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Assessing Risk Indicators of Allograft Survival of Renal Transplant: An Application of Joint Modeling of Longitudinal and Time-to-Event Analysis

Hojjat Sayyadi,[1] Farid Zayeri,[1,*] Ahmad Reza Baghestani,[1] Taban Baghfalaki,[2] Ali Taghizadeh Afshari,[3] Mohsen Mohammadrahimi,[3] Javid Fereidoni,[4] and Khadijeh Makhdoomi[5]

[1]Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[2]Department of Statistics, Faculty of Mathematical Sciences, Tarbiat Modares University, Tehran, IR Iran
[3]Department of Kidney Transplantation, School of Medicine, Urmia University of Medical Sciences, Urmia, IR Iran
[4]Department of English Language, School of Medicine, Urmia University of Medical Sciences, Urmia, IR Iran
[5]Department of Nephrology, Nephrology and Kidney Transplant Research Center, Urmia University of Medical Sciences, Urmia, IR Iran

[*]*Corresponding author*: Farid Zayeri, Department of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122707347, E-mail: fzayeri@yahoo.com

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Abstract

Background: After kidney transplantation, many risk factors can lead to graft rejection and force the patient to return to dialysis treatment.
Objectives: This study aims to identify risk indicators of renal graft failure, such as serum creatinine, on long-term graft survival, using a novel statistical technique.
Methods: In this historical cohort study, 129 patients who underwent kidney transplants were assessed and followed up from September 2003 to December 2014 in Urmia, Iran. The main outcome of the study was assessing the survival rate of kidney transplant in these subjects. In addition, the serum creatinine levels were measured repeatedly for one year after the operation, as the most important risk indicator of graft failure. In addition, the effect of other indicators on graft survival were assessed using a joint modeling of longitudinal and survival technique, using the R software, version 3.0.2.
Results: One-, three-, five-, and ten-year graft survival was 93.8%, 86.8%, 76.6%, and 37.4%, respectively. The results of the joint model showed that risk indicators, such as serum creatinine level ($P < 0.0001$, HR = 1.82), patient's age ($P = 0.006$, HR = 1.03), and anti-thymocytes globulin ($P = 0.019$, HR = 2.57) had a significant relationship to graft survival.
Conclusions: In general, our study showed that short-term graft failure in Iran is almost equal to the reported rates in some developed countries, but its long-term failure is rather high compared to these same countries. In this context, monitoring the post-operative risk indicators of graft rejection, such as the serum creatinine level, plays an important role in increasing the survival rate of kidney transplantation. The present model can be used to design similarly structured datasets.

Keywords: Risk Factors, Kidney Transplantation, Survival Analysis, Joint Modeling

1. Background

Chronic renal failure is defined as a glomerular filtration index rate of less than 60 mL/minute in 1.73 m^2 of body area for at least three months. It is a public health problem with a significant financial burden (1). Recent research indicates that 10% to 15% of American adults were diagnosed with chronic renal failure in 2009 (2). The rate of diagnosis was 11.2%, 10.1%, and 18.7% for Australia, Singapore, and Japan, respectively, in 2006 (3-5). In Iran, the number of patients with progressive renal disease was 25,000 in 2006, with an annual increase of approximately 12%. It is also predicted that, by the end of 2016, the prevalence and incidence of end-stage renal disease patients (ESRD) will be 357 and 57 subjects per million, respectively (6).

The main causes of long-term graft loss are chronic kidney dysfunction, recurrence of glomerulonephritis, and death from other health problems (except those related to kidney functioning) (7, 8). Moreover, chronic graft loss has immunologic and non-immunologic causes. The immunological factors are leukopenia and human leukocyte antigen (HLA) type, while the donor's non-immunologic factors include type of donor (e.g., living or cadaver) and donor's age and race. Also, the recipient's immunological factors include serum creatinine level, hemodynamic status, age, sex, race, and health complaints, such as hyperuricemia, acute tubular necrosis, heart attack, hypertension, and diabetes (9).

In practice, three categories of treatment are available for these patients: hemodialysis, peritoneal dialysis, and

kidney transplantation. Recent studies show that kidney transplantation is the most effective therapy for ESRD patients. It reduces the risk of mortality and enhances patients' quality of life (10). Living donors (relative or non-relative) and cadavers are the usual sources for kidney transplantation (11). In this context, the variety of research shows that the survival rate of a transplant received from a living donor is significantly higher than from a deceased donor (12, 13). In the past two decades, the short-term outcomes of transplant have improved notably, while the long-term outcomes have not remarkably improved.

