

Longitudinal Serum Creatinine Levels in Relation to Graft Loss Following Renal Transplantation: Robust Joint Modeling of Longitudinal Measurements and Survival Time Data

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Abstract

Background: Chronic kidney disease (CKD) is a major public health problem that may lead to end-stage renal disease (ESRD). Renal transplantation has become the treatment modality of choice for the majority of patients with ESRD. It is therefore necessary to monitor the disease progression of patients who have undergone renal transplantation. In order to monitor the disease progression, the continuous assessment of kidney function over time is considered.

Objectives: This study aimed to investigate the etiological role of recipient characteristics in serum creatinine changes within the follow-up period and in relation to the graft failure risk, as well as to evaluate whether or not the serum creatinine level represents an indicator of graft failure following renal transplantation.

Methods: This retrospective cohort study was conducted at the department of nephrology, Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, between April 2005 and December 2008. The study involved 413 renal transplantation patients. The primary outcomes were the determination of the serum creatinine levels at each attendance and the time to graft failure. Robust joint modeling of the longitudinal measurements (serum creatinine level) and time-to-event data (time to graft failure) were used for the analysis in the presence of outliers in the serum creatinine levels. The data analysis was implemented in WinBUGS 1.4.3.

Results: There was a positive association between the serum creatinine level and graft failure (HR = 5.13, $P < 0.001$). A one unit increase in the serum creatinine level suggests an increased risk of graft failure of up to 5.13 times. The serum creatinine level significantly decreased over time (95% CI: (-1.58, -1.08)). The recipient's age was negatively associated with the serum creatinine level (95% CI: (-0.02, -0.001)).

Conclusions: Graft failure is more likely to occur in patients with higher serum creatinine levels.

Keywords: End-Stage Renal Disease (ESRD), Graft Loss, Serum Creatinine Level, Robust Joint Modeling, Bayesian Approach

1. Background

Chronic kidney disease (CKD) is a major public health problem worldwide, and it may lead to end-stage renal disease (ESRD). ESRD is defined as an irreversible reduction in kidney function, and the high mortality rate is one of the main challenges associated with the treatment of these patients (1). According to recent reports, the total number of patients with ESRD has been increasing dramatically (2). Renal replacement therapy is required for the survival of patients with ESRD. Renal transplantation is the preferred treatment modality for renal replacement therapy in patients with ESRD due to the high rate of patient survival, improved quality of life, and low health care costs. Accord-

ing to a report by the management center for transplantation and special diseases of Iran, the frequency of patients with ESRD undergoing renal replacement therapy (RRT) was 32,686 in 2007 (prevalence of 435.8 per million population (pmp)). This number is very high when compared to the frequency in both 1997 and 2000, when the prevalence of ESRD was 137 pmp and 238 pmp, respectively. The incidence of patients with ESRD also seems to have increased from 13.82 pmp in 1997 to 49.9 pmp in 2000 and then 63.8 pmp in 2006 (3). Patient survival has significantly improved over the last three decades. However, despite significant efforts being made to improve the survival of renal grafts, many patients still experience graft failure. The rate

of five-year survival of kidney allografts was estimated to be 82.5% in Iran in 2011 (4). Graft failure is a major clinical event, and it is defined as a return to dialysis, or death with a functioning graft (5). Unfortunately, the main determinants of both the patient's and the graft's survival are not yet completely understood (6, 7).

In medical research, it is common to observe a time-to-event outcome, together with longitudinal measurements of a disease marker. Since it is essential to monitor the disease progression of patients who have undergone renal transplantation, the continuous assessment of kidney function over time is important (8, 9). For renal transplantation patients, the serum creatinine level is the simplest biomarker that is routinely measured to monitor the disease progression of a kidney transplant recipient. Once a patient experiences graft failure, measurements of the serum creatinine level will not be recorded and the patients will no longer be monitored for kidney function, which results in missing data. The longitudinal serum creatinine level and the time to graft failure are typically correlated, with both types of data being associated through unobserved random effects. Separate analyses of longitudinal measurements and survival data may lead to biased estimates (10-12). The joint modeling of survival data and longitudinal measurements takes into account the dependence between both processes, and it can handle non-ignorable missing data. It also enables simultaneous statistical inference regarding both outcomes. Using this method, more accurate parameter estimates and efficient inferences concerning the effect of the covariates on the longitudinal and survival processes can therefore be obtained (13, 14). The existing methods for the joint modeling of longitudinal outcomes and time-to-event data can be highly influenced by the presence of outlying observations in the longitudinal data (i.e., serum creatinine level). Robust joint modeling can be used to investigate the relationship between both the serum creatinine levels and the time to graft failure in the presence of outliers in the serum creatinine values (15-17).

