Joint Modeling of Longitudinal Renal Function and Graft Survival Data in Kidney Transplantation

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TTS 2024 September 22-25 Istanbul/Turkey

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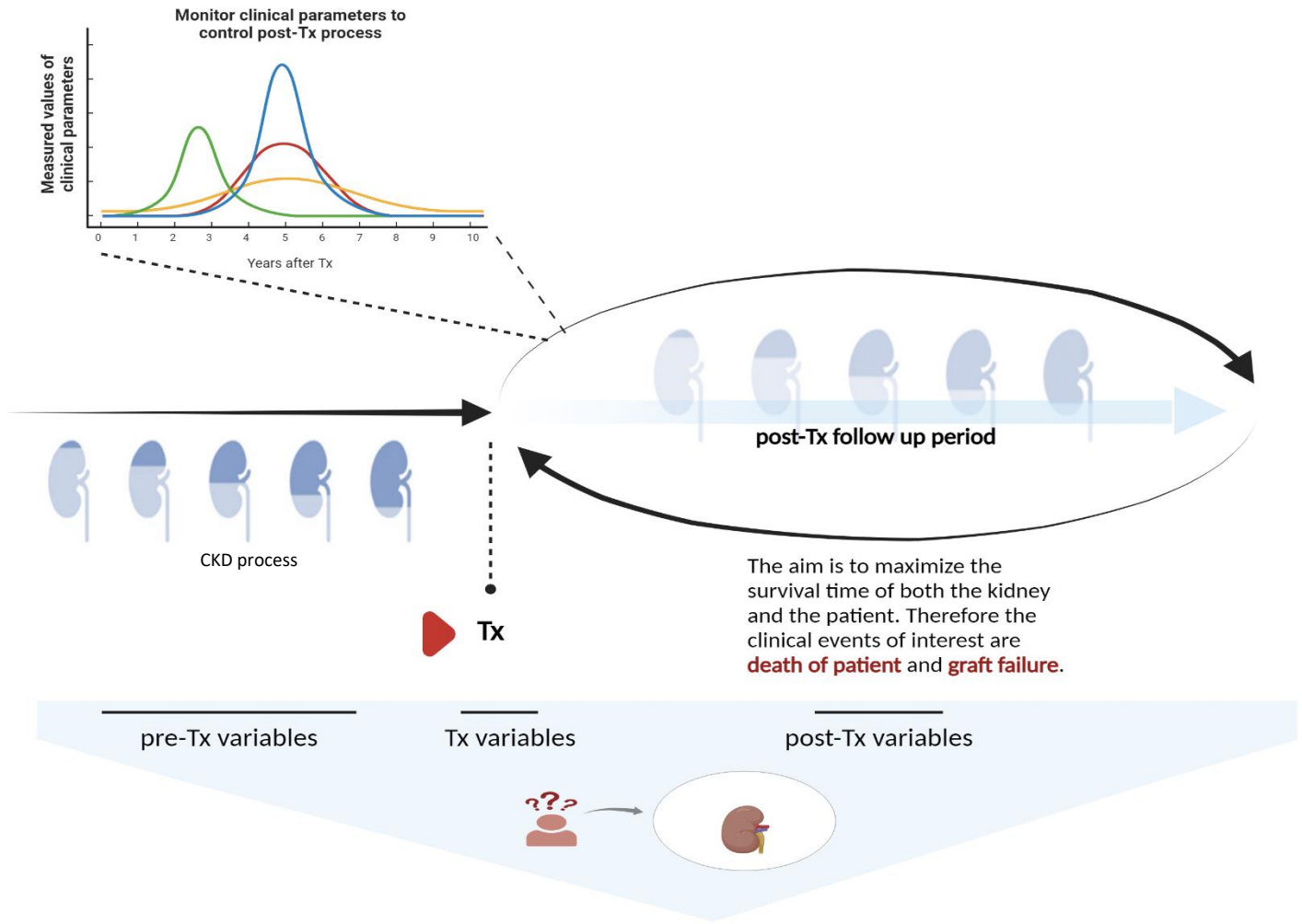

- What are the risk factors affecting graft failure?
- Can clinical parameters predicting late graft failure be identified?
- Do the curve changes of clinical parameters indicating kidney function predict graft failure?

