Iranian J Publ Health, Vol. 43, No.3, Mar 2014, pp. 316-322

Original Article

Multi-State Survival Analysis in Renal Transplantation Recipients

Moghaddameh MIRZAEE [1], ***Kazem MOHAMMAD*** [1], ****Mahmood MAHMOODI*** [1], ***Hojjat ZERAATI*** [1], ***Mohammad-Reza EBADZADEH*** [2], ***Abbas ETMINAN*** [2], ***Faramarz FAZELI*** [3], ***Mohammad Hasan DEHGHANI FIROUZABADI*** [2], ***Hossein SATTARY*** [2], ***Mahdiyeh HAGHPARAST*** [2], ***Abbas RAHIMI FOROUSHANI*** [1]

1. *Dept. of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran*
2. *Physiology Research Center, Departments of Nephrology, Urology and Renal Transplantation, Kerman University of Medical Sciences, Kerman, Iran*
3. *Dept. of Urology, Zahedan University of Medical Sciences, Zahedan, Iran*

***Corresponding Author:** Tel: +98–21–88989127 Email: mahmoodim@tums.ac.ir

(Received 19 Aug 2013; accepted 15 Dec 2013)

Abstract

Background: Renal transplantation is a therapy for end-stage renal disease. During the study of recipients' survival after renal transplantation, there are some events as intermediate events that not only affect the recipients' survival but also events which are affected by various factors. The aim of this study was to handle these intermediate events in order to identify factors that affect recipients' survival by using multi-state models.

Methods: This retrospective cohort study included 405 renal transplant patients from Afzalipour Hospital, Kerman, Iran, from 2004 to 2010. The survival time of these recipients was determined after transplantation and the effect of various factors on the death hazard with and without renal allograft failure and hazard of renal allograft failure was studied by using multi-state models.

Results: During 4.06 years (median) of follow-up; 28 (6.9%) recipients died and allograft failure occurred in 51 (12.6%) recipients. Based on the results of multi-state model, receiving a living kidney transplantation decreased the hazard of renal allograft failure (HR=0.38; 95% CI: 0.17- 0.87), pre-transplant hypertension (HR=2.94; 95% CI: 1.54- 5.63) and serum creatinine levels >1.6 upon discharge from the hospital (HR=7.38; 95% CI: 3.87- 7.08) increased the hazard of renal allograft failure. Receiving living kidney transplantation decreased the hazard of death directly (HR=0.18; 95% CI: 0.04- 0.93).

Conclusions: It was concluded that the effect of donor type, pre-transplant hypertension and having serum creatinine >1.6 upon discharge from the hospital was significant on hazard of renal allograft failure. The only variable that had a direct significant effect on hazard of death was donor type.

Keywords: Renal transplantation, Intermediate event, Multi-state model, Death hazard

Introduction

The number of patients with end-stage renal disease (ESRD) increases yearly at a rate of 7-8% (1). Most of these patients choose renal transplantation (RT) since it improves the quality of life and is cost-effective compared to other therapies such as dialysis (1-3). Canada has the first rank of RT in the world (4) and Iran has the first rank of RT in the Middle East (3). Although RT decreases the mortality of patients with ESRD, their survival remains less than the general population (5). Therefore, in order to improve the survival of RT recipients it is important to identify which varia-

bles affect this survival. In this context, some studies have shown that variables such as receiving a living kidney transplant, pre-transplant hypertension, renal allograft failure (RAF) and serum creatinine have significant effects on recipients' survival (6-8). Some of these variables may undergo no change over time, e.g. recipients' gender, measured at the beginning of the study. However, there are some variables that should be measured during the study and their value changes over time; therefore, they are often called time-dependent variables.

These variables not only affect patients' survival as a time-dependent variable but their occurrence is also influenced by different factors. One of the statistical models designed to consider such variables is to assume them time-dependent variables and to model survival data based on them (9-12). This approach has limitations because we can consider only the effect of these variables on occurrence of death and we cannot detect which variables have an effect on occurrence of time-dependent variables.

