Eur J Epidemiol (2016) 31:469–479
DOI 10.1007/s10654-016-0121-2

CLINICAL EPIDEMIOLOGY

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

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Received: 26 August 2015 / Accepted: 16 January 2016 / Published online: 1 February 2016

Abstract In renal transplantation, serum creatinine (SCr) is the main biomarker routinely measured to assess patient's health, with chronic increases being strongly associated with long-term graft failure risk (death with a functioning graft or return to dialysis). Joint modeling may be useful to identify the specific role of risk factors on chronic evolution of kidney transplant recipients: some can be related to the SCr evolution, finally leading to graft failure, whereas others can be associated with graft failure without any modification of SCr. Sample data for 2749 patients transplanted between 2000 and 2013 with a functioning kidney at 1-year post-transplantation were obtained from the DIVAT cohort. A shared random effect joint model for longitudinal SCr values and time to graft failure was performed. We show that graft failure risk depended on both the current value and slope of the SCr. Deceased donor graft patient seemed to have a higher SCr increase, similar to patient with diabetes history, while no significant association of these two features with graft failure risk was found. Patient with a second graft was at higher risk of graft failure, independent of changes in SCr values. Anti-HLA immunization was associated with both processes simultaneously. Joint models for repeated and time-to-event data bring new opportunities to improve the epidemiological knowledge of chronic diseases. For instance in renal transplantation, several features should receive additional attention as we demonstrated their correlation with graft failure risk was independent of the SCr evolution.

Keywords Joint modeling · Time-to-event data · Repeated measurements · Serum creatinine · Graft failure · Kidney transplantation

Introduction

Recently, Asar et al. [1] pointed out that joint models for repeated and time-to-event data should be used to correctly consider longitudinal and survival processes and their relationship when they are strongly dependent [2, 3]. Joint models could allow identification of specific associations for each risk factor: (1) association with an event risk, (2) association with an event risk throughout a previous marker evolution modification, and (3) associations on both longitudinal and survival processes. With this type of suitable model, the precise description of specific associations could provide new insights in the knowledge of a disease pathway mechanism.

Indeed, from a methodological standpoint, longitudinal measurements and time-to-event data are typically analyzed separately, using a mixed model and survival model

Electronic supplementary material The online version of this article (doi:10.1007/s10654-016-0121-2) contains supplementary material, which is available to authorized users.

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respectively, without considering their possible relationship [2]. However, it is known that these two processes are often mutually dependent in a chronic disease context. Inferences from mixed models may be biased in cases of an informative censoring process [4–6]. Similarly, the time-dependent Cox model fails to correctly handle a time-dependent endogenous variable, which is a variable generated by the patient themselves (e.g. creatinine) in contrast to an exogenous variable which is not (e.g. air pollution level) [7–9]. It also often fails to correctly account for measurement error.

In many chronic diseases, the occurrence of major events and the assessment of corresponding risk factors guide physicians in implementing the most beneficial care for patients. In renal transplantation, serum creatinine (SCr) is a well-known longitudinal marker used to assess the health of kidney transplant recipients especially after the first year post-transplantation, i.e. in the chronic phase of the disease evolution [10]. In the chronic phase, graft failure, defined as return to dialysis or death with a functioning graft, is often preceded by a continuous deterioration in renal function and is associated with an irreversible increase in SCr levels. In contrast, during the first year post-transplantation, patients are submitted to a risk of early graft failure due to acute clinical events such as delayed graft function, acute rejection episode, and infections or complications. Therefore the disease evolution mechanism is very different between the acute and chronic phases [11, 12]. Few authors have studied the association of risk factors on renal function evolution [13, 14] while the risk factors associated with long-term graft failure have been well described [12, 15, 16]. Renal function has been shown to be one of the most important risk factors [17, 18]. However, the precise mechanism is not well known: the majority of risk factors leading to graft failure may be associated with chronic SCr changes, finally leading to graft failure, but one can also hypothesize that some features may be related to graft failure risk independently from their association on SCr evolution.

Whilst several authors have used joint models for longitudinal and time-to-event data in renal transplantation [19–22], none have precisely studied the specific association of each baseline explicative variable. The precise study of such associations would be of primary importance for physicians in order to improve their appraisal of kidney transplant recipients' health. Therefore, we present for the first time a shared random effect multivariable joint model to study the baseline characteristics that could be related to long-term kidney graft outcomes. By studying SCr evolution and graft failure from one year post-transplantation, it brings an epidemiological approach to understand the risk factors associated with the disease evolution in its chronic phase.

Materials and methods

Study population

Data were extracted from the French observational and prospective DIVAT cohort (www.divat.fr) of kidney transplant recipients from 6 University hospitals (French Research Ministry: RC12_0452, last agreement No 13 334, No CNIL for the cohort: 891735, No CNIL for the study: 914226). According to the following inclusion criteria, 2749 patients were studied: adult recipients who received a first or second renal transplant 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 Mycofenolic acid. All study participants gave informed consent.

