Prediction of Long-term Kidney Failure in Renal Transplant With Chronic Allograft Dysfunction Using Stage-Specific Hazard Rates

Hamid Reza Khalkhali,[1] Ali Ghafari[2]

Abstract

Objectives: **The process of kidney failure in renal transplant recipients with chronic allograft dysfunction is characterized by a progressive decline in glomerular filtration rate over time that it is determined by the 5-stage model. This study used stage-based statistical survival analysis to predict graft survival in renal transplant recipients with chronic allograft dysfunction.**

Materials and Methods: **In a single-center, retrospective study, 214 renal transplant recipients with chronic allograft dysfunction were investigated at a university hospital in Iran from 1997 to 2005. At each patient visit, kidney function was assessed using glomerular filtration rate and stage of disease.**

Results: **The estimated stage-specific hazard rates of disease progression are stage one, 453.936; stage two, 485.040; stage three, 545.808; and stage four; 649.488 per 1000 person-years. The estimated mean times in each stage were as follows: kidney damage with normal or increased glomerular filtration rate, 26.43 months; kidney damage with mildly decreased glomerular filtration rate, 24.74 months; moderate kidney disease, 21.98 months; and severe kidney disease; 18.48 months. These estimates yield a mean time from stage 1 to kidney failure of 91.63 months. The probability of graft survival was predicted using estimated stage-specific hazard rates. The 18th, 58th, 118th, and 155th months' death-censored graft survival probabilities were 0.99, 0.75, 0.25, and 0.10.**

Conclusions: **In this method of survival analysis, we can determine a statistical model according to a real clinical model in renal transplant recipients with chronic allograft dysfunction. It enables us to determine the stage-specific hazard rates of disease progression. These findings can help nephrologists to understand the kidney disease process and better predict graft survival.**

Key words: *Graft survival, 5-stage model, Phase-type distribution, Markov model, Survival analysis*

Introduction

Globally, more than 500 million individuals, or about 1 in 10 adults in the general population, have some form of chronic kidney disease.1 Worldwide, more than 1.5 million people are currently alive through either dialysis or transplant.[1] The cumulative global cost for renal replacement therapy is predicted to exceed US $1 trillion.[1] In addition to its costs, chronic kidney disease leads to substantial patient morbidity and mortality. Unfortunately, many of these patients die before the initiation of renal replacement therapy.[2-4] Kidney transplant is considered the treatment modality of choice for most patients with end-stage renal disease. Yet recent evidence demonstrates that despite optimistic earlier estimates, long-term outcomes have not greatly improved in these patients.[5-8]

For many chronic diseases, clinicians are interested in studying the prognosis of disease to understand the mechanisms of disease progression.

From the [1]Department of Epidemiology and Biostatistics and the Center of Research in Nephrology and Transplantation, and the [2]Department of Nephrology, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran

Acknowledgements: *The authors thank the Center of Research in Nephrology and Transplantation of Urmia University of Medical Sciences. None of the authors declares any conflicts of interest. The authors would like to thank the Vice-chancellor of the Center of Research in Nephrology of Urmia University of Medical Sciences, Urmia-Iran, for financial support.*

Address reprint requests to: *Hamid Reza Khalkhali, PhD in Biostatistics, Department of Epidemiology and Biostatistics and the Center of Research in Nephrology and Transplantation, Public Health, Urmia University of Medical Sciences Urmia, 57147, I.R. Iran*
Phone: *+98 914 4432420* ***Fax:*** *+98 441 2770047* ***E-mail:*** *khalkhali@umsu.ac.ir*

