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

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ABSTRACT

Background. Informing kidney transplant recipients of their prognosis and disease progression is of primary importance in a patient-centred 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 Données Informatisées et VAlidées en Transplantation (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 of six baseline parameters, in addition to the SCr evolution. We validated the dynamic predictions by evaluating both discrimination and calibration accuracy. The area under the receiver operating characteristic 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 provided an online application tool (https://shiny.idbc.fr/DynPG).
Conclusion. We have created a tool that, for the first time in kidney transplantation, predicts graft failure risk both at an individual patient level and dynamically. We believe that this tool would encourage willing patients into participative medicine.

Keywords: dynamic prediction, graft failure, kidney transplantation, patient-centred care, shared decision-making

INTRODUCTION

Health researchers and policy-makers are increasingly encouraged to promote patient-centred 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 as 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.* [5] that in kidney transplantation, patient preferences prioritize graft survival before any risk of adverse outcomes such as infections or cancers. Therefore, providing individual graft survival prediction could be a first step towards improving patient health status information and promoting patient-centred 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 risk factors for graft failure. In this context, we proposed the Kidney Transplant Failure Score to predict at 1 year post-transplantation the probability of graft survival over the seven following years [6]. The usefulness of this score is currently being studied in a randomized clinical trial to drive patient follow-up between 1 and 3 years post-transplantation [7]. However, its main limitation was the lack of update after 1 year post-transplantation. Moreover, informing willing patients at each outpatient visit of their mid-term prognosis could help to increase their understanding of a reinforced burden of treatment and follow-up, and commit them to 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 in 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, joint modelling of both marker evolution and time to failure has recently been developed [10, 11]. A few studies have been based on such approaches in kidney transplantation [12–14]. Nevertheless, none of these models has been used for dynamic predictions.

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

The objective of the present study was to enable willing patients to determine their mid-term risk for 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.

MATERIALS 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, 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 mycophenolate. This whole sample was randomly split as follows: two-thirds of the patients ($n = 2749$) were used as a learning sample to estimate models; and the remaining third ($n = 1372$) 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 an 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 restricted the visit to be within 8 to 16 months post-transplantation. The endpoint was time to graft failure defined as the first event including return to dialysis, pre-emptive re-transplantation and death with a functioning graft. We considered 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 mid-term prognosis.

Statistical analyses

The high number of predictors in the joint model we initially proposed (Supplementary Table S1) [15] was due to the etiologic objective of our previous study, that is, to describe the factors associated with both SCr evolution and/or graft failure risk.

In the present prognostic context, with 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, donor gender initially associated with graft failure risk was removed 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 measurements and six 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 latter 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 or complement-dependent cytotoxicity) was positive pre-transplantation.

The DynPG was defined as the probability of being graft failure-free over the next 5 years, for each prediction time from 1 to 6 years post-transplantation, as formally defined in Supplementary Materials. This maximum prediction time of 6 years post-transplantation was retained since there were 178 patients still at risk of graft failure at 11 years post-transplantation in the validation sample.

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

Variables	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/m^2)	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 ischaemia time (h)	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-month SCr (μmol/L)	38	138.30 ± 53.38	36	138.77 ± 55.10	0.7528
6-month SCr (μmol/L)	75	136.64 ± 53.18	73	135.43 ± 48.91	0.3930
3-month proteinuria (g/day)	669	0.34 ± 0.87	1151	0.33 ± 0.70	0.7079
6-month proteinuria (g/day)	759	0.30 ± 0.52	1273	0.32 ± 0.76	0.5526
12-month 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)	
Haemodialysis		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 dyslipidaemia	0	860 (31.28)	0	957 (36.96)	<0.0001
History of neoplasia	0	228 (8.29)	0	284 (10.97)	0.0009
>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

BMI, body mass index; NA, not available (missing data); HLA, human leucocyte antigen; SCr, serum creatinine; SD, standard deviation.

