Original Article

Multivariate Longitudinal Assessment of Kidney Function Outcomes on Graft Survival after Kidney Transplantation Using Multivariate Joint Modeling Approach: A Retrospective Cohort Study

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Received: 10 August 2019
Revised: 22 January 2020
Accepted: 07 March 2020

What's Known

- After kidney transplantation, key markers are measured longitudinally over time to prevent the risk of kidney failure due to the allograft rejection. These markers are correlated to ensure accurate assessment of kidney function.
- Previous studies focused mainly on joint modeling of one longitudinal marker and time-to-event (allograft rejection) data.

What's New

- The effect of multiple markers, such as serum creatinine and blood urea nitrogen, on allograft survival was evaluated by using multivariate joint models.
- The results showed that the blood urea nitrogen marker played a more important role than serum creatinine in preventing allograft rejection.

Abstract

Background: The performance of a transplanted kidney is evaluated by monitoring variations in the value of the most important markers. These markers are measured longitudinally, and their variation is influenced by other factors. The simultaneous use of these markers increases the predictive power of the analytical model. This study aimed to determine the simultaneous longitudinal effect of serum creatinine and blood urea nitrogen (BUN) markers, and other risk factors on allograft survival after kidney transplantation.

Methods: In a retrospective cohort study, the medical records of 731 renal transplant patients, dated July 2000 to December 2013, from various transplant centers in Mashhad (Iran) were examined. Univariate and multivariate joint models of longitudinal and survival data were used, and the results from both models were compared. The R package joineRML was used to implement joint models. P values <0.05 were considered statistically significant.

Results: Results of the multivariate model showed that allograft rejection occurred more frequently in patients with elevated BUN levels (HR=1.68, 95% CI: 1.24-2.27). In contrast, despite a positive correlation between serum creatinine and allograft rejection (HR=1.49, 95% CI: 0.99-2.22), this relationship was not statistically significant.

Conclusion: Results of the multivariate model showed that longitudinal measurements of BUN marker play a more important role in the investigation of the allograft rejection.

Introduction

Chronic kidney disease causes gradual loss of kidney function, leading to the so-called end-stage renal disease (ESRD). At this advanced stage, kidney transplantation is the main treatment modality to improve patients' quality of life and reduce mortality.[1, 2] Considering the high prevalence of ESRD, it is important to address the social impact and financial burden of this medical condition.[3]

Kidney transplantation is performed under specific conditions, as it is often difficult, and at times impossible to find a compatible kidney for patients in need of a transplant. Therefore, it is important to identify risk factors associated with graft failure, most of which are predictable and preventable. One such risk factor is the rejection of a donated kidney due to the renal allograft failure.[4] To assess the progression of renal disease in transplant patients, kidney markers such as blood urea nitrogen (BUN), serum creatinine, and glomerular filtration rate (GFR) are measured periodically after transplantation.[5,6] These markers are measured over time to monitor changes in their levels and to prevent the risk of kidney failure due to allograft rejection.

While some tend to give a prognosis solely based on the baseline measure of these markers, the advantages of repeated measurements over an extended period of follow-up have been reported.[7] The true potential of a marker in determining severity of the disease and subsequent prognosis can only be illustrated with longitudinal measurements.[8] In fact, physicians require access to both baseline and follow-up data to accurately determine the progress of a disease and provide an accurate prognosis.[9] However, the main challenge is to correctly relate longitudinal measurements of kidney markers to the prognosis.

A useful tool to analyze such data is the time-dependent Cox model.[10] In this model, it is assumed that longitudinal outcomes are measured over time and without error. However, given that longitudinal outcomes are measured periodically, and the generated errors are not considered, the hypotheses of this model are violated.[11] An alternative method is to use joint models of longitudinal and time-to-event data. Joint models calculate the dependence between the longitudinal and survival process and provide estimates with reduced standard error. With a more accurate estimate of parameters, valid conclusions can be drawn regarding the impact of covariates on the longitudinal and survival process.[12] A previous study, using theoretical and simulated data, demonstrated the advantages of joint models over the time-dependent Cox model.[13]

In practice, the collected data often have a more complex structure, including several longitudinal responses.[14,15] There are some advantages in simultaneous modeling of multiple longitudinal responses in joint models over individual modeling of each longitudinal response. First, for correlated longitudinal responses, the adjusted estimation of each longitudinal response is more appropriate with the risk of occurrence of the event.[16] In other words, by measuring multiple longitudinal variables, the relationship between a longitudinal variable and time-to-event data with or without the effect of other longitudinal variables may vary greatly. Second, the predictive ability of joint models would significantly increase when the correlation between longitudinal variables is taken into account.[16,17] Several studies also showed bias in the estimated parameters, if the correlation between longitudinal variables and the separate fitting of joint models for each longitudinal outcome is ignored.[6,14] The multivariate joint model has become an attractive tool in medical research, as it provides physicians with a good insight in the dynamics of the underlying disease and to opt for the most appropriate treatment at any given time during follow-up.