Experimental and Clinical Transplantation (2012) 1: 8-13

DOI: 10.6002/ect.2011.0049

It may often be natural to think that the development of many medical and health-related conditions can be characterized as underlying processes that go through a set of stages. For example, chronic diseases such as cancer or human immunodeficiency virus (HIV) and AIDS progress with time from an early stage (sometimes) through intermediate and advanced stages to death. The progression of cancer can be determined by the size of tumor and by metastasis. The progression of AIDS can be characterized by methods such as CD4 and CD8 T-cell counts. Marker covariates are often measured repeatedly over time, such that they may not even effectively influence the underlying process but may rather be a measure of how far this process has advanced. Several studies are among those that have proposed analyzing HIV progression by modeling CD4 cell counts using the Markov model.[9-12] In another example, Escolano and associates[13] used a 5-stage model to study hospital-acquired infections in intensive care units. Hansen and associates[14] designed a 9-stage model to analyze liver transplant data. Other scenarios have been modeled by staging, including mortality in diabetes,[15] treatment of burns,[16] and treatment of diabetic retinopathy.[17, 18] Graft loss owing to chronic allograft dysfunction is a major concern in renal transplant recipients.[19, 20] Clinically, chronic allograft dysfunction is characterized by a progressive decline in the glomerular filtration rate (GFR) over time.[21]

Understanding the chronic kidney disease process in renal transplant recipients with chronic allograft dysfunction helps us to acquire knowledge and new insights about disease pathophysiology and the postoperative care of patients, which, in turn, will improve long-term graft survival. The aim of this study was to predict graft survival probability using stage-specific hazard rates. The statistical model was assumed according to a clinical 5-stage model for renal transplant recipients with chronic allograft dysfunction.

Materials and Methods

Population, data collection, and measurements

We performed a single-center, retrospective study in 214 renal transplant recipients with chronic allograft dysfunction, enrolled from among 1534 renal transplant recipients treated at the Urmia University of Medical Sciences Hospital, Urmia, Iran, from 1997 to 2005. The selection criteria were a functional renal allograft for at least 1 year and a progressive decline in allograft function. The Cockcroft-Gault estimation of creatinine clearance [(140-age) × (body weight)]/(serum creatinine × 72), was used to estimate kidney function.[22] Creatinine clearance was a marker covariate in which each renal transplant recipient had several visits (creatinine clearance measurement) during the study.

Staged progression based on clinical phases

Renal transplant recipients with chronic allograft dysfunction have a progressive decline in GFR, which was used to stage disease progression based on clinical phases according to the 5-stage model (Figure 1). We applied this staging system to determine pattern of disease progression per stage in this group of patients, according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease.[23]

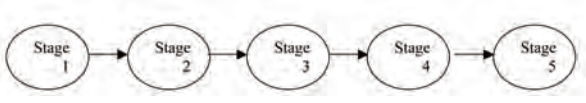

Figure 1. The 5-stage model for kidney disease progression according to National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease. Stage 1 (glomerular filtration rate, or GFR, ≥ 90 mL/min/1.73 m^2) indicates kidney damage with normal or increased GFR, stage 2 (GFR, 60-89 mL/min/1.73 m^2) indicates kidney damage with mildly decreased GFR, stage 3 (GFR, 30-59) indicates moderate kidney disease, stage 4 (GFR, 15-29) indicates severe kidney disease, and stage 5 (GFR, < 15 mL/min/1.73 m^2) indicates kidney failure or dialysis.

Statistical model and parameters estimation

The phase-type distributions are appropriate tools for modeling survival time in situations where the overall survival time is a progression through several stages.[24] We assumed the statistical model according to a clinical 5-stage model. Clinically, chronic allograft dysfunction is characterized by a decline in GFR over time, which in most of the studies can be described by linear or exponential functions.[25-29] We found in many studies, that for data analysis use of the Markov property by modeling the exponential distribution is not unreasonable for multistage disease progression of cancer or chronic disease by Markov assumption.[30-33] Therefore, we constructed the likelihood function using a time-homogeneous Markov model with a negative exponential waiting time (hereafter called *time*) in each stage (Table 1). The stage-specific hazard rates were estimated by

maximizing overall likelihood to time to kidney failure, using the following formula:

$$L(\lambda_1,\lambda_2,\lambda_3,\lambda_4|\text{data}) = \prod_{k=1}^{117} f_1(t_{k1}/\lambda_1) \times \prod_{k=1}^{176} f_2(t_{k2}/\lambda_2) \times \prod_{k=1}^{22} S_2(t^*_{k2}/\lambda_2)$$
$$\times \prod_{k=1}^{107} f_3(t_{k3}/\lambda_3) \times \prod_{k=1}^{85} S_3(t^*_{k3}/\lambda_3) \times \prod_{k=1}^{57} f_4(t_{k4}/\lambda_4) \times \prod_{k=1}^{50} S_4(t^*_{k4}/\lambda_4)$$