In many medical studies, the common objective is to estimate the time between an intervention (such as surgery, chemotherapy, or transplantation) and the occurrence of an event (such as full recovery, death, or recurrence of a disease). The statistical method used for such data is known as survival analysis. The goals of survival analysis can be divided into three categories: estimation and interpretation of risk (hazard) and survival functions, comparison of the survival and hazard functions, and assessment of the relationship between predictor variables and survival time. In some studies, in addition to recording the time-to-event data (as a primary response variable), some of the other variables affecting the survival time (which, in turn, are influenced by a variety of risk factors and markers) are measured repeatedly over time. These longitudinal markers play a mediating role in such analysis. They play the role of predictor variable, for better description of the main outcome variable (for instance, the survival of the patients). At the same time, they are influenced by other indicators, and thus act as the secondary outcome variable.

In this context, recent considerable attention has been focused on so-called joint models. In comparison with separate analysis of survival and longitudinal data, the joint model gives us more accurate estimates for assessing the effect of covariates under study. In the joint modeling field, usually a linear mixed effects model is applied for the longitudinal analysis and a Cox regression model is used for the survival portion of the data (14).

Foroushani et al., in 2015, assessed long-term kidney graft failure and evaluated the risk factors of graft survival of patients who had malignancy after transplantation (15). Ghanei et al., in a historical cohort study, evaluated short- and long-term graft survival of patients who underwent kidney transplants from living or deceased donors. They assessed the serum creatinine level only for one month after transplantation. They reported that the age and sex of the donor, along with the serum creatinine level of the recipient, were the most important factors affecting the graft survival rate (16). Morales et al., in a multi-center study, reported the risk factors for graft loss and mortality after renal transplantation based on patient age. They found that the main causes of graft loss were chronic allograft dysfunction in younger patients and death with functioning graft in older patients. They also reported the significance of elevated creatinine levels more than 1g at six months post-transplantation (17). Ghoneim et al., in their single-center study, showed that some factors, such as donor's age, genetic considerations, type of primary immunosuppression, number of acute rejection episodes, and total steroid dose during the first three months after transplantation affect the kidney graft survival of subjects (18).

In our literature review, we did not find any published articles about assessing the longitudinal effect of creatinine level on long-term graft survival of patients after renal transplantation using the joint modeling of longitudinal and time-to-event data framework. Thus, we decided to conduct the present study in a sample of patients in the kidney transplantation center in the Urmia University of Medical Sciences in northwest Iran. The novelty of our work is the use of a complex and powerful statistical model for analyzing this complicated data.

2. Objectives

In this study, by using the joint modeling approach, our focus was on two main objectives: to estimate the ten-year graft survival rate of the patients after renal transplantation and to determine the longitudinal effect of serum creatinine level and other indicators on graft loss in these patients.

3. Methods

3.1. Study Sample

In this historical cohort study, a total number of 129 files of patients who were referred to the kidney transplant center of the Imam Khomeini Hospital of Urmia University of Medical Sciences during 2003 to 2014 were studied. The inclusion criteria were 1) patients who had kidney transplant surgery during 2003 to 2014 in the above-mentioned transplant center, 2) registration of 12 repeated measures of serum creatinine level after surgery and, 3) complete registration of the covariates under study. Patients' files with incomplete records were excluded from the study (less than 10% of the files). The sample size was computed using the STATA software, version 11 (sample size for Cox proportional hazard model) with type I error = 0.05, test power = 0.90, hazard ratio for the creatinine level of 1.4 (estimated from a pilot study) and standard deviation = 1.0. The obtained sample size was about 93 subjects and, considering 20% missing or lost to follow up, at least a sample

of 112 subjects were added for assessing the effect of creatinine level on the survival of renal grafts as the main outcome of the study. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Human Research Committee of the Urmia University of Medical Sciences (ethical code: ir.umsu.rcc.1392.233, Date: January 2014). Figure 1 shows the flowchart of the study.

