Short-term and Long-term Survival of Kidney Allograft
Cure Model Analysis

Moghaddameh Mirzaee,[1] Jalal Azmandian,[2] Hojjat Zeraati,[1]
Mahmood Mahmoodi,[1] Kazem Mohammad,[1] Abbas Etminan,[2]
Mohammad Hasan Dehghani Firouzabadi,[2]
Simindokht Habibzade,[2] Mahdiyeh Haghparast[2]

1Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran
2Departments of Nephrology, Urology and Renal Transplantation, Kerman University of Medical Sciences, Kerman, Iran

Keywords. kidney transplantation, kidney allograft failure, survival models, Cox proportional hazard models

Introduction. Kidney allograft failure is a major concern in kidney transplant recipients. We separately assessed risk factors for long-term and short-term survival of death-censored kidney allograft.
Materials and Methods. This study included 397 kidney recipients who underwent surgery in Afzalipour Hospital, Kerman, Iran, from 2004 to 2010. The Cox mixture cure model was used to fit independent variables for prediction of graft survival in short-term and long-term.
Results. Allograft failure occurred in 43 kidney transplant recipients (10.8%). Among the long-term survivors, hypertension (odds ratio, 3.35; 95% confidence interval [CI], 1.6 to 6.7), a serum creatinine level greater than 1.6 at hospital discharge (odds ratio, 15.1; 95% CI, 7.2 to 31.9), and donor age (odds ratio, 1.14; 95% CI, 1.09 to 1.18) were significant predictors of allograft failure. Overweight, obesity, and male donor were associated with better survival. In short-term survivors, a high body mass index (hazard ratio, 3.59; 95% CI, 1.2 to 10.7) and longer duration of pretransplant dialysis (hazard ratio, 2.4; 95% CI, 1.07 to 5.7) were associated with graft failure, while the risk of allograft failure decreased in recipients who received kidney transplants from living donors versus deceased donors (hazard ratio, 0.3; 95% CI: 0.11 to 0.78) and with each 1-year increase in donor age (hazard ratio, 0.91; 95% CI, 0.86 to 0.96).
Conclusions. Many efforts have been made to improve short-term survival of kidney allograft. The cure analysis extends the knowledge by showing that control of which variables can improve both long-term and short-term survival rates.

IJKD 2014;8:225-30
www.ijkd.org

Original Paper

INTRODUCTION

The destination of chronic kidney disease (CKD) is end-stage renal disease and most of patients with end-stage renal disease choose kidney transplantation as a therapy, because it improves quality of life and offers greater longevity for them compared to dialysis therapy.[1] This is in spite of the fact that the cost of kidney transplantation is high, for example it is US $ 60 000 in the United States and US $ 10 000 in Iran.[2,3]

The history of the first kidney transplantation in Iran goes back to 1967 and only 112 kidney transplantation were performed until 1985.[4,5] But now Iran has the first rank of kidney transplantation in the Middle East and 4th rank in the world.[6]

Generally "prevention is better than cure," so we should screen patients with CKD. Because end-stage renal disease patients are frequently diagnosed as having kidney function impairment in advanced

stage of CKD.[7] Other than screening CKD patients in order to prevent end-stage of it, the next question is how to improve survival of kidney allograft in patients who choose kidney transplantation. The rate of 5-year survival of kidney allograft was estimated to be 82.5% in Iran in 2011; therefore, nearly 20% of patients had allograft failure during the 5-year period after kidney transplant.[8]

In order to improve survival of kidney allograft, it is important to identify which factors are associated with it. Several studies have been carried out to this end, identifying variables such as hypertension, donor sex, donor age, body mass index (BMI), and serum creatinine after transplant as factors associated with allograft survival.[6,9,10] These studies have used multivariate Cox proportional hazards model, which is one of the most popular methods to analyze survival data.[11] In this model, it is assumed that all the subjects in the population experience the event, but in some studies a considerable proportion of subjects may be long-term survivors. In these situations, in spite of the fact that the follow-up period is long, a fraction of patients do not experience the event, so the censoring rate increases and rate of survival is overestimated.