In likelihood function, λ_i, f_i, and S_i denote the stage-specific hazard rate, probability distribution function, and survival function of the time in stage i i→ i + 1. Let be the *k*th uncensored observation, t^*_{ki} be the *k*th censored observation where censoring occurred from stage i to stage i + 1. The likelihood was maximized using the general optim R code.[34]

Results

Data were available for 214 renal transplant recipients with chronic allograft dysfunction; the mean time (± standard deviation) to start of the chronic allograft dysfunction process was 9.8 ± 2.4 months after transplant. Renal transplant recipients had 12 to 56 visits (creatinine clearance measurements) during the study. For 6870 patient visits and grading, 614 transitions between stages of GFR occurred during the study. Among 614 observed transitions, 457 were completed, and 157 were censored, because there was no change in the stage between the last 2 visits. Table 1 shows the time censoring and descriptive information.

According to the clinical model, renal transplant recipients with chronic allograft dysfunction have a progressive decline in GFR. Therefore, we must assume a series' structure of phase-type distributions. There are 2 kinds of these models. The first assumption is that stage-specific hazard rates are equal in each stage: $\lambda_1 = \lambda_2 = \lambda_3 = \lambda_4 = \lambda$. The second assumption is that stage-specific hazard rates are different in each stage: $\lambda_i \neq \lambda_j$. The estimates of stage-specific hazard rates and other statistical indexes are shown in Table 2.

The hazard rate for each stage was estimated at 534.576 per 1000 person-years according to equal assumed rates. It means that we expected an average of 22.5 months in each stage before the patient's disease would progress to the next stage. According to unequal-assumed rates, estimated stage-specific hazard rates of disease progression were as follows: stage one, 453.936; stage two, 485.040; stage three, 545.808; and stage four; 649.488 per 1000 person-years.

Table 1. Waiting time censoring and descriptive information.

Transition	No censoring (n)	Right censoring (n)	Total transitions (n)
1 → 2	117	0	117
2 → 3	176	22	198
3 → 4	107	85	192
4→ 5	57	50	107
Total	457	157	614

Table 2. Transition rate estimation and other statistical indexes.

Distribution	Parameters (transition rate)	Estimate	Standard error	Rate*	Mean waiting time (mo)
Equal-assumed rate	λ	0.044548	0.0021	534.576	89.8
Unequal-assumed rate	λ_1	0.037828	0.00350	453.936	26.4
	λ_2	0.040420	0.00305	485.040	24.7
	λ_3	0.045484	0.00439	545.808	21.9
	λ_4	0.054124	0.00720	649.488	18.5

*Rate is the stage-specific hazard rate per 1000 person-years: $\lambda_i \times 12 \times 1000$.

The estimated mean times in each stage of kidney disease were as follows: kidney damage with normal or increased GFR, 26.4 months; kidney damage with mildly decreased GFR, 24.7 months; moderate kidney disease, 21.9 months; and severe kidney disease, 18.5 months. We used stage-specific hazard rates to predict stage-survival probability (Table 3).

According to unequal-assumed rates, about 50% to 60% of patients in 1 year will stay in the same stage; it means that about 40% to 50%, [1-S_i(t)], will progress to the next stage. Probability of disease progression over 2 years was as follows: stage one, 59.7%; stage two, 62.1%; stage three, 66.4%; and stage four; 72.7%. These probabilities of disease progression over 3 years were predicted as follows: stage one, 74.4%; stage two, 76.7%; stage three, 80.6%; and stage four, 85.8%. One of the main objectives of this study was to describe time to kidney failure by using estimated stage-specific hazard rates. According to equal-assumed rates, that is T, overall time from stage 1 to kidney failure have an Erlang (m = 4, λ) distribution; the second, λ_i, λ_j that is T,

Table 3. Prediction of stage-survival probability over time, according to 2 models.