Available data

Most classical risk factors susceptible to influence SCr evolution and/or graft failure risk were extracted from the database. Donor features included: age, gender, last SCr level, deceased (from cardiovascular cause vs. other)/living donation. Recipient characteristics were: age, gender, body mass index (BMI), history of comorbidities (diabetes, hypertension, dyslipidemia, neoplasia, cardiovascular), duration of dialysis before transplantation, preemptive graft, hemodialysis or peritoneal dialysis, pre-transplant anti-class I or class II Human Leucocyte Antigen (HLA) immunization and cause of initial renal disease (recurrent nephropathy or not). Transplantation parameters were: cold ischemia time and number of HLA-A-B-DR incompatibilities. The following variables were collected within the first year post-transplantation: occurrence of delayed graft function (defined as the need for dialysis after transplantation), occurrence of acute rejection episodes and SCr levels at 3 and 6 months post-transplantation.

Outcomes

The baseline was the 1-year post-transplantation anniversary. The best marker of renal function should be the measured GFR (mGFR) [23]. Unfortunately, this measurement is costly and is not performed in practice for routine patient follow-up. Different equations to estimate GFR (eGFR) have been proposed [24–27], and are principally based on SCr values adjusted on recipient age, gender and ethnicity. A major limitation lies in the fact that these eGFR formulae have been developed from general population data or from patients with chronic kidney disease and thus may not be applicable to kidney transplant patients [28–30]. Despite this, SCr or eGFR are equivalent

in terms of relative evolution, the second resulting from a transformation of the first parameter. We decided to study the SCr (μmol/L), which was the longitudinal marker routinely recorded yearly until patient death with a functioning graft or return to dialysis. The time-to-event (graft failure) was defined as the delay between 1-year post-transplantation and the first event between return to dialysis or death with a functioning graft.

Statistical analysis

We used a shared random effect model. It combines a mixed model for the longitudinal process and a parametric survival model for the time-to-event process, for which underlying hypotheses were checked in an independent manner. For the longitudinal assessment, we used a logarithmic transformation of SCr values in order to respect both assumptions related to residual's homoscedasticity and linear relationship over time. Two random effects were considered for the baseline value and the slope. For survival, hazard proportionality and log-linearity were assessed.

In a joint shared random effect framework, longitudinal and survival processes are linked through common random effects. Rizopoulos has previously described the possible parameterizations to model this dependence [2]. For instance, the survival process can be modeled as dependent on the current level of the marker, on the intensity of marker evolution (i.e. the slope), on both current level and slope, on cumulative effects or on lagged effects.

In the first step of model building, we defined a baseline risk function and the dependence between the two processes from a joint model without baseline explicative variables. We graphically retained a Weibull distribution for the baseline risk function. According to the Bayesian Information Criteria (BIC), the dependence between the two processes was characterized by the instantaneous hazard of graft failure depending on both the level and the slope of the longitudinal marker at the current time. As recommended by Rizopoulos to solve optimization difficulties, all quantitative variables were standardized in order to scale the coefficients [2].

In the second step, we performed the selection of baseline explicative variables. Univariable models were composed using three effects of each variable: on baseline value, on the slope (interaction with time) and on the graft failure risk. Among these parameters, those which were not significant ($p > 0.05$) were removed in a hierarchical manner: if the association on the slope was significant, the corresponding association on baseline value was also considered. Finally, a multivariable joint model was generated by including effects retained in the univariable models, and a forward stepwise selection was performed (always using a 5 % type-I error rate).

In order to study the relevance of the joint modeling, we also performed separate analyses: (1) a linear mixed model to study the SCr evolution and (2) a time-dependent Cox model to study the graft failure risk. We used the same variables selection procedure.

As sensitivity analyses, we performed two joint models in a cause specific approach: (1) time-to-return to dialysis by censoring death, and in contrast (2) time-to-death with a functioning graft by censoring return to dialysis.

Joint model parameters were estimated by likelihood maximization. The complete mathematical formulation of the joint model is shown in "Appendix 1". Due to the logarithmic transformation of SCr, coefficients for the longitudinal process have an interpretation as relative change rather than absolute change. Details related to interpretations are presented in "Appendix 2". Confidence intervals for relative change were obtained using parametric simulations (5000 iterations) [31]. All analyses were performed using the 3.0.1 version of the R software [32] with the 1.3-0 version of the JM package [33].

