quantiles of predictions.

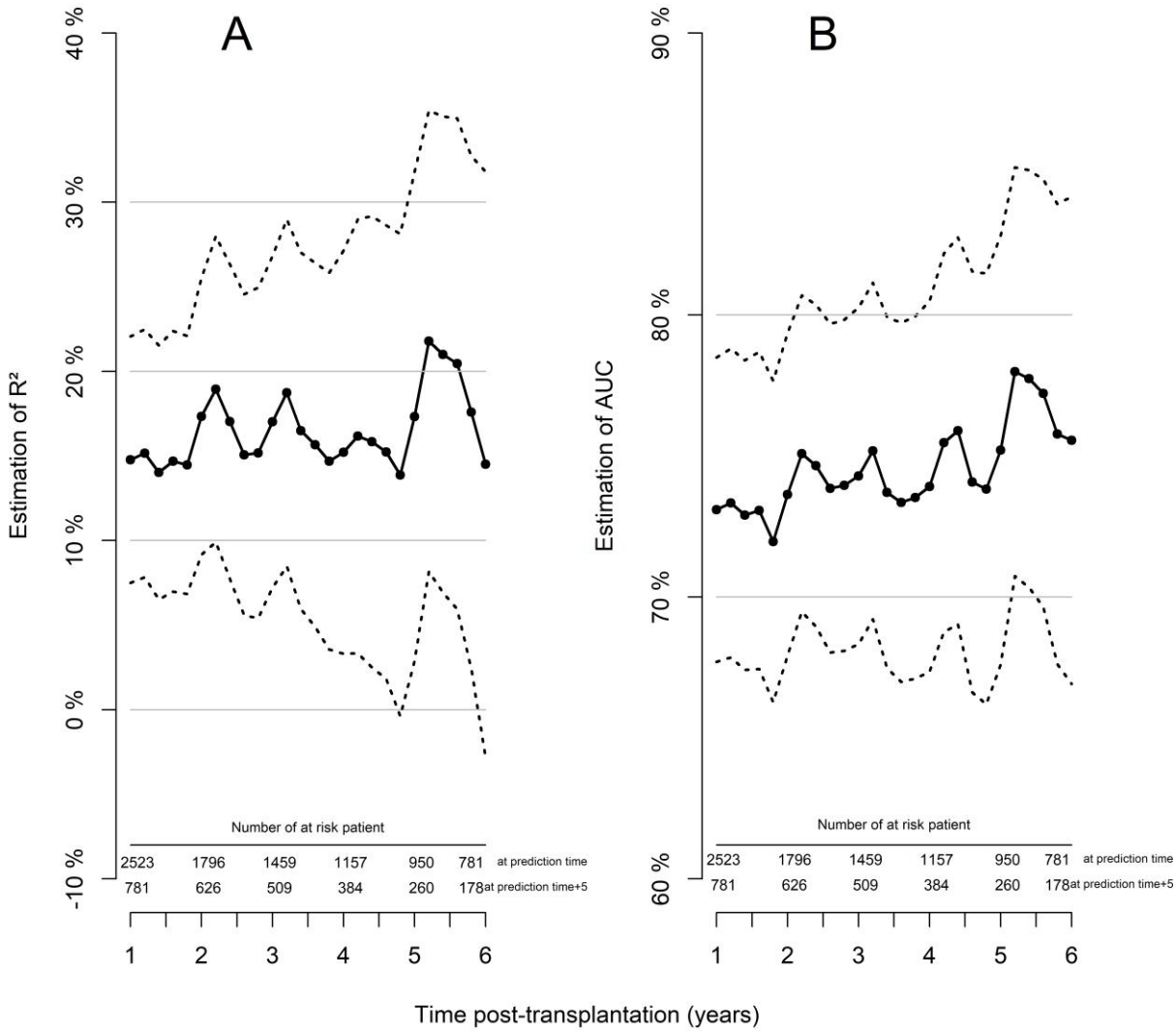

Figure 2: Prognostic capacities of the dynamic predictions (n=2523, 66 observations deleted due to missing data concerning covariates) estimated for prediction times from 1 to 6-years post-transplantation for a given horizon window of 5 years, R^2 supplied global performance (Part A) while Area under ROC curve (AUC) appraised discrimination accuracy (Part B). Estimations are drawn in solid lines and the corresponding 95% confidence interval is drawn in dashed lines.