		Time (mo)						
	Stage-specific hazard rate	0	6	12	18	24	30	36
Equal-assumed rate	0.044548	1	0.765	0.586	0.448	0.343	0.263	0.201
Unequal-assumed rate	0.037828	1	0.797	0.635	0.506	0.403	0.321	0.256
	0.040420	1	0.785	0.616	0.483	0.379	0.297	0.233
	0.045484	1	0.761	0.579	0.441	0.379	0.255	0.194
	0.054124	1	0.723	0.522	0.377	0.273	0.197	0.142

overall time has a hypoexponential distribution.[35, 36] Both models were compared with the Akaike information criterion.[37] This information criterion of the hypoexponential was less than the Erlang distribution (649.44 vs 683.33); therefore, the hypoexponential distribution was appropriate to study overall time for progression from stage 1 to kidney failure.

The probability of graft survival was estimated. The 13-month graft survival probability was 0.997; 18-month survival was 0.991; 2-year, 0.976; 3-year, 0.92; 5-year, 0.709; and 94-month, 0.409. For 100 months or longer, we also predicted the probability of graft survival. The 100-month graft survival was 0.364; 120-month, 0.293; and 140-month, 0.142. The hazard function for kidney failure in renal transplant recipients with chronic allograft dysfunction monotonically increased, that is, it converted to Min (λ_1, λ_2, λ_3 λ_4) in hypoexponential distribution.

Figure 2 shows the curves of survival function S(t) and hazard function h(t) for *T*, overall time for progression from stage 1 to kidney failure according to the hypoexponential distribution.

The mean time for progression to kidney failure was 91.6 months, and the median time was 84 months. The 18th, 58th, 118th, and 155th months' death-censored graft survival probabilities were 0.99, 0.75, 0.25, and 0.10.

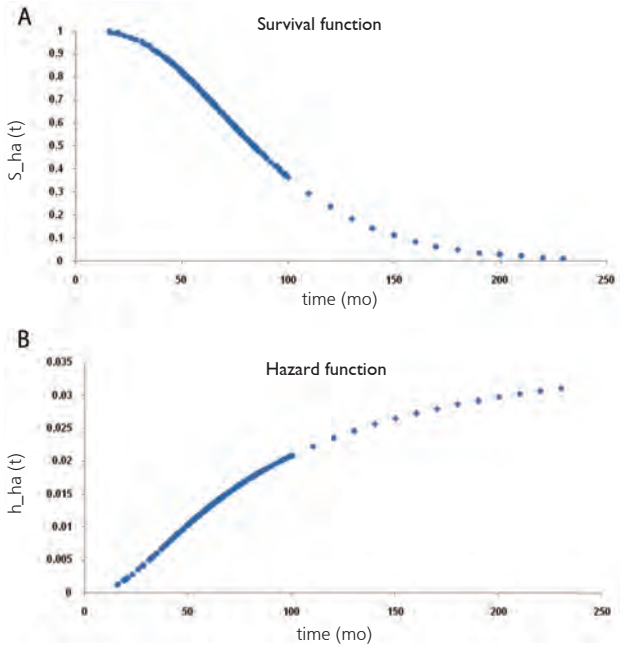

Figure 2. Survival function (A) and hazard function (B) curves for T, overall waiting time from stage one to kidney failure according to the hypoexponential distribution. Dots show the predictive value at times above 100 months, according to fitted distribution.

Discussion

In this study, we determined stage-specific hazard rates according to the 5-stage model in renal transplant recipients with chronic allograft dysfunction. These results showed that the rate of progression between stages became greater in more-advanced stages, which means that the rate of progression from stage 1 to 2 was slower than progression from stage 2 to 3, and so on. This finding is compatible with the hyperfiltration theory in chronic kidney disease.[38] According to this theory, loss of a number of glomeruli leads to hyperfiltration in remaining glomeruli. This hyperfiltration could destroy the remaining glomeruli, and this process could become more serious when the number of remaining glomeruli become fewer and fewer. We computed probability function, hazard function, mean, median, and other percentile for time to kidney failure in these patients using estimated stage-specific hazard rates. The mean and median times to kidney failure were 91.6 and 84 months. The 18th, 58th, 118th, and 155th months' death-censored graft survival probabilities were 0.99, 0.75, 0.25, and 0.10. Kukla and associates[28] found that the death-censored kidney survival in renal transplant recipients was 1-year 100%, 5-year 89%, and 9-year 50%. Consequently, using estimated GFR-based progression the half-life graft survival was 9.6 years. Sijpkens and associates[29] assessed deterioration of kidney function with creatinine clearance at 6 months. They found the death-censored kidney graft survival in the group with a creatinine clearance above mL/s/m^2 (> 50 mL/min/1.73 m^2), with a negative slope of creatinine clearance after 6 months, to be 1-year 98% survival, 5-year 86%, and 8-year 87%.