Prognostic performances were reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (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 receiver operating characteristic 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 survival (computed using the Kaplan–Meier estimator). All analyses were performed using R (v3.3.0) and 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, while the validation sample comprised 2589 patients. Table 1 compares these two samples. Compared with the learning sample, the validation sample had higher rates of patients immunized against HLA class I (40.3% versus 32.7%) and II (35.5% versus 29.8%) and comorbidities (14.1% versus 11.6% for history of diabetes; 37.0% versus 31.3% for history of dyslipidaemia; 11.0% versus 8.3% for history of neoplasia), as well as shorter mean cold ischaemia times (16.0 ± 9.5 h versus 17.8 ± 9.8 h). These differences may be explained by the inclusion in the validation sample of 1217 recipients who were more recently transplanted.

During 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 to 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) 68.8–74.1%] for the validation sample versus 71.8% (95% CI 69.3–74.5%) for the learning sample (log-rank test, P = 0.5191) (Supplementary Figure S1).

Table 2. Simplified multivariate joint model for longitudinal evolution of logarithmic transformation of 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)

Variables	Survival process	
	HR (95% CI)	P-value
Current SCr for an increase of 25% (μmol/L)	1.96 (1.79– 2.15)	<0.0001
Current SCr increase for a growth of 25% in 1 year (μmol/L)	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 disease: yes versus no	1.41 (1.16–1.71)	0.0007
3-month 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

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

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

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 that was estimated using the learning sample and required six fewer covariates than the initially proposed model [15]. Recipient age at transplantation, history of cardiovascular disease, 3-month SCr values, occurrence of acute rejection episode(s) in the first year post-transplantation, pre-transplantation anti-HLA class I immunization and graft rank were significantly associated with graft failure risk ($P < 0.05$). For any time from 1 year post-transplantation, graft failure was dependent on both the current SCr value and current SCr slope. If a patient had a 25% higher SCr value, the graft failure risk was twice as high [hazard ratio (HR) = 1.96, 95% CI 1.79–2.15]. Moreover, for a given SCr value, where a patient had a steeper increase in SCr, the graft failure risk was significantly increased (HR = 1.84, 95% CI 1.11–3.04).

Prognostic capacities of 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 (Supplementary Table S2). As illustrated in Figure 1, the data did not present major concerns regarding calibration, even though more accurate predictions were observed at earlier prediction times. The overall prognostic capacities (discrimination and calibration) for predicting patient and graft survival at each transplantation anniversary up to 5 years post-transplantation seemed relatively similar for making predictions over the years (Figure 2A). R^2 values ranged from 14% (95% CI 7–21%) to 15% (95% CI −2% to 33%) at 1 and 6 years post-transplantation, respectively. At 6 years post-transplantation, regarding the acceptable calibration, patient and graft survival was, on average, 15% lower for patients who actually had graft failure, compared with those who did not. The corresponding discriminative capacities increased with post-transplantation time (Figure 2B). The AUC values ranged from 0.72 (95% CI 0.67–0.78) to 0.76 (95% CI 0.68–0.85) 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 was lower than that of a subject who did not. Of note, accuracy plots revealed a similar performance in terms of discrimination and calibration, when compared with the joint model previously proposed by Fournier *et al.* (Supplementary Figure S2) as well as the model without any variable selection in the survival sub-model (Supplementary Table S3 and Figure S3).

Examples of dynamic predictions. In order to illustrate how the DynPG could be used in practice, we selected two illustrative clinical cases from the validation sample. We computed their DynPG on each occasion they attended the hospital, using the online application tool we developed (available at https://shiny.idbc.fr/DynPG). The SCr measurements and evolution were plotted on the left side of the plot, and the corresponding prediction of graft and patient survival was plotted on the right side. We also considered 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 using the Kaplan–Meier estimator on the learning sample. In order to produce results interpretable for the large majority of patients, this online application also offers visual aids including smileys and short sentences.