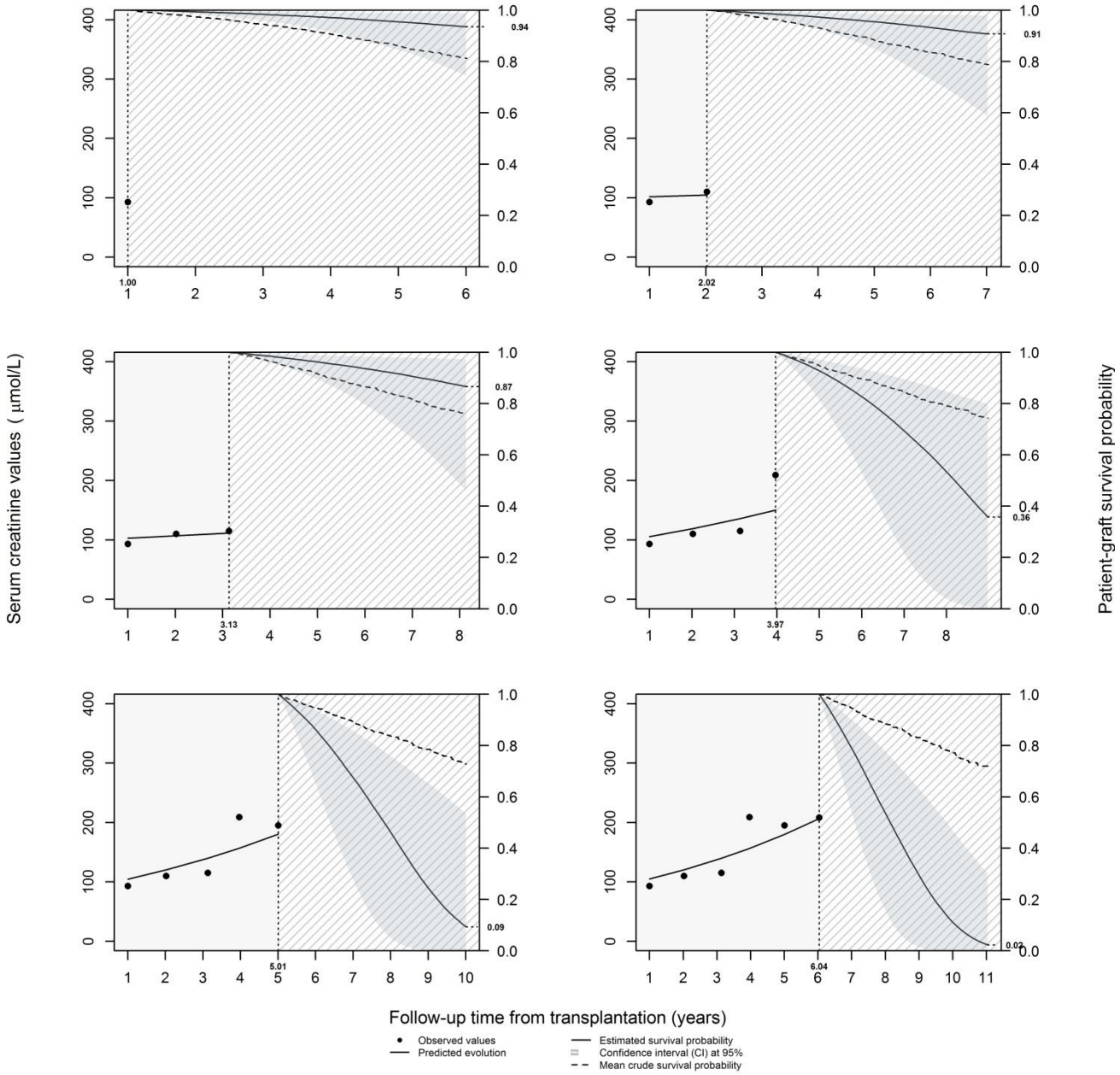

Figure 3: Individual dynamic predictions obtained from the simplified joint model for prediction times from 1 to 6 years post-transplantation for a particular individual (A woman aged 51 years transplanted in 2005 for the first time, without history of cardiovascular disease, anti-class I immunized, with SCr measurement at 3-months post-transplantation at 88 µmol/L and no acute rejection episode in the first year post-transplantation). The recipient was returned in dialysis at 9.3 years after transplantation. The mean crude survival probabilities can be used as a benchmark (it is the non-parametric Kaplan-Meier survival probabilities conditioning on the survival until the prediction time, estimated from data of Fournier et al.(15)).