In the group with a creatinine clearance under mL/s/m^2 (< 50 mL/min/1.73 m^2), with negative slope of creatinine clearance after 6 months), survival was found to be 1-year 83%; 5-year 55%; 8-year 45%; and 10-year 39%. Djamali and associates[25] the kidney survival in renal transplant recipients was found in 1-year 100%, 5-year 88%, 8-year 76%, and 13-year 49%. The kidney survival in chronic kidney disease was found in 1-year 96%, 5-year 62%, and 14-year 17%. According to findings by Gill and associates,[26] assuming that the mean annualized decline in GFR remains constant and that return to dialysis occurs at 10 mL/min/1.73 m^2, the expected allograft survival

would be approximately 22.5 years for deceased-donor recipients and 27.3 years for live-donor recipients. Hariharan and associates[39] published estimates of allograft survival (11.0 to 19.0 years for deceased-donor grafts vs 16.9 to 35.9 years for living-donor grafts).

Conclusions

Despite the former survival data analyses (nonparametric survival analyses that were preferred by researchers in the medical sciences), in this method of data analysis, we can determine statistical model according to a real clinical model in renal transplant recipients with chronic allograft dysfunction. It enables us to determine the stage-specific hazard rates of disease progression. These findings may help nephrologists to better understand the kidney disease process and improve graft survival prediction.