2. Objectives

The aim of the current study is to investigate the etiological role of recipient characteristics in serum creatinine changes within the follow-up period and in relation to the graft failure risk, as well as to evaluate whether or not the serum creatinine level represents an indicator of graft failure following renal transplantation.

3. Methods

This retrospective cohort study included 413 patients with ESRD who underwent renal transplantation at the Baqiyatallah transplant center, Baqiyatallah hospital, Tehran, Iran, between April 2005 and December 2008. The study parameters were retrieved from a computerized database of transplant patients that includes the recipient's age, gender, BMI, blood group, history of diabetes, history of dialysis therapy prior to transplantation, and donor type. The primary outcomes of the study were the determination of the serum creatinine levels at each attendance and the time to graft failure. The serum creatinine levels were recorded at several time points (before renal transplantation, 15 days after transplantation, and one, three, six, 12, and 24 months after renal transplantation).

3.1. Statistical Analysis

In many medical studies, survival data and longitudinal biomarkers are collected together. In this study, the serum creatinine level was measured intermittently over time for each recipient, while the time to graft failure was another outcome of interest. The time to graft failure may be associated with the longitudinal biomarker trajectories. However, separate analyses of survival and longitudinal outcomes may lead to biased results. Using the joint modeling approach, all information from the survival and longitudinal processes is included simultaneously in the model so as to provide valid and efficient estimates (14). A joint model can link two processes by un-observed random effects through the use of a shared parameter model (18). Within the joint modeling framework, the linear mixed effects model was applied to model the longitudinal serum creatinine levels, while the Cox proportional hazard model was used to model the time to graft failure. In the current data, there were outlying observations in the serum creatinine levels, and the existing methods for joint modeling can be highly influenced by outliers in the longitudinal data. To overcome this problem, a joint model is proposed that is robust against outlying longitudinal measurements due to assuming a t-distributed measurement error in the linear mixed effects sub-model. The Bayesian estimation method was applied to estimate the model parameters. In this study, Bayesian parameter estimates, the posterior mean (standard deviation), and a 95% credible interval are reported. According to the Bayesian approach, the parameter estimates are significant when the 95% credible interval does not contain a zero. The proposed robust joint model was implemented using WinBUGS 1.4.3 statistical software (19).

4. Results

This study included 413 renal transplantation patients. The baseline characteristics of the recipients are summarized in Table 1. The median follow-up time was 6.80 months. The results of the robust joint modeling of the serum creatinine levels and the time to graft failure are presented in Table 2.

Table 1. Baseline Characteristics of 413 Renal Transplant Recipients^a

Characteristics	Results
Recipient age, y	42 (18 to 75)
Recipient BMI, kg/m ²	22.84 (12.80 to 37.11)
Recipient gender, male	277 (67.1)
Positive history of diabetes	80 (19.4)
Living donor	358 (86.7)
Positive history of dialysis before transplantation	346 (83.8)
Graft failure	295 (71.4)

Abbreviations: BMI, Body Mass Index.

^aValues are expressed as median (range) or No. (%).

According to the results of the survival sub-model, patients who received a living donor kidney had a higher risk of graft failure than patients who received a deceased donor kidney transplant (HR = 1.82; 95% HPD: (1.39 to 3)). The time to graft failure was not significantly associated with the recipient's age, gender, history of dialysis prior to transplantation, or history of diabetes (Table 2). Based on the results of the longitudinal sub-model, the serum creatinine values significantly decreased over time (Table 2). The recipient's age was negatively associated with the serum creatinine values (Table 2). However, no significant association was found between the serum creatinine levels and the recipient's BMI, gender, or history of dialysis (Table 2).