Case A. This was a 51-year-old female transplanted with a first graft in 2005, immunized against HLA class I pre-transplantation, without a history of cardiovascular disease or acute rejection episodes during the first year post-transplantation and with a 3-month SCr value of 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 46–97%; Figure 3). At that prediction time, 3 years post-transplantation, her estimated survival curve was above the entire population at risk at that same time. One year later (i.e. 4 years post-transplantation), a significant increase in SCr values was observed, resulting in a significant decrease in predicted graft and patient survival. Despite subsequent stabilization of the SCr values (5 and 6 years post-transplantation), her prognosis did not improve. At 6 years post-transplantation, the patient had a 98% predicted

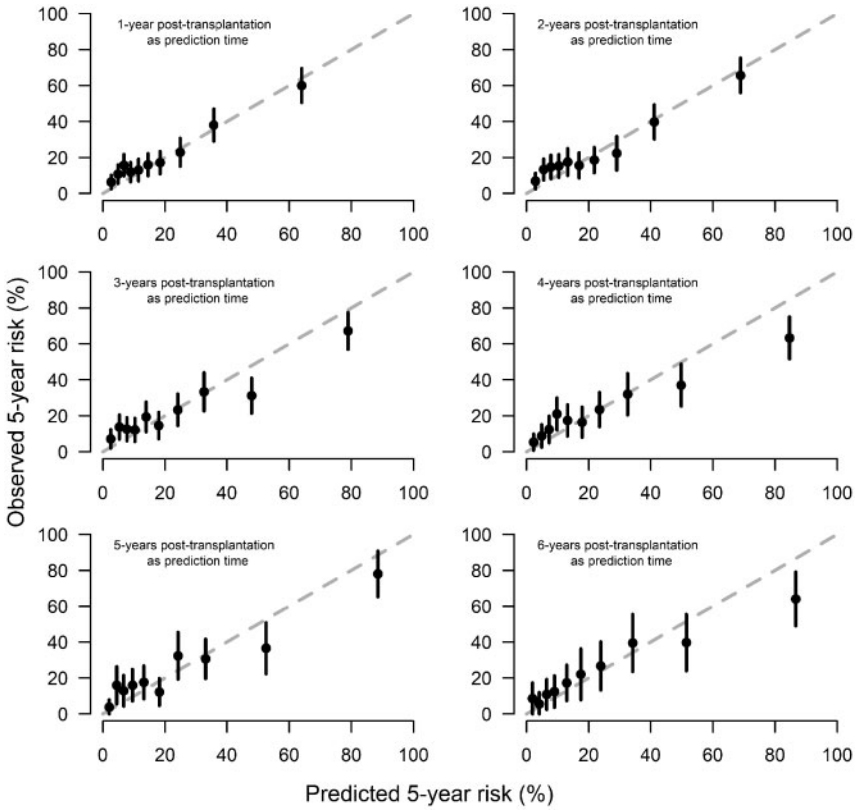

FIGURE 1: Calibration plot of dynamic predictions using the validation sample ($n = 2523$, 66 observations deleted due to missing data concerning covariates) for prediction times from 1 to 6 years post-transplantation. Mean predicted risks and observed risks (Kaplan–Meier) are displayed for each subgroup,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