Introduction

Chronic kidney disease (CKD) is a condition in which the kidneys gradually lose their function due to damage, eventually leading to the need for dialysis or kidney transplantation (Tx). Although a kidney transplant is a treatment, it is not a permanent solution; after a certain period, the patient may need to undergo dialysis or another transplant. Globally, the prevalence of CKD is estimated at 9.1% (Cockwell & Fisher, 2020). In our country, its prevalence is 15.7%. It ranks as the twelfth leading cause of death worldwide (Cockwell & Fisher, 2020).

The transplanted kidney has a certain lifetime and it depends on recipient and donor related, and many other clinical factors. Considering graft failure risk, patients are followed over years to monitor their kidney function during the post-transplantation period. This longitudinal observational period provides longitudinal and survival outcomes which are related and allow to model graft failure mechanism.

In this study, the relationship between kidney survival and temporal changes in creatinine and hematocrit, which are kidney function biomarkers, was examined with multivariate joint models.

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Method

Study design
Retrospective cohort

Study data
The application data used in this study was obtained by applying to the Non-Interventional Ethics Committee of Acıbadem Bursa Hospital.
There is cross-sectional and longitudinal data (~88,000 rows) for a total of 1002 patients who underwent kidney transplantation between December 2011 and January 2021.

Study outcomes

Survival Outcome Variables:

Graft failure: Defined as the absence of kidney function occurring at any time after transplantation due to irreversible graft damage that requires chronic dialysis and/or re-transplantation, or the patient's death.

Longitudinal Outcome Variables:
Serum creatinine level (CRE: mg/dl)
Hematocrit level (HCT: %)
Proteinuria (Positive/Negative)

Independent Variables of the Study
•Gender, Age at transplantation, Donor type, Total number of mismatches, Dialysis type and duration, History of any type of rejection, Etiology types

Statistical Models

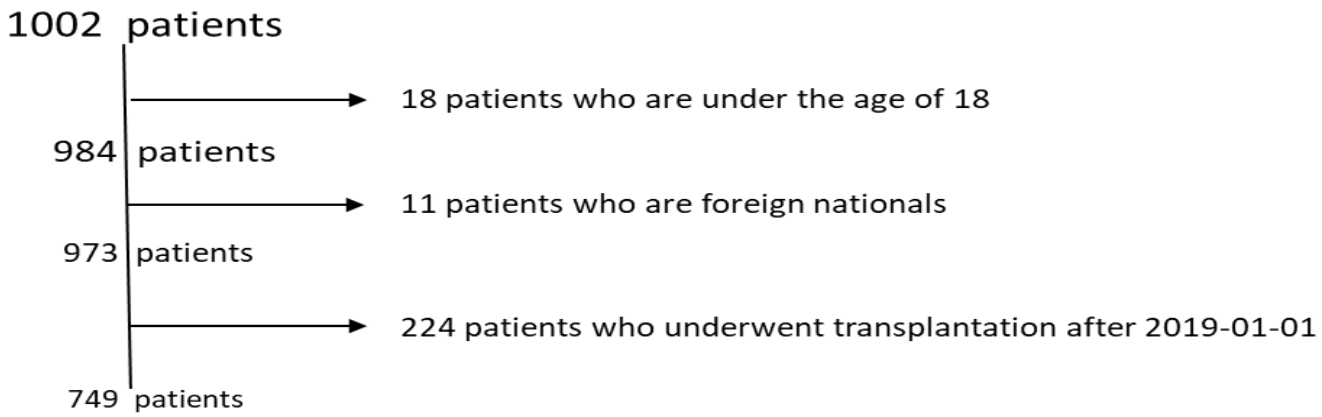
A significance level of 0.05 was used in all analyses. R software (R software, version 4.0.5, packages: arsenal, JMbayes2 for joint modeling, survival for proportional hazard tests, MuMIn for mixed model R^2 calculation, GLMMadaptive, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org) was used.

Survival Submodel: The variable selection for the Cox regression model was based on clinical knowledge and the completeness and accuracy of the data content. The Cox regression assumption was examined using the proportional hazard Schoenfeld residual test. Since the baseline hazard function in joint models must be defined parametrically, a B-spline was used within the joint model.

Longitudinal Submodel: The time-dependent variation of numerical longitudinal variables was modeled using a natural spline with four knots. In this model, fixed effects for age, gender, and donor type, along with random intercepts and random slopes, were included. The conditional variance explained by the model (fixed effects + random effects) and the normality of the residuals were checked. For proteinuria, a generalized linear mixed model (with a binomial logit link function) was used, including random intercepts and slopes with only the fixed effect of time.