Multi-state models are alternative approaches for analyzing such events. Such analyses have been used in RT recently. Kramer et al used multi-state model for renal recipients' survival by starting the state as alive on dialysis and using alive after first kidney transplant as intermediate event and death was considered an event (13).

In studying the renal recipients' survival, one of the most important variables that can affect this survival is RAF.

Knoll et al. showed that RAF increased the risk of death by over three folds compared to patients who maintained transplant function (6); they used multivariate time-dependent analysis to detect the effect of RAF on recipients' survival because the value of RAF can change at any time after transplantation. In recent analyses, it was not shown that the variables can affect RAF but there are studies showing that only the variables such as pre-transplant hypertension, donor age, and serum creatinine after transplant can affect RAF as factors associated with allograft survival (14-16).

The aim of this study was to identify factors that affect death hazard with and without RAF and hazard of RAF in RT recipients by using a multi-state model.

Materials and Methods

Setting and Participants

This retrospective cohort study was carried out on 405 patients with ESRD, who had chosen RT therapy in Afzalipour Hospital, Kerman, Iran from 2004 to 2010. Patients undergoing repeated transplants were excluded from the study. The date of RAF was recorded and RAF was defined as relapsing into dialysis or re-transplantation. The patients were followed from the date of RT until death or up to 2011. The patients were followed to see whether they were alive at the end of the study or dead by any cause other than RT, such as accidents, stroke or cardiovascular diseases. In this study, we considered deaths caused only by infection or malignancy.

Risk Factors

The following risk factors were assessed in multivariate analysis: recipients' gender (male, female), donor type (living, deceased), pre-transplant hypertension (yes, no), pre-transplant diabetes (yes, no) and serum creatinine upon discharge from the hospital (mL/min) ($\leq$1.6, >1.6). This cut-point of serum creatinine was identified by the hospital laboratory.

Clinical and demographic data were collected from recipient records in the hospital and follow-ups were carried out by nephrology clinic.

Statistical Analysis

To examine the effect of different risk factors on patients' survival, multi-state models were used. Multi-state models are alternative and innovative approaches for analyzing time-to-event data. According to this model, patients experience different states during the study from the beginning to death event and transition times between states have different distributions such as Exponential, Weibull, Gamma, etc.

Survival analyses commonly focus only on factors that affect time of occurrence of death event.

In these models, all RT recipients are alive at the beginning of the study and then move toward death. Therefore, in this manner we consider only two states.

However, in this study an additional state (called intermediate event) such as RAF was considered. In fact we assume RT recipients move toward death from two paths; 1) without RAF and 2) with RAF. These transitions are illustrated in Fig. 1.

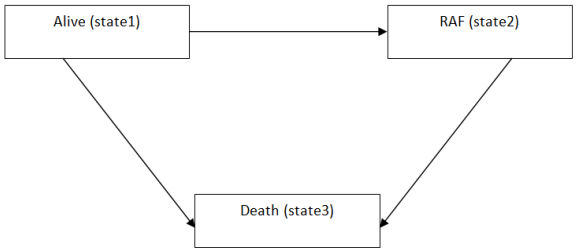

Fig. 1: Multi-state model for death of kidney recipients

There are three transitions for RT recipients during the study in the above model.

1. Death without RAF (transition from state1 to state 3)
2. RAF (transition from state 1 to state 2)
3. Death with RAF (transition from state 2 to state 3)

Disregarding intermediate events and the time of their occurrence influences the results of the study, resulting in bias in data analysis (12, 17, 18).

In this study we assume RT recipients move from state 1 to state 3 by probability of P and by probability (1-P) move from state 1 to state 2. Different exponential distributions were used for transition times between different states. Therefore, there were different hazards for transition between states and the effects of risk factors on these hazards were evaluated. Statistical model is more explained in appendix.

All the statistical analyses were performed using SAS 9.2 software. A significance level of 5% was considered statistically significant.

Results

This study evaluated 405 RT recipients. Most of the recipients were male (226, 55.8%), had pre-transplant hypertension (279, 68.9%) and pre-transplant diabetes (330, 81.5%). The mean and median age of recipients at transplantation time were 37.96±14.72 and 37 years (range: 5 to 73 years). Recipients received mostly living kidney transplantation (351, 86.7%) and had serum creatinine ≤1.6 (mL/min) upon discharge from the hospital (287, 70.9%).