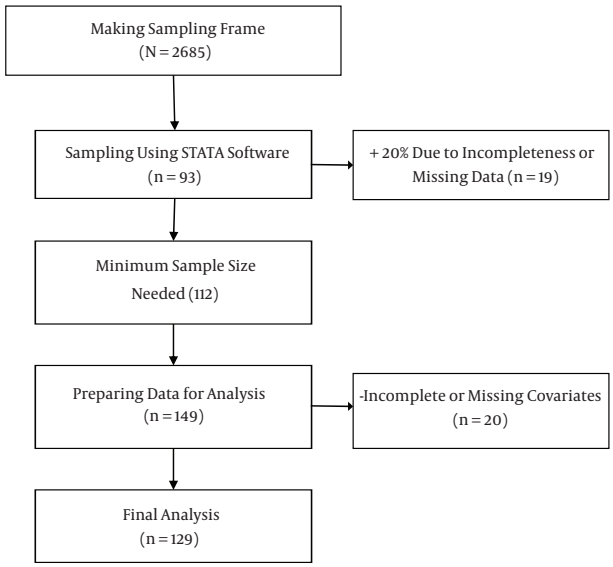

Figure 1. Flow Diagram of Sampling Process

3.2. Variables Under Study

In the present study, the main outcome was the kidney transplant survival time. The time between surgery and total graft loss and return to dialysis was determined as the survival time. The patients who did not experience graft loss were considered the censored. In addition, the serum creatinine level of the patients was recorded monthly, using urine and blood tests, for one year after transplantation. This repeated measure (the longitudinal variable) was one of the most important indicators of the survival of the transplant in the survival analysis. It also was used as the outcome variable in the longitudinal portion of the modeling process.

Moreover, other risk indicators, such as the type of kidney donor, recipient's age and sex, anemia, type of medication, diabetes, and anti-thymocyte globulin, as well as complications after transplantation, such as proteinuria, hyperkalemia, hyperuricemia, leukopenia, myocardial infarction, delayed graft function, acute tubular necrosis, urinary tract infection, chronic allograft necrosis, dyslipidemia, liver dysfunction, and hypercalcemia, were included as the explanatory variables in the statistical models.

3.3. Statistical Analysis

As mentioned, a joint analysis of survival and longitudinal data was used to assess the relationship between explanatory variables and the response variable. To illustrate the joint model, let Y_{it} denote the t^{th} repeated observation for i^{th} subject under study (I = 1, 2,…, n; t = 1, 2,…, T_i) and X_{it} and Z_{it} are the p-dimensional and q-dimensional ($q \leq P$) covariate vectors for the fixed and random part of the model. Thus, the following linear mixed effect model can be written for analyzing the longitudinal part of the statistical model:

$$Y_{it} = x'_{it}\beta_1 + z'_{it}b_i + \varepsilon_{it}$$

where β_1 is a p-dimensional longitudinal fixed effect parameter and b_i is a q-dimensional random effect. As usual, ε_{it} shows the error term for i^{th} subject in t^{th} situation. In addition, let T_i indicate the observed survival time for subject i ($T_i = \min [T_i^*, C_i]$) where T_i^* is true event time and C_i is the censoring time. The following model was assumed for the time-to-event (survival) part of the statistical model.

$$h(t_i) = h_0(t) \exp [x'_{it}\beta_2 + \alpha Y_{it}]$$

where $h_0(t)$ is the baseline hazard function, β_2 is a P_2-dimensional vector of survival fixed effects parameters, and α is a coefficient called shared parameter that must be significant in the context of joint modeling. This modeling process enables us to assess the effect of the variety of explanatory variables on the longitudinal and survival parts of the joint model simultaneously, while assessing the effect of longitudinal outcome on the time-to-event (survival) part. The JM package in open source R software, version 3.0.2, was utilized for fitting the described joint model (19).

4. Results

In this historical cohort study, 129 patients who received kidney transplants from live donors from September 2003 to December 2014 were enrolled in the study. A total of 79 patients (62.7%) were male and 47 (37.3%) were female, and 93 patients (72%) had hypertension. In addition, 14 donors (10.9%) were relatives, and three patients suffered a heart attack after transplantation. The mean (SD) age, weight, and follow-up time (years) of the subjects was 39.18 (1.216), 57.0 (1.0), and 6.7 (1.8), respectively. Table 1 shows other characteristics of the patients under study. In addition, Table 2 shows descriptive statistics about the monthly trend of creatinine levels of the patients during the first year after transplantation.