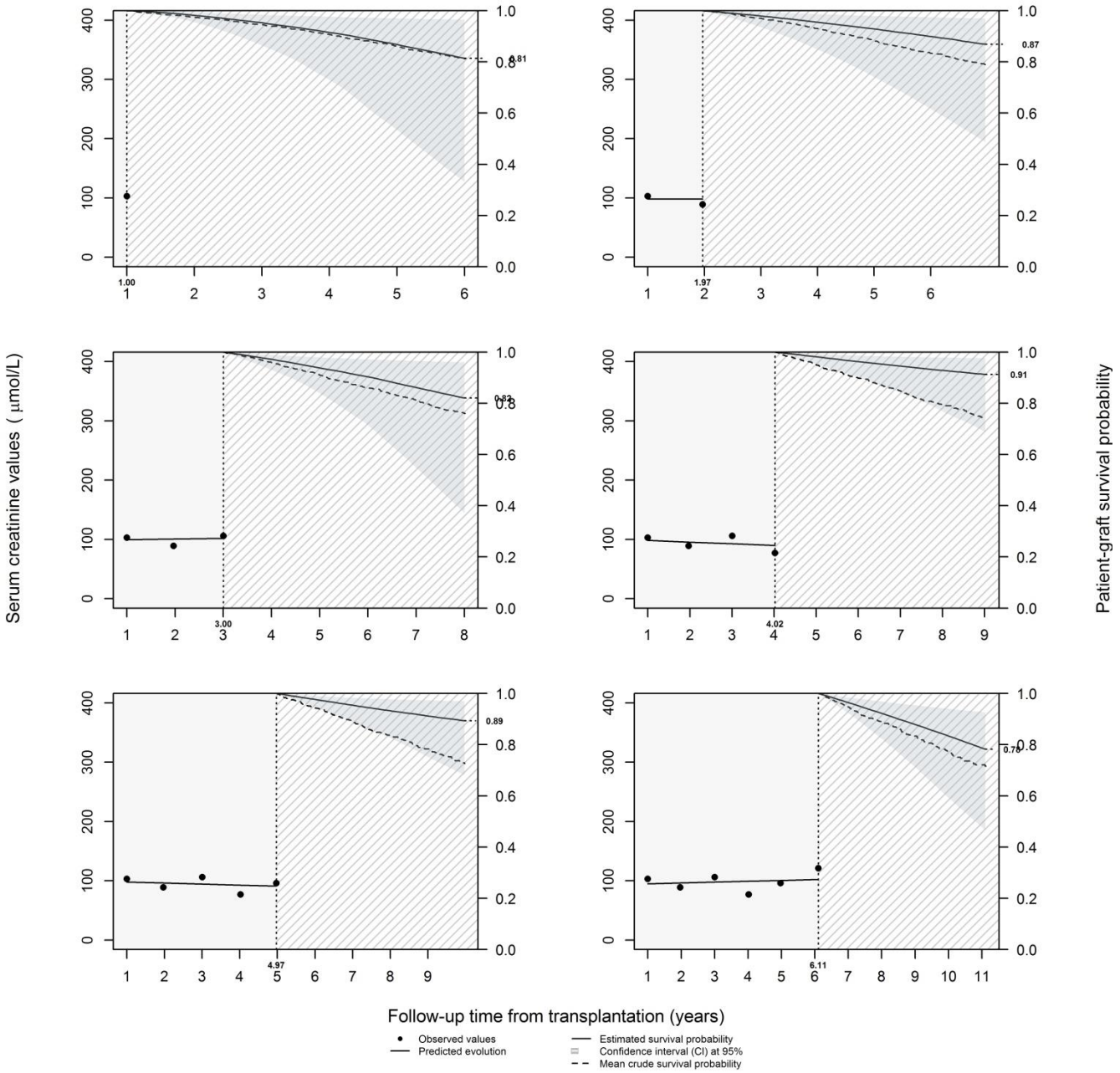

Figure 4: Individual dynamic predictions obtained from the simplified joint model for prediction times from 1 to 6 years post-transplantation for a particular patient (case B): A woman aged 60 years transplanted in 2007 for the second time, without history of cardiovascular disease, anti-class I immunized, with SCr measurements at 3-months post-transplantation at 100 µmol/L and with at least one acute rejection episode in the first year post-transplantation. The recipient was still alive with a functioning graft at 10 years post-transplantation. The mean crude survival probabilities can be used as a benchmark (it is the non-parametric Kaplan-Meier survival probabilities conditioning on the survival until the prediction time, estimated from data of Fournier et al.(15)).

Web supplementary materials

Definition of the Dynamic prediction of Patient and Graft survival (DynPG)

We defined the Dynamic prediction of Patient and Graft survival (DynPG) as the probability, calculated at a given prediction time s, to be free of graft failure within the next 5 years as:

$$\pi_s = P(T_i^* > s + 5 \mid T_i^* > s, Y_i(s), X_i; \theta, b_i) \quad (1)$$

with T_i^* the time to kidney graft failure of subject i, s the prediction time, $Y_i(s)$ the longitudinal measurements of serum creatinine until time s, X_i a matrix of baseline risk factors, θ the fixed parameters of the joint model, and b_i the random effects. We used a shared random effect joint model for longitudinal and survival data:

$$\begin{cases} Y_i(s) = \log(SCr)_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \varepsilon_{ij} = m_i(t_{ij}) + \varepsilon_{ij} \\ h_i(t) = h_0(t)\exp\left(\alpha_1 m_i(t) + \alpha_2 \frac{dm_i(t)}{dt} + \gamma X_i\right) \end{cases} \quad (2)$$

where β_0 and β_1 are respectively the mean values of $\log(SCr)$ at baseline (1-year post-transplantation) and the evolution slope, b_{0i} and b_{1i} are the corresponding random effects for subject i, ε_{ij} is the residual error of subject i at time t_{ij} ($m_i(t_{ij})$ is thus the true level of $\log(SCr)$ at time t_{ij}), $h_i(t)$ is the instantaneous risk function at time t with $h_0(t)$ the baseline risk function, α_1 and α_2 are respectively the regression coefficients for the effect on the patient-graft failure risk of current level and current slope of SCr, and γ are the regression coefficients associated with the baseline risk factors X_i.