One approach to model long-term survival studies is using *mixture cure models*.[12] A cure model is a mixed model, composed of two parts: the cure part which estimates cure fraction and variables which affect the odds ratio (OR) of not curing for long-term survivors, and the second part is the survival estimates using the variables that affect the hazard ratio (HR) of the event happening for short-term survivors. The aim of this study was to estimate the fraction of recipients who had long-term survival of kidney allograft and to determine which variables affect the odds of failure or survival of kidney allograft for uncured recipients. In this study, Cox mixture cure model was used because it is highly flexible and proportionality of the HR is assumed for all the variables.[13-15]

MATERIALS AND METHODS

Setting and Participants

This retrospective cohort study included 397 kidney transplant recipients undergoing surgery between 2004 and 2010 in Afzalipour Hospital, Kerman, Iran. Recipients undergoing repeated transplant operations were excluded. The recipients were followed from the date of the transplant until allograft failure or 2011, and dead recipients with functioning kidney allograft were considered as censored. Kidney allograft failure was defined by returning to dialysis or retransplantation.

Covariates

The following recipient covariates were assessed in multivariate analysis: age, sex, BMI (< 18.5 kg/m^2, 18.5 kg/m^2 to 25 kg/m^2, and ≥ 25 kg/m^2), pretransplant duration on dialysis (≤ 6 months, 6 to 24 months, and ≥ 24 months), donor source (living versus deceased), pretransplant hypertension, and serum creatinine level upon discharge from the hospital (≤ 1.6 mg/dL versus > 1.6 mg/dL). The included donor factors were age and sex. Clinical and demographic data were collected from recipient records in the hospital and follow-ups were carried out by the nephrology clinic staff.

Statistical Analysis

Using the Kaplan-Meier curve (Figure), it can be seen that the survival function estimates leveled off at nonzero proportion (approximately 80%) after a median of 3.82 years of follow-up and that no further event of interest occurred after 6.37 years. In this situation it was assumed that a fraction of recipients had long-term survival of kidney allograft; therefore, mixture cure model was used. By using the Cox mixture cure model, it was possible to estimate the fraction of patients with long-term survival (cured) and detect which variables affected the odds of failure by logit part or which variables were associated with short-term survivors. A SAS macro was used, which was written by Corbiere and Joly for data analysis.[16] Statistical significance was defined at a *P* value less than .05.

RESULTS

This study evaluated 397 kidney transplant recipients. Allograft failure occurred in 43 (10.8%) recipients during the median 3.82-year follow-up period. The median age of the recipients at transplant was 37 years (range, 5 to 73 years). The majority of the recipients did not have pretransplant hypertension (59%). Body mass index was in the reference range in 52.9% of the recipients. The majority of the recipients (41%) were on dialysis for 6 months or less and received kidney transplants from a living donor. Serum creatinine on discharge from the hospital was 1.6 mg/dL or less for most

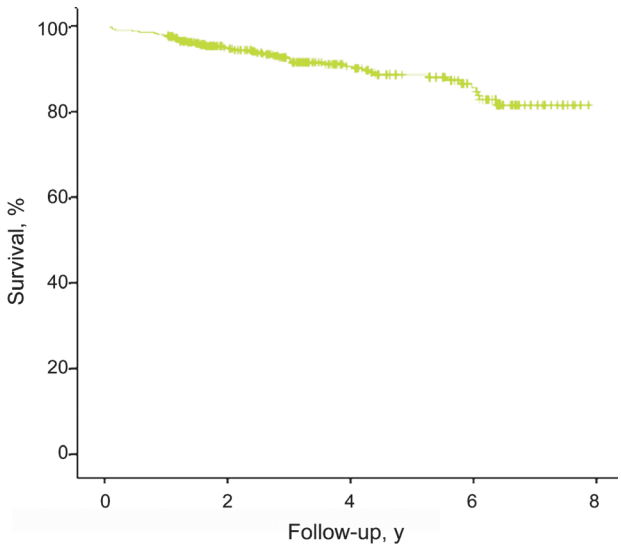
of them (72%). The median age of the donors was 26 years (range, 12 to 57 years). Kidney donors were mostly males (72.8%; Table 1).