Table 1. Characteristics of the Patients

Variables	Category	Frequency (%)
Delayed graft function	Yes	4 (3.1)
	No	125 (96.9)
Acute tubular necrosis	Yes	7 (5.4)
	No	122 (94.6)
Myocardial infarction	Yes	3 (2.4)
	No	123 (97.6)
Urinary tract infection	Yes	69 (54.8)
	No	57 (45.2)
Chronic allograft necrosis	Yes	88 (68.2)
	No	41 (31.8)
Hyperuricemia	Yes	78 (61.9)
	No	48 (38.1)
Atg	Yes	25 (19.4)
	No	104 (80.6)
Proteinuria	Yes	84 (65.1)
	No	45 (34.9)
Hyperkalemia	Yes	8 (6.2)
	No	121 (93.8)
Liver dysfunction	BIL-T	51 (39.5)
	BIL-D	78 (60.5)
Dyslipidemia	TG	106 (82.2)
	CHOL	23 (17.8)
Hypercalcemia	Yes	22 (17.1)
	No	107 (82.9)
Anemia	Yes	63 (48.8)
	No	66 (51.2)
Diabetes	Yes	28 (21.7)
	No	101 (78.3)

The mean (SD) serum creatinine levels at all time points measured in the study were 1.28 (0.86), which was reported at every month (see Table 2).

Among 129 patients under study, 63 patients (48.8%) experienced graft rejection during the follow-up period. The minimum rejection time after surgery was 15 days. The mean (SD) time of follow-up and duration of dialysis before allograft in this study was 75.2 (32.2) and 15.29 (1.22) months, respectively. The mean and median survival times were 75.2 (32.2) and 73.2 months, respectively. Preliminary analysis of time-to-event (rejection of graft) data using the Kaplan-Meier method revealed that one-, three-, five-, seven-, and ten-year survival rates of the grafts were 93.8%, 86.8%, 76.6%, 58.7%, and 37.4% respectively (Figure 2).

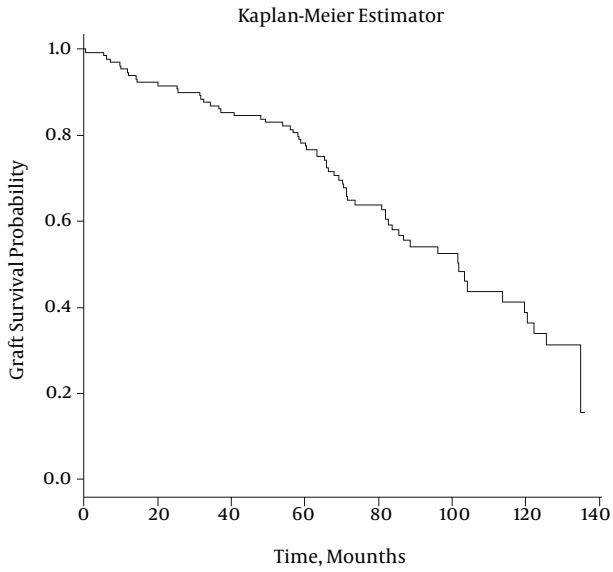

Figure 2. Survival Rate of Graft Among Patients Under Study

In the next step of data analysis, we used a univariate random intercept model to screen the potential indicators of the longitudinal section (creatinine). The univariate Cox regression model was used to screen the potential indicators of the second section (i.e., graft survival). In this stage, variables with $P < 0.15$ were included in the joint modeling of longitudinal and survival analysis.

In the final step of statistical analysis, the described joint model was fitted to the data. Table 3 shows the results of the longitudinal part of the model, and Table 4 shows the results obtained from the survival part.

In Table 3, one can observe that leukopenia, chronic allograft necrosis, and observation times were significantly associated with the creatinine levels of the patients. The interpretation of results can be performed with the estimates. For instance, the obtained estimate of -0.0132 for the observation time variable means that the mean level of creatinine decreases about 0.13 unit every month after transplantation ($P < 0.001$). In addition, the estimate of + 0.379 for the presence of leukopenia means that patients with leukopenia had a higher mean level of creatinine (about 0.38 unit) compared to those without leukopenia ($P = 0.001$).