Results

Baseline characteristics

Baseline characteristics are presented in Table 1. Sixty percent of the recipients were male, with a mean age of 49.7 ± 13.6 years. Histories of cardiovascular disease or dyslipidemia were observed in one third of recipients, 11.6 % had history of diabetes, 82.6 % had hypertension, and 8.3 % had a cancer before the transplantation. Second transplantations were realized in 17.2 % of studied patients. Immunologic characteristics included: 12.8 % of patients presented more than 4 HLA–A-B-DR incompatibilities, and around one third were immunized against class I or class II HLA prior to transplantation. Donors were mainly deceased (84.8 %) with a mean age of 50.7 ± 15.5 years and 56.4 % were male. Delayed graft function occurred for 714 patients (26.1 %). SCr at 3 and 6 months were on average 138.3 ± 53.4 and 136.6 ± 53.2 μmol/L respectively. Finally, 21.5 % of recipients presented at least one episode of acute rejection before the first anniversary of the graft.

Follow-up description

During follow-up, 278 patients returned to dialysis and 203 died with a functioning graft. The median event-free follow-up time was 3.99 years. The patient-graft survival curve and its corresponding 95 % confidence interval (95 % CI) are presented in Fig. 1. Patient-graft survival rates at 10 years after the first anniversary of the graft was

Table 1 Description of recipients, donors, and transplantation characteristics of the studied population (n = 2749)

	Missing	Estimations
Quantitative characteristics: mean ± SD		
Recipient age (years)	0	49.7 ± 13.6
Recipient BMI (kg/m^2)	10	24.0 ± 4.2
Donor age (years)	1	50.7 ± 15.5
Last donor SCr (μmol/L)	25	89.9 ± 52.8
Cold ischemia time (h)	10	17.8 ± 9.8
3-month SCr (μmol/L)	38	138.3 ± 53.4
6-month SCr (μmol/L)	75	136.6 ± 53.2
Categorical characteristics: N (%)		
Recipient men	0	1674 (60.9)
Transplanted before 2008	0	1369 (49.8)
Second transplantation	0	474 (17.2)
Dialysis technique	3	
Pre-emptive transplantation		342 (12.5)
Hemodialysis		2192 (79.8)
Peritoneal dialysis		212 (7.7)
Time to dialysis prior to transplantation (at least 1 year)	36	1948 (71.8)
Recurrent causal nephropathy	0	899 (29.1)
Diabetes history	0	319 (11.6)
Hypertension history	0	2272 (82.6)
Cardiovascular history	0	933 (33.9)
History of dyslipidemia	0	860 (31.3)
History of cancer	0	228 (8.3)
HLA A-B-DR incompatibilities (>4)	7	350 (12.8)
Positive anti-class I immunisation	66	876 (32.6)
Positive anti-class II immunisation	87	792 (29.8)
Donor men	8	1545 (56.4)
Status	6	
Living donor		418 (15.2)
Cerebrovascular donor death		1309 (47.7)
Non cerebrovascular donor death		1016 (37.1)
Delayed graft function	15	714 (26.1)
Acute rejection episode during the first year	0	591 (21.5)

SD standard deviation, *BMI* body mass index, *SCr* serum creatinine, *HLA* human leukocyte antigen

58.4 % [95 % CI 54.8 %; 62.3 %]. Additionally, 12 843 SCr measurements were collected, with a median of 4 measurements per patient (ranging from 1 to 14). The median time between two measurements was 11.7 months (interquartile range: 9.2, 12.5).

Joint modeling

Table 2 presents the estimations related to the final multivariable joint model.

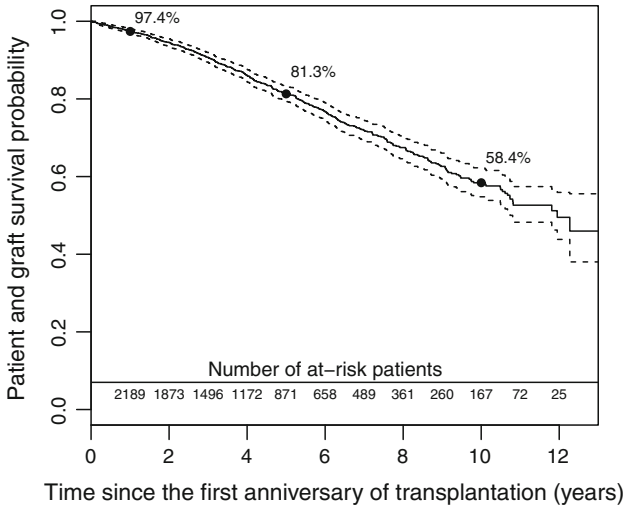

Fig. 1 Patient and graft survival according to the time since the first anniversary of the transplantation (n = 2749) from Kaplan–Meier estimator and their corresponding 95 % CI

Dependence between SCr dynamic and graft failure risk

For any time 1 year after transplantation (t > 1), the graft failure risk 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 = 1.92, 95 % CI [1.75; 2.11]). Moreover, for a given SCr value, where a patient had a steeper increase in SCr graft failure risk was significantly worse (HR = 1.89, 95 % CI [1.17; 3.06] for an increase of 25 % in SCr value in 1 year).