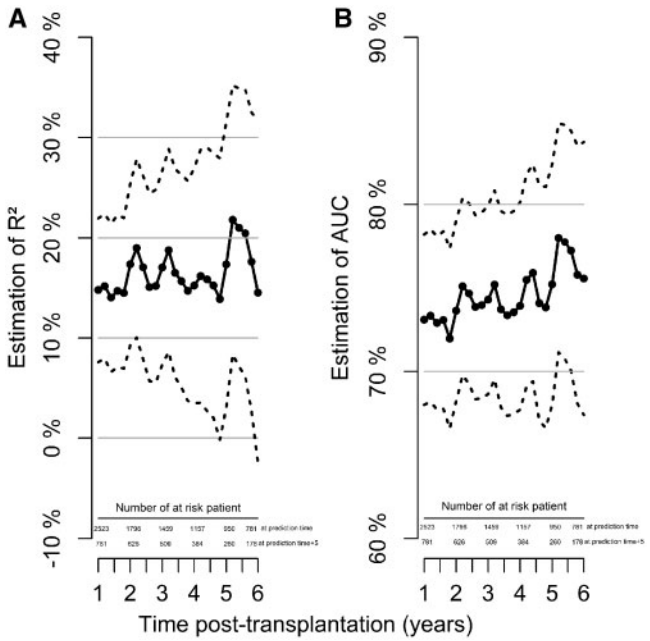

FIGURE 2: Prognostic capacities of the dynamic predictions ($n = 2523$, 66 observations deleted due to missing data concerning covariates) estimated for prediction times from 1 to 6 years post-transplantation for a given horizon window of 5 years; R^2 evaluated global performance (**A**) and the AUC appraised the discrimination accuracy (**B**). Estimations are drawn in solid lines and the corresponding 95% CIs are shown in dashed lines.

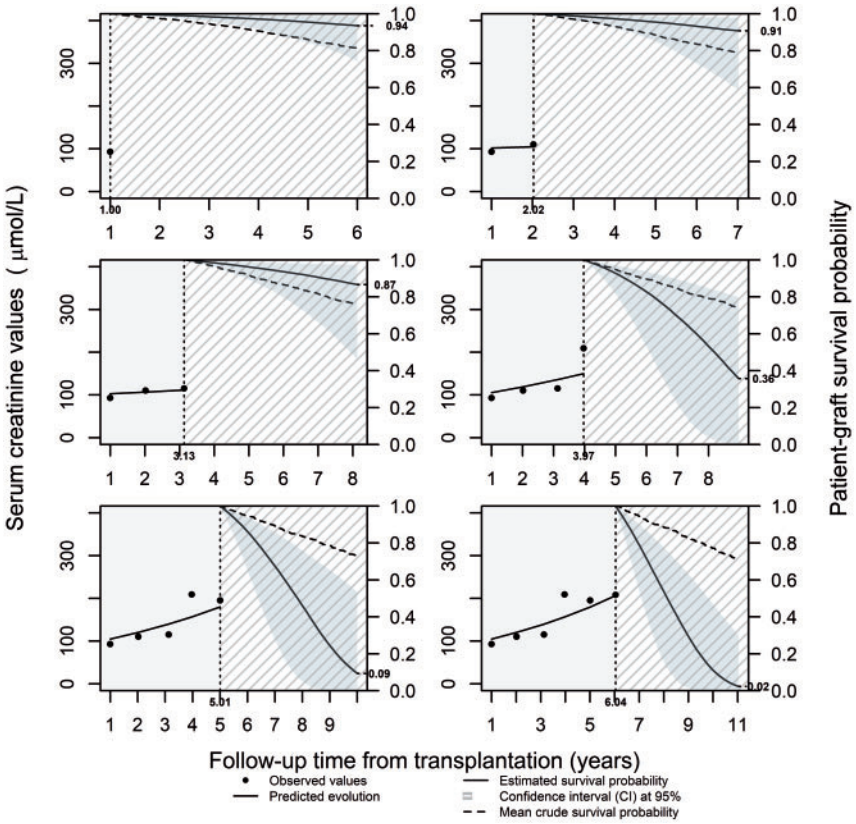

FIGURE 3: Individual dynamic predictions obtained from the simplified joint model for prediction times from 1 to 6 years post-transplantation for a particular individual (Case A: woman aged 51 years transplanted in 2005 for the first time, with no history of cardiovascular disease, anti-HLA class I immunized, with SCr measurement at 3 months post-transplantation of 88 µmol/L and no acute rejection episode in the first year post-transplantation). The recipient was returned to 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]).

