



## Identify Survival Predictors of the First Kidney Transplantation: A Retrospective Cohort Study

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### Abstract

**Background:** The first kidney transplant survival is very important. We know that short-term survival of kidney transplantation is improved over the past two decades in Iran; however, no information is available on long-term survival and predictors. This study explored factors influencing long-term renal transplant survival at northwest of Iran.

**Methods:** In this single-center, study, survival rates and half-life of 201 the first kidney transplants between 1999 and 2008 were measured by a historical-cohort study in Imam Khomeini Hospital in Urmia, Iran. The log-rank test and Cox-regression model were used to compare survival curves and determine factor affecting graft survival time, respectively.

**Results:** First graft survival from one, five, and 10 years was 96%, 89%, and 46%, respectively. Mean±se and median±se of first graft survival time was 3061±105.01 day (95% CI: 2855.47-3267.11 day) and 3411±282.1 day (95%CI: 2858.08-3963.92), respectively. Predictors of first graft rejection were recipient age ( $P=0.001$ ), LDL cholesterol ( $P=0.008$ ), immunosuppressive drugs ( $P=0.047$ ), serum creatinine three and six months ( $P=0.042$  and  $0.001$ , respectively) and related donor family ( $P=0.037$ ).

**Conclusion:** Patients with first graft transplantation had a moderate long-term survival. The study showed that small age at transplant, low LDL cholesterol before transplant, and relative to donor, could be decrease the risk graft loss.

**Keywords:** Graft survival, Kidney transplantation, Surgery

### Introduction

Results of previous studies indicate numbers of patients with end stage of renal disease (ESRD) who need to renal transplant, are increasing (1-2). Around the world, treatment of most patients of ESRD is renal transplant (3-4). If graft loss occurs, would be increasing both mortality rate and health care costs in population (4).

Incidence of ESRD increased from 38.5 (in per million populations) in 1998 to 49.9-53 in 2000 (2, 5). In addition, number of renal transplant in Iran increased from 6 in 1984 to 1422 in 2000 (2). In Iran, number of cadaveric transplant has been very low in the last two decades (between 0.1% and 0.8%), and most of donors were non-relative and men (2, 5).

Although the kidney transplantation returns patients to daily living, and increases patient's quality of life compare to dialysis (2, 5-7), but long-term graft survival and its predictors are unclear (8). Surgical procedures, postoperative care, and use immunosuppressive drugs for kidney transplant increases short-time graft survival rate (6, 9). Immunological and non-immunological factors are involved in rejection of kidney transplants (10), that identify factors affecting graft rejection reduces need for repeated kidney transplantation. Such the factors reduce disability and years of life lost due to dialysis (11).

Because of recurrent renal transplant can be performed under certain conditions (12) and provide kidney for transplant is difficult and sometimes impossible, so determining factors affecting long-term survival of first graft is very important. Finally, it can be inferred that the first kidney transplant survival is very important because renal transplantation is a therapy for end-stage renal disease (2, 13). We know that short-term survival of kidney transplantation is improved over the past two decades in Iran (2); however, no information is available on long-term survival and predictors of renal transplantation in northwest of Iran, Imam Khomeini center, Urmia, Iran (14). This study explored factors influencing long-term renal transplant survival at northwest of Iran.

## Materials and Methods

### Setting and Participants

In this single-center study, a retrospective cohort study, medical records of 201 patients which receiving renal grafts for the first time between 1999 and 2008 in Imam Khomeini Hospital, Urmia, Iran, were reviewed and analyzed. We used demographic and clinical characteristics of patients (Table 1 and 2). For the purpose of the first graft survival analysis, graft failure was defined as return to dialysis, and death due to the functioning graft.

Patients undergoing repeated renal transplants were excluded from this study. Only right-censored occurred at graft survival time. Recipients were followed from the date of renal transplant until graft loss or up to 2008. Dead recipients with

functioning kidney graft loss were considered as censored. Clinical and demographic data were collected from recipient records in the hospital files of patients and follow-ups were carried out by nephrology clinic section.