Factors associated with 1-year post-transplantation SCr

Several factors appeared significantly correlated with a higher 1-year SCr without significant association with the SCr evolution or with graft failure risk. An increase of 50 μmol/L in the 6-month SCr level was associated with a 1-year SCr increase of 17.99 % (95 % CI [16.62 %; 19.34 %]). Patient with a graft provided from a donor 10 years older compared to other donor had a 3.68 % higher SCr at 1 year (95 % CI [2.97 %; 4.39 %]).

Factors associated with SCr evolution during follow-up

A history of diabetes was associated with a higher SCr increase. After 5 years, the presence of this comorbidity for a patient was associated with a SCr 14.45 % higher (95 % CI [7.76 %; 21.46 %]) compared to its absence, while we did not observe any significant difference at 1 year. For a given patient, a graft from a deceased donor due to a cerebrovascular cause was associated with a relative increase of 12.52 % in expected 5-year SCr (95 % CI [6.50 %; 18.89 %]), compared to a graft from a living

Table 2 Multivariable 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)

	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 (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 versus female	0.074	[0.057; 0.091]	<0.0001	−0.007	[−0.014; 0.000]	0.0392			
Diabetes history: yes versus no	0.000	[−0.026; 0.025]	0.9866	0.027	[0.016; 0.039]	<0.0001			
Cardiovascular history: yes versus no	0.000	[−0.017; 0.017]	0.9812	0.008	[0.000; 0.015]	0.0371	1.39	[1.14; 1.69]	0.0011
3-month SCr (µmol/L, standardized)	0.083	[0.071; 0.096]	<0.0001				0.84	[0.74; 0.95]	0.0062
6-month SCr (µmol/L, standardized)	0.176	[0.164; 0.189]	<0.0001						
Acute rejection episode during the first year: yes versus no	0.055	[0.036; 0.074]	<0.0001				1.46	[1.17; 1.83]	0.0010
Anti-class I immunization: positive versus 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 versus 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 versus female							0.83	[0.69; 1.01]	0.0589
Donor age (years, standardized)	0.056	[0.045; 0.066]	<0.0001						

Referential value for 1-year SCr was 4.024, 95 % CI [3.982; 4.065]. Referential value for 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. $\alpha = 2.93$; $\alpha_2 = 3.29$

Coef coefficient, *HR* hazard ratio, *CI* confidence interval

donor, but only a 7.14 % increase when compared to a deceased donor due to another cause (95 % CI [1.48 %; 13.00 %]).

Factors associated with both 1-year post-transplantation SCr and SCr evolution during the follow-up

Male recipient had a 7.68 % higher 1-year SCr (95 % CI [5.83 %; 9.51 %]). Nevertheless, he was likely to have a slower increase: after 5 years follow-up the gap reduced to 3.98 % (95 % CI [0.18 %; 7.81 %]).

Factors associated with the graft failure risk

Two factors were significantly associated with graft failure risk. Without significant correlation with the SCr, a patient transplanted for the second time had a higher graft failure risk compared to his first transplantation (HR = 1.32, 95 % CI [1.02; 1.73]). On the contrary, for a given patient, graft from male tended to be associated with a smaller risk of graft failure compared to graft from female donor (HR = 0.83, 95 % CI [0.69; 1.01]).

Factors associated with both SCr and the graft failure processes

A 10-year older patient was associated with a 2.04 % lower 1-year SCr (95 % CI [1.31 %; 2.77 %]). Moreover, this difference increased during the follow-up, i.e. 5.57 % lower at 5-years post-transplantation (95 % CI [4.20 %; 6.95 %]). This could be explained by lower creatinine production in the elderly population due to a smaller muscle mass. However, for a given SCr evolution during the follow-up, the situation where the recipient is older was associated with a higher graft failure risk (HR = 1.35 for a 10-year older patient, 95 % CI [1.25; 1.46]).

For a given patient, higher 3-month SCr was associated with a significantly higher 1-year SCr level. For instance, for a 50 µmol/L difference at 3-months, the 1-year SCr level increased by 8.08 % (95 % CI [6.83; 9.32]). Additionally, for a given evolution of SCr from 1-year post-transplantation, a higher 3-month SCr was associated with a lower graft failure risk (HR = 0.85 for an increase of 50 µmol/L in 3-month SCr level, 95 % CI [0.75; 0.95]).