Table S1: Multivariate joint model for longitudinal evolution of logarithmic transformation of serum creatinine (SCr) and risk of graft failure (return to dialysis or death with a functioning graft) in kidney transplant patients (n=2584 patients, 165 patients excluded due to missing data), i.e. Table 2 in Fournier et al.(15)

	Longitudinal process						Survival process		
	Association with the log(1-year SCr) (baseline effect)			Association with the log(SCr evolution) (slope effect)					
	coef	95%CI	p-value	coef	95%CI	p-value	HR	95%CI	p-value
Current SCr (µmol/L), for an increase of 25%							1.92	[1.75 ; 2.11]	<0.0001
Current SCr increase (µmol/L), for a growth of 25% in 1-year							1.89	[1.17 ; 3.06]	0.0097
Recipient age at transplantation (years, standardized)	-0.028	[-0.038 ; -0.018]	<0.0001	-0.010	[-0.014 ; -0.006]	<0.0001	1.51	[1.35 ; 1.68]	<0.0001
Recipient gender: male vs female	0.074	[0.057 ; 0.091]	<0.0001	-0.007	[-0.014 ; 0.000]	0.0392			
History of diabetes: yes vs no	0.001	[-0.026 ; 0.025]	0.9866	0.027	[0.016 ; 0.039]	<0.0001			
History of cardiovascular diseases: yes vs no	0.001	[-0.017 ; 0.017]	0.9812	0.008	[0.001 ; 0.015]	0.0371	1.39	[1.14 ; 1.69]	0.0011
3-months SCr (µmol/L, standardized)	0.083	[0.071 ; 0.096]	<0.0001				0.84	[0.74 ; 0.95]	0.0062
6-months SCr (µmol/L, standardized)	0.176	[0.165 ; 0.189]	<0.0001						
Acute rejection episode(s) during the first year: yes vs no	0.055	[0.035 ; 0.073]	<0.0001				1.46	[1.17 ; 1.83]	0.0010
Anti-class I immunization: positive vs negative	0.010	[-0.008 ; 0.027]	0.2707	0.011	[0.004 ; 0.019]	0.0036	1.50	[1.19 ; 1.90]	0.0006
Rank of graft: second vs first							1.32	[1.02 ; 1.73]	0.0381
Donor type (ref : living donor)			0.0773			0.0022			
Cerebrovascular death	0.028	[0.004 ; 0.052]		0.018	[0.007 ; 0.028]				
Non cerebrovascular death	0.019	[-0.005 ; 0.043]		0.010	[-0.001 ; 0.020]				
Donor gender: male vs female							0.83	[0.69 ; 1.01]	0.0589
Donor age (years, standardized)	0.056	[0.045 ; 0.066]	<0.0001						

Referential value for log(1-year SCr) was 4.024, 95%CI: [3.982; 4.065]. Referential value for log(SCr) evolution was 0.034 95%CI: [0.018 ; 0.050]. This model is adjusted on a time effect with a threshold at 2008 (before 2008 vs after): coefficient for the relation to the SCr at 1- year: 0.018 95%CI: [0.002 ; 0.034]and to the SCr evolution: 0.013 95%CI: [0.005; 0.020] and HR = 0.73 [0.57 ; 0.94]. Parameters of the Weibull baseline risk function were: intercept -20.247 ± 0.982 ; log(shape): 0.337 ± 0.046. α= 2.93 ; α_2 = 3.29
Coef: coefficient; HR: Hazard Ratio ; CI: confidence interval.

Table S2: Description of recipients, donors and transplantation characteristics (n=2589) and comparison between included patients for whom dynPG can be computed and excluded patients due to at least one missing value.