Accurate assessment of kidney function requires a correlation between the measured serum creatinine and BUN markers, since each marker can be influenced by the demographic and physiological characteristics of a patient.[18,19] Current studies on renal diseases have mainly focused on methodological development and clinical application of the multivariate joint model.[5,15,16,20,21] To the best of our knowledge, no study has previously evaluated the effect of multiple markers and other risk factors on allograft survival. Hence, using the multivariate joint model, this study aimed to determine the simultaneous longitudinal effects of serum creatinine and BUN markers, in combination with other risk factors on allograft survival after kidney transplantation.

Materials and Methods

In a retrospective cohort study, medical records of 731 recipients of kidney transplants, dated July 2000 to December 2013, from various transplant centers in Mashhad (Iran) were examined. An accurate estimate of allograft survival was anticipated, since the patients were followed up for two years after kidney transplantation. Initial assessment of the records led to the exclusion of 113 patients, because they had less than three months of follow-up, had other types of organ transplants, or had kidney transplants more than once. Eventually, the medical records of 618 recipients of kidney transplants were included in the study. Allograft failure was defined as creatinine levels >6 mg/dL for more than three months or clinical diagnosis, and the need for peritoneal dialysis or hemodialysis.

The records showed that the serum creatinine and BUN levels of the patients were measured longitudinally over time. These

repeated measurements (longitudinal variables) were important indicators in the analysis of allograft survival and were used as response variables in the longitudinal sub-model of the joint modeling process. The included risk factors of the recipients were age, sex, donor source, history of hypertension (systolic hypertension >140 mmHg or diastolic hypertension >90 mmHg), serum creatinine level within one month after transplantation, duration of dialysis, types of immunosuppressant drugs (patients receiving prednisolone, CellCept®, and cyclosporine were assigned to group A, and those receiving prednisone, cyclosporine, and imuran to group B), and body mass index (BMI) on the last visit. Patients with BMI <18.5 were considered as underweight, 18.5≤BMI≤24.9 as normal, and >24.9 as overweight.

To analyze longitudinal and survival data, multivariate mixed-effects models were used for longitudinal multivariate responses, and the Cox model for the time-to-event response was used to evaluate the relationship between explanatory variables and response variables.[11]

Longitudinal Models

The l-th longitudinal data sub-model is given by:

$$y_l(t_i)=y_l^*(t_i)+\epsilon_{il}=X_l^T(t_i)\beta_l+Z_l^T(t_i)b_{il}+\epsilon_{il} \qquad (1)$$

Where $y_l^*(t_i)=(y_l(t_{i1}),\ y_l(t_{i2}),\ ...,\ y_l(t_{in_i}))^T$ is the corresponding true underlying longitudinal measures of l–th biomarker ($l=1, ..., L$) for the i–th subject ($i=1, ..., n$) at time points t_{ij} ($j=1, ..., n$), where n and n_i are the number of subjects and number of longitudinal repeated measures for each subject respectively.

$X_l^T(t_i)$ is the design matrix of fixed effects; $Z_l^T(t_i)$ is the design matrix for the random effects, $b_i=(b_{i1},\ b_{i2},\ ...,\ b_{il})^T \sim N(0,\ D)$; measurement error is distributed as $\epsilon_{il} \sim N(0,\ \sigma_l^2\ I_{ni})$.

In the variance-covariance matrix of random effects D, the between- and within-subject correlations for longitudinal markers are represented.

The Survival Model

Let T_i^* be the true event time and C_i be the censoring time for the i-th subject, respectively. The observed event time is $T_i=min\ (T_i^*,\ C_i)$, and the event indicator is $\delta_i=min\ (T_i^*,\ C_i)$. The hazard function can be written as:

$$h(t_i) = h_0(t) \exp\left\{\gamma^T w_i + \sum_{l=1}^{L} \alpha_l\ y_l^*(t_i)\right\} \qquad (2)$$

Where $h_0(t)$ denotes the baseline hazard function, and α_l and γ are coefficients for the function of the l-th biomarker and baseline risk

factors. The correlation between the multivariate mixed-effects models and time-to-event sub-models is induced by the shared random effects through $y_l^*(t_i)$.