Major risk factors included acute rejection in the first year post-transplantation, immunization, and cardiovascular history. When a patient had an acute rejection episode during the first year post-transplantation, a 5.65 % higher 1-year SCr was observed compared to cases where no acute rejection occurred (95 % CI [3.65; 7.71]). Nevertheless, independently of the current value and the slope of SCr, the situation where acute rejection has occurred appeared with a higher risk of graft failure (HR = 1.46, 95 % CI [1.17; 1.83]). A patient with cardiovascular history was more likely to have an increased SCr compared to the same patient without this history, and a higher graft failure risk independently from this increase (HR = 1.39, 95 % CI [1.14; 1.69]). Similarly, a significant SCr increase was demonstrated for pre-transplant immunized patient, with an additional graft failure risk not related to this SCr increase, compared to the same patient non-immunized.

Separate models

The linear mixed model estimations and those of the time-dependent Cox model are presented in Tables 3 and 4 respectively. One can note differences in the retained variables. An acute rejection episode in the first year post-transplantation was significantly associated with the SCr evolution by using a linear mixed model, in opposition to the results obtained by using joint models. No relationship between cardiovascular history or donor type with SCr evolution were retained by using the linear mixed model, while we concluded from the final joint model that patients with cardiovascular history may have a significantly higher SCr increase during the follow-up ($p = 0.0371$) and SCr evolution could be different given the donor type status ($p = 0.0022$). Slight underestimations of hazard ratios were obtained from the time-dependent Cox model compared to the joint model. For example, the hazard ratio related to the recipient age was 1.25 (95 % CI [1.19–1.38]) for 10 years older by using the time-dependent Cox model against 1.35 (95 % CI [1.25; 1.46]) by using the joint model. Additionally, diabetes was retained as a risk factor for graft failure by using the Cox model, while it does not by using the joint model. In contrast, acute rejection episode was not retained as a risk factor for graft failure by using the time-dependent Cox model, while it was by using the joint model.

Cause specific approach

Using a cause specific approach (Tables S1 and S2 in supplementary materials), we observed that current SCr level was more importantly associated with return to dialysis (HR = 2.51, 95 % CI [2.22; 2.84]) compared to death with a functioning graft (HR = 1.47, 95 % CI [1.24; 1.74]). As expected, this higher association was also observed for acute rejection episode (HR = 1.63, 95 % CI [1.20; 2.20] vs. HR = 1.24, 95 % CI [0.86; 1.80]). In contrast, cardiovascular history (HR = 1.07, 95 % CI [0.81; 1.41] vs. HR = 2.01, 95 % CI [1.49; 2.70]) and recipient age (HR = 1.20, 95 % CI [1.05; 1.39] vs. HR = 2.36, 95 % CI [1.95; 2.86]) were strongly associated with the time-to-death.

Table 3 Multivariable analysis for the logarithmic transformation of SCr

	Longitudinal 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
Recipient age (years, standardized)	−0.025	[−0.035; −0.015]	<0.0001	−0.010	[−0.013; −0.006]	<0.0001
Recipient gender: male versus female	0.073	[0.056; 0.090]	<0.0001	−0.007	[−0.013; 0.001]	0.0441
History of diabetes: yes versus no	0.003	[−0.022; 0.028]	0.7987	0.026	[0.015; 0.038]	<0.0001
3 month SCr (μmol/L, standardized)	0.085	[0.072; 0.097]	<0.0001			
6 month SCr (μmol/L, standardized)	0.176	[0.164; 0.189]	<0.0001			
Acute rejection episode <1 year: yes versus no	0.055	[0.036; 0.075]	<0.0001	−0.009	[−0.017; −0.001]	0.0233
Anti class I immunization: positive versus negative	0.010	[−0.007; 0.028]	0.2344	0.010	[0.002; 0.017]	0.0111
Donor age (years, standardized)	0.057	[0.046; 0.067]	<0.0001			
Cold ischemia time (h)—standardized	0.002	[−0.006; 0.010]	0.6717	0.004	[0.001; 0.007]	0.0253

12,241 observations from 2583 patients

Referential value for 1-year SCr was 4.024, 95 % CI [3.985, 4.064]. Referential value for SCr evolution was 0.040 95 % CI [0.025; 0.055]. This model is adjusted on a time effect with a threshold at 2008 (before 2008 vs. after): coefficient for relation to the 1-year SCr: 0.020 95 % CI [0.004; 0.037] and to the SCr evolution: 0.011 95 % CI [0.003; 0.018]

Coef coefficient, *CI* confidence interval, *SCr* serum creatinine

Table 4 Multivariable time-dependent Cox model for patient-graft failure risk (2604 patients, 455 events observed)

	Survival process		
	HR	95 % CI	*p* value
Last observation of SCr carried forward (LOCF), (μmol/L), for an increase of 25 %	2.07	[1.97; 2.18]	<0.0001
Recipient age (years, standardized)	1.40	[1.26; 1.55]	<0.0001
Diabetes history: yes versus no	1.50	[1.15; 1.95]	0.0031
Cardiovascular history: yes versus no	1.36	[1.12; 1.65]	0.0021
3-month SCr (μmol/L, standardized)	0.80	[0.73; 0.89]	<0.0001
Anti class I immunization: positive versus negative	1.44	[1.15; 1.81]	0.0015
Graft rank: second versus first	1.37	[1.05; 1.80]	0.0221
Donor gender: male versus female	0.82	[0.68; 1.00]	0.0456
Time to dialysis prior transplantation (≥1 year vs. <1)	1.27	[1.00; 1.60]	0.0500