	Whole cohort (n=2589)		Included DynPG (n=2523)		Excluded patients (n=66)		p-value
	NA	estimations	NA	estimations	NA	estimations	
Quantitative characteristics :mean (SD)							
Recipient age at transplantation (years)	0	50.6 (14.3)	0	50.7 (14.2)	0	47.8 (14.6)	0.1176
Recipient body mass index (kg/m²)	7	24.7 (4.4)	6	24.7 (4.4)	1	24.6 (5.1)	0.9920
Donor age (years)	4	52.1 (15.9)	4	52.1 (16.0)	0	49.4 (15.3)	0.1530
Last donor SCr (µmol/L)	21	88.2 (53.5)	21	88.5 (53.9)	0	80.2 (32.8)	0.0524
Cold ischemia time (hours)	7	16.0 (9.5)	7	16.0 (9.5)	0	13.3 (10.6)	0.0435
Time spent on dialysis (years)	23	2.9 (3.2)	22	2.9 (3.1)	1	3.0 (4.6)	0.9070
3-months SCr (µmol/L)	36	138.8 (55.1)	0	138.8 (55.2)	36	139.4 (51.4)	0.9464
6-months SCr (µmol/L)	73	135.4 (48.9)	56	135.5 (48.9)	17	131.1 (51.0)	0.5485
3-months proteinuria (g/day)	1151	0.3 (0.7)	1103	0.3 (0.7)	48	0.4 (1.1)	0.6880
6-months proteinuria (g/day)	1273	0.3 (0.8)	1238	0.3 (0.8)	35	0.3 (0.4)	0.5176
12-months proteinuria (g/day)	1224	0.3 (0.5)	1190	0.3 (0.5)	34	0.2 (0.4)	0.1235
Categorical characteristics: N (%)							
Recipient men	0	1596 (61.65)	0	1558 (61.8)	0	38 (57.6)	0.4910
Second transplantation	0	442 (17.07)	0	434 (17.2)	0	8 (12.1)	0.2789
Dialysis technique	0		0		0		0.0338
Pre-emptive transplantation		346 (13.36)		331 (13.1)		15 (22.7)	
Hemodialysis		2032 (78.49)		1983 (78.6)		49 (74.2)	
Peritoneal dialysis		211 (8.15)		209 (8.3)		2 (3.0)	
Relapsing initial disease	0	687 (26.54)	0	661 (26.2)	0	26 (39.4)	0.0165
History of diabetes	0	353 (14.10)	0	348 (14.2)	0	17 (12.3)	0.6056
History of hypertension	0	2120 (81.88)	0	2069 (82.0)	0	51 (77.3)	0.3244
History of cardiovascular diseases	0	911 (35.19)	0	889 (35.2)	0	22 (33.3)	0.7494
History of dyslipidemia	0	957 (36.96)	0	928 (36.8)	0	29 (43.9)	0.2344
History of neoplasia	0	284 (10.97)	0	276 (10.9)	0	8 (12.1)	0.7617
HLA A-B-DR incompatibilities (>4)	3	399 (15.43)	2	381 (15.1)	1	18 (27.7)	0.0056
Daily anti-HLA immunization of class I	30	1032 (40.33)	0	1015 (40.2)	30	17 (47.2)	0.3958
Daily anti-HLA immunization of class II	45	904 (35.53)	18	886 (35.4)	27	18 (46.2)	0.1626
Donor men	3	1468 (56.77)	3	1432 (56.8)	0	36 (54.6)	0.7121
Donor vital status	7		0		7		0.0204
Living donor		481 (18.63)		460 (18.2)		21 (31.8)	
Cerebrovascular donor death		1151 (44.58)		1126 (44.6)		25 (37.9)	
Non cerebrovascular donor death		950 (36.79)		930 (36.9)		20 (30.3)	
Delayed graft function	9	714 (27.67)	8	696 (27.7)	1	18 (27.7)	0.9974
Acute rejection during the first year	0	499 (19.27)	0	491 (19.5)	0	8 (12.1)	0.1356
Transplanted before 2008	0	722 (27.89)	0	706 (28.0)	0	16 (24.2)	0.5036

Abbreviations: HLA human leukocyte antigen; NA missing value, SD standard deviation; SCr serum creatinine.

Table S3: Multivariate joint model for longitudinal evolution of logarithmic transformation of serum creatinine (SCr) and risk of graft failure (return to dialysis or death with a functioning graft) in kidney transplant patients (n=2584 patients, 165 patients excluded due to missing data), without any variable in the longitudinal sub-model and without any variable selection in the survival sub-model.