Joint Model: Due to the difficulty in calculating the maximum likelihood estimator in multivariate joint models, estimation was performed using a Bayesian approach.
Model results and model selection were based on the Deviance Information Criterion (DIC), trace plots, and posterior density plots.

Flow chart



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Results

Recipient characteristics

	(N=749)
Gender	
Male	**475 (63.4%)**
Female	274 (36.6%)
Age	
Mean (SD)	44.5 (11.9)
Median (Min-Max)	**46.0 (18.0 - 79.0)**
BMI	
Missing	16
Mean (SD)	25.4 (4.7)
Median (Min-Max)	24.8 (11.8 - 47.6)
Blood type	
A	334 (44.6%)
AB	64 (8.5%)
B	139 (18.6%)
O	212 (28.3%)
Second Tx	**15 (2.0%)**
Smoking	
Yes	220 (29.4%)
No	49 (6.5%)
Former-smoker	116 (15.5%)
Unknown	364 (48.6%)
Alcohol	
Yes	358 (47.8%)
No	6 (0.8%)
Former-drinker	21 (2.8%)
Unknown	364 (48.6%)
Coronary artery disease (CAD)	
Missing	2
Yes	238 (31.9%)
No	147 (19.7%)
Unknown	362 (48.5%)
Hypertension (HT)	
Missing	2
Yes	127 (17.0%)
No	298 (39.9%)
Unknown	322 (43.1%)

	(N=749)
CKD etiology	
Glomerulonephritis	58 (7.7%)
Seconder Glomerulonephritis	32 (4.3%)
Tubulointerstitial nephritis	13 (1.7%)
Polycystic kidney	**48 (6.4%)**
Genetic	9 (1.2%)
Diabetes	**85 (11.3%)**
Neurogenic Bladder	4 (0.5%)
Vesicoureteral reflux	28 (3.7%)
Dialysis type	
Peritoneal dialysis (PD)	50 (6.7%)
Hemodialysis (HD)	**481 (64.2%)**
HD+PD	30 (4.0%)
Preemptive	**188 (25.1%)**
Total dialysis duration	
Mean (SD)	44.7 (57.0)
Median (Min-Max)	**13.0 (0.0 - 324.0)**
Pre-Tx CRE	
Missing	117
Mean (SD)	7.5 (2.8%)
Median (Min-Max)	7.0 (1.2 - 20.0%)
Celluluar Rejection	30 (4.0%)
Humoral Rejection	72 (9.6%)
Hyperacute Rejection	3 (0.4%)
Rejection	99 (13.2%)
Ex	**105 (14.0%)**
Graft loss	**60 (8.0%)**
Follow up duration (years)	
Mean (SD)	3.5 (2.1)
Median (Min-Max)	3.3 (0.01 - 8.0)

Donor characteristics

	(N=749)
Gender	
Male	**396 (52.9%)**
Female	353 (47.1%)
Age	
Mean (SD)	**54.1 (14.7)**
Median (Min-Max)	54.0 (17.0 - 89.0)
BMI	
Missing	37
Mean (SD)	27.8 (4.9)
Median (Min-Max)	**27.1 (16.7 - 57.9)**
Blood type	
A	302 (40.3%)
AB	37 (4.9%)
B	111 (14.8%)
O	299 (39.9%)
Donor type	
Alive	**427 (57.0%)**
Cadeveric	322 (43.0%)
HT	
Missing	440
Yes	117 (37.9%)
No	181 (58.6%)
Unknown	11 (3.6%)
Diabetes	
Missing	440
Yes	46 (14.9%)
No	253 (81.9%)
Unknown	10 (3.2%)

	(N=749)
Dual kidney	**13 (1.7%)**
A missmatch	
0	68 (9.1%)
1	**396 (52.9%)**
2	285 (38.1%)
B missmatch	
0	64 (8.5%)
1	**362 (48.3%)**
2	323 (43.1%)
DR missmatch	
0	135 (18.0%)
1	**501 (66.9%)**
2	113 (15.1%)
Total missmatch	
Mean (SD)	3.6 (1.3%)
Median (Min-Max)	**4 (0-6%)**
Cadaver cause of death	
Missing	11
Cerebrovascular event	**193 (62.1%)**
Other	118 (37.9%)
Cadaveric Cold Ischemia Time (hours)	
Missing	4
Mean (SD)	19.3 (4.2%)
Median (Min-Max)	**18.9 (9.2 - 39.1%)**

The mean graft survival time was 6.3 95% CI [6.1-6.5].