The results obtained from the survival part of the model (Table 4), which is our main interest, show that the variables of serum creatinine level ($P < 0.001$), patient age ($P = 0.006$), and anti-thymocytes globulin treatment ($P =$

Table 2. Descriptive Statistics of Serum Creatinine in the First Year After Transplantation

Month	Min	Max	Mean	SD
1	0.6	9.1	1.410	0.8598
2	0.5	13.9	1.440	1.2849
3	0.5	5.0	1.316	0.6489
4	0.6	6.4	1.285	0.8125
5	0.6	5.5	1.202	0.6377
6	0.1	8.4	1.244	0.9984
7	0.5	8.4	1.161	0.7688
8	0.2	9.3	1.198	0.9027
9	0.1	10.6	1.240	0.9447
10	0.6	11.6	1.320	1.1766
11	0.5	2.7	1.185	0.4472
12	0.5	6.9	1.315	0.8080

Table 3. Results of Joint Model (Longitudinal Submodel with Creatinine Level as Response Variable)

Variable	Factor Level	Coefficient	SE	95% Confidence Interval	P Value
Observation times	-	-0.013	0.005	(-0.023, -0.003)	0.005
Age at transplant	-	0.002	0.003	(-0.004, 0.008)	0.609
Drug use (Azathioprine vs Cellcept)	-	-0.252	0.203	(-0.650, 0.146)	0.215
Sex	Female	-0.115	0.090	(-0.291, 0.061)	0.202
	Male	reference category			
Hyperkalemia	Yes	0.098	0.219	(-0.331, 0.527)	0.656
	No	reference category			
Leukopenia	Yes	0.379	0.113	(0.158, 0.601)	0.001
	No	reference category			
Anemia	Yes	0.0971	0.088	(-0.075, 0.270)	0.271
	No	reference category			
Anti-thymocytes globulin	Yes	0.151	0.121	(-0.086, 0.388)	0.213
	No	reference category			
Chronic Allograft Necrosis	Yes	0.181	0.092	(0.001, 0.361)	0.049
	No	reference category			

0.019) were significantly related to graft survival. By using the exponential of the estimates, the results can be interpreted as the hazard ratios (HR column in Table 4). For creatinine level, the HR=1.82 tells us that, by any increase in creatinine levels of the patients, the hazard of graft rejection increases about 82%. In addition, by every one-year increase in patient age, the hazard of graft rejection increases approximately 3%. Finally, taking anti-thymocytes globulin increases the graft rejection hazard by about 2.5 times.

5. Discussion

In this study, we used the survival data of patients with kidney transplants to identify the short- and long-term survival of the grafts as well as to determine important risk indicators of graft rejection, using powerful statistical methods. Regarding the first objective of the present study, it was found that less than one-fourth of the grafts were rejected until five years after surgery. In addition, a little more than one-third of the grafts were re-

Table 4. Results of Joint Model (Survival Submodel) for Kidney Transplant Patients

Variable	Factor level	Coefficient	SE	95% Confidence interval	HR	P Value
Shared parameter	-	-0.045	0.019	(-0.082, -0.008)	-	0.023
Creatinine Index	-	0.600	0.120	(0.365, 0.835)	1.82	< 0.001
Age at Transplant	-	0.0280	0.010	(0.008, 0.048)	1.03	0.006
Drug use (Azathioprine vs Cellcept)	-	0.992	0.607	(-0.198, 2.182)	2.69	0.237
Donor Type	Relative	0.550	0.516	(-0.461, 1.561)	1.73	0.286
	Non relative	reference category				
Hyperuricemia	Yes	-0.179	0.309	(-0.785, 0.427)	0.836	0.561
	No	reference category				
Leukopenia	Yes	0.621	0.367	(-0.098, 1.340)	1.86	0.091
	No	reference category				
Myocardial Infarction	Yes	0.735	0.715	(-0.666, 2.136)	2.09	0.303
	No	reference category				
Acute Tubular Necrosis	Yes	-0.379	0.594	(-1.543, 0.785)	0.684	0.523
	No	reference category				
Anti-Thymocytes Globulin	Yes	0.945	0.404	(0.153, 1.737)	2.57	0.023
	No	reference category				

jected in a ten-year period after kidney transplantation. Although these findings are in agreement with several studies in Iran and other developed countries, the reports from other countries highlight that the long-term survival rate of kidney transplantation is considerably higher than our results. For instance, Ghanei et al. (2012) reported one- and five-year graft survival rates of 89% and 82.5%, respectively. Soylu et al. (2015) conducted a retrospective study in Turkey in which most of the recipients (82.6%) received their organs from living donors. One-year and five-year graft survival rates were 87.5% and 78.3%, respectively. For the 2005 to 2008 period, one-year graft survival was equal (91%) between Europeans and white and Hispanic Americans, whereas it was slightly lower for African Americans (89%). In contrast, overall five- and ten-year graft survival rates were considerably higher in Europe (77% and 56%, respectively) than for any of the three U.S. populations (whites: 71% and 46%, Hispanics: 73% and 48%, and African Americans, 62% and 34%) (16, 20, 21).