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 deterioration in 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 patients' queries about their chances of keeping their graft alive in the near future. The DynPG is designed to make such predictions and could also be informatively beneficial in supporting clinical decision-making for the patient. From a patient-centred care view, this tool could also be useful for willing patients, to slowly and carefully prepare them psychologically and emotionally in terms of their mid-term outcomes and allow them to be a participant in their transplantation health status.

Case B. This was a 60-year-old female, recipient of a second transplantation in 2007, with no history of cardiovascular disease, immunized against HLA class I pre-transplantation, with at least one acute rejection episode during the first year post-transplantation and with a 3-month SCr value of 100 µmol/L. In 2017, this recipient was still alive with a functioning graft.

In contrast to Case A, no increase in the SCr level was observed with respect to time post-transplantation, as illustrated in Figure 4. At 5 years post-transplantation, the 10-year patient and graft survival was estimated to be 89% (95% CI 68–97%). While the baseline prognosis was worse for Case B compared with Case A, consideration of the SCr evolution illustrates the importance of updating the initial prediction. This example emphasizes the usefulness of the proposed dynamic model, compared with the existing fixed-time models [6, 27–29]. Providing these predictions and their disseminated interpretation could be important in reassuring this patient about her mid-term prognosis.

DISCUSSION

While clinical decisions are usually made by physicians on behalf of their patients, shared decision-making is increasingly considered as an essential part of quality healthcare delivery [1]. The P4-medicine descriptor, that is, 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 patient adherence to treatment plans, as patients recognize having an active role in the decision-making process [1, 8]. The multiplicity of risk factors in kidney transplantation requires synthetic tools to estimate the graft failure risk. To our knowledge, this study is

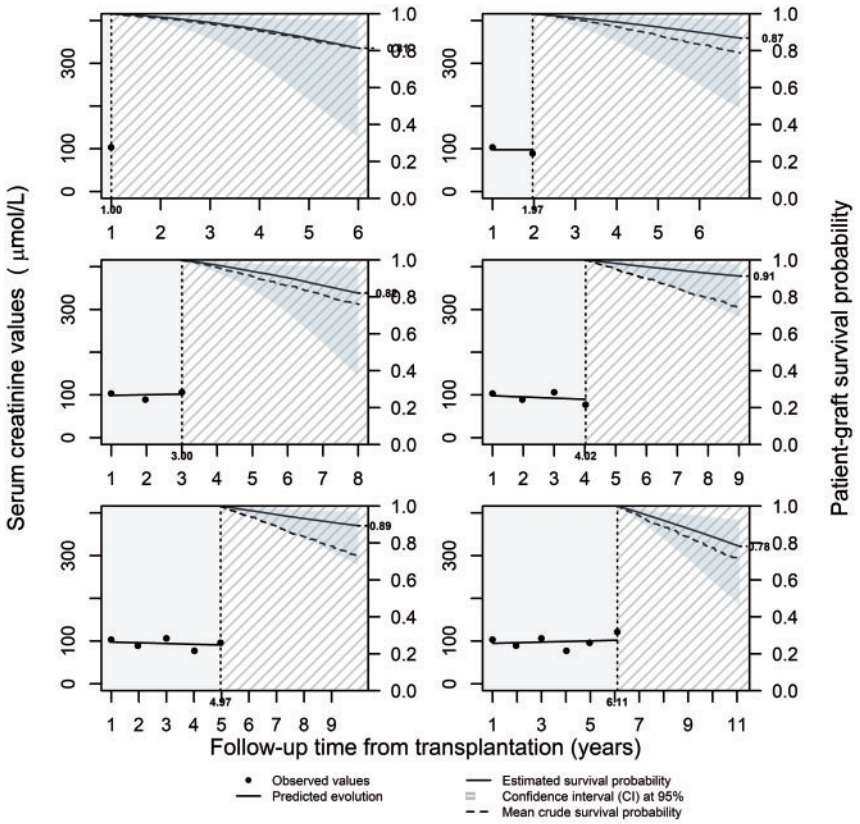

FIGURE 4: Individual dynamic predictions obtained from the simplified joint model for prediction times from 1 to 6 years post-transplantation for a particular patient (Case B: woman aged 60 years transplanted in 2007 for the second time, with no history of cardiovascular disease, immunized against HLA class I, with SCr measurement at 3 months post-transplantation of 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]).

the first to propose and validate a simple model to dynamically predict patient and graft survival. We also propose an online application tool (https://shiny.idbc.fr/DynPG) that is similar to the one proposed for patients suffering from chronic heart failure [31].