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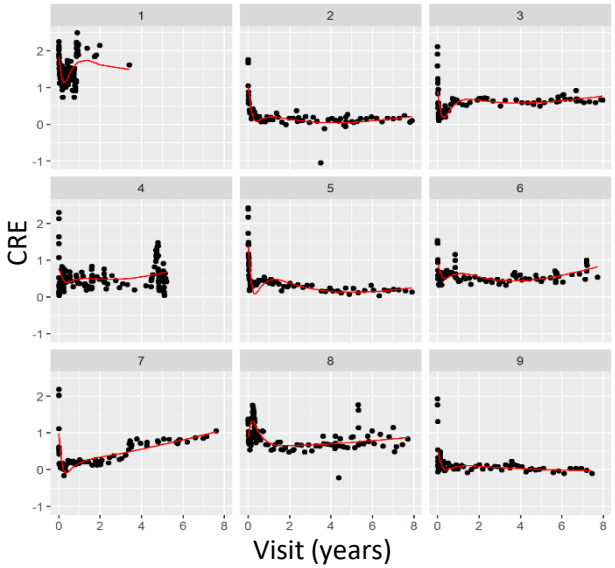
In the multivariate joint model that incorporating both longitudinal submodels for CRE and HCT, along with a survival submodel, the risk of kidney loss increased as the age at transplantation was high (hazard ratio 1.02) and the donor type was cadaver (hazard ratio 1.08), but only the age at transplantation was found to be statistically significant (p<0.001). No effect of gender and total number of missmatches was observed (p>0.05). When the effect of longitudinal variables on survival was examined, an increase in creatinine on the logarithmic scale increased the risk, while an increase in hematocrit reduced the risk (hazard ratios 4.52 and 0.84, respectively; p<0.001).

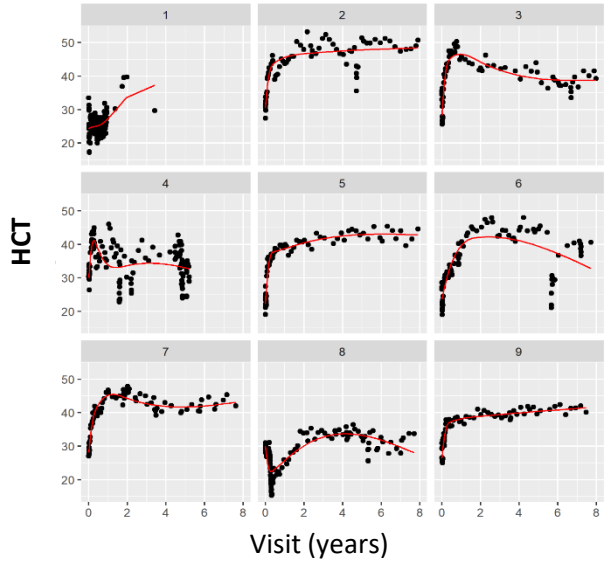
Log(CRE) Longitudinal Submodel results

Variable	Coefficient/SE	95% Credible Interval	P value
Visit			
Intercept	1.3056/0.0559	1.1960; 1.4142	<0.0001
$\beta_{11}^{..}$	-0.6465/0.0230	-0.6916; -0.6010	<0.0001
$\beta_{12}^{..}$	-0.7372/0.0388	-0.8127; -0.6622	<0.0001
$\beta_{13}^{..}$	-1.4616/0.0519	-1.5612; -1.3584	<0.0001
$\beta_{14}^{..}$	0.3635/0.0791	0.2270; 0.5329	<0.0001
Gender (ref: Male/ Female)	-0.2685/0.0267	-0.3204; -0.2164	<0.0001
Age at Tx (years)	-0.0006/0.0011	-0.0028; 0.0017	0.6194
Donor type (ref: Alive/Cadeveric)	0.2833/00353	0.2120; 0.3505	<0.0001
σ_1	02921/00011	0.2900; 0.2944	<0.0001