Mean and median age of donors were 28.08±7.22 and 26 years (range: 12 to 57 years) and most of them were male (295, 72.8%). The recipients' five-year rate was 0.89 (95% CI: 0.84- 0.92).

The baseline characteristics of recipients have been shown according to renal allograft status in Table 1.

The probability of death without RAF was estimated at 0.3 (95% CI: 0.05- 0.54).

During the 4.06-year (median) follow-up, death occurred in 28 (6.9%) recipients. RAF occurred in 51 (12.6%) recipients (transition from state 1 to state 2). In this study death without RAF occurred in 8 (28.6%) recipients (transition from state 1 to state 3) and 20 (39.2%) recipients had death with RAF (transition from state 2 to state 3).

The effect of different variables on death hazard without RAF, hazard of RAF and death hazard with RAF has been shown in Table 2. The effects of pre-transplant hypertension, serum creatinine upon discharge from the hospital and donor type were statistically significant on hazard of RAF (transition from state 1 to state 2). Based on these results, having pre-transplant hypertension increased the hazard of RAF by 2.94 (95% CI: 1.54- 5.63) times. Having serum creatinine >1.6 upon discharge from the hospital increased the hazard of RAF by 7.38 (95% CI: 3.87- 7.08) times.

Receiving living kidney transplantation decreased the hazard of RAF by 0.38 (95% CI: 0.17- 0.87) times.

As shown in Table 2, the effect of recipient's gender and serum creatinine upon discharge from the hospital was statistically significant on death hazard with RAF (transition from state 2 to state 3). The death hazard with RAF increased in male recipients by 2.55 (95% CI: 1.01- 6.50) times compared to female recipients. Serum creatinine >1.6

upon discharge from the hospital increased this hazard by 3.52 (95% CI: 1.15- 8.72) times.

The analysis of the effect of different variables on death hazard without RAF (transition from state 1 to state 3) revealed that only the effect of donor type was significant. The death hazard without renal failure decreased in recipients who received a living kidney transplantation by 0.18 (95% CI: 0.04- 0.93) times.

Table1: Baseline characteristics of patients with renal transplantation

Risk factors		Renal allograft status		
		Renal allograft failure	No renal allograft failure	
Gender	Female	25 (49)	154 (43.5)	179 (44.2)
	Male	26 (51)	200 (56.5)	226 (55.8)
Donor type	Deceased	11 (21.6)	43 (12.1)	54 (13.3)
	Living	40 (78.4)	311 (87.9)	351 (86.7)
Pre-transplant hypertension	No	25 (49)	254 (71.8)	279 (68.9)
	Yes	26 (51)	100 (28.2)	126 (31.1)
Pre-transplant diabetes	No	36 (70.6)	305 (86.2)	341 (84.2)
	Yes	15 (29.4)	49 (13.8)	64 (15.8)
Serum creatinine upon discharge from the hospital (mL/min)	≤1.6	15 (29.4)	273 (76.7)	288 (71.1)
	>1.6	34 (70.6)	83 (23.3)	117 (28.9)
Donor age (years)	≤28	35 (68.6)	243 (68.3)	278 (68.6)
	>28	16 (31.4)	111 (31.7)	127 (31.4)

Table 2: Multi-state analysis for effect of different variables on allograft failure, death with/ without allograft failure