	Survival process		
	HR	95%CI	p-value
Current SCr (µmol/L), for an increase of 25%	2.07	[1.87; 2.29]	<0.0001
Current SCr increase (µmol/L), for a growth of 25% in 1 year	1.54	[0.90; 2.65]	0.1146
Recipient age at transplantation (years, standardized)	1.73	[1.49; 2.01]	<0.0001
History of cardiovascular diseases: yes versus no	1.36	[1.11; 1.68]	0.0038
3-months SCr (µmol/L, standardized)	0.92	[0.81; 1.04]	0.1735
Acute rejection episode(s) during the first year: yes versus no	1.39	[1.10; 1.76]	0.0067
Anti-class I immunization: positive versus negative	1.46	[1.11; 1.92]	0.0063
Rank of graft: second versus first	1.31	[0.96; 1.79]	0.0883
Recipient gender	0.91	[0.72; 1.15]	0.4265
Relapsing initial disease	0.85	[0.68; 1.06]	0.1470
Dialysis technique (ref: Pre-emptive transplantation)			0.5381
Peritoneal dialysis	1.27	[0.72; 2.22]	
Hemodialysis	1.24	[0.84; 1.84]	
History of diabetes	1.48	[1.10; 1.99]	0.0088
History of hypertension	0.92	[0.70; 1.21]	0.5505
History of dyslipidemia	1.21	[0.98; 1.50]	0.0801
History of neoplasia	0.96	[0.67; 1.37]	0.8148
Donor men	0.84	[0.68; 1.03]	0.0879
Donor vital status (ref: Living donor)			0.7266
Cerebrovascular donor death	0.92	[0.56; 1.50]	
Non cerebrovascular donor death	1.01	[0.61; 1.65]	
More than 5 HLA A-B-DR incompatibilities	1.10	[0.84; 1.46]	0.4870
Anti-class II immunization: positive versus negative	1.07	[0.80; 1.42]	0.6490
6-months SCr (µmol/L, standardized)	0.93	[0.82; 1.06]	0.2810
Donor age (years, standardized)	0.87	[0.75; 1.00]	0.0560
Cold ischemia time (hours, standardized)	0.95	[0.83; 1.09]	0.4738
Recipient BMI (kg/m², standardized)	0.79	[0.70; 0.88]	<0.0001
Last donor SCr (µmol/L)	1.03	[0.94; 1.13]	0.5043

Referential value for log(SCr) at 1-year post-transplantation was 4.861, 95%CI : [4.847; 4.874]. Referential value for the slope of log(SCr) was 0.024 95%CI : [0.020; 0.027]. This model is adjusted on a period effect with a threshold at 2008 (before 2008 versus after): HR=0.77 [0.59 ; 1.00]

Parameters of the Weibull baseline risk function were: intercept : -20.74 ± 1.12; log(shape): 0.32 ± 0.05; $alpha_1$ = 3.26 ± 0.23 95%CI[2.81 ; 3.71] and $alpha_2$ = 2.18 ± 1.38 95%CI[-0.53 ; 4.89]