In addition, a separate joint analysis of each of the longitudinal markers was considered for the survival response. An important assumption in using mixed-effects models is that the observations of longitudinal responses are normal. Due to the lack of normal distribution of BUN marker observations, we used the square transformation of this marker. In the analysis of joint models, if one or more observations are missing for any of the variables used in the analysis for an individual, then all the relevant information for that individual is excluded from the study, ultimately leading to a reduction in sample size and bias in the results. Therefore, the estimation of missing observations was initially conducted using the multiple imputation method. Parameter estimates and inferences were then made using the maximum likelihood method, and based on the expectation-maximization algorithm.

The R package joineRML (version 3.3.2) was used to implement the joint models. P values <0.05 were considered statistically significant. The study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (code: IR.MUMS.REC.1395.232).

Results

A total of 618 medical records of recipients of kidney transplants were analyzed. Among the patients, who were followed up during the 13 years, 35 (5.66%) cases had irreversible transplant rejection leading to dialysis and death occurred in 7 (1.13%) of the cases. The median time of patient follow-up was 6.36±4.97 years. The demographic and clinical characteristics of the patients are presented in table 1.

For each patient, the longitudinal profiles of the square root of BUN and serum creatinine with respect to the event status are presented in figure 1. The fitted curves represent moderate population profiles for the event and non-event groups using linear mixed-effects models. We observed that the mean population of BUN and serum creatinine markers measured over time was larger in the event group than the non-event group. This indicated the potential association between the risk of occurrence, and the longitudinal measurements of BUN and serum creatinine. The difference in marker values at the beginning of the study was negligible between the groups. Therefore, by only using the baseline values of BUN and serum creatinine markers, the analysis may not detect

Table 1: Demographic and clinical characteristics of renal transplant patients

Variables		Event	Non-event	Total	Variables		Event	Non-event	Total
		N (%)		N			N (%)		N
Sex	Male	25 (59.52)	316 (54.86)	618	Donor source	Living donor	27 (67.50)	393 (71.07)	593
	Female	17 (40.48)	260 (45.14)			Deceased donor	13 (32.50)	160 (28.93)	
Age	≤40	35 (85.37)	374 (66.20)	606	BMI	Underweight	6 22.22)	27 (7.28)	398
	>40	6 (14.63)	191 (33.80)			Normal	15 (55.56)	182 (49.06)	
Serum creatinine after transplantation	≤1.6	24 (57.14)	479 (83.16)	618		Overweight	6 (22.22)	162 (43.66)	
	>1.6	18 (42.86)	97 (16.84)		Months of pre-transplantation dialysis	≤24	33 (82.50)	414 (76.24)	583
Hypertension	Yes	26 (61.91)	243 (42.19)	618		>24	7 (17.50)	129 (23.76)	
	No	16 (38.09)	333 (57.81)		Types of immu-nosuppressant drugs	A	36 (85.71)	546 (94.79)	618
						B	6 (14.29)	30 (5.21)	

BMI: Body Mass Index; A: Patients receiving prednisolone, CellCept®, and cyclosporine; B: Patients receiving prednisone, cyclosporine, and Imuran
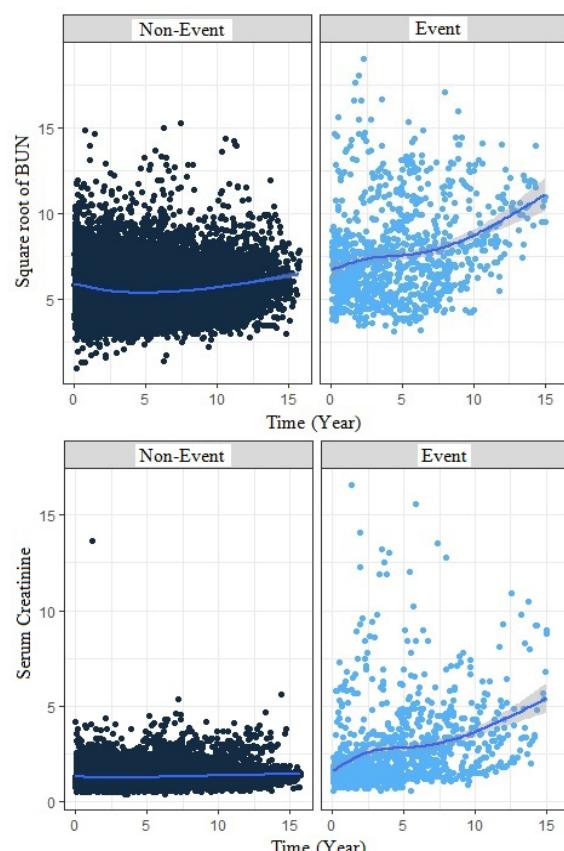
Figure 1: Longitudinal profiles of the square root of BUN and serum creatinine with respect to the event status. The curves represent moderate population profiles for the event and non-event groups. The mean population of BUN and serum creatinine markers measured over time was larger in the event group than the non-event group. This indicated the potential association between the risk of occurrence and the longitudinal measurements of BUN and serum creatinine.