HCT Longitudinal Submodel results

	Coefficient/SE	95% Credible Interval	P value
Visit	28.8476/0.5811	27.7081; 29.9835	<0.0001
Intercept	10.8027/0.3396	10.1493; 11.4848	<0.0001
$\beta_{11}^{..}$	6.7234/0.6978	5.3237; 8.0852	<0.0001
$\beta_{12}^{..}$	13.6235/0.6974	12.2592; 14.9774	<0.0001
$\beta_{13}^{..}$	5.6669/1.3665	3.0780; 8.3651	<0.0001
$\beta_{14}^{..}$	-2.2854/0.2856	-2.8480; -1.7248	<0.0001
Gender (ref: Male/ Female)	0.0136/0.0122	-0.0100; 0.0374	0.2654
Age at Tx	-0.4980/0.3506	27.7081; 29.9835	<0.0001
Donor type (ref: Alive/Cadeveric)	3.2892/0.0127	10.1493; 11.4848	<0.0001
σ_1	28.8476/0.5811	5.3237; 8.0852	<0.0001





Survival Submodel results

Variable	Coefficient/SE	95% Credible Interval	HR	P value
CRE	1.5141/0.2001	1.1217; 1.8999	45.453	<0.0001
HCT	-0.1696/0.0229	-0.2149; -0.1269	0.844	**<0.0001**
Gender (ref: Male/ Female)	-0.0465/0.2384	-0.5264; 0.3992	0.9546	0.8646
Age at Tx (years)	0.0226/0.0076	0.0079; 0.0379	10.229	**0.0028**
Donor type (ref: Alive/Cadeveric)	0.0804/0.1907	-0.2966; 0.4710	10.837	0.6752
Rejection (ref:Yok/Var)	0.0536/0.1953	-0.3384; 0.4253	10.551	0.776
Total missmatch	0.0484/0.0674	-0.0824; 0.1838	10.496	0.4744
Total dialysis duration	0.0012/0.0015	-0.0018; 0.0040	10.012	0.4212

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Discussion

Studies investigating the effect of multiple longitudinal biomarkers on graft survival using joint models are limited due to computational complexity. Sayyadi et al. (Sayyadi et al., 2016) found a hazard ratio (HR) of 1.82 (95% CI 1.4-2.3; p<0.001) for graft loss associated with serum CRE levels measured monthly over one year in a survival model that included factors such as age at transplantation, donor type, immunosuppressive drug type, anemia, leukopenia, hyperkalemia, myocardial infarction, acute tubular necrosis, and anti-thymocyte globulin. Similarly, Fournier et al. (Fournier et al., 2016) found an HR of 1.89 (95% CI 1.2-3.1; p=0.01) for serum CRE measured at 3, 6, and 12 months post-transplant in a survival submodel accounting for age at transplantation, cardiovascular history, the presence of acute rejection in the first year, and donor gender.

Two studies have investigated multiple longitudinal biomarkers in joint models. The first, by Rasoul Alimi et al. (Alimi et al., 2021b)) modelled serum CRE and blood urea nitrogen with linearly in longitudinal submodels. They found an HR of 1.49 (95% CI 1.0-2.2; p=0.051) for serum CRE and 1.68 (95% CI 1.2-2.3; p<0.001) for blood urea nitrogen in a survival submodel that included age at transplantation, gender, and hypertension. Serum creatinine was not statistically significant in the presence of blood urea nitrogen. Lastly, Rizopoulos and Ghosh (Rizopoulos & Ghosh, 2011) identified eGFR, proteinuria, and hematocrit levels as being associated with graft survival in a survival submodel that included gender, age at transplantation, and weight. They modelled longitudinal biomarkes with splines in longitudinal submodels. Despite differences in risk factors and longitudinal and survival submodels, these studies consistently associated changes in serum CRE with graft survival, while hematocrit has only been associated in two studies, including the present study. Since it is known that kidney biomarkers exhibit nonlinear changes, it is important to model them using splines in joint models. This study is the second multivariate joint model to use splines for modeling kidney biomarkers and presents a realiable predictive model from a clinical perspective due to its single-center patient series.

Conclusion

The relationship between longitudinal data of kidney function biomarkers and kidney survival has been demonstrated. It is beneficial to incorporate all available information in this type of multivariate model. It is expected that dynamic predictions will be integrated into current systems in the future, with these models utilizing all data from a patient's medical history. This makes multivariate joint modeling a valuable tool in the era of personalized medicine as it provides doctors with a deeper understanding of disease progression and the ability to select the most suitable treatment at a specific follow-up time.

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