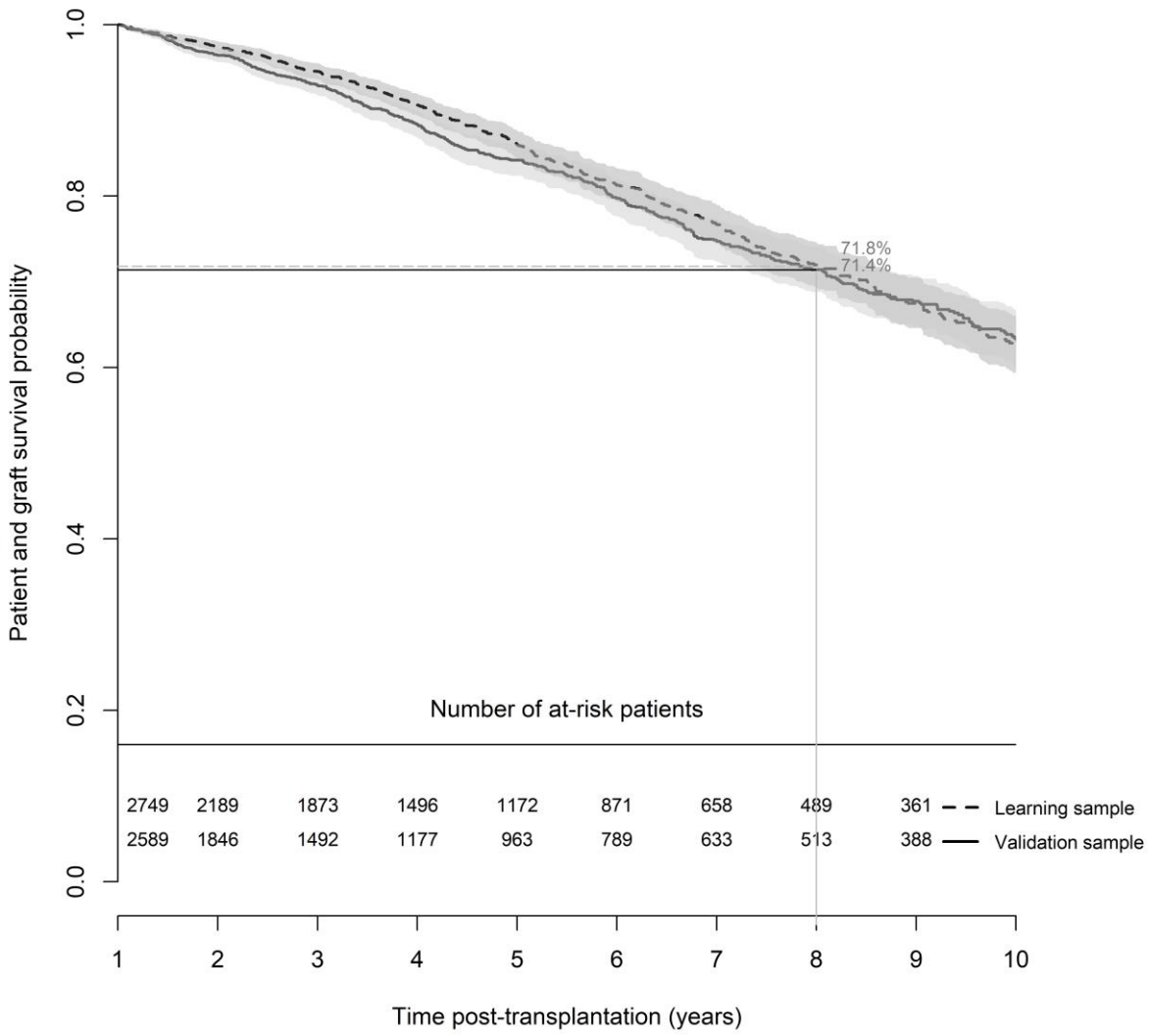

Figure S1: Patient and graft survival from Kaplan-Meier estimator and their corresponding 95%CI according to the learning and validation samples (Log-Rank test: p=0.5191).

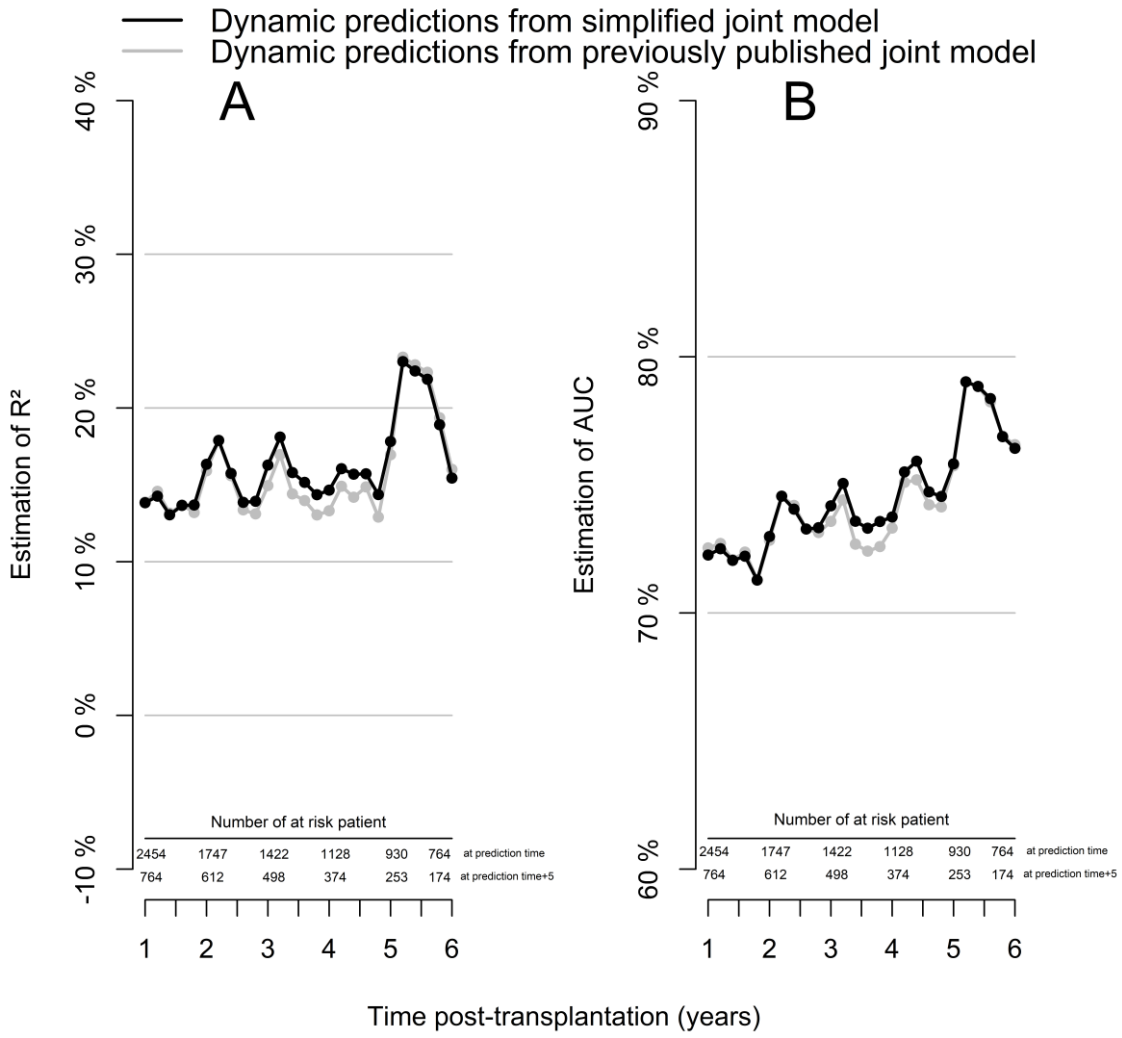

Figure S2: Prognostic capacities of the dynamic predictions from the joint model published in Fournier et al. compared to those obtained from the simplified joint model. These predictions are computed on the validation sample (n=2454 individuals, 135 observations deleted due to missing data concerning covariates) for prediction times from 1 to 6-years post-transplantation for a given horizon window of 5 years. R^2 supplied global performance (Part A) while Area under ROC curve (AUC) appraised discrimination accuracy (Part B).