In addition, the significant model association parameter revealed a positive association between the serum creatinine levels and graft failure, which means that graft failure is more likely to occur in patients with higher serum creatinine levels (HR = 5.13, $P < 0.001$).

5. Discussion

The annual frequency of patients with ESRD seems to be increasing at a rate of 7% - 8% (20). The increasing incidence of ESRD patients in Iran suggests that it is a significant medical, social, and economic problem (3, 21). Monitoring the disease progression of ESRD transplantation patients is a necessity. The continuous assessment of kidney function over time is performed in order to monitor

Table 2. Results of the Robust Joint Modeling of the Serum Creatinine Level and the Time to Graft Failure^a

	Mean (SD)	95% CI
Longitudinal sub-model		
Intercept	4.44 (0.70)	(3.06, 5.81)
Time	-1.32 (0.13)	(-1.58, -1.08)
Recipient age, year	-0.01 (0.005)	(-0.02, -0.001)
Recipient BMI	0.03 (0.03)	(-0.02, 0.08)
Recipient gender, male	0.19 (0.22)	(-0.25, 0.62)
History of dialysis	0.40 (0.28)	(-0.15, 0.94)
Survival sub-model		
	Hazard Ratio	95% CI for Hazard Ratio
Recipient age, year	0.99	(0.98, 1.01)
Recipient gender, male	1.13	(0.83, 1.55)
Living donor	1.82	(1.39, 3.00)
History of dialysis	0.84	(0.57, 1.23)
History of diabetes	0.89	(0.60, 1.30)

Abbreviations: BMI, body mass index; CI: credible interval; SD, standard deviation.

^aAccording to the Bayesian approach and the longitudinal sub-model, the parameter estimates are significant when the 95% credible interval does not contain a zero. In the survival sub-model, the credible intervals that do not contain a 1 represent the significant effect of the corresponding parameter.

the disease progression. The progression of renal disease is usually determined by changes in the levels of various markers. In this regard, a decrease in the serum creatinine level indicates an improvement in kidney function over time (22).

The current study aimed to investigate the etiological role of recipient characteristics in serum creatinine changes within the follow-up period and in relation to the graft failure risk, as well as to evaluate the association between the serum creatinine level and graft failure following renal transplantation. The current study utilized a new statistical methodology, the robust joint modeling of survival data and longitudinal biomarker measurements, to assess whether changes in the serum creatinine level over time were associated with the time to graft failure following renal transplantation.

In the current study, the time to graft failure was not significantly correlated with the recipient's age, gender, history of dialysis prior to transplantation, or history of diabetes. According to the results of this study, the serum creatinine levels significantly decreased over time. The patients appeared to have improved kidney function over time, as evidenced by the negative slope of the serum creatinine level in the longitudinal sub-model. The recipient's age was inversely associated with the serum creatinine values. The current study's findings in the longitudi-

nal sub-model regarding time and age are consistent with those of other studies (22). A statistically significant relationship between age and the serum creatinine levels was found in some reports (22, 23). In our research, no significant association was found between the recipient's gender and the serum creatinine values. However, a previous study found that male patients have inferior kidney function when compared to females (22).

The main finding of the current study is the direct association between serum creatinine levels and graft failure, which means that graft failure is more likely to occur in patients with higher serum creatinine levels. A one unit increase in the serum creatinine level suggests an increased risk of graft failure of up to 5.13 times. Therefore, measuring the serum creatinine levels in order to monitor the outcome of renal transplantation is a very important issue. In general, there is agreement between studies in the nephrology field regarding the role of the serum creatinine level in the likelihood of experiencing graft failure following renal transplantation (24, 25).

The main advantages of this study were the investigation of the influential parameters on both the longitudinal serum creatinine levels and the time to graft failure outcomes following renal transplantation, as well as the evaluation of the dependence between the serum creatinine levels and graft failure through the simultaneous joint model. Additionally, in the current study the existing methods for joint modeling were modified to produce more efficient estimates of the model parameters in the presence of outlying observations in the serum creatinine levels.

Only a few prior studies have focused on the factors that influence the serum creatinine levels over time (22).

5.1. Limitations

There were some missing values in the records of the serum creatinine levels for some transplantation patients. Thus, we were forced to ignore such patients.

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Footnotes

Authors' Contribution: All authors' contributed equally to this study.

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