To achieve the second objective of this study, a joint modeling approach was utilized to more accurately screen the potential risk indicators of graft rejection. The findings from this model showed that repeated creatinine levels, as well as patient age and anti-thymocytes globulin, had a significant relationship to the hazard of graft rejection.

For the patient age variable, our findings revealed that the older patients had lower survival rates than the younger ones. It seems that, with increasing age, the number of nephrons reduces while atherosclerosis increases, thus it can reduce the survival of the graft.

This result is in agreement with other reports from different parts of the world. For instance, Ghanei et al. (2012) reported subjects' age as one of the most important factors for good graft survival. Also, Ghoneim et al. (2013), in their study among patients receiving kidneys from live donors, showed that recipient age had a significant negative impact on graft survival (16, 18). In contrast, other research did not find a significant relationship between patient age and graft survival. For example, Briganti et al. (2002) and Orsenigo et al. (2005) reported no significant effect of age on graft survival (7, 22).

With increasing age of patients, the rates of morbidity and mortality increase as well, thus it is necessary to moderate the dose of immunosuppressive drugs. On the other hand, decreasing the dose of immunosuppressive drugs can have a negative effect on graft survival. In addition, cardiovascular diseases and vascular atherosclerotic changes can increase with aging, which can have adverse effects on graft survival (6).

Anti-thymocytes globulin is a common medication used for preventing allograft rejection, and it is also used to treat patients with aplastic anemia (i.e., those who are not candidates for bone marrow transplant). This medicine can also be used to decrease the immune system in kid-

ney, liver, bone marrow, heart, and other organ transplantations. The effect of this product has not been sufficiently clarified, but its effect on graft failure was significant in our study. Based on our experience, the use of this medication in the above-mentioned cases can decrease the creatinine level, and it also can improve the renal status. However, it should be used with caution and only in limited cases.

In this study, the hazard of graft rejection in the subjects who received the ATG drug was 3.23 times that of subjects who did not receive the medicine. Specifically, this medicine is prescribed 1) for patients who have experienced transplantation more than once, 2) for patients who experience an increase in creatinine after transplantation, and 3) for patients who experience a very slow decrease in creatinine level after surgery. It is clear that patients with critical conditions receive this medicine and, consequently, observing a low survival rate in these subjects is not completely due to use of this drug. Instead, it might be attributable to their poor condition after transplantation. Finally, it is highly recommended to prescribe ATG to transplant patients who have high risk of rejection, have had a previous transplantation, or have received a kidney from a cadaver. Broad studies should be carried out to prescribe ATG to other low risk patients.

As the most important aim of the present study, we investigated the longitudinal effect of the serum creatinine level on survival of grafts. The results revealed that patients with a higher level of creatinine in the first year after transplantation had a remarkably higher hazard of graft rejection. Although we did not find any published articles about the longitudinal effects of creatinine level on survival of kidney graft, numerous studies are available about its cross-sectional effect. In a study conducted in Shiraz, Iran, on cadaveric transplant patients, it was shown that the risk of graft loss in subjects with creatinine greater than 2 mg/dL was 3.23 times more than for subjects who had a serum creatinine less than the mentioned amount (23).

In most studies, the cross-sectional effect of serum creatinine was investigated on short-term survival. However, some studies reported serum creatinine to be one of the important risk factors of graft loss for short- and long-term survival (16, 24-27). In this study, the effect of serum creatinine was examined in longitudinal (i.e., repeated measurements every month in the first year after transplant) format, and this longitudinal variable was one of the significant variables in our joint model. It means that, for every unit increase in the creatinine index, the risk of graft failure increases 82%. This point is contrary to the study of Rayhill et al., while it is consistent with the results of McLaren et al., which revealed that serum creatinine levels at six months after transplant were not predictive of the risk of developing chronic allograft failure. Rayhill et al. compared the outcome of simultaneous pancreas-kidney transplantation (SPK) and living related donor renal transplantation (LRD) in patients with diabetes, and they found discharge creatinine, the strongest predictor of graft survival, was highest in the SPK group and lowest in the HLA-identical LRD group (28, 29).