References

1. World Kidney Day March 10, 2011 Web site. National Kidney and Transplant Institute Web site. http://www.worldkidneyday.org: Accessed November 18, 2011.
2. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med.* 2004;351(13):1285-1295.
3. Shlipak MG, Fried LF, Stehman-Breen C, Siscovick D, Newman AB. Chronic renal insufficiency and cardiovascular events in the elderly: findings from the Cardiovascular Health Study. *Am J Geriatr Cardiol.* 2004;13(2):81-90.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296-1305.
5. Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *Am J Transplant.* 2004;4(3):378-383.
6. Meier-Kriesche HU, Schold JD, Kaplan B. Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? *Am J Transplant*. 2004;4(8):1289-1295.
7. Sayegh MH, Carpenter CB. Transplantation 50 years later—progress, challenges, and promises. *N Engl J Med.* 2004;351(26):2761-2766.
8. Keith DS, DeMattos A, Golconda M, et al. Factors associated with improvement in deceased donor renal allograft function in the 1990s. *J Am Soc Nephrol*. 2005;16(5):1512-1521.
9. Longini IM Jr, Clark WS, Byers RH, et al. Statistical analysis of the stages of HIV infection using a Markov model. *Stat Med*. 1989;8 (7):831-843.
10. Gentleman RC, Lawless JF, Lindsey JC, Yan P. Multi-state Markov models for analyzing incomplete disease history data with illustrations for HIV disease. *Stat Med*. 1994;13(3):805-821.
11. Brookmeyer R, Liao J. Statistical modeling of the AIDS epidemic for forecasting health care needs. *Biometrics*. 1990;46(4):1151-1163.
12. Aalen OO, Farewell VT, De Angelis D, Day NE, Gill ON. A Markov model for HIV disease progression including the effect of HIV diagnosis and treatment: application to AIDS prediction in England and Wales. *Stat Med*. 1997;16(19):2191-2210.
13. Escolano S, Golmard JL, Korinek AM, Mallet A. A multi-state model for evolution of intensive care unit patient: prediction of nosocomial infections and deaths. *Stat Med*. 2000;19(24):3465-3482.
14. Hansen BE, Thorogood J, Hermans J, Ploeg RJ, Van Bockel JH, Van Houwelingen JC. Multistate modeling of liver transplantation data. *Stat Med*. 1994;13(23-24):2517-2529.
15. Andersen PK. Multistate models in survival analysis: a study of nephropathy and mortality in diabetes. *Stat Med*. 1988;7:661-670.
16. Satten GA, Datta S. Marginal estimation for multi-stage models: waiting time distributions and competing risks analysis. *Stat Med*. 2002;21(1):3-19.
17. Marshall G, Jones RH. Multi-state models and diabetic retinopathy. *Stat Med*. 1995;14(18):1975-1983.
18. Yau CL, Huzerbazar AV. Analysis of censored and incomplete survival data using flowgraph models. *Stat Med*. 2002;21:3727-3743.
19. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. *N Engl J Med*. 2002;347(2):103-109.
20. Chapman JR, O'Connell PJ, Nankivell BJ. Chronic renal allograft dysfunction. *J Am Soc Nephrol.* 2005;16(10):3015-3026.
21. Paul LC. Chronic allograft nephropathy: an update. *Kidney Int*. 1999;56(3):783-793.
22. Cockcrorft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16(1):31-41.
23. Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification: Part 4. Definition and classification of stages of chronic kidney disease. *Am J Kidney Dis*. 2002;39(2):S46-S75.
24. Aalen OO, Borgan O, Gjessing K. *Survival and Event History Analysis: A Process Point of View*. Springer Science+Business Media; 2008.
25. Djamali A, Kendziorski C, Brazy PC, Becker BN. Disease progression and outcomes in chronic kidney disease and renal transplantation. *Kidney Int*. 2003;64(5):1800-1807.
26. Gill JS, Tonelli M, Mix CH, Pereita BJG. The change in allograft functions among long-term kidney transplant recipients. *J Am Soc Nephrol.* 2003;14(6):1636-1642.
27. Gourishankar S, Hunsicker LG, Jhangri GS, Cockfield SM, Halloran PF. The stability of the glomerular filtration rate after renal transplantation is improving, *J Am Soc Nephrol*. 2003;14(9):2387-2394.
28. Kukla A, Adulla M, Pascual J, et al. CKD stage-to-stage progression in native and transplant kidney disease. *Nephrol Dial Transplant*. 2008;23(2):693-700.
29. Sijpkens YWJ, Zwinderman AH, Mallat MJK, Boom H, Fijter JWD, Leendert PC. Intercept and slope analysis of risk factors in chronic renal allograft nephropathy. *Graft*. 2002;5(2):108-113.
30. Faddy M J, Taylor GJ. Stochastic modeling of the onset of bronchiolitis obliterans syndrome after lung transplantation: an analysis of risk factors, mathematical and computer modeling. *Mathematical and Computer Modelling.* 2003;38(11-13):1185-1189.
31. Weijnen TJ, van Hamersvelt HW, Just PM, et al. Economic impact of extended time on peritoneal dialysis as a result of using polyglucose: the application of a Markov chain model to forecast changes in the development of the ESRD programme over time. *Nephrol Dial Transplant.* 2003;18(2):390-396.
32. Littlewood KJ, Greiner W, Baum D, Zoellner Y. Adjunctive treatment with moxonidine versus nitrendipine for hypertensive patients with advanced renal failure: a cost-effectiveness analysis. *BMC Nephrol*. 2007;8:9.
33. Hui-Min W, Ming-Fang Y, Chen TH. SAS macro program for non-homogeneous Markov process in modeling multi-state disease progression. *Comput Methods Programs Biomed*. 2004;75(2):95-105.
34. Maindonald J, Braun WJ. *Data Analysis and Graphics Using R: An Example-Based Approach*. Cambridge, England: Cambridge University Press; 2003.
35. Neuts MF. Probability distributions of phase-type. In: Liber amicorum Prof. Emeritus H. Florin, ed. *Chap Matrix-Geometric Solutions in Stochastic Models*, Department of Mathematics, University of Louvain, Louvain, France; 1975.

36. Bladt M, Neuts MF. Matrix-exponential distributions: calculus and interpretations va flow. *Commun Stat Stochastic Models*. 2003;19(3):115-129.
37. Akaike H. A new look at the statistical model identification. *IEEE Trans Automatic Control*. 1974;19:716-723.
38. Brenner BM. *Brenner and Rector's The Kidney*. 8th ed. New York, NY: Saunders; 2008.
39. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med*. 2000;342(9):605-612.