Risk factors		Adjusted hazard ratio(95% confidence interval)		
		State 1 to State 2[1]	State 2 to State 3[2]	State 1 to State 3[3]
Gender	Female[4]	1	1	1
	Male	0.76 (0.39- 1.50)	2.55 (1.01- 6.50)	0.66 (0.11- 3.90)
Donor type	Deceased	1	1	1
	Living	0.38 (0.17- 0.87)	0.63 (0.23- 1.17)	0.18 (0.04- 0.93)
Pre-transplant hypertension	No	1	1	1
	Yes	2.94 (1.54- 5.63)	0.47 (0.10- 1.00)	4.07 (0.75- 4.03)
Pre-transplant diabetes	No	1	1	1
	Yes	0.94 (0.41- 2.12)	2.41 (0.88- 6.63)	1.12 (0.23- 5.59)
Serum creatinine upon discharge from the hospital (mL/min)	≤1.6	1	1	1
	>1.6	7.38 (3.87- 7.08)	3.52 (1.15- 8.72)	3.80 (0.76- 6.96)
Donor age (years)	≤28	1	1	1
	>28	0.76 (0.39- 1.50)	2.55 (1.00- 6.51)	0.66 (0.11- 3.90)

1- Transition from alive state to allograft failure state
2- Transition from allograft failure state to death state
3- Transition from alive state to death state
4- The first category is considered a reference group.

Discussion

This is the first study to use multi-state analysis for considering the effect of renal allograft failure on recipients' death. This analysis helps us discover which variables can directly affect transition from RT to death without RAF or indirectly affect transition from RT with RAF to death.

During the 4.06 years (median) of follow-up 28 recipients (6.9%) died and 51 (12.6%) recipients had RAF and death occurred in 20 (39.21%) recipients with allograft failure. The results of this study are almost consistent with those of other studies. US Renal Data System reported that 25% of patients with renal allograft transplant had AF after 5 years. Therefore, it was reported that the five-year survival rate of renal allograft in deceased kidney transplant was 75% (4); the rate of AF after 7 years in all the patients (living and deceased kidney transplants) in this study was 12.6%. In this study the follow-up period was longer and all the patients (not merely deceased kidney transplant patients) were considered in the analysis, resulting in the difference between 12.6% and 25%.

For improving the survival rate of renal recipients, we should identify which variables can affect it. There are many statistical methods for investigating different factors that can affect this survival. Many studies, by using standard survival models such as Cox regression, have identified factors that affect survival of renal recipients (19-21). These models only focus on identifying factors affecting the time of occurrence of death event. However, in many situations, events occur for patients during the study which may affect the interest event.

Ignoring these events or intermediate events and time of their occurrence can affect the final results. Use of complex survival models such as multi-state models has a great advantage in considering intermediate events and the effect of them on interest event directly or indirectly and also investigate the variables that effect on intermediate events.

Applying a complex model like multi-state instead of the standard survival models in medical researches makes us to understand the natural process of the disease and help researchers to take closer look at the behavior of diseases. In the present study, the effect of different variables on recipients' death hazard was studied according to a multi-state model with three states of recipients "being alive at RT" (state 1), "alive with RAF" (state 2) and "death" (state 3).

Therefore, RAF was considered as an intermediate event in the present study; in contrast, Knoll et al used time-dependent analysis and considered RAF as a time-dependent variable and reported that RAF had a direct and significant effect on death hazard (6). However, by using multi-state model in the present study it was possible to identify which variables affect RAF hazard and the effect of RAF on death hazard directly and indirectly. The analysis for identifying the effect of different variables by multi-state models showed that donor type had a significant effect on hazard death without RAF (state 1 to state 3) as well as RAF (state 1 to state 2). This variable had no significant effect on death hazard due to allograft failure (state 2 to state 3). Most studies on death hazard of recipients have shown that living kidney transplantation decreased recipients' death hazard (22). The results of the present study showed the same results but this factor affected death hazard without renal allograft and its effect on death hazard with RAF was through occurrence of RAF hazard. So we recommend to recipients to get a living kidney compared to deceased kidney.

By using multi-state models, Kramer et al showed that donor type did not affect death hazard either directly or indirectly (13). This study used data only on children but we evaluated all the recipients in all the ages.

Pre-transplant hypertension had a significant effect on death hazard directly without RAF (state 1 to state 3). This factor had a direct impact on death hazard and it increased the death hazard like other studies (6-8). So it is important to extend the preventive programming for hypertension in whole population.