HR hazard ratio, *CI* confidence interval, *SCr* serum creatinine

A period effect is included with a HR = 0.71, 95 % CI [0.55; 0.92]

Discussion

Our results show that during the chronic phase of renal transplantation, elevated SCr levels as well as the magnitude of SCr increases are associated with a higher risk of graft failure. Accordingly, physicians routinely supervise both the current SCr level and its increase. The large majority of baseline explicative variables are firstly associated with the baseline SCr level or its evolution, finally leading to graft failure. Interestingly, we demonstrated that besides the association of cardiovascular history with increased SCr, this risk factor was additionally associated with an increase in the risk of graft failure. Therefore, at a given time for a given SCr level and slope, the presence of cardiovascular history should be considered as a risk factor for graft failure. Similarly, patient transplanted for a second time seemed at higher risk of graft failure, regardless of the SCr level or its slope, compared to its first graft. Other factors independent of SCr leading to increased graft failure risk may result from stronger immunosuppression or undetected immunization against donor specific antigens. In addition to retransplantation or the presence of cardiovascular history, particular attention should also be paid to patients with a high 3-month SCr level, transplantation in older patients or when an acute rejection episode during the first year has occurred. These patients may be more

susceptible to graft failure without having previously displayed aberrant SCr levels. On the contrary, if a patient received a deceased donor graft but had a SCr evolution analogous to those which would be observed if the graft had come from a living donor, the monitoring of this patient should be the same regardless of the donor status.

In renal transplantation, numerous studies have focused on only one or two measurements of renal function to study their association with graft failure [34–36]. However, the joint modeling approach allows the whole trajectory of longitudinal SCr measurements to be taken into account. In this paper, we used for the first time a shared random effect joint modeling to more precisely specify the association between chronic SCr evolution and graft failure risk. Different types of dependence can be considered such as the current marker level, the evolution intensity during the follow-up, cumulative effects or lagged effects [2].

More generally, our approach illustrates that joint modeling constitutes a powerful approach for time-to-event analysis with endogenous time-dependent variable [1], which supports a real mechanistic evolution for many chronic diseases. However, their use in observational studies is still uncommon. As previously acknowledged by Asar et al. [1], differing results and interpretations between the joint modeling and the separate approaches reinforce the necessity to use joint modeling in the presence of endogenous variable. We also highlighted the differences in our application in kidney transplantation. In other diseases, the informative censoring or the endogenous nature for the longitudinal variable can result in even higher differences.

One limitation in our study may be the graft failure definition: the first event between the return to dialysis and death with a functioning graft. Because it is very difficult to distinguish the cause of death related or not to the disease, we performed a sensitivity analyses. The results illustrated the overall robustness of the results but with a probable underestimation of the association between the SCr and the acute rejection episode on the risk of graft failure.

In conclusion, our results illustrate the importance of joint models and their potential usefulness in improving chronic disease research. It brings a more complete epidemiological view of the risk factors and the related natural disease history mechanisms. The use of this novel statistical model on a large cohort of kidney transplant recipients highlights that several risk factors were associated with SCr evolution while others were associated with graft failure risk independently of the initial SCr value or its subsequent evolution. These included elderly or immunized recipients, second transplantations, grafts coming from female donors, patients experiencing an acute rejection episode in the first year post-transplantation, patients with cardiovascular history or with a high gap between 3 and 12 month SCr measurements, features that should receive additional attention.

Acknowledgments We wish to thank the DIVAT scientific board (C. Legendre, H. Kreis, L. Rostaing, N. Kamar, E. Morelon, G. Mourad, V. Garrigue, M. Kessler and M. Ladrière) as well as members of the clinical research assistant team (S. Le Floch, A. Petit, J. Posson, C. Scellier, V. Eschbach, K. Zurbonsen, C. Dagot, F. M'Raiagh, V. Godel, X. Longy and P. Przednowed). The DIVAT cohort is partially supported by Roche Laboratory since 1994.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix 1: Mathematical formulation of the shared random effect joint model

Let Y be the longitudinal marker and t_{ij} the time of measurement of the jth ($j = 1, \ldots, n_i$) measure for the patient i ($i = 1, \ldots, N$). Let $h(\cdot)$ denotes the instantaneous risk function of graft failure. The joint model combines a linear mixed model (Eq. 1) with a parametric regression model (Eq. 2). They share the random effects (b_{0i}; b_{1i}).