Table 1. Characteristics of Kidney Allograft Recipients

Parameter	Value*
Number of patients	397
Kidney allograft failure	43 (10.8)
Recipient age, y	38.0 ± 14.7
Male recipient s	218 (54.9)
Pretransplant hypertension	123 (31.0)
Body mass index, kg/cm2	
< 18.5	102 (25.7)
18.5 to 25	210 (52.9)
≥ 25	85 (21.4)
Pretransplant dialysis time, mo	
≤ 6	163 (41)
6 to 24	144 (36.3)
≥ 24	90 (22.7)
Serum creatinine at hospital discharge	
≤ 1.6	286 (72)
> 1.6	111 (28)
Donor source	
Living	345 (86.9)
Deceased	52 (13.1)
Donor age, y	28.1 ± 7.2
Male donor	289 (72.8)

*Values are frequencies (percent) for categorical variables and mean ± standard deviation for continuous variables.

As the Figure shows, a notable proportion of the recipients were long-term survivors. The proportionality hazard assumption for the variables was checked, which was appropriate for all the variables; therefore, Cox mixture cure model was used with a logit link. Table 2 shows the ORs and confidence intervals for long-term survivors by using the Cox mixture cure model with a logit link



Kaplan-Meier curve for survival of kidney allograft.

Table 2. Estimates of Odds Ratio and Probability of Being Long-Term Survivor

Variable	Odds Ratio (95% Confidence Interval)	*P*	Survival Probability (95% Confidence Interval)
Recipient age, y	1.02 (1.00 to 1.04)	.18	…
Male recipient	0.59 (0.29 to 1.16)	.12	…
Pretransplant hypertension			
Yes	3.35 (1.60 to 6.70)	.001	0.70 (0.62 to 0.78)
No	1	…	0.84 (0.79 to 0.88)
Body mass index, kg/cm2			
< 18.5	1.60 (0.96 to 4.28)	.06	0.74 (0.65 to 0.82)
18.5 to 25	1	…	0.77 (0.71 to 0.82)
≥ 25	0.34 (0.24 to 0.70)	.03	0.89 (0.82 to 0.95)
Pretransplant dialysis time, mo			
≤ 6	1	…	…
6 to 24	1.10 (0.52 to 2.30)	.78	…
≥ 24	1.90 (0.84 to 4.50)	.78	…
Serum creatinine at hospital discharge			
≤ 1.6	1	…	0.55 (0.45 to 0.64)
> 1.6	15.10 (7.20 to 31.90)	< .001	0.89 (0.85 to 0.92)
Donor source			
Living	0.56	.26	…
Deceased	1	…	…
Donor age, y	1.14	< .001	…
Donor sex			
Male	0.28	< .001	0.84 (0.79 to 0.88)
Female	1	…	0.70 (0.61 to 0.78)

and probability of being a long-term survivor. The average fraction of being a long -term survivor was estimated to be 0.77 ($P < .001$). Among the long-term survivors, the OR for recipients with pretransplant hypertension was 3.35, meaning that the risk of allograft failure was significantly higher in them, compared to those not having pretransplant hypertension. Overweight and obese recipients had a low risk of failure compared to recipients with normal weight. The OR for recipients who had a serum creatinine level greater than 1.6 upon discharge from the hospital was 15.1, indicating a high risk of failure compared to the reference group (serum creatinine, ≤ 1.6). A 1-year increase in donor age increased the risk of failure (OR, 1.14; Table 2).

Table 3 shows the HRs and confidence intervals for short-term survivors. According to this table, the HR was 3.59 for recipients who had a BMI higher than normal, indicating that kidney allograft failure happened faster than in the normal group. In short-term survivors, when the duration of pretransplant dialysis increased to24 months and longer, allograft failure happened faster compared to recipients who had dialysis duration of 6 months or shorter (HR, 2.4). Risk of allograft failure decreased (HR, 0.3) in recipients who received kidney transplants from living donors versus deceased donors. A 1-year increase in donor age decreased the risk of allograft failure (HR, 0.91).