It did not have any significant effect on occurrence of RAF hazard or death hazard with RAF. Serum creatinine >1.6 upon discharge from the hospital increased the death hazard without RAF and had a direct effect on death hazard. It is consistent with findings reported by studies on standard models of

survival (6-8). Its effect on death hazard with RAF was indirect and through the effect on RAF hazard.
Applying a complex model like multi-state, instead of the standard survival models, leads to a better understanding of the natural process of the disease and helps the researcher take a closer look at the behavior of variables. By using multi-state analysis, it was shown that the effects of donor type, pre-transplant hypertension and serum creatinine levels of >1.6 upon discharge from the hospital were significant on hazard of renal allograft failure. Having serum creatinine levels >1.6 upon discharge from the hospital had an indirectly significant effect on death hazard. The only variable that had a direct and significant effect on death hazard was the donor type.
This study had some limitations. First, no information was available about matching factors between donors and recipients. It is possible that mismatching between donors and recipients was associated with patient survival. Second, there was no access to laboratory data at the time of AF in order to explain why these patients ran a higher risk of death.

Conclusion

By using multi-state analysis, it was concluded that the effect of donor type, pre-transplant hypertension and having serum creatinine were significant on hazard of renal allograft failure. The only variable that had a direct significant effect on hazard of death was donor type.

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.

Acknowledgements

This paper is a part of a research for a PhD degree at School of Public, Tehran University of Medical Sciences (TUMS) and was financially supported by the university. We would like to express our gratitude to Kerman University of Medical Science, Kerman, Iran, for data acquisition. The authors declare that there is no conflict of interests.

References

1. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ,Stablein D (2000). Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med,* 342:605-12.
2. Mendeloff J, Ko K, Roberts MS, Byrne M,Dew MA (2004). Procuring organ donors as a health investment: how much should we be willing to spend? *Transplantation,* 78:1704-10.
3. Simforoosh N, Basiri A, Tabibi A,Shakhssalim N (2004). Laparoscopic donor nephrectomy--an Iranian model for developing countries: a cost-effective no-rush approach. *Exp Clin Transplant,* 2:249-53.
4. Alirahmi H, Farahnak A, Golmohamadi T,Esharghian MR (2010). Comparative assay of glutathione S-transferase (GSTs) activity of excretory-secretory materials and somatic extract of Fasciola spp parasites. *Acta Med Iran,* 48:367-70.
5. Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ,van Es LA (1997). Patient survival after renal transplantation; more than 25 years follow-up. *Nephrol Dial Transplant,* 12:1672-9.
6. Knoll G, Muirhead N, Trpeski L, Zhu N,Badovinac K (2005). Patient survival following renal transplant failure in Canada. *Am J Transplant,* 5:1719-24.
7. Meier-Kriesche HU, Baliga R, Kaplan B (2003). Decreased renal function is a strong risk factor for cardiovascular death after renal transplantation. *Transplantation,* 75:1291-5.
8. Molnar MZ, Streja E, Kovesdy CP et al.(2012). Age and the associations of living donor and expanded criteria donor kidneys with kidney transplant outcomes. *Am J Kidney Dis,* 59:841-8.
9. Andersen PK, Borgan O, Gill RD,Keiding N (1993). *Statistical models based on counting processes.* ed. 2nd ed,Springer New York.
10. Kalbfleisch JD,Prentice RL (2002). *The statistical analysis of failure time data.* ed. 2nd ed,,john Wiley &Sons, New Jersey.
11. Klein jP,Moeschberger ML (2003). *Survival analysis : techniques for censored and truncated data.* ed. 2nd ed,Springer, New York.