any relationship between the marker values and the risk of allograft failure.

The missing observations were estimated using the multiple imputation method. In the first stage, a univariate linear mixed-effects model was used to identify the effective variables in the longitudinal markers (BUN and serum creatinine). The Cox multivariate regression model was used to identify the factors affecting allograft survival. Variables with P<0.15 were used in the analysis of joint models. In the final stage of statistical analysis, univariate and multivariate joint models were fitted to the data. The results of the univariate joint model fitted to the serum creatinine and BUN markers are shown in table 1. Moreover, the results of the multivariate joint models fitted to both markers are shown in table 2.

Risk Factors Associated with Serum Creatinine Levels

There was a significant increasing linear trend in creatinine values over time in the univariate (P<0.001) and multivariate (P=0.008) models. Furthermore, female patients had lower serum creatinine levels in both univariate and multivariate models (P<0.001). After transplantation, serum creatinine greater than 1.6 mg/dL had a significant positive effect on the creatinine value over time in the univariate (P=0.013) and multivariate (P=0.025) models. Based on the univariate model, the BMI was significantly positively correlated with higher values of creatinine levels over time (P=0.004 and P=0.014, respectively) (table 2). Based on the multivariate model, an increase in the BMI of recipients of kidney transplants led to an increase in the serum creatinine level over time. However, the increase was not statistically significant (P=0.207 and P=0.164, repectively) (table 3). The donor source (living or deceased donor)

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Table 2: The results of univariate joint modeling of serum creatinine level, square root of blood urea nitrogen level, and time to graft failure

Longitudinal sub-model for serum creatinine				
Variables	**Coefficient**	**S.E**	**95% CI**	**P value**
Intercept	0.93	0.11	(0.72, 1.14)	<0.001
Observation time	0.11	0.03	(0.04, 0.17)	<0.001
Sex (female)	-0.31	0.06	(-0.44, -0.19)	<0.001
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.17	0.07	(0.04, 0.31)	0.013
BMI (kg/m^2)				
Normal weight versus underweight	0.27	0.09	(0.09, 0.46)	0.004
Overweight versus underweight	0.25	0.10	(0.05, 0.46)	0.014
Donor source (deceased versus living)	0.15	0.08	(-0.02, 0.31)	0.084
Survival sub-model for serum creatinine				
Variables	**Coefficient**	**S.E**	**HR (95% CI)**	**P value**
Association parameter	0.92	0.06	2.51 (2.25, 2.80)	<0.001
Age of recipients (years) (≥40 versus <40)	-0.95	0.55	0.39 (0.13, 1.13)	0.082
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.41	0.42	1.50 (0.66, 3.42)	0.336
Hypertension (Yes versus No)	1.46	0.38	4.31 (2.04, 9.10)	<0.001
Longitudinal sub-model for the square root of BUN				
Variables	**Coefficient**	**S.E**	**95% CI**	**P value**
Intercept	5.02	0.12	(4.78, 5.27)	<0.001
Observation time	0.13	0.02	(0.09, 0.17)	<0.001
Sex (female)	-0.44	0.13	(-0.68, -0.19)	<0.001
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.56	0.16	(0.24, 0.87)	<0.001
Months of pre-transplantation dialysis (>24 months versus ≤24 months)	0.36	0.14	(0.10, 0.63)	0.008
Hypertension (Yes versus No)	0.32	0.13	(0.60, 0.57)	0.016
Types of immunosuppressant drugs	-0.55	0.06	(-0.68, -0.43)	<0.001
Survival sub-model for the square root of BUN				
Variables	**Coefficient**	**S.E**	**HR (95% CI)**	**P value**
Association parameter	0.86	0.05	2.35 (2.15, 2.57)	<0.001
Age of recipients (years) (≥40 versus <40)	-1.93	0.44	0.15 (0.06, 0.35)	<0.001
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.30	0.42	1.35 (0.60, 3.06)	0.473
Hypertension (Yes versus No)	1.72	0.41	5.57 (2.49, 13.23)	<0.001

BMI: Body mass index; BUN: Blood urea nitrogen; S.E: Standard error; HR: Hazard ratio

variable in both univariate (P=0.084) and multivariate (P=0.110) models were not statistically significant (tables 2 and 3).