$$Y_{ij}(t_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 X_{1i} + \beta_3 X_{2i} t_{ij} + \varepsilon_{ij} \quad (1)$$

$$h_i(t) = h_0(t)\ \exp(\gamma^T X_{3i} + g(m_i(t); \alpha)) \quad (2)$$

with $(b_{0i}; b_{1i})^T \sim \mathrm{MVN}(0,B)$, B an unstructured variance–covariance matrix, X_{1i} a vector of baseline covariates influencing the baseline value of longitudinal marker, X_{2i} another vector of baseline covariates that may change marker evolution over time and β_0, β_1 two scalars defining the referential value of the baseline level and the slope of the longitudinal biomarker $Y(\cdot)$ respectively, and β_2, β_3 two p-vectors of the same dimension as X_1 and X_2 respectively. The evolution of the measurements $Y_{ij}(t_{ij})$ are defined by the sum of a subject specific trend $m_i(t_{ij})$ plus an error term $\varepsilon_{ij} \sim N(0, \sigma^2_\varepsilon)$. For the instantaneous risk function of graft failure, $h_0(t)$ denotes the baseline risk function, and X_{3i} is a vector of baseline covariates that could influence the graft failure risk, with a corresponding vector of fixed regression coefficients γ. g is a function of the true level of the marker m_i, which specifies the type of dependence between the longitudinal and the survival processes. Classically, it may be the current level of the marker ($g(m_i(t)) = \alpha m_i(t)$), the intensity of marker deterioration during the follow-up i.e. the slope ($g(m_i(t)) = \alpha_2 m_i'(t)$), or both ($g(m_i(t)) = \alpha_1 m_i(t) + \alpha_2 m_i'(t)$) [2]. This latter is the retained association of the model presented in Table 2.

Appendix 2: Clinical interpretations of the joint model parameters

Parameters of the longitudinal process

Due to the log transformation of the longitudinal marker SCr, the parameters in the linear mixed submodel should be interpreted as the log of relative change. The longitudinal equation can be written as follows:

$$\log\left(\mathrm{SCr}\left(t_{ij}\right)\right) = \beta_0 + b_{0i} + (\beta_1 + b_{1i})t_{ij} + \beta_2 X_{1i} + \beta_3 X_{2i} t_{ij}$$

and the SCr evolution can be re-written as:

$$\mathrm{SCr}\left(t_{ij}\right) = \exp(\beta_0 + b_{0i})\ \exp\left((\beta_1 + b_{1i})t_{ij}\right) \exp(\beta_2 X_{1i})\exp\left(\beta_3 X_{2i} t_{ij}\right)$$

Qualitative variables

Let Z be a qualitative variable associated with:

- the 1-year SCr only ($Z \subseteq X_1;\ Z \nsubseteq X_2$). The excess of SCr for a patient with $Z = 1$ as compared to the case where $Z = 0$ for the same patient is:

$$\frac{\mathrm{SCr}(t_{ij})_{[Z_i=1 \text{ vs } Z_i=0]}}{\mathrm{SCr}(t_{ij})_{[Z_i=1 \text{ vs } Z_i=0]}} = \frac{\exp(\beta_0 + b_{0i})\exp\left((\beta_1 + b_{1i})t_{ij}\right)\exp(\beta_2)}{\exp(\beta_0 + b_{0i})\exp\left((\beta_1 + b_{1i})t_{ij}\right)}$$

This gap of SCr is constant beyond 1-year post-transplantation.

- Both the 1-year SCr and the SCr increase during the follow-up ($Z \subseteq X_1;\ Z \subseteq X_2$)

$$\mathrm{SCr}(t_{ij})_{[Z_i=1 \text{ vs } Z_i=0]} = \exp\left(\beta_2 + \beta_3 t_{ij}\right)$$

This gap of SCr value is increasing or decreasing during the follow-up according to the sign of β_3. For clinical purposes, in the interpretations, we used the time $t = 5$ to quantify a relative change at 5 years after the first year post-transplantation.

Quantitative variables

Let W_1 be a quantitative variable with sd_{W1} its standard deviation, w a value of W_1 and Δ a relevant clinical increase.