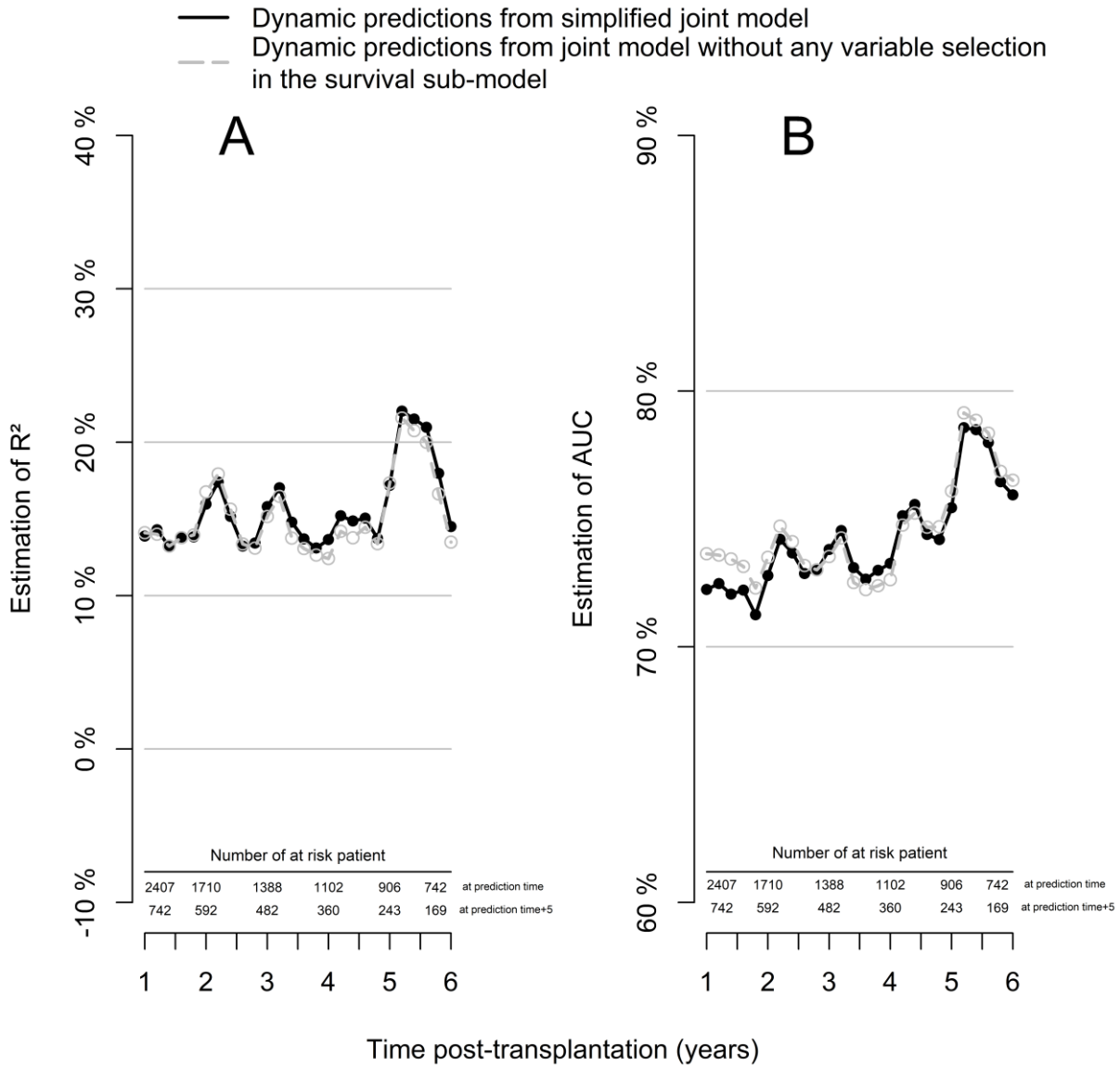

Figure S3: Prognostic capacities of the dynamic predictions from the joint model without any variable selection in the survival sub-model compared to those obtained from the simplified joint model. These predictions are computed on the validation sample (n=2407 individuals, 182 observations deleted due to missing data concerning covariates) for prediction times from 1 to 6-years post-transplantation for a given horizon window of 5 years. R^2 supplied global performance (Part A) while Area under ROC curve (AUC) appraised discrimination accuracy (Part B).