Risk Factors Associated with BUN Levels

In both univariate and multivariate models, there was a significant increasing linear trend in BUN values over time (P<0.001). Female patients had lower BUN levels than males (P<0.001). After transplantation, serum creatinine greater than 1.6 mg/dL had a significant positive effect on BUN levels over time in both univariate (P<0.001) and multivariate (P=0.037) models. Before transplantation, dialysis for more than 24 months was associated with higher levels of BUN over time in both univariate (P=0.008) and multivariate (P=0.023) models. High blood pressure was also significantly associated with increased BUN levels in both univariate

(P=0.016) and multivariate (P=0.021) models. In both univariate and multivariate models (P<0.001), the levels of BUN marker for the recipients of type B immunosuppressant drugs decreased significantly over time compared with the recipients of type A drugs (tables 2 and 3).

Risk Factors for Time to Graft Failure

In terms of graft failure risks, there was no significant difference in the age of patients (hazard ratio [HR]=0.39, 95% CI: 0.13-1.13) in the univariate joint model with serum creatinine as a marker (table 1). However, this variable was significant in the univariate joint model (HR=0.15, 95% CI: 0.06-0.35) (table 2) and multivariate joint model (HR=0.26, 95% CI: 0.08-0.87) with BUN as a marker (table 3). Serum creatinine after transplantation was not significant in either model. Patients with high blood pressure had

Table 3: The results of multivariate joint modeling of the serum creatinine level, square root of blood urea nitrogen level, and time to graft failure

Variables	Coefficient	S.E	95% CI	P value
Longitudinal sub-model serum creatinine				
Intercept	1.04	0.12	(0.80, 1.27)	<0.001
Observation time	0.10	0.04	(0.03, 0.18)	0.008
Sex (female)	-0.31	0.07	(-0.44, -0.17)	<0.001
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.16	0.07	(0.02, 0.30)	0.025
BMI (kg/m^2)				
Normal weight versus underweight	0.13	0.11	(-0.07, 0.34)	0.207
Overweight versus underweight	0.16	0.11	(-0.07, 0.38)	0.164
Donor source (deceased versus living)	0.12	0.07	(-0.02, 0.26)	0.110
Longitudinal sub-model the square root of BUN				
Variables	Coefficient	S.E	95% CI	P value
Intercept	5.07	0.14	(4.79, 5.35)	<0.001
Observation time	0.16	0.04	(0.08, 0.24)	<0.001
Sex (female)	-0.45	0.13	(-0.70, -0.20)	<0.001
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.33	0.16	(0.02, 0.64)	0.037
Months of pre-transplantation dialysis (>24 months versus ≤24 months)	0.26	0.11	(0.04, 0.48)	0.023
Hypertension (Yes versus No)	0.23	0.10	(0.04, 0.43)	0.021
Types of immunosuppressant drugs	-0.56	0.06	(-0.68, -0.43)	<0.001
Survival sub-model				
Variables	Coefficient	S.E	HR (95% CI)	P value
Association parameter (serum creatinine)	0.40	0.20	1.49 (0.99, 2.22)	0.051
Association parameter (square root of BUN)	0.52	0.15	1.68 (1.24, 2.27)	<0.001
Age of recipients (years) (≥40 versus <40)	-1.35	0.62	0.26 (0.08, 0.87)	0.029
Female versus male serum creatinine after transplantation (mg/dL) (≥1.6 versus <1.6)	0.09	0.56	1.09 (0.37, 3.26)	0.870
Hypertension (Yes versus No)	1.60	0.49	4.94 (1.89, 12.90)	0.001

BMI: Body mass index; BUN: Blood urea nitrogen; S.E: Standard error; HR: Hazard ratio

a higher risk of graft failure (HR=4.94, 95% CI: 1.89-12.90) in the multivariate joint model (table 3). Moreover, this variable was significant in both univariate joint models. Additionally, in the multivariate joint model, the significant model association parameter revealed a positive correlation between BUN levels and graft failure (HR=1.68, 95% CI: 1.24-2.27) (table 3). This indicated that graft failure was more likely to occur in patients with higher BUN levels. The association parameter was also significant in the univariate joint model (HR=2.35, 95% CI: 2.15-2.57) (table 2). In the multivariate joint model, unlike the univariate joint model (HR=2.51, 95% CI: 2.25-2.80) (table 2), the association parameter was not significant despite a positive correlation between serum creatinine levels and graft failure (HR=1.49, 95% CI: 0.99-2.22) (table 3).