### Covariates

Based on patient's files the following risk factors were assessed in Cox-regression model: recipients' age ( $\geq 50$  years) and sex (male, female), patient's smoking status (yes, no), hypercalcemia (yes, no), diabetes disease (yes, no), hypertension (systolic blood pressure  $>140$  or diastolic blood pressure  $>90$  versus else), blood transfusion before transplant (yes, no), time on the waiting list ( $\geq 2$  versus  $< 2$  year), glomerulonephritis (yes, no), weight (gr), dialysis duration (year), type of immunosuppressants drugs (Patients who received drugs prednisolone, azathioprine and cyclosporine denoted "1", patients who received drugs prednisolone, cyclosporine and cellcept denoted "0"), Relative to donor (yes, no), LDL-cholesterol (mg/dl), Serum creatinine at transplant ( $\geq 1.6$  versus  $< 1.6$  mg/dL). The measurements were confirmed by nephrologists of Imam Khomeini Hospital. The data compiled to a checklist by expert medical evidence. In the study, there was not special confounder. The results adjusted based on demographic and clinical characteristics.

### Statistical Analysis

Cox-regression model was used to crude (univariate) and adjusted (multivariate) risks, using independent variables found to have  $P < 0.1$  based on univariate analysis. The proportionality of hazard assumption was evaluated by direct visualization of log [-log (survival time)] versus log (survival time). Kaplan-Meier used to show cumulative survival cure by gender. All of the variables listed above were included in the Cox regression model, and those that were not significantly associated with graft survival are listed in Table 1. In addition, the adjusted association of independent variables, which were significantly associated with graft survival, is showed in Table 3. To estimate death-censored half-life time and 95% confidence interval Exponential model was used. To analysis of

data, we used software R version 2.12.1 statistical software. Statistical significance was defined at a *P*-value less than 0.05.

## Results

### Demographic and clinical characteristics of patients

A total of 201 kidney transplant recipients were included in the study between 1999 and 2008. Sex ratio of 201 kidney transplant patients was 1.7. Third quartile of male age was 49 years and it for female was 45 years. Taken at last visit, renal transplant rejection rate was 53.8% (54.8% in male and 53.9% in female; Table 2). In addition, mean±se and median±se for first graft survival time were 3061±105.01 (95%CI: 2855.47-3267.11) and 3411±282.1 day (95%CI: 2858.08-3963.92) day, respectively. In addition, percentiles 25±se

and 75±se were 4051±113.5 and 2319±142.9 day. None of the patients had splenectomy before transplantation. Hypertension was observed in 94 of patients. The univariate Cox-regression model showed that demographic and clinical characteristics of patients had not statistical significant effect on first graft survival time (Table 1). In this study, all donors were alive and had not received any cadaveric renal transplant, and interactions between covariates were not statistical significant. Most of patients (85.57%) received drugs prednisolone, azathioprine and cyclosporine, and rest received prednisolone, cyclosporine and cellcept. In the study, delayed graft function was observed in 4 cases. Graft survival rate was not significantly different in men and women (*P*=0.838).

**Table 1:** Univariate Cox-regression analysis for effect of demographic and clinical characteristics of patients (n=201)

Variable	Value	HR <sup>e</sup>	95% CI	<i>P</i> value
Sex (% male)	62.3	1.24 <sup>a</sup>	0.631-2.47	0.534
Smoking (%yes)	10.45	1.03	0.584-1.48	0.221
Hypercalcemia (% yes)	6.2	3.52	0.240-7.782	0.085
Diabetes (% yes)	28 (13.93) <sup>b</sup>	1.91	0.884-4.145	0.108
Hypertension (% yes)	46.77	1.43 <sup>b</sup>	0.619-3.308	0.402
Blood transfusion before transplant (% yes)	43.78	1.07	0.520- 3.901	0.312
Time on the waiting list (% ≥ 2 year)	23.64 <sup>c</sup>	0.86	0.788-0.904	0.165
Glomerulonephritis (% yes)	69.65 <sup>c</sup>	1.62	0.91-2.81	0.11
Weight (gr)	57.1± 11.05 <sup>d</sup>	1.01	0.984-1.039	0.426
Dialysis duration (year)	4.78±4.12 <sup>d</sup>	1.01	0.999-1.002	0.371

<sup>a</sup> Male versus female; <sup>b</sup> yes versus no; <sup>c</sup> ≥2 versus <2; <sup>d</sup> mean±sd; <sup>e</sup> unadjusted hazard ratios were obtained by univariate proportional Cox-regression.