12. Andersen PK (1988). Multistate models in survival analysis: a study of nephropathy and mortality in diabetes. *Stat Med,* 7:661-70.
13. Kramer A, Stel VS, Geskus RB, Tizard EJ, Verrina E, Schaefer F, Heaf JG, Kramar R, Krischock L, Leivestad T, Palsson R, Ravani P,Jager KJ (2012). The effect of timing of the first kidney transplantation on survival in children initiating renal replacement therapy. *Nephrol Dial Transplant,* 27:1256-64.
14. Chang SH, Coates PT,McDonald SP (2007). Effects of body mass index at transplant on outcomes of kidney transplantation. *Transplantation,* 84:981-7.
15. Keith DS, Cantarovich M, Paraskevas S,Tchervenkov J (2006). Recipient age and risk of chronic allograft nephropathy in primary deceased donor kidney transplant. *Transpl Int,* 19:649-56.
16. Zhang J,Peng Y (2009). Accelerated hazards mixture cure model. *Lifetime Data Anal,* 15:455-67.
17. Andersen PK,Keiding N (2002). Multi-state models for event history analysis. *Stat Methods Med Res,* 11:91-115.
18. Kay R (1986). A Markov model for analysing cancer markers and disease states in survival studies. *Biometrics,* 42:855-65.
19. Narayanan R, Cardella CJ, Cattran DC, Cole EH, Tinckam KJ, Schiff J,Kim SJ (2010). Delayed graft function and the risk of death with graft function in living donor kidney transplant recipients. *Am J Kidney Dis,* 56:961-70.
20. Smavatkul C, Pascual J, Desai AG et al. (2007). Disease progression and outcomes in type 1 diabetic kidney transplant recipients based on posttransplantation CKD staging. *Am J Kidney Dis,* 50:631-40.
21. Tang H, Chelamcharla M, Baird BC, Shihab FS, Koford JK,Goldfarb-Rumyantzev AS (2008). Factors affecting kidney-transplant outcome in recipients with lupus nephritis. *Clin Transplant,* 22:263-72.
22. Noppakun K, Cosio FG, Dean PG, Taler SJ, Wauters R,Grande JP (2011). Living donor age and kidney transplant outcomes. *Am J Transplant,* 11:1279-86.

Appendix

Transition time distribution between state 1(Alive) and state 2 (RAF) is Exponential with parameter λ_{12} , transition time between state 1(Alive) and state 3 (Death) has Exponential distribution with parameter λ_{13} and transition time distribution from state 2(RAF) to state 3(Death) is Exponential with parameter λ_{23} . So these times have density function, hazard function and distribution function such as bellow:

Density functions:

$$f_{12i}(t_{12i}) = \lambda_{12}\exp(-\lambda_{12}t_{12i})$$

$$f_{13i}(t_{13i}) = \lambda_{13}\exp(-\lambda_{13}t_{13i})$$

$$f_{23i}(t_{23i}) = \lambda_{23}\exp(-\lambda_{23}t_{23i})$$

Hazard functions:

$$h_{12i}(t_{12i}) = \lambda_{12}$$

$$h_{13i}(t_{13i}) = \lambda_{13}$$

$$h_{23i}(t_{23i}) = \lambda_{23}$$

Distribution functions:

$$F_{12i}(t_{12i}) = 1-\exp(-\lambda_{12}t_{12i})$$

$$F_{13i}(t_{13i}) = 1-\exp(-\lambda_{13}t_{13i})$$

$$F_{23i}(t_{23i}) = 1-\exp(-\lambda_{23}t_{23i})$$

For incorporating covariates x1, x2,….., x_n in model, we identify the effect of them on parameters of Exponential distributions (λ_{12}, λ_{13}, λ_{23}) that they are hazard functions.

$$\lambda_{12} = \exp(\beta_{012} + \beta_{112}x_1 + ... + \beta_{n12}x_n)$$

$$\lambda_{13} = \exp(\beta_{013} + \beta_{113}x_1 + ... + \beta_{n13}x_n)$$

$$\lambda_{23} = \exp(\beta_{023} + \beta_{123}x_1 + ... + \beta_{n23}x_n)$$

Likelihood function is written as follows

p is the probability of transition from state 1 to state 3. If the transition occurred between two states then the density function is used, otherwise the distribution function is used.

$$L = \prod_{i=1}^{n_{12}}(1-p)f_{12i}(t_{12i})\prod_{i=1}^{n_{13}}pf_{13i}(t_{13i})\prod_{i=1}^{n_{12}^*}1-[(1-p)F_{12i}(t_{12i})+pF_{13i}(t_{13i})]\prod_{i=1}^{n_{23}}f_{23i}(t_{23i})\prod_{i=1}^{n_{23}^*}1-[F_{23i}(t_{23i})]$$