Table 3. Estimates of Hazard Ratios for Short-Term Survivors

Variable	Hazard Ratio (95% Confidence Interval)	*P*
Recipient age, y	0.99 (0.97 to 1.02)	.67
Male recipient	0.61 (0.28 to 1.28)	.18
Pretransplant hypertension	1.15 (0.58 to 2.3)	.67
Body mass index, kg/cm^2		
< 18.5	0.85 (0.37 to 1.9)	.71
18.5 to 25	1	…
≥ 25	3.59 (1.2 to 10.7)	.02
Pretransplant dialysis time, mo		
≤ 6	1	…
6 to 24	1.49 (0.64 to 3.1)	.38
≥ 24	2.4 (1.07 to 5.7)	.03
Serum creatinine at hospital discharge		
≤ 1.6	1	…
> 1.6	0.89 (0.41 to 1.7)	.62
Donor source		
Living	0.3 (0.11 to 0.78)	.01
Deceased	1	…
Donor age, y	0.91 (0.86 to 0.96)	.004
Male donor	1.33 (0.67 to 2.6)	.42

DISCUSSION

The results of this study showed that pretransplant hypertension, BMI, serum creatinine upon discharge from the hospital, and donor age and sex had significant association with odds of allograft failure in long-term survivors. In addition, it was demonstrated that BMI, donor source, donor age, and pretransplant dialysis duration were associated with survival of kidney allograft in short-term survivors.

Many studies have been carried out in Iran and other countries to determine which variables are associated with kidney allograft survival. These studies have used Cox proportional hazard model for the analysis of their data. The Cox model is an appropriate and popular analysis for short-term survival. When an event is encountered and there is a high censoring rate after sufficient follow-up duration, use of mixture cure models are better than usual analyses such as the Cox model. Mixture cure model divides people into two groups: long-term and short-term survivors. These studies have shown only 1-year kidney allograft survival rate as short-term survival and more than 1 year as long-term survival and used the Cox model for identifying which variables affect on kidney allograft survival overlay on long-term and short-term survival rates.

In Iran, several studies have shown that donor age and sex, serum creatinine after kidney transplant during the first month, and serum creatinine upon discharge from the hospital are significantly associated with kidney allograft survival.[8,17] Studies in other countries have shown that BMI, pretransplant hypertension, and donor age affect allograft survival.[10,18] A study evaluated 13 671 kidney allograft recipients and showed the effect of serum creatinine on long-term survival of kidney allograft indirectly by estimated glomerular filtration rate at 12-month postoperative interval.[19] Raiss Jalali and coworkers showed that low blood pressure before kidney transplantation was associated with improved graft survival.[18] Fattahi and colleagues showed 2-year graft survival was lower among recipients of deceased donor kidney transplant. In this study, we showed that the risk of allograft failure decreased in recipients who received

kidney transplants from living donors versus deceased.[20] In addition, the results of the present study showed that pretransplant hypertension increased the odds of allograft failure in long-term survivors. Furthermore, an increase in donor age was associated with a decrease in the long-term survival of allograft, consistent with the results of a study by Keith and colleagues.[9]

Chang and colleagues confirmed that overweight and obese recipients had higher risks of allograft failure compared to recipients with normal weight.[21] However, this study showed that overweight and obese recipients had a high risk for allograft failure in short-term survival, but they had low odds of allograft failure in long-term survivors compared to recipient with normal weight. Body mass index at the time of transplant was used in this study because it was possible that overweight and obese recipients lost their weights after transplant and reached ideal weight and had better long-term survival.

The results of this study are consistent with those of other studies in some aspects, but in some aspects they are different. Our analysis was divided into two parts of long-term and short-term survivors; thus, some variables had significant association with one part only or their effect was reverse on the second part. There was no other study in the literature review, which has used mixture cure model in kidney allograft survival for further discussion. Despite improvements in immunologic conformity between donors and recipients, surgical methods and attention to recipients after transplantation have increased short-term survival rate of allograft. The results of this study will help us to improve long-term kidney allograft survival by controlling effective variables. Findings of this study, however, should be interpreted considering some limitations, such as the fact that there was not any information about human leukocyte antigen antibody matching between recipients and donors or several other potentially important factors.