The proposed online application provides meaningful predictions for both clinician and patient. For instance, for the patient presented in Case A, at 5 years post-transplantation, one can predict a 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 in their disease treatment. In contrast, for the patient presented in Case B, the DynPG could be useful in reducing anxiety and stress and improving the patient's well-being.

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

Some important limitations have to be considered. First, the DynPG is based on SCr values (µmol/L) as the only longitudinal marker for dynamic predictions. We chose SCr, instead of the estimated glomerular filtration rate, because a number of studies have shown that, although the two markers have equivalent prognostic capacities, SCr values are 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 immunization, 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 biostatistics community [37]. Second, 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 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 compared with the initially published Fournier model and the joint model without variable selection in the survival sub-model. Third, the prediction of graft failure can be seen as a limitation because a non-negligible part of cause of death with a functioning graft was associated with a

cause other than transplantation. Despite this, it is noteworthy that an alternative solution consisting of right-censoring death would have been also open to criticism. Fourth, 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, it should be noted that our results may be valid for cohorts with inclusion criteria similar to those used in our study and with comparable patient characteristics; otherwise, the interpretation of predictions can be misleading. Finally, we arbitrarily chose 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 onto waiting lists for pre-emptive re-transplantation if a patient's predicted risk is particularly high in a smaller horizon window of 1 year.

Finally, predictive tools of this type where the patient is actively involved raise significant ethical and practical questions in terms of their smart and safe use in a patient-centred point of view, such as how to transmit prediction information to the patient and which information has to be given. With regard to our online application tool, we proposed an interpretation inspired by Hollnagel's proposal [41]. For instance, for the patient in Case A presenting at 3 years post-transplantation with 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 graft failure. Among these 13 patients, we don't know if it is a return to dialysis, a pre-emptive re-transplantation or death with a functioning graft. We also do not know which group you will belong to'. Henderson and Keiding also recognized that punctual prediction should be communicated with caution, since it ignores the variability surrounding the prediction [42]. In that sense, it may be relevant to provide prediction intervals. Accordingly, we believe that the first step would be to trial the DynPG among nephrologists as a tool to inform and prepare their willing patients regarding their probability of future graft survival and their clinical management strategy. In parallel, we are working on patient perception and emotions when confronted with their predicted risk of graft failure in order to avoid to leave alone the patients with their predicted result and potentially a cognitive or psychological misinterpretation of their outcome. One may envisage the use of our online application tool as an educational motivation. For instance, presenting one patient with different hypothetical scenarios about their SCr evolution may illustrate the modification of the incurred graft failure risk and thus encourage the patient to be more compliant. We also plan to evaluate the possible impact of the DynPG by focusing on the well-being of patients through measuring their anxiety, stress and adherence levels.

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

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

M.-C.F. participated in the conceptualization, methodology, formal analysis, writing—original draft, review and editing. Y.F. performed conceptualization, methodology, writing—review and editing. P.B. undertook formal analysis, writing—review and editing. C.L., S.G., M.L., E.M., F.B., L.R., N.K., G.M., V.G. and G.C.-D. were involved in data acquisition, writing—review and editing. M.G. contributed to the conceptualization, provided clinical mentorship, and undertook writing—review and editing. E.D. was involved in project administration, conceptualization, methodology, writing—original draft, review and editing.

CONFLICT OF INTEREST STATEMENT

None declared.

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