### Ten-year Survival Rates

The survival rates of kidney transplantation over 10 years are shown in Table 2 after transplant. In

10 years follow up log-rank test was not showed significant different survival rate between male and female (Table 2)

**Table 2:** The first graft survival rate among patients from 1999 to 2008, Urmia, Iran (n=201)

Sex	First graft survival rates (%)									
	1year	2year	3year	4year	5year	6year	7year	8year	9year	10year
Male	95.4 (92.5-98.3)	94.7 (91.6-97.8)	91.1 (87.2-95.1)	90.8 (86.8-94.8)	88.4 (83.9-92.8)	75.2 (69.2-81.1)	72 (65.8-78.2)	58.1 (51.3-64.9)	50.9 (43.9-57.8)	45.2 (38.3-52.1)
Female	98.2 (96.4-99.9)	96 (93.4-98.7)	92.8 (89.3-96.3)	92.5 (88.9-96.1)	92.3 (88.7-95.9)	79.1 (73.6-84.6)	67.4 (61.1-73.7)	62.3 (55.7-68.9)	53.2 (46.4-59.9)	46.1 (39.4-52.8)
Total	96.7 (94.3-99.1)	95.2 (92.3-98.1)	92.1 (88.4-95.7)	91.6 (87.8-95.3)	89 (84.8-93.2)	77.3 (71.6-82.9)	70.2 (64.1-76.4)	60.8 (54.2-67.5)	52.4 (45.6-59.1)	46.2 (39.5-52.9)

Numbers in parentheses represent 95% confidence intervals for graft survival rates.

### Predictors of the first graft survival

Adjusted results from multivariate Cox regression analysis showed that influence factors of graft survival were recipient age  $\geq 50$  years [hazard ratio (HR)=2.58,  $P=0.001$ , Table 3], serum creatinine [HR=2.35,  $P=0.042$ , Table 3] and LDL cholesterol [HR=1.02,  $P=0.008$ , Table 3], a relative of donor [HR=4.90,  $P=0.037$ , Table 3], and type of

immunosuppressant drugs [HR=4.51,  $P=0.047$ , Table 3]. A unit increase in creatinine after transplantation, risk of graft rejection would be increase about two times (Table 3). Relative lack of donor and recipient kidneys increased rejection risk to 5 times. In addition, elderly recipients were at higher risk of graft loss ( $P=0.001$ ).

**Table 3:** Variables associated with survival in kidney transplantation patients using multivariate Cox proportional hazard model (n=201)

Variable	Crude HR	95% CI	Adjusted HR*	95% CI**	Pvalue
Recipient age ( $\geq 50$ yr versus $<50$ )	2.04	0.374-3.706	2.579	2.519-2.639	0.001
Relative to donor (yes=0, no=1)	1.59	0.708-2.472	4.903	4.783-5.023	0.037
Type of immunosuppressants drugs <sup>a</sup>	1.06	0.139-1.981	4.521	4.391-4.651	0.047
LDL-cholesterol (mg/dl)	0.017	0.001-0.033	1.017	1.006-1.028	0.008
Serum creatinine at transplant ( $\geq 1.6$ versus $<1.6$ mg/dL)	1.855	0.111-3.599	2.351	2.339-2.472	0.002

\*Adjusted HR by backward method.

\*\*CI for the adjusted Hazard Ratio.

<sup>a</sup>Patients who received drugs prednisolone, azathioprine and cyclosporine denoted "1", patients who received drugs prednisolone, cyclosporine and cellcept denoted "0".

## Discussion

Kidney transplantation is the treatment of choice in patients with ESRD, and reduces mortality rate significantly compared with those with chronic dialysis (15, 16). For improving the survival rate of first graft loss, we should identify which variables can affect it. Although many studies have been done for determination of graft loss causes, but still there is challenge among them. The first transplant rejection and related factors are very important. May there be no opportunity to re-transplant for some patients. This is why it is necessary to determine the factor affecting the first kidney transplant rejection. In this study, all donors were alive and had not received any cadaveric renal transplant, therefore we cannot compare between survival rate of alive and cadaveric donors.

### Predictors of the first graft survival

In the present study, where cause of ESRD was clear, most common cause was glomerulonephritis.

This result was observed in previous study in Iran (5, 17) and other parts of the world (15). Multivariate Cox-regression analysis showed that recipient age is an important factor affecting graft survival rate. This result was reported by previous studies (15, 18, 19). Some studies (4, 19, 20) have shown that gender of recipients related to graft survival. In contrast to mentioned studies, our study with some studies (13, 21, 22) has showed that gender of recipients did not predict graft survival. Therefore, we cannot say certainly that gender has associated with graft loss. Some of study (13, 23) confirmed that recipients' weight had effected on allograft failure; but this study did not confirmed the result. Unlike the results of Massy et al (9) we did not find association between blood pressure and graft survival. Although, multivariate Cox-regression model showed that type of anti-immunosuppressant drugs can be predicted graft survival time, but based on the estimated significant measure ( $P=0.047$ ) we cannot exactly cyclosporine, cellcept, and prednisolone are the most positive influential factors on graft survival (Table

3). We observed that increasing in serum creatinine level, hazard ratio of renal failure would rise. Hence, it can say that serum creatinine levels are highly predictive hazard rate of graft loss. Such results were observed in previous study (6). Cox-regression model showed that factors such as the type of medication received, donor-type, creatinine and LDL cholesterol can be predicted graft survival.

### **Ten-year survival rates**

It seems survival rate of kidney transplants improved with new surgical techniques and immunosuppressant drugs. The study indicates that transplant short-term survival rates in Urmia have been highly successful (Table 2). In a Iranian study (20), on 3028 patients transplanted during 1984 to 2005, survival rates after one, three, five, ten and fifteen years were 85.4%, 76.4%, 68.3%, 46.4%, and 23.8%, respectively. According to the study results, survival rates of one-, three- and five-year in our study were higher than them (21), but 10-year survival rate was similar. Also, in a study conducted in west of Iran (5) from 1989 to 2001, survival rate after one-, three- and ten-year were reported 91.5%, 84.8% and 46.9%, respectively, that survival rates obtained in our study show a greater degree than in West of Iran.

Short-term survival of renal transplantation in the present study is consistent with USA and Japan studies (24, 25). Our results were showed that long-term survival of first graft loss in Urmia (46%) was lower than Japan (59%) and USA (74%) (24, 25). Therefore, we can say short-term survival obtained in this study was similar (in Japan and USA) (24, 25) or higher than some studies (in European and South American) (26-29), but long-term survival rate in our study was shorter than them (18-19). Therefore, based on short-term survival rates, it can be said that the skill of surgical in Iran is similar to development countries (21-26); while, long-term results showed that may treatment services providing or follow-upping devices in Urmia comparison development countries (24-26) is not appropriate or recipients' behaviors may be not suitable.

### **Limitation**

Rate of missing value in demographic characteristics was high. Therefore, we selected three demographic variables such sex, smoking status and weight. The study was a retrospective cohort study analysis, and we did not dominance to complete monitoring and data registration. Another limitation of this study is no information about some viral and infection diseases such as cold and influenza, which led to the development of renal transplant failure. The recipients were recruited from a single-center, Imam Khomeini Hospital, and the results cannot generalize to all recipients in Iran. For this work, we suggest a Meta study on survival rates among renal transplantation recipients or a big cohort in Iran. In addition, sample size in the study was approximately small. We recommend to next studies were done by large sample in prospective study design not retrospective cohort.

### **Ethical considerations**

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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