CONCLUSIONS

Many efforts have been made to improve short-term survival of kidney allograft. The cure analysis extends the knowledge by showing that control of which variables can improve both long-term and short-term survival rates.

ACKNOWLEDGMENTS

This article is a part of PhD thesis supported by Tehran University of Medical Sciences. We would like to thank the Deputy of Research and Technology of Tehran University of Medical Sciences for financial support of this study. The authors thank Kerman University of Medical Science for supporting data collection.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wolfe RA, Ashby VB, Milford EL, et al. Comparisonof mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaverictransplant. N Engl J Med. 1999;341:1725-30.
2. Nourbala MH EB, Kardavani B, et al. The cost of kidney transplantation in Iran. Transplant Proc. 2007;39:927-9.
3. Pourfarziani VNM, Azizabadi Farahani M, Moghani Lankarani MAS. Costs and length of hospitalizations following kidney transplantation. Iran J Kidney Dis. 2009;3:103-8.
4. Einollahi B. Iranian experience with the non-related renal transplantation. Saudi J Kidney Dis Transpl. 2004;15:421-28.
5. Ghods AJ. Iranian model of paid and regulated living-unrelated kidney donation. Clin J Am Soc Nephrol. 2006;1:1136-45.
6. Jiajia ZH, Yinwei P. Accelerated hazards mixture cure model. Lifetime Data Anal. 2009;14:455-67.
7. Mahdavi Mazdeh M. Why do we need chronic kidney disease screening and which way to go? Iran J Kidney Dis. 2010;4:275-81.
8. Ghanei E, Nasrolahi A, Razaghi M. Evaluation Short and Long term Graft and survival rates in kidney transplanted patients between 1995-2011. J Army Univ Med Sci. 2011;9:251-5.
9. Keith DS, Cantarovich M, Paraskevas S, Tchervenkov J. Recipient age and risk of chronic allograft nephropathy in primary deceased donor kidney transplant. Transpl Int. 2006;19:649-56.
10. Chang S, McDonald SP. Effects of body mass index at transplant on outcomes of kidney transplantation. Transplant Proc. 2007;84.
11. Cox DR. Regression models and life tables. J R Statist Soc B. 1972;34:187-220.
12. perperoglou A, keramopoullos A, houwelingen H. Approaches in modeling long-term survival:an application to breast cancer. Statist Med. 2007;26:2666-85.
13. Fleming T, Harrington D. Counting processes and survival analysis. New York: Wiley; 1991.
14. Kleinbaum D, Klein M. Survival analysis: a self-learning text. New York: Springer-Verlag; 2005.
15. Tsiatis A. A large sample study of Cox's regression model.

Ann Statistics. 1981;9:93-108.

16. Corbière F, Joly P. A SAS macro for parametric and semiparametric mixture cure models. Comput Methods Programs Biomed. 2007;85:173-80.
17. Hassanzade J, Salahi H, Rajaeefard A, Zeighami B, Almasi Hashiani A. 10-year graft survival analysis of renal transplantation and factors affecting it in patients transplanted from live donor in shiraz transplant research center during 1999-2009. J Kerman Univ Med Sci. 2011;18:28-39.
18. Raiss Jalali GA, Fazelzadeh A, Mehdizadeh AR. Effect of hypertension on transplant kidney function: three year of follow-up. Transplant Proc. 2007;39:941-2.
19. Kasiske BL, Israni AK, Snyder JJ, Skeans MA. The relationship between kidney function and long-term graft survival after kidney transplant. Am J Kidney Dis.57:466-75.
20. Fattahi MR NM, Rostami Z, Einollahi B. Patient and graft outcomes in deceased-donor kidney transplantation. Iran J Kidney Dis. 2012;6:291-9.
21. Sean H, Chang P, Toby HC, Stephen PM. Effects of body mass index at transplant on outcomes of kidney transplantation. Transplant Proc. 2007;84.

Correspondence to:
Jalal Azmandian, MD
Departments of Nephrology, Urology and Renal Transplantation, Kerman University of Medical Sciences, Kerman, Iran
E-mail: j_azmandian@yahoo.com

Received April 2013
Revised August 2013
Accepted September 2013