- Let X_1 be the standardized version of W_1, X_2 be null (W_1 was associated with the 1-year SCr only).

$$\begin{aligned}&\mathrm{SCr}\left(t_{ij}\right)\left[W_{1i} = w + \Delta \text{ vs } W'_{1i} = w\right]\\ &= \frac{\exp(\beta_0 + b_{0i})\exp\left((\beta_1 + b_{1i})t_{ij}\right)\exp\left(\beta_2\left(\frac{(w+\Delta)}{sd_{W1}}\right)\right)}{\exp(\beta_0 + b_{0i})\exp\left((\beta_1 + b_{1i})t_{ij}\right)\exp(\beta_2(w/sd_{W1}))}\\ &= \frac{\exp(\beta_2 w/sd_{W1} + \beta_2\Delta/sd_{W1})}{\exp(\beta_2(w/sd_{W1}))}\\ &= \exp(\beta_2\Delta/sd_{W1})\end{aligned}$$

- Now, let $X_1 = X_2$ be the standardized version of W_1 (W_1 was associated with both the 1-year SCr and the SCr evolution).

$$\begin{aligned}\mathrm{SCr}\left(t_{ij}\right)\left[W_{1i} = w + \Delta \text{ vs } W'_{1i} = w\right] &= \frac{\exp(\beta_0 + b_{0i})\exp\left((\beta_1 + b_{1i})t_{ij}\right)\exp\left(\beta_2\left(\frac{(w+\Delta)}{sd_{W1}}\right)\right)\exp\left(\beta_3 t_{ij}\left(\frac{(w+\Delta)}{sd_{W1}}\right)\right)}{\exp(\beta_0 + b_{0i})\exp\left((\beta_1 + b_{1i})t_{ij}\right)\exp(\beta_2(w/sd_{W1}))\exp\left(\beta_3 t_{ij}(w/sd_{W1})\right)}\\ &= \exp(\beta_2\Delta/sd_{W1})\exp\left(\beta_3 t_{ij}\Delta/sd_{W1}\right))\end{aligned}$$

Hazard ratio for the longitudinal marker

As we have seen in "Appendix 1", the instantaneous risk function is written as follows:

$$\begin{aligned}h_i(t) &= h_0(t)\ \exp\left(\gamma^T X_{3i} + \alpha_1 m_i(t) + \alpha_2 m'_i(t)\right)\\ &= h_0(t)\ \exp\left(\gamma^T X_{3i} + \alpha_1 m_i(t)\ + \alpha_2 \frac{\delta m_i(t)}{\delta t}\right)\end{aligned}$$

With $m_i(t) = \beta_{0i} + \beta_{1i} t$ and $\frac{\delta m_i(t)}{\delta t} = \beta_{1i}$

As we use a log transformation of SCr measurement ($Y(t) = \log(\mathrm{SCr}(t))$), the hazard ratio which quantifies the association between the longitudinal marker and the risk of event was expressed for a clinically relevant difference.

- For the current level of the marker, we can rewrite the HR for a difference of 25 % in SCr values at the same time for the same patient and the same slope:

$$\begin{aligned}&HR_{1.25\mathrm{SCr}(t)\text{vs}\mathrm{SCr}(t)}\\ &= \frac{h_0(t)\exp\left(\gamma^T X_{3i} + \alpha_1 \log(1.25\mathrm{SCr}(t)) + \alpha_2 m'_i(t)\right)}{h_0(t)\exp\left(\gamma^T X_{3i} + \alpha_1 \log(\mathrm{SCr}(t)) + \alpha_2 m'_i(t)\right)}\\ &= \exp(\alpha_1(\log(1.25\mathrm{SCr}(t)) - \log(\mathrm{SCr}(t))))\\ &= 1.25^{\alpha_1}\end{aligned}$$

- For the intensity of the marker, the HR which compares the situation in which $\frac{\delta}{\delta t}\log(SCr_i(t)) = s_1$ to another in which $\frac{\delta}{\delta t}\log(SCr_i(t)) = s_2$, for same covariates X_{3i} and level of SCr at time t is equal. $HR = \exp(\alpha_2(s_2 - s_1))$. Besides, because we assume a linear model, $\frac{\delta}{\delta t}\log(SCr_i(t))$ is constant, that is $\forall t$, $\frac{\delta}{\delta t}\log(SCr_i(t)) =$ s for some $s \in \mathbb{R}$. This implies $\forall t' > t$:

  $SCr_i(t') = SCr_i(t)\exp(s(t' - t))$.

  If the SCr increases by x % between t-1 and t, then $s = \log(1 + x/100)$ because $s = \log\left(\frac{SCr_i(t)}{SCr_i(t-1)}\right)$

  This leads to: $HR = \exp(\alpha_2(\log(1 + x/100) - \log(1 + y/100)))$ which is the HR which compares an increase of x % between t-1 and t to an increase of y %. In our paper, we choose to compare an increase of 25 % compare to the mean evolution (a growth of 3 % each year).

Hazard ratio for the quantitative variables

Because the quantitative variables have been standardized, the HR for these factors were expressed for an increase of one standard deviation. In order to calculate them for an increase of relevant threshold in the variable unit, we can proceed as follows:

Let X_1 be the standardization of W_1 with sd_1 its standard deviation. HR_X is the HR obtained for the standardized variable and HR_W is the one for an increase of Δ unit of W_1.

$$HR_W = HR_X^{\left(\frac{\Delta}{sd_1}\right)}$$

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