In general, it can be concluded that increasing the level of creatinine after kidney transplantation can affect long-term graft survival. The effect of hyperuricemia on survival was significant, which agrees with Huang et al.'s study. This could be due to the direct effect on cell function (30). Regarding the effect of hyperuricosuria on graft survival, uric acid-lowering drugs can be used to compare the survival of these patients with a control group. Also, to obtain more precise results, the glomerular filtration rate of patients who have a high level of uric acid can be contrasted with patients who have normal levels.

It should be mentioned that the increasing of the follow up period can be a sign of acute rejection, delayed graft function, and acute tubular necrosis. In turn, these conditions can be the cause of ischemia on the transplanted kidney, even after creatinine normalization. They can also cause inflammation reactions and loss of nephrons and hypertrophy of the remaining nephrons, as well as glomerul sclerosiation, which can have a severe negative effect on graft survival. The long-term increase of creatinine is a sign of chronic rejection, which is the main cause of graft loss. Fortunately, by increasing the serum creatinine, some recently discovered drugs can be added to the treatment protocol which, in turn, can have a positive effect on patient survival (31).

As a result of the joint modeling process, we found that, by every unit increase in the monthly recorded creatinine levels during the first year after kidney transplantation, the hazard of graft rejection increased about two times. Reported significant hazard ratios (HR) from different studies were 2.23, 1.72, 3.69, and 1.57 (25-27, 32). However, the reported effect size of creatinine level (HR = 1.82) in the current study might be more reliable than similar studies, because it was computed from repeated measures of creatinine levels (via longitudinal study), which is more comprehensive than a single observation (e.g., a cross-sectional study).

In recent decades, a large volume of medical and statistical research has been performed to identify the effective factors for the survival rate of renal graft throughout the world (15, 16, 18, 22, 25, 26, 28, 33). In these studies, the data analysts generally applied the usual statistical models, such as Cox proportional hazards or other well-known parametric or semi-parametric survival models. Here, we applied a more complex and powerful statistical model for

joint analysis of longitudinal and survival data. This modeling approach yields less bias and more accuracy, compared to other common techniques.

A number of statisticians have recommended the strict use of joint modeling approaches for better describing the longitudinal effects of different markers on time-to-event data (34-36). In our study, we modeled the longitudinal effect of subjects' post-operation creatinine levels on survival of kidney grafts, using a joint modeling technique. According to our literature review, this is the first attempt to use joint analysis of longitudinal creatinine and long-term survival of kidney transplantation.

One of the limitations of this study was the lack of access to a larger sample size. In addition, the model has its limitations. First, long-term follow-up of patients after transplantation is time-consuming, and second, the records of patients admitted to the medical centers may be incomplete. Moreover, the patients in this study did not return to the hospital for long-term follow-up, the data was not completely registered in the patients' files, the HLA matching was not done before transplantation in the patient files, and the side effects of immunosuppressive drugs were not assessed on the graft survival. Therefore, these findings should be interpreted with caution.

On the other hand, the study does offer the following advantages: it was completed on a large observation (1,560 observations). Compared to similar studies conducted in other provinces, the collected data was highly reliable and advanced, and powerful statistical approaches were utilized for analyzing the available data. In addition, the study was carried out in a center which has a favorable reputation, based on its more than 25 years of experience.

For future studies, the authors suggest assessing larger sample sizes or using substitute modeling, such as Bayesian joint modeling and/or any other similarly structured multi-center analysis. Also, the model presented herein can be applied to design similarly structured datasets.

5.1. Conclusion

In general, the results obtained from the present study revealed that the short-term survival of renal graft is in an acceptable range, while the long-term survival of kidney transplantation is still low, especially compared with reported estimates in developed countries. In this context, paying more attention to the risk indicators and risk factors of graft rejection, as well as promoting the level of post-operative care (including monitoring the markers, nursing, and medication) are of great importance.

Finally, to present more accurate estimates about the survival of the renal graft and survival rate of the patients (which was not assessed in our study) and to identify a wider range of factors related to graft survival, a multi-center study is recommended at the various referral kidney transplantation centers in different parts of Iran.

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Footnotes

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