Correlation Between Multiple Longitudinal Data

The difference in deviance was used to determine the significance of a given effect. Deviance is defined as twice the difference in the maximized log-likelihood between models with and without the inclusion of the effect of the assessed parameters. The association between the square root of BUN and serum creatinine was examined by setting D12 elements in the covariance matrix to zero. This resulted into a difference in deviance of 605.06 with nine degrees of freedom, indicating a significant correlation between the two longitudinal variables.

Discussion

According to the analysis of the patients' data, we found that the results obtained from a model based on multivariate longitudinal markers of both BUN and serum creatinine differed from the two separate univariate analysis of each marker. We also found a direct association between BUN levels and allograft rejection, indicating a greater possibility of transplant rejection in patients with higher levels of BUN. In comparison with the results obtained from the univariate joint model, the effect of serum creatinine was not statistically significant in the multivariate model.

Compared to joint models with univariate longitudinal data, joint models with multivariate

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longitudinal data correlated longitudinal values of these markers to generate more accurate estimates, and control for type 1 error that might emanate from a univariate analysis when conducted without accounting for multiple comparisons.[6, 19, 22] Lin and colleagues showed that if the correlation between multiple longitudinal variables is negligible, the result of joint models with longitudinal multivariate variables should be similar to that of univariate joint models with each marker taken into account separately.[23] Therefore, the reported effect size from serum creatinine level in the multivariate model might be more reliable and comprehensive than in the univariate model as it includes the correlation between markers.

The results of the multivariate model showed that the BUN marker had a greater impact on the risk of transplant rejection than the serum creatinine marker. In addition, the levels of BUN marker increased slowly over time (beta=0.158, P=0.001). Therefore, repeated measurements of BUN levels are important to monitor the outcome of kidney transplants.

Based on our literature review, no study has previously investigated the effect of BUN as a longitudinal marker on kidney transplantation. Most studies evaluated the cross-sectional effect of serum creatinine, which is one of the most important risk factors, on allograft survival.[24, 25] In the present study, the effect of creatinine after transplantation was not statistically significant. This could be due to the effect of this variable as a longitudinal marker on allograft survival. Studies that examined the impact of this variable longitudinally, reported a significant risk of allograft rejection in patients with a higher level of creatinine than in other patients.[1, 26]

The age of recipients was an important factor affecting the allograft survival rate. In line with other studies, our results showed that the risk of rejection in the older age group was lower than in the younger age group.[27, 28] In contrast, some other studies reported either no significant relationship between age and survival rate[29, 30] or reduced survival rate with an increase in age.[31, 32] High blood pressure was also found to be one of the main causes of ESRD and an indicator of increased risk of rejection. This was in line with the finding of some studies,[33, 34] but in contrast to a report by Veroux and colleagues.[32]

The main strength of the present study is the evaluation of the effect of multiple longitudinal markers (serum creatinine and BUN) on allograft survival using multivariate joint models. However, the study is subject to three main limitations. First, estimation of survival rates and the associated prognostic factors require reliable sources in the form of a prospective study, whereas we performed a retrospective cohort study using medical records of patients. Second, some medical records were excluded from the study due to loss to follow-up of the patients. This negatively affected our findings, since transplant rejection, as one of the important parameters in our study, was not available for those patients. Third, the records were often incomplete with regard to some important variables such as ischemic time, age, cause of ESRD, and human leukocyte antigen typing of patients. Consequently, we were unable to assess their effect on the allograft survival rate.

Conclusion

The results of the multivariate model showed that the BUN marker played a more important role than serum creatinine in investigating allograft rejection. Elevation of BUN marker in transplant patients can be prevented by monitoring variables such as sex, serum creatinine level after transplant, dialysis period before transplant, history of hypertension, and types of drugs.

Acknowledgment

Conflict of